CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022372Orig1s000

MEDICAL REVIEW(S)

Cross-Discipline Team Leader Review

Date	June 28, 2010
From	John E. Hyde, Ph.D., M.D., Clinical Team Leader, DGP
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement #**	NDA 22-372 N000
Applicant	Braintree Laboratories
Date of Submission	July 1, 2008; Received July 2, 2008
PDUFA Goal Date	August 2, 2009
Proprietary Name / **Established (USAN) names**	SUPREP BOWEL PREP KIT Sodium sulfate, potassium sulfate, magnesium sulfate
Dosage forms / Strength	Oral Solution, 6 oz. bottle with 17.51 g sodium sulfate, 3.13 g potassium sulfate, and 1.6 g magnesium sulfate
Proposed Indication	Cleansing of the colon as a preparation for colonoscopy in adults.
Recommended:	Complete Response.

1. Introduction

This application, received July 2, 2008, is for a product consisting of a combination of sulfate salts proposed as a bowel preparation for "cleansing of the colon as a preparation for colonoscopy in adults," using (b) (4) overnight (b) (4) dosing regimens. The application is not for a new molecular entity.

The original PDUFA goal date for the application was 5/2/09. The goal date was extended to 8/2/09 based on a major amendment, but the review was delayed by a number of complications (see Submission and Review, under Background, below). The application was the subject of a Regulatory Briefing on 8/28/09.

The primary reviewing disciplines all recommended the product for approval. However, this CDTL Reviewer (Clinical Team Leader) concludes that the safety evaluations in the application do not satisfy the statutory standard and recommends a Complete Response action to require additional safety data. If the product is approved on this review cycle, this Reviewer recommends that the NDA should be subjected to significant postmarketing requirements to collect additional safety data.

2. Background

General Background

Bowel Cleansing Products
See the Clinical Review by J. Gatti for information about the approval history of the various bowel preparation products. The Applicant's rationale for developing this product was to provide a product that required a smaller volume of fluid compared to the PEG plus electrolytes products (2.8 L for Suprep vs. 4 L for Colyte and GoLytely, but MoviPrep requires only 3L), without using a concurrent stimulant laxative (which has been implication in ischemic colitis), and avoiding use of sodium phosphate (which has been implicated in phosphate nephropathy).

Sulfate Salts
Certain sulfate salts (sodium sulfate) were initially approved as an ingredient in bowel preparations in the U.S. in 1984 (on 7/13/84 with the approval of GoLytely, NDA 19-011, and on 10/26/84 with the approval of Colyte, NDA 18-983). Sulfate is also present in the bowel preparation MoviPrep (NDA 21-881). Both sodium sulfate and magnesium sulfate appear as active ingredients in approved products. Potassium sulfate is not listed as an active ingredient in any other approved drug (per current Orange Book). However, the approved products Colyte, GoLytely, and MoviPrep contain salts of potassium (KCl) and salts of sulfate (Na_2SO_4) together in solution, which is effectively the same as having potassium sulfate as part of solution.

Product
The product is a solution, with each 6 oz. bottle containing as the active ingredients 17.51 g sodium sulfate, 3.13 g potassium sulfate, and 1.6 g magnesium sulfate. The preparation involves taking two doses, (b) (4) as an overnight split dose separated by about 12 hours. Each dose is taken by diluting the solution in water to a volume of 16 oz. and consuming that plus an additional 32 oz. water over about an hour. This reviewer calculates that if the solutes are considered dissolved in water to the approximately 1.4 L recommended, each dose is effectively a volume of 1.4 L of a 325 mOsm/L solution with 176 mEq/L Na, 26 mEq/L K, 23 mg/dL Mg, and 110 mmol/L SO_4.

For the complete dose used for a bowel prep, MoviPrep contains 106 mmol SO_4, and GoLytely and Colyte contain 160 mmol of SO_4. Suprep contains nearly twice as much SO_4 as the latter two, with a total of 309 mmol in the total bowel prep dose.

Presubmission Activity

Suprep was developed under IND 74,808, which was received on 4/10/06. The IND was sponsored by the Applicant. The initial studies involved the investigation of several variations of bowel prep formulations based on sulfate salts.

An End-of-Phase-2 teleconference was held on 3/26/07. The meeting package included two study protocols, one comparing Suprep to MoviPrep (b) (4) . Both protocols had no follow-up evaluations

after the colonoscopy day visit. The meeting package cited data from Phase 2 studies showing that Suprep produced little change in urinary calcium. Further, tests showed that $CaSO_4$ should not precipitate at the urine concentration and pH observed in Phase 2.

Selected items of note from the 3/26/07 meeting were:

- Because the proposed sulfate dose exceeded amounts allowed as food additives, The FDA requested four-week oral toxicity testing in rodent and non-rodent species.
- The Division stated they viewed the drug as a combination product, but felt the company might be able to address it.
- The FDA requested additional studies in patients with hepatic and renal dysfunction and in geriatric patients to evaluate pharmacokinetics and effect on renal function. The Division agreed that renal and hepatic impairment could be addressed as a separate Phase 2 study and that geriatrics could be addressed as part of Phase 3 studies.
- The Applicant asked if 360 subjects would be adequate to address safety. The minutes do not record a direct response to that question. (b) (4)

  Because of recent reports of renal failure with phosphate nephropathy that were associated with sodium phosphate agents, the FDA requested evaluation of renal function at 1, 3, and 6 months after colonoscopy.
- The FDA stated that MoviPrep, (b) (4) were all acceptable comparators, and that the use of only one for both of the Phase 3 studies would be acceptable.
- The FDA commented that the dosing regimens were acceptable, but dose in labeling would depend on results.
- There was discussion of the advisability of enrolling patients with higher seizure risk due to reports with sodium phosphate products. The issue was resolved with agreement that such patients could be enrolled but should be balanced.
- The primary endpoint (as defined in the study descriptions below) was the same as used in NuLytely and HalfLytely and was acceptable to the FDA.
- The FDA advised the company about certain additional details that should be provided in the statistical sections of the protocols.

Two special protocol assessments were received on 4/9/07. The protocols used MoviPrep as the comparator for both protocols, (b) (4), and a follow-up visit at 30 days was added. The study designs were those described for Study 301 and Study 302 below, and the questions were essentially identical for the two protocols. In the SPA response letters sent on 5/21/07, Question 1 pointed to the addition of a follow-up visit at Day 30 and asked "Is this follow-up acceptable?" The FDA response acknowledged the evidence that calcium salt precipitation should not be expected with Suprep, and responded "… With this in mind, the proposed 30-day follow-up visit and lab testing is acceptable for the proposed study protocol." There was no other comment on the safety assessment plan. The SPA response letters also listed deficiencies that remained in the statistical section of the protocols, including the lack of justification for the non-inferiority margin.

No pre-NDA meeting was held between the FDA and the Applicant.

Submission and Review

The original NDA was dated July 1, 2008, and was received on July 2, 2008. It was given Standard review status with an action date of May 2, 2009.

The application was submitted in paper. During the filing review it was determined that the organization and tabbing were insufficient. Also, the Applicant had not provided electronic data sets for any of the safety or efficacy data. Electronic datasets were received by the end of August 2008, but it took a few cycles of interaction to get datasets and definition files that the clinical and statistical reviewer felt were adequate. Satisfactory datasets were received in December 2009.

The original PDUFA goal date for the application was 5/2/09. The PDUFA goal date was extended on 4/28/09 based on a major amendment received 4/21/09. Several factors created delays in the review of the application: satisfactory electronic datasets were not received until five months into the review cycle. Safety concerns raised by the clinical reviewer and certain omissions in the safety datasets and tabulations led to information requests for additional safety analyses in April 2009. Controversy concerning the adequacy of the safety evaluation led to the Division taking the application to a CDER Regulatory Briefing on August 28, 2009. Subsequently, substantial postmarketing requirements had to be negotiated. The reviewing Team's receipt of two Priority Review applications overlapping the end of the review cycle further delayed final work on this application until actions were taken on the priority applications.

The submission was considered by the Pediatric Review Committee (PeRC) on 4/29/09. The pediatric plan and Committee's recommendations are discussed in the Pediatrics section, below.

No Advisory Committee meeting was convened to discuss this application, but the application was presented in at CDER Regulatory Briefing on August 28, 2009.

The relevant review disciplines have all written review documents. The primary review documents relied upon are the following:

Clinical Review, by J. Gatti, dated 8/19/09.
Statistical Review and Evaluation, by M. Fan, dated 7/7/09.
Pharmacology/Toxicology Review and Evaluation, by T. Chakraborti, dated 3/6/09.
Office of Clinical Pharmacology Review, by P. Bai, dated 4/10/09.
Initial Quality Assessment, by M. Kowblansky, dated 8/25/08.
Chemistry Review, by T. Mehta, dated 7/16/09.
Chemistry Review (labels), by T. Mehta, dated 8/6/09.
Product Quality Microbiology Review, by V. Pawar, dated 4/7/09.
OSE Consult memo, by A. Mackey, dated 3/26/09.
Division of Cardiovascular and Renal Products Consult, by M. Blank, dated 10/14/09.
Office of Biostatistics Quantitative Safety Review, by B. Neustifter, dated 10/26/09.
Regulatory Project Manager Review (PLR Review) by M. Scherer, dated 3/25/09.
Regulatory Briefing Minutes, by M. Scherer, draft.

REMS Memorandum, by D. Griebel, dated 6/22/10
DSI Review by K. Malek, dated 3/24/09.
DMEPA Proprietary Name and Labeling Review, by A. Crandall, dated 4/16/09.
DMEPA Proprietary Name Review, by A. Crandall, dated 8/10/09.
DMEPA Proprietary Name Review, by A. Crandall, dated 1/15/10.
DMEPA Proprietary Name Review, by A. Crandall, dated 5/6/10.
DRISK Review of Patient Labeling, by B. Fuller, dated 8/7/09.
DDMAC Labeling Comments, by S. Doshi and K. Klemm, dated 4/14/09.
DDMAC Labeling Comments (MedGuide), by S. Doshi, dated 6/9/10.

The reviews should be consulted for more specific details of the application and review conclusions. This memorandum summarizes selected information from the primary review documents.

3. CMC

The product is a solution, with each 6 oz. bottle of solution containing 17.51 g sodium sulfate (123 mmol Na_2SO_4, MW 142.04), 3.13 g potassium sulfate (18 mmol K_2SO_4, MW 174.26), and 1.6 g magnesium sulfate (13 mmol $MgSO_4$, MW 120.37) as the active ingredients. It also contains sodium benzoate (b) (4), sucralose (b) (4), malic acid (b) (4), and (b) (4) flavoring agents. (b) (4) purified water. The solution is clear to slightly hazy. The product is packaged in an amber (b) (4) container.

(b) (4) the manufacturer for sodium sulfate and magnesium sulfate. For potassium sulfate, (b) (4) Braintree Laboratories performs the commercial scale manufacturing and packaging of the drug product. Several commercial laboratories are used for a variety of QC tests.

(b) (4)

The CMC Reviewer found there was sufficient information provided to assure the identity, strength, purity, and quality of the product. There was sufficient stability data to support an expiry of 24 months. The Reviewer found the Applicant's post-approval stability protocol for the drug product to be acceptable. A categorical exemption was granted for the environmental assessment requirement. In his initial review (7/16/09), the CMC Reviewer identified deficiencies in the container labels that required correction. In his review dated 8/6/09, he found the labels received on 8/3/09 to be acceptable.

The Office of Compliance made an "Acceptable" recommendation.

The Microbiology Reviewer confirmed the effectiveness (b) (4) and found the stability data were acceptable.

Because the product required dilution before administration, there was discussion within ONDQA (documented in the CMC review dated 7/16/09) about whether the dosage form nomenclature should include the word (b) (4) The final recommendation was to use the dosage form designation "oral solution," in keeping with USP conventions.

Conclusions and Recommendations
The Chemistry Reviewer recommended the application for approval. The dosage form designation recommended by ONDQA was "oral solution." The Microbiology Reviewer recommended the application for approval. No Phase 4 commitments, agreements, or risk management steps were recommended by the Reviewers.

4. Nonclinical Pharmacology/Toxicology

The application contained two 28-day, repeated-dose, oral toxicity studies, one in rats and one in dogs. Animals were dosed by oral gavage with a combination of sulfate salts, similar to the combination in Suprep, dissolved in vehicle (deionized water) and administered in a volume of 15 mL/kg.

In the rat study, the doses were 1.25, 2.5, and 5.0 g/kg/day. Vehicle and 5.13 g/kg/day of oral sodium phosphate (OSP, the ingredient in Fleet Phospho Soda) were used as controls. The animals developed diarrhea and swollen abdomens. There were no significant hematology changes. Serum chemistry changes were decreased chloride, potassium, sodium, and serum osmolality, and increased bicarbonate. Urine showed increased sodium, potassium, and pH. Calcium and phosphorus were unchanged. Creatinine clearance was not altered except at the highest dose in females, but there were dose-related increases in the clearances of sodium and potassium. Necropsy findings were dose-related dilation of colon and jejunum and minimal to mild adrenal cortical vacuolization. Renal mineralization was only seen in females; it was minimal in two animals on test article and mild in one treated with vehicle. In the group treated with the OSP control, there was moderate to severe renal mineralization at necropsy. Chemistry data in the sodium phosphate group were limited due to early animal losses, but the available data showed decreased calcium, increased phosphate, decreased creatinine clearance, and increased clearance of sodium and potassium.

In the dog study, the doses were 1.25, 2.5, and 5 g/kg/day. Vehicle was used as a control. The animals exhibited emesis, excessive drinking of water, and abnormal excreta (soft and/or mucoid feces and/or diarrhea). There were no significant changes in hematology or clinical chemistry results. The urine showed increased pH and increased sodium. The sodium clearance was increased from baseline, but the increase was not clearly dose-related. There were no significant ECG findings. There were no significant gross or histopathology findings on necropsy.

CDTL Comment: The finding in the rat study of increased fractional excretion of sodium and potassium in the face of decreased serum sodium and potassium suggest dose-related renal

tubular toxicity. The findings in dogs are less clear, but the increased sodium clearance suggests there may have also been a renal tubular effect in dogs. Although a dramatic difference in renal calcification was seen, the other renal effects were not that clearly different between the sodium phosphate and sulfate salt preps.

The Nonclinical Reviewer recommended changes to the labeling in Section 8.1 (Pregnancy) and 8.3 (Nursing Mothers) to comply with required regulatory wording. He also recommended several changes to Section 13 (Nonclinical Toxicology) to provide more complete information about the nonclinical studies and remove statements (b) (4)

Conclusions and Recommendations
The Nonclinical Reviewer concluded that the nonclinical studies in the application were adequate to support the proposed use and recommended that the application could be approved from the nonclinical perspective. The Reviewer stated the Applicant should be asked to make the labeling changes as described in his review. He did not recommend any Phase 4 commitments.

5. Clinical Pharmacology/Biopharmaceutics

General clinical pharmacology/biopharmaceutics.
In response to requests made at the End-of-Phase 2 teleconference, the Applicant conducted Study 202, which evaluated pharmacokinetics and pharmacodynamics in six healthy subjects, six subjects with moderate renal impairment (GFR 42 to 48 mL/min), and six patients with mild or moderate hepatic impairment (Child-Pugh A in five patients, B in one patient). Subjects received a split dosing regimen, with one dose at 6 am and the second dose at 6 pm. They were allowed only clear liquids during that day until 2 hours after the second dose. Evaluations included serum and urine sulfate, serum chemistry, hematology, vital signs, and ECGs.

The baseline serum sulfate means were 335 µmol/L in normals (normal range cited as 240 to 420 µmol/L), 607 µmol/L for the renal impairment group, and 407 µmol/L for the hepatic impairment group. The sulfate PK parameters (corrected for baseline concentrations) are shown in the table below:

Study 202: Serum Sulfate PK Parameters Corrected for Pre-dose Sulfate

Mean (% CV)

	Healthy normal (n = 6)	Moderate Renal impairment (n = 6)	Mild/moderate hepatic impairment (n = 6)
C_{max} (µmol/L)	500 (33%)	717 (38%)	560 (27%)
AUC_T (mmol*hr/L)	8.0 (43%)	12.3 (34%)	10.8 (27%)
T_{max} (hr)*	16.8 (48%)	17.5 (17%)	14.2 (35%)
$T_{1/2}$ (hr)	8.5 (54%)	10.2 (92%)	5.6 (41%)

* T_{max} is expressed as hours after the *first* of the two doses, which was 12 hours before the second dose.
Table is adapted from table in Section 1.4 of Office Clinical Pharmacology Review.

For all groups, sulfate levels generally increased within an hour after the first dose. They returned to pre-dose levels by Day 6, and any elevations on Day 3 were not statistically distinguishable from pre-dose levels. Urine sulfate levels were higher on Day 3 than predose, but declined to close to pre-dose levels by Day 6. The Applicant estimated that the cumulative % dose of sulfate secreted in the urine within 30 hours was approximately 20% in healthy subjects, but the CV was large (62%) and the estimate did not correct for baseline endogenous sulfate excretion.

Serum sodium, potassium, and magnesium remained relatively constant during the study period as shown in the table below:

Study 202: Mean Serum Sodium (mEq/L), Potassium (mEq/L), and Magnesium (mg/dL) over Study Period

	Pre-dose	12 hrs after Dose 2	Day 3	Day 6
Healthy Normal (n=6)				
Sodium	141.0	140.3	139.8	140.0
Potassium	4.0	4.0	3.9	4.0
Magnesium	1.76	1.70	1.67	1.64
Renal Impaired (n=6)				
Sodium	138.8	139.3	141.2	140.3
Potassium	4.2	4.2	4.2	4.2
Magnesium	1.56	1.58	1.56	1.50
Hepatic Impaired (n=6)				
Sodium	140.8	141.8	141.0	140.8
Potassium	4.0	4.1	4.2	4.2
Magnesium	1.75	1.71	1.67	1.72

Table is adapted from table in Section 2.2.4 of Office Clinical Pharmacology Review. Data source is Applicant's Table 15.2.1.1, Clinical Chemistry Assessments, in vol. 4.1 of Module 5.

From these results, the Reviewer concluded that there was no difference between the three subject groups regarding serum sodium, potassium, or magnesium.

Serum creatinine also remained fairly stable and stayed within the normal range for healthy and hepatic impairment patients. Of note is one healthy normal patient (006) with baseline creatinine of 1.0 mg/dL that rose to 1.4 at 30 hours and then returned to normal.

Drug-drug interactions

No drug-drug interaction studies were conducted.

Demographic interactions/intrinsic factors/special populations

Study 202 was too small to permit demographic or other analysis apart from disease group. There was only one elderly patient in the study. Sulfate levels were not measured in the Phase 3 studies, so there are no other assessments of sulfate PK parameters.

Conclusions and Recommendations

The Clinical Pharmacology Reviewer found the information in the NDA acceptable from the clinical pharmacology perspective. Her recommended labeling changes were deletion of section

12.2 (Pharmacodynamics) and revisions to section 12.3 (Pharmacokinetics) to provide more complete information about the findings of Study 202. The Reviewer did not recommend any Phase 4 commitments in her review document.

The Clinical Pharmacology Reviewer participated in the Postmarketing Requirement negotiations with the Applicant that followed the Regulatory Briefing. For the clinical trial that was being considered, she recommended that the ECG and laboratory testing being planned as part of the safety evaluations should be timed to try to capture any effects at the peak of sulfate exposure, which she estimated to be between 5 and 8 hours after completing dosing.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application, because it is not intended as an antimicrobial product.

7. Clinical/Statistical-Efficacy

This submission contained two primary Phase 3 efficacy studies. Both studies compared Suprep to MoviPrep, which is an approved PEG plus electrolytes osmotic laxative. The studies differed only in the dosing regimen. For each dose of Suprep, the procedure was to dilute the contents of a 6 oz. bottle in water to a volume of 16 oz and consume it, to be followed by two additional 16 oz. volumes of water consumed over the following hour (total volume of 1.4 L). Two doses are required for the complete prep, so the total required volume for a prep is 2.8 L. MoviPrep was taken according to labeled instructions (described in under the individual studies); the total volume required for MoviPrep prep was 3 L. In Study 301 two doses of each drug were taken on the evening before colonoscopy ("consecutive dose" for purposes of this review), whereas in Study 302 one dose was taken in the evening and the second the following morning ("split dose").

In both studies, different dietary instructions were given for the two different treatments: Those randomized to Suprep were instructed to have a light breakfast the day before colonoscopy followed only by clear liquids until after the colonoscopy. Patients randomized to MoviPrep were allowed to have a normal breakfast, light lunch, and clear soup or plain yogurt for supper, to be completed at least one hour before starting dosing. Only clear liquids were allowed after supper until colonoscopy was completed.

Consecutive-Dose Study BLI800-301 (Study 301)

This study was a randomized, single-blind, active-controlled, multicenter, non-inferiority study in adult scheduled to undergo colonoscopy. The study enrolled 408 patients at 11 sites. Patients were randomized to Suprep Bowel Prep Kit or to MoviPrep. Patients took two consecutive doses of the drug the evening before colonoscopy.

Eligibility, treatment, and assessments

To be eligible, patients needed to be undergoing colonoscopy for a routine indication, including screening, diagnostic workup, or other follow-up, but otherwise in good health. Patients were excluded for severe GI conditions, foreign body removal, significant electrolyte abnormalities (but without specific criteria), aspiration predisposition, history of renal or hepatic insufficiency, CHF, or previous GI surgery. A urine pregnancy test and contraceptive measures were required for females of child-bearing potential. See the Clinical Review for additional details of the eligibility criteria.

Patients were randomized with equal probability to receive Suprep or MoviPrep. Those randomized to Suprep were instructed to take the first dose starting about 6 pm, and to take the second dose at about 7 pm, but no later than 9 pm. For those randomized to MoviPrep, dosing was to begin at approximately 6 pm. Patients were to take the first liter of solution as divided doses over an hour (~8 oz every 15 minutes). The second liter was to taken in a similar manner starting about 7:30 pm. An additional 1 L of clear fluid was to be taken during the evening. Concomitant medications were not restricted but their use was recorded.

A screening visit (Visit 1) was to take place about two weeks before the colonoscopy. Screening consisted of physical exam, history, blood chemistry and hematology testing, and urine pregnancy test. Patients were dispensed medication at this visit, but those who were later found to be disqualified on the basis of screening lab results were instructed to return the medication. On the day of colonoscopy (Visit 2), but prior the procedure, patients had physical exam and repeat blood testing. A follow-up visit approximately one month after the procedure (Visit 3) consisted of physical exam and final blood tests. Adverse event data were collected at Visits 2 and 3; this included a special Symptom Scale questionnaire targeting GI symptoms that was to be completed during the prep and returned at Visit 2.

Endpoints

The primary endpoint was the quality of the preparation, with success defined by a colonoscopy grading score of 3 or 4, where 3 = "good" (small amount of feces or fluid not interfering with exam), and 4 = "excellent" (not more than small bits of adherent feces, fluid). Endoscopists were blinded to treatment assignment. The primary analysis was a non-inferiority comparison to MoviPrep with a margin of 15%; acceptance of the non-inferiority hypothesis was to be followed by a test for superiority. Patients who took any of the drug were considered to be in the (Applicant's) "ITT" population.

Protocol-specified secondary endpoints were adequacy of cleaning and need for re-preparation. No multiplicity adjustment was proposed.

Results

From 416 patients screened, 408 patients from 11 sites were randomized in Study 301. Of these, 204 were assigned to Suprep and 204 to MoviPrep. Among those randomized, the mean age was 57, with 26% 65 years or older, the mean weight was 185 lbs, percent male was 45%, and percent Caucasian was 88%. The three most common specified reasons for colonoscopy were screening (66%), GI bleeding (7%), and constipation/diarrhea (5%). The proportion considered to be "high risk" was 48%; this was imbalanced, with 43% in Suprep and 53% in MoviPrep.

Of the 408 randomized, 387 took the study medication, and 382 completed colonoscopy. By the Applicant's ITT analysis, the study met the pre-specified non-inferiority margin, but did not demonstrate superiority of Suprep over MoviPrep:

Proportion of Preparation Success in Study 301
Applicant's "ITT" Analysis

Suprep	MoviPrep	Difference	C.I. for difference
82.0% (159/194)	**80.3%** (155/193)	**1.6%**	**(-5.7%, 9.8%)**

For the secondary endpoint of "adequate preparation," calculated only for patients who completed colonoscopy, the proportions were 93.7% for Suprep and 94.8% for MoviPrep.

The Statistical Reviewer calculated the success rates using the true ITT population of all randomized patients, counting as failures those who did not take the medication. By that analysis, success rates were 77.9% for Suprep and 76.0% for MoviPrep. The difference, and confidence interval for the difference, were similar to those from the Applicant's analysis and also met the non-inferiority margin with a lower limit of -6.2%. The Statistical Reviewer observed that the treatment differences were consistent among subgroups of gender and age. He could not draw a conclusion about efficacy in racial subgroups due to the low representation.

The Statistical Reviewer noted that a -15% non-inferiority margin (absolute difference) could imply a relative difference as large as 20.5%, and he felt the Applicant had not justified the choice adequately. However, he noted that a *relative* difference of 10% would lead to an absolute non-inferiority margin of -7%, which the study met, so he found the results provided adequate evidence of non-inferiority.

Conclusions and Recommendations
The Statistical Reviewer concluded that the study supported a finding of non-inferiority of Suprep compared to MoviPrep. The Clinical Reviewer concluded that the results showed evidence of efficacy, but she noted that the difference in concomitant diet favored Suprep. She felt a claim of comparability of the two preparations was not supported, because the comparison was not made on the background of similar diets.

Split-Dose Study BLI800-302 (Study 302)

This study was a randomized, single-blind, active-controlled, multicenter, non-inferiority study in adults scheduled to undergo colonoscopy. The study enrolled 379 patients at 10 sites. Patients were randomized to Suprep or to MoviPrep. Patients took one dose of the drug the evening before colonoscopy and the second dose the next morning.

Eligibility, treatment, and assessments
The eligibility criteria were the same as for Study 301, above.

Patients were randomized with equal probability to receive Suprep or MoviPrep. Those randomized to Suprep were instructed to take the first dose starting about 6 pm. At about 6 am the next morning they were to take the second dose and complete the preparation at least one

hour prior to colonoscopy. For those randomized to MoviPrep, dosing was to begin at approximately 6 pm. Patients were to take the first liter of solution as divided doses over an hour (~8 oz every 15 minutes). An additional 0.5 L of clear fluid was to be taken during the evening. The second liter of solution was to be taken in similar divided doses starting about 6 am the next morning, followed by an additional 0.5 L of clear liquids. The preparation was to be completed at least one hour before the colonoscopy. Concomitant medications were not restricted but their use was recorded.

The visits and monitoring plan were the same as described for Study 301, above.

Endpoints

The primary endpoint was success, defined in the same way as for Study 301, above. The analysis plan was essentially identical, except that only patients who completed colonoscopy were considered to be in the (Applicant's) "ITT" population.

Results

From 379 patients screened at 10 sites, all 379 patients were randomized in Study 302. Of these, 190 were assigned to Suprep and 189 to MoviPrep. Among those randomized, the mean age was 56, with 22% 65 years or older, the mean weight was 184 lbs, percent male was 46%, and percent Caucasian was 87%. The three most common specified reasons for colonoscopy were screening (61%), GI bleeding (15%), and constipation/diarrhea (7%). The proportion considered to be "high risk" was 46%. No major demographic imbalances were noted.

Of the 379 randomized, 364 took the study medication, and 363 completed colonoscopy. For this study, the Applicant's "ITT" analysis included only patients who completed colonoscopy. By that analysis, the study met the pre-specified non-inferiority margin, but did not demonstrate superiority of Suprep over MoviPrep:

Proportion of Preparation Success in Study 302
Applicant's "ITT" Analysis

Suprep	MoviPrep	Difference	C.I. for difference
97.2% (175/180)	**95.6%** (175/183)	**1.6%**	**(-2.2%, 5.4%)**

For the secondary endpoint of "adequate preparation," calculated only for patients who completed colonoscopy, the proportions were 98.9% for both Suprep and MoviPrep.

The Statistical Reviewer calculated the true ITT success rates using all randomized patients, counting as failures those who did not take the medication. By that analysis, success rates were 92.1% for Suprep and 92.6% for MoviPrep. The confidence interval for the difference was wider, with a lower limit of -5.8%. That still met the pre-specified non-inferiority margin. The Statistical Reviewer observed that treatment differences were consistent among subgroups of gender and age. He could not draw a conclusion about efficacy in racial subgroups due to the low representation.

The Statistical Reviewer also noted that an analysis of cleansing score using the full 4-point scale (as opposed to dichotomizing into success of failure) showed Suprep to be slightly superior to

MoviPrep (nominal p = 0.034), due to the fact that Suprep had a higher proportion of "excellent" scores.

The Statistical Reviewer expressed the same reservations about the Applicant's choice of non-inferiority margin as he had for Study 301. For the high success proportions seen in this study, he noted that a *relative* difference of 5% would be more reasonable. That would lead to a non-inferiority margin of -4%, which was not met by the true ITT analysis.

Conclusions and Recommendations
The Statistical Reviewer concluded that the study met its pre-defined non-inferiority margin, but did not feel the margin was adequately justified. The Clinical Reviewer concluded that the results showed evidence of efficacy, but, as in Study 301, she noted that the difference in concomitant diet favored Suprep, so that a claim of comparability of the two preparations was not supported.

8. Safety

The bulk of the safety data came from the two Phase 3 studies described above. These studies included 751 treated patients, of whom 375 were exposed to Suprep. The Applicant also provided safety data from 18 patients who took Suprep in the PK study (Study 202), described in the Clinical Pharmacology section, above. Supplemental safety information came from the Applicant's Phase 1 and 2 studies. Although those studies included more extensive safety monitoring than the two Phase 3 studies, all of that experience involved various earlier formulations that were not the to-be-marketed product, and the studies used various doses. (One of these studies, Study 101, is reviewed more fully in the Clinical Pharmacology Review because it included pharmacodynamic evaluations.)

The only death reported in the application was a 76 year old male who receive MoviPrep and died two months after the colonoscopy from respiratory arrest with acute renal failure as a complication of colonic resection. The Applicant reported two serious adverse events (SAEs) in the Phase 3 studies; both were in the MoviPrep group: hospitalization for atypical chest pain with MI ruled out, and colonic perforation (of note, the perforation was not reported by the investigator to the Applicant until 16 months after the event).

The Clinical Reviewer also commented on two other significant AEs: mild ischemic colitis noted on colonoscopy in a patient who receive MoviPrep, and third degree AV block in an 83 year old male who took Suprep. This latter patient took Suprep in Study 301 using the consecutive dose regimen. He had a history of gout and hypertension; he was taking allopurinol, fosinopril, and prophylactic aspirin. At screening, he had normal vital signs and potassium was 5.2. When presenting for colonoscopy he complained only of nausea and bloating. His physical exam was normal, and potassium was 4.8, but he was found to be in third degree heart block. He was referred for treatment and did not have colonoscopy. The investigator considered the event unrelated to treatment and probably due to a pre-existing medical condition.

Adverse events in the clinical studies were collected from spontaneous reports, but patients were also given a Symptoms Scale questionnaire more specifically targeting the expected GI adverse reactions known to occur with bowel preps (nausea, vomiting, abdominal symptoms). In the initial datasets and tabulations the Applicant provided, GI symptoms were included only if rated "bothersome," "distressing," or "severely distressing" by the patients on the questionnaire. The Clinical Reviewer requested a re-analysis of the safety data with all events included. The following is the revised tabulation of common adverse events from the Clinical Review (Section 7.1.5.4). Common adverse reactions (≥ 3%) in the two Phase 3 studies were overall discomfort, abdominal fullness, nausea, abdominal cramping, and vomiting. A table of adverse reactions occurring at a rate of ≥ 1% is shown below:

Studies 301 & 302: Common Adverse Events (Incidence > 1%)

	Same (One) Day Regimen		Split Day Regimen	
Symptom	Suprep (n=194)	MoviPrep (n=193)	Suprep (n=181)	MoviPrep (n=183)
Discomfort	63%	60%	56%	69%
Abdominal Distension	57%	55%	43%	54%
Abdominal Pain	37%	35%	38%	44%
Nausea	46%	39%	38%	34%
Vomiting	13%	4%	9%	4%
Headache	2%	2%	1%	<1%

Adapted from Clinical Review, Section 7.1.5.4, Table 21.

It is noteworthy that all the vomiting cases with Suprep that were rated greater than mild in severity were females.

Chemistry measurements at screening and the colonoscopy visit were obtained on 352 Suprep patients (94% of those treated) and 364 MoviPrep patients (97% of treated). Mean changes in serum chemistries were generally mild, but a few contrasts between the two products deserve mention:

- Mean bicarbonate fell by less than 1.0 mEq/L for Suprep in either study, while MoviPrep decreases were 1.6 to 1.7.
- Chloride tended to fall by 0.6 mEq/L with Suprep but rose by 0.8 to 1.6 with MoviPrep.
- Mean osmolality fell by 1.8 and 2.6 mOsm/kg in the two studies for Suprep, but fell by 1.0 or less with MoviPrep.
- Total protein rose by 0.12 to 0.18 g/dL for Suprep, but rose by 0 to 0.07 g/dL for MoviPrep.
- Notably, uric acid rose by 0.45 to 0.55 mg/dL for Suprep, but by 0.0 to 0.02 for MoviPrep.

See Clinical Review, section 7.1.7, for detailed tabulations of mean chemistry values at each visit and their changes. See also the Quantitative Safety Review (consult) for additional safety analyses.

The frequencies of abnormal (i.e., outside normal range) chemistry values of interest at the colonoscopy visit are shown in the following table:

Studies 301 & 302: Prevalence of Selected Abnormal Chemistry Results on Day of Colonoscopy

	Na ↓	Na ↑	K ↓	K ↑	Bicarb ↓	Bicarb ↑
Suprep (n=352)	2.8%	1.4%	0.9%	3.4%	11%	0.3%
MoviPrep (n=364)	2.2%	2.2%	1.9%	2.7%	16%	0.3%
	Ca ↓	Ca ↑	Phos ↓	Phos ↑	BUN ↑	Creat ↑
Suprep (n=352)	0.9%	9.1%	4.3%	2.6%	7.1%	8.2%
MoviPrep (n=364)	0.0%	3.8%	3.6%	1.4%	8.8%	9.6%

Derived from Applicant's Table 14.3.6.1, p. 137-139 in vol. 8.1 of Module 5.

The two products were generally similar by this analysis, although Suprep had fewer patients with abnormally low bicarbonate, but more patients with elevated calcium.

Several of the abnormalities tabulated above were in patients with pre-existing abnormalities. The frequencies of *new* abnormal chemistry values at the colonoscopy visit among patents whose values (for that analyte) were normal at screening are given in the table below:

Studies 301 & 302: Incidence of Abnormal Chemistry Results in Patients with Normal Values at Screening Visit (Only Events with Proportion ≥ 5% for Suprep)

	Bicarb ↓	Ca ↑	Gluc ↑	bili ↑	T. prot ↑	Uric Acid ↑
Suprep	11%	7.2%	9.6%	9.1%	5.1%	26%
MoviPrep	15%	2.7%	11.1%	13.2%	1.1%	12%

Derived from Applicant's Table 14.3.6.1, p. 137-139 in vol. 8.1 of Module 5.

The partly reflects findings of the preceding table, but also shows a large proportion of patients who developed elevations of uric acid. The latter finding accords with the elevation in mean uric acid mentioned above.

In each of the two studies, patients taking Suprep had a mean weight loss of 2.8 lbs at the day of colonoscopy, while patients taking MoviPrep had a mean loss of 2.2 lbs in each study; the p-values for the differences between treatments were 0.04 in Study 301 and 0.067 in Study 302. For both treatments, and in both studies, mean systolic blood pressures at day of colonoscopy were within 4 mmHg of baseline, and mean diastolic pressures were within 2 mmHg of baseline. Mean pulses rose by about 2 bpm in Study 301 and fell by less than 1 bpm Study 302. There were no significant differences between the treatment groups for blood pressures or pulse.

The Clinical Reviewer noted a relatively high frequency of bradycardia (heart rate < 60) in the adverse event database, and requested further analyses from the Applicant. The frequency of bradycardia at the colonoscopy visit was 9.7%, only slightly higher than the baseline prevalence of 7.8% and lower than the frequency for MoviPrep. No obvious clinical correlates were identified (see Clinical Review, section 7.1.8.3).

The Clinical Reviewer did additional investigations prompted by the observation of several instances of CK elevations for both drugs in Studies 301 and 302. In several cases the elevation was most pronounced at the one-month follow-up visit. The Clinical Reviewer requested additional analysis and information regarding the cases. CK isoenzymes were not available. None of the cases was associated with cardiac symptoms or any sequelae on follow-up. The

Applicant proposed that the cases could be explained by medications (several patients were taken statins, which can elevate CK) or exercise. No other clinical correlates were identified by the Clinical Reviewer.

The Statistical Reviewer performed some supplemental analyses of the safety data (using the database as initially reported by the Applicant) and noted that the proportion of elderly with an adverse event was higher for Suprep (28%, compared to 6% for MoviPrep). He also noted that mean symptom severity tended to be higher for Suprep, but with only vomiting reaching statistical significance. He found that females had more vomiting symptoms with Suprep vs. MoviPrep, and there was a similar trend for nausea symptoms. In his analysis, more high risk patients had adverse events with Suprep than MoviPrep (16% vs. 5%), and GI symptoms tended to be higher with Suprep (12% vs. 5%).

Consults

Quantitative Safety Review

The Quantitative Safety Reviewer evaluated the safety data from Studies 301 and 302 to assess the frequency and relationship to treatment for new elevations of BUN, creatinine, uric acid, and magnesium; new decreases in bicarbonate; and any new abnormalities of sodium, potassium, chloride, calcium, phosphorus, and osmolality (with new defined as occurring in a patient with baseline (Visit 1) value that was normal or in the direction opposite of the post-treatment abnormality). He also looked for associations of the abnormalities with demographic factors and adverse events.

Extensive tabulations of rates of abnormalities can be found in the consult review. Findings that the reviewer noted in his summary were the following:

- Suprep appeared to have more frequent abnormal calcium values than MoviPrep (12% vs., 7%) and more frequent uric acid elevations than MoviPrep (22% vs. 15%). Abnormal calcium was found more frequently with the split dosing vs. the one-day dosing for both products (17% vs. 8% for Suprep, 9% vs. 6% for MoviPrep). [*CDTL Note: this was the opposite of the relationship of adverse events with dosing regimen.*] Suprep had a lower frequency of abnormal chloride (6%, vs. 15% for MoviPrep).
- There appeared to be a relationship between gender and elevated creatinine (3% for females, 10% for males) but no visible confounding with treatment or regimen. The Reviewer felt this was the only analyte that appeared to have a relationship with gender.
- Vomiting was more common with Suprep (11%, vs. 4% for MoviPrep). Among patients taking Suprep, abdominal distention was more common with the one-day dosing than split dosing (57% vs. 43%).
- Females had a higher risk of abdominal distension, abdominal pain, discomfort, nausea, and vomiting. The risk increase did not differ significantly by treatment.
- Abnormal serum osmolality appeared to be associated with abdominal pain, with an odds ratio of 1.9. Abnormal sodium was associated with vomiting with an odds ratio of 3.2.
- A small number of patients had redrawn blood samples (overall, around 2% of samples were redrawn, ranging from 0% to 2.8% depending on study, treatment group, and visit), but there was lack of recorded justification for a large portion of them.

The Quantitative Safety Reviewer regarded all of the findings as exploratory, but recommended giving consideration to requesting post-marketing trials to determine the strength of effects of Suprep on calcium and uric acid and to investigate the evidence of an abnormal creatinine response in men. Because of concern over undocumented blood redraws, he strongly supported requesting a methodical post-marketing study to evaluate safety with strict adherence to protocol.

Cardiorenal Consult

The Division of Cardiovascular and Renal Products was consulted for advice on developing requirements for a safety study to investigate the renal effects of Suprep. The Reviewer recommended that the study include patients with renal insufficiency to improve the ability to detect any renal effects, because patients with normal renal function might not show much change in function despite renal injury. In addition to creatinine, she recommended testing BUN and urine albumin. She further recommended that evaluations include fractional excretion of uric acid and urine pH, that the studies monitor calcium and magnesium, and that they include ECGs at C_{max}. She suggested also including the novel biomarkers Cystatin C and KIM 1. She recommended testing be done at baseline, day of colonoscopy, and at 72 hours, one week, and one month post colonoscopy.

The Reviewer recommended that any patients who have creatinine elevations after Suprep exposure be treated with adequate volume resuscitation, discontinuation of medications that could contribute (diuretics, NSAIDs, ACE inhibitors, ARBs) and other standard management, as well as being evaluated for other causes of renal dysfunction. The Reviewer noted that there was no known direct effect of sulfate on the kidney, but that sulfate can induce metabolic acidosis that in turn can cause decreased calcium and magnesium reabsorption as well as decreased uric acid excretion.

The Reviewer suggested that another PK study, designed to look at serum pH, urine pH, anion gap, serum calcium, serum magnesium, and uric acid measured at several intervals post-ingestion, would be useful for understanding the metabolic effects of Suprep.

The Reviewer made several additional observations:

- While Suprep showed a greater increase in uric acid compared to MoviPrep, it also showed greater variation and exhibited some greater decreases
- Elevated urine pH (as was seen in animal studies) would cause a uricosuric effect and decrease serum uric acid. The observation of decreased bicarbonate in Suprep-treated patients suggests patients had a metabolic acidosis and that their urine may not have been alkaline. Also there might have been volume contraction due to vomiting, which may have decreased uric acid clearance (volume contraction decreases uric acid excretion in rats). There is no literature to support a direct effect of sulfate on uric acid excretion.
- It is not clear from the available study data whether the uric acid increase is a consequence of increased formation or decreased excretion. Measuring fractional excretion of uric acid would be useful to distinguish these possibilities.
- The Reviewer suggested consideration of including wording in the labeling cautioning about use in gout, although no cases were seen in the clinical studies.

- Metabolic acidosis has been shown to result from consumption of sulfur, so that it would be important to study patients with renal insufficiently to see if Suprep could cause a severe worsening of their usual metabolic acidosis.
- There is experience with sulfate exposure from the use of magnesium sulfate for preeclampsia. The few reported deaths in the literature appear to be cardiac and are likely related to magnesium rather than sulfate.
- Increased sulfate can complete with calcium, and the Reviewer noted patients in the PK study (Study 202) had a slight decrease in calcium. She recommended that the follow-up study look at serum calcium closely.
- The reviewer noted that excess colonic lumen sulfide is thought to result in colonic epithelial inflammation. She suggested consideration recommending against its use in ulcerative colitis pending further study.

Overall Safety Conclusions and Recommendations

The Clinical Reviewer concluded that a higher frequency of nausea and vomiting was noted with Suprep compared to MoviPrep and that, for both products, the consecutive dose regimen produced a greater number of adverse events than the split dose regimen. The Statistical Reviewer drew a similar conclusion. The Clinical Reviewer felt the extent of drug doses and duration of exposure were adequate. She identified as inadequacies the length of follow-up of abnormal labs and the lack of analysis of sulfates. She felt the Applicant should have had post-dose follow-up labs between the dose and day 30. She recommended that the Applicant be asked for a Phase 4 commitment to do a study of additional patients using ECGs to further evaluate bradycardia, including follow-up CK with fractionation, and with more frequent measurements of sulfate, BUN, creatinine, electrolytes, and urinalysis after dosing.

9. Advisory Committee Meeting

This application was not presented to an FDA Advisory Committee.

Regulatory Briefing

Advice on this application from outside the Division was sought in a CDER Regulatory Briefing on August 28, 2009. Presentations included an overview of the history of cathartics and a background of recent bowel prep approvals and safety issues, as well as the findings of the nonclinical, clinical, and clinical pharmacology reviews for Suprep. Discussion centered on the adequacy of the Suprep safety database, what additional assessments should be required, and whether additional data should be collected pre- or postapproval.

Panel members noted that safety monitoring deficiencies should have been addressed at the time of the SPA. They commented that if the Division now decides to require additional safety information before approval, it would need to explain why the information is needed to label the drug properly and why the SPA agreement is no longer valid. They also remarked that postmarketing data should not be substituted for data that are really needed prior to approval. Some members said they felt more safety data were needed prior to approval; one specifically recommended a study of a couple thousand to characterize safety better.

10. Pediatrics

PeRC & PREA
The application was presented to the Pediatric Research Committee (PeRC) on 4/29/09. The committee recommended that, because this product represented a new therapeutic option, studies in pediatric patients should be required. One bowel prep (NuLytely, a PEG product) is approved for use down to the age of 6 months (the approval was based on literature review). In light of that, it was felt that studies down to that age should be required for Suprep.

The Applicant provided a pediatric study plan on 3/30/09 containing the following elements:

1. Retrospective survey of colonoscopy rates in the pediatric population.
2. Open-label tolerability and effectiveness study in 20 patients 12 to 16 years.
3. Randomized dose-ranging study of three different doses of Suprep compared to NuLytely in patients 12 to 16 years.
4. Randomized dose-ranging study of three different doses of Suprep compared to NuLytely in patients 3 to 11 years, if supported by the study in item 3.
5. Randomized dose-ranging study of three different doses of Suprep compared to NuLytely in patients birth to 2 years, if supported by the study in item 4.

11. Other Relevant Regulatory Issues

Standard of Evidence for Efficacy
Evidence of efficacy was provided in two single-blind, active-control studies. For evaluation of bowel prep products, placebo controls are impractical and not necessary. It is generally accepted, and reasonable from common experience, that bowel preparation through dietary manipulations alone cannot reliably provide an adequate prep. Reasonable comparability to a proven effective bowel prep should be adequate to establish efficacy.

For Study 302, the Statistical Reviewer felt a 5% relative margin would be more appropriate in light of the low failure rates. This CDTL agrees that claims of comparability should be based on smaller margins in such situations. When the comparator product is only a few % away from 100% success, the competitor needs to show near perfect performance also to be considered the "same" clinically. However, in this case, the margin needed for establishing *efficacy* need not be as tight, since a 98% success rate is above the success rates seen in trials of other products that are considered efficacious; a product could be clinically inferior to such a high performing comparator and still be efficacious. In fact, the success rates in Study 302 were well above those in Study 301, and both arms in Study 301 were accepted as efficacious.

Adequacy of Safety Evaluation
The Clinical Reviewer noted deficiencies in the safety evaluations, but recommended the application for approval with postmarketing requirements for additional safety data. This CDTL feels the safety evaluations were not adequate, and recommends a Complete Response action to

require additional safety data. See **13. Recommendations/Risk Benefit Assessment**, below, for a detailed discussion of the CDTL assessment of the adequacy of the safety evaluation.

Combination Policy
As stated in the ONDQA Filing Review by M. Kowblansky of 8/25/08:

> The proposed product contains three active ingredients: sodium sulfate and magnesium sulfate, which have been approved for use in other products, and potassium sulfate, which is a new active ingredient. However, it should be noted that both sulfate ions and potassium ions function as active moieties, as has been the case in other approved applications.
>
> The applicant identifies sodium sulfate as the dominant osmotic agent, with the product requiring at least 250 mmoles of sulfate ion for acceptable efficacy. The role of the other ionic components in the formulation is not explicitly discussed in the application, but based on first principles it is a reasonable conclusion that all are osmotically active. The sponsor's statement that sodium sulfate is the dominant osmotic agent no doubt is based on the fact that it is the most abundant component in the formulation, not that sulfate is the primary active moiety in the formulation; all of the ions from the active ingredients (sodium, magnesium, potassium, and sulfate) are active moieties

In effect, all of the ions, Na, K, Mg, and SO_4 contribute to the osmotic effects, much in the same way that each fraction of a dose of a single entity contributes to the effect of the whole dose. Further, the Applicant's Phase 1 investigations of different sulfate salt formulations and the effect on patients' blood electrolytes provided a rationale for using a mixture of salts. For this product, the combination policy's requirement that each component contributes can be satisfied on the basis of scientific principles, and does not necessarily require factorial efficacy studies.

Requirement for a Medication Guide
The Applicant proposed a brief FDA-Approved Patient Labeling with the initial labeling proposal. In the course of labeling discussions it was decided that patient information in the form of a Medication Guide should be required for this application when it is approved. The product carries warnings about the risk of fluid and electrolyte disturbances, which can, in turn, increase the risk of cardiac arrhythmias, seizures, and renal impairment. The product is self-administered, and there are certain patient factors that can exacerbate the risk. There is a concern that bowel preparation products for screening colonoscopy are often prescribed by someone other than the regular healthcare provider, so there is an opportunity for gaps in continuity of care for which patient labeling could help reduce risk. The reasons for including patient labeling as a Medication Guide are that:

- The product has serious risks, relative to benefits, of which patients should be made aware because information concerning the risks could affect patients' decisions to use the product.
- Patient labeling could help give patients a starting point for discussions with their healthcare providers about the decision to use the product or about complications from use of the product, which could help prevent serious adverse effects.

DSI Audits
Inspections were conducted at Laurel, MD (Dr. Richard Chasen, Study 301, 75 patients), Orange, CA (Dr. Steven Duckor, Study 302, 46 patients), Anaheim, CA (Dr. Dennis Riff, Study 302, 80 patients), and Germantown, TN (Dr. Lawrence Wruble, Study 302, 40 patients). All four sites received a final classification of VAI (deviations from regulations), but the DSI reviewer's

assessment was the violations would not affect the validity of the data, and he concluded that data from all four sites appeared valid and could be used in support of the NDA.

12. Labeling

Labeling Consults
The Division of Drug Marketing, Advertising, and Communications (DDMAC) made several recommendations to improve clarity and formatting and alerted the Division to statements that could be promotional or that might need substantiation. DDMAC also provided recommendations for the proposed Medication Guide to help maintain consistency with the Package Insert, ensure that risks were not minimized, and make the language more consumer-friendly. See the DDMAC Reviews for details. The Division of Risk Management (DRISK) also provided detailed recommendations for improving the patient instructions in the labels and labeling.

DMEPA identified deficiencies in the carton and container labels and also recommended improvements to sections of those labels to improve the comprehension of the instructions for use.

Proprietary Name
In the name reviews conducted on 4/16/09, 8/10/09, 1/15/10, and 5/6/10, DMEPA had no objections to the proposed proprietary name of Suprep Bowel Prep Kit. The review considered the possibilities of the "p" in the middle of Suprep appearing either as upper or lower case. The review identified 15 names with some similarity, but concluded that the similarities were unlikely to result in medication errors.

Specific Labeling Issues

- The Applicant proposed dosing instructions that were different from the way the drug had been used in the clinical studies; (b) (4) The labeling should provide instructions for use that match the way the product was evaluated. Since the consecutive-dose regimen appeared to have lower efficacy and a higher frequency of adverse reactions than the split-dose regimen, the dosing section of labeling should describe those differences and encourage use of the split-dose regimen when possible.

- The Applicant's proposed labeling had only a warning for serious pre-existing GI conditions and a warning not to drink the solution undiluted. Some currently approved osmotic laxatives have more complete descriptions in the warnings of the adverse reactions that may complicate the electrolyte abnormalities that can occur. The wording of warnings from these related products should be adapted as applicable for Suprep. Specifically, the labeling should have warnings regarding fluid and chemistry abnormalities, cardiac arrhythmias, seizures, and risk when used in patients with renal impairment. The warning regarding chemistry abnormalities should make explicit mention of the elevation of uric acid that can occur and comment on its potential for precipitating an acute flair in patients with gout. Because

aphthous ulcerations and ischemic colitis have been reported with some bowel preps and there are no studies that eliminate those concerns for this product, a warning with information regarding those risks should be included.

- The Applicant initially proposed labeling that only reported the more pronounced ("bothersome" or worse) adverse reactions (AR). This differs from reporting of ARs in other bowel prep products, and also obscures the greater frequency of some ARs, such vomiting, compared to the active control. The AR reporting in the labeling should include ARs regardless of severity.

- Because some of the risks of the product relate the effects on electrolytes, information about the magnitude of those effects should be included in labeling, either under Section 6 (Adverse Reactions) or 12.2 (Pharmacodynamics).

- Several of the warnings for marketed osmotic laxatives include partial lists of drugs that may increase the likelihood of fluid and electrolyte abnormalities or that may increase the risks of resulting complications. It would be reasonable to include a subsection in Section 7 (Drug Interactions) to call attention to the possibility of this type of drug interaction and cross-reference the warnings.

- Section 12.3 (Pharmacokinetics) should be revised as recommended by the Clinical Pharmacology Reviewer to include additional information about sulfate kinetics.

- Section 13 (Nonclinical Toxicology) should be revised as recommended by the Nonclinical Reviewer to provide more complete information about the toxicities seen in the nonclinical studies and to remove statements (b) (4) .

- The Applicant proposed statements and tables in Section 14 (Clinical Studies) comparing Suprep's safety and effectiveness characteristics to those of the active comparator, MoviPrep. Because the treatment regimens in both studies used different diets for the two products, and because the difference in diets favored Suprep, direct comparisons between these two products are not supported. The comparator should only be described in generic terms, and the differences in diet should be clearly described.

- The product carton and container labels were revised as recommended in the CMC review.

- The Applicant was initially asked to provide FDA-Approved Patient Labeling that provided more complete information about how to prepare and use the product. In the process the labeling negotiations, the Division decided that the additional patient information should take the form of a Medication Guide (see **11. Other Relevant Regulatory Issues** for rationale).

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
The primary reviewers recommended the application for approval, in some cases contingent on certain labeling changes or postmarketing requirements. However, this CDTL Reviewer recommends the Applicant be sent a Complete Response letter requesting additional safety studies. Should the decision be made to approve the application on this review cycle, this Reviewer recommends that there be postmarketing requirements to do additional safety studies. See below for a discussion of the CDTL assessment of deficiencies and recommended requirements.

Risk Benefit Assessment
The benefit of Suprep for preparation for colonoscopy has been established in the clinical trials, and it appears to be about as effective as other approved products in this pharmacologic class. Based on what was found in clinical trials and what is known about pharmacologically related products, no unacceptable risks were identified with this product. However, because the risks of Suprep have not been assessed adequately, in this Reviewer's view, a complete risk/benefit assessment cannot be made. The CDTL Reviewer's concerns regarding the safety assessments are set out below.

CDTL's Discussion of Deficiencies in Safety Assessments
This Reviewer finds the Suprep safety assessment has the following deficiencies:

- Lack of ECG data
  The few ECGs that were collected in the development program were mostly on formulations other than Suprep, and were mostly in young adults. No ECG data were collected for Studies 301 and 302. The average age in those studies was in the late 50's, and the target population for this product includes a substantial proportion that is elderly. For a new bowel prep product with a new combination of ingredients, ECG assessment is reasonably applicable. And for an application in a pharmacologic class in which at least some other members carry warnings about the risk of arrhythmias, routine ECG collection is especially applicable. In fact, the guidance on QT testing (ICH E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, Section III) states:

  > Evaluation of the effects of a drug on the standard ECG intervals and waveforms is considered a fundamental component of the safety database of any new drug application.

  ECGs were included in the evaluation for the Visicol NDA approved in 2000, and some QT changes were identified. Apparently ECGs were not done for subsequent bowel prep applications; in some cases, but not all, the products had close similarities to previously approved products. The primary clinical reviewers of the recent HalfLytely and MoviPrep applications considered the lack of ECG data to be a deficiency in those applications. This Reviewer does not accept that prior approval of bowel preps without ECG data provides an adequate argument that ECGs are not applicable for the current application.

This Reviewer does agree, however, that a thorough QT study should not be a requirement for this product, because sulfate and the other components of Suprep have long been present in approved products, and a formal thorough QT study would be impractical for a product such as a bowel prep.

- Inadequate evaluation of blood chemistry
  An effect on certain blood chemistries is an expected event with bowel preps, although one of the considerations in their design is to minimize those effects. The effect of bowel preps on the kidney is a current issue of concern. Although blood chemistry was evaluated on the day of colonoscopy at a time when the effect of the prep would be anticipated to be its greatest, short-term follow-up testing to determine the persistence of the changes and to look for any transient effects that may be slightly delayed (such a creatinine elevation) would be reasonably applicable, but was not done. Samples were taken for sulfate levels, but the analyses were never run by the Applicant. Further, some patients in the study were found to have elevation in CK; without fractionation or more complete laboratory follow-up, the interpretation of those findings is unclear.

- Lack of urinalysis
  Urinalysis was not done in either of the pivotal studies. Urinalysis is readily available and a common component of a new drug development program. Such testing is reasonably applicable on routine grounds. Given that other bowel preps have had reports of an effect on renal function, and that the nonclinical findings with Suprep suggested a renal tubular effect, the need for urinalysis with microscopic and urine chemistries seems clear. Interpretation of the effects of Suprep on blood chemistry was frustrated by the lack of data on urine chemistry (or volume status, see next bullet point) to help understand what the observed changes implied regarding effects on renal function.

- Failure to obtain orthostatic vital signs
  Although vital sign data were collected, there was no collection of data on orthostatic changes, which could have provided information about volume status. In recent bowel prep applications, clinical reviews mention orthostatic vital sign data only for Osmoprep. While not a routine evaluation for most drug development, orthostatic vital signs are readily obtainable. For a product expected to affect fluid and electrolytes, an assessment of volume status using vital signs is particularly applicable. Like urinalysis, information on volume status would have been particularly helpful for interpreting the blood chemistry changes and better assessing effects on renal function.

- Lack of systematic collection of endoscopic findings other than cleansing
  From the information reported in the application, it appears there was no systemic collection of potential adverse events relating to endoscopic findings, in particular whether there were findings of aphthous ulceration or ischemic colitis. Studies for the Visicol NDA identified an increased frequency of aphthous ulceration compared to a PEG-based product. It does not appear that the studies in this application required collection of data regarding that adverse event. Although the study reports noted ischemic colitis in one MoviPrep patient, it is not clear how methodically such adverse events were assessed. The gut is the major target organ for efficacy, ergo, a reasonable candidate for scrutiny for toxicity. It would have been

appropriate for the studies to have included specific, systematic assessment and recording of adverse effects on the colon, rather than relying on apparently spontaneous reporting by the endoscopists.

- Lack of coagulation testing
  The effects of Suprep on coagulation were not evaluated at any phase of this development program. While no special concerns have arisen for this pharmacologic class regarding an effect on coagulation, and there is no a priori expectation of a safety issue based on the composition of Suprep, coagulation testing is readily available and a reasonably applicable test to incorporate into new drug development.

- Inadequate body of safety experience
  Because Suprep is not directly therapeutic, but, in a sense, an adjunct to prophylaxis, there is a large "number needed to treat" to obtain the benefits of routine endoscopic cancer screening. Therefore, a high bar for safety is appropriate, and the safety database requirement for bowel preps should be greater than the general minimum expectation for a new therapeutic drug. The rate for serious complications of colonoscopy without biopsy is cited at around 0.1%[1]. It would be appropriate to expect that a new bowel prep for colonoscopy should not substantially contribute to that risk, but to do so would take an experience in at least 3,000 patients (just to be 95% confident of a risk < 0.1% if no event is seen). The size of the safety database in this application cannot provide confidence that the incidence of serious reactions is much less than 1%. In this Reviewer's view, a substantially larger safety database is reasonably applicable to a product of this kind.

CDTL's Consideration of the Role of the SPAs

The Applicant requested SPAs in April 2007 for the two pivotal studies, and the Applicant was told that the safety evaluations for those studies were adequate. A SPA is intended to be specific to a protocol and not an entire development program; therefore the SPA is not a formal agreement on adequacy of the safety database in the development program. It might have been reasonable for Applicant to infer, based on the End-of Phase-2 meeting and the SPAs, that the FDA had not identified any deficiencies in the safety component of the development program. Nonetheless, this Reviewer does not view the requirement for additional safety data to be a breach of any explicit contract regarding the safety database.

Further, the FD&C Act has to be viewed as having priority over any SPA agreement. In any assessment of what constitutes "adequacy" it is to be expected that there will be areas subject to judgment; there a SPA can provide an official decision on how those judgments should be made. It is appropriate for a reviewer to defer to those judgments, even if different from his or her own preferences, as long as they can be viewed as reasonable alternative interpretations. However, if the requirements of the Act cannot be viewed as being reconcilable with SPA judgments or with other implied agreements, as this Reviewer feels is the case here, then the recommended action needs to be in accordance with the requirements of the Act.

[1] Nelson DB, KR McQuaid, JH Bond, DA Lieberman, DG Weiss, et al., 2002, Procedural success and complications of large-scale screening colonoscopy, Gastrointest Endosc, 55:307-14.

CDTL's Conclusions about Adequacy of Safety Program
The statutory requirement (FD&C Act 505(d)(1)) is that an application shall not be approved if there is a finding that the investigations "do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use…"

Some of the deficiencies cited above, such as lack of coagulation testing or orthostatic vital signs, might not be considered as making the testing inadequate. However, given the *a priori* concerns for drugs in this class regarding fluid and electrolyte imbalance and renal function, this Reviewer finds it very difficult to justify, as being adequate for approval, the lack of ECGs, lack of short-term follow-up of blood chemistry, and lack of urinalysis. Also, this Reviewer considers the small size of the overall safety database to be inadequate to support approval.

Bowel preps involve ingestion of a large amount of fluid and electrolytes. Although one goal in their design is to minimize effects on chemical and hemodynamic homeostasis, shifts do occur. Products in this class carry warnings about ECG changes, seizures, and risks of use in patients with renal impairment. Further, products in this class can have physiologic effects that go beyond simple transient electrolyte disturbances, as evidence by the aphthous ulcerations seen with Visicol, the nephrocalcinosis associated with the sodium phosphate preps, the ischemic colitis associated with HalfLytely, and the effects on uric acid seen with the subject of this current application.

This Reviewer finds the past decade's experience with bowel preps sufficient to reject the notion that a simplified safety screen is acceptable for new drug products in this pharmacologic category, rather, they deserve to be subjected to the same thorough evaluation expected of any other new drug product, including targeted evaluations as indicated by known safety issues with others in the pharmacologic class.

This Reviewer sees the safety deficiencies in this application as reflecting failings in confronting safety problems known to occur with this class of drugs. This Reviewer does not view the safety data included in the application as representing adequate testing by all methods reasonably applicable to show whether or not Suprep is safe for use, and therefore cannot recommend the application for approval.

CDTL's Recommendations for Required Safety Studies
Before this product is approved, the Applicant should conduct a study substantially similar to Study 301 or 302 but incorporating baseline and post-dosing ECGs; blood chemistry testing, including sulfate and CK with fractionation, at one or more occasions following the day of colonoscopy, and preferably with longer-term follow-up; urinalysis with microscopic and chemistry, including uric acid; orthostatic vital signs; and coagulation testing. The trial should involve recording of colonoscopic observations regarding extent of aphthous ulceration and evidence of ischemic colitis, and there should be follow-up contact after several months to obtain adverse event information. This should be done for both dosing regimens. In addition, there should be a large safety database with at least the capability of detecting and obtaining reasonably reliable estimates of the frequency of serious or other significant adverse events that may occur in about 0.1% of treated patients.

Recommendation for Postmarketing Risk Evaluation and Management Strategies
Should this product be approved, it should be accompanied by a Medication Guide, and therefore will require a MedGuide-only REMS. No other special postmarketing risk evaluation and management strategies are recommended.

Recommendation for other Postmarketing Requirements and Commitments
If the application is approved, the Applicant should be required to carry out the pediatric plan described above under Pediatrics. In addition, this Reviewer recommends that the Applicant should be required to conduct studies such as those describe under *CDTL Conclusions about Adequacy of the Safety Program*, above. If the product is marketed, a large, suitably designed epidemiology study might be used to address the recommended requirement for a large safety database.

Recommended Comments to Applicant
Apart from communication of deficiencies or post-marketing requirements, there are no recommended comments to the Applicant.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22372	ORIG-1	BRAINTREE LABORATORIES INC	SUPREP BOWEL PREP KIT

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN E HYDE
06/28/2010

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-372
Submission Code	N000
Letter Date	7-1-08
Stamp Date	7-2-08
PDUFA Goal Date	Major Amendment 8-2-09
Reviewer Name	Jasmine Chen Gatti, M.D.
Review Completion Date	8/7/09
Established Name	Sodium sulfate, magnesium sulfate, potassium sulfate
(Proposed) Trade Name	Suprep Bowel Prep Kit®
Therapeutic Class	Osmotic Laxative
Applicant	Braintree Laboratories, Inc.
Priority Designation	Standard
Formulation	Oral solution
Dosing Regimen	Two six ounce bottles of Suprep with water
Indication	Colonic Bowel Prep/ Gastrointestinal Lavage Prior to Colonoscopy
Intended Population	Adults 18 years and older

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective, this medical officer recommends an **Approval Action** of BLI800, Suprep Bowel Prep Kit ® (sodium sulfate, potassium sulfate and magnesium sulfate) Oral Solution for bowel cleansing prior to routine or diagnostic colonoscopy. This Approval action should occur only if the Applicant agrees to certain labeling changes and to post-marketing commitments. The Applicant should not state that BLI800 is superior to MoviPrep and remove any labeling that might imply this. In addition, Braintree must indicate their studies were not well controlled for dietary consistency, had diminished sensitivity and specificity lacking confirmatory and pooled endoscopic findings, and that populations that dropped out were greater than expected with their product. Braintree must also agree to post-marketing studies for safety follow-up for adverse events and abnormal laboratory tests. Instances of bradycardia were noted. No Phase 3 requirements for ECG studies were previously requested to provide further information on these patients.

1) Justification for Efficacy Equivalence and Non-inferiority Margin Since the dietary restrictions used in the pivotal studies BLI800-301 and BLI800-302 comparing MoviPrep and the product BLI800 used vastly different diet requirements and the impact of diet on efficacy is inevitable, the efficacy comparisons are found to be inconclusive. *See Section 10.1.8 Concomitant Medications.* Furthermore, Applicant attempted to justify the non-inferiority margin after multiple requests. *See Statistics Review*. The drop-out rate proved to be higher than was expected at 7%. Inconsistencies in ratings by colonoscopists were noted for the poor and fair findings.

2) Inadequate quantification and follow-up of laboratory tests especially serum sulfates
This reviewer recommends Braintree agree to do **PMC studies** for safety follow-up for adverse events and **abnormal laboratory tests** especially the creatine kinase, glucoses, urinalysis, and others and do additional sampling of **sulfates**. Although serum sulfates were drawn and frozen for analysis for over 700 patients in the two pivotal BLI800-301 and 302 studies, the Applicant chose not to analyze these samples based on their assessment of BLI800-202. Applicant acknowledges that they did not notify FDA of the change in the protocol nor submit an amendment. FDA's assessment of BLI800-202 finds inadequate normalization of some of the serum sulfates at the end of the study. Further study of the serum sulfate PK and correlation with any potential adverse events in Phase 3 studies with a broad general population is recommended. Safety signals for CK, renal function, urinalysis, and sulfate for follow-up immediately after drug ingestion to 50 days post-colonoscopy should be done. Follow-up of CK, creatinine, BUN, GFR, electrolytes and adverse events at 8 to 14 hours, at 24 to 36 hours, 72 hours and at 4 to 8 weeks is recommended. In discussion with Dr. Jane Bai, due to the lack of sufficient data of the Study 202 renal impairment patients who had elevations up to 50% in sulfate levels, proposed

measurements of renal function, sulfate levels and correlation with CK fractionated components such as CK-MB is sought. *See Clinical Pharmacology Review.*

During the SPA negotiations, follow-up of laboratory tests to 3 and 6 months and 1 month was agreed upon. Excluded from the prior SPA discussion, are requests for lab monitoring on a daily basis post-dose for one week and for serum sulfate sampling post-dose. We highly recommend laboratory monitoring extend past the one month monitoring to 3 months. During SPA negotiations, the regulatory action of removing the OSP from the OTC market for nephropathy had not occurred. As FDA continues to monitor all oral colonic cleansers for post-approval adverse events the changing milieu mandates requests for frequent monitoring of post-dose adverse events not only at one month time, but, up until that time. Likewise, with the implementation of new PMC for OsmoPrep and Visicol and the change to NDA approval process for Fleet's products these drugs are undergoing close scrutiny.

3) Greater frequency of nausea and vomiting

This reviewer requests that Applicant agrees to clearly label that adverse events may be **increased with the same day dosing** regimen and both regimens **induce greater frequency of nausea and vomiting** than MoviPrep. Because the safety profile of patients taking the same day dose was less favorable than for the patients taking the split-day dose, patients will be informed that this split day dosing may be safer than the same day dosing. This reviewer recommends the elimination of the same day dose regimen due to higher adverse event rates and lower efficacy. The rare instances where this lavage would be used on an emergent basis can be included as an option for the provider in the Dosage and Administration whereupon the "Same Day Regimen: For Emergent Use Only As Instructed by Provider" would be designated. Using the Split dose regimen would eliminate confusion in instructions for use found in the label (b) (4) decrease adverse events, and improve efficacy for the larger population.

4) Higher Risks in Subpopulations

The labeling should not allow use in populations the Applicant did not study.

This reviewer also recommends adding **Warnings** to the labeling for subpopulations at high risk for dehydration, electrolyte changes, or liver impairment and additional symptom warnings such as potential tonic-clonic seizures due to electrolyte changes, caution with concomitant medications use of diuretics, ACEI (angiotensin converting enzyme inhibitors), ARB (angiotensin receptor blockers) as potentiators of the electrolyte changes and dehydration. Patients with other comorbidities such as diabetes or hypercholesterolemia who are using cholesterol lowering agents may be warned that BLI800 may exacerbate glucose or CK levels. An analysis of high use patients--those adults over 50 years using routine colonoscopy for screening and on those who are at high risk of developing complications—those with renal or hepatic failure should be studied in greater numbers.

5) Data Follow-up for Bradycardia Safety Concerns

In BLI800-101, a Phase 2 study of three groups of patients given either OSP (Oral Sodium Phosphate), OSS (Oral Sodium Sulfate), and healthy volunteers, the ECGs obtained showed sinus bradycardia and some QTC prolongation that was less than 450msec. No further cardiac studies were requested in the Phase 3 studies. About 40 patients had bradycardia that appeared after taking the treatment drugs. Some of the patients were taking concomitant beta-blockers and many were taking hypertensive and hypercholesterolemia medications. In BLI 800-202, clinically insignificant ECG changes were noted in 4 renal impaired patients, 4 hepatic impaired patients, and two healthy volunteers. Further delineation of the significance of these changes in

larger populations and in the population that will most likely use this product is warranted. *See Section 7.1.8 and 7.1.9 on Vital signs and ECG.*

6) Pediatric Waivers

In the classes of oral sodium phosphate and PEG (polyethylene glycol) products in the pediatric population waivers had been granted in the past. What was well known to the market cannot be applied to this product as it is a new drug entity that has not been studied in the pediatric population. With the recent withdrawal of OTC Fleet's products due to oral sodium phosphate inducing acute nephrocalcinosis and Suprep's heightened potential for greater use in light of the current market changes, we request that further pediatric studies be done by the Applicant.

If the Applicant **does not agree to these important changes in labeling and post-marketing and pediatric studies, then this reviewer recommends a Complete Response.**

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No applicable risk management activity is recommended for this NDA.

1.2.2 Required Phase 4 Commitments

This reviewer requires a phase 4 commitment to do a well controlled randomized study of 400 patients to further delineate the type of bradycardia with ECGs occurring after ingestion of the prep and to follow-up to 50 days post-colonoscopy based on OSP follow-up findings for nephropathy to delineate further adverse events and safety signals for abnormal lab results. This includes an analysis of sub-group populations of patients who are most likely to be using routine colonoscopy for screening (adults over the age of 50 years) and on those who are at high risk of developing complications of renal failure, electrolyte imbalance, rhabdomyolysis, or nephropathy related to calcification should be sub-divided for analysis. Follow-up of CK and fractionation of CK, sulfates, creatinine, BUN, GFR, electrolytes, urinalysis at 8 to 14 hours, at 24 to 36 hours, 72 hours, and at 4 to 8 weeks and adverse events are requirements still under discussion.. Deputy Director of Safety, Dr. Joyce Korvick, was consulted on the REMS plans. The Applicant is required to perform pediatric clinical trials that the Applicant initially did not submit. *See Pediatrics section 8.4*.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Braintree Laboratories, Inc. submitted this new drug application under 505 (b) (1) of the Federal Food, drug, and Cosmetic Act on July 1, 2008 to support the approval of BLI800, Suprep, (sodium sulfate, potassium sulfate and magnesium sulfate) for "gastrointestinal lavage for cleansing of the colon in preparation for colonoscopy in adults". The proposed BLI800 dosage is

(b) (4) a two day split dose (BLI800-302) (b) (4). BLI800 is being compared to MoviPrep®. It is indicated for bowel cleansing prior to colonoscopy, intestinal surgery, and barium enema X-ray examination.
Braintree submitted a total of eight completed clinical studies. The Phase 1 and Phase 2 studies consisted of about 100 patients. Some patients were eliminated from analysis by the sponsor, some were used multiple times for the different drug formulations and not clearly sub-identified in the submission with unclear wash-out periods and missing data. The majority of findings to support efficacy and safety involved two pivotal studies BLI800-301 (Study 301) and BLI800-302 (Study 302).

1.3.2 Efficacy

This reviewer believes that the efficacy results from Study 301 and 302 were found to be less robust when compared to MoviPrep's study design for efficacy. Applicant claims a greater number of successful preps assessed by descriptions of the degree colonic visualization during endoscopy based on a 4 point scale in BLI800 compared to MoviPrep in their labeling (77.9% versus 76.0% in Study 301) (92.1% versus 92.6% in Study 302). Adequacy of cleaning was also assessed by visualization and rated as adequate or inadequate.

The dietary restrictions used in the pivotal studies comparing MoviPrep and the product BLI800 used vastly different diet requirements and the impact of diet on efficacy is inevitable, and therefore the subsequent results are unreliable. Inconsistencies occurred between ratings of some "fair" grade 2 exams as inadequate and some as adequate. Even some "poor" grade 1 exams were rated as adequate but not needing re-prepping. In addition, the lack of endoscopist verification by second expert or by video recording also diminished the sensitivity and specificity of the efficacy results. The comparator was changed (b) (4) to PEG product after the Phase 2 studies. *See Appendix 10.1.1, 10.1.2, 10.1.3, and 10.1.4 for Study 301 and 302 study results.*

This reviewer believes that Suprep may be less efficacious even though the comparative rates of successful preparations appear comparable. Suprep had an advantage with a lighter diet prior to bowel preparation, the descriptive endoscopic assessments were unverified and did not come from a pooled number of evaluators, and there were inconsistencies in adequacy ratings. The pivotal studies of Suprep® Oral Solution demonstrated safety in the majority of patients during the time of ingestion. The entire (N) database of the eight studies was approximately 903. Since the earlier studies were small, did not have clear wash-out periods or indications, had missing data, and did not always use to to-be–marketed formulation, the focus will be on the pivotal studies.

1.3.3 Safety

A higher frequency of nausea and vomiting was noted in BLI800 than in patients taking MoviPrep. For the same day regimen in both osmotic laxatives there were greater numbers of adverse events. Sub-populations of the elderly also had greater adverse events. There was only one death in a Moviprep patient who had respiratory arrest and 2 serious adverse events that included an atypical chest pain and colonic perforation. One patient on Suprep developed AV block and was discontinued from the study. Applicant's original labeling did not include the

patient reported gastrointestinal adverse events and the TEAE combined together in their labeling tables as well as report mild and moderate gastrointestinal AE's. Applicant did not report the colonic perforation until over one year from its occurrence. Applicant did not submit an amendment to not analyze more than 700 serum sulfate samples that they collected and left frozen in a lab. As of result of these issues the last of which generated a 10 fold increase in adverse events a major amendment was obtained.

1.3.4 Dosing Regimen and Administration

Two 6 ounce bottles of oral sulfate solution were given as a same day dose prior to colonoscopy (Study 301) or as a split dose one day prior with the second dose on the day of colonoscopy (Study 302). Each dose was followed by 32 oz. of water. The study protocol differed only in the dose regimens. Since the same day dose was less efficacious (77.9%) as compared to the split day dose (92.1%) and it had more adverse events such as nausea and vomiting, this reviewer believes that the same day dose should be eliminated. Dose-response studies were done in hepatic impaired, renal impaired, and healthy patients. The Phase 2 Study 202 which was the same day dose, measured PK correlated parameters of bowel movement (weight, volume, water percentage, consistency, color, cleansing time) and laboratory changes including serum sulfate over a 30 hour (then post-dose 3 and 6 days) interval.

1.3.5 Drug-Drug Interactions

Drug-drug interactions were not studied.

1.3.6 Special Populations

Special populations of moderate renal impairment subjects and mild-to-moderate hepatic disease patients were studied for PK in BLI800-202 revealing higher serum sulfate concentrations for the moderate renal impairment group, then the healthy volunteers. It was lowest in the mild to moderate hepatic impairment group. Subpopulations such as geriatric patients and high risk populations with cardiac, renal, vascular or diabetic disease were separately analyzed and showed higher incidences of nausea and vomiting and abnormal laboratory tests.

2 Introduction and Background

2.1 Product Information

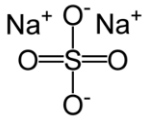
Proposed Trade Name (established name) Suprep Bowel Prep Kit® (trade name) or BLI800, a new drug formulation consisting of sodium sulfate, potassium sulfate, and magnesium sulfate salts with a dominant active ingredient of sodium sulfate.
Proposed Indication is for bowel cleansing prior to routine and diagnostic colonoscopy

Pharmacologic Class an osmotic laxative solution. Because sulfates are poorly absorbed in the intestinal tract, these agents act somatically to increase water content of stool and induce watery diarrhea.

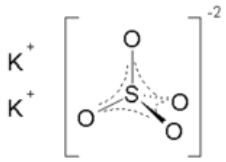
Proposed Age Group Adults

Molecular and Structural formulas of main Suprep ingredients:

Sodium Sulfate, USP
The chemical formula is Na2SO4. The average Molecular Weight is 142.04. The structural formula is:



Potassium Sulfate, FCC, purified
The chemical formula is K_2SO_4 The average Molecular Weight is 174.26. The structural formula is:



Magnesium Sulfate, USP
The chemical formula is $MgSO_4$ The average Molecular Weight: 120.37. The structural formula is:

The active ingredients of BLI800 consist of potassium sulfate, sodium sulfate, and magnesium sulfate. Sodium sulfate is the most abundant agent which osmotically increases the content of stool and causes diarrhea. Its intent is not to change the electrolyte balance. [redacted] sucralose [redacted], citric acid, malic acid, [redacted] flavors. [redacted] sodium benzoate. Purified water is used [redacted]

The drug will be in a carton with two 6 oz. [redacted] bottles [redacted]. A 16 oz. [redacted] container with a fill line will also be included.

Sodium sulfate is anhydrous and USP grade consisting of large, colorless, odorless, transparent crystals or granular powder. It has a density = 2.68 g/cm3, a melting point =844OC. It is freely

soluble in water, soluble in glycerin and insoluble in alcohol. For more details see the (b) (4) Drug Master File (b) (4).

Early Phase 1 studies 001-022 determined the effectiveness of five oral sulfate salts without phosphates as compared to an oral phosphate solution and measured any electrolyte and fluid shifts that resulted. The second Phase 1 study, 005-082, further refined the sulfate solution by comparing 4 sulfate solutions to 3 laxatives and 3 cleansers. It set the cut point as 2400g or greater of stool output and 3% or less remaining stool solids as to what was to be considered the standard for sufficient cleansing based on the amount of stool solids and stool output produced by colonic cleansers known to be effective. The third Phase 1 study, 006-181, used an optimal sulfate solution compared to marketed Fleet EZ-Prep and 4L NuLytely to measure efficacy based on stool output and % stool solids.

Table 1: Drug Composition

Table 1. Drug Product Composition

Raw Material and Grade Quality	Quantity per 6 oz bottle	Quantity per Dose (2-6 oz bottles)	Function
Sodium Sulfate, USP	17.510 g	35.020 g	Active ingredient
Potassium Sulfate, FCC	3.130 g	6.260 g	Active ingredient
Magnesium Sulfate Anhydrous, USP	1.600 g	3.200 g	Active ingredient
Sodium Benzoate, NF	(b) (4)		
Sucralose (b) (4)			
Malic Acid, FCC			
Citric Acid, USP			
(b) (4)			
Purified Water, USP			

2.2 Currently Available Treatment for Indications

Colorectal cancer (CRC) is a leading cause of mortality with a 6% risk of occurring in one's lifetime. CRC screening is recommended for secondary prevention by the US Preventive Services Task Force (USPSTF) either by annual fecal occult blood testing, sigmoidoscopy every 3 to 5 years or colonoscopy every 10 years beginning at the age of 50 and sooner in high risk patients. In recent years, colonoscopy is becoming a more frequent procedure due to the raise in inflammatory bowel disease, Crohn's disease, and ulcerative colitis.

Colonoscopy is also used for follow-up of barium enemas, work-up of anemias of unknown etiology, follow-up for high-risk polyps, or for localizing sources of bleeding. The newer technology of virtual colonoscopy using a capsule that is swallowed and then expelled in the feces has developed as a alternative to routine colonoscopy, but still requires bowel preparation like the traditional colonoscopy.

OSMOTIC CLEANSERS
Osmotic cleansers are not broken down and the poorly absorbed ions increases intestinal water secretion and peristalsis. Osmotic laxatives include lactulose, mannitol, and sorbitol. Short chain organic acids are produced by bacterial degradation in the colon which lowers the pH and possibly causes stimulation of peristalsis that increases stool microbial bulk. The common saline laxatives used for bowel prep include magnesium hydroxide or magnesium sulfate and sodium sulfates. Magnesium sulfate seems to be most potent and its action may be mediated by cholecystokinin (CCK).

Two major categories of colonic cleansers, PEG plus electrolytes or oral sodium phosphates, rely to some degree on osmotic cleansing. PEG preparations are non-absorbed, non-degraded polymers prepared with iso-osmotic solutions such as sodium bicarbonate, sodium chloride and potassium chlorides, providing fluid that softens stools and accelerating gut transit time. Bowel cleansing products can often be used in the same formulation as in laxatives but, at different doses. Other phosphate containing bowel cleansers include Osmoprep and Visicol.

Products may also be combined to utilize different mechanisms of action or introduce changes based on volume or added electrolytes. Stool softeners-- Bisacodyl (Dulcolax), Senna (Senokot) -- that stimulate peristalsis can be combined with PEG and electrolytes for maximum cleansing-composing products such as GoLytely, NuLytely, and Halflytely. (All currently FDA bowel preps have PEG 3350 and electrolytes).

Additionally, physicians prescribe off-label use of these laxatives as colonic cleansers for preparation of for radiologic and surgical procedures. Unapproved dosage regimens and a variety of amounts of concomitant fluid intake during the procedures are also prescribed.

Table 2: A summary of marketed bowel preparations

Drug Name	Applicant And NDA #	Formulation	Advantage & Total Fluid	Approval Date	Comments
PEG + Electrolytes					
Colyte	Schwartz Pharma NDA 18-983	PEG-3350+ NaCL,KCL, Sodium bicarbonate, sodium sulfate, powder	4L/Little net absorption, flavors	1984	GI bleed, esophageal perforation /tear, pulmonary edema, can use in ileus. Caution in severe UC
GoLytely	Braintree NDA 19-011	236 or 227 gms PEG 3350 +sodium sulfate & bicarbonate, NaCl, KCL, powder.	Up to 4L/ Decrease salt and water absorption	1984	Too salty , later formulation with flavor evolved into Nulytely (Golytely RSS)
Nulytely (TriLyte-Schwatz Pharma) Half-lytely*	Braintree NDA 19-797 ANDA 76-491	420 grams of PEG 3350 with KCL, sodium bicarbonate, NaCL, powder	Up to 4L /No sodium sulfate, increased PEG, flavored *Halflytely in 2 L	1991	Lower salt content, GI obstruction, gastric retention, bowel perforation, toxic colitis, toxic megacolon, ileus
Moviprep	Salix/ Norgine BV NDA 21-881	PEG 3350 sodium sulfate, NaCL, potassium chloride, sodium ascorbate and ascorbic acid in powder; has aspartame	2L	2006	Tonic-clonic seizure & severe hypersensitivity. Warnings are same as for NuLytely includes UC, excludes ileus
Miralax	Schering Plough NDA 22015	PEG 3350, oral solution -17 grams/tbs	Laxative (17 gms in 8 oz. fluid for 2 weeks) prescribed as colonic cleansers,	2006, currently OTC	Original NDA withdrawn. Used off label as colonic cleanser
Oral Sodium Phosphates					
Visicol,	In-Kline NDA 21-097(Salix)	At least 3.4L Sodium phosphate tablets (60 gms)		2001-2002, 2008	20-33 tablets; Tonic-clonic seizures, hyponatremia
Osmoprep	Salix/In-Kline NDA 21-892	Sodium phosphate tablets (48 gm and PEG 8000	Gluten-free	2006	
Fleets	C.B. Fleet	Fleets Phospho-soda, prep kits, enemas, oral laxatives, suppositories with sodium phosphate (Pedia Lax Chews , Pedia Lax Enema) Removed as OTC	Easier to ingest	OTC mono-graph Now Under NDA with REMS	Contraindicated in CHF, MI, ascites, renal insufficiency. AE: Electrolyte and metabolic changes, Acute phosphate nephropathy

2.3 Availability of Proposed Active Ingredient in the United States

Sodium sulfate and potassium sulfate has been used as laxatives such as in Glauber's salt. But, The potassium sulfate component has not been used in other formulations whereas the other sodium sulfate and magnesium sulfate have been used. The two major groups of osmotic cleansers, the oral sodium phosphates and the PEG plus electrolytes products generally rely on poor sulfate ion absorption. Among the approved osmotic laxatives, sodium sulfates in Golytely,

Colyte, MoviPrep—have been used together with oral PEG components. [2] See Table 2: Summary of marketed osmotic lavages.

2.4 Important Issues With Pharmacologically Related Products

Oral Sodium Phosphate Bowel Preps

On December 10, 2008 a Supplementary Response Letter was issued from FDA following 30 cases of renal complications related to acute phosphate nephropathy stating that all prescription oral sodium phosphates specifically, OsmoPrep and Visicol must have a risk management or REMS proposal. This included medication guides, doctor letters or a communication plan, elements to assure safe use, an implementation system with a timetable for assessment. Furthermore, the requirement of a PMR of a prospective, randomized, active-controlled, trial comparing the risk of developing acute kidney injury in patients undergoing bowel cleansing using Visicol or Osmoprep compared to patients undergoing bowel cleansing using PEG products was implemented. The OTC oral sodium phosphates, mostly the Fleets preparations, have been pulled from the market. Aside from renal complications, significant electrolyte shifts especially in the elderly such as hypocalcemia with precipitation of calcium phosphate, hypokalemia, hyperphosphatemia, and hypernatriemia can also occur. These are not to be used in patients with congestive heart failure, renal impairment, ascites patients, gastrointestinal obstruction, megacolon, perforation, ileus or inflammatory bowel disease. Caution is exercised in patients taking medications known to prolong the QT interval, and in patients with heart disease, acute myocardial infarction, unstable angina, dehydration, hypertensive medications, gastric retention, colitis, or colostomy or ileostomy.

PEG plus Electrolyte Bowel Preps

In Halflytely and its similar PEG products, precautions include use in patients with impaired gag reflex, and in patients prone to regurgitation or aspiration. Mallory-Weiss tears and gastrointestinal bleeding can also occur. Large volumes cleansers caused more adverse events especially nausea, vomiting, cramping, and bloating. Patients who have impaired water handling that experience severe vomiting or nausea should be monitored especially for electrolytes. Halflytely is contraindicated in patients with ileus, gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis, or toxic megacolon.

In Moviprep, there are additional warnings of generalized tonic-clonic seizures associated with electrolyte abnormalities such as hypokalemia and hyponatremia which resolved with fluid and electrolyte correction that have occurred. Caution should be exercised in patients with severe ulcerative colitis, ileus, gastrointestinal obstruction or perforation, gastric retention, toxic colitis, or toxic megacolon.

Current warnings and precautions in both types of bowel preps

- Use with concomitant medications such as diuretics, ACEI that increase the risk of electrolyte abnormalities or have a history of hyponatremia is included. Testing of electrolytes at baseline and post-colonoscopy is recommended.
- Potentially fatal and severe electrolyte derangements may occur in subpopulations such as the elderly who have comorbidities or are prone to dehydration.

Proposed advantages of BLI800

- Lower volume (2.84 L) can effectively induce osmotic gastrointestinal lavage effectively with fewer adverse events.
- Poor sulfate absorption in the gastrointestinal tract increases water & stool output.
- No expected acute phosphate nephropathy or nephrocalcinosis.
- Mild or minimal electrolyte derangements after taking the drug.

2.5 Presubmission Regulatory Activity

Important decisions and agreements were made at the End of Phase 2 Teleconference on March 26, 2007, and in two Special Protocol Assessments for IND 74,808 sequence 004 and sequence 005 submitted April 10, 2007 for Phase 3 protocols BLI800-301 and BLI800-302. In the End-of- Phase 2 meeting the following were recommended by the FDA:

- 4 week oral toxicity studies in rodent and non-rodent.
- Pharmacokinetic studies (P2) for electrolytes and sulfate in patients with hepatic and renal disease. (No further (P1) non-clinical pharmacokinetic studies were required.)
- Subpopulation studies of geriatric and high risk patients with cardiac disease during Phase 3 trials.
- Primary efficacy endpoint could be a binary outcome (success/failure).
- Further clarification for primary and secondary endpoints in the protocols, analysis populations, and the handling of missing data or dropouts was requested. Phase 3 protocols would be intended for non-inferiority designs.
- Follow-up at 1, 3, & 6 months was suggested because of the history of acute phosphate nephropathy in OPS.
- Applicant requested control be changed from (b) (4) to Moviprep.

On 5/24/07, FDA responded to the two SPA requests for Study 301 and 302 with the following:
Braintree asked if a 30 day follow-up for serious AE and blood samples for labs including creatinine were acceptable. FDA responded with the following: "the occurrence of acute nephrocalcinosis with the sulfate product is theoretical and we have not seen any data to raise significant concern regarding the oral sulfate product to this point. You performed an analysis which showed no significant change in urinary calcium output in patients exposed to BLI800, and further chemical tests of the saturation index (SI) for $CaSO_4$ (the precipitant that would theoretically be of concern for causing renal injury) showed that sulfate concentrations could be safely increased by a factor of 10 without approaching saturation."

On April 6, 2007, two SPA Phase 3 submissions-- Protocol BLI800-301 and BLI800-302-- compared BLI800 to MoviPrep using two dosing regimens in a non-inferiority approach concluded with these important decisions:

- Further justification of the non-inferiority margin at (b) (4) and not 15% was requested.
- Clarification of the basis of the proposed non-inferiority margin was requested.
- Significance level would be 0.25% for a one-sided hypothesis testing.
- Multiplicity adjustment method for the secondary endpoints should be used.

- Consideration to include a low dose bowel preparation solution as a control agent with the intent of showing superiority of BLI800 was requested.

In addition, FDA accepted the change from (b) (4) to MoviPrep as the comparator and allowed follow-up of patients to 30 days only.

FDA responded to the pre-meeting package for the type A (August 13, 2007) meeting for studies 301and 302 that the use of a (b) (4) effect size may be appropriate to calculate sample size; however, from a clinical standpoint, an improvement of at least 15% to demonstrate superiority was requested. The final determination on the inclusion of a superiority or non-inferiority claim in labeling would be a review issue.

On July 23, 2007, FDA responded to a protocol review request for BLI800-202, a proposed Phase 2 trial titled "An Open Label, Single Dose Study to Assess the Effect of BLI800 on Safety and Clinical Chemistry Parameters in Patients with Renal Dysfunction and Hepatic Impairment" using the proposed Phase 3 dosing. The responses to the above are summarized below:

On August 22, 2007, FDA's response to the Applicant was that blood and urine samples were to be analyzed for chemistry parameters and sulfate levels and collected about 10 minutes prior to dose 2 and at 1, 2, 4, 8, 12, and 18 hours post-dose, and about 10 minutes before dose 1 and at 1, 2, 4, 8, and 10 hours post-dose. Samples will also be collected before noon on Days 3 and 6. The adequacy of the proposed sample size of six depended on the PK variability in the renal impairment patients. The analytical method for the assay of serum sulfate was validated except for long-term stability studies, which at the time were yielding acceptable results. The Applicant chose to include mild-moderate hepatic impairment patients since this type of patient was rarely enrolled in Phase 3 studies. The protocol was modified to include Group 3 moderately impaired patients instead of testing in end stage renal disease (ESRD) patients.

2.6 Other Relevant Background Information

There is no other foreign use of this product that is currently known and no studies are being conducted at foreign sites.

3 Significant Findings from Other Review Disciplines

3.1 CMC

BLI800 has three active ingredients, two of which, sodium sulfate and magnesium sulfate, have been approved for use in other products. Potassium sulfate is a new active ingredient. Note that both sulfate ions and potassium ions function as active moieties, as has been the case in other approved applications. See the CMC filing review by Marie Kowblansky which states, "The Applicant identifies sodium sulfate as the dominant osmotic agent, with the product requiring at

least 250 mmoles of sulfate ion for acceptable efficacy. The role of the other ionic components in the formulation is not explicitly discussed in the application, but based on first principles it is a reasonable conclusion that all are osmotically active. The Applicant's statement that sodium sulfate is the dominant osmotic agent no doubt is based on the fact that it is the most abundant component in the formulation, not that sulfate is the primary active moiety in the formulation; all of the ions from the active ingredients (sodium, magnesium, potassium, and sulfate) are active moieties."

The Microbiology review performed by Dr. Vinayak Pawar found Suprep acceptable for approval from a microbiology product quality standpoint.

3.2 Animal Pharmacology/Toxicology

The toxicology studies included a 7 day and a 28 day repeat-dose toxicity study by oral gavage of BLI800 in rat and dog species for up to 28 days with a maximum daily dose of 5 g/kg/day (approximately 0.9 times in rat and 3 times in dog, the recommended human dose of 44.48 g/day or 0.89 g/kg based on the body surface area). BLI800 caused diarrhea, electrolyte, and metabolic changes (hypochloremia, hypokalemia, hyponatremia and lower serum osmolality, higher urine sodium and potassium, alkaline urine and high serum bicarbonate indicative of metabolic alkalosis) in rats. The target organs in rats appeared to be the adrenal cortex (alteration of vacuolation), colon (dilated colon), jejunum (dilated) and kidney (minimal mineralization). The mineralization was minimal in the kidney in females at mid- and high-dose. It was seen in one placebo animal versus severe mineralization in the oral sodium phosphate group. See Pharmacologist, Dr. Tamal Chakraborti's review.

Table 3:Histopathologic Findings in Rats

Text Table 11. Incidence Of Selected Histopathologic Findings, Study Day 28 Scheduled Necropsy[a]

	Males					Females				
	BLI800				OSP	BLI800				OSP
Dosage (g/kg/day):	**0**	**1.25**	**2.5**	**5.0**	**5.13**	**0**	**1.25**	**2.5**	**5.0**	**5.13**
Kidney[b]	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Degeneration, tubular	0	0	0	0	10	0	0	0	0	10
Severe	0	0	0	0	2	0	0	0	0	4
Moderate	0	0	0	0	8	0	0	0	0	5
Mild	0	0	0	0	0	0	0	0	0	1
Mineralization	0	0	0	0	10	1[c]	0	1[c]	1[c]	10
Severe	0	0	0	0	5	0	0	0	0	4
Moderate	0	0	0	0	5	0	0	0	0	5
Mild	0	0	0	0	0	1[c]	0	0	0	1
Minimal	0	0	0	0	0	0	0	1[c]	1[c]	0
Stomach[b]	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Mineralization	0	0	0	0	8	0	0	0	0	8
Severe	0	0	0	0	0	0	0	0	0	1
Moderate	0	0	0	0	5	0	0	0	0	5
Mild	0	0	0	0	2	0	0	0	0	2
Minimal	0	0	0	0	1	0	0	0	0	0
Heart[b]	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Degeneration, myocardial	0	0	0	0	7	0	0	0	0	9
Severe	0	0	0	0	0	0	0	0	0	2
Moderate	0	0	0	0	4	0	0	0	0	1
Mild	0	0	0	0	2	0	0	0	0	2
Minimal	0	0	0	0	1	0	0	0	0	4
Aorta[b]	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Mineralization	0	0	0	0	2	0	0	0	0	1
Moderate	0	0	0	0	1	0	0	0	0	1
Mild	0	0	0	0	1	0	0	0	0	0

[a] = Incidences for the 5.13 g/kg/day OSP group (Group 5) includes animals found dead, euthanized in extremis and euthanized at the scheduled necropsy.

[b] = Number of tissues examined from each group.

[c] = Background level of mineralization with no test article significance.

As shown in the table above, administration of OSP at 5.13 g/k/day caused mortality and toxicity-- seen as renal tubular degeneration and mineral deposition, mineralization in the stomach and aorta, and cardiac and hepatic degeneration /necrosis. In dogs, BLI800 caused emesis, excessive salivation, excessive drinking of water and abnormal excreta (soft and/or mucoid feces and/or diarrhea) and increased urine pH and sodium excretion. No significant organ toxicities were observed. Clinical signs of diarrhea and electrolyte and metabolic changes appeared to be secondary to the pharmacological actions or homeostatic adaptation to the osmotic load. There were no significant nonclinical safety concerns for the indication. For more detailed study results and conclusions, see the full Pharmacology/Toxicology review by Dr. Chakraborti.

4 Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

Aside from the two pivotal Phase 3 studies, Applicant also submitted six Phase 1 and 2 studies. Applicant enclosed literature with the submission. Ann Corken Mackey was consulted from Office of Safety and Epidemiology (OSE) for assessment of the reported elevations in creatine kinases in BLI800 and Moviprep. The AERS database was searched for elevation in CK's of other bowel preps such as oral sodium phosphates and PEG products. Concomitant medications such as propofol, midazolam, fentanyl and Demerol were also investigated as contributing factors to the elevation in CK's. See OSE Consult by Ann Corken Mackey and section 4.4.

4.2 Tables of Clinical Studies

Table 4 summarizes the clinical studies and trials submitted for the review of NDA 22-372.

Table 4: Summary of Clinical Trials for BLI800

Study	Design	Patient Population/Group Description	Formulation /dosing
001-022: S	SS, OL, NR,AC, Phase 1	N=5 H A, each subject received ≥ 2 solutions	5 sulfates vs. Fleet's, split dose
005-082: S	SS, OL, NR, AC, Phase 1	N=27 H A: Solution (Sln) 1, 2, 4: n=1 each Sln 3: n=3 Sln 5: n=5.	5 sulfates vs. 6 laxatives:Senna,MOM, NuLytely-2L & 4L, HalfLytely & bisacolyl,2 doses,1 day
006-181 S & E	SS, OL, NR, AC, Phase 1	N=9 H A (1 excluded) used for 1 to 3 of preparations for n=5 each group	BLI800 vs. Fleet's vs. NuLytely-4L, split doses
BLI800-101	SS, randomized, O L, A C, Phase 2 effects of colonic cleanser on symptoms, stool and plasma electrolytes, fecal volume, fluid balance over approx. 3 weeks	N=18-24 males: 2 Gps of 6 HA: 6 split doses (OSS, Fleets). Added 6 HA: 6 doses every 15 minute Day 1. Gp1: split dose (3 glasses Fleet with 3 water) Gp2: OSS 3 doses in 2L with 1 glass water, repeat AM Gp3: OSS to 2L: 6 glasses in one day, with 2 glasses water Gp4: OSS diluted 1L in 3 glasses & up to 6 glasses water	Early sulfate formulation similar to BLI800 vs. Fleet's in split dose, same day dose
BLI800-101	amendment	N=18-24, 6 H A, OPS; 12-18 H A, OSS Gp1, 3 ,4: same ; Gp 2 (in 2L): Fleet's 3 doses, 1 glass water, repeat AM	
BLI800-201:E	SS, OL , unC, Phase 2: 4 cleansing scores, post-colonoscopy	N= 9 H A	Early sulfate solution in split dose
BLI800-202:S	SS, OL, study on PK effects, Phase 2	Healthy control, 6 mild to moderate hepatic impairment 6 moderate renal impairment	To-be-marketed formulation, 12 hour between 2 doses
BLI800-301:S, E	R, P, MC, SB , AC, Phase 3	N=387 A, routine and diagnostic colonoscopy	BLI800 vs. MoviPrep; Same day dose
BLI800-302: S,E	R, P , MC, SB, AC, Phase 3	N=364 A undergoing routine and diagnostic colonoscopy	BLI800 vs. MoviPrep ; Split dose

single site= SS, multi-center= MC, open-label= OL, single-blind= SB, non-randomized= NR, randomized= R, parallel =P, active control=AC, healthy= H, adults =A, safety=S, efficacy=E

4.3 Review Strategy

Efficacy Studies
Two Phase 3 pivotal studies, BLI 800-301 and BLI 800-302 for safety and efficacy and one pilot phase 2 efficacy study, BLI800-201 (as reference for supporting better efficacy results), form the basis of the efficacy review.

Safety Studies
Other than the two pivotal studies, six other Applicant conducted trials were evaluated for potential safety data. The phase 1 studies provided safety data that were not relied upon due to small sample size and poor adherence to protocol thereby generating unclear wash-out periods and missing data. The Phase 2 studies (BLI800-101) provided mostly safety data. BLI800-201 is

a Phase 2 efficacy study on the adequacy of cleansing post-colonoscopy. BLI800-202 is a sub-population hepatic and renal impairment (PK) study which was important for information about serum sulfates and changes in electrolytes during the first 30 hour interval.
The only PK study, BLI800-202, was reviewed for short-term safety by the Clinical Pharmacology Reviewer, Jane Bai, see Section Clinical Pharmacology. A safety review was also performed by this medical reviewer in this special renal and hepatic impaired population.

This medical officer was responsible for reviewing NDA 22-372 efficacy and safety data. The pivotal studies BLI800-301 and BLI800-302 comparing BLI800 to Moviprep in adult patients as a colonic cleanser prior to colonoscopy for routine and diagnostic indications formed the basis for the majority of safety and efficacy conclusions. The reliance on two adequately, well-controlled, randomized, parallel studies is consistent with NDA criteria for submission review under the 21 CFR.

Review of labeling for currently approved products GoLytely, HalfLytely, Colyte, NuLytely, Osmoprep, Visicol, Fleet's E-Z Prep and Prep Kits, and MoviPrep were done as well as review of Applicant Special Protocol Amendments, meeting minutes, IND meetings communications during the investigational phase of this drug.

A consult was obtained from Office of Safety and Epidemiology (OSE), Ann Corken Mackey, for post-marketing reports related to elevations in creatine kinase values and Adverse Event Reporting System (AERS) data. *Reviewer's comments: A review of NDA 21-881 (Moviprep) for any PEG product class effects associated with elevated creatine kinases or other laboratory abnormalities referred to in Module 5, Volume 9.3, tabs 16.2.20.1 and 16.2.20.2 and Module 5, Vol. 10.3 tabs 16.2.20.1 and 16.2 .20.2 and discussed in IR sent 2/10/09 was done. Discussion with Deputy Director of Safety, Joyce Korvick, was also done. Preliminary consult on REMS plan included JMP search for elevated BUN and creatinines. Mild elevations in BUN and creatinines were noted in approximately 50 patients, some with trends. See Section 7.1.4 Other Search Strategies. A preliminary JMP analysis of electrolyte changes associated with vomiting did not show substantial changes. See Section 7.1.4. DMMAC were also consulted. Refer to section 4.4 for DSI and OSE conclusions.*

4.4 Data Quality and Integrity

Table 5: DSI sites audited

Investigators	Site #	Protocol #	No. Patients	Location	Rationale
Richard Chasen, M.D.	3	BLI800-301	75	Laurel, MD USA	Second largest number of patients East coast
Steven Duckor, M.D.	13	BLI800-302	46	Orange, CA USA	Associated with site 15, West Coast
Dennis Riff, M.D.	15	BLI800-302	80	Anaheim, CA USA	Largest number of patients West Coast

Investigators	Site #	Protocol #	No. Patients	Location	Rationale
Lawrence Wruble, M.D.	20	BLI800-302	40	Germantown, Tn USA	Death reported Southern locale

Site Selection
Four inspection sites were chosen based on the largest number of subjects (site 3 and 15), the occurrence of death (site 20), and the regional locale (rural vs. urban; West coast vs. East coast vs. Southern regions). Also, sites that reported highly robust results as compared to Moviprep or other sites were investigated.

Site 3, Laurel, Maryland
Inspectors found discrepancies in drug kit numbers assigned to seven subjects. Two patients (03-17 and 0318) were switched in treatment assignment.
Five patients did not receive pregnancy tests. Four of these patients did have tubal ligations. The dispensing of drugs was also found to be discrepant.

Site 13, Orange, CA
At this site the investigator did not report five adverse events related to elevated uric acids and a discrepancy in symptom reporting as GI bleed in the eCRF was in actuality "bleeding from hemorrhoids" for patient #13026.

Site 15, Anaheim,CA
At this site protocol violation occurred when a patient was given the test drug and colonoscopy prior to receiving the screening labs.

Site 20, Germantown, TN
Because a Medwatch form was submitted 1 year and 4 months after the occurrence of a colonic perforation during a mandatory safety update when the Applicant was preparing for the DSI inspection at site 20, Dr. Antoine El Hage from DSI was contacted and the site thoroughly investigated with audits of all CRFs. One death had been reported at site 20 of a patient who had died from respiratory distress.
Patient #006 was given the study drug before the screening labs were done, and two male patients were checked off as having had pregnancy tests done.

Khairy Malek, of DSI stated all the sites received VAI Deviation from Regulations ratings, and appear valid for the support of the NDA.

Submission Quality and Integrity
The initial submission for NDA 22-372 was only a paper submission without electronic datasets. The submission was poorly organized and information was difficult to locate. Requests for re-pagination and electronic datasets were partly fulfilled. Applicant's initial paper submission of datasets required more than 15 further clinical information requests excluding other requests by the other disciplines and review of at least seven revised electronic and/or paper datasets that

were unsatisfactory before the one submitted on May and June 2009 was adequate for review. This review was hampered by incomplete information.

Infromation request	Date Received	Brief Description
1	10/28/08	Lack test drug given dates, Phase 1 and some further SAS datasets-still incomplete
2	11/21/08	NI margin, SAS datasets with gender, treatment group, age, study number, Stats efficacy dataset info, error in AE tables; CRF's requested SAE.
3 (safety update)	12/12/08	Unreported colonic perforation from 8/07 reported
4	12/24/08	SAS datasets lack drug adminstration /f/u dates-still incomplete
5	2/3/09	Same as "4" due to formatting –still incomplete; SAE clarifications
6	2/10/09	Further clarifications of "5"
7	2/23/09	Further narratives of SAE's , incidence for AE tables by FDA differ from Applicants; CK elevation analysis
8	3/9/09	Additional CK elevation analysis
9	3/11/09	Submit pediatric development plan
10	4/3/09	Missing serum sulfate analysis, clarify screen failures, (b) (4)
11	4/21/09	Sulfates not analyzed—no amendment, drop outs clarified, bradycardia analysis, exclusion of mild/moderate GI severity in AE tables
12	5/6/09	TEAE and Pt. reported Symptoms not combined, new SAS AE datasets
13	5/14/09	new SAS AE datasets with all AE's
14	6/12/09	New complete TEAE datasets using all randomized patients

During labeling/PMC meetings it was discovered that the Applicant had not combined their adverse events reported by the patient with the TEAE (reported by investigator) tables. Since these were reported separately and partially in the label this requested final complied dataset submitted May 2009 combined the patient reported adverse events with the observer reported adverse events that resulted in a 10x increase in the number of total adverse events and 8 fold increases in the number of patients with adverse events in the BLI800 group were complied. for analysis. This ultimately resulted in a major amendment.

The electronic datasets lacked numeric format, lacked labeling of demographic details, labeling of date of drug ingestion and correlation with AE's, lack of accurate safety reporting and analysis prior to the last dataset. Applicant did not follow their protocol in not processing serum sulfate samples, nor did they submit an amendment or note this omission in their summary. Applicant did not report all AE in their tables, selecting on severe or moderate AE's in their tables. Applicant did not report a SAE until more than one year later.

Applicant did not supply datasets on a Phase 1 study until requested (study sited "4 solutions were used" and Applicant excluded one solution's dataset), did not report to Medwatch a MoviPrep patient who had a SAE of colonic perforation until 1 year and 4 months later until Applicant was preparing for a DSI inspection. Narrative reports of the atypical chest pain (#12002) as well as the narrative report on the patient with respiratory arrest (# 20013) resulting in death were requested in Information Request (IR) of 2/10/09 , but were of insufficient detail and IR #7 was sent. Applicant also had errors in statistical calculations of the two-day dosing for treatment emergent adverse events which hampered the review of this submission. 22 other CRF's were requested.

Applicant did not supply a detailed Integrated Summary of Safety and Integrated Summary of Efficacy in Module 5 with initial submission and this was complicated by the re-calculations of

the True ITT and TEAE and associated datasets so that the Module 2 ISS and ISE tables were substantially different at the final review.

4.5 Good Clinical Practices

According to the Applicant, all studies were conducted in full compliance to the Code of Federal Regulations (CFR) including the Good Clinical Practices (GCP) Guidelines, which is consistent with ethical principles set forth in the International Conference on Harmonization (ICH) and HIPAA Privacy Regulations. With the exception of protocol violations described in section 4.4 on DSI inspections, serum samples that were collected per protocol but never analyzed, and a Medwatch report for SAE not submitted until more than one year after occurrence when it was found upon Applicant audit of site 20, the investigators and study staff were compliant in their study protocol in accordance with 21CFR parts 50 and 56 which governs the protections of human patients and 21 CRF regulates IRBs. The Applicant states they explained the purpose, nature, potential risks of the study to each patient. In accordance with 21CFR parts 50 and 56, Applicant states patients had to sign an informed consent at pre-screening before evaluation and enrollment (An example was submitted). Applicant states the consent forms were kept on file by the site staff. Applicant states that an Institutional Review Board reviewed and approved the study protocol and informed consent form prior to starting the study.

4.6 Financial Disclosures

For Study BLI800-301 and BLI800-302, the Applicant provided a signed 3454 form for certification of Financial Interests and Arrangements of Clinical Investigators denying any financial arrangements with the clinical investigators from sites 1 to 21 that performed all studies included in Study BLI800-301 and BLI800-302.

5 Clinical Pharmacology

5.1 Pharmacokinetics

One pharmacokinetic study was performed by Braintree to evaluate the PK properties. BLI800 - 202 studied PK in moderate renal impairment patients and mild to moderate hepatic impairment patients. In three groups of 6 normal healthy volunteers (NHV), 6 mild/moderate hepatic (MHD) impairment patients or 6 moderate renal impairment patients ingesting either OPS or OSS. BLI800 was well-tolerated by these patients with types and severity of adverse events similar to those seen in Phase 3 trials. Patients with (Moderate Renal Disease) MRD had elevated serum sulfate levels at baseline and after BLI800 when compared to healthy subjects, the elevations were less than the patients with renal failure and were insufficient to alter biochemical parameters indicative clinically of hypersulfatemia. After adjustments for these baseline sulfate levels, there were no differences in sulfate PK parameters. See Pharmacology review by Dr. Jane Bai.

No specific pharmacodynamic studies or efficacy studies in animals were performed by the Applicant to delineate the mechanism of action or other physiologic effects. The only human PK study performed is described in *section 5.1.*

5.2 Exposure-Response Relationships

Exposure-response relationships and pharmacodynamics were not assessed in NDA 22-372. No dose ranging studies were performed in the BLI800-202, the only PK study. Serum sulfate levels were measured at different timepoints. See section 5.1.

6 Integrated Review of Efficacy

The individual studies for BLI800-301 and BLI800- 302 study design protocols and study results are reviewed in Appendices 10.1.1 to 10.1.4.

6.1 Indication: Colonic Cleanser

Suprep Bowel Prep Kit is a gastrointestinal lavage indicated for cleansing of the colon in preparation for colonoscopy in adults.

6.1.1 Methods

Two Phase 3 pivotal studies, BLI 800-301 and BLI 800-302 form the basis of the efficacy review. One pilot phase 2 non-controlled efficacy study using an early sulfate (not the to-be-marketed) formulation, BLI800-201, was reviewed for the sensitivity of efficacy evaluations subdivided into segmental colonic assessments. Since this was a non-controlled study it was not included for statistical calculation, but, it could have been used to increase sensitivity of the pivotal trials (See Appendix 10. 6). The 2 pivotal studies, under IND 74808, involved 2 randomized 1:1, parallel, multi-center, single-blind Phase 3 studies of BLI800 vs. MoviPrep® in 400 adults using a same day (Study 301) and a two day split dose (Study 302) regimen of 1 gm/dose oral sulfate solution.

6.1.2 General Discussion of Endpoints

Primary efficacy endpoint
In both pivotal studies the primary efficacy endpoint was identical. The efficacy findings were subject to one endoscopist's visual assessment without verification by another gastroenterologist or colonoscopist either by direct re-visualization or video recording. Neither were distinct assessments by 4 point analysis of the colon at the ascending, transverse, descending, sigmoid areas or rectum performed. The primary efficacy endpoint grades and corresponding description are described below in a 4 point scale but pooled to a binary outcome of success or failure.

Table 6: Degree of Colonic Preparation Success--Graded Descriptions

Score	Grade	Description
1	Poor	Large amounts of fecal residue, additional cleansing required
2	Fair	Enough feces or fluid to prevent a completely reliable exam
3	Good	Small amounts of feces or fluid not interfering with exam
4	Excellent	No more than small bits of adherent feces/fluid

- grades 1 or 2 = failures
- grades 3 or 4 = successes.

This 4 point cleansing scores were also used to support the approval of GoLYTELY, NuLYTELY and HalfLYTELY. This is an invalidated scoring system. No placebo studies have ever been performed in any colonic cleanser clinical studies.

Diminished Specificity and Sensitivity of Colonic Results

Reviewer's Comments: This reviewer believes that the binary outcome of success or failure used in this NDA diluted the sensitivity of the grade of cleansing and the computation of efficacy results based on sections of colonic and the clearer distinctions of degree of cleansing. These results were also not substantiated by other endoscopists. It is highly likely that the specialists who did the assessments were gastroenterologists. In the German and French studies from the MoviPrep NDA, some of the colonoscopists may not have been gastroenterologists whereby operator experience and frequency of endoscopy may influence results.

The German and French studies from the MoviPrep NDA are presented as a reference for discussion of recommendations. It illustrates how the current NDA could have increased its sensitivity and specificity by using the VRS (Verbal Rating Scale) for five colonic segments (the ascending, transverse, descending, and sigmoid colon and rectum). This was used in the MoviPrep German and French studies as well as utilizing a 4-level overall colon cleansing scale that incorporates the VRS.

The responders with grades A or B were defined as having an overall effective preparation. Grades C or D patients were considered non-responders.

Table 7: 4-level Colon Scale in the German and French Studies (NDA 21-881 review)

Overall Colon Cleansing Scale (level)	Colon Segment with VRS score	VRS Score
A	All segments	3 or 4
B	At least one	2
C	At least one	1
D	At least one	0

This scale was in turn based on a 5-point VRS that assessed the five colonic segments.

Table 8: The 5-point VRS cleansing in the German and French studies (colonic segments: ascending, transverse, descending, sigmoid and rectum from NDA 21-881 review)

Point VRS	DEFINITION	Description
4	**Very Good**	Empty and clean
3	**Good**	Presence of clear liquid in the gut, but easily to be removed by suction*
2	**Moderate**	Brown liquid or semisolid remaining amounts of stool, fully removable by suction**
1	**Bad**	Semisolid amounts of stool, only partially removable with a risk of incomplete visualization of gut mucosa
0	**Very Bad**	Semisolid or solid amounts of stool; consequently colonoscopy incomplete or needs to be terminated

* In the French study, the good (3) rating was defined as "clear liquid (transparent, yellow, or green)".
** In the French study, the moderate (2) rating was defined as "brown liquid or semisolid remaining small amounts of stool, fully removable by suction or displaceable."

In the German study, three blinded gastroenterologists graded cleansing of each colonic segment by video-recording. In the French study, one blinded gastroenterologist and one colonoscopist reviewed video recordings. In the present NDA, no verification of the colonic cleansing score is performed by another endoscopist or gastroenterologist by video recording or during the procedure. Separate segments of the colon are not rated on a VRS scale.

In the Phase 2 pilot un-controlled efficacy BLI800-201, the separate segments of the colon were rated, but, this was not done in the Phase 3 studies. In BLI800-201 (study 201), colonoscopists rated the cleansing with a four point scale ranging from 1= poor to 4=excellent and assessed the amounts of residual stool and fluid as 1=absent, 2=small, 3=moderate, 4=excess in each of 5 colon segments (cecum, ascending, transverse and descending, and sigmoid/rectal colon).

Secondary Endpoint
The secondary endpoint (independent of the primary endpoint) included the adequacy of cleaning and the need for re-preparation as assessed by the colonoscopist at the time of exam. Ratings of 2 or 1 were considered adequate or inadequate. Some assessments "1" ratings were designated as needing re-preparation and some were not.
Reviewer's Comments: The rating of adequacy of cleaning could have utilized a Visual Analog Scale (VAS) that would measure a scale of 0 to 100 in degree of adequacy. It may also have measured the degree of water injection into the colon during colonoscopy as well as the degree of liquid aspirated.

6.1.3 Study Design

The pivotal studies BLI800-301 and BLI800-302 comparing BLI800 to Moviprep in adult patients as a colonic cleanser prior to colonoscopy for routine and diagnostic indications formed the basis for the majority of safety and efficacy conclusions. The reliance on two adequately, well-controlled randomized parallel studies is consistent with NDA criteria for submission review under the 21 CFR.

The pivotal studies were randomized (1:1), single-blinded (to the colonoscopist), active-controlled, parallel-group, efficacy trials of approximately 400 male and female adults in 10 to 11 sites comparing Suprep to MoviPrep in those patients who were undergoing routine and diagnostic colonoscopy. BLI800 or MoviPrep were administered orally as a same day or split dose.

With the exception of dose regimens both study 301 and study 302 were designed exactly alike. The studies were identical in study design, inclusion/exclusion criteria, study schedule, and efficacy endpoints. It replicated the indicated use of the colonic preparation in the proposed population for elective and non-elective colonoscopy.

The eligibility criteria are presented in Table 9, followed by the Study Visits and Procedures in Table 10.
Reviewer comments: Dose finding studies in Phase 1 and 2 were adequate for doses and dose regimens used in the pivotal studies.

The lack of a placebo control group in any past colonic cleanser clinical trial and the discrepancies in dietary restrictions, the change in comparator, and the "biocreep" that may have occurred with a delta of 15% in prior non-inferiority PEG and OSP studies are to be considered.
The duration of the controlled study to assess benefit was acceptable. The entry criteria was acceptable. Some of those patients excluded in the study were not excluded in the patient population in the label. Exclusion and inclusion criteria have evolved based on the other colonic cleanser labeling such as for MoviPrep, NuLytely, HalfLytely, and Fleet's EZ Prep.
Further study of subpopulations of high risk patients, elderly with co-morbidities and concomitant medications are needed to weigh the benefits versus the risks of Suprep.

Unblinding
Randomization and blinding occurred as specified in Appendix 10 under Randomization.
If there was un-blinding by the staff during the study, these were considered protocol violations.
To prevent unblinding, only the unblinded staff performed drug accountability by measuring the remaining amount of MoviPrep bottle and assessing the number of BLI800 bottles used.
After using the preparation, the patient would return all the drug preparation components on Visit 2. *Reviewer's comment: Other than the endoscopist who is blinded, the other staff that were blinded were not specified.* To maintain blinding of the colonoscopist, he did not perform randomization, drug dispensing, return and drug accountability. Patients were instructed not to talk with their staff about their preparation.

For further discussion on endpoints, blinding, randomization, statistical analytic plan see the efficacy results and statistician review by Dr. Milton Fan.

Table 9 : Eligibility Criteria for Study 301 and 302

Inclusion Criteria	Exclusion Criteria
Adult male and female patients, ages 18 years and older, were included if they were undergoing colonoscopy for routine indications or for follow-up of barium enema results, gastrointestinal bleed, anemia of unknown etiology, cancer surveillance, endosonography, inflammatory bowel disease (IBD), unknown etiology of diarrhea or constipation, polypectomy, laser therapy or routine screening. Patients must have: • Otherwise, good health. • If female, and of child-bearing potential, using acceptable form of birth control such as hormonal birth control, IUD, double-barrier method, depot contraception, abstinence or vasectomized spouse. • Negative urine pregnancy test at screening. • According to investigator judgment, mentally competent to provide informed consent for participation.	Patients were excluded for any one of the following reasons: • Known or suspected ileus, severe Ulcerative Colitis (UC), gastrointestinal (GI) obstruction, gastric retention, bowel perforation, toxic colitis, or megacolon. • Predisposed to aspiration based on impaired consciousness. • Undergoing colonoscopy for foreign body removal/decompression. • Patients with clinically significant electrolyte abnormalities on Visit 1 labs (↓K+, ↑↓Na+, ↓Ca+, ↑phosphate, dehydration or those secondary to use of diuretics or angiotensin converting enzyme inhibitors) • Patients with phenylketonuria, an investigational study within the last 30 days. • History of renal or hepatic insufficiency, history of CHF, previous GI surgeries, or G-6-PD deficiency. • Subjects who are pregnant or lactating or intend to become pregnant. • Subjects of childbearing potential who refuse a pregnancy test. • Subjects allergic to any components of BLI800: sodium sulfate, potassium sulfate, magnesium sulfate and sucralose or of Moviprep: polyethylene glycol, sodium sulfate, sodium chloride, potassium chloride, ascorbic acid, sodium ascorbate, aspartame and acesulfame potassium. • Subjects determined by Investigator to not be suitable for any reason. • Subject in another investigational study.

Reviewer's comment: Applicant did not specify the limits for electrolyte abnormalities. They reported 2.5 ULN as abnormal in safety data.

Table 10:Study 301 and 302 Visits and Procedures

Procedures	Visit 1 Screen	Day Before Endo-scope	Visit 2 Day of Endo-scope	Visit 3 30 Day F/U
Informed Consent	x			
Inclusion/Exclusion Criteria Review	x			
Medical History	x			
Physical Exam	x		x	
Concomitant Med Review	x		x	
Chemistry/Hematology	x		x	x
Urine Pregnancy Test (if applicable)	x			
Randomization	x			
Drug dispensed	x			
Subject Instructed	x			
Subject's First Dose		X (studies 301, 302)		
Subject's Second Dose		X (study 301)	X (study 302)	
Treatment Questionnaire		x	x	
Symptom Scale			x	
Review of Subject Questionnaires			x	
Drug Accountability			x	
Perform Colonoscopy			x	
Assess Safety			x	x

The study duration was approximately 60 days with screening (Visit 1), Day of Colonoscopy (Visit 2), and ~30 day follow-up or phone contact (Visit 3). Protocol violation was not considered for patients who fell outside of these time windows: Visit 2 was not made within 14 days from Visit 1; Visit 3 did not fall between 25 to 45 days.

Reviewer's Comments: Because the dietary restrictions of BLI800 were more stringent than for MoviPrep, the efficacy findings are less robust. This was also true for the MoviPrep studies where inconsistent dietary restrictions were used among the other PEG and OSP comparators.

6.1.4 Efficacy Findings

Primary Endpoint Analysis

Both the Suprep and Moviprep same day regimens (77.9% vs. 76% for successful preparations) had poorer efficacy than both the split dose regimens (92.1% vs. 92.6% for successful preparations).

Suprep and Moviprep Split day regimens (92.1% vs. 92.6%) had very small differences between each other. The confidence interval falls between the pre-determined equivalence margins of ± 15%. Furthermore, the absolute value of the lower limit of the confidence interval was slightly greater than 4%, the more desired non-inferiority margin recommended by Dr. Fan.

Table 11: Responder's Rate for Colon Cleansing Preparation in Study 301 and 302

Treatment Group	True ITT (all randomized pts)			Applicant ITT			
	Responder n/N (5)	BLI800 – MoviPrep	95% C.I.	Responder n/N (5)	(BLI800 – MoviPrep)	95% C.I.	95% Confidence Interval
Suprep Same day	159/204 (77.9%)	1.9%	(-6.2%, 10.1%)	159/194 (82.0%)	1.6%	(-5.7%, 9.8%)	75.8% - 87.1%
MoviPrep Same day	155/204 (76 %)			155/193 (80.3%)			74.0% - 85.7%
Suprep Split dose	175/190 (92.1%)	-0.5%	(-5.8%, 4.9%)	175/180 (97.2%)	1.6%	(-2.2%, 5.4%)	93.6% - 99.1%
MoviPrep Split dose	175/189 (92.6%)			175/183 (95.6%)			91.6% - 98.1%

* Table complied by Milton Fan and this reviewer

See appendices 10.1 and 10.2 for further details.

The Applicant did not use a true ITT that included all randomized patients.

Applicant submitted in response to an IR in the table below that showed the success rate of all Suprep patients at 84.8% compared to all MoviPrep patients at 84% with 95% CI =-4.3,5.9 and verified the other rates calculated by Dr. Fan and this reviewer.

Primary Efficacy Responder Analysis
BLI800-301/302 Studies

Responder[1]	BLI800 n (%)	MoviPrep n (%)	95% CI[2]	p[3]	p[4]
All Patients (n)	394	393			
Success	334 (84.8%)	330 (84.0%)	-4.3, 5.9	0.755	<0.001
Fail	60 (15.2%)	63 (16.0%)			
301 Patients (n)	204	204			
Success	159 (77.9%)	155 (76.0%)	-6.2, 10.1	0.634	<0.001
Fail	45 (22.1%)	49 (24.0%)			
302 Patients (n)	190	189			
Success	175 (92.1%)	175 (92.6%)	-5.8, 4.9	0.862	<0.001
Fail	15 (7.9%)	14 (7.4%)			

(1) A successful treatment is defined as bowel cleansing graded either excellent or good by the blinded colonoscopist (grading score = 3 or 4).
(2) Confidence interval (CI) for the difference between treatments was by Chi-Square Test.
(3) P-value for the difference between treatments is from a Cochran-Mantel-Haenzsel Chi-Square, controlling for site.
(4) P-value for the non-inferiority hypothesis using an equivalence margin of 15 percent (reference Tables 14.2.1b in this submission)

Primary Efficacy Endpoint By Cleansing Scores: Study 301 and 302

From IR #14, received 6/12/09

Preparation Cleansing Score
BLI800-301/302 Studies

	All Patients		301 Patients		302 Patients	
Score	BLI800 n (%)	MoviPrep n (%)	BLI800 n (%)	MoviPrep n (%)	BLI800 n (%)	MoviPrep n (%)
4 Excellent	200 (50.8%)	168 (42.7%)	86 (42.2%)	72 (35.3%)	114 (60.0%)	96 (50.8%)
3 Good	134 (34.0%)	162 (41.2%)	73 (35.8%)	83 (40.7%)	61 (32.1%)	79 (41.8%)
2 Fair	25 (6.3%)	37 (9.4%)	22 (10.8%)	31 (15.2%)	3 (1.6%)	6 (3.2%)
1 Poor	11 (2.8%)	8 (2.0%)	9 (4.4%)	6 (2.9%)	2 (1.1%)	2 (1.1%)
Mean Score	3.41	3.31	3.24	3.15	3.59	3.47
p value[1]	0.049		0.278		0.050	

1) P-value for Mean Preparation Score is from a one-way ANOVA with term for treatment for the continuous variable.
(reference Tables 14.2.1.1b in this submission)

The split day dose of Suprep was more efficacious at 60% than the same day dose regimen at 42.2% for excellent scores. The same day dose had more "poor" scores than the split dose regimen (4.4% versus 1.1%).

Secondary Endpoint Analysis

The secondary endpoint of adequacy of preparations was a binary outcome with "2" being adequate and "1" being inadequate. The need for re-preparation and colonoscopy was noted. Some "1" ratings for inadequate were noted as needing re-preparation and some were not. Using the truee ITT, in the Suprep same day population, 87.3% had adequate preps as compared to a slightly higher 89.2 % in the Moviprep group. In the Suprep split day population 93.7% has adequate preps compared to a slightly higher incidence in the MoviPrep group of 95.8%. MoviPrep was slightly more efficacious in producing adequate cleansing.

Table 12: Secondary Endpoint: Number and Percent of Adequate Preparations

Number and Percent of Adequate Preparations Protocol BLI800						
	Applicant **ITT**			**True ITT (all randomized pats)**		
Treatment	Rate	(BLI800 – MoviPrep)	95% C.I.	Rate	(BLI800 – MoviPrep	95% C.I.
Suprep Same day	178/190 (93.7%)	-1. 1%	(-5.8%, 3.6%)	178/204 (87.3%)	-2.0%	(-8.2%, 4.3%)
MoviPrep Same Day	182/201 (89.2%)			182/204 (89.2%)		
Suprep Split Day	178/180 (98.9%)	-0.0%	(-2.2%, 2.1%)	178/190 (93.7%)	-2.1%	(-6.6%, 2.4%)
MoviPrep Split Day	181/183 (98.9%)			181/189 (95.8%)		

from Table 302-7 and
Compiled by Milton Fan and this reviewer

In IR #14, received 6/12/09, Applicant confirmed that the adequacy of successful cleansing was 87.3 % in the Suprep group and 89.2% in the MoviPrep group using the True ITT values. In addition, there were 6.9% (14/204) in the Suprep group and 4.9% (12/204) in the MoviPrep group who had missing data. Of those patients listed as failures, 66.7% (8/12) in the Suprep group and 7/10 (70%) were noted as needing re-preparation.

In Study 301, there were 26 patients (14 in BLI800 and 12 in MoviPrep) who were excluded from the Applicant's ITT analyses. There were 26 patients (14 in BLI800 and 12 in MoviPrep) who were excluded from the Applicant's ITT analyses. In Study 302, there were 16 patients (10 in BLI800 and 6 in MoviPrep) who were excluded from the Applicant's ITT analyses.

Dr. Fan performed an analysis of the superiority of Suprep to placebo as if it had been an arm in this study. The lower limit of the two-sided 95% confidence intervals on the success rate for BLI800 of 87.3% was computed based on 95% CI on the success rate of BLI800 for the true ITT population. If we set the lower limit of the two-sided 95% confidence intervals on the success rate for BLI800 higher than the upper limit of 95% confidence interval on the historical success rate for placebo (if it exists), then BLI800 would be considered as effective.

Applicant attempted to justify the non-inferiority margin by referring to the previously listed studies summarized in Table 13: Historical Non-inferiority Margins of Other Studies and NDAs. They assumed that since no placebo studies exist and such a study probably would not be IRB approved if attempted now due to the risks associated with a failed colonoscopy procedure, that the success rate of placebo in these studies would be 0%. Applicant states that the generally accepted success rate of cleansing is 70%. [1,3,4]

Table 13: Historical Non-inferiority Margins of Other Studies and NDAs (From Applicant)

Study Drug NDA/Study#			Success Rate %	Non-inferiority % or delta	Primary EP tool	Secondary EP tool
MoviPrep # N-21881		Same Day	73	15	Primary: VRS, 4-point colon segment scale Secondary: ≥ 15, includes modified adequate/inadequate rating	
		Split Day	88.9	15		
Halflytely #N-21551			79.3	16	4 point	adequate/inadequate rating
Nulytely			76.8			
Halflytely with Bisacodyl	S-006 Study F-3826	10 mg	86.9	15		
Halflytely with Bisacodyl		20 mg	87.9			

Subgroup Analyses

Subgroup analysis of gender, age, and site as shown below were consistent for minimal site treatment differences for gender and age between Suprep and MoviPrep in Study 301 and 302. Patients with missing data were considered "failures".

Table 14 and 15 : Subgroup Analysis of Successful Preparations in Study 301 and 302 (note correction of site 11 is site 21 in Dr. Milton Fan's table)

Number and Percent of Successful Preparations
Protocol BLI800-301
True ITT Analysis

Subgroup	BLI800	MoviPrep	Diff	95% CI
Gender				
Male	73/90 (81.1%)	71/94 (75.5%)	5.6%	(-6.3%, 17.4%)
Female	86/114 (75.4%)	84/110 (76.4%)	-0.9%	(-12.1%, 10.3%)
Age (yrs)				
< 65	116/150 (77.3%)	120/150 (80.0%)	-2.7%	(-11.9%, 6.6%)
≥ 65	43/54 (79.6%)	35/54 (64.8%)	14.8%	(-1.9%, 31.5%)
Site				
1	16/23 (69.6%)	17/24 (70.8%)	1.3%	(-27.4%, 24.9%)
2	16/20 (80.0%)	18/20 (90.0%)	-10.0%	(-31.9%, 11.9%)
3	28/38 (73.7%)	23/37 (62.2%)	11.5%	(-9.5%, 32.5%)
4	17/20 (85.0%)	15/20 (75.0%)	10.0%	(-14.6%, 34.6%)
5	15/18 (83.3%)	14/18 (77.8%)	5.6%	(-20.2%, 31.4%)
6	1/2 (50.0%)	1/2 (50.0%)	0.0%	(-98.0%, 98.0%)
7	14/24 (58.3%)	17/24 (70.8%)	-12.5%	(-39.3%, 14.3%)
8	1/3 (33.3%)	2/3 (66.7%)	-33.3%	(-100.0%, 42.1%)
9	26/27/ (96.3%)	22/26 (84.6%)	11.7%	(-3.9%, 27.3%)
10	24/27 (88.9%)	24/28 (85.7%)	3.2%	(-14.4%, 20.7%)
11	1/2 (50.0%)	2/2 (100.0%)	-50.0%	(-100.0%, 19.3%)

Number and Percent of Successful Preparations
Protocol BLI800-302
True ITT Analysis

Subgroup	BLI800	MoviPrep	Diff	95% CI
Gender				
Male	81/87 (93.1%)	82/87 (94.3%)	-1.1%	(-8.4%, 6.1%)
Female	94/103 (91.3%)	93/102 (91.2%)	0.1%	(-7.7%, 7.8%)
Age (yrs)				
< 65	134/144 (93.1%)	141/150 (94.0%)	-0.9%	(-6.6%, 4.7%)
≥ 65	41/46 (89.1%)	34/39 (87.2%)	1.9%	(-11.9%, 15.8%)
Site				
11	18/23 (90.0%)	18/20 (90.0%)	0.0%	(-18.6%, 18.6%)
12	13/15 (86.7%)	15/15 (100.0%)	-13.3%	(-30.5%, 3.9%)
13	22/23 (95.7%)	23/23 (100.0%)	-4.3%	(-12.7%, 4.0%)
14	14/15 (93.3%)	15/15 (100.0%)	-6.7%	(-19.3%, 6.0%)
15	38/40 (95.0%)	35/40 (87.5%)	7.5%	(-4.8%, 19.8%)
16	12/14 (85.7%)	12/13 (92.3%)	-6.6%	(-30.0%, 16.8%)
17	7/7 (100.0%)	5/6 (83.3%)	16.7%	(-13.2%, 46.5%)
18	14/15 (93.3%)	12/15 (80.0%)	13.3%	(-10.5%, 37.2%)
19	19/21/ (90.5%)	20/22 (90.9%)	-0.4%	(-17.8%, 16.9%)
20	18/20 (90.0%)	20/20 (100.0%)	-10.0%	(-23.2%, 3.2%)

Compiled by Milton Fan.

From the response to IR#14 received 6/12/09, the female success rate for BLI800 was 83% (83.4% in MoviPrep female patients, 95% CI -7.5,6.7) and the male success rate for BLI800 was 86.9% (84.6% in Moviprep, 95% CI -4.9,9.5). The colonoscopy success rates for the Caucasian group were 85.2% (BLI800) vs. 84.3% (MoviPrep). In the non-Caucasian group, success rates were 81.5% (Suprep) vs. 81.8% (MoviPrep).

The sub-group by age in Study 301 from the Applicant, showed similar percentages for the ≥65 yr old group: greater success rate at 79.6% for Suprep and lower success rate 64.8% for MoviPrep (95% CI= -1.8 to 31.5 for total of both groups). With the ≥ 75 year old group, greater success rate at 61.5% for Suprep and lower success rate 57.9% for MoviPrep (95% CI= -30.9 to 38.2 for total of both groups). Study 302 from the Applicant showed similar percentages for the ≥65 yr old group: greater success rate at 89.1% for Suprep and lower success rate of 87.2% for MoviPrep (95% CI= -11.9 to 15.8 for total of both groups). With the ≥ 75 year old group, greater success rate at 86.7% for Suprep and lower success rate 70% for MoviPrep (95% CI= -16.5 to 49.9 for total of both groups).

Disposition of Patients: The studies were conducted at 21 centers with 787 randomized patients who were dispensed medication. The screen failures included patients who did not meet criteria and those who withdrew consent (see Drop Out section). There were no notable differences between the screen failures and withdrawals as compared with the randomized patients. Of these patients, the Applicant subdivided the patients into Non-ITT and ITT patients that incorporated Completers and Non-completers. *See Section 7.1.3.1 Overall Profile of Drop-outs.*

A summary of the successful preparation rates comparing both dose regimens and each treatment group concludes better efficacy in the split dose regimen as compared to the same day dose

regimen for BLI800 and MoviPrep. It also demonstrated comparable efficacy of the two treatment groups within the split dose regimen. MoviPrep may be slightly more efficacious in both the same day and split dose for adequacy of cleansing.

Since the dietary restrictions used in the pivotal studies BLI800-301 and BLI800-302 comparing MoviPrep and the product BLI800 used vastly different diet requirements and the impact of diet on efficacy is inevitable, the efficacy comparisons are found to be inconclusive. *See Section 10.1.6 or 10.2.6 Concomitant Medications* FDA request removal from the labeling any equivalence efficacy comparison between MoviPrep and the product or placebo. Efficacy results were based on a four point scale of degree of cleansing that was not verified by a second or third impartial operator at time of procedure or at time of video recording viewing. Exact identification and number of segments of colon that were inadequately cleansed were also not identified, although the Phase 2 pilot study did do these specific scales. Inconsistencies in ratings by colonoscopists were noted for the poor and fair findings. Although the non-inferiority margin falls within the acceptable confidence intervals considered to be adequate, the Applicant justification for the non-inferiority margin of 15% was provided based on historical use of similar margins and the Applicant did use all randomized patients (the True ITT) until IR#14. *See Appendix 10.6.1 for further details*.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

In Studies 301 and 302, the Suprep and Moviprep, same day regimens (77.9% vs. 76%) had poorer efficacy than both the split day regimens (92.1% vs. 92.6%). Suprep and Moviprep split day regimens (92.1% vs. 92.6%) had very small differences between each other.
This reviewer concludes that Suprep is efficacious in preparation for colonoscopy and that the split dose is superior to the same day dose. Moviprep may have slightly better adequate preparations. The determination of adequacy of preparation and the descriptions of successful preparations based on a 4 point scale are subject to the operator's assessment. In this study, this subjectivity was not reduced by confirmatory or pooled visual assessments by other colonoscopists. These scales are not validated, but, they have been historically used in approval of the PEG products. An additional scale to assess the portion of the colon that was cleansed (in different degrees) would also have increased specificity and sensitivity of results. *See Appendix 10.6.3.*

Dietary requirements varied in this study favoring the results of Suprep. Historically, this variability in dietary requirements exists in other past colonic lavage clinical trials such as with MoviPrep.

7 Integrated Review of Safety

The Integrated Review of Safety includes pivotal studies, BLI800-301 and BLI 800-302 in approximately 800 male and female adult patients in 21 sites for bowel cleansing prior to routine or diagnostic colonoscopy. Study 301 enrolled 416 patients of which 408 were randomized, 387 took all or part of the study drug, and 382 underwent colonoscopy. Patients averaged 95% compliance in Study 301. Study 302 enrolled 379 patients, all of which were randomized, 364 took all or part of the study drug, and 363 underwent colonoscopy. Patients averaged greater than 98% compliance in Study 302.

Five other Phase 1 and Phase 2 studies using developing formulations of sodium sulfate (Studies 001-022, 005-082, 006-181, BLI800-101 & 201, BLI800-202) used more proximate versions of the to-be-marketed BLI800 formulation. These studies included safety data that did not demonstrate substantial safety concerns although Study 101, 201,202 will be discussed in more detail. The established safety parameters were lacking for complete datasets and unclear about wash-out periods which were not clearly identified when the same subjects were placed into more than one treatment group.

7.1 Methods and Findings

Safety Endpoints: Day before colonoscopy to Visit 2
Safety Endpoints included a Symptom Questionnaire given on the day before colonoscopy and reviewed on Visit 2 or Day of colonoscopy. It was completed from the time the prep was started until the subject returned for Visit 2. Protocol violations for food were assessed. *See section on Protocol Violations 10.1.2.5.*
The Symptom Questionnaire was completed during Visit 2 prior to sedation and colonoscopy. It is based on the following scale of symptoms rated from 1 to 5 (1- none; 2-mild; 3-bothersome 4-distressing; 5-severely distressing) to describe the intensity of the following symptoms**:**

- Nausea,
- Vomiting
- Stomach bloating
- Cramping
- Overall discomfort .

Safety Assessments During Visits 2 and 3
Safety assessments were performed at Visits 2 and 3. They consisted of serum laboratory measurements at post-dose (times lab drawn before colonoscopy was variable) immediately prior to colonoscopy and on follow-up Visit 3. These would be compared to the screening labs done on Visit 1. Sites would attempt to schedule Visit 2 within 14 days of the screening date, but, those who fell outside of this window would not be considered protocol violators. On Visit 2, Symptom Questionnaires would be returned and reviewed with staff. Before the colonoscopy, the patient would complete the Symptom Scale portion, the vital signs would be taken, a physical exam be performed, and review of any adverse events or change in concomitant medications. Lab work without a specific pre-determined time would be obtained and serum sulfate sent to a

second lab. The blood was frozen and sent to (b) (4) for analysis of serum sulfate. *Comments: The Applicant decided not to analyze sulfates in the pivotal studies, without a formal amendment to the FDA. An IR was sent requesting the status of the frozen serum sulfate and the possibility of performing an analysis. Samples were found to be inadequately frozen since 2007 and were sub-optimal for analysis.*

The thirty day follow-up was chosen because of the history of renal complications occurring one to 6 months post-OSP dose. A complete metabolic panel, with renal and liver function tests, and a complete blood count with differential were done by (b) (4).

Adverse Events Reporting

The definition of an adverse event is the untoward or unexpected occurrence of a medical event in a subject undergoing investigation and having been administered a study product. This includes unfavorable or unintended signs including laboratory results, symptoms, or disease associated with the use of a study drug or investigational product. The following standard rating tables for severity and relatedness to study treatment are from the Applicant submission, Module 5, Volume 6.2, Tab 5.3.5.1B, 16.1.1, p.22):

Grade	Severity	Description
1	Mild	Barely noticeable, does not influence functioning, causing no limitations of usual activities
2	Moderate	Makes participant uncomfortable, influences functioning causing some limitations of usual activities
3	Severe	Severe discomfort, treatment needed Severe and undesirable, causing inability to carry out usual activities
4	Life-threatening	Immediate risk of death, life threatening or disabling (Must be reported as serious adverse event)
5	Fatal	Causes death of participant (Must be reported as serious adverse event)

Categories of Attribution:	Description: relationship of the study drug
Unrelated	There is NO evidence of any causal relationship
Possible	There is SOME evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of OTHER Factors May Have Contributed to the event (e.g., the subject's clinical condition, other concomitant events)
Probable	There IS Evidence to suggest a causal relationship, and the influence of other factors is Unl kely.
Definite	There is CLEAR evidence to suggest a causal relationship, and other possible contr buting factors can be Ruled Out.

Serious Adverse events (SAE) are any untoward medical occurrence that occurred subsequent to signing of informed consent until the follow-up visit and is described according to standard SAE definitions.

Collection of adverse events began with signing of the informed consent to the end of Visit 2. It includes prompt reporting of subjects' observation of symptoms. The investigator includes the time of report, date of onset, description of event, severity of event, actions and treatment resulting from the event, action on study participation, duration of event, and investigator correlation of event to study treatment.

7.1.1 Deaths

Only one fatality occurred in a MoviPrep patient, 20013, from site 20 from Study 302 who died as a result of respiratory arrest. This patient was a 76 year old male who took the study drug on 7/26/07 and 7/27/07 and underwent a laparoscopic colonic resection (b) (6) for a transverse colon neoplasm found by colonoscopy (b) (6). The patient had a respiratory arrest with acute renal failure and cardiac arrest post-surgery (b) (6) and the investigator did not relate the SAE to MoviPrep treatment. Patient expired (b) (6). This reviewer believes this was not related to Moviprep treatment and cannot positively relate the acute renal failure to the MoviPrep.

7.1.2 Other Serious Adverse Events

Applicant states that there were no serious treatment-emergent adverse events (TEAE's) for the BLI800 group in Study 301 and Study 302. Three serious TEAE's occurred in the MoviPrep Study 302 group. The first two cases were reported by Braintree along with the fatality patient (BH) #20013 as the only three cases of SAE's (IR from January 2009).

Patient 12002 ((b) (6)) was a 52 year old male who had atypical chest pain. Patient took MoviPrep from site 12 on 8/2/07 and 8/3/07. The patient was admitted (b) (6) for observance of atypical chest pain associated with numbness in the fingers and squeezing chest pain. Patient had blood tests and ECG done which ruled out a cardiac etiology and he was discharged on (b) (6). Investigator states this was unrelated to the study drug.

Patient 20030 ((b) (6)) was a late-reported colonic perforation in a 59 year old male The original Medwatch report for subject 20030 was not submitted until 1 year and 4 months after the event, when the Applicant was doing a routine audit in preparation for the DSI inspection. Applicant states they were not previously informed of this incident. Patient took MoviPrep (b) (6) and had rapid onset of severe right lower abdominal pain after his colonoscopy (b) (6) that was due to a perforation of bowel. The CT scan showed intraperitoneal air and patient went to the emergency room. Patient was admitted to the hospital where he had an emergent right colectomy to repair the perforation and included removal of a non-resectable polyp identified on colonoscopy which would have necessitated elective surgery. Patient did well post-op and was discharged (b) (6) in good condition. Patient did not return for a follow-up visit. The investigator concluded that this was unrelated to MoviPrep treatment.

7.1.3 Dropouts and Other Significant Adverse Events

In each Study 301 and 302, 360 patients were randomized in (1:1) one of two preparations. The expected drop out rate was 5%. This medical reviewer calculated the drop out rate at 7%.

7.1.3.1 Overall profile of dropouts

There were 9 screen failures and 4 drop outs due to adverse events, 3 in the Suprep group and 1 in the MoviPrep group. There were a combined total of 51 discontinuations: 34 drop outs --9 screen failures & 26 after randomization-- from Study 301 and 16 drop outs from Study 302. If it is based on n=787, the overall incidence of drop out would be about 7% with a 1% drop-out incidence based on treatment emergent adverse events.

Screen Failures

Out of the 416 eligible patients included in Study 301, 8 patients were identified as screen failures: "did not meet criteria" (5 patients), and "withdrew consent" (3 patients)
None of these 8 patients were dispensed medications. They provided informed consent but did not complete screening procedures.

Table 16: Summary of Screen Failures

Summary of Screen Failures

Patient	Age	Gender	ITT Status	Was Drug Dispensed?	Reason for Discontinuation
02011	71	M	Non-ITT	No	Patient withdrew consent
02026	30	F	Non-ITT	No	Patient withdrew consent
03008	62	M	Non-ITT	No	Patient met exclusion #13 – patient participated in an investigational clinical, surgical, drug, or device study within 30 days of screening.
03071	55	M	Non-ITT	No	Patient met exclusion #5 – patient had a history of hepatic insufficiency
07034	84	F	Non-ITT	No	Patient withdrew consent
10012	64	M	Non-ITT	No	Patient met exclusion #12 – patient was excluded by the investigator due to uncontrolled hypertension
10019	71	M	Non-ITT	No	Patient met exclusion #7 – patient had a history of significant GI surgery (subtotal gastrectromy)
10023	46	F	Non-ITT	No	Patient met exclusion #12 – patient was excluded by the investigator due to uncontrolled hypertension

Received on 4/2/09 from Braintree in email information request.

Reviewer Comments: During the search of SAS, there was 1 more patient not included in Table 16 in the screen failures, subject 2014 (clinically significant electrolyte abnormalities, visit 1 in BLI800 group).

Total Number of Drop Outs

A Summary of Drop Outs: Non-ITT patients which were excluded from the ITT population despite randomization and ITT Non-Completers who received full or partial treatment are listed in the Appendix 10.6.1 (continued over 4 tables). In IR of 6/12/09, Applicant submited an (exploratory) dataset using the True ITT.

Reasons for Drop Out

Unrandomized patients and screen failures
In study 301, there were 8 screening failures that were not randomized. The Applicant stated in their protocol that these could include some patients that received study medication and did not take it and returned it. According to the Applicant IR response of April 3, 2009, none of the eight patients had medication dispensed leaving 408 of the 416 to be randomized.
Randomized patients
Of the randomized patients, 10 from the BLI800 group (8 withdrew, 2 did not met study criteria) and 11 from the Moviprep group (6 withdrew, 4 did not meet study criteria, one was non-compliant) dropped out. Four more dropped out (3 from AE and 1 from insurance issue) from the BLI800 group and 1 dropped out from the Moviprep group due to an AE. See Applicants randomization charts under individual studies in *Appendix 10.1 and 10.2.*

Based on the Applicant's speculation of 5% drop out rate of 787 patients or a total of 39 patients, the drop out rate was higher=51 patients with the incidence about 7%. If it is based on n=787, the incidence would be about 1% drop-out based on treatment emergent adverse events.

7.1.3.2 Adverse events associated with dropouts

Drop outs due to treatment emergent adverse events

The crucial 4 dropouts due to treatment emergent adverse events are summarized in Table 15.
Table 17: Dropouts due to AE

Patient	Age	Treatment	Adverse Event	Received drug
2032	59	Suprep	Nausea	Yes
5034	59	Suprep	Vomiting	Yes
10011	31	MoviPrep	Bloating, nausea	Yes
10038	83	Suprep	AV block	Yes

Taken from Braintree's Information Request Response received 4/21/09. The first three patients had partial treatment in Study 301 and were called ITT Non-Completers

- Pt 2032: 60 year old (yo) F had routine colonoscopy, PMH: HTN, arrhythmias, high cholesterol on Lipitor, Hyzaar, Inderal had one dose of Suprep. Discontinued due to moderate nausea, no scope performed.
- Pt 5034: 59 yo F had routine colonoscopy, PMH: HTN, polypectomy tubular adenoma,diverticulosis, GERD, hiatal hernia on Atacand, Norvasc, Zaroxolyn, Vitamin) received Suprep at 6pm 10/24/07 had mild vomiting, did not take second dose No scope or Visit 3 occurred.
- Pt 10011: 32 yo F had GI bleed, PMH: heartburn, SOB on VIT C, Lexapro, Lamictal, Trazodone, Yasmin) had MoviPrep on 7/20/07, unable to tolerate prep, had severely distressing bloating and nausea, no second dose or scope occurred.
- Pt 10038: received Suprep had AV block (see prior narrative report)

Reviewer comment:
All of the patients who dropped out due to AE's were from Study 301 using the same day regimen. There were no clear drug-demographic, drug-disease, and drug-drug interactions noted.

There were no other rarer events that may have represented an important treatment induced adverse event.

7.1.3.3 Other significant adverse events

This reviewer found two cases of significant AE's reported: one for MoviPrep and one for BLI800.
Patient 11007 (b) (6) was reported in Study 302 Synopsis as a SAE but not reported as SAE in other areas of the submission. This 52 year old female received MoviPrep on (b) (6) During colonoscopy (b) (6), the investigator noted mild ischemic colitis in the descending colon. This was confirmed by biopsy. The event was resolved by the end of the study without complications. It was considered possibly related to MoviPrep treatment.

Patient 10038 was an 83 year old male who had third degree heart block who took BLI800 on the same day regimen (Study 301). He had past medical history of mild gout treated with Allopurinol, hypertension treated with Fosinopril and was using aspirin to prevent stroke. He took his first dose (b) (6) at 6 pm and his second dose at 7:05 pm, no colonoscopy was performed. He developed moderate AE of third degree heart block (b) (6) He had a normal physical exam on Visit 2 (b) (6) with a BP= 110/66 and pulse of 60. Patient had a normal PE on Visit 1 (screening) with BP=120/70 and pulse of 60. One day post-dose he developed the heart block and reported on his symptom scale on Visit 2 some mild stomach bloating and nausea. No other symptoms were noted nor how the patient was diagnosed. He had continuing symptoms that were deemed moderate, unrelated, and unresolved. He was discontinued from the study. He received other medication for treatment of his symptoms and was considered an ITT Non-Completer. Patient had elevated BUN/creatinine and potassium on Visit 1 (29/1.6, K+=5.2) Visit 2 (17/1.4, K+=4.8) and Visit 3 (22/1.5, K+= 5.2). Applicant states this was not a SAE. This reviewer believes this AE may have been related to the study drug.

Two additional cases of note were not listed as discontinuations, drop-outs, or SAE. They occurred in the **MoviPrep** group:

- Mild sinus tachycardia (Study 302) occurred in patient 12008. This 66 yo female took Moviprep on 8/5/07 and developed mild sinus tachycardia on 8/6/07. Visit 1 BP=122/72, p=86. Visit 2 BP= 147/83, p=100. It was deemed unrelated to the drug and resolved without treatment.
- Mild bradycardia (Study 302) occurred in patient 14012. This 55yo male took Moviprep 8/16/07 and developed AE on 8/17/07 which was mild, unresolved, and unrelated. Visit 1 BP=122/88, pulse=64 and Visit 2 BP=120/80, pulse=60.

7.1.4 Other Search Strategies

In Phase 2, BLI800-201 (study 201), evaluated 9 patients with an earlier Fordtran formulation. Adverse events occurred in two female subjects where nausea, vomiting, bloating and headache were reported. No serious or unexpected adverse events were reported. The vomiting resolved prior to colonoscopy and small non-clinically significant laboratory changes were noted.

Comments: After Information requests, Applicant supplied partially missing safety datasets on Phase 1 and 2 patients. Missing electronic datasets for Phase 3 studies required multiple further requests for usability and clarification. See Appendix 10.6.2 Summary of Information Request. The Medwatch report of the SAE of colonic perforation was submitted over 1 year after it occurred. Other detailed case report forms of the patient with atypical chest pain and of the patient with respiratory arrest resulting in death were requested in IR of 2/10/09. Applicant referred back to narratives in submission without further case details. Also, Applicant's errors in statistical calculations of the two-day dosing for treatment emergent adverse events and lack of clear designation of whether a AE was treatment related or not was clarified in two further IR's. During clarification of the discrepancies in incidence rates of Adverse Events found in our calculations as compared to their submission, it was then discovered that the Applicant did not include combined treatment adverse events from patient reported AE's and observer reported AE's. They were received in IR #14 on 6/12/09 when the Applicant noted exploratory inclusion of all randomized patients. Further Applicant justification for elevations in CK's and bradycardia were also part of the safety review.

The following searches were constructed to analyze combinations of clinical findings that were considered markers of particular toxicities. This included postmarketing searches for class effects of colonic cleansers on creatine kinases and electrolytes and/or concomitant medications and correlation with adverse events such as myalgias. Other searches analyzed renal function changes post-dose on Visit 2 or 3 in patients with vomiting and bradycardia changes and any correlation with hyperkalemia or hypokalemia.

<u>Creatine Kinases</u>
A consult was obtained from, Office of Safety and Epidemiology (OSE), Ann Corken Mackey for post-marketing reports related to elevations in creatine kinase values and Adverse Event Reporting System (AERS) data. AERS searched for cases of elevated CK associated with bowel preparations (sodium phosphate, PEG) as well as concomitant medications that might have been given for a procedure (Midazolam, Propofol, Demerol and Fentanyl). No cases were associated with PEG, Propofol or Demerol. One case of a 79 year old female who used sodium phosphate, became acidotic and died (increased CK, troponin, phosphorus, sodium, creatinine, glucose, SGOT and decreased calcium and magnesium were noted). Another case of a 46 year old female who used sodium phosphate and midazolam before colonoscopy and experienced a myocardial infarct was also cited. The patient was also taking Baclofen which is known to increase CK according to the reporter.

The unofficial update stated: "A search of AERS for fentanyl identified 61 reports (note raw data, duplicates could exist). None of these patients were using fentanyl for a colonoscopy; the

indications for use included chronic pain associated with malignancy or short term use for surgery. Approximately 30% of the cases were associated with an overdose of fentanyl and other substances. Most of the patients had underlying conditions known to increase CK, including rhabdomyolysis, myocardial infarction, malignant hyperthermia, myalgia, etc. At least one patient's CK returned to normal when a concomitant statin drug was discontinued (statin drugs are known to increase CK)."

In Ann Corken's review she states that in the study reports provided, it was noted that a couple of patients who experienced increased CK were receiving statin drugs and this could have played a role. Most of the investigators stated that the increases in CK were not clinically significant. It may be reasonable to ask the Applicant to explain these cases (including any events experienced because of the increased CK). Applicant stated and summarized the elevations of CK's with correlation to concomitant medications and stated that the investigators in general did not think there were any significant clinical signs associated with the elevations or particular patterns with the medications. *This reviewer believes the cumulative effect of statins or other medications that may elevate CK, and other comorbidity, exercise, stress and electrolyte changes probably have contributed to these elevations in CK and their clinical significance needs further data.*

Mild BUN and Creatinine Abnormalities

This reviewer did a search of the SAS files for both Study 301 and 302. The search was conducted for Visit 2 and Visit 3 electrolyte changes. See Appendix 10.6.5 for tables of BUN and creatinine changes

Other Mild Electrolyte Abnormalities in Patients with Vomiting

This reviewer did another search of the above SAS file for patients with vomiting and noted the following (See Appendix 10.6.5 for tables of BUN and creatinine changes):

:

- Four patients had hyponatriema ranging from 132 to 135 (136-145 normal). Two patients had hypernatriemia at 145 and 146.
- One patient had hypocalcemia at 7.9 (8.4 -10.2), 7 patients had hypercalcemia ranging from 10.3 to 10.9.
- Five patients had phosphorus (2.6-4.5) changes: one patient at 5.5 and one patient at 2.5. The rest had mild elevations up to 4.7
- Three patients had magnesium changes (1.3-2.1) in the 1.1 to 1.2 range.
- Chloride (96-108) changes were also mild ranging from 94-113. Bicarbonates (22-29) had wider ranges from one patient with 11 and the rest from 18 to 21.
- Two patients had hyperkalemia at 5.4.

In the Suprep group, twelve patients had BUN abnormalities ranging from 20 to 38 (ULN 19). Only 4 of these patients had an abnormal creatinine ranging from 1.2 to 1.5 (ULN 1.1). in the Moviprep group two patients had abnormal BUN values (20 to 25) and none had any creatinine abnormalities.

To summarize, this search revealed only mild changes in electrolytes for most patients who had vomiting at Visit 2 or 3. There were 10 more Suprep patients with vomiting who had renal function changes than those who vomited in the Moviprep group.

Studies on bradycardia before dose and post-dose are detailed in Section 7.1.8 and did not reveal large number of patients with decreases in pulse.

Study 202: PK study of sulfates in Hepatic and Renal Impairment Patients showed that out of 18 subjects, subject 12, 15, 17 and 18 did not resolve to first serum sulfate levels by the end of study monitoring. As expected, the group of normal volunteers (NHV) had total sulfate excreted in urine over collection intervals up to 30 hours of a median of 5257 (17.7%) whereas MRD (moderate renal disease) patients had medians of 4816 (16.3%) and M/MHD (Mild/moderate hepatic disease) patients had 6266 (21%). Renal impaired patients retained more sulfate than the normal patients and hepatic impaired patients excreted more than the normal patients. There is normalization of serum sulfate to pre-dose levels at the end of the study. *This reviewer recommends further serum sulfate monitoring after Visit 2 and after Visit 3.*

There were only mild adverse events noted among the 18 patients: among the NHV, one event each occurred with chest congestion, chills, emesis, elevated serum creatinine; among the M/MHD , one event each of sore throat, abnormal urinalysis, elevated serum creatinine occurred; among the MRD group, one event each of constipation, fatigue, perianal irritation, and symptomatic hypoglycemia. There was only one elderly subject (#5) who was 66 years old, therefore the effects on the elderly cannot be determined.
See Table 4.2 for a summary of other studies searched.
See Section 7.1.7 Laboratory Findings for a detailed review of the electrolyte changes associated with this study. See section 7.2 for further details of each study.

7.1.5 Common Adverse Events

The common adverse events profile for BLI800 included nausea, vomiting and to a lesser degree abdominal pain, abdominal distension and headache. They were found to be worse in the same day regimen in both groups. Nausea and vomiting were worse for the BLI800 group. Adverse Events Tables are included.

7.1.5.1 Eliciting adverse events data in the development program

The Symptom Questionnaire
The Symptom Questionnaire was completed by the patient during Visit 2 at variable times prior to sedation and colonoscopy. It is based on the following scale of symptoms rated from 1 to 5 (1-none; 2-mild; 3-bothersome 4-distressing; 5-severely distressing) to describe intensity of the nausea, vomiting, stomach bloating, cramping, and overall discomfort. Both studies used checklists that included the symptom scale. Data were individually collected for overall experience and a mean score for cramping, stomach bloating, nausea, vomiting and overall discomfort.

Safety Endpoint Results
Safety endpoints were used by the Applicant to elicit adverse event data.

In both studies and treatment groups, during Visit 2 and 3, analysis was based on adverse event and laboratory results, preferred term (MEDRA dictionary terms), severity, and relationship of treatment to Treatment Emergent Adverse Events. Differences in adverse event rates were tested by Chi-Square or Fisher's exact test with 95% CI. Laboratory tests for change from screening and group differences were tested by ANOVA. AE collection began at the time informed consent was obtained until completion of Visit 2.

Reviewer's Comments: According to their definition of AE reporting, AE collection was concluded at the completion of Visit 2, therefore not extending to Visit 3 or beyond. Serious AE reporting commenced at time of signed inform consent and concluded with the follow-up visit performed at 30 days after colonoscopy.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

AE may be defined as any untoward medical event that occurs in a patient or patient receiving study medication. It can be any unfavorable and unintended sign including laboratory finding, symptoms or disease temporally associated with use of the drug.

Reports of Serious AE would be triggered by the investigator informing Braintree and IRB immediately. The investigator would decide if the patient would continue in the study and be provided appropriate medical therapy. These subjects were followed until resolution and Braintree and IRB would be informed of patient course.

Reviewer's Comments: Applicant submitted in their five datasets and initial submission varying adverse events, different levels of preferred terms. For instance in tables included in section 7.1.5.3 the combined BLI800 301-302 were found to be in error by the Applicant , and preferred terms in tables sometimes did not include major systems such as "general disorders, renal, skin and tissue." The Table 18 found in Appendix 10.6.7 (done after IR received 1/09 and before inclusion of the patient reported GI symptoms) included other higher level terms such as sinus tachycardia, diarrhea and dizziness not included in the original tables. There were more events in the BLI800 group for gastrointestinal events: vomiting, nausea, abdominal distension and pain, and diarrhea. There were renal events: dysuria, kidney enlargement, urinary tract infection, blood in urine. There was one cardiac event in BLI800 group: AV block. Other events in the BLI800 group included headache, pruritis, mouth ulceration, dry mouth, nasopharyngitis, and chills.

During Labeling review it was noted that the Applicant submitted (b) (4) [redacted] *It was discovered that the Applicant did not include patient reported symptoms from their questionnaires and the "mild and moderate"*

Upon IR request, Applicant compiled a comprehensive table that included mild and moderate GI symptoms. The combined TEAE studies 301 and 302 compared the BLI800 group (N=375) as 35 patients (9.3%) and the number of events as 43. For MoviPrep, there were 27(7.2%) patients with 33 events.

Upon further request, when Applicant compiled tables (IR of May 2009) of total TEAE both observer and patient reported the following results were obtained:

- *The number of patient in the BLI800 group increased to 278 (74.1%) with 566 events. This reflected a 64.8% increase in TEAE in the BLI800 group. In the MoviPrep group, the number of patients increased to 278 patients (73.9%) with 536 events, reflecting a 66.7% increase in TEAE.*
- *Overall the number of TEAE's were similar between the two groups, but, patients in the BLI800 group did poorer in certain symptoms such as in nausea and vomiting. Specifically, there were 42.1% of the BLI800 patients compared to 36.4% of the MoviPrep patients who had nausea and 10.9% compared to 3.7% respectively who had vomiting.*

The Applicant did not present the full range of severities of gastrointestinal symptoms in one table and compile the observer and patient-reported symptoms for accurate analysis for adverse event labeling.

7.1.5.3 Incidence of common adverse events

The Symptom Questionnaire was completed during Visit 2 prior to sedation and colonoscopy. It is based on the following scale of symptoms rated from 1 to 5 (1- none; 2-mild; 3-bothersome 4-distressing; 5-severely distressing) to describe intensity of the following**:**
nausea, vomiting, stomach bloating, cramping, overall discomfort.

The Symptom questionnaire data assessed the overall experience and a mean score for cramping, stomach bloating, nausea, vomiting and overall discomfort.

The preferred terms used by the investigator in the symptom questionnaire differed from the preferred terms used by the observer reported terms. Stomach bloating was also recorded as abdominal distension. Cramping was also reported as abdominal pain. Initial tables omitted body systems and the mild and moderate gastrointestinal gradations but, included all grades of other body systems.

Initially data from this questionnaire was not combined with observer recorded events: TEAE. In the 6/12/09 submission the following tables were generated which showed that the number of events increased by 8 to 10 fold. See section 7.1.5.3. for further tables of causality assessments and severity ratings with particular attention to incidence rates based on the Study 301 and 302 Phase 3 studies that provided the best estimates of rates.

Common Adverse Events based on Severity: Patient Reported Adverse Symptoms

In Study 301, vomiting was noted to be greater in all categories of severity in BLI800 and in particular for females. No correlation was seen between age and weight. Table 301-11 from Applicant page 40 Volume 5.1 titled "BLI800 Patients Experiencing Bothersome to Severely Distressing Vomiting" showed that 11 of the 13 patients who ingested the two doses up to 1.5 hours had vomiting. Applicant attributed this increase in vomiting to the hypertonicity of taking two doses in a short period of time and thus inducing delays in gastric emptying.

Reviewer's Comments:
The Table 1 (Applicant table 301-8 from the Applicant in July 2008 without corrections) is found in Appendix 10.6.8. It is the original TREATMENT EMERGENT ADVERSE EVENTS in BLI800 group only. It did not incorporate the patient reported outcomes and illustrates the vastly different incidences from the table received in IR#14 on 6/12/09.

Table 1 or 301-8 was re-tabulated as well as an integrated summary of preferred terms to include the true ITT and the mild and moderate GI AE. The Applicant included all the non-gastrointestinal symptoms regardless of severity. Other AE that were omitted from the above list of terms included colitis ischemic, large intestine perforation and abdominal pain upper which each had one case in the Moviprep group. Additional Preferred Terms that were omitted were: anxiety, blood urine present, bradycardia, colitis ischemic, discomfort, dizziness, feeling hot, influenza, kidney enlargement, non-cardiac chest pain, respiratory distress sinus tachycardia, urinary tract infection. Just among the TEAE (without the patient symptom questionnaire reports) there were:

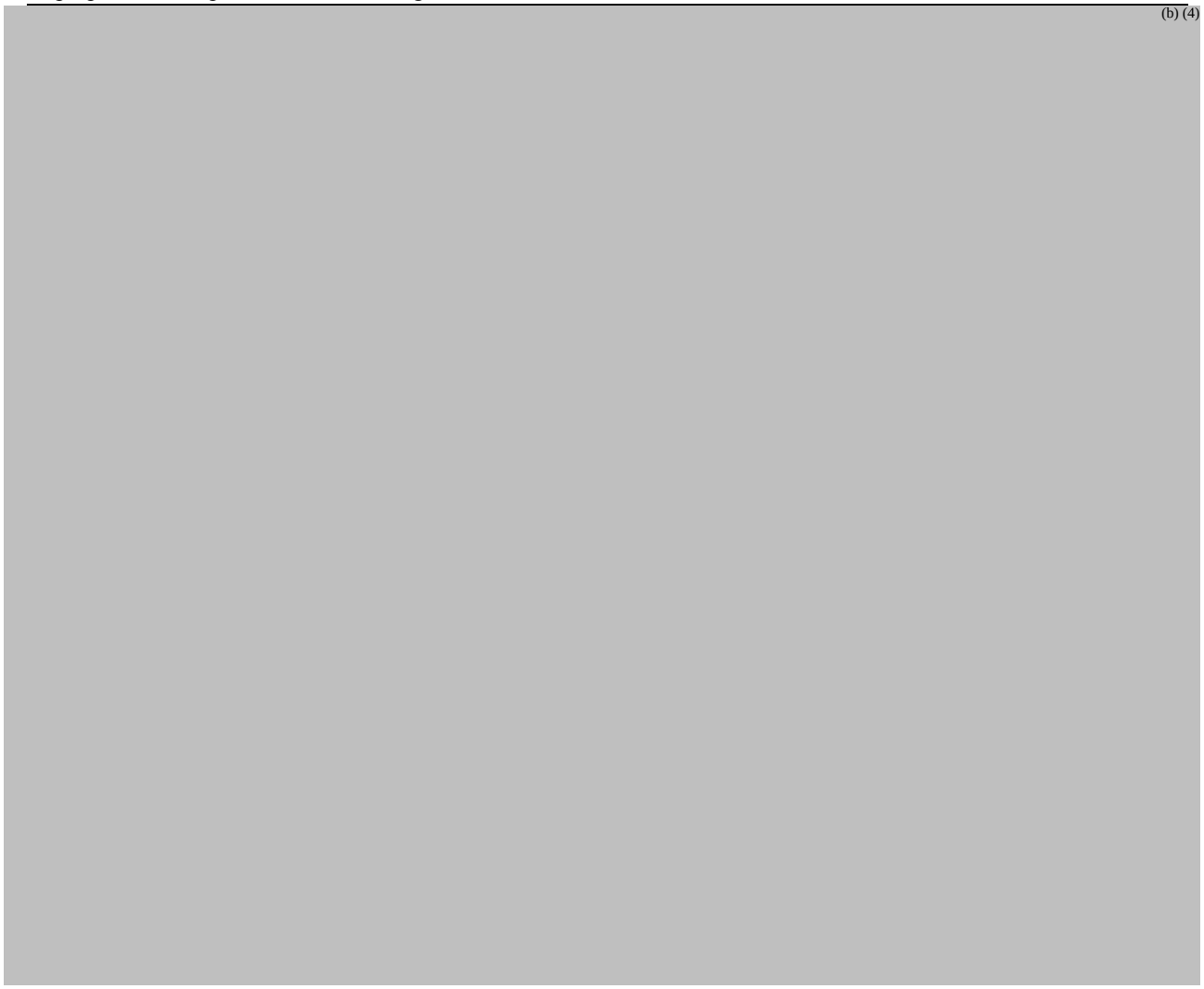
- *One additional case each of moderate nausea and vomiting;*
- *One added case each of mild chills, headache, and nasopharyngitis,*
- *One added case of severe abdominal distention*
- *2 additional cases of severe abdominal pain*

The pivotal studies 301 and 302 demonstrated more nausea and vomiting in SuPrep patients than in MoviPrep patients. There were potential substantial safety concerns about the abnormal creatine kinases, lack of serum sulfate studied in Phase 3, and other labs without follow-up to normalization. The unknown outcome of these abnormal laboratory tests needs further established post-marketing studies and correlation with any potential adverse events. There remain areas of safety concerns for sub-populations of product users who may also have concomitant use of other medications, pre-disposing factors for electrolyte imbalances or elevated CK levels or renal failure.

7.1.5.4 Common adverse event tables

The best overall display of common adverse events are presented for labeling.
Table 19, from the submitted label, was the investigator reported adverse events. Table 20 is the reviewer's submitted label for patient and observer reported adverse symptoms. Table 21 is the label under discussion which utilizes the Applicant ITT.

(b) (4)



The following are comparison table of both studies and both regimens.

Table 21: Same Day versus Split Day Regimens: Percentage of Patients with Treatment Emergent Adverse Events of >1% (All randomized patients, IR 6/12/09)

Symptom	Same (One) Day Regimen		Split Day Regimen	
	Suprep N=204	PEG-product N=204	Suprep N=190	PEG-product N=189
Discomfort	60.3%	56.9%	53.7 %	66.7%
Abdominal Distension	54.4%	52.5%	40.5%	51.9%
Abdominal Pain	34.8%	33.3%	36.3%	42.9%
Nausea	43.6%	36.8%	36.3%	32.8%
Vomiting	12.3%	3.4%	8.4%	3.7%
Headache	2.0 %	1.5%	1.1 %	0.5%

* In both studies, Suprep patients were permitted to have a light breakfast followed by clear liquids and PEG-product patients were permitted to have a normal breakfast, light lunch, followed by clear liquids. Data from Applicant submitted Tables from IR#14 on June 16, 2009.

During labeling discussions it was recommended that the following table be incorporated utilizing the applicant's original ITT.

(b) (4)

7.1.5.5 Identifying common and drug-related adverse events

The following Table 25: Total TEAE and Symptoms Scores by MedDRA Body Systems and Preferred Terms in Study 301 and 302 from response to IR #14 received 6/12/09, represent the combined pivotal studies in each treatment group analyzed for causality consistency between the dose and control in each group and occurrence of adverse events. The gastrointestinal differences from the two treatment groups were discussed in Section 7.1.5.4. Briefly, nausea and vomiting were slightly higher in incidences than MoviPrep and MoviPrep was higher for abdominal distension, abdominal pain and overall discomfort. Since the p-values are without significance in the majority of the tables, only significant p-values are noted. Comparisons are based on percentage, patient, or event numbers. The prior cardiac cases were discussed in Section 7.1.3.: only one BLI800 patient had any cardiac event (AVB). Headaches were both in the 1% range with a slightly higher incidence for BLI800. Likewise, <1% patient had increased incidences of pruritis, dysuria, CK elevation, ALT, AST, and LDH elevations in the BLI800 group.

Table 25: Total TEAE and Symptoms Scores by MedDRA Body Systems and Preferred Terms in Study 301 and 302 (IR 6/12/09)

Treatment Emergent Adverse Events and Symptom Scores by
MedDRA Body System and Preferred Term
BLI800-301/302 Studies

Body System/Preferred Term[1]	BLI800 (N= 394)	MoviPrep (N= 393)	95% CI[2]	p-Value
Number of Patients with Any Event	294 (74.6)	298 (75.8)	(-7.2, 4.8)	0.741
Number of Events	773	763		
CARDİAC DISORDERS	1 (0.3)	2 (0.5)	(-1.1, 0.6)	0.624
Atrioventricular Block Complete	1 (0.3)	0	(-0.2, 0.8)	1.000
Bradycardia	0	1 (0.3)	(-0.8, 0.2)	0.499
Sinus Tachycardia	0	1 (0.3)	(-0.8, 0.2)	0.499
GASTROINTESTINAL	274 (69.5)	277 (70.5)	(-7.3, 5.5)	0.816
Abdominal Distension	188 (47.7)	205 (52.2)	(-11.4, 2.5)	0.226
Abdominal Pain	140 (35.5)	149 (37.9)	(-9.1, 4.4)	0.506
Anal Discomfort	1 (0.3)	2 (0.5)	(-1.1, 0.6)	0.624
Ischemic Colitis	0	1 (0.3)	(-0.8, 0.2)	0.499
Diarrhea	1 (0.3)	0	(-0.2, 0.8)	1.000
Dry Mouth	1 (0.3)	0	(-0.2, 0.8)	1.000
Large Intestine Performation	0	1 (0.3)	(-0.8, 0.2)	0.499
Mouth Ulceration	1 (0.3)	0	(-0.2, 0.8)	1.000
Nausea	158 (40.1)	137 (34.9)	(-1.5, 12.0)	0.141
Vomiting	41 (10.4)	14 (3.6)	(13.3 10.4)	0.000
GENERAL DISORDERS	226 (57.4)	242 (61.6)	(-11.1, 2.6)	0.246
Chills	2 (0.5)	2 (0.5)	(-1.0, 1.0)	1.000
Discomfort	225 (57.1)	242 (61.6)	(-11.3, 2.6)	0.217
Feeling Hot	0	1 (0.3)	(-0.8, 0.2)	0.499
Non-cardiac Chest Pain	0	1 (0.3)	(-0.8, 0.2)	0.499
INFECTIONS & INFESTATIONS	1 (0.3)	0	(-0.2, 0.8)	1.000
Nasopharyngitis	1 (0.3)	0	(-0.2, 0.8)	1.000
INVESTIGATIONS	3 (0.8)	0	(-0.1, 1.6)	0.249
ALT Increased	1 (0.3)	0	(-0.2, 0.8)	1.000
AST Increased	2 (0.5)	0	(-0.2, 1.2)	0.449
CPK Increased	1 (0.3)	0	(-0.2, 0.8)	1.000
LDH Increased	1 (0.3)	0	(-0.2, 0.8)	1.000
NERVOUS SYSTEM	6 (1.5)	5 (1.3)	(-1.4, 1.9)	1.000
Dizziness	0	1 (0.3)	(-0.8, 0.2)	0.499
Headache	6 (1.5)	4 (1.1)	(-1.1, 2.1)	0.752

Treatment Emergent Adverse Events and Symptom Scores by
MedDRA Body System and Preferred Term
BLI800-301/302 Studies

Body System/Preferred Term[1]	BLI800 (N= 394)	MoviPrep (N= 393)	95% CI[2]	p-Value
RENAL AND URINARY	1 (0.3)	0	(-0.2, 0.8)	1.000
Dysuria	1 (0.3)	0	(-0.2, 0.8)	1.000
RESPIRATORY	0	1 (0.3)	(-0.8, 0.2)	0.499
Respiratory Distress	0	1 (0.3)	(-0.8, 0.2)	0.499
SKIN AND TISSUE	1 (0.3)	0	(-0.2, 0.8)	1.000
Pruritis	1 (0.3)	0	(-0.2, 0.8)	1.000

(1) Totals by MedDRA Body System represent the total number and percentage of patients that experienced an AE within that Body System. Preferred Term counts listed beneath the Body System represent the number and percentage of patients that experienced each individual event. The same patient can report multiple symptoms each of which would be counted under multiple Preferred Terms. However, the overall Body System total will only count such a patient once.
(2) 95% confidence interval for difference in proportion and p-value from Fisher's Exact test.
(reference ISS Table 14.3.1b in this submission)

7.1.5.6 Additional Analyses

Adverse events that are clearly drug-related are analyzed further. No explorations for delay in onset of treatment and adaption were done. Brief comment on severity analysis is included. Subgroups of patients analyzed for TEAE include high risk, gender, race and age analyses. Tables 26, 27, and 28 are from IR 6/12/09.

In an earlier version of Applicant supplied datasets, there were a total of 686 events in the adverse events reported by the investigator. A table that was compiled by this reviewer showed the breakdown in severity with each body system. Among the moderate to fatal symptoms major categories of body systems effected were GI, cardiac, and respiratory the last two categories being unrelated to study drug.

In the BLI800 group, the following systems had MODERATE symptoms

- One case AV Block;
- Four cases abdominal distension
- Three cases abdominal pain (equal in number to Moviprep)
- Three cases vomiting
- One headache
- One dysuria

In the BLI800 group, the following systems had SEVERE symptoms

- One case abdominal distension
- Two cases abdominal pain
- One case nausea

In the MoviPrep group, the following were FATAL or SEVERE symptoms

- One case was fatal for respiratory distress
- Severe for intestinal perforation, abdominal distension, nausea, vomiting, general discomfort, and non-cardiac chest pain.

In the elderly, there was one patient with AVB in the Suprep group and one patient with respiratory distress in the MoviPrep group. *See section 7.1.1 and 7.1.2 Serious and fatal AE's*.

Table 26: TEAE and Symptom Scores by MedDra Terms in Elderly

Treatment Emergent Adverse Events and Symptom Scores by
MedDRA Body System and Preferred Term – Elderly Patients
BLI800-301/302 Studies

Body System/Preferred Term[1]	BLI800 (N= 100)	MoviPrep (N= 93)	95% CI[2]	p-Value
Number of Patients with Any Event	65 (65.0)	65 (69.9)	(-18.1, 8.3)	0.540
Number of Events	161	148		
CARDIAC DISORDERS	1 (1.0)	1 (1.1)	(-2.9, 2.8)	1.000
Atrioventricular Block Complete	1 (1.0)	0	(-1.0, 3.0)	1.000
Sinus Tachycardia	0	1 (1.1)	(-3.2, 1.0)	0.482
GASTROINTESTINAL	59 (59.0)	56 (60.2)	(-15.1, 12.6)	0.884
Abdominal Distension	41 (41.0)	39 (41.9)	(-14.8, 13.0)	1.000
Abdominal Pain	31 (31.0)	29 (31.2)	(-13.3, 12.9)	1.000
Anal Discomfort	0	1 (1.1)	(-3.2, 1.0)	0.482
Diarrhea	1 (1.0)	0	(-1.0, 3.0)	1.000
Dry Mouth	1 (1.0)	0	(-1.0, 3.0)	1.000
Mouth Ulceration	1 (1.0)	0	(-1.0, 3.0)	1.000
Nausea	26 (26.0)	24 (25.8)	(-12.2, 12.6)	1.000
Vomiting	10 (10.0)	0	(4.1, 15.9)	0.002
GENERAL	47 (47.0)	52 (55.9)	(-23.0, 5.1)	0.250
Chills	1 (1.0)	0	(-1.0, 3.0)	1.000
Discomfort	47 (47.0)	52 (55.9)	(-23.0, 5.1)	0.250
NERVOUS SYSTEM	1 (1.0)	1 (1.1)	(-2.9, 2.8)	1.000
Dizziness	0	1 (1.1)	(-3.2, 1.0)	0.482
Headache	1 (1.0)	0	(-1.0, 3.0)	1.000
RESPIRATORY	0	1 (1.1)	(-3.2, 1.0)	0.482
Respiratory Distress	0	1 (1.1)	(-3.2, 1.0)	0.482

(1) Totals by MedDRA Body System represent the total number and percentage of patients that experienced an AE within that Body System. Preferred Term counts listed beneath the Body System represent the number and percentage of patients that experienced each individual event. The same patient can report multiple symptoms each of which would be counted under multiple Preferred Terms. However, the overall Body System total will only count such a patient once.
(2) 95% confidence interval for difference in proportion and p-value from Fisher's Exact test.
(reference ISS Table 14.3.1.1b in this submission)

In the elderly, rare cardiac TEAE's were noted: one case of AVB for Suprep and one sinus tachycardia for Moviprep. *For details see 7.1.3.3 Other significant events*. For GI TEAE's both groups had equal incidences of abdominal distension (about 41%), abdominal pain (about 31%), and nausea (about 26%). But, Suprep caused 10% more vomiting than Moviprep in the elderly.

Suprep had fewer incidences of chills (47% for Suprep versus 56% for Moviprep) and discomfort (47% for Suprep versus 56% for Moviprep). Suprep had 1% more headaches than Moviprep, but, Moviprep had 1% more dizziness than Suprep. There was a 1% greater incidence of respiratory distress in Moviprep. The increased incidence of vomiting was the most notable TEAE for the elderly using Suprep.

Table 27 and 28: TEAE and Symptom Scores in MedDRA terms in males and females
In males, MoviPrep had greater incidences of abdominal distention, abdominal pain and one case of large bowel perforation. Suprep had more nausea at 9.7% and vomiting at 11.4%. There were one case each of elevations in AST and LDH. (Applicant used 2.5 ULN as abnormal labs). In females, MoviPrep had greater incidences of abdominal distention, abdominal pain, and one case of ischemic colitis. Suprep had more nausea at 9.7% and vomiting at 9.4%. There were one case each of elevations in AST, ALT, and CPK.

Treatment Emergent Adverse Events and Symptom Scores by
MedDRA Body System and Preferred Term – *Male* Patients
BLI800-301/302 Studies

Body System/Preferred Term[1]	BLI800 (N= 176)	MoviPrep (N= 182)	95% CI[2]	p-Value
Number of Patients with Any Event	113 (64.2)	128 (70.3)	(-15.8, 3.6)	0.260
Number of Events	267	303		
CARDIAC DISORDERS	1 (0.6)	1 (0.5)	(-1.5, 1.6)	1.000
Atrioventricular Block Complete	1 (0.6)	0	(-0.5, 1.7)	0.492
Bradycardia	0	1 (0.5)	(-1.6, 0.5)	1.000
GASTROINTESTINAL	104 (59.1)	115 (63.2)	(-14.2, 6.0)	0.449
Abdominal Distension	70 (39.8)	79 (43.4)	(-13.8, 6.6)	0.521
Abdominal Pain	50 (28.4)	58 (31.9)	(-13.0, 6.0)	0.492
Large Intestine Perforation	0	1 (0.5)	(-1.6, 0.5)	1.000
Nausea	52 (29.5)	55 (30.2)	(-10.2, 8.8)	0.908
Vomiting	8 (4.5)	2 (1.1)	(0.0, 6.9)	0.058
GENERAL DISORDERS	83 (47.2)	103 (56.6)	(-19.7, 0.9)	0.090
Discomfort	83 (47.2)	103 (56.6)	(-19.7, 0.9)	0.090
Feeling Hot	0	1 (0.5)	(-1.6, 0.5)	1.000
Non-cardiac Chest Pain	0	1 (0.5)	(-1.6, 0.5)	1.000
INVESTIGATIONS	1 (0.6)	0	(-0.5, 1.7)	0.492
AST Increased	1 (0.6)	0	(-0.5, 1.7)	0.492
LDH Increased	1 (0.6)	0	(-0.5, 1.7)	0.492
NERVOUS SYSTEM	1 (0.6)	1 (0.5)	(-1.5, 1.6)	1.000
Headache	1 (0.6)	1 (0.5)	(-1.5, 1.6)	1.000
RESPIRATORY	0	1 (0.5)	(-1.6, 0.5)	1.000
Respiratory Distress	0	1 (0.5)	(-1.6, 0.5)	1.000

(1) Totals by MedDRA Body System represent the total number and percentage of patients that experienced an AE within that Body System. Preferred Term counts listed beneath the Body System represent the number and percentage of patients that experienced each individual event. The same patient can report multiple symptoms each of which would be counted under multiple Preferred Terms. However, the overall Body System total will only count such a patient once.
(2) 95% confidence interval for difference in proportion and p-value from Fisher's Exact test.
(reference ISS Table 14.3.1.2b in this submission)

In females, one rare cardiac TEAE's was noted as sinus tachycardia for Moviprep. *For details see 7.1.3.3 Other significant events*. For GI TEAE's both groups had comparable incidences of abdominal distension (about 5.6% difference favoring Suprep) and abdominal pain (about 1.8% difference favoring Suprep). Suprep caused 9.4% more vomiting and 9.7% more nausea in the Suprep group than Moviprep in females. Suprep had equal incidences of chills (2% for both) and discomfort (65.1% for Suprep versus 65.9% for Moviprep). Suprep had .9% more headaches than Moviprep, but, Moviprep had .5% more dizziness than Suprep. There was a .5% greater incidence of diarrhea, dry mouth, mouth ulceration, nasopharyngitis, ALT elevation, AST elevation, CPK elevation, dysuria, and pruritis in Suprep. Moviprep had .5% greater incidence of ischemic colitis, and .4% greater incidence of anal discomfort. The increased incidence of nausea and vomiting was most notable TEAE in females using Suprep. There were fewer incidences of abdominal pain and abdominal distension in the females in the Suprep group.

Treatment Emergent Adverse Events and Symptom Scores by
MedDRA Body System and Preferred Term – *Female* Patients
BLI800-301/302 Studies

Body System/Preferred Term[1]	BLI800 (N= 218)	MoviPrep (N= 211)	95% CI[2]	p-Value
Number of Patients with Any Event	181 (83.0)	170 (80.6)	(-4.8, 9.8)	0.533
Number of Events	506	460		
CARDIAC DISORDERS	0	1 (0.5)	(-1.4, 0.5)	0.492
Sinus Tachycardia	0	1 (0.5)	(-1.4, 0.5)	0.492
GASTROINTESTINAL	170 (78.0)	162 (76.8)	(-6.7, 9.1)	0.818
Abdominal Distension	118 (54.1)	126 (59.7)	(-14.9, 3.8)	0.283
Abdominal Pain	90 (41.3)	91 (43.1)	(-11.2, 7.5)	0.769
Anal Discomfort	1 (0.5)	2 (0.9)	(-2.1, 1.1)	0.618
Ischemic Colitis	0	1 (0.5)	(-1.4, 0.5)	0.492
Diarrhea	1 (0.5)	0	(-0.4, 1.4)	1.000
Dry Mouth	1 (0.5)	0	(-0.4, 1.4)	1.000
Mouth Ulceration	1 (0.5)	0	(-0.4, 1.4)	1.000
Nausea	106 (48.6)	82 (38.9)	(0.4, 19.1)	0.051
Vomiting	33 (15.1)	12 (5.7)	(3.8, 15.1)	0.001
GENERAL DISORDERS	143 (65.6)	139 (65.9)	(-9.3, 8.7)	1.000
Chills	2 (0.9)	2 (0.9)	(-1.9, 1.8)	1.000
Discomfort	142 (65.1)	139 (65.9)	(-9.7, 8.3)	0.919
INFECTIONS & INFESTATIONS	1 (0.5)	0	(-0.4, 1.4)	1.000
Nasopharyngitis	1 (0.5)	0	(-0.4, 1.4)	1.000
INVESTIGATIONS	2 (0.9)	0	(-0.3, 2.2)	0.499
ALT Increased	1 (0.5)	0	(-0.4, 1.4)	1.000
AST Increased	1 (0.5)	0	(-0.4, 1.4)	1.000
CPK Increased	1 (0.5)	0	(-0.4, 1.4)	1.000
NERVOUS SYSTEM	5 (2.3)	4 (1.9)	(-2.3, 3.1)	1.000
Dizziness	0	1 (0.5)	(-1.4, 0.5)	0.492
Headache	5 (2.3)	3 (1.4)	(-1.7, 3.4)	0.724
RENAL AND URINARY	1 (0.5)	0	(-0.4, 1.4)	1.000
Dysuria	1 (0.5)	0	(-0.4, 1.4)	1.000
SKIN AND TISSUE	1 (0.5)	0	(-0.4, 1.4)	1.000
Pruritis	1 (0.5)	0	(-0.4, 1.4)	1.000

(1) Totals by MedDRA Body System represent the total number and percentage of patients that experienced an AE within that Body System. Preferred Term counts listed beneath the Body System represent the number and percentage of patients that experienced each individual event. The same patient can report multiple symptoms each of which would be counted under multiple Preferred Terms. However, the overall Body System total will only count such a patient once.
(2) 95% confidence interval for difference in proportion and p-value from Fisher's Exact test.
(reference ISS Table 14.3.1.2b in this submission)

Table 29: TEAE's and Symptom Scores in MedDRA terms in Caucasian and Non-Caucasian

Body System/Preferred Term[1]	Caucasian (N= 338)	Non-Caucasian (N=54)
Number of Patients with Any Event	256 (75.7)	36 (66.7)
Number of Events	683	86
CARDIAC DISORDERS	1 (0.3)	0
Atrioventricular Block Complete	1 (0.3)	0
GASTROINTESTINAL	240 (71.0)	33 (61.1)
Abdominal Distension	165 (48.8)	22 (40.7)
Abdominal Pain	122 (36.1)	17 (31.5)
Anal Discomfort	0	1 (1.9)
Diarrhea	1 (0.3)	0
Dry Mouth	1 (0.3)	0
Mouth Ulceration	1 (0.3)	0
Nausea	142 (42.0)	16 (29.6)
Vomiting	36 (10.7)	5 (9.3)
GENERAL DISORDERS	199 (58.9)	25 (46.3)
Chills	2 (0.6)	0
Discomfort	198 (58.6)	25 (46.3)

There were greater incidences in the Caucasian group of abdominal distension (8.1%), abdominal pain (4.6%), nausea (12.4%), vomiting (1.4%) and discomfort (12.3%) than in the Non-Caucasian group. The Caucasian group had .3% greater incidences of AVB, diarrhea, dry mouth, mouth ulceration compared to the Non-Caucasian group. The Caucasian group had the most AE's among all the subgroups analyzed.

Table 30: TEAE and Symptom Scores in MedDRA terms in High Risk Group (Cardiac, Renal, Vascular or Diabetic Disease)

In the high risk group, The Suprep group had higher incidences of abdominal distension (1.7%), abdominal pain (1.9%), nausea (5.1%), and vomiting (9.4%). One cardiac TEAE's was noted as AVB for Suprep. *Reviewer comment: These incidences are the same as the cardiac and GI (the 4 four listed above) TEAE's as for the elderly. For details see 7.1.3.3 Other significant events.* Suprep had almost equal incidences of discomfort (55.7% for Suprep versus 56. 9% for

Moviprep) and headaches (.6% for Suprep and .5% for Moviprep). Moviprep had .5% more respiratory distress, non-cardiac chest pain, large intestine perforation, ischemic colitis, anal discomfort than Suprep. There was a .6% greater incidence in Suprep of dry mouth, mouth ulceration, dysuria, and pruritis. Moviprep had .5% greater incidence of ischemic colitis, and .4% greater incidence of anal discomfort. The high risk group and the elderly group were the same in incidences for abdominal distension, abdominal pain, nausea, vomiting and AVB. The other more significant AE's such as respiratory distress, ischemic colitis and large intestine perforation occurred in the Moviprep group. Greater incidences of vomiting and nausea are again noted in the Suprep as compared to the Moviprep group among the high risk patients.

Treatment Emergent Adverse Events and Symptom Scores by
MedDRA Body System and Preferred Term – High Risk Patients
BLI800-301/302 Studies

BEST AVAILABLE COPY

Body System/Preferred Term[1]	BLI800 (N= 176)	MoviPrep (N= 195)	95% CI[2]	p-Value
Number of Patients with Any Event	132 (75.0)	141 (72.3)	(-6.3, 11.7)	0.637
Number of Events	347	351		
CARDIAC DISORDERS	1 (0.6)	0	(-0.5, 1.7)	0.474
Atrioventricular Block Complete	1 (0.6)	0	(-0.5, 1.7)	0.474
GASTROINTESTINAL	122 (69.3)	130 (66.7)	(-6.8, 12.1)	0.656
Abdominal Distension	86 (48.9)	92 (47.2)	(-8.5, 11.9)	0.756
Abdominal Pain	61 (34.7)	64 (32.8)	(-7.8, 11.5)	0.742
Anal Discomfort	0	1 (0.5)	(-1.5, 0.5)	1.000
Ischemic Colitis	0	1 (0.5)	(-1.5, 0.5)	1.000
Dry Mouth	1 (0.6)	0	(-0.5, 1.7)	0.474
Large Intestine Perforation	0	1 (0.5)	(-1.5, 0.5)	1.000
Mouth Ulceration	1 (0.6)	0	(-0.5, 1.7)	0.474
Nausea	74 (42.0)	72 (36.9)	(-4.8, 15.1)	0.339
Vomiting	22 (12.5)	6 (3.1)	(4.0, 14.9)	0.001
GENERAL DISORDERS	98 (55.7)	111 (56.9)	(-11.3, 8.9)	0.834
Discomfort	98 (55.7)	111 (56.9)	(-11.3, 8.9)	0.834
Non-cardiac Chest Pain	0	1 (0.5)	(-1.5, 0.5)	1.000
NERVOUS SYSTEM	1 (0.6)	1 (0.5)	(-1.4, 1.6)	1.000
Headache	1 (0.6)	1 (0.5)	(-1.4, 1.6)	1.000
RENAL AND URINARY	1 (0.6)	0	(-0.5, 1.7)	0.474
Dysuria	1 (0.6)	0	(-0.5, 1.7)	0.474
RESPIRATORY	0	1 (0.5)	(-1.5, 0.5)	1.000
Respiratory Distress	0	1 (0.5)	(-1.5, 0.5)	1.000
SKIN AND TISSUE	1 (0.6)	0	(-0.5, 1.7)	0.474
Pruritis	1 (0.6)	0	(-0.5, 1.7)	0.474

(1) Totals by MedDRA Body System represent the total number and percentage of patients that experienced an AE within that Body System. Preferred Term counts listed beneath the Body System represent the number and percentage of patients that experienced each individual event. The same patient can report multiple symptoms each of which would be counted under multiple Preferred Terms. However the overall Body System total will only count such a patient once.
(2) 95% confidence interval for difference in proportion and p-value from Fisher's Exact test.
(reference ISS Table 14.3.1.4b in this submission)

Table 30: Study 301 (Same Day Dose Regimen) TEAE and Symptom Scores by MedDRA terms

Table 301-8 (Exploratory)
Treatment Emergent Adverse Events and Symptom Scores
by MedDRA Body System and Preferred Term

Body System/Preferred Term[1]	BLI800 (N= 204)	MoviPrep (N= 204)	95% CI[2]	p-Value[2]
Number of Patients with Any Event	162 (79.4)	149 (73.0)	(-1.9,14.6)	0.163
Number of Events	434	381		
CARDIAC				
Atrioventricular Block Complete	1 (0.5)	0	(-0.5, 1.4)	1.000
GASTROINTESTINAL	155 (76.0)	139 (68.1)	(-0.8, 16.5)	0.098
Abdominal Distension	111 (54.4)	107 (52.5)	(-7.7, 11.6)	0.766
Abdominal Pain	71 (34.8)	68 (33.3)	(-7.7, 10.7)	0.835
Anal Discomfort	1 (0.5)	2 (1.0)	(-2.1, 1.2)	1.000
Diarrhea	1 (0.5)	0	(-0.5, 1.4)	1.000
Dry Mouth	1 (0.5)	0	(-0.5, 1.4)	1.000
Mouth Ulceration	1 (0.5)	0	(-0.5, 1.4)	1.000
Nausea	89 (43.6)	75 (36.8)	(-2.6, 16.4)	0.189
Vomiting	25 (12.3)	7 (3.4)	(3.7, 14.0)	0.001
GENERAL DISORDERS	123 (60.3)	116 (56.9)	(-6.1, 13.0)	0.547
Chills	1 (0.5)	2 (1.0)	(-2.1, 1.2)	1.000
Discomfort	123 (60.3)	116 (56.9)	(-6.1, 13.0)	0.547
INVESTIGATIONS	2 (1.0)	0	(-0.4, 2.3)	0.499
AST Increased	1 (0.5)	0	(-0.5, 1.4)	1.000
CPK Increased	1 (0.5)	0	(-0.5, 1.4)	1.000
LDH Increased	1 (0.5)	0	(-0.5, 1.4)	1.000
NERVOUS SYSTEM	4 (2.0)	4 (2.0)	(-2.7, 2.7)	1.000
Dizziness	0	1 (0.5)	(-1.4, 0.5)	1.000
Headache	4 (2.0)	3 (1.5)	(-2.0, 3.0)	1.000
RENAL AND URINARY	1 (0.5)	0	(-0.5, 1.4)	1.000
Dysuria	1 (0.5)	0	(-0.5, 1.4)	1.000
SKIN AND TISSUE	1 (0.5)	0	(-0.5, 1.4)	1.000
Pruritis	1 (0.5)	0	(-0.5, 1.4)	1.000

(1) Totals by MedDRA Body System represent the total number and percentage of patients that experienced an AE within that Body System. Preferred Term counts listed beneath the Body System represent the number and percentage of patients that experienced each individual event. The same patient can report multiple symptoms each of which would be counted under multiple Preferred Terms. However, the overall Body System total will only count such a patient once.
(2) 95% confidence interval for difference in proportion and p-value from Fisher's Exact test.
(reference Table 14.3.1b in this submission)

Table 31: Study 302 (Split Day Dose Regimen) TEAE and Symptom Scores by MedDRA terms

Treatment Emergent Adverse Events and Symptom Scores
by MedDRA Body System and Preferred Term

Body System/Preferred Term[1]	BLI800 (N= 190)	MoviPrep (N= 189)	95% CI[2]	p-Value[2]
Number of Patients with Any Event	132 (69.5)	149 (78.8)	(-18.1, -0.6)	0.046
Number of Events	339	382		
CARDIAC	0	2 (1.1)	(-2.5, 0.4)	0.248
Bradycardia	0	1 (0.5)	(-1.6, 0.5)	0.499
Sinus tachycardia	0	1 (0.5)	(-1.6, 0.5)	0.499
GASTROINTESTINAL	119 (62.6)	138 (73.0)	(-19.7, -1.0)	0.037
Abdominal distension	77 (40.5)	98 (51.9)	(-21.3, -1.4)	0.031
Abdominal pain	69 (36.3)	81 (42.9)	(-16.4, 3.3)	0.208
Ischemic colitis	0 (0.0)	1 (0.5)	(-1.6, 0.5)	0.499
Large Intestine Perforation	0 (0.0)	1 (0.5)	(-1.6, 0.5)	0.499
Nausea	69 (36.3)	62 (32.8)	(-6.1, 13.1)	0.517
Vomiting	16 (8.4)	7 (3.7)	(-0.1, 9.5)	0.083
GENERAL DISORDERS	103 (54.2)	126 (66.7)	(-22.2, -2.7)	0.016
Chills	1 (0.5)	0	(-0.5, 1.6)	1.000
Discomfort	102 (53.7)	126 (66.7)	(-22.8, -3.2)	0.012
Feeling hot	0	1 (0.5)	(-1.6, 0.5)	0.499
Non-cardiac chest pain	0	1 (0.5)	(-1.6, 0.5)	0.499
INFECTIONS	1 (0.5)	0	(-0.5, 1.6)	1.000
Nasopharyngitis	1 (0.5)	0	(-0.5, 1.6)	1.000
INVESTIGATIONS	1 (0.5)	0	(-0.5, 1.6)	1.000
ALT increased	1 (0.5)	0	(-0.5, 1.6)	1.000
AST increased	1 (0.5)	0	(-0.5, 1.6)	1.000
NERVOUS SYSTEM	2 (1.1)	1 (0.5)	(-1.3, 2.3)	1.000
Headache	2 (1.1)	1 (0.5)	(-1.3, 2.3)	1.000
RESPIRATORY	0	1 (0.5)	(-1.6, 0.5)	0.499
Respiratory distress	0	1 (0.5)	(-1.6, 0.5)	0.499

(1) Totals by MedDRA Body System represent the total number and percentage of patients that experienced an AE within that Body System. Preferred Term counts listed beneath the Body System represent the number and percentage of patients that experienced each individual event. The same patient can report multiple symptoms each of which would be counted under multiple Preferred Terms. However, the overall Body System total will only count such a patient once.
(2) 95% confidence interval for difference in proportion and p-value from Fisher's Exact test.
(reference Table 14.3.1b in this submission)

idential 1

Reviewer's Comments: The Study 302 table was also re-tabulated for Applicant error of non-inclusion of treatment emergent AE during the first day of administration of the study drug in Study 302 (split dosing) from IR 11/20/08.

Comparison of Suprep for Same Day Dose Regimen (Study 301) versus Split Day Dose Regimen

Comparison of Suprep for Same Day Dose Regimen (Study 301) versus Split Day Dose Regimen (Study 302) TEAE and Symptom Scores by MedDRA terms was analyzed. *See Table 20,21 Section 7.1.5.4 for comparisons of most common GI TEAE and headaches.* It

demonstrated that the same day regimen had more abdominal distension (13.9%), less abdominal pain (-1.5%), more nausea (7.3%), more vomiting (3.9%), more headache (.9%) and more discomfort (6.6%) compared to the split day dose regimen. The other TEAE's that occurred between the two groups were .5%. In the same day regimen, there was .5% more AVB, anal discomfort, diarrhea, dry mouth, mouth ulceration, elevated CPK, elevated LDH, dysuria, and pruritis. There was equal incidence of chills and elevated AST at .5%. The split day regimen had .5% greater incidence of nasopharyngitis and elevated ALT.
In summary, the same day regimen produced greater abdominal distension by 14%, more nausea by 7% and more vomiting by 4%.

7.1.6 Less Common Adverse Events

The Applicant originally listed the common adverse event of Headache in at least 1% of patients at 1.3% in Suprep and 1.1% in MoviPrep (see sect 7.1.5.4). From 6/12/09 IR recalculations, the following frequencies of less common adverse events are noted for Suprep:
Table 32: Frequencies of less common adverse events

Frequencies	Suprep in Study 301 (%)	Suprep in Study 302	Moviprep in Study 301	Moviprep in Study 302
≤ 2%	Headache (2)	Headache (1.1)	Headache (1.5)	
≤ 1%	(0.5) : chills, nasopharyngitis, increased CPK, LDH, AST, dysuria, pruritis, AVB, anal discomfort, diarrhea, mouth ulceration	(0.5) : chills, nasopharyngitis, increased ALT and AST	Anal discomfort (1) chills (1)	(0.5):ischemic colitis, feels hot, non-cardiac CP, respiratory distress, bradycardia, sinus tachycardia, large intestine perforation, headache
0.1 % to 1%	----	----	Dizziness (0.5)	---

7.1.7 Laboratory Findings

The approach to review of the abnormal laboratory findings and the methods used to assess, discuss and review the findings are detailed in this section to follow. Also refer to section *7.1.2 and 7.1.3 for Other Serious Adverse Events and Dropouts and Other Significant Adverse Events.*

7.1.7.1 Overview of laboratory testing in the development program

For both Study 301 and 302, laboratory testing of chemistry, hematology, creatine kinases was done at (b) (4) and some additional labs (serum osmolality) were sent to (b) (4). Screening labs at visit 1, colonoscopy labs at visit 2 and follow-up labs at visit 3 were performed. Serum levels of sulfates were planned. No follow-up of abnormal labs were planned in the protocol. (b) (4) received frozen sulfate specimens that were not analyzed as stated in protocol and no amendment was submitted to modify this.
Of 6 patients who received Visit 1 baseline labs, took study drug, but, later dropped out, three had Visit 3 follow-up labs. For detailed summary table of these patients see Appendix 10.6.1: Summary of Randomized Patients (IR 4/14/09.

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

Based on the lack of placebo-controlled studies for any colonic cleansers and the preferred selection of longer-term data to provide the best data for decision of any effect of the drug on a lab test abnormality, pooled studies included the pivotal study 301 and 302 and study 202 data. Selection of the pivotal trials and Study 202 for lab test monitoring is based on concerns about OSP nephropathy and first-time use of this sulfate combination resulting in analyses for sulfate testing and renal function monitoring during the interval post-dose to Day 6 to Day 30.

No direct measurements of the drug in serum or stool were planned. Early Phase 1 and 2 studies did not measure the drug solution amounts, but did measure the individual electrolyte components. In Table 33 (Tables 301-17, 302-16), mean chemistry values by Visit per Applicant's initial ITT population showed significant drop in chloride is noted and increase in uric acid from Visit 1 to Visit 2.

Table 33: (Table 301-17 & 302-16) Mean (SD) Chemistry Values by Visit (ITT Population) from Module 5, Vol. 5.1 page 47 and Vol. 6.1, page 45.

Table 301-17
Mean (SD) Chemistry Values by Visit (ITT Population)

Analyte (units)	Normal Range[1]	Drug	Baseline	Visit 2	Visit 3	Δ to Visit 2	Δ to Visit 3	P (Δ V2)
Albumin (g/dL)	3.8-5.2	BLI800 MoviPrep	4.49 (0.28) 4.46 (0.27)	4.56 (0.28) 4.48 (0.28)	4.42 (0.29) 4.42 (0.28)	0.07 (0.25) 0.01 (0.23)	-0.07 (0.22) -0.04 (0.23)	**0.025**
Alk Phos (U/L)	F 35-104 M 40-129	BLI800 MoviPrep	69.8 (22.0) 69.2 (20.2)	69.4 (23.5) 68.7 (21.5)	68.7 (27.4) 68.0 (20.5)	0.23 (8.6) -0.51 (7.4)	-0.94 (15.0) -0.89 (7.6)	0.379
ALT (U/L)	7-52	BLI800 MoviPrep	23.2 (22.6) 21.3 (12.4)	25.8 (38.4) 22.9 (13.0)	30.2 (115.0) 21.2 (12.6)	2.19 (17.9) 1.60 (8.1)	7.14 (94.0) 0.18 (9.3)	0.681
Amylase (U/L)	28-100	BLI800 MoviPrep	50.4 (20.1) 52.4 (23.0)	43.1 (16.6) 45.9 (18.5)	50.6 (21.5) 53.0 (21.6)	-7.35 (8.4) -6.45 (10.5)	0.01 (11.2) 0.68 (14.7)	0.364
AST (U/L)	13-39	BLI800 MoviPrep	22.2 (18.7) 21.1 (8.3)	25.7 (27.7) 23.0 (8.8)	36.3 (196.3) 21.0 (9.4)	3.39 (10.9) 2.01 (7.6)	14.0 (177.9) 0.02 (8.5)	0.155
Bicarbonate (mEq/L)	22-29	BLI800 MoviPrep	25.2 (2.3) 25.3 (2.1)	24.3 (2.5) 23.7 (2.4)	25.1 (2.2) 25.2 (2.2)	-0.83 (2.7) -1.68 (2.8)	-0.16 (2.2) -0.12 (2.2)	**0.003**
BUN (mg/dL)	6-19	BLI800 MoviPrep	16.7 (5.0) 17.1 (5.0)	13.5 (3.9) 14.2 (4.6)	16.6 (5.0) 17.4 (5.5)	-3.29 (4.1) -2.89 (3.9)	-0.15 (3.8) 0.23 (4.1)	0.329
Calcium (mg/dL)	8.4-10.2	BLI800 MoviPrep	9.74 (0.36) 9.74 (0.38)	9.69 (0.39) 9.62 (0.37)	9.66 (0.39) 9.66 (0.39)	-0.06 (0.38) -0.13 (0.38)	-0.09 (0.33) -0.09 (0.37)	0.068
Chloride (mEq/L)	96-108	BLI800 MoviPrep	104.5 (2.6) 103.8 (2.5)	103.9 (2.7) 105.4 (2.7)	105.1 (2.7) 104.6 (2.5)	-0.71 (2.6) 1.61 (2.4)	0.73 (2.2) 0.75 (2.4)	**< 0.001**
Creatine Kinase (U/L)	30-223	BLI800 MoviPrep	113.3 (74) 128.4 (165)	123.6 (117) 110.5 (93)	139.0 (389) 128.1 (161)	10.0 (109) -16.0 (139)	26.7 (383) 1.18 (203)	**0.048**
Creatinine (mg/dL)	F 0.4-1.1 M 0.5-1.2	BLI800 MoviPrep	0.95 (0.21) 0.99 (0.25)	0.97 (0.20) 0.99 (0.24)	0.95 (0.21) 1.01 (0.24)	0.03 (0.13) 0.00 (0.12)	0.01 (0.12) 0.03 (0.12)	0.061
Bilirubin (mg/dL)	0-0.25	BLI800 MoviPrep	0.11 (0.07) 0.11 (0.05)	0.15 (0.08) 0.14 (0.08)	0.17 (0.92) 0.10 (0.06)	0.04 (0.06) 0.04 (0.06)	0.06 (0.91) -0.01 (0.05)	0.300
GGT (U/L)	F 5-36 M 8-61	BLI800 MoviPrep	27.3 (19.3) 30.8 (25.3)	27.8 (20.7) 30.8 (25.1)	25.9 (27.4) 30.3 (26.9)	0.42 (9.2) -0.26 (7.7)	-0.66 (23.0) -0.19 (10.1)	0.441
Glucose (mg/dL)	70-105	BLI800 MoviPrep	104.7 (33) 106.5 (31)	101.4 (31) 101.0 (27)	109.6 (37) 112.9 (36)	-3.16 (32) -5.73 (27)	4.99 (26) 6.71 (31)	0.409
LDH (U/L)	118-273	BLI800 MoviPrep	164.1 (33) 162.8 (32)	176.5 (55) 172.5 (45)	166.5 (68) 158.6 (31)	13.0 (48) 9.66 (44)	1.98 (54) -3.34 (28)	0.488
Magnesium (mEq/L)	1.3-2.1	BLI800 MoviPrep	1.68 (0.14) 1.68 (0.15)	1.70 (0.15) 1.63 (0.14)	1.64 (0.14) 1.65 (0.14)	0.02 (0.12) -0.05 (0.12)	-0.05 (0.12) -0.03 (0.14)	**<0.001**
Osmolality mOsm/kg	275-301	BLI800 MoviPrep	292.0 (5.7) 291.3 (6.0)	290.2 (5.3) 290.3 (5.7)		-1.85 (5.5) -1.06 (5.7)		0.172
Phosphorus (mg/dL)	2.6-4.5	BLI800 MoviPrep	3.47 (0.52) 3.47 (0.53)	3.52 (0.51) 3.44 (0.47)	3.42 (0.54) 3.44 (0.53)	0.06 (0.54) -0.04 (0.51)	-0.05 (0.52) -0.02 (0.57)	0.079
Potassium (mEq/L)	3.5-5.1	BLI800 MoviPrep	4.40 (0.44) 4.40 (0.45)	4.32 (0.43) 4.29 (0.40)	4.41 (0.45) 4.39 (0.40)	-0.08 (0.48) -0.11 (0.51)	0.01 (0.43) -0.01 (0.49)	0.552
Sodium (mEq/L)	136-145	BLI800 MoviPrep	140.3 (2.5) 139.8 (2.4)	140.4 (2.7) 140.5 (2.5)	140.5 (2.3) 140.4 (2.4)	0.11 (2.7) 0.72 (2.7)	0.28 (2.4) 0.55 (2.5)	**0.029**
T. Bilirubin (mg/dL)	0.1-1.2	BLI800 MoviPrep	0.61 (0.40) 0.59 (0.25)	0.93 (0.56) 0.85 (0.39)	0.75 (2.08) 0.58 (0.26)	0.32 (0.26) 0.26 (0.25)	0.14 (2.06) -0.01 (0.18)	**0.034**
T. Protein (g/dL)	6.4-8.3	BLI800 MoviPrep	7.30 (0.42) 7.30 (0.41)	7.42 (0.47) 7.30 (0.44)	7.16 (0.44) 7.18 (0.42)	0.13 (0.41) 0.00 (0.38)	-0.15 (0.36) -0.12 (0.37)	**0.001**
Uric Acid (mg/dL)	F 2.4-5.7 M 3.4-7.0	BLI800 MoviPrep	5.67 (1.5) 5.78 (1.7)	6.22 (1.5) 5.78 (1.7)	5.87 (1.5) 5.94 (1.8)	0.59 (0.81) -0.01 (0.81)	0.20 (0.78) 0.18 (0.75)	**<0.001**

1) M = male, F = female (reference table 14.3.6, Section 14)

Table 302-16
Mean (SD) Chemistry Values by Visit (ITT Population)

Analyte (units)	Normal Range[1]	Drug	Baseline	Visit 2	Visit 3	Δ to Visit 2	Δ to Visit 3	P (Δ V2)
Albumin (g/dL)	3.8-5.2	BLI800 MoviPrep	4.51 (0.25) 4.47 (0.26)	4.63 (0.37) 4.54 (0.28)	4.45 (0.28) 4.47 (0.28)	0.12 (0.31) 0.07 (0.26)	-0.06 (0.22) -0.01 (0.23)	0.129
Alk Phos (U/L)	F 35-104 M 10-129	BLI800 MoviPrep	67.8 (17.8) 67.7 (20.7)	68.2 (19.4) 67.6 (21.4)	67.2 (18.3) 67.4 (22.3)	0.37 (7.8) 0.02 (8.4)	-0.65 (7.0) 0.06 (9.9)	0.687
ALT (U/L)	7-52	BLI800 MoviPrep	20.8 (10.0) 22.4 (17.0)	23.4 (13.3) 26.7 (25.3)	21.0 (10.4) 23.4 (20.8)	2.50 (7.7) 4.70 (13.4)	0.25 (7.6) 0.65 (10.8)	0.065
Amylase (U/L)	28-100	BLI800 MoviPrep	49.0 (24.4) 48.1 (17.8)	40.8 (17.2) 41.5 (15.2)	50.1 (22.5) 51.2 (19.3)	-8.21 (18.2) -6.38 (9.1)	0.42 (17.5) 2.49 (9.8)	0.235
AST (U/L)	13-39	BLI800 MoviPrep	20.5 (6.9) 21.5 (12.2)	24.1 (8.9) 26.9 (17.2)	20.6 (6.4) 22.6 (15.4)	3.54 (7.2) 5.43 (13.8)	0.05 (6.8) 1.35 (11.8)	0.114
Bicarbonate (mEq/L)	22-29	BLI800 MoviPrep	25.2 (2.3) 25.2 (2.3)	24.3 (2.4) 23.5 (2.5)	25.6 (2.2) 25.6 (2.3)	-0.89 (2.9) -1.68 (2.7)	0.33 (2.3) 0.35 (2.3)	**0.011**
BUN (mg/dL)	6-19	BLI800 MoviPrep	16.8 (5.0) 16.3 (5.3)	13.3 (3.9) 13.5 (4.5)	16.6 (5.1) 16.7 (5.1)	-3.61 (4.2) -2.84 (3.8)	-0.29 (4.0) 0.17 (3.5)	0.068
Calcium (mg/dL)	8.4-10.2	BLI800 MoviPrep	9.73 (0.35) 9.73 (0.39)	9.66 (0.53) 9.57 (0.41)	9.68 (0.40) 9.66 (0.39)	-0.06 (0.48) -0.16 (0.41)	-0.04 (0.37) -0.08 (0.37)	**0.040**
Chloride (mEq/L)	96-108	BLI800 MoviPrep	104.1 (2.5) 104.4 (2.6)	103.5 (3.1) 105.2 (3.1)	104.1 (2.8) 104.2 (2.7)	-0.75 (3.1) 0.89 (2.8)	0.05 (2.6) -0.15 (2.5)	**<0.001**
Creatine Kinase (U/L)	30-223	BLI800 MoviPrep	115.9 (95) 116.7 (122)	114.1 (89) 114.0 (91)	122.6 (196) 187.9 (704)	-0.9 (66) -2.6 (105)	5.7 (157) 68.9 (676)	0.856
Creatinine (mg/dL)	F 0.4-1.1 M 0.5-1.2	BLI800 MoviPrep	0.95 (0.20) 0.97 (0.26)	0.96 (0.19) 0.95 (0.21)	0.95 (0.19) 0.98 (0.24)	0.00 (0.12) -0.02 (0.13)	0.00 (0.12) 0.01 (0.13)	0.190
D. Bilirubin (mg/dL)	0-0.25	BLI800 MoviPrep	0.11 (0.05) 0.10 (0.05)	0.14 (0.07) 0.15 (0.08)	0.11 (0.05) 0.11 (0.06)	0.03 (0.06) 0.04 (0.06)	0.00 (0.04) 0.00 (0.05)	**0.024**
GGT (U/L)	F 5-36 M 8-61	BLI800 MoviPrep	31.5 (34.8) 29.8 (31.9)	31.9 (35.5) 34.6 (56.5)	31.6 (35.8) 31.9 (39.0)	-0.19 (11.5) 4.65 (30.0)	-0.26 (14.8) 1.89 (20.7)	0.050
Glucose (mg/dL)	70-105	BLI800 MoviPrep	101.1 (26) 99.4 (24)	95.1 (19) 94.9 (21)	105.3 (32) 103.6 (30)	-4.98 (23) -4.61 (20)	3.93 (31) 5.34 (28)	0.878
LDH (U/L)	118-273	BLI800 MoviPrep	161.2 (30) 161.1 (53)	179.6 (53) 179.0 (80)	163.0 (42) 171.5 (70)	18.8 (51) 17.7 (55)	1.71 (37) 9.19 (47)	0.851
Magnesium (mEq/L)	1.3-2.1	BLI800 MoviPrep	1.67 (0.14) 1.67 (0.13)	1.73 (0.15) 1.65 (0.13)	1.65 (0.15) 1.65 (0.14)	0.06 (0.14) -0.01 (0.13)	-0.01 (0.13) -0.01 (0.13)	**<0.001**
Osmolality		BLI800 MoviPrep	291.4 (6.1) 290.8 (6.0)	288.8 (5.3) 290.4 (5.6)		-2.71 (6.3) -0.27(5.7)		**<0.001**
Phosphorus (mg/dL)	2.6-4.5	BLI800 MoviPrep	3.47 (0.53) 3.45 (0.55)	3.37 (0.50) 3.42 (0.53)	3.48 (0.53) 3.48 (0.64)	-0.10 (0.59) -0.04 (0.52)	0.01 (0.60) 0.01 (0.58)	0.304
Potassium (mEq/L)	3.5-5.1	BLI800 MoviPrep	4.35 (0.42) 4.31 (0.43)	4.27 (0.41) 4.29 (0.45)	4.39 (0.38) 4.38 (0.42)	-0.07 (0.43) -0.02 (0.48)	0.05 (0.48) 0.06 (0.45)	0.382
Sodium (mEq/L)	136-145	BLI800 MoviPrep	139.9 (2.4) 139.9 (2.3)	140.2 (2.3) 140.5 (2.5)	140.1 (2.3) 140.0 (2.3)	0.14 (2.5) 0.57 (2.6)	0.19 (2.4) 0.12 (2.4)	0.123
T. Bilirubin (mg/dL)	0.1-1.2	BLI800 MoviPrep	0.56 (0.26) 0.60 (0.31)	0.85 (0.44) 0.87 (0.52)	0.57 (0.27) 0.60 (0.29)	0.29 (0.26) 0.27 (0.30)	0.01 (0.17) -0.00 (0.19)	0.694
T. Protein (g/dL)	6.4-8.3	BLI800 MoviPrep	7.32 (0.45) 7.25 (0.40)	7.50 (0.59) 7.32 (0.45)	7.19 (0.44) 7.17 (0.43)	0.18 (0.51) 0.07 (0.44)	-0.13 (0.37) -0.07 (0.38)	**0.037**
Uric Acid (mg/dL)	F 2.4-5.7 M 3.4-7.0	BLI800 MoviPrep	5.81 (1.6) 5.68 (1.6)	6.27 (1.6) 5.70 (1.5)	5.93 (1.4) 5.97 (1.7)	0.44 (0.84) -0.02 (0.82)	0.14 (0.91) 0.28 (0.84)	**<0.001**

1) M = male, F = female (reference table 14.3.6, Section 14)

7.1.7.3 Standard analyses and explorations of laboratory data

Site personnel entered data into Oracle clinical Version 4.5 remote date capture database which is compliant with 21 CFR Part 11 by (b) (4). Medical records were reviewed to verify all data points including potential AE and to ensure consistency with the database. Investigator will retain copies of data, consent forms, and other study documents for 2 years after NDA approval.

Records are available with notice to proper personnel from Braintree or to the necessary authorities under Department of HHS in accordance with federal regulations.

7.1.7.4 Additional analyses and explorations

Elevations of CK up to 3 times upper limit of normal were used to identify the following cases. The majority of elevated CK's were attributed by the Applicant to exercise, 5% higher prevalence in black males, hemolyzed labs, or unknown etiology. The Applicant stated that random elevations are seen in the general population and appear to be unrelated to study medication.

Table 34 A &B (table 2 below and additional cases in following table sent in another IR): Post-treatment CK elevations >3X ULN

Table 2: Patients in Phase 3 studies with post-treatment CK elevations >3 X ULN

PT	TREATC	Screening visit CK, U/L	Visit 2 (colonoscopy) CK, U/L	Follow-up visit CK, U/L (post-treatment day)	Concomitant medications	Age (yrs)
01002	BLI-800	90	1325	116 (27)	Paxil	51
05013	BLI-800	132	211	5064 (44)	Crestor, Zetia	56
09049	BLI-800	447	274	756 (25)	Hyzaar, Toprol XL, ASA	60
17004	BLI-800	692	414	2404 (25)	Simvastatin, fenofibrate	50
18021	BLI-800	665	844	138 (32)	Clonidine, esomeprazole, montelukast, naproxen	61
19021	BLI-800	212	121	684 (33)	Fish oil	44
04009	MoviPrep	953	900	1035 (30)	ASA, terazosin, amlodipine, benzapril	75
05002	MoviPrep	117	109	1682 (21)	none	53
11014	MoviPrep	505	719	8730 (57)	none	45
15024	MoviPrep	53	64	2873 (42)	L-thyroxine	57

ULN = 223 U/L
Data Source: ISS datasets LABS.xpt, CM.xpt, VisDtISS.xpt (VisDtISS.xpt submitted December 23, 2008)

Pt	Treatment	Ck, Visit 1	CK, Visit 2	CK, Visit 3	Concomitant Meds	Age	Comments
13039	BLI800	607	107	125 (34)	Dymetadrine	50	Elev. At pre-dose
3063	BLI800	424	618	540 (16)	ASA, fenofibrate, esomeprazole, beconamine,omacor	50	5% elevation. In black males
3029	Moviprep	516	659	ND	Insulin, atorvastin	48	
10031	Moviprep	1534	209	101 (32)	Doxazosin,calcium,Vitamin C &D, saw palmetto,fish oil	65	exercised
13005	Moviprep	104	636	630 33)	Paracetamol	62	
14007	Moviprep	363	363	630 (33)	Atenolol, olmesartan, medoxomil, amlodipine, dutaseride, HCTZ	64	Uncertain etiology.
15025	Moviprep	1437	309	648 (42)	L-thyroxine, ASA, testosterone, quetiapine, somatropin	53	exercised

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In the pivotal studies, vital signs were monitored at screening, Visit 1, under the table of Study Visits and Procedures.
Reviewer's comments: In searching the CRF, the vital signs were also taken on Visit 2 but not on Visit 3 which included lab work and safety assessments only.

7.1.8.2 Standard analyses and explorations of vital signs data

The vitals signs were compared for mean and absolute change between visit 1 and 2. Other than the findings with bradycardia (see Section 7.1.8.3) vital signs (blood pressure and respiratory rate) did not reveal substantial fluctuations.

7.1.8.3 Additional analyses and explorations

Safety questions from the BLI800-101 study were not previously found to be of concern and Phase 3 ECG studies were not pursued. This reviewer surveyed the Phase 3 study vital signs to do a preliminary safety assessment of any signs of bradycardia as an indicator of potential arrhythmia or prolong QT. In searching the Visit 2 pulses for bradycardia (pulse less than 60 bpm), this reviewer found 73 cases of bradycardia which through investigations of baseline pulse, concomitant medications and potassium levels, she was able to eliminate 30 cases that were originally bradycardic at screening leaving 40 cases of bradycardia after drug treatment and colonoscopy.
An Information request #8 was generated for the Applicant to compile a contingency table of percentages of patients who had bradycardia (< 50 and < 60) at screening and measure the percentage of patients who had dropped by Visit 2. The results were not remarkable for a large percentage of bradycardia on Visit 2 that was not already present. Of the 375 patients who had normal pulses (>60) at screening, only 1 (0.3%) developed bradycardia <50 on visit 2 and 24 patients (6.4%) developed bradycardia <60 on Visit 2. These percentages were lower than those for the MoviPrep patients and the overall shift in the number of patients who were bradycardiac at Visit 2 in the Suprep group was not substantially different than the number at Visit 1. (29 patients had pulses that normalized or were improved on Visit 2 who were bradycardic at Visit 1, and 25 patients who were normal at Visit1 became bradycardic at Visit 2 for the Suprep group). The number of patients who became bradycardic from normal pulse was essentially equivalent to the number of patients who were bradycardic and normalized or improved. Applicant notes that Patient 12017 only had pulse taken at screening and this was read as normal. Applicant also notes that in the table the <60 pulse also includes the <50 pulse patients.

Table 35:Pooled pulse changes after visit 2

	BLI-800 (N=375) Visit 2						MoviPrep (N=376) Visit 2					
	< 50		< 60		Normal		< 50		< 60		Normal	
Screening	N	%	N	%	N	%	N	%	N	%	N	%
< 50	0		1	(0.3)	0		0		1	(0.3)	2	(0.5)
< 60	0		10	(2.7)	18	(4.8)	4	(1.1)	18	(4.8)	15	(4.0)
Normal	1	(0.3)	24	(6.4)	319	(85.1)	3	(0.8)	28	(7.4)	315	(83.8)

Table 35: Individual study pulse changes contingency tables are presented below:

Study 301

Screening Pulse (BPM)	BLI800 (N=194) Visit 2 pulse (BPM)			MoviPrep (N=194) Visit 2 pulse (BPM)		
	<50 (n) (%)	<60 (n) (%)	Normal (n) (%)	<50 (n) (%)	<60 (n) (%)	Normal (n) (%)
<50	0	0	0	0	1 (0.5)	0
<60	0	2 (1.0)	11 (5.7)	1 (0.5)	7 (3.6)	6 (3.1)
normal	1 (0.5)	6 (3.1)	172 (88.7)	1 (0.5)	7 (3.6)	173 (89.6)

Study 302

Screening Pulse (BPM)	BLI800 (N= 181) Visit 2 pulse (BPM)			MoviPrep (N= 183) Visit 2 pulse (BPM)		
	<50 (n) (%)	<60 (n) (%)	Normal (n) (%)	<50 (n) (%)	<60 (n) (%)	Normal (n) (%)
<50	0	1 (0.6)	0	0	0	2 (1.1)
<60	0	8 (4.4)	7 (3.9)	3 (1.6)	11 (6.0)	9 (4.9)
normal	0	18 (9.9)	147 (81.2)	2 (1.1)	21 (11.5)	142 (77.6)

When Study 301 and 302 are analyzed separately, Suprep had 3.1% (Study 301) and 9.9% (Study 302) decreases from normal to < 60 and Moviprep had 3.6% (Study 301) 11.5% (Study 302) decreases from normal to < 60. The decreases from normal to < 50 were from 0 to 1.1% in Study 302 for both groups and equal (.5%) for both groups in Study 301. *See Section 7.1.*9 ECG

Patients who developed bradycardia at Visit 2 (59 to 42 bpm, had at least 5 beat declines below 60 bpm after test drug) were correlated with potassium levels and significant concomitant medications.

Table 36: Sample patients with bradycardia and potassium changes and their concomitant medications (-- represent normals)

Patient ID#	Treatment M= Moviprep S= BLI800	Visit 1 Pulse (bpm)	Visit 2 Pulse (bpm)	Screen K+	Visit 2 K+	Visit 3 K+	Significant PMH
Suprep group							
2003	S 301	78	53	--	--	5.1	Neurontin,Prozac
3004	S 301	68	54	--	--	5.6	64 yo, Dyazide
15064	S 302	64	56	5.0	--	5.2	
20036	S 302	72	53	3.2	--	--	55 yo,Atacand
12023	S 302	72	58	--	5.3	--	Paxil, Procardia
13032	S 302	73	59	--	5.1	--	Metformin,Glyburide
Moviprep group							
14022	M 302	80	50	--	5.1	--	58 yo
15015	M 302	60	55	--	5.4	--	Lisinopril
15040	M 302	55	49	--	5.0	--	Adalat
18007	M 302	64	53	5.1	--	--	Altace, Coreg
20017	M 302	76	52	6.5	--	--	52 yo, Insulin
20035	M 302	78	51	--	5.2	--	--
8005	M 301	56	47	7.4	--	--	HCTZ

Five patients with abnormal screening potassiums were not noted as having been "discontinued" from the study. Applicant submitted lists for non-ITT, ITT non-completers that were discontinued. Nine patients showed hyperkalemia at Visit 2 and Visit 3: seven were on concomitant hypertensive, diabetic, and cholesterol medications.

According to the MoviPrep Review a lack of any colonic cleanser ECG studies during Phase 3 has been the accepted practice. Dr. Brodsky stated that, 'A thorough QT/QTc study was not performed in this NDA'. According to the October 2005 Guidance for Industry entitled, *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs,* "Drugs are expected to receive a clinical electrocardiographic evaluation, beginning early in clinical development, typically including a single trial dedicated to evaluating their effect on cardiac repolarization."Additionally, PEG-based colon preparations have been associated with electrolyte disorders (including hypokalemia and hypocalcemia) on the day of the colonoscopy and several days after the colonoscopy. Since hypokalemia and hypocalcemia have been associated with QT prolongation, PEG-based colon preparations may be more likely to be associated with QT prolongation.Unfortunately, no thorough QT/QTc study of a PEG-based or sodium phosphate-based colon preparation (including GoLYTELY, NuLYTELY, HalfLYTELY, Visicol, and OsmoPrep) has been performed and submitted to the DGP.However, several PEG-based colon preparations, on the market for over 20 years, have not been associated with a significant number of post-marketing cases of prolonged QT or arrhythmias.

7.1.9 Electrocardiograms (ECGs)

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

ECGs were analyzed in BLI800 Study 101 where the QTc effect was discussed in Module 5 Volume 3.2, Appendix B (Table 27, 28, 29) and Appendix C (Listing 32 and Figure 2). Some patients showed abnormal ECGs at baseline and/or post-dose—mostly sinus bradycardia. There were statistically significant increases in QT and QT_C intervals in those patients taking OPS, but not in those taking OSS (see Applicant Table 72.2). *See section 7.1.9.3 for ECG details.*

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

BLI800-101 and 202 were the only studies that performed ECGs and therefore were selected for study. Inferred data based of pulse rates of patients in the pivotal studies were used for analysis of bradycardia as discussed in *sections 7.1.8.3 and 7.1.9.3*.

7.1.9.3 Standard analyses and explorations of ECG data

In BLI800 Study 101, some patients showed abnormal ECGs at baseline and/or post-dose—mostly sinus bradycardia. There were statistically significant increases in QT and QT_C intervals in those patients taking OPS, but not in those taking OSS (see Applicant Table 72.2). In the OSS group, no changes exceeded 450ms in QTc prolongation and none were considered statistically significant. Individual and mean ECG parameters versus time showed no clear trends. Subjects in the OSS and OPS group showed sinus bradycardia. In the Phase 3 datasets, bradycardia (pulses less than 60) ranged from pulses of 59 to 42 in 73 cases of which 30 were in the BLI800 group and 41 cases were in the Moviprep group (2 did not have the treatment identified). About 40 patients had bradycardia that appeared after taking the treatment drugs. Some of the patients were taking concomitant beta-blockers and many were taking hypertensive and cholesterol medications.

In BLI Study 202, 6 healthy volunteers, 6 moderately renal impaired, 6 moderately hepatic impaired patients received screening, pre-dose and post-dose ECGs at Days 2, 3, and 6. Three renal impaired patients had abnormal ECGs on screening consisting of left ventricular hypertrophy (LVH), sinus bradycardia with premature atrial complexes (PAC), and normal sinus rhythm (NSR) with low voltage which all resolved to (NSR) or remained stable without clinical significance. One patient (007) at Day -1, developed NSR with LVH with comments that it may be normal variant. On the discharge physical exam, the comment of "prolong QT was added" and on Day 3 and 6 no mention of any prolongation was noted. Two hepatic impaired patients (004,009) had abnormal screening ECGs (marked sinus bradycardia and non-specific t-wave abnormality). On Day-1, two other hepatic impaired patients (010,013) developed abnormalities (left axis deviation, non-specific ST abnormality) that resolved to sinus rhythm with PAC on Day 6 and sinus rhythm with occasional premature ventricular contractions PVC's on Day 3 (no ECG abnormalities were noted on Day 6 for patient 013). Two healthy volunteers (008,017) developed low voltage QRS on Day 6 and sinus bradycardia with sinus arrhythmia on discharge ECG who did not have any ECG abnormalities noted on Day 6.

In summary, there were a variety of changes noted on the ECG's post-dose, but, no clinically significant findings were associated with these ECGs.

7.1.9.4 Additional analyses and explorations

Other than the ECGs done in Studies 101 and 202, no further data was available for analysis and no additional analyses were performed.

7.1.10 Immunogenicity

No studies for immunogenicity are needed since no increase in immune sensitization is expected or detected in other colonic cleansers. Hypersensitivity reactions to the prep have been noted with PEG products resulting in rhinitis, pruritis, and rashes.

7.1.11 Human Carcinogenicity

Since this product is given as a one time regimen as two 6 ounce sulfate doses, long term exposure leading to cumulative carcinogenicity is not expected, nor has carcinogenicity been studied.

7.1.12 Special Safety Studies

See prior sections on ECG.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No expected abuse potential exists for the colonic preparation.

7.1.14 Human Reproduction and Pregnancy Data

Pregnant and females of child-bearing potential are excluded from this study. No reproductive studies are expected to be performed and there is no available information on drug exposure for this drug.

7.1.15 Assessment of Effect on Growth

Since this preparation is used on a short term basis as a one time dose, no long term effects on growth are expected. This has not been studied. The Applicant proposes deferral of pediatric studies until after NDA approval. *See Section 8.4 Pediatrics.* No assessment-- by height or weight-- on growth was outlined in the pediatric Development plan.

7.1.16 Overdose Experience

In a Phase 1 trial, the patients were inadvertently administered excess amounts of the study drug. Patient had no complications other than gastrointestinal symptoms that completely resolved. No

other experience with overdose of this study drug is known to this reviewer. No clear renal impairment (*see section 7.1.7.4 Additional analyses: Bun and creatinine*) or isoenzyme genetic differences have been seen with this drug.

7.1.17 Postmarketing Experience

The postmarketing safety assessment on CK elevations with other bowel preparations can be found in Section 7.1.4 by Ann Corken.

7.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS

The adverse events seen during the development were largely related to gastrointestinal symptoms of nausea and vomiting with fewer incidences of abdominal distention, pain, and discomfort. Nausea and vomiting are prevalent in the elderly, high risk and Caucasian subgroups. Gastrointestinal adverse events are anticipated as is a slight amount of dehydration and electrolyte shift. Due to the prevalence of future use in the older than 50 year age group for disease and screening, further follow-up studies of electrolyte changes are need. There was one fatality due to respiratory distress in the MoviPrep group. The single case of AVB seem to be possibly related to BLI800. Other common adverse events such as headache can also be slightly higher in incidence in the BLI800 group.

There was adequate drug exposure but, inadequate safety evaluation because not all tests were followed to normalization (Bun, creatinine, CK) or analyzed (serum sulfates). Adequate numbers and demographic subsets should include those with certain concomitant medications. Labeling should only include those who were included in the studies. Doses and duration of drug use was adequate. Further ECG studies should elicit any correlation of bradycardia with ECG changes. No drug-drug interaction studies were carried out. *See sect. 7.1 for list of additional analyses for safety: CK, renal function changes, vomiting and electrolyte changes, and bradycardia analyses.*

The Phase 1 and 2 studies are supporting and non-pivotal information for safety only:
In Phase 1 Study 001-022, was a single site, open-label non-randomized, active control study in 5 healthy volunteers comparing 5 sulfate formulations without phosphates to Fleet's Phospho-soda in split doses. It was to determine the safest preparation that did not produce clinically significant electrolyte and fluid shifts yet produced adequate cleansing. This was measured by serum and stool electrolytes. Using a stool production of 2400g based on what the known effective colonic cleanser for what Fleets Phospho-soda produced, the sulfate formulation that provided 250mmole or more of sulfate (based on the prior sulfate formulations tested) with a stool output of 2400g was the target for selecting the best sulfate formulation. Fewest electrolyte changes also were considered and this led investigators to determine the best formulation among the 4. Although the Applicant stated there were no unexpected or serious adverse events reported, the datasets did not include AE symptoms of Solution A to D. In Solution E, 3 subjects had slight nausea, 4 had severe thirst, one had moderate thirst, and 5 had bad taste. Cleanout of

colon was designated as 3=clear, 2=dark/clear. Solution E had pre-12 hour electrolyte data only for subject 3017, 3020, 3022 but, did not include 11 and 18 hour post-dose data. In the hemo1.xpt, subject numbers are missing for the Solution A to D. It is unclear if there would be any changes in Tables 14 of Module 5 volume 8.1, if the ITT groups were re-tabulated (see Stats review for efficacy). The exact location of the statement on page 4 of section 2.5, table 8 and 9 is not labeled. The dataset for serum electrolytes (serum1.xpt) is unclear for time given, such as subject 3017 or 3020 at time 67500 who both had hyperkalemia. It is unclear what the wash-out period may have been for subjects who were utilized in more than one study group with a different product.

In Phase 1 Study 005-082, was single site, open-label, non-randomized, active control study in 27 healthy adults that continued to develop the sulfate formulation and use thin layer chromatography to detect laxatives. Initial dataset for this study was also missing symptom reports of Solution 1 and 2 and later submitted. According to the 12/24/08, IR response, no site questionnaires were administered to Solution 5 subjects, therefore, no data is available. Solution 5 was chosen as the best solution because it showed the least effect on electrolytes. It is also unclear what the wash-out period was for subjects who participated in different treatments although the consent form states that "the intervals between the various test days will be at least 1 week, to allow your gastrointestinal tract to get over the effect of the previous laxative." Subjects who were the same individuals were given new subject identification number when placed into a new treatment group.

Reviewer's comment: In this study, the 5 sulfate formulations were given at "half the final expected dose" which makes it less likely that the adverse effects might be seen as in the to-be-marketed dose. The measure of effectiveness was based on the stool output and % stool solids.

It was also noted that Solution 4 data results were omitted from the original submission and an information request for that data was submitted. From the 12/24/08 submission, it appears all or part of serum and stool electrolyte data is missing for Solution 1, 2, 3, and 4 of the sulfate solutions. No unexpected or serious side effects were reported. The subject taking Solution 1 had moderate cramping, one of three subjects taking Solution 3 had mild gas, and the subject taking Solution 4 had moderate boating and mild gas. No data for symptoms from Solution 5 were gathered (see IR).

See Table taken from Applicant Module5, volume 6.2, Tab 5.3.5.1B, 16.1.1

The Percent Stool Solids were low ranging from 17.9 to 3.6 % for all the sulfate solutions, and with Solution 5 ranging from 14.3 to 10.2% as a measure for efficacy of cleansing.

Reviewer comment: The original comparator for NDA 22372 was (b) (4) *and later was changed to Moviprep in a SPA.*

In Phase 1 study 006-181, the to-be-marketed formulation was compared to Fleet's EZ-Prep and NuLYTELY in normal volunteers. In the 12/24/08 IR response, FDA was informed that the investigator, John Fortran, submitted these results to a journal who then requested the investigator do further subjects so that all the subjects received all three treatments. The new subjects were submitted as a XPT. File to replace and give further detail to Table 14: Subject Questionnaires. The subjects who were the same individuals were given new subject identification numbers when placed into a new treatment group.

The results of the updated files included n=7 for BLI800, n=7 for EZ-Prep, and n=6 for NuLytely (missing one subject). Among those who received BLI800, one had moderate gas, 4 had mild gas and mild nausea, and one had mild gas with a "bothersome" overall treatment. All

the other 6 considered the overall treatment easy. Stool and serum electrolytes compared to the other preparations were done.

The following Table is from Applicant's Module 2, table 2.7.2-12. Serum sulfates were compared in the OSP, PEG and BLI800 groups in Study 101. The 5:00 am sulfate mean was 2x the baseline mean for Suprep sulfates. This increased to 3x the baseline mean for Suprep sulfates at 8:00am. These were significant accumulations compared to baseline.

Table 37: Mean Serum Analytes

Mean Serum Analytes (SD)

Analyte (units)	Normal Range	Prep	Baseline	5:00am	8:00am
Albumin (g/dL)	3.5-5.0	BLI800 EZ-Prep NuLYTELY	4.7 (0.2) 4.6 (0.4) 4.7 (0.4)	4.5 (0.3) 4.3 (0.3) 4.3 (0.3)	4.7 (0.2) 4.5 (0.2) 4.4 (0.3)
Bicarbonate (mEq/L)	22-30	BLI800 EZ-Prep NuLYTELY	28 (2) 28 (1) 29 (1)	27 (1) 27 (2) 27 (1)	28 (2) 27 (3) 28 (1)
BUN (mEq/dL)	9-20	BLI800 EZ-Prep NuLYTELY	15 (4) 14 (4) 14 (2)	11 (2) 10 (2) 11 (3)	11 (2) 10 (2) 11 (2)
Calcium (mg/dL)	8.4-10.2	BLI800 EZ-Prep NuLYTELY	9.7 (0.3) 9.4 (0.4) 9.9 (0.4)	9.5 (0.5) 9.1 (0.3) 9.1 (0.2)	9.7 (0.4) 9.2 (0.3) 9.3 (0.2)
Chloride (mEq/L)	98-107	BLI800 EZ-Prep NuLYTELY	101 (1) 101 (3) 101 (2)	101 (2) 99 (1) 102 (1)	99 (2) 99 (3) 101 (3)
Creatinine (mg/dL)	0.7-1.2	BLI800 EZ-Prep NuLYTELY	1.0 (0.2) 1.0 (0.2) 1.0 (0.2)	1.0 (0.2) 1.0 (0.2) 1.0 (0.2)	1.0 (0.2) 1.1 (0.2) 1.0 (0.2)
Hematocrit (%)	40.0-52.0	BLI800 EZ-Prep NuLYTELY	43.2[1] 45.6 (3.6)[3] 46.3 (4.2)	45.1 (2.4)[2] 44.0 (3.6)[3] 42.5 (2.5)	45.6 (1.8)[2] 45.2 (2.1)[3] 43.3 (2.1)
Magnesium (mg/dL)	1.7-2.6	BLI800 EZ-Prep NuLYTELY	2.1 (0.1) 2.1 (0.2) 2.2 (0.1)	2.1 (0.2) 2.1 (0.1) 2.1 (0.2)	2.2 (0.1) 2.0 (0.1)* 2.2 (0.1)
Osmolarity[4] (mOsm)		BLI800 EZ-Prep NuLYTELY	289 (2) 291 (4) 291 (3)	286 (1) 287 (3) 286 (3)	285 (3) 284 (3) 288 (5)
Phosphorus (mg/dL)	2.7-4.5	BLI800 EZ-Prep NuLYTELY	3.3 (0.6) 3.4 (0.2) 3.1 (0.8)	4.1 (0.7) 5.6 (0.3)* 3.9 (0.5)	3.4 (0.5) 6.6 (1.5)* 3.6 (0.4)
Potassium (mEq/L)	3.6-5.0	BLI800 EZ-Prep NuLYTELY	4.2 (0.4) 4.1 (0.3) 4.2 (0.3)	4.1 (0.3) 3.7 (0.3) 3.9 (0.1)	4.1 (0.2) 3.8 (0.2) 4.1 (0.3)
PTH, 1-84	14.0-72.0	BLI800 EZ-Prep[1] NuLYTELY[1]	NA 80.7 73.4	NA 129.4 69.2	NA 179.1 76.0
Sodium (mEq/L)	136-145	BLI800 EZ-Prep NuLYTELY	140 (1) 139 (2) 140 (2)	139 (1) 139 (2) 139 (1)	139 (1) 139 (1) 139 (2)
Sulfate[4] (mg/dL)		BLI800 EZ-Prep NuLYTELY	0.61 (0.34) 0.46 (0.17) 0.64 (0.15)	1.20 (0.28) 0.59 (0.30)* 0.67 (0.08)*	1.94 (0.22) 0.57 (0.22)* 0.56 (0.14)*

* t test vs BLI800 $p \leq 0.05$
1 = values from 1 study subject; 2 = values from 2 study subjects; 3 = values from 4 study subjects
4 = normal range not established See CTD Section 5.3.4.1C for the full report.

In Phase 2 Study BLI 800-101 a dose finding randomized, parallel, multicenter, open label study was performed in 60 healthy subjects of both genders for up to 8 days. Doses ranged from 10 ml (1.2 g), 30 ml (3.7 g), 50 ml (6.2 g), and 70 ml (8.7g) of oral sulfate solution for patients who

were being treated for constipation. Pharmacodynamic characteristics and safety was compared between OPS and OSS groups.

Table 38: BLI 800-101 Mean Changes From baseline For Serum Electrolyte Concentrations (%)

BLI800-101 Mean Changes From Baseline For Serum Electrolyte Concentrations (%)

Analyte	OPS Group 1		OSS Group 2		OSS Group 3			
	T = 16 hr	T = 22 hr	T = 16 hr	T = 22 hr	T = 16 hr	T = 22 hr	p 16 hr	p 22 hr
Ca (mmol/L)	-2.85	-1.86	0.78	-1.15	1.83	-1.60	* #	-
Ca x P (mg^2*dl^2)	25.0	18.3	-7.93	4.88	-5.72	5.84	* #	-
Cl (mmol/L)	-1.75	-0.44	-1.28	-0.96	-0.97	-0.15	-	-
HCO_3 (mmol/L)	-8.90	-1.44	-5.53	-3.97	-5.50	-0.86	-	-
K (mmol/L)	-5.12	-6.91	0.82	1.22	4.77	3.95	# $	#
Mg (mmol/L)	-6.28	1.41	-0.75	3.28	-0.63	5.28	* #	-
Na (mmol/L)	0.84	0.25	0.97	-0.72	-0.35	-0.24	-	-
PO_4 (mmol/L)	28.7	20.4	-8.76	5.96	-7.38	7.64	* #	-
SO_4 (mg/dL)	-21.0	-8.60	106	66.6	71.5	59.7	* #	* #

* = Group 2 significantly different from Group 1; p value < 0.05
# = Group 3 significantly different from Group 1; p value < 0.05
$ =Group 3 significantly different from Group 2; p value < 0.05
(See Study report Synopsis, CTD Section 5.3.4.1D)

Taken from Applicant's Module 2, Table 2.7.2-17

The amount of Ca phosphate accumulation was significant for the OPS group at 16 and 22 hours with some accumulation of the substance at 22 hours in the OSS groups 2 and 3.

Comments: Applicant previously used the Ca phosphate accumulation of OPS versus OSS as justification for only one month post-dose monitoring for acute nephrocalcinosis during SPA negotiations.

For Phase 2 BLI800-202, where special populations of renal and hepatic impairment patients were studied for PK, see section 8.3.

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

Pivotal Studies 301 and 302 were the primary data sources used in conducting the review.

7.2.1.1 Study type and design/patient enumeration

See Table 4 in section 4.2 for all patients across the entire development program in Phase 1 to 3 with study design, treatment groups, general doses and numbers of patients. Other than study 202, no other special subpopulations were isolated into one study.

7.2.1.2 Demographics

In the phase 3 pivotal studies:
The overall population had more females (54%) in study 302. Both treatment groups were comparable for race, age, and baseline weight. The average age was 55 years (20 to 84 years). Study patients weighed about 184 pounds. *See section 10.1.2.2 and 10.1.5. (Patient Disposition)* The Phase 1 and 2 studies, which consisted of 98 patients, patients were closely matched in some studies, but, others had missing data, and had unclear wash-out periods.

7.2.1.3 Extent of exposure (dose/duration)

Patients were generally exposed to this drug for less than 24 hours usually between 12 to 18 hours. There were no variable doses. There were longer intervals of exposure in Study 302 where patients took one dose the following morning instead of both on the same day.
Reviewer's comments: Inconsistencies existed on the submitted label and the actual way the patients were instructed to take the study medication. (b) (4)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Some secondary clinical data sources were used to evaluate safety. Review included the safety update on the SAE of colonic perforation. Medline, PDR& other sources of approved colonic cleansers, Orange Book, searches for label information, review of Applicant protocol study 303 and other cited studies in Phase 1 and 2 that used virtual colonoscopy. MoviPrep & NuLytely reviews were performed. Labels of currently marketed PEG and OSP products were reviewed.

7.2.2.1 Other studies

No additional data was used. Phase 1 studies were not included due to poor data collection and study design.

7.2.2.2 Postmarketing experience

Since Suprep has not been approved and no other sulfate predominant oral lavage is approved, there is no postmarketing experience.

7.2.2.3 Literature

For MoviPrep, published articles support reports of serious AE in patients over 60 years of age who used PEG based products. AE included upper gastrointestinal bleeds from Mallory-Weiss tear, esophageal perforation, asystole, and acute pulmonary edema after PEG aspiration. These products also produce allergic reactions characterized by urticaria, rhinorhea, dermatitis, and

anaphylaxis. There were rare reports of generalized tonic-clonic seizures associated with electrolyte abnormalities in patients without history of seizures. These resolved with the normalization of electrolytes. ACE inhibitors or underlying hyponatremic patients. Applicant included case-report forms for a study with virtual capsule colonoscopy to support study design. In the safety update, Applicant submitted the study protocol for Study BLI800-303 under another IND.

7.2.3 Adequacy of Overall Clinical Experience

In accordance to the ICH guidance such as ICH-E1A, the extent of dose and duration of exposure to assess safety was adequate in number for subjects with elderly, racial, gender and high risk subgroups who were exposed to the drug for its oral lavage indication. The study was adequate except for the following:

- the length of follow-up of abnormal labs
- the lack of inclusion of populations studied in the label
- more targeted studies on patients who have particular concomitant medication and risk factors
- further analysis of sulfates
- Study 202 performed sulfate measurement on only a small number of normal healthy volunteers
- bradycardia could be more clearly defined in Phase 3 studies with ECGs

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The preclinical testing was adequate to explore potential adverse events.

7.2.5 Adequacy of Routine Clinical Testing

Other than the clinical assessments and laboratory analysis requested for follow-up of abnormal labs and analysis of serum sulfates under *Section 8.7 and 9.3.2 on PMC*, the other Visit 1, 2 and 3 laboratory testing were adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No further studies were performed to assess metabolic, clearance and interaction of the study drug other than Study 202. Drug to drug interaction (substrate /inducer/inhibitor) and clearance (CYP450 enzymes and p-glycoproteins) was not characterized by the Applicant nor requested in earlier planning.

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

Applicant should have made attempts to detect adverse effects related to potential nephropathy and excess sulfate accumulation in general and sub-populations by doing post-dose lab follow-up between dose and day 30 and preferably beyond Day 30 to Month 6. Applicant did attempt study of sulfates in Study 202 but, they did not carry out the planned sulfate studies in Phase 3.

7.2.8 Assessment of Quality and Completeness of Data

Applicant submitted incomplete and poor quality summary tables with incomplete data and electronic datasets throughout the review for both safety (and efficacy) assessment. *See Appendix 10.6.2 for Summary of IR submissions.*

7.2.9 Additional Submissions, Including Safety Update

The safety update provided the SAE of colonic perforation over one year after the event. The last IR's received in May and June 2009 had critical integrated summary tables and was the basis of a major amendment. See section 7.1 for the 8 to 10 fold increase in AE's after the last two IR #13 and 14.

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

Table 38: Summary Table of Important and treatment-related AE's.

Patient ID	AE Brief summary	Reference
20013	Death from respiratory arrest	Sections 7.1, 7.2,7.3.
12002	Atypical chest pain	
20030	Late-report colonic perforation	
11007	Mild ischemic colitis	
10038	Third degree heart block	
2032	Nausea	
5034	Vomiting	
10011	Bloating and nausea	

The pivotal studies 301 and 302 demonstrated more nausea and vomiting in Suprep patients than in MoviPrep patients. Though more substantial safety concerns were not obvious with the data submitted, there were potential substantial safety concerns involving the abnormal creatine kinases, lack of sulfate data in the Phase 3 studies, and other labs follow-up including renal function and uric acid period. The unknown outcome of these abnormal laboratory tests needs further established post-marketing studies and correlation with any potential adverse events. Safety concerns remain for sub-populations of product users who may use concomitant

medications, have pre-disposing factors for electrolyte imbalances or elevated CK levels or renal failure.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Study 301 and 302 were pooled across studies to estimate and compare incidences for safety and efficacy.

7.4.1.1 Pooled data vs. individual study data

Study 301 and 302 were analyzed separately due to the different safety profiles whereupon the patients who took the same day dose regimen had more nausea and vomiting.

7.4.1.2 Combining data

The numerator events and denominators for the pivotal studies were combined. Study 202 was not combined.

7.4.2 Explorations for Predictive Factors

No further explorations for dose dependency, time dependency, drug-demographic interactions, drug-disease interactions and drug-drug interactions were done except for CK's and concomitant medication use by the OSE consult.

7.4.2.1 Explorations for dose dependency for adverse findings

No further explorations for dose dependency were performed.

7.4.2.2 Explorations for time dependency for adverse findings

No further explorations for time dependency were performed.

7.4.2.3 Explorations for drug-demographic interactions

No further explorations for drug-demographic interactions were performed.

7.4.2.4 Explorations for drug-disease interactions

No further explorations for drug-disease interactions were performed.

7.4.2.5 Explorations for drug-drug interactions

No further explorations for drug-drug interactions were performed.

7.4.3 Causality Determination

No causality determination was done.

8 Additional Clinical Issues

8.1 Dosing Regimen and Administration

(b) (4)

Reviewer's comments: NDA 21-881 MoviPrep review also states that "Since MoviPrep patients received food closer to the colonoscopy, they were less likely to have a clean colonoscopy

preparation compared to the OSPS patients." The differences in dietary restrictions for the two treatment groups, whereupon the BLI800 treatment group followed a more restricted diet before the colonoscopy than did the Moviprep treatment group, may have resulted in the initial effectiveness comparisons to be weighted to BLI800 and, therefore, may have favored theBLI800 treatment group for the primary efficacy outcome measure. Theoretically, the patients in the Moviprep group, may have required more aggressive colonic cleansing than in the BLI800 group.

On the MoviPrep label, instructions for the use of Moviprep included three steps. The first two steps for mixing the 2 pouches of A and 2 pouches of B up to one liter solution with water were identical for both dosing regimens. Step 3 incorporates a choice of instructions for the split-dose versus Evening-only (full dose) regimen. The following instructions for patient use were submitted by the Applicant:

For the Study 301 Same Day Dose Regimen

BLI800

Dosing Instructions (day before colonoscopy):

- At approximately 6:00 PM: pour the content of one 6 oz bottle of BLI800 into the mixing cup provided. Fill the cup with water to the 16 oz fill line and drink the entire 16 oz volume.
- Drink two additional 16 oz cups of water over the next hour.
- At approximately 7:00 PM (but no later than 9:00 PM): pour the contents of the second 6 oz bottle of BLI800 into the mixing cup provided. Fill the cup with water to the 16 oz fill line and drink the entire 16 oz volume.
- Drink two additional 16 oz cups of water over the next hour.

Dietary Restrictions (day before colonoscopy):

- Light breakfast, clear liquid lunch and clear liquid dinner
- Red and purple liquids, milk and alcoholic beverages are prohibited

MoviPrep

Dosing Instructions (day before colonoscopy):

- At approximately 6:00 PM: Take the first liter of MoviPrep solution over one hour at a rate of 8 oz every 15 minutes until complete.
- Approximately 1.5 hours after completing the first dose, take the second liter of MoviPrep solution over one hour at a rate of 8 oz every 15 minutes until complete.
- Drink 1 liter (approximately 32 ounces) of additional clear liquid during the evening before the colonoscopy.

For the Study 302 Split Dose Regimen

BLI800: Day before colonoscopy:

- At approximately 6:00PM: pour the content of one 6 oz bottle of BLI800 into the mixing cup provided. Fill the cup with water to the 16 oz fill line and drink the entire 16 oz volume.
- Drink two additional 16 oz cups of water over the next hour.

Day of colonoscopy:

- At approximately 6:00 AM (10-12 hours after evening dose): pour the content of the second 6 oz bottle of BLI800 into the mixing cup provided. Fill the cup with water to the 16 oz fill line and drink the entire 16 oz volume.
- Drink two additional 16 oz cups of water over the next hour.
- Complete all study preparation and required water at least one hour prior to colonoscopy.

Dietary Restrictions:

- Light breakfast, clear liquid lunch and clear liquid dinner on the day before colonoscopy.
- Red and purple liquids, milk and alcoholic beverages are prohibited.
- Clear liquids only from the time the BLI800 preparation is started until after colonoscopy.

MoviPrep

Day before colonoscopy:

- At approximately 6:00PM: Take the first liter of MoviPrep solution over one hour at a rate of 8 oz every 15 minutes until complete.
- Drink another 0.5 liters of clear liquid.

Day of colonoscopy:

- At approximately 6:00 AM: take the second liter of MoviPrep solution over one hour at a rate of 8 oz every 15 minutes until complete.
- Drink 0.5 liters of additional clear liquid. The additional clear liquid must be finished at least one hour prior to colonoscopy.

Dietary Restrictions:

- Day before colonoscopy: normal breakfast, light lunch and clear soup and/or plain yogurt for dinner. Dinner should be completed by approximately 5:00 PM, and must be completed at least an hour prior to starting the MoviPrep solution.
- Red and purple liquids, milk and alcoholic beverages are prohibited.
- Clear liquids only from the time the MoviPrep preparation is started until after colonoscopy.

See section 10.1.1.5 and 10.1.3.8.

8.2 Drug-Drug Interactions

No specific drug-drug interactions have been studied for pharmacodynamics.

8.3 Special Populations

In BLI800-202, the PK's in patients with moderate renal and hepatic disease were studied. No differences were seen in the safety profile, electrolytes, urine and serum sulfate PK's. The same day regimen group had more intense and longer abdominal pain, discomfort, distension, nausea. OPS and OSS were almost equally effective. Lower doses should be considered for renal and hepatic impaired patients, elderly patients, and patients who may have predisposing electrolyte or dehydrating diseases, high risk or medications. Caucasians may be more predisposed to GI symptoms and may require lower doses. Pediatric studies most likely will show a need for

modified dosing based on weight. This treatment should be avoided in pregnant and lactating females.

8.4 Pediatrics

Historical Osmotic Laxative Pediatric Waivers
Pediatric waivers in the classes of oral sodium phosphate and PEG (polyethylene glycol) products for the pediatric populations had been granted in the past based on historical use and not on sufficient and adequate well-controlled clinical trials. Since this product is a new drug entity that has not been studied in the pediatric population, the prior historical use pediatric waivers are not applicable. With the recent withdrawal of OTC Fleet's products due to oral sodium phosphate inducing acute nephrocalcinosis and its heightened potential for greater use of Suprep in light of the current safety concerns of the OSP and PEG products, we request that further pediatric studies be done by the Applicant.
This reviewer notes that NuLytely has labeling for use in children and Fleets OTC products also has been used in children. Neither Osmoprep nor Visicol is labeled for use in children.

Deferral and Development Plan
The Applicant submitted a deferral with the original submissThe plan was received 3/11/09 by email and revised 3/30/09. It stratifies the study of the pediatric population into 5 studies as follows, to commence no later than one year from approval of Suprep.
Study 1 is a Retrospective Survey of Colonoscopy Rates in The Pediatric Population (birth to 16 years). It will determine the number of colonoscopies being performed in various pediatric age groups. The need to develop an age appropriate formulation will be based on the utilization data that is gathered from Study 1. They plan to submit the protocol within 3 months of approval and have the final report within 9 months of approval.
Study 2 is An Open-label Pilot Study Assessing the efficacy and tolerability of Suprep in Pediatric Patients (age 12 to 16) to evaluate the adult formulation and any age appropriate formulation for tolerability and efficacy. There will be up to 20 patients in each arm. Stratification will be performed for multiple subgroups. If more pilot studies are needed to refine the formulation, they will be performed before Study 3. (b) (4)

Study 3 is a randomized, single-blind multicenter dose-ranging study comparing safety and efficacy of Suprep (3 doses) versus NuLytely in adolescents (ages 12 to 16). (b) (4)

Study 4 is a randomized, single-blind multicenter dose-ranging study comparing safety and efficacy of Suprep (3 doses) versus NuLytely in children (3-11years) and will be performed if the data from Study 3 supports evaluation of Suprep in this age group. (b) (4)

Study 5 is a randomized, single-blind multicenter dose-ranging study comparing safety and efficacy of Suprep (3 doses) versus NuLytely in children (Birth – 2 years) and will be performed if the data from Study 4 supports evaluation of Suprep in this age group. (b) (4)

Table 41: Summary Study Design (Studies 2 - 5) of Development Plan

(b) (4)

Reviewer Comments: No specific age appropriate dose formulation or PK/PD studies were included. Reference to other colonic cleanser products approved or tested in Pediatric populations are not included. There were no specific times of assessments for monitoring of adverse events and lab work.

PeRC Consultation

After PeRC consultation and discussion, it was decided that the Pediatric development plan would be deferred until more information was derived from Study 1. (b) (4)

A toxicology study of juvenile rodent and non-rodents of one month duration would also be requested.

Written Request

No written request has been made as of the date of this review. Applicant was to be notified to collect data to begin Study 1.

8.5 Advisory Committee Meeting

No Advisory Committee has been deemed necessary as osmotic cleaners have been used routinely and widely accepted by the public and the medical community as necessary bowel preparation prior to routine and diagnostic colonoscopy.

8.6 Literature Review

Any literature related to application was referenced throughout the review. *See References in section 10.5.*

8.7 Postmarketing Risk Management Plan

No postmarketing risk management plan by the Applicant was submitted. See section 9.3.1 for postmarketing risk management recommendations.

8.8 Other Relevant Materials

The review from Division of Drug Marketing, Advertising, and Communications (DDMAC) Shefali Doshi and Kathleen Klemm, Regulatory Review Officers, had comments on the proposed product labeling, bottle label, carton label and (English only) (b) (4) which were included in the labeling review in section 9.4.
No other relevant materials were reviewed. Other than the OSE review of database of adverse events related to abnormalities in lab work, no other review of proposed and completed epidemiologic studies were performed.

9 Overall Assessment

9.1 Conclusion

The Applicant should not state that BLI800 is superior to MoviPrep and remove any labeling that might imply this. In addition, Braintree must indicate their studies were not well controlled for dietary consistency, had diminished sensitivity and specificity lacking confirmatory and pooled endoscopic findings, and that populations that dropped out were greater than expected with their product.
Braintree must also agree to post-marketing studies for safety follow-up for adverse events and abnormal laboratory tests. Instances of bradycardia were noted. No Phase 3 requirements for ECG studies were previously requested to provide further information on these patients.
Applicant label also does not adequately warn and contraindicate certain groups that may be predisposed to seizures, cardiac arrhythmias, and have renal impairment. Certain concomitant medications or underlying electrolyte abnormalities also need to be identified for careful lab monitoring post-dose. Applicant should agree to clearly label that adverse events may be **increased with the same day dosing** regimen and both regimens **induce greater frequency of nausea and vomiting** than MoviPrep.

9.2 Recommendation on Regulatory Action

From a clinical perspective, this medical officer recommends an **Approval Actiom** of BLI800, Suprep Bowel Prep Kit ® (sodium sulfate, potassium sulfate and magnesium sulfate) Oral

Solution for bowel cleansing prior to routine or diagnostic colonoscopy, if the Applicant agrees to certain labeling changes and to post-marketing commitments. The Applicant should not state that BLI800 is superior to MoviPrep and remove any labeling that might imply this. In addition, Braintree must indicate their studies were not well controlled for dietary consistency, had diminished sensitivity and specificity lacking confirmatory and pooled endoscopic findings, and that populations that dropped out were greater than expected with their product. Braintree must also agree to post-marketing studies for safety follow-up for adverse events and abnormal laboratory tests. Instances of bradycardia were noted. No Phase 3 requirements for ECG studies were previously requested to provide further information on these patients. If the Applicant does not agree to these important changes in labeling and post-marketing and pediatric studies, then this reviewer recommends a Complete Response. The risk-benefit analysis BLI800 benefits outweigh safety risks for approval as explained below:

The two pivotal trials revealed that the split dose regimen, Suprep is slightly more efficacious than the PEG without adjusting for the differences in diet that favored Suprep. Since the dietary restrictions used in the pivotal studies used vastly different diet requirements and the impact of diet on efficacy is inevitable, the efficacy comparisons are found to be inconclusive. *See Section 10.1.8 Concomitant Medications.* Furthermore, Applicant attempted to justify the non-inferiority margin after multiple requests. *See Statistics Review*. The drop-out rate proved to be higher than was expected at 7%. Inconsistencies in ratings by colonoscopists were noted for the poor and fair findings.

Because the safety profile of patients taking the same day dose was less favorable than for the patients taking the split-day dose, patients will be informed that this split day dosing may be safer than the same day dosing. This reviewer recommends the elimination of the same day dose regimen due to higher adverse event rates and lower efficacy. The rare instances where this lavage would be used on an emergent basis can be included as an option for the provider in the Dosage and Administration whereupon the "Same Day Regimen: For Emergent Use Only As Instructed by Provider" would be designated. Using the Split dose regimen would eliminate confusion in instructions for use found in the label and patient instruction sheet, decrease adverse events, and improve efficacy for the larger population. There appears to be no overt safety signals that have led to serious or fatal outcomes. There appears to be a greater amount of nausea and vomiting but, a lesser amount of abdominal pain and distension and headache as compared to the PEG product.

The labeling should not allow use in populations the Applicant did not study.

This reviewer also recommends adding **Warnings** to the labeling for subpopulations at high risk for dehydration, electrolyte changes, or liver impairment and additional symptom warnings such as potential tonic-clonic seizures due to electrolyte changes, caution with concomitant medications use of diuretics, ACEI (angiotensin converting enzyme inhibitors), ARB (angiotensin receptor blockers) as potentiators of the electrolyte changes and dehydration. Patients with other comorbidities such as diabetes or hypercholesterolemia who are using cholesterol lowering agents may be warned that BLI800 may exacerbate glucose or CK levels. An analysis of high use patients--those adults over 50 years using routine colonoscopy for screening and on those who are at high risk of developing complications—those with renal or hepatic failure should be studied in greater numbers.

The gray area remains in the labs values that were inadequately pursued to normalization, or not pursued at all. Postmarketing follow-up that includes stringent post-dose to

3 month follow-up is required to answer these unknowns. Selection of a non-stratified healthy population may be desired for initial follow-up lab for safety then followed by the high risk, elderly populations with careful attention to concomitant medication use.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Risk management activity should include clinical **studies** for safety follow-up. They should evaluate adverse events and **abnormal laboratory tests.** This should include creatine kinase, glucoses, renal function, urinalysis, and additional sampling of **sulfates**. Serum sulfates were drawn and frozen for analysis and the sponsor chose not to analyze these samples. Likewise, elevated CK's were never followed to resolution: based on the OSE consult, this review of data and Applicant response, no pattern could be established. Further follow-up of patients with elevated CK, renal function, sulfates are warranted immediately after drug ingestion to 50 days post-colonoscopy based on OSP follow-up findings for nephropathy. CK elevations especially CK fractionates to distinguish myocardial damage from gastric CK changes may be indicated.

9.3.2 Required Phase 4 Commitments

PMR meetings are currently in progress. This reviewer recommends Braintree agree to do **PMC studies** for safety follow-up for adverse events and **abnormal laboratory tests** especially the creatine kinase, glucoses, urinalysis, and others and do additional sampling of **sulfates**. Although serum sulfates were drawn and frozen for analysis for over 700 patients in the two pivotal BLI800-301 and 302 studies, the Applicant chose not to analyze these samples based on their assessment of BLI800-202. Applicant acknowledges that they did not notify FDA of the change in the protocol nor submit an amendment. Further study of the serum sulfate PK and correlation with any potential adverse events in Phase 3 studies with a broad general population is recommended. Safety signals for CK, renal function, urinalysis, and sulfate for follow-up immediately after drug ingestion to 50 days post-colonoscopy should be done. Follow-up of CK, creatinine, BUN, GFR, electrolytes and adverse events at 8 to 14 hours, at 24 to 36 hours, 72 hours and at 4 to 8 weeks is recommended. In discussion with Dr. Jane Bai, due to the lack of sufficient data of the Study 202 renal impairment patients who had elevations up to 50% in sulfate levels, proposed measurements of renal function, sulfate levels and correlation with CK fractionated components such as CK-MB is sought. *See Clinical Pharmacology Review.* During the SPA negotiations, follow-up of laboratory tests to 3 and 6 months and 1 month was agreed upon. Excluded from the prior SPA discussion, are requests for lab monitoring on a daily basis post-dose for one week and for serum sulfate sampling post-dose. We highly recommend laboratory monitoring extend past the one month monitoring to 3 months. During SPA negotiations, the regulatory action of removing the OSP from the OTC market for nephropathy had not occurred. As FDA continues to monitor all oral colonic cleansers for post-approval adverse events the changing milieu mandates requests for frequent monitoring of post-dose adverse events not only at one month time, but, up until that time. Likewise, with the

implementation of new PMC for OsmoPrep and Visicol and the change to NDA approval process for Fleet's products these drugs are undergoing close scrutiny.

In BLI800-101, a Phase 2 study of three groups of patients given either OSP (Oral Sodium Phosphate), OSS (Oral Sodium Sulfate), and healthy volunteers, the ECGs obtained showed sinus bradycardia and some QTC prolongation that was less than 450msec. No further cardiac studies were requested in the Phase 3 studies. About 40 patients had bradycardia that appeared after taking the treatment drugs. Some of the patients were taking concomitant beta-blockers and many were taking hypertensive and hypercholesterolemia medications. In BLI 800-202, clinically insignificant ECG changes were noted in 4 renal impaired patients, 4 hepatic impaired patients, and two healthy volunteers. Further delineation of the significance of these changes in larger populations and in the population that will most likely use this product is warranted. *See Section 7.1.8 and 7.1.9 on Vital signs and ECG.*

In the classes of oral sodium phosphate and PEG (polyethylene glycol) products in the pediatric populations waivers had been granted in the past. What was well known to the market cannot be applied to this product as it is a new drug entity that has not been studied in the pediatric population. With the recent withdrawal of OTC Fleet's products due to oral sodium phosphate inducing acute nephrocalcinosis and Suprep's heightened potential for greater use in light of the current market changes. PREA commitments are under discussion with a pediatric development plan submitted 4/09 and current waiver status until approval. Further pediatric studies will be requested of the Applicant.
See section 8.4.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests.

9.4 Labeling Review

Labeling discussions are in process. Changes and clarifications in the product name and inclusion of chemistry information was done. Major revisions in the packaging that included adding patient instructions for same day regimen use were requested. Instructions for patient use were also inconsistent with the study protocol instructions and were corrected on packaging and label. Large sections of the "Contraindications and Warnings and Precautions" were expanded. Warnings include sections for suspected gastric obstruction, seizures, renal impairment, electrolyte abnormalities, ischemic colitis, and cardiac arrhythmias. The Applicant's original label adverse event tables did not reflect the full range of adverse events and were removed and new ones tabulated. *See Section 6.1 and 7.1* Patient Counseling Information was modified based on the added warnings and precautions. Additional specifications were included by CMC.

DMEA Review
Anne Crandall, PharmD. Safety Evaluator, in the Division of Medication Error Prevention and Analysis (DMEPA) stated the proposed name was not vulnerable to name confusion that could lead to medication errors. Additionally, DMEA prefers the "P" in Suprep to be lower case, and the 15 identified potential similar names that potentially can be confused with the product were unlikely to result in medication errors. Labeling Risk Assessment identified the following areas

that needed improvement: inadequate instructions for use on container labels, lack of required content in grams or milligrams of each active ingredient in accordance with 21 CFR 201.57 (c) (4), dose form and strength on Package Insert was needed, and elimination duplicative container label information. From the Label and Labeling Risk Assessment other recommendations are included such as (b) (4) the need for dilution. For carton label, the instructions for (b) (4) overnight regimen should appear. The strength should be stated (b) (4) . The package insert also had to display strength of each ingredient in accordance with Physician labeling Requirements (PLR) 21 CFR 201.57 ©(4)(i). See DMEPA review for further details.

DRISK was consulted on the Applicant's intent to include the patient instructions along with the Full Prescribing Information as part of a (b) (4) It will be updated with the final label information as agreed upon through label negotiations.

9.5 Comments to Applicant

There are no important deficiencies that preclude the approval of the application. See Section 9.3.1 and 9.3.2 regarding Risk management activities and Phase 4 commitments. See Section 4.5 for comments on Quality of Submission.

The Applicant should have:

- submitted electronic datasets with the original submission ensuring that numeric formatting is usable and that the gender, treatment groups, sex, date of treatment compared to onset of adverse events are incorporated.
- carefully incorporated all adverse events, both patient reported and observer reported in combined tables for labeling.
- included Narrative case reports of all serious adverse events and Applicant should have ensured that their sites reported all adverse events to MedWatch in the designated time period, not more than one year later.
- requested amendments for protocol changes when they decided not to analyze the serum sulfates.
- Designed Protocols to reflect their labeling and not changed the labeling (b) (4) This statement was substantiated by table 301-11 in the original submission. The label they submitted reflected adjustments in their desired mode of administration to decrease adverse events.
- Followed abnormal lab results after the last visit until normalization.
- Submitted Phase 1 and phase 2 data in as complete fashion as possible

10 Appendices

10.1 A Efficacy Evaluation of BLI800 Oral Sulfate versus MoviPrep® as Same Day Dose Bowel Cleansing Preparations in Adult Subjects: Protocol BLI-800-301

This section will review the efficacy study design and results for BLI800 Study 301 compared to MoviPrep in adult patients utilizing the bowel preparation before colonoscopy.

10.1.1 Study Design

Study BLI800-301 (Study 301) was a Phase 3, randomized (1:1), endoscopist single-blind, parallel-group, non-inferiority, efficacy clinical trial of BLI800 compared to MoviPrep® in approximately 400 male and female adults patients in 11 sites who underwent routine and diagnostic colonoscopy. BLI800 (Suprep) or MoviPrep were administered orally as a same day dose. Two doses each of a 6 ounce bottle of oral sulfate solution was given as a bowel preparation (bowel prep) on the day of colonoscopy. Subject participation in this study may last up to 60 days. A screening visit (Visit 1) should be performed within 15 days of the colonoscopy. Follow-up (Visit 3) was at 30 days post-colonoscopy.

10.1.2 Study Objectives

The primary objective of the study was to determine the effectiveness of BLI800 compared to Moviprep as a bowel preparation in adult patients undergoing routine colonoscopy. The secondary objective was to determine the safety and tolerability of BLI800 compared to Moviprep patients.

10.1.3 Patient Population

Inclusion Criteria
Adult male and female patients, ages 18 years and older, were included if they were undergoing colonoscopy for routine indications or for follow-up of barium enema results, gastrointestinal bleed, anemia of unknown etiology, cancer surveillance, endosonography, inflammatory bowel disease (IBD), unknown etiology of diarrhea or constipation, polypectomy, laser therapy or routine screening. Patients must have:

- If female, and of child-bearing potential, used acceptable form of birth control such as hormonal birth control, IUD, double-barrier method, depot contraception, abstinence or vasectomized spouse.
- Had negative urine pregnancy test at screening.
- Been mentally competent to provide informed consent for participation.

Exclusion Criteria
Patients were excluded for any one of the following reasons:

- Known or suspected ileus, severe ulcerative colitis, gastrointestinal (GI) obstruction, gastric retention, bowel perforation, toxic colitis, or megacolon.
- Predisposed to aspiration based on impaired consciousness.
- Undergoing colonoscopy for foreign body removal/decompression.
- Patients with clinically significant electrolyte abnormalities on Visit 1 labs (↓K+, ↑↓Na+, ↓Ca+, ↑phosphate, dehydration or those secondary to use of diuretics or angiotensin converting enzyme inhibitors)
  Reviewer's comment: Protocol did not have specific ranges for the electrolyte abnormalities. Applicant reported 2.5 ULN in safety data as abnormal.
- Patients with phenylketonuria, history of renal or hepatic insufficiency, history of CHF, previous GI surgeries, or G-6-PD deficiency.
- Subjects who are pregnant or lactating or intend to become pregnant.
- Subjects of childbearing potential who refuse a pregnancy test.
- Subjects allergic to BLI800: sodium sulfate, potassium sulfate, magnesium sulfate and sucralose or to Moviprep: polyethylene glycol, sodium sulfate, sodium chloride, potassium chloride, ascorbic acid, sodium ascorbate, aspartame and acesulfame potassium.
- Subjects determined by Investigator to not be suitable for any reason.
- Subject in another investigational study, an investigational study within the last 30 days.

10.1.4 Treatment Plan

Randomization and Controls

During the baseline visit, patients who met the inclusion and exclusion criteria were randomized to receive BLI800 or Moviprep. The lowest drug kit number available at that site will be dispensed and all patients will be randomized in a 1:1 ratio of 180 patients in each treatment arm. Each site had balanced BLI800 and MoviPrep patients with no intentional stratification at site, for high risk patients with cardiac, diabetes or renal disease, geriatric patients older than 65 years. This was a single-blind study where the colonoscopist would not perform randomization, drug dispensing, drug return, and accountability. There were some blinded study personnel—who exactly was blinded was not designated. Failure to maintain blinding was considered a protocol violation. The patients were not blinded. Patients were not to discuss their study drug with any staff member and if staff did not remain blinded, a protocol violation would be cited.

Dietary Restrictions

Subjects are instructed to have a light breakfast, a clear liquid lunch (no red and purple liquids, milk or alcoholic drinks are allowed) on the day prior to colonoscopy. The subject will self-administer the first dose of the bowel prep the day before the colonoscopy at approximately 6 pm. The contents of one 6 ounce bottle of BLI800 will be poured into a mixing cup that is then filled to the 16 ounce fill line with water and completely ingested. This is followed by two 16 ounce cups of water ingested within the next hour. At approximately 6:00 am the following day, 10 to 12 hours after the first dose, the second dose and post-dose water intake must be completed one hour prior to colonoscopy. Subjects will consume only clear liquids from the time of BLI800 ingestion until after the colonoscopy is completed.

Moviprep® (Salix Pharmaceuticals, Inc.) has a clinical label with a caution statement, study code, study Applicant, address, and kit number attached. All subjects received the lemon flavored.

This was dispensed in its marketed package which consists of a total of 4 pouches (2 of Pouch A, 2 of pouch B) re-constituted to a total of 2 L. One Pouch A is combined with one pouch B in an enclosed container followed by 1 liter lukewarm water for the total combined two dose regimen. The preparation should be completely dissolved and may be refrigerated prior to drinking and used within 24 hours. Instructions are according to approved labeling. Subjects will have a normal breakfast, a light lunch and clear soup and/or plain yogurt for dinner on the evening before colonoscopy.

Dinner should be consumed at least one hour prior to the start of Moviprep. At approximately 6 pm the first liter of the solution will be ingested at a rate of 8 ounces every 15 minutes until finished, followed by half a liter of clear liquid (approximately 16 ounces). At approximately 6 AM the day of colonoscopy, the second liter of Moviprep will be ingested at the same rate followed by half a liter of liquid at least one hour prior to the colonoscopy. No solid foods will be taken once Moviprep is begun until after the colonoscopy.

10.1.5 Study Visits and Procedure

1) During Visit 1 (Baseline visit) patients were given instructions on use of medication. The patients self-administered the study drug according dose instructions. Patients returned the used preparation components on Visit 2 (Day of Colonoscopy visit). See Section 8.1 for dietary restrictions and dosing regimen.

The unblinded staff will perform drug accountability on all drug supplies returned to the site on the day of colonoscopy. They will measure the remaining amount of liquid in the Moviprep bottle, and assess the number of BLI800 bottles used. There were no mandatory or prohibited medications, only dietary requirements.

At Visit 1 (or before Visit 2) a signed consent was obtained following the informed consent process. Medical history and vital signs were obtained and a physical exam performed. *Reviewer's Comments: The protocol does not specify the exact time this will be done.* Concomitant medications used were obtained. Serum chemistry, hematology and sulfate blood work were to be done. A urine pregnancy test will be done on appropriate female patients. If patients have clinically significant electrolyte abnormalities, the investigator can determine if this will be the basis of discontinuation from the study after the baseline visit. Those who were discontinued were contacted after the labs were reviewed by the investigator and patients were to return the unopened bowel prep and were classified as "screen failures".
Reviewer's Comments: Though it does not explicitly state that patients received medications at Visit 1, it does state that if patients were told to discontinue from the study that they return the study drug. These patients were not randomized by the Applicant even though they had been given a study drug that they didn't ingest.
Serum laboratory samples for hematology and chemistry will be tested at the central laboratory. *Reviewer's comments: From the study results and the submitted CRF, serum sulfates were never tested. Another lab* (b) (4) *ran results seen in the CRFs for serum osmolality.*

2) At Visit 2, subjects returned the Treatment Questionnaire that was reviewed for completeness and, if needed, completed with staff. On Visit 2, a 30-day follow-up appointment was scheduled. *Reviewer's Comments: On Visit 2, patients attempted to return to the site within 14 days, to obtain the colonoscopy following completion of the second dose of drug. If they did not return within 14 days, they would not be considered protocol violators.* (Please note that in Study 301, the subject's second dose is given 1 to 3 hours after completing the first dose on the Day before colonoscopy.

Symptom Scales that reported overall experience were to be filled out prior to colonoscopy. Vital signs and a physical exam will be performed. Any changes in concomitant medications and occurrence of adverse events will be obtained. Serum chemistry, hematology and sulfate blood work will be done. Subjects were dropped for illness interfering with visits, investigator determination or withdrawal by subject. *Reviewer's Comments: See Section 7.1.3 regarding Dropouts.*

3) Visit 3 was a follow-up visit to assess safety AE's and have chemistry and hematology tests performed. They were expected to occur between 25 and 45 days following colonoscopy, and visits occurring outside this window were not considered protocol violations. *Reviewer's Comments: The Special Protocol Assessments stated that this timeframe did not have to be strictly followed.*

The 3 study visits and one colonoscopy procedure are summarized in the following table (table from Applicant's submission Module 5, Volume 6.2, Tab 5.3.5.1B, 16.1.1).

Table 42: Study 301 Visits and Procedures

Procedures	Visit 1	Day Before Endo-scope	Visit 2 Day of Endo-scope	Visit 3 30 Day F/U
Informed Consent	x			
Inclusion/Exclusion Criteria Review	x			
Medical History	x			
Physical Exam	x		x	
Concomitant Med Review	x		x	
Chemistry/Hematology Lab work	x		x	x
Urine Pregnancy Test (if applicable)	x			
Randomization	x			
Drug dispensed	x			
Subject Instructed	x			
Subject's First Dose		x		
Subject's Second Dose		x		
Treatment Questionnaire		x	x	
Symptom Scale			x	
Review of Subject Questionnaires			x	
Drug Accountability			x	
Perform Colonoscopy			x	
Assess Safety			x	x

Since 30 days has been identified as the critical time point for renal assessment for complications in oral phosphate cleansers, a third serum level for chemistry and hematology will be drawn at Visit 3. This will be drawn on all patients regardless of whether they completed the study. Occurrence of adverse events will also be done. Patients will report the onset of treatment for

serious adverse events following the colonoscopy and report AE's that were still ongoing at the time of study completion.

10.1.6 Concomitant Medications

Entry criteria did not restrict any use of any concomitant medications and no consistent medication regimens were noted except that sedatives, anxiolytics, analgesics used for the colonoscopy itself are listed as concomitant medications.
Concomitant medications would be recorded for 7 days prior to screening until Visit 2 and varied only in instances when adverse events required treatment (also considered concomitant medication). The differences in dietary requirements are again noted. Food violations are noted in the following section.

10.1.7 Compliance with Study Medication

Since patients were allowed to take any concomitant medications, there were no medication violations. See below for food violations. One patient was considered non-compliant in the MoviPrep group. Some patients were described as being non-compliant to the study protocol. See Disposition table.

10.1.8 Protocol Deviations and Violations

From the Treatment Questionnaire, there were 26 food violations in the BLI800 treatment group or 6.7% and 28 food violations in the MoviPrep group or 7.6%. Specifics of the violations were not described in the electronic datasets since the results reflected binary outcomes.
The following questions were asked:

1. Record the date that you took the first dose of preparation.
2. What time did you take the first dose of preparation?
3. Record the date that you took the second dose of preparation.
4. What time did you take the second dose of preparation?
5. Record what you eat on the day of your preparation and specify time.

Reviewer's Comments: In Applicant submission, two sections in Module 5 Volumes 9.3 and 10.3 (both Tab 16.2.21) state that times outside the window of follow-up and between Visit 1 and visit 2 are protocol violations, yet in the SPA these are deemed non-protocol violations.

10.1.9 Primary Endpoints

The primary endpoint measured the efficacy of BLI800 compared to Moviprep® in producing clinically adequate bowel prep for colonoscopy. The adequacy and the quality of the bowel prep were measured visually by the endoscopist according to the following scale. The colonoscopist was asked to rate the quality of the bowel preparation based on the colon cleansing scores that are summarized in the following table 43 (electronically copied from the Applicant's submission, Module 5, Volume 6.2, Tab 5.3.5.1B, 16.1.1, p. 19).

Table 43: Colon Cleansing Scores

Score	Grade	Description
1	Poor	Large amounts of fecal residue, additional cleansing required
2	Fair	Enough feces or fluid to prevent a completely reliable exam
3	Good	Small amounts of feces or fluid not interfering with exam
4	Excellent	No more than small bits of adherent feces/fluid

Scores of grades 1 or 2 were considered as treatment failures, and scores of grades 3 or 4 were considered to be successes. According to the primary endpoint based on a binary outcome of success or failure, it was defined as failure if the following occurred:

1. Bowel cleansing grade of poor=1 or fair=2
2. Patient did not have an adequate bowel prep for colonoscopy as determined by investigator as insufficient fecal output, unclear fecal discharge or due to preparation AE
3. Patient did not have adequate cleansing for evaluation

10.1.10 Secondary Efficacy Endpoints

As a secondary endpoint, each colonoscopist was also asked to rate whether or not the bowel preparation was adequate or inadequate in a binary outcome measure.
If the bowel prep was rated as inadequate, the need for repeat bowel preparation was noted.

10.1.11 Statistical considerations

The statistical considerations for efficacy for Study 301, involve adequate cleansing and quality of successful cleansing as determined by colonoscopist assessments on a poor=1 to excellent=4 rating as primary analysis that included the ITT group only and not all randomized patients. Subjects who completely or partially took study drug, but, did not have a colonoscopy due to reasons unrelated to the prep were not originally included in the primary and secondary efficacy analysis and were included only in the safety analysis (IR #14 of 6/12/09 included all randomized patients).

Both studies included several defined groups in their original submission:
Screen Failures in Study 301 included 8 patients identified as "did not meet criteria" (five patients) or "withdrew consent" (3 patients). None of these 8 patients were dispensed medications. They provided informed consent but did not complete screening procedures because they either withdrew consent or were found ineligible during the visit.
Intention to treat (ITT) population included randomized patients who took the study drug and either completed and did not complete the protocol. The **True ITT** that had to be re-calculated for Study 301 and included all randomized patients who were assigned a study treatment.

Completed patients are ones who ingests BLI800 and has a colonoscopy. A **Non-Completer** was one who did not have a colonoscopy.
Discontinued patients could include patients lost to follow-up, non-completers, non-compliant to medication or protocol, adverse events, withdrew consent, non-evaluable, or did not meet criteria.

For Study BLI800-301, the Applicant proposed the15% of non-inferiority marginal without any justification. A more detailed justification on the selection of non-inferiority margin of 15% was requested at the prior March 23, 2007 and provided in IR of 11/21/08.
If the assumed expected event for the control was larger (e.g. 90% or more), the non-inferiority margin should be tightened. The margin would be much less than 15%.

If no colonoscopy was done due to poor prep or if there were prep related adverse events then the patient was considered a failure rating. All patients were determined by the colonoscopist as success or failure which was then analyzed as the primary efficacy endpoint and tested sequentially in a hierarchical structure with the first test being a non-inferiority test based upon the D=P1-P2. Using the Null hypothesis HO: P1-P2<=D0 versus H1: P1-P2=D1>D0. P1 is Bli800 group and P2 is Moviprep group and D0 is the acceptable margin of equivalence to an absolute margin of 15%. The 15% margin was established as an acceptable non-inferiority margin for Braintree's prior applications of HalfLytely, NDA 19-797; NuLytely, NDA 21-551) and other products. [2,3]

Subjects who completely or partially took study drug but did not have a colonoscopy due to reasons unrelated to the prep were not included in the primary and secondary efficacy analysis but, along with all other subjects, were included in the safety analysis.
This reviewer agrees with comments from Dr. Milton Fan, Statistician, whose review included concern about "biocreep" that may have resulted from comparison of MoviPrep as it was compared to a standard regimen of Golytely (PEG+E) that was used in prior approval studies. The success rate of effective gut cleansing was 88.9% in the MoviPrep group compared with 94.8% in the Golytely (PEG+E) group. This resulted in a difference of -5.9% in favor of Golytely with a lower bound of 95% confidence interval of -12.0%. The Applicant did not justify the non-inferiority margin when requested on multiple requests (pre-NDA, NDA, and SPA meetings) and sent in an IR of 11/08 based on a historical non-inferiority margins used in other marketed products. Their choice of a 15 % margin implies that as much as a 20.5% relative decrease of assumed expect event rate of 73% might occur in patients prepared with BLI800. In Study 301, if we were to choose a 10% relative decrease as the worse acceptable case scenario, then there would be a 5% chance of the worst case and the margin would be 7% which the Applicant's results falls within.

10.1.12 Protocol Amendments

No protocol amendments were submitted after the initial submission.

10.1.13 Patient Disposition

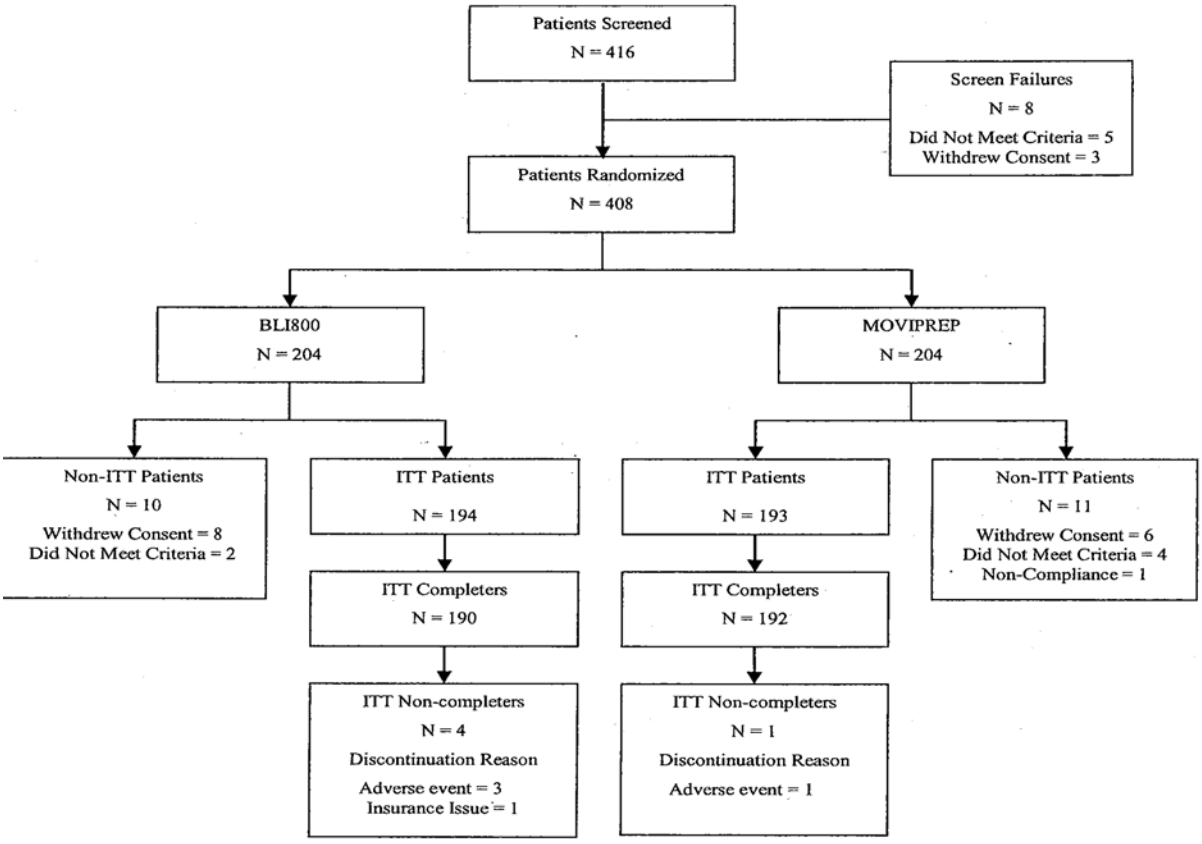
The study was conducted at ten centers with 416 screened patients and 408 randomized patients who were dispensed medication. The screen failures included patients who did not meet criteria and those who withdrew consent. There were no notable differences between the screen failures

and withdrawals as compared with the randomized patients. In each group there were 204 patients. Of these patients, the Applicant subdivided the patients into Non-ITT and ITT patients that incorporated Completers and Non-completers (see Figure 2: Patient Disposition Taken from Module 5, Volume 5.1 tab 5.3.5.1.A page 27.)

Successful completers were defined as: compliance with study-related procedures, considered part of ITT, compliance with taking the medication under the protocol. A "completed" subject is one who ingests BLI800 and has a colonoscopy. Any of the following were not included: screen failures before randomization, those who did not take study medication were not included in the ITT group, those who withdrew for consent, did not meet criteria, were lost to follow-up, or had discontinuation (insurance issue, adverse event). All except one was considered non-ITT (therefore not completing protocol) or a non-completer patient. S*ee section on "Overall Profile of Drop outs"*

Table 44: Patient Disposition for Study 301

Figure 2: Patient Disposition



Reviewer's Comments: Upon inclusion of the true ITT patients the Applicant ITT number increased from 387 to 408 patients.

Table 45: Demographics (Complied by Milton Fan)

Table 1 Summary of Demographic and Baseline Characteristics --- Protocol BL800-301

All Randomized Patients

Characteristics	BL800 (N=204)	MoviPrep (N=204)	Between Treatment p-value
Sex			
Male	90 (44.1%)	94 (46.1%)	0.6906
Female	114 (55.9%)	110 (53.9%)	
Race			
N	202	203	0.5341
White	178 (88.1%)	178 (87.7%)	
Black	22 (10.9%)	25 (12.3%)	
Asian	1 (0.5%)	0 (0.0%)	
Other Races	1 (0.5%)	0 (0.2%)	
Age (yr)			0.6622
Mean (SD)	57.7 (10.9)	57.2 (11.9)	
Age			1.000
<65	150 (73.5%)	150 (73.5%)	
≥65	54 (26.5%)	54 (26.5%)	
High Risk			0.0375
Yes	88 (43.1%)	109 (53.4%)	
No	116 (56.9%)	95 (46.6%)	

Compiled by this reviewer
P-values were computed by this reviewer.
P-value for categorical data was obtained using Chi-square test.
P-value for continuous data was obtained using t-test.

Age is calculated as DOB from screening visit, Percentage of race does not equal 100% since Hispanic or Latino patients may not have reported a race.

There were more females (54%) than males (46%) in the study population, although they were evenly distributed between the two treatment groups. Likewise the two groups were similar in age, race and weight. Fifty-five years was the average age with 81 ITT patients age 65 or older and 23 patients 75years of age or older. Eighty–six percent were Caucasian and 9% were African American. The average weight was about 184 pounds.

Indications for the procedure included routine screening for colorectal cancer, follow-up of colonic polyps, gastrointestinal bleeds, and other radiologic procedures.

10.1.14 Primary Efficacy Results

Primary Efficacy Endpoints Results

Applicant's results of the primary efficacy endpoints show about an 8% improvement over the cleansing with MoviPrep for the 4 or "excellent" score. MoviPrep is about 5% better for the 3 or "good" score.

Table 46: Preparation efficacy results

Preparation Cleansing Score		
	BLI800 n=194 (%)	MoviPrep n=193 (%)
4	86 (44.6%)	72 (37.3%)
3	73 (37.8%)	83 (43%)
2	22 (11.4%)	31 (16.1%)
1	9 (4.7%)	6 (3.1%)
mean	3.25	3.15

Applicant's table from Module 5, Volume 5.1, page 30

Updated Preparation efficacy results based on IR #14 of 6/12/09

Preparation Cleansing Score		
	BLI800 n=204 (%)	MoviPrep n=204 (%)
4	86 (42.2%)	72 (35.3%)
3	73 (35.8%)	83 (40.7%)
2	22 (10.8%)	31 (15.2%)
1	9 (4.4%)	6 (2.9%)

Applicant concludes that BLI800 has more "excellent" scores. The mean average cleansing score was consistent with other colonic cleansers especially 4L preparations. Combining the scores for 3 and 4 composed the "successful" versus "failure" group and resulted in very little difference in responder analysis by geographic area on a site by site basis. (See Module 5, 5.1, page 33)

Table 47: Successful Preparations Per Applicant ITT Analysis: Study-301 Applicant's ITT

Copied from Table 301-5, Milton Fan's Review

Treatment	Rate	Diff (BLI800 – MoviPrep)	95% C.I.
BLI800	159/194 (82.0%)	1.6%	(-5.7%, 9.8%)
MoviPrep	155/193 (80.3%)		

Table 48: Study-301 Number and Percent Successful Preparations Per True ITT (See prior definition of True ITT in Statistical Section)

The table shows less favorable results of 77.9% and 76.0% as opposed to 82% and 80% "successful" for BLI800 and MoviPrep respectively.

Compiled by Milton Fan.

Treatment	Rate	Diff (BLI800 – MoviPrep)	95% C.I.
BLI800	159/204 (77.9%)	1.9%	(-6.2%, 10.1%)
MoviPrep	155/204 (76.0%)		

Reviewer's Comments: Applicant subsequently sent in these efficacy results in IR #14 of 6/12/09.

10.1.15 Secondary Efficacy Results

For the secondary efficacy results of Study 301, colonoscopists were asked on a colonoscopy exam form "Was cleansing adequate for evaluation" and most were considered by the endoscopist as adequate. Grades of "2" and "1" both were sometimes rated adequate. These were included in the ITT and considered a completed study. Thirteen patients who were designated as inadequate were noted to need a repeat prep (9 in the MoviPrep group and 4 in the BLI800 group)

Table 49: Secondary Efficacy Endpoint for Study 301: Number and Percent of Adequate Preparations (per sponsor ITT)

	BLI800 n (%)	**MoviPrep n (%)**	**95% CI[1]**	**P**
Adequate?[2] (n)	190	192		
Yes	178 (94%)	182 (95%)	-5.8, 3.6	0.667
No	12 (6%)	10 (5%)		

(1) Confidence interval (CI) for the difference between treatments was by Chi-Square Test.
(2) Patients 02032, 05034, 07029, 10011 and 10038 are not included because they did not undergo colonoscopy.
(reference table 14.2.3 in Section 14)

Table 50: Number and Percent of Adequate Preparations: Study-301 True ITT Analysis
Compiled by Milton Fan

Treatment	Rate	Diff (BLI800 – MoviPrep)	95% C.I.
BLI800	178/204 (87.3%)	-2.0%	(-8.2%, 4.3%)
MoviPrep	182/204 (89.2%)		

Study 301, the true ITT was recalculated and resulted in slightly lower efficacy results in the efficacy comparisons were different for the dietary requirements. Other flaws in the study design included food protocol violations, unconfirmed colonoscopy cleansing and adequacy scores for efficacy.

In sub-populations based on gender, race, geographic region, and age the following Applicant reported no difference in efficacy success in females of 79% for BLI800 and 81% for MoviPrep. More males were successful with BLI800 at 87% than with MoviPrep at 80% although it is not statistically significant. In the >65 years age group, BLI800 had a success rate of 86% compared to MoviPrep at 73%. Overall the >65 years age group using BLI800 had greater success rates at 86% compared to the < 65 year age group with a 81% success rate. The >65 year age group using MoviPrep had a decrease of about 10% compared to the <65 year age group. No statistically significantly differences were noted between races and between sites (1 to 10, 21). Table 51: Sub-Populations and Primary efficacy Response
Number and percent of Successful Preparations

Table 301-5
Primary Efficacy Responder Analysis
Number and Percent of Successful Preparations

Responder[1]	BLI800 n (%)	MoviPrep n (%)	95% CI[2]	p[3]	p[4]
All Patients (n)	194	193			
Success	159 (82.4%)	155 (80.3%)	-5.7, 9.8	0.614	**<0.001**
Fail	34 (17.6%)	38 (19.7%)			
Elderly (≥65 y)	50	48			
Success	43 (86.0%)	35 (72.9%)	-2.7, 28.9	0.073	-
Fail	7 (14.0%)	13 (27.1%)			
Males	84	89			
Success	73 (86.9%)	71 (79.8%)	-3.9, 18.2	0.246	-
Fail	11 (13.1%)	18 (20.2%)			
Females	109	104			
Success	86 (78.9%)	84 (80.8%)	-12.6, 8.9	0.893	-
Fail	23 (21.1%)	20 (19.2%)			

(1) A successful treatment is defined as bowel cleansing graded either excellent or good by the blinded colonoscopist (grading score = 3 or 4).
(2) Confidence interval (CI) for the difference between treatments was by Chi-Square Test.
(3) P-value for the difference between treatments is from a Cochran-Mantel-Haenzsel Chi-Square, controlling for site.
(4) P-value for the non-inferiority hypothesis using an equivalence margin of 15 percent

The Applicant concluded that the efficacy of the same day preparation of BLI800 is equivalent to the same day preparation of MoviPrep.

Results from subgroup analyses of primary efficacy endpoint by gender, age, and site are given below for true ITT analysis. In this true analysis, patients with missing data were considered "failures".

Table 51: Number and Percent of Successful Preparations :Protocol BLI800-301 (True ITT Analysis**)** Compiled by Milton Fan

Subgroup	BLI800	MoviPrep	Diff	95% CI
Gender				
Male	73/90 (81.1%)	71/94 (75.5%)	5.6%	(-6.3%, 17.4%)
Female	86/114 (75.4%)	84/110 (76.4%)	-0.9%	(-12.1%, 10.3%)
Age (yrs)				
< 65	116/150 (77.3%)		120/150 (80.0%)	-2.7% (-11.9%, 6.6%)
≥ 65	43/54 (79.6%)	35/54 (64.8%)	14.8%	(-1.9%, 31.5%)
Site				
1	16/23 (69.6%)	17/24 (70.8%)	1.3%	(-27.4%, 24.9%)
2	16/20 (80.0%)	18/20 (90.0%)	-10.0%	(-31.9%, 11.9%)
3	28/38 (73.7%)	23/37 (62.2%)	11.5%	(-9.5%, 32.5%)
4	17/20 (85.0%)	15/20 (75.0%)	10.0%	(-14.6%, 34.6%)
5	15/18 (83.3%)	14/18 (77.8%)	5.6%	(-20.2%, 31.4%)
6	1/2 (50.0%)	1/2 (50.0%)	0.0%	(-98.0%, 98.0%)
7	14/24 (58.3%)	17/24 (70.8%)	-12.5%	(-39.3%, 14.3%)
8	1/3 (33.3%)	2/3 (66.7%)	-33.3%	(-100.0%, 42.1%)
9	26/27/ (96.3%)	22/26 (84.6%)	11.7%	(-3.9%, 27.3%)
10	24/27 (88.9%)	24/28 (85.7%)	3.2%	(-14.4%, 20.7%)
11	1/2 (50.0%)	2/2 (100.0%)	-50.0%	(-100.0%, 19.3%)

As seen from above, treatment differences were consistent among subgroups of gender and age. Note correction for site 11 is site 21.

10.1.16 Summary and Conclusions for Study 301 with Comments on Safety

Applicant's results of the primary efficacy endpoints show about a 1.9% improvement over the cleansing with MoviPrep for the successful preps. In the 4 or "excellent" score category Suprep was about 7% better than MoviPrep. But, for the 3 or "good" score Suprep was about 5% worse than Moviprep. Applicant states these results are consistent with other approved preparation cleaning scores. When ratings were consolidated into a "success" versus "failure" score the two preparations showed no difference. The Applicant concludes that BLI800 and MoviPrep have similar preparation success which is better than other reported colonic preparation. The mean average cleansing score was consistent with other colonic cleansers especially 4L preparations. Combining the scores for 3 and 4 and sub grouping this "successful" versus "failure" group resulted in very little difference in responder analysis by geographic area on a site by site basis. (See Module 5, 5.1, page 33). This efficacy rates for the same day regimen was not as high as for the split day dose regimen for both Suprep and Moviprep.

In the labeling for Moviprep, under "Information for patients" it states that "Patients may have clear soup and/or plain yogurt for dinner, finishing the meal at least one hour prior to the start of Moviprep treatment. No solid food should be taken from the start of Moviprep treatment until after the colonoscopy". In the two treatments groups, patients had different type of meals. Patients who received MoviPrep were allowed to eat a full breakfast, a light lunch, and a clear liquid dinner; in contrast, patients who received Suprep were instructed not to eat a light breakfast and clear liquids afterwards until the day of the colonoscopy. It is inevitable that the amount of food and the type of solid food before the colonoscopy can influence the efficacy of colon cleansing. Since Moviprep is the comparator product for BLI800 and the same issue of incomparable dietary requirements arises for the comparator as when Moviprep was reviewed for its NDA approval. The Applicant should have considered the impact of the different dietary requirements in their assertion of superiority and in their study design.

10.2 Study BLI800-302 (Study 302) Efficacy Review

10.2.1 Study Design

The pivotal study BLI800-302 (Study 302) was a Phase 3, randomized (1:1), endoscopist single-blind, parallel-group, non-inferiority, efficacy clinical trial of BLI800 compared to MoviPrep® in approximately 400 male and female adults patients in 11 sites who were undergoing routine and diagnostic colonoscopy. BLI800 (Suprep) or MoviPrep were administered orally as a given in the evening then repeated in the AM.
Two doses each of a 6 ounce bottle of oral sulfate solution was given as a bowel preparation (bowel prep) on the day of colonoscopy. Subject participation in this study may last up to 60 days. A screening visit (Visit 1) was performed within 15 days of the colonoscopy. Follow-up (Visit 3) was at 30 days post-colonoscopy.

10.2.2 Study Objectives

The primary objective of the study was to determine the effectiveness of BLI800 compared to Moviprep as a bowel preparation in adult patients undergoing routine colonoscopy. The secondary objective was to determine the safety and tolerability of BLI800 compared to Moviprep.

10.2.3 Patient Population

Inclusion Criteria
Adult male and female patients, ages 18 years and older, were included if they were undergoing colonoscopy for routine indications or for follow-up of barium enema results, gastrointestinal bleed, anemia of unknown etiology, cancer surveillance, endosonography, inflammatory bowel disease (IBD), unknown etiology of diarrhea or constipation, polypectomy, laser therapy or routine screening. Patients must have:

- If female, and of child-bearing potential, used acceptable form of birth control such as hormonal birth control, IUD, double-barrier method, depot contraception, abstinence or vasectomized spouse.
- Had negative urine pregnancy test at screening.
- Be mentally competent to provide informed consent for participation.

Exclusion Criteria

Patients were excluded for any one of the following reasons:

- Known or suspected ileus, severe ulcerative colitis, gastrointestinal (GI) obstruction, gastric retention, bowel perforation, toxic colitis, or megacolon.
- Predisposed to aspiration based on impaired consciousness.
- Undergoing colonoscopy for foreign body removal/decompression.
- Patients with clinically significant electrolyte abnormalities on Visit 1 labs (↓K+, ↑↓Na+, ↓Ca+, ↑phosphate, dehydration or those secondary to use of diuretics or angiotensin converting enzyme inhibitors)
  Reviewer's comment: Protocol did not have specific ranges for the electrolyte abnormalities. Applicant reported 2.5 ULN in safety data as abnormal.
- Patients with phenylketonuria, history of renal or hepatic insufficiency, history of CHF, previous GI surgeries, or G-6-PD deficiency.
- Subjects who are pregnant or lactating or intend to become pregnant.
- Subjects of childbearing potential who refuse a pregnancy test.
- Subjects allergic to BLI800: sodium sulfate, potassium sulfate, magnesium sulfate and sucralose or to Moviprep: polyethylene glycol, sodium sulfate, sodium chloride, potassium chloride, ascorbic acid, sodium ascorbate, aspartame and acesulfame potassium.
- Subjects determined by Investigator to not be suitable for any reason.
- Subject in another investigational study, an investigational study within the last 30 days.

10.2.4 Treatment Plan

Randomization and Controls

During the baseline visit, patients who met the inclusion and exclusion criteria were randomized to receive BLI800 or Moviprep. The lowest drug kit number available at that site will be dispensed and all patients will be randomized in a 1:1 ratio of 180 patients in each treatment arm. Each site had balanced BLI800 and MoviPrep patients with no intentional stratification at site, for high risk patients with cardiac, diabetes or renal disease, geriatric patients older than 65 years. This was a single-blind study where the colonoscopist would not perform randomization, drug dispensing, drug return, and accountability. There were some blinded study personnel--who was blinded was not designated. Failure to maintain blinding was considered a protocol violation. The patients were not blinded. Patients were not to discuss their study drug with any staff member and if staff did not remain blinded, a protocol violation would be cited.

Dietary Restrictions

Subjects are instructed to have a light breakfast, a clear liquid lunch (no red and purple liquids, milk or alcoholic drinks are allowed) on the day prior to colonoscopy. The subject will self-

administer the first dose of the bowel prep the day before the colonoscopy at approximately 6 pm. The contents of one 6 ounce bottle of BLI800 will be poured into a mixing cup that is then filled to the 16 ounce fill line with water and completely ingested. This is followed by two 16 ounce cups of water ingested within the next hour. At approximately 6:00 am the following day, 10 to 12 hours after the first dose, the second dose and post-dose water intake must be completed one hour prior to colonoscopy. Subjects will consume only clear liquids from the time of BLI800 ingestion until after the colonoscopy is completed.

Moviprep® (Salix Pharmaceuticals, Inc.) had a clinical label with a caution statement, study code, study Applicant, address, and kit number attached. All subjects received the lemon flavored.

This was dispensed in its marketed package which consists of a total of 4 pouches (2 of Pouch A, 2 of pouch B) re-constituted to a total of 2 L. One Pouch A is combined with one pouch B in an enclosed container followed by 1 liter lukewarm water for the total combined two dose regimen. The preparation should be completely dissolved and may be refrigerated prior to drinking and used within 24 hours. Instructions are according to approved labeling. Subjects will have a normal breakfast, a light lunch and clear soup and/or plain yogurt for dinner on the evening before colonoscopy.

Dinner should be consumed at least one hour prior to the start of Moviprep. At approximately 6 pm the first liter of the solution will be ingested at a rate of 8 ounces every 15 minutes until finished, followed by half a liter of clear liquid (approximately 16 ounces). At approximately 6 AM the day of colonoscopy, the second liter of Moviprep will be ingested at the same rate followed by half a liter of liquid at least one hour prior to the colonoscopy. No solid foods will be taken once Moviprep is begun until after the colonoscopy.

10.2.5 Study Visits and Procedures

1) During Visit 1 (Baseline visit) patients were given instructions on use of medication. The patients self-administered the study drug according dose instructions. Patients returned the used preparation components on Visit 2 (Day of Colonoscopy visit). See Section 8.1 for dietary restrictions and dosing regimen.

The unblinded staff will perform drug accountability on all drug supplies returned to the site on the day of colonoscopy. They will measure the remaining amount of liquid in the Moviprep bottle, and assess the number of BLI800 bottles used. There were no mandatory or prohibited medications, only dietary requirements.

At Visit 1 (or before Visit 2) a signed consent was obtained following the informed consent process. Medical history and vital signs were obtained and a physical exam performed. *Reviewer's Comments: The protocol does not specify the exact time this will be done.* Concomitant medications used were obtained. Serum chemistry, hematology and sulfate blood work were to be done. A urine pregnancy test will be done on appropriate female patients. If patients have clinically significant electrolyte abnormalities, the investigator can determine if this will be the basis of discontinuation from the study after the baseline visit. Those who were discontinued were contacted after the labs were reviewed by the investigator and patients were to return the unopened bowel prep and were classified as "screen failures".
Reviewer's Comments: Though it does not explicitly state that patients received medications at Visit 1, it does state that if patients were told to discontinue from the study that they return the

study drug. These patients were not randomized by the Applicant even though they had been given a study drug that they didn't ingest.
Serum laboratory samples for hematology and chemistry will be tested at the central laboratory. *Reviewer's comments: From the study results and the submitted CRF, serum sulfates were never tested. Another lab* (b) (4) *ran results seen in the CRF's for serum osmolality.*

2) At Visit 2, subjects returned the Treatment Questionnaire that was reviewed for completeness and, if needed, completed with staff. On Visit 2, a 30-day follow-up appointment was scheduled. *Reviewer's Comments: On Visit 2, patients attempted to return to the site within 14 days, to obtain the colonoscopy following completion of the second dose of drug. If they did not return within 14 days, they would not be considered protocol violators.* (Please note that in Study 301, the subject's second dose is given 1 to 3 hours after completing the first dose on the Day before colonoscopy).

Symptom Scales that reported overall experience were to be filled out prior to colonoscopy. Vital signs and a physical exam will be performed. Any changes in concomitant medications and occurrence of adverse events will be obtained. Serum chemistry, hematology and sulfate blood work will be done. Subjects were dropped for illness interfering with visits, investigator determination or withdrawal by subject. *Reviewer's Comments: See Section 7.1.3 regarding Dropouts*

3) On Visit 3 was a follow-up visit to assess safety AE's and have chemistry and hematology tests performed. They were expected to occur between 25 and 45 days following colonoscopy, and visits occurring outside this window were not considered protocol violations. *Reviewer's Comments: The Special Protocol Assessments stated that this timeframe did not have to be strictly followed.*

The 3 study visits and one colonoscopy procedure are summarized in the following table (table from Applicant's submission Module 5, Volume 6.2, Tab 5.3.5.1B, 16.1.1).

Table 52: Study 302 Visits and Procedures

Procedures	Visit 1	Day Before Endo-scope	Visit 2 Day of Endo-scope	Visit 3 30 Day F/U
Informed Consent	x			
Inclusion/Exclusion Criteria Review	x			
Medical History	x			
Physical Exam	x		x	
Concomitant Med Review	x		x	
Chemistry/Hematology Lab work	x		x	x
Urine Pregnancy Test (if applicable)	x			
Randomization	x			
Drug dispensed	x			
Subject Instructed	x			
Subject's First Dose		x		
Subject's Second Dose			x	
Treatment Questionnaire		x	x	
Symptom Scale			x	
Review of Subject Questionnaires			x	
Drug Accountability			x	
Perform Colonoscopy			x	
Assess Safety			x	x

Table from Applicant Module5, Volume 6.2, Tab 5.3.5.1B, 16.1.1

10.2.6 Concomitant Medications and Medication Dispensing and Compliance

Entry criteria did not restrict any use of any concomitant medications and no consistent medication regimens were noted except that sedatives, anxiolytics, analgesics used for the colonoscopy itself are listed as concomitant medications.
Concomitant medications would be recorded for 7 days prior to screening until Visit 2 and varied only in instances when adverse events required treatment (also considered concomitant medication). The differences in dietary requirements are again noted. Food violations are noted in the following section.

10.2.7 Compliance with Study Medication

Since patients were allowed to take any concomitant medications, there were no medication violations. See below for food violations. One patient was considered non-compliant in the MoviPrep group. Some patients were described as being non-compliant to the study protocol. See Disposition table.

10.2.8 Protocol Deviations and Violations

From the Treatment Questionnaire, there were 26 food violations in the BLI800 treatment group or 6.7% and 28 food violations in the MoviPrep group or 7.6%. Specifics of the violations were not described in the electronic datasets since the results reflected binary outcomes.
The following questions were asked:

- To record the date that you took the first dose of preparation.

- What time did you take the first dose of preparation?
- To record the date that you took the second dose of preparation.
- What time did you take the second dose of preparation?
- Record what you eat on the day of your preparation and specify time.

Reviewer's Comments: In Applicant submission, two sections in Module 5 Volumes 9.3 and 10.3 (both Tab 16.2.21) state that times outside the window of follow-up and between Visit 1 and visit 2 are protocol violations, yet in the SPA these are deemed non-protocol violations.

10.2.9 Primary Endpoints

The primary endpoint measured the efficacy of BLI800 compared to Moviprep® in producing clinically adequate bowel prep for colonoscopy. The adequacy and the quality of the bowel preparation we measured visually by the endoscopist according to the following scale. The colonoscopist was asked to rate the quality of the bowel preparation based on the colon cleansing scores that are summarized in the following table 43 (electronically copied from the Applicant's submission, Module 5, Volume 6.2, Tab 5.3.5.1B, 16.1.1, p. 19).

Table 53: Colon Cleansing Scores

Score	Grade	Description
1	Poor	Large amounts of fecal residue, additional cleansing required
2	Fair	Enough feces or fluid to prevent a completely reliable exam
3	Good	Small amounts of feces or fluid not interfering with exam
4	Excellent	No more than small bits of adherent feces/fluid

Scores of grades 1 or 2 were considered as treatment failures, and scores of grades 3 or 4 were considered to be successes. According to the primary endpoint based on a binary outcome of success or failure, it was defined as failure if the following occurred:

- Bowel cleansing grade of poor=1 or fair=2
- Patient did not have an adequate bowel prep for colonoscopy as determined by investigator as insufficient fecal output, unclear fecal discharge or due to preparation AE
- Patient did not have adequate cleansing for evaluation

10.2.10 Secondary Efficacy Endpoints

As a secondary endpoint, each colonoscopist was also asked to rate whether or not the bowel preparation was adequate or inadequate in a binary outcome measure.
If the bowel prep was rated as inadequate, the need for repeat bowel preparation was noted.

10.2.11 Statistical considerations

The statistical considerations for efficacy for Study 301, involve adequate cleansing and quality of successful cleansing as determined by colonoscopist assessments on a poor=1 to excellent=4 rating as primary analysis that included the ITT group only and not all randomized patients. Subjects who completely or partially took study drug, but, did not have a colonoscopy due to reasons unrelated to the prep were not originally included in the primary and secondary efficacy analysis and were included only in the safety analysis (IR #14 of 6/12/09 included all randomized patients).

Both studies included several defined groups in their original submission:
Screen Failures in Study 301 included 8 patients identified as "did not meet criteria" (five patients) or "withdrew consent" (three patients). None of these 8 patients were dispensed medications. They provided informed consent but did not complete screening procedures because they either withdrew consent or were found ineligible during the visit.
Intention to treat (ITT) population included randomized patients who took the study drug and either completed and did not complete the protocol. The **True ITT** that had to be re-calculated for Study 301 and included all randomized patients who were assigned a study treatment.
Completed patients are ones who ingests BLI800 and has a colonoscopy. A **Non-Completer** was one who did not have a colonoscopy.
Discontinued patients could include patients lost to follow-up, non-completers, non-compliant to medication or protocol, adverse events, withdrew consent, non-evaluable, or did not meet criteria.

For Study BLI800-301, the Applicant proposed the 15% of non-inferiority marginal without any justification. A more detailed justification on the selection of non-inferiority margin of 15% was requested at the prior March 23, 2007, and provided in IR of 11/21/08.

If the assumed expected event for the control was larger (e.g. 90% or more), the non-inferiority margin should be tightened. The margin would be much less than 15%.

By choosing δ=15%, it implied that as much as a 16.8% relative decrease of the assumed expected event rate of 89% might occur in patients with BLI800. See Statistics Review by Dr. Milton Fan for a more detailed description.

If no colonoscopy was done due to poor prep or if there were prep related adverse events then the patient was considered a failure rating. All patients were determined by the colonoscopist as success or failure which was then analyzed as the primary efficacy endpoint and tested sequentially in a hierarchical structure with the first test being a non-inferiority test based upon the D=P1-P2. Using the Null hypothesis HO: P1-P2<=D0 versus H1: P1-P2=D1>D0. P1 is BLI800 group and P2 is Moviprep group and D0 is the acceptable margin of equivalence to an absolute margin of 15%. The 15% margin was established as an acceptable non-inferiority margin for Braintree's prior applications of HalfLytely, NDA 19-797; NuLytely, NDA 21-551) and other products. [2,3,8]

Subjects who completely or partially took study drug but did not have a colonoscopy due to reasons unrelated to the prep were not included in the primary and secondary efficacy analysis but, along with all other subjects, were included in the safety analysis.
This reviewer agrees with comments from Dr. Milton Fan, Statistician, whose review included concern about "biocreep" that may have resulted from comparison of MoviPrep as it was compared to a standard regimen of Golytely (PEG+E) that was used in prior approval studies.

The success rate of effective gut cleansing was 88.9% in the MoviPrep group compared with 94.8% in the Golytely (PEG+E) group. This resulted in a difference of -5.9% in favor of Golytely with a lower bound of 95% confidence interval of -12.0%. The Applicant did not justify the non-inferiority margin when requested on multiple requests (pre-NDA, NDA, and SPA meetings) and sent in an IR in 11/08 based on historical non-inferiority margins used in other marketed products. Their choice of a 15 % margin implies that as much as a 20.5% relative decrease of assumed expect event rate of 73% might occur in patients prepared with BLI800. In Study 302, if we were to choose a 10% relative decrease as the worse acceptable case scenario, then there would be a 5% chance of the worst case and the margin would be 7% which the Applicant's results falls within.

10.2.12 Protocol Amendments

No protocol amendments were submitted after the initial submission.

10.2.13 Patient Disposition

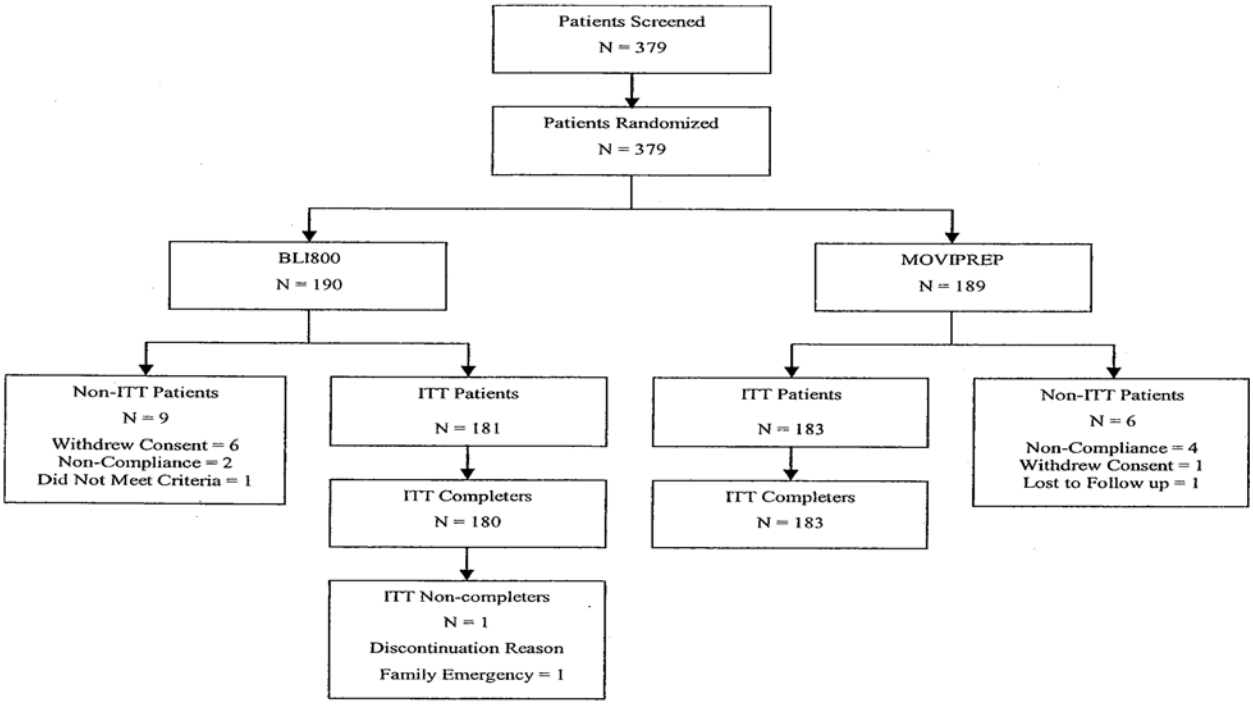
Study 302 enrolled new patients in 11 sites that were eligible with all 379 screened patients also having been randomized. Successful completers being defined as: (compliance with study-related procedures), considered part of ITT, compliance with taking the medication under the protocol. Those who did not take study medication were not included in the ITT group. Likewise, those who withdrew for consent, did not meet criteria, were lost to follow-up, or had family emergency were discontinued.

In the following chart, successful completers were defined as: compliance with study-related procedures, considered part of ITT, compliance with taking the medication under the protocol. A "completed" subject is one who ingests BLI800 and has a colonoscopy. Those who did not take study medication were not included in the ITT group. Those who withdrew for consent, did not meet criteria, were lost to follow-up, or had discontinuation (insurance issue, adverse event) and non-compliance was not included. All except one was considered non-ITT (therefore not completing protocol) or a non-completer patient. See section on "Overall Profile of Drop outs" There were a total of 379 randomized patients, 190 in the BLI800 group and 189 in the MoviPrep group that were single blinded.

Reviewer's comments: IR #8 response to clarification on the exact point at which the patients received medication, had visits completed, colonoscopy completed and when they dropped out resulted in the tables Appendix 12.1.

Table 55: Study 302 Patient Disposition

Figure 2: Patient Disposition



10.2 Protocol Deviations: See Appendix 16.2.21 for all protocol deviations.

Patient disposition consisted of 379 screened and randomized patients of which 190 were in the Suprep group and 189 in the MoviPrep group. Applicant further separated out those who did not receive any partial or full dose medication resulting in 181 in the Suprep group and 183 in the MoviPrep group.

Study 302 initial submitted tables used an ITT that did not include all randomized patients. Upon inclusion of the true ITT patients the original number increased from 180 to 190 in the BLI800 group and from 183 to 189 patients in the MoviPrep treatment group. They were single blinded, randomized, and received study drug in each group. Of the total of 9 Non-ITT patients in the BLI800 group, 6 withdrew consent, 2 were non-compliant and 1 did not meet criteria. Only 1 other patient (12017) in this group did not complete the study due to a family emergency. In the MoviPrep group, of the total 6 Non-ITT patients, 4 were non-compliant (11016, 16004, 17011, 18028 by taking both doses on the day prior to colonoscopy), 1 withdrew consent, one was lost to follow-up. All other patients completed the study.

10.2.14 Demographics

There were more females (54%) than males (46%) in the study population, although they were evenly distributed between the two treatment groups. Likewise the two groups were similar in age, race and weight. Fifty-five years was the average age with 81 ITT patients age 65 or older and 23 patients 75years of age or older. Eighty –six percent were Caucasian and 9% were African American. The average weight was about 184 pounds. ITT patient 12017 was excluded in the efficacy analysis being classified as non-evaluable.

Table 56: Study 302 Demographics (Complied by Milton Fan)

Table 2 Summary of Demographic and Baseline Characteristics --- Protocol BL800-302

All Randomized Patients

Characteristics	BL800 (N=190)	MoviPrep (N=189)	Between Treatment p-value
Sex			
Male	87 (45.8%)	87 (46.0%)	0.9623
Female	103 (54.2%)	102 (54.0%)	
Race			
N	190	185	0.0952
White	160 (84.2%)	166 (89.7%)	
Black	19 (10.0%)	16 (8.6%)	
Asian	8 (4.2%)	2 (1.1%)	
Native American	0 (0.0%)	1 (0.5%)	
Other Races	3 (1.6%)	0 (0.0%)	
Age (yr)			0.9749
Mean (SD)	55.9 (12.3)	55.9 (10.8)	
Age			0.4040
<65	144 (75.8%)	150 (79.4%)	
≥65	46 (24.2%)	39 (20.6%)	
High Risk			0.8738
Yes	88 (46.3%)	86 (45.5%)	
No	102 (53.7%)	103 (54.5%)	

Compiled by this reviewer
P-values were computed by this reviewer.
P-value for categorical data was obtained using Chi-square test.
P-value for continuous data was obtained using t-test.

10.2.15 Primary Efficacy Endpoints Results for Study 302

Primary Efficacy Endpoints Results
Applicant's results of the primary efficacy endpoints show about a 10.8% improvement over the cleansing with MoviPrep for the 4 or "excellent" score. MoviPrep is about 9.3% better for the 3 or "good" score. Applicant states these results are consistent with other approved preparation cleaning scores. When ratings were consolidated into a "success" versus "failure" score the two preparations showed no difference.

Table 57: BLI800-302 Colonoscopy Assessment Analysis by Cleansing Grade-Primary Efficacy Endpoint

Grade	BLI800 (N=180)	MoviPrep (N=183)	All Patients (N=364)
Excellent	114 (63.3)	96 (52.5)	210 (57.9)
Good	61 (33.9)	79 (43.2)	140 (38.6)
Fair	3 (1.7)	6 (3.3)	9 (2.5)
Poor	2 (1.1)	2 (1.1)	4 (1.1)
Mean Score	3.59	3.47	3.53

Taken from Applicant's Module 5.3.5.1, table 14.2.1.1, excludes patient 12017 (had to reschedule colonoscopy due to family emergency)

Table 58: BLI800-302 Colonoscopy Assessment of Success and Failure: Primary Efficacy Endpoint ITT Population

Assessment	BLI800 (N=180)	MoviPrep (N=183)	All Patients (N=364)	95% CI	Diff (BLI800-Moviprep)
Success	175 (97.2)	175 (95.6)	350 (96.4)	-2.2 -5.4	1.6%
Failure	5 (2.8)	8 (4.4)	13 (3.6)		

Taken from Applicant's Module 5.3.5.1, table 14.2.1

The Applicant's table does not include patients who did not undergo colonoscopy: patient 12017 was excluded. Applicant concluded that BLI800 and MoviPrep have similar preparation success which is better than other reported colonic preparation. The mean average cleansing score was consistent with other colonic cleansers especially 4L preparations. Combining the scores for 3 and 4 and sub grouping this "successful" versus "failure" group resulted in very little difference in responder analysis by geographic area on a site by site basis. (See Module 5, 5.1 page 33)

Re-calculation of Applicant Primary Efficacy Endpoints for Study 302 with true ITT which included an additional 16 randomized patients (10 in BLI8000 and 6 in Moviprep) that the Applicant excluded.

Table 59: Study 302 True ITT Re-calculated Colonoscopy Assessment by Cleansing Grade

Grade	BLI800 (n= 190)	MoviPrep (n=189)	All patients (n=379)
Excellent	114/190 (60.0)	96/189 (50.8)	210/374 (56.1)
Good	61/190 (32.1)	79/189 (41.8)	140/374 (37.4)
Fair	3/190 (1.6)	6/189 (3.2)	9/374 (2.4)
Poor	2/190 (1.1)	2/189 (1.1)	4/374 (1.1)

Calculated by this reviewer, also see Stats review.

Table 60: Successful Primary Endpoint With True ITT

Number and Percent of Successful Preparations
Protocol BLI800-302
True ITT Analysis Compiled by Milton Fan

Treatment	Rate	Diff	95% C.I.
BLI800	175/190 (92.1%)	-0.5%	(-5.8%, 4.9%)
MoviPrep	175/189 (92.6%)		

For the true ITT analysis which included all randomized subjects, BL800 patients experienced similar preparation success to MoviPrep.

The total success percentage defined by combining the excellent and good grades of BLI 800 was 92.1% as compared to MoviPrep at 92.6%, a difference of -0.5% favoring MoviPrep. The 95% CI was (-5.8%, 4.9%).

The Applicant's sub-group analysis by gender, age and site of Study 302 did not include the true ITT which incorporated all missing data as a failure.

Subgroup Analysis

Table 61: Primary Efficacy Responder Analysis, Number and Percent of Successful Preparations (from Applicant Table 302-5)

Responder	BLI800 n (%)	MoviPrep n (%)	95% CI	p	p
All Patients (n)	180	183	-2.2, 5.4	0.391	<0.001
Success	175 (97.2%)	175 (95.6%)			
Fail	5 (2.8%)	8 (4.4%)			
Elderly (>65 y)	43	38	-5.7 , 17.5	0.403	--
Success	41 (95.3%)	34 (89.5%)			
Fail	2 (4.7%)	4 (10.5%)			
Males	83	85	-4.0 ,6.2	0.718	--
Success	81 (97.6%)	82 (96.5%)			
Fail	2 (2.4%)	3 (3.5%)			
Females	97	98	-3.5, 7.6	0.296	--
Success	94 (96.9%)	93 (94.9%)			
Fail	3 (3.1%)	5 (5.1 %)			

Of the Applicant's calculations based on 363 patients that underwent colonoscopy, there was little difference in gender (both treatment groups and sexes had about 95% response). In the ≥ 65 year of age group, success rates were 95% and 90% in BLI800 and MoviPrep groups. This was consistent with a 97% success rate in the < 65 year age group. No differences were noted based on race.

Based on Applicant Table 302-6, no site specific differences were noted by the Applicant between sites 11 to 20.

Table 302-6
Responder Analysis by Geographic Region

Site	Score[1]	BLI800	MoviPrep	95% CI[2]	p[2]
11	Success Fail	18 (95%) 1 (5%)	18 (95%) 1 (5%)	-14.2, 14.2	1.000
12	Success Fail	13 (100%) 0 (0%)	15 (100%) 0 (0%)	-	-
13	Success Fail	22 (100%) 0	23 (100%) 0	-	-
14	Success Fail	14 (93%) 1 (7%)	15 (100%) 0	-19.3, 6.0	1.000
15	Success Fail	38 (97%) 1 (3%)	35 (92%) 3 (8%)	-4.6, 15.2	0.358
16	Success Fail	12 (100%) 0	12 (100%) 0	-	-
17	Success Fail	7 (100%) 0	5 (83%) 1 (17%)	-13.2, 46.5	0.462
18	Success Fail	14 (100%) 0	12 (86%) 2 (14%)	-4.0, 32.6	0.481
19	Success Fail	19 (95%) 1 (5%)	20 (95%) 1 (5%)	-13.4, 13.0	1.000
20	Success Fail	18 (95%) 1 (5%)	20 (100%) 0	-15.3, 4.8	0.487

(1) A successful preparation was defined as as colonoscopy cleansing score of 3 or 4.
(2) Confidence interval (CI) and P-value for the difference between BLI800 and MoviPrep are from a Chi Square test. (reference table 14.2.1.5, Section 14)

Subgroup analyses of the primary efficacy endpoint by gender, age, and site follow for true ITT analysis. In this true ITT analysis, patients who had missing data were considered "failures".

Table 62: Number and Percent of Successful Preparations Study-302: True ITT Analysis
Complied by Milton Fan

Subgroup	BLI800	MoviPrep	Diff	95% CI
Gender				
Male	81/87 (93.1%)	82/87 (94.3%)	-1.1%	(-8.4%, 6.1%)
Female	94/103 (91.3%)	93/102 (91.2%)	0.1%	(-7.7%, 7.8%)
Age (yrs)				
< 65	134/144 (93.1%)		141/150 (94.0%)	-0.9% (-6.6%, 4.7%)
≥ 65	41/46 (89.1%)	34/39 (87.2%)	1.9%	(-11.9%, 15.8%)
Site				
11	18/23 (90.0%)	18/20 (90.0%)	0.0%	(-18.6%, 18.6%)
12	13/15 (86.7%)	15/15 (100.0%)	-13.3%	(-30.5%, 3.9%)
13	22/23 (95.7%)	23/23 (100.0%)	-4.3%	(-12.7%, 4.0%)
14	14/15 (93.3%)	15/15 (100.0%)	-6.7%	(-19.3%, 6.0%)
15	38/40 (95.0%)	35/40 (87.5%)	7.5%	(-4.8%, 19.8%)
16	12/14 (85.7%)	12/13 (92.3%)	-6.6%	(-30.0%, 16.8%)
17	7/7 (100.0%)	5/6 (83.3%)	16.7%	(-13.2%, 46.5%)
18	14/15 (93.3%)	12/15 (80.0%)	13.3%	(-10.5%, 37.2%)
19	19/21/ (90.5%)	20/22 (90.9%)	-0.4%	(-17.8%, 16.9%)
20	18/20 (90.0%)	20/20 (100.0%)	-10.0%	(-23.2%, 3.2%)

Compiled by Milton Fan
As seen from table above, the treatment difference was consistent among subgroups for gender and age.

10.2.16 Secondary Endpoints Results

BL800 patients experienced similar number of "adequate" preparations compared to MoviPrep.
Table 63: Number and Percent of Adequate Preparations Protocol BLI800-302
Applicant's ITT Analysis

Treatment	Rate	Diff (BLI800 – MoviPrep)	95% C.I.
BLI800	178/180 (98.9%)	-0.0%	(-2.2%, 2.1%)
MoviPrep	181/183 (98.9%)		

Copied from Table 302-7

As seen from table above, BL800 patients experienced similar adequate preparations to MoviPrep. The confidence interval falls between the pre-determined equivalence margins of ± 15%.

Table 64 (includes the following 2 tables): Secondary Endpoint for Study 302 with True ITT

Reference: Table 14.2.3, Section 14	BLI800 N=190 (%)	MoviPrep N=189 (%)	95% CI= -2.2,2.1	P= 1.000
Adequate (n)	180	183		
Yes	178 (93.7%)	181 (95.8%)		
No	2 (1.1%)	2 (3.2%)		
Missing	10 (5.3%)	6 (3.2%)		
Need for Re-Prep			-100, 19.3	
Yes	0	1 (50)		
No	2 (100)	1 (50)		

Taken from Applicant with above reference from IR #14 of 6/12/09

For the secondary efficacy results of Study 302, colonoscopists were asked on a colonoscopy exam form "Was cleansing adequate for evaluation" and most were considered by them as being adequate.

The secondary efficacy endpoint initially did not include all randomized patients. There were 16 patients (10 in BLI800 and 6 in MoviPrep) who were excluded from the Applicant's ITT analyses. If these 16 patients were considered to be" failed," then the sponsor recently submitted results from secondary efficacy responder analysis for true ITT population is consistent with the results given below.

Number and Percent of Adequate Preparations
Protocol BLI800-302
True ITT Analysis
Complied by Milton Fan

Treatment	Rate	Diff (BLI800 – MoviPrep)	95% C.I.
BLI800	178/190 (93.7%)	-2.1%	(-6.6%, 2.4%)
MoviPrep	181/189 (95.8%)		

In the True ITT, both treatment groups experienced similar adequate preparations.

10.2.17 Summary and Conclusions

Applicant's results of the primary efficacy endpoints show about a 10% improvement over the cleansing with MoviPrep for the 4 or "excellent" score. MoviPrep is about 10% better for the 3 or "good" score. If combined as a successful score there is a 2.9% difference between treatments. The split day dose regimen had higher efficacy rates for both treatment groups than did the same day dose regimen. Applicant states these results are consistent with other approved preparation cleaning scores. When ratings were consolidated into a "success" versus "failure" score the two preparations showed no difference. The Applicant concludes that BLI800 and MoviPrep have similar preparation success which is better than other reported colonic preparation. The mean average cleansing score was consistent with other colonic cleansers especially 4L preparations. Combining the scores for 3 and 4 and sub grouping this "successful" versus "failure" group resulted in very little difference in responder analysis by geographic area on a site by site basis (See Module 5, 5.1 page 33).

In the labeling for Moviprep, under "Information for patients" it states that "Patients may have clear soup and/or plain yogurt for dinner, finishing the meal at least one hour prior to the start of Moviprep treatment. No solid food should be taken from the start of Moviprep treatment until after the colonoscopy". In the two treatments groups, patients had different type of meals.

Patients who received MoviPrep were allowed to eat a full breakfast, a light lunch, and a clear liquid dinner; in contrast, patients who received Suprep were instructed not to eat a light breakfast and clear liquids afterwards until the day of the colonoscopy. It is inevitable that the amount of food and the type of solid food before the colonoscopy can influence the efficacy of colon cleansing. Since Moviprep is the comparator product for BLI800 and the same issue of incomparable dietary requirements arises for the comparator as when Moviprep was reviewed for its NDA approval. The Applicant should have considered the impact of the different dietary requirements in their assertion of superiority and in their study design.

10.3 Line-by-Line Labeling Review

The labeling submitted by the Applicant was reviewed line-by-line and modifications were sought from the Applicant. This is a summary of the major changes recommended for the Applicant's proposed labeling with justifications for these changes. The final labeling will not be complete at the time of completion of this review and continual discussion of the labeling per GRMPs will occur throughout the review cycle. Minor changes to the font of the product name and particular changes in dosage and administration were made so that they conformed to what was used during the study in the study protocol and patient instructions. Major additions were made to the Contraindications, Warnings and Precautions section to comprehensively include concerns that are found in other osmotic laxative labels and that may also be concerns for this product. Concerns included warnings and precautions for aspiration, serious fluid and electrolyte abnormalities, cardiac arrhythmia, seizures, renal impairment, colonic mucosal ulcerations and ischemic colitis. (b) (4) Drugs that interact to increase risks due to fluid and electrolyte abnormalities, affect absorption and the withholding of stimulant laxative use were also incorporated. More precaution with the elderly was also recommended and with those on concomitant medications such as diuretics, ACEI's, and ARB's.

The consult by Shefali Doshi and Kathleen Klemm, Regulatory Review Officers in the Division of Medication Errors and Technical Support (DMETS) has been completed and are highlighted as follows:

- General comment: (b) (4)
- Indications and Usage: Specify age arrange for term "adults"

(b) (4) . The current Medication Guide should be clearer in its designation as "Split-Dose Instructions"

Reviewer's Comments: (b) (4)

10.4 List of Investigator Name, Location and Site Number

1
Charles Barish, MD
Wake Research Associates, LLC
3100 Blue Ridge Road, Suite 200
Raleigh, NC 27612
2
Raj Bhandari, MD
Delta Research Partners
611 Grammont Street
Monroe, LA 71201
3
Richard Chasen, MD
Maryland Digestive Disease Research, LLC
7350 Van Drusen Road, Suite 360
Laurel, MD 20707
4
Daniel Connell, MD
Regional Gastroenterology Associates of Lancaster
2104 Harrisburg Pike, Suite 300
Lancaster, PA 17604
5
Michael Goldstein, MD
Long Island GI Research Group
310 East Shore Rd. Suite 206
Great Neck, NY 11023
6
Pramod Malik, MD
Chesapeake, Virgina Offce
Gastroenterology Associates of Tidewater
112 Gainsborough Square, Suite 101
Chesapeake, VA 23320
7
Mark Nagrani, MD
United Medical Research
612 Palmetto Street,
New Smyrna Beach, FL, 32168
8
Julio Salcedo, MD
Washington Gastroenterology
106 Irving Street, NW, suite 205,
Washington DC, 20010
9
Howard Schwartz, MD

Miami Research Associates
6141 Sunset Drive; Suite 301
Miami FL, 33143
10
Michael Schwarz, MD
Jupiter Research Inc.
1002 South Old Dixie Highway, Suite 301
Jupiter FL, 33458
11
William Burch, MD
Franklin Gastroenterology, PLLC
740 Cool Springs Blvd. Suite 210
Franklin, TN 37067
12
Roland Bennetts, MD
Northwest Gastroenterology Clinic
1130 NW 22nd Ave. Suite 410
Portland, OR 97210
13
Steven Duckor, MD
Advanced Clinical Research Institute
2617 East Chapman Ave. Suite 302
Orange, CA, 92869

14
Ronald Kotfila, MD
Gastrointestinal Associates
1421 N State Street Suite 203
Jackson, MS, 39202
15
Dennis Riff, MD
Advanced Clinical Research Institute
1211 West La Palma Avenue, Suite 602
Anaheim, CA 92801
16
Robert Souder, MD
Regional Research Institute
45 Physicians Drive
Jackson, TN 38305
17
Ira Stein, MD
Gastrointestinal Institute, PLLC
2400 Patterson Street, Suite 515
Nashville, TN 37203

18
Barr Winston, MD
Houston Medical Research Associates
1140 Cypress Station Drive, Suite 305
Houston, TX 77090
19
Robert Wohlman, MD
Northwest Gastroenterology Associates
1135 116th Avenue NE, LL-160
Bellevue, W A 98004 USA
20
Investigator Name and Location
Lawrence Wruble, MD
Memphis Gastroenterology Group
8000 Wolf River Blvd
Germantown, TN 38138
21
Reynaldo Rodriguez, DO
University of South Alabama
Knollwood Physician Pavilion
5600 Girby Road
Mobile, AL 36693

10.5 References

1 Bitoun A, Ponchon T, Barthet M, Coffins B, Dugue C, Halphen M; Results of a prospective randomized multicenter controlled trial comparing a new 2-L ascorbic acid plus polyethylene glycol and electrolyte Solution vs. sodium phosphate solution in patients undergoing elective colonoscopy. Aliment. Pharmacol. Ther. 2006: 1631-1642.

2 Doyle D, Hanks G, Cherny N, Calman, K; Oxford Textbook of Palliative Medicine, Third Edition, Oxford University Press, New York, 2005.

3 Brodsky E: Clinical MoviPrep NDA 21-881 Review completed 3/30/06.

4 Temple, R: FDA experience and perspective on non-inferiority trials. FDA workshop CAP. January 18, 2008.

10.6 REFERENCED TABLES

10.6.1 Section 7.1.5.1 Table 16 (continued over next 4 tables): Summary of Non-ITT patients which were excluded from the ITT population despite randomization. ITT Non-Completers who received full or partial treatment were included as ITT.

Braintree Laboratories, Inc.
NDA 22, 372: SuPrep®

FDA Information Request – 04/14/09
Item 1 – Summary of Randomized Patients

Patient ID	Age	Sex	Study	Treatment	ITT Status	Drug Treatment Full/Partial/None	Visit 2 Labs done?	Colonoscopy Done?	Visit 3 Done?	Reason for Discontinuation	When Dropout Occurred
01042	75	F	BLI800-301	MoviPrep	Non-ITT	No Treatment	No	No	No	Patient withdrawn due to clinically significant Visit 1 labs	Before Visit 2
02015	63	F	BLI800-301	BLI800	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2
02024	38	M	BLI800-301	BLI800	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2
02032	59	F	BLI800-301	BLI800	ITT Non-Completer	Partial Treatment	No	No	No	Adverse event: nausea	Before Visit 2
02040	69	M	BLI800-301	MoviPrep	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2
03005	50	M	BLI800-301	BLI800	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2
03013	84	F	BLI800-301	MoviPrep	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2
03057	86	M	BLI800-301	MoviPrep	Non-ITT	No Treatment	No	No	No	Non-compliance: no Visit 1 lab results obtained	Before Visit 2
03065	79	M	BLI800-301	BLI800	Non-ITT	No Treatment	No	No	No	Patient withdrawn due to clinically significant Visit 1 labs	Before Visit 2
04017	54	F	BLI800-301	BLI800	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2
05001	39	F	BLI800-301	BLI800	Non-ITT	No Treatment	No	No	No	Non-compliance: no Visit 1 chemistry results obtained	Before Visit 2
05007	49	F	BLI800-301	MoviPrep	Non-ITT	No Treatment	No	No	No	Non-compliance: patient refused to return for preg. test	Before Visit 2

Patient ID	Age	Sex	Study	Treatment	ITT Status	Drug Treatment Full/Partial/None	Visit 2 Labs done?	Colonoscopy Done?	Visit 3 Done?	Reason for Discontinuation	When Dropout Occurred
05011	56	F	BLI800-301	MoviPrep	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2
05020	75	M	BLI800-301	MoviPrep	Non-ITT	No Treatment	No	No	No	Non-compliance: no Visit 1 lab results obtained	Before Visit 2
05032	78	M	BLI800-301	BLI800	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2
05034	59	F	BLI800-301	BLI800	ITT Non-Completer	Partial Treatment	Yes	No	No	Adverse event: vomiting	Before Visit 2
06003	48	F	BLI800-301	MoviPrep	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2
07003	46	F	BLI800-301	BLI800	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2
07013	50	M	BLI800-301	BLI800	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2
07022	60	F	BLI800-301	MoviPrep	Non-ITT	No Treatment	No	No	No	Non-compliance: no Visit 1 lab results obtained	Before Visit 2
07029	75	M	BLI800-301	BLI800	ITT Non-Completer	Full Treatment	No	No	No	Patient withdrew due to lack of insurance coverage for colonoscopy	Before Visit 2
09022	79	M	BLI800-301	MoviPrep	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2
09039	49	M	BLI800-301	MoviPrep	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2
10006	66	F	BLI800-301	BLI800	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2

Patient ID	Age	Sex	Study	Treatment	ITT Status	Drug Treatment Full/Partial/None	Visit 2 Labs done?	Colonoscopy Done?	Visit 3 Done?	Reason for Discontinuation	When Dropout Occurred
10011	31	F	BLI800-301	MoviPrep	ITT Non-Completer	Partial Treatment	Yes	No	Yes – labs drawn	Adverse event: bloating, nausea	Before Visit 2
10038	83	M	BLI800-301	BLI800	ITT Non-Completer	Full Treatment	Yes	No	Yes – labs drawn	Adverse event: atrioventricular block	During Visit 2
11032	53	F	BLI800-302	MoviPrep	Non-ITT	No Treatment	No	No	No	Lost to Follow up	Before Visit 2
11033	43	F	BLI800-302	BLI800	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2
12014	54	M	BLI800-302	BLI800	Non-ITT	No Treatment	No	No	No	Patient withdrawn due to clinically significant Visit 1 labs	Before Visit 2
12017	54	F	BLI800-302	BLI800	ITT Non-Completer	Full Treatment	No	No	Yes – labs drawn	Patient had a family emergency and had to reschedule colonoscopy	Before Visit 2
13006	77	M	BLI800-302	BLI800	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2
15012	45	M	BLI800-302	MoviPrep	Non-ITT	No Treatment	No	No	No	Non-compliance: patient could not complete colonoscopy during study window	Before Visit 2
15026	52	M	BLI800-302	BLI800	Non-ITT	No Treatment	No	No	No	Non-compliance: patient could not complete colonoscopy during study window	Before Visit 2

Patient ID	Age	Sex	Study	Treatment	ITT Status	Drug Treatment Full/Partial/None	Visit 2 Labs done?	Colonoscopy Done?	Visit 3 Done?	Reason for Discontinuation	When Dropout Occurred
15071	77	F	BLI800-302	MoviPrep	Non-ITT	No Treatment	No	No	No	Non-compliance: patient could not complete colonoscopy during study window	Before Visit 2
16007	69	F	BLI800-302	BLI800	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2
16009	43	F	BLI800-302	BLI800	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2
16019	56	F	BLI800-302	MoviPrep	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2
18004	58	F	BLI800-302	BLI800	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2
18023	61	M	BLI800-302	MoviPrep	Non-ITT	No Treatment	No	No	No	Non-compliance: patient refused to take study preparation	Before Visit 2
19006	57	F	BLI800-302	MoviPrep	Non-ITT	No Treatment	No	No	No	Non-compliance: patient could not complete colonoscopy during study window	Before Visit 2
19025	61	F	BLI800-302	BLI800	Non-ITT	No Treatment	No	No	No	Non-compliance: patient could not complete colonoscopy during study window	Before Visit 2
20026	67	M	BLI800-302	BLI800	Non-ITT	No Treatment	No	No	No	Patient withdrew consent	Before Visit 2

10.6.2 Summary of Information Requests to Applicant

Infromation request	Date Received	Brief Description
1	10/28/08	Lack test drug given dates, Phase 1 and some further SAS datasets-still incomplete
2	11/21/08	NI margin, SAS datasets with gender, treatment group, age, study number, Stats efficacy dataset info, error in AE tables; CRF's requested SAE.
3 (safety update)	12/12/08	Unreported colonic perforation from 8/07 reported
4	12/24/08	SAS datasets lack drug adminstration /f/u dates-still incomplete
5	2/3/09	Same as "4" due to formatting –still incomplete; SAE clarifications
6	2/10/09	Further clarifications of "5"
7	2/23/09	Further narratives of SAE's , incidence for AE tables by FDA differ from Applicants; CK elevation analysis
8	3/9/09	Additional CK elevation analysis
9	3/11/09	Submit pediatric development plan
10	4/3/09	Missing serum sulfate analysis, clarify screen failures, (b) (4)
11	4/21/09	Sulfates not analyzed—no amendment, drop outs clarified, bradycardia analysis, exclusion of mild/moderate GI severity in AE tables
12	5/6/09	TEAE and Pt. reported Symptoms not combined, new SAS AE datasets
13	5/14/09	new SAS AE datasets with all AE's
14	6/12/09	New complete TEAE datasets using all randomized patients

10.6.3 Study 201 Efficacy Results

Colonoscopy Residual Fluid Score

Colon Segment	Cecum	Ascending	Transverse	Descending	Sigmoid/ Rectum
Mean (SD)	1.11 (0.31)	1.11 (0.31)	1.89 (0.74)	1.11 (0.31)	1.22 (0.42)
Range	1-2	1-2	1-3	1-2	
N (%) of patients 1 = absent 2 =small					
	8 (89%)	8 (89%)	3 (33%)	8 (89%)	7 (77%)
	1 (11%)	1 (11%)	4 (44%)	1 (11%)	2 (23%)
3 = moderate	0	0	2 (22%)	0	0
4 = excess	0	0	0	0	0

10.6.4 Identifying common and drug-related adverse events

Table 22, 23 The Most Frequent TEAE >3% for Study 301: (received 6/12/09 from Applicant)

Body system	Preferred Term	BLI800 # (%) N= 204	MoviPrep # (%) N= 204	95% CI
# of patient with event		162 (79.4)	149 (73)	-1.9 to 14.6
Total # event		434	301	
Gastrointestinal Disorders		155 (76)	139 (69.1)	-.8 to 16.5
	Abdominal distension	111 (54.4)	107 (52.5)	-7.7 to 11.6
	Abdominal Pain	71 (34.8)	40 (33.3)	-7.7 to 10.7
	Nausea	85 (43.6)	75 (36)	-2.4 to 16.4
	Vomiting	25 (12.3)	7 (3.4)	3.7 to14
General Disorders and Administration Site Conditions		123 (40.3)	116 (56.9)	-6.1 to 13
	Overall Discomfort	123 (40.3)	116 (56.9)	-6.1 to 13

.

Study 302: (received 6/12/09 from Applicant): Most Frequent TEAE >3%

	Preferred Term	BLI800 # (%) N= 190	MoviPrep # (%) N=189	95% CI
# of patient with event		132 (69.5)	149 (78.8)	-18.1to -.6
Total # event		339	182	
Gastrointestinal Disorders		119 (62.6)	138 (73.0)	-19.7 to -1.0
	Abdominal distension	79 (40.5)	98 (51.9)	-21.3 to-1.4
	Abdominal Pain	69 (36.3)	81 (42.9)	-16.4 to 3.3
	Nausea	69 (36.3)	62 (32.8)	-6.1 to 13.1
	Vomiting	16 (8.4)	7 (3.7)	-.1 to 9.5
General Disorders and Administration Site Conditions		103 (54.2)	126 (66.7)	-22.2 to -2.7
	Overall Discomfort	102 (53.7)	126 (66.7)	-22.8 to -3.2

10.6.5 BUN and Creatinine Changes Tables (1), (2) and Subgroup of Suprep patients with BUN and Creatinine Elevations and Vomiting in (3)

Bun and Creatinine Changes (1)

BUN (6-19) and Creatinine (.4 -1.1) changes VISIT 1, 2, 3				
Patient ID	Treatment Group	Visit 1 (screen)	Visit 2 (colonoscopy)	Visit 3 (F/U)
5008	S1	20/.9	15/1	20/1.1
5014	M1	35/1.8	38/2*	35/1.9
5015	S1	20/1.1	18/1.2	27/1.4
5018	M1	14/1.1	17/1.9*	15/1.2
5025	M1	14/1.1	14/1.2	17/1.3
5030	S1	18/.7	12/.9	20/.9
7011	M1	18/1.1	20/1.3	23/1.1
7039	S1	22/1.2	21/2.1	24/1.4
8007	S1	18/1.1	22/1.5*	20/1.2
9008	S1	10/.7	11/.8	21/.9
9020	M1	24/1.1	17/1.3	23/1.3
9025	S1	17/.8	18/.9	22/.9
10001	S 1	22/1.1	18/1.2	21/1.3
10007	M1	15/.9	15/.9	25/.9
10008	M1	20/.9	16/1	21/1
10028	S1	19/1.2	25/1.3	24/1.3
10052	S1	18/1.2	14/1.1	16/1.3
10054	M1	20/1.2	19/1.3	23/1.5
11010	S2	13/.8	13/.9	20/.9
11011	M2	42/1.7	18/1.4	35/2
11030	S2	22/1.2	15/1	27/1.2
11034	M2	21/1.1	16/1.2	18/1.3
11039	S2	19/1.1	15/1.1	20/1
13001	M2	15/1.2	14/1.2	16/1.4
13022	S2	15/1	18/1.2	30/1.3
13032	S2	30/1.1	21/.9	33/.8

25

BUN and Creatinine Changes (2)

BUN (6-19) and Creatinine (.4 -1.1) changes VISIT 1, 2, 3				
Patient ID	Treatment Group	Visit 1 (screen)	Visit 2 (colonoscopy)	Visit 3 (F/U)
13037	S 302	16/1	15/1.2	15/1
14007	M 302	21/2.2	21/2	26/2.3
15008	M 302	16/1.1	17/1.2	22/1.2
15009	S 302	26/1.5	21/1.4	36/1.7
15015	M 302	23/1.2	25/1.1	30/1.3
15025	M 302	18/1.1	22/1.2	16/1.3
15045	S 302	15/1	14/.8	26/.9
15050	S 302	21/.8	18/.8	25/1.4
15062	M 302	20/1	17/1.1	21/1.2
18021	S 302	21/1.3	18/1.4	22/1.4
19010	S 302	19/1.1	16/1.3	24/1
19019	M 302	17/.9	13/.9	20/1
19022	M 302	23/1.5	17/1.5	27/1.6
19038	M 302	18/1	17/1.1	23/1.1
20017	S 301	17/.8	14/.8	20/1
21003	S 301	17/.8	22/1	none

25

Treatment Group	BUN (Visit 2 or 3)	Creatinine (Visit 1,2,3	Patient ID
Suprep	23		1034
	20		2007
	22, 23	1.5,1.2	8007
	22		9001
	23		12006
	--	1.4	13004
	20,20,29	1.5,1.5,1.4	15035
	20 (Visit 1), 20	--	15047
	32, 20, 20	--	15076
	21(Visit 1), 22	1.3,1.4,1.4	18021
	24 (Visit 1), 23		19012
	27,20,38		20014
Moviprep			
	20		12005
	25 (Visit 1), 20		18025

10.6.6 Interim TEAE Table Excluding Patient Reports in Diaries

Table 1: AE incidence table derived from ISS AE.xpt dataset

Treatment Group	Total	BLI-800	Moviprep
N =	770	388	382
AEDECOD	n(%)	n(%)	n(%)
NAUSEA	14 (2)	6 (2)	8 (2)
HEADACHE	10 (1)	6 (2)	4 (1)
VOMITING	9 (1)	6 (2)	3 (1)
ABDOMINAL DISTENSION	8 (1)	5 (1)	3 (1)
ABDOMINAL PAIN	8 (1)	5 (1)	3 (1)
CHILLS	4 (1)	2 (1)	2 (1)
ANAL DISCOMFORT	3 (<1)	1 (<1)	2 (1)
ASPARTATE AMINOTRANSFERASE INCREASED	2 (<1)	2 (1)	0
NASOPHARYNGITIS	2 (<1)	2 (1)	0
ABDOMINAL PAIN UPPER	1 (<1)	0	1 (<1)
ALANINE AMINOTRANSFERASE INCREASED	1 (<1)	1 (<1)	0
ANXIETY	1 (<1)	0	1 (<1)
ATRIOVENTRICULAR BLOCK COMPLETE	1 (<1)	1 (<1)	0
BLOOD CREATINE PHOSPHOKINASE INCREASED	1 (<1)	1 (<1)	0
BLOOD LACTATE DEHYDROGENASE INCREASED	1 <1)	1 (<1)	0
BLOOD URINE PRESENT	1 (<1)	1 (<1)	0
BRADYCARDIA	1 (<1)	0	1 (<1)
COLITIS ISCHAEMIC	1 (<1)	0	1 (<1)
DIARRHOEA	1 (<1)	1 (<1)	0
DISCOMFORT	1 (<1)	0	1 (<1)
DIZZINESS	1 (<1)	0	1 (<1)
DRY MOUTH	1 (<1)	1 (<1)	0
DYSURIA	1 (<1)	1 (<1)	0
FEELING HOT	1 (<1)	0	1 (<1)
INFLUENZA	1 (<1)	0	1 (<1)
KIDNEY ENLARGEMENT	1 (<1)	1 (<1)	0
LARGE INTESTINE PERFORATION	1 (<1)	0 (0)	1 (<1)
MOUTH ULCERATION	1 (<1)	1 (<1)	0
NON-CARDIAC CHEST PAIN	1 (<1)	0	1 (<1)
PRURITUS	1 (<1)	1 (<1)	0
RESPIRATORY DISTRESS	1 (<1)	0	1 (<1)
SINUS TACHYCARDIA	1 (<1)	0	1 (<1)
URINARY TRACT INFECTION	1 (<1)	1 (<1)	0

10.6.7 Table 18: Added Major Body System AE ,Preferred Terms in Interim Table Re-Calculated BLI800 -301and 302 Studies: Inclusion of Mild/Mod Severe GI AE from AE.xpt files submitted 1/09

Body System Preferred Term	BLI800 (n= 388)	MoviPrep (n=382)
# of patients with any event		
# of events	40	32
CARDIAC	1	2
AV Block	1	0
Sinus Tachycardia	0	1
Added CARDIAC		
Bradycardia	0	1
GASTROINTESTINAL (excludes Applicant's dry mouth and mouth ulceration)	27	22
Abdominal Distension	5	3
Abdominal Pain	5	3
Anal Discomfort	1	2
Diarrhea	1	0
Nausea	6	8
Vomiting	6	3
ADDED GI TERMS		
Abdominal Pain Upper	0	1
Colitis Ischemic	0	1
Large Intestine Perforation	0	1
INVESTIGATIONS Alanine Aminotransferase Increased	1	0
Aspartate Aminotransferase Increased	1	0
Blood Lactate Dehydrogenase Increased	1	0
Blood Creatine Phosphokinase Increased	1	0
GENERAL	2	2
Chills	2	2
NERVOUS SYSTEM	6	5
Dizziness	0	1
Headache	6	4
RESPIRATORY SYSTEM	0	1
Respiratory Distress	0	1
RENAL SYSTEM	4	0
Kidney Enlargement	1	0
Blood Urine Present	1	0
Urinary Tract Infection	1	0

10.6.8 Table 1: TEAE subdivided by preferred terms and severity

All BLI800 Patients (n=375)

Preferred Term	Severity Mild	Moderate	Severe
Number of Patients with Any Event	17 (4.5)	11 (2.9)	1 (0.3)
Number of Events	22	13	1
Abdominal distension	0	4 (1.1)	0
Abdominal pain	0	3 (0.8)	0
ALT increased	1 (0.3)	0	0
Anal discomfort	1 (0.3)	0	0
AST increased	2 (0.5)	0	0
Atrioventricular block complete	0	1 (0.3)	0
CK increased	1 (0.3)	0	0
LDH increased	1 (0.3)	0	0
Chills	1 (0.3)	0	0
Diarrhea	1 (0.3)	0	0
Dry mouth	1 (0.3)	0	0
Dysuria	0	1 (0.3)	0
Headache	4 (1.1)	1 (0.3)	0
Mouth ulceration	1 (0.3)	0	0
Nasopharyngitis	1 (0.3)	0	0
Nausea	3 (0.8)	1 (0.3)	1 (0.3)
Pruritis	1 (0.3)	0	0
Vomiting	3 (0.8)	2 (0.5)	0

Taken from Applicant's Table 301-8 from Module 5, Volume 5.1

10.6.9 Further Detailed data of Table 20: Pooled Study 301 and 302 Reviewer Calculated Most Common Adverse Events Observed in At Least 1%

Symptoms	Total Number events of symptom	BLI800 N = 394 (%)	MoviPrep N=393 (%)
Abdominal Pain	289	140 (35.5)	149 (37.9)
Abdominal Distension	393	188 (47.7)	205 (52.2)
Nausea	295	158 (40.1)	137 (34.9)
Vomiting	55	41(10.4)	14 (3.6)
Headache	10	6 (1.5)	4 (1.0)
Discomfort	467	225 (57.1)	242 (61.6)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22372	ORIG 1	BRAINTREE LABORATORIES INC	SUPREP BOWEL PREP KIT

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JASMINE C GATTI
08/13/2009

JOHN E HYDE
08/19/2009
Do not concur with recommendation for Approval. See separate Cross-Discipline Team Leader Review.