CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203595Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 18, 2013
From	Robert P. Fiorentino, M.D., M.P.H.
Subject	Cross-Discipline Team Leader Review
NDA#	203595
Applicant	Braintree Laboratories, Inc.
Date of Submission	December 16, 2011
PDUFA Goal Date	January 19, 2013, originally October 19, 2012 (review extension on Oct. 10, 2012)
Proprietary Name / Established (USAN) names	SUCLEAR / Sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution
Dosage forms	Oral solution, and powder for oral solution
Proposed Indication(s)	Colon cleansing in preparation for colonoscopy
Recommended:	*Approval*

Table of Contents

1. Introduction

On December 16, 2011, Braintree Laboratories submitted a 505(b)(1) NDA for a new oral bowel cleansing agent used in preparation for colonoscopy. The preparation of BLI850 prior to ingestion results in a separate sulfate salt solution and a polyethylene glycol (PEG) plus electrolyte solution, thereby making this a combination product under 21 CFR 300.50.

The Applicant's proposed indication is "for cleansing of the colon in preparation for colonoscopy in adults." The Applicant seeks approval of two dosing regimens, in which BLI850 is either taken in a 2-day Split Dose regimen or as a Day Before (b) (4) regimen. The results of two adequate and well controlled clinical trials were submitted to the NDA to support approval.

The review was conducted as a Standard review with a review extension on Oct. 10, 2012 due to a major amendment. Reviews were submitted by multiple disciplines described in Section 2.

2. Background

General Background: Bowel Cleansing Products

Compounds used for bowel cleansing can be divided into 3 broad categories according to their mechanism of action: *isosmotic, hyperosmotic* and *stimulant*.

Isosmotic preparations that contain PEG are considered osmotically balanced, high-volume (4L liters), non-absorbable, and non-fermentable electrolyte solutions. These solutions cleanse the bowel with less water and electrolyte shifts and provide evacuation primarily by the mechanical effect of large-volume lavage.

Hyperosmotic preparations draw water into the bowel lumen, which stimulates peristalsis and evacuation. These are smaller-volume preparations but their hyperosmotic nature can cause fluid shifts, accompanied by transient serum electrolyte alterations or dehydration.

Stimulant laxatives promote colonic motility through variable mechanisms that are incompletely characterized. Bisacodyl is a commonly used over-the-counter laxative and is used in combination with lower volume (2 liters) PEG plus electrolyte solutions (PEG-ELS) as a bowel cleansing agent, such as in HalfLytely. Bisacodyl's active metabolite stimulates colonic motility.

Adverse events following bowel preparation are uncommon but potentially serious. Because many patients undergoing colorectal cancer screening are otherwise healthy, the benefit:risk ratio must be carefully considered when deciding which preparation to prescribe to which patient. The adverse effects of bowel preparations can be magnified

when there is inadequate hydration, inappropriate dosing or inappropriate patient selection.[1]

As also discussed in detail in Dr. Lee's Clinical Review, the importance of a high-quality bowel preparation for the detection of colon polyps has been demonstrated in several studies[2,3]. Patients who are either unable or unwilling to complete a colon-cleansing regimen may have inadequate bowel cleansing, which can result in incomplete visualization of the colon and failure to detect colon pathology. Furthermore, poor bowel preparation can prolong procedure time and increasing the chance of an aborted examination, thereby necessitating a repeat colonoscopy at an interval sooner than that recommended by screening guidelines. Improvements in bowel preparation tolerability are important for increasing patient compliance with colorectal cancer screening guidelines, which in turn can lead to improved health outcomes.

As further addressed in Dr. Lee's review, split dosing (or 2-day dosing) of bowel preparations for colonoscopy has recently emerged as an important factor in bowel cleansing efficacy and may also impact patient tolerability. In an effort to improve the quality of colonoscopy, the 2008 American College of Gastroenterology guidelines for colorectal cancer screening recommend that bowel preparations be given in split doses and that this regimen become the standard of care[3]. One of the main concerns with respect to bowel preparations administered entirely the day before the procedure is the potential for impaired visualization of the colon because of residual fecal matter, particularly in the right colon. Passage of chyme from the small intestine to the cecum and ascending colon during the interval between final administration of the purgative and onset of the procedure may make the visualization of mucosal detail difficult. In addition, continuous gastric, intestinal, pancreatic, and biliary secretions also may result in re-accumulation of small intestinal effluent in the colon[4].

Product Background

BLI850 is a combination product containing the following two components:

(1) sodium sulfate, potassium sulfate and magnesium sulfate oral solution that must be diluted prior to ingestion; and
(2) PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride powder that must be constituted into an oral solution prior to ingestion.

<u>First component or Dose 1 (oral solution)</u>
6-oz liquid concentrate contains sodium sulfate, potassium sulfate, and magnesium sulfate, as well as inactive ingredients. The liquid concentrate must be diluted with 10 oz

[1] Adamcewicz, M et al Mechanism of Action and Toxicities of Purgatives Used for Colonoscopy Preparation, Expert Opin Drug Metab Toxicol. 2011 January; 7(1): 89-101
[2] Leaper et al. Reasons for failure to diagnose colorectal carcinoma at colonoscopy. Endoscopy. 204;36:499-503
[3] Harewood GC et al. Impact of colonoscopy preparation quality on detection of suspected colonic neoplasia. Gastrointest Endosc.2003;58:76-79.
[4] Frommer D. Cleansing ability and tolerance of three bowel preparations for colonoscopy. Dis Colon Rectum.1997;40:100-104.

of water prior to use (total of 16 oz). Sodium sulfate is the primary, osmotically active ingredient in this sulfate concentrate component. The sulfate liquid concentrate has the same formulation as the approved SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate and magnesium sulfate) Oral Solution (NDA 22-372, approved August 5, 2010), but uses half the amount (i.e., one 6-oz bottle or half of the total 12-oz dose of SUPREP).

Table 1: BLI850 product composition: First component or Dose 1 (Sulfate Solution)

Raw material and Grade quality	Quantity per dose (6-oz bottle)	Function
Sodium Sulfate, USP	17.51 g	active ingredient
Potassium Sulfate, (b) (4)	3.13 g	active ingredient
Magnesium Sulfate Anhydrous, USP	1.6 g	active ingredient
Sodium Benzoate, NF	(b) (4)	(b) (4)
Sucralose (b) (4)		
Malic Acid, FCC		
Citric Acid, USP		
(b) (4) Flavor		
		(b) (4)
Purified Water, USP		(b) (4)

Source: Adapted from the Applicant's NDA 203-595 submission, Module 2, 2.3P, Table 1.

Second component or Dose 2 (for oral solution)

2 liters of polyethylene glycol and electrolytes (PEG-ELS) for oral solution is comprised of 4 drug substances: polyethylene glycol 3350 (PEG-3350), sodium chloride, sodium bicarbonate, and potassium chloride. PEG-3350 is the primary, osmotically active ingredient in this PEG-ELS component. The 2L PEG-ELS component is part of the FDA-approved NuLYTELY (NDA 19-797, approved April 22, 1991), but uses half the amount (i.e., 2L or half of the 4L dose of NuLYTELY). This formulation is also identical to the PEG solution part of HalfLytely and Bisacodyl Tablets Bowel Prep Kit (NDA 21-551, approved May 10, 2004) without bisacodyl tablets.

Table 2: BLI850 product composition: Second component or Dose 2 (PEG-ELS)

Raw material and Grade quality	Quantity per dose (2L bottle)	Function
Polyethylene Glycol 3350, NF	210 g	active ingredient
Sodium Chloride, USP	5.6 g	active ingredient
Sodium Bicarbonate, USP	2.86 g	active ingredient
Potassium Chloride, USP	0.74 g	(b) (4)
Flavor ingredients (optional)	1.00 g	flavoring agent

Source: Adapted from the Applicant's NDA 203-595 submission, Module 2, 2.3P, Table 2.

Key Regulatory Background

BLI850 has been developed under IND 102894.

January 30, 2009
The Division sent an advice letter to the Applicant detailing the following key clinical and statistical comments for Studies 301 and 302:

- The Division recommended that the Applicant use a non-inferiority margin based on the historical evidence of the efficacy of the active control and other clinical and statistical considerations relevant to the new treatment and the current trials. In addition, the Division requested that the Applicant provide a justification for selecting a 15% non-inferiority margin and address assay sensitivity and constancy assumptions.
- The Applicant was advised to clearly pre-specify the Intent to treat (ITT) and per-protocol (PP) populations for the primary and secondary analyses.
- The Division recommended that the non-inferiority analysis of the primary efficacy endpoint be conducted on both the ITT and PP populations. The comparison of the difference in the primary efficacy endpoint should be made using a confidence interval approach, which should be pre-specified in the protocol.
- The Applicant was asked to propose several sensitivity analyses to address missing data. The Division advised the Applicant that sensitivity analyses and handling of missing data should be pre-specified in the protocol.

June 9, 2009: The Division sent an advice letter to the Applicant to provide statistical comments for the submitted SAP for Studies 301 and 302. The following were the key recommendations provided to the Applicant:

- The Division recommended using a pre-specified non-inferiority margin of 9% instead of 15%.
- The Division recommended that the Applicant perform primary efficacy analysis using the PP population, which should be defined as patients who met the inclusion and exclusion criteria, adhered to the protocol and consumed at least 75% of the colon preparation product.

The Applicant did not request a pre-NDA meeting prior to submitting the NDA application.

Submission & Review
Original NDA study reports were submitted by paper on December 16, 2011; datasets were submitted electronically. Application was granted a Standard Review. The assigned PDUFA goal date was October 19, 2012 and was not extended during the review. The proposed pediatric plan was considered by the Pediatric Review Committee (PeRC) on August 1, 2012. The pediatric plan and Committee's recommendations are discussed in the Pediatrics section, below.

No Advisory Committee meeting or CDER Regulatory Briefing was convened to discuss this application.

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

DGIEP Clinical Review
- Jessica J. Lee, M.D. and Helen Sile, M.D., joint review signed 01/03/2013

Office of Clinical Pharmacology, DCP III
- Sandhya Apparaju, Ph.D., review signed 9/18/2012

DGIEP Nonclinical Review
- Yuk-Chow Ng, Ph.D., review signed 9/14/2012 and addendum added 10/04/2012

ONDQA (CMC)
- Gene W. Holbert, Ph.D., review signed 8/17/2012, addendum signed 01/17/2013

Division of Biometrics 3 (Efficacy Statistics Review)
- Wen Jen Chen, Ph.D., review signed 10/13/2012

Division of Biometrics 3 (Safety Statistics Review)
- Bradley McEvoy, MS, DrPH, review dated 09/12/2012

Pediatric and Maternal Health Staff
- Erica Radden, M.D., review signed 10/22/2012

Division of Medication Error Prevention and Analysis (DMEPA)
- Anne Tobenkin, PharmD, Prop. Name Review dated 05/03/2012
- Teresa McMillan, PharmD
    - Proprietary name review signed 09/17/2012
    - Label, Labeling and Packaging Review signed 09/14/2012
- Nitin Patel, Administrative File Memo, 6/29/2012

Division of Medical Policy Programs (DMPP) / Patient Labeling
- Karen Dowdy, RN, BSN, MedGuide reviews dated 10/02/2012 & 12/14/2012

Office of Prescription Drug Promotion (OPDP), Division of Consumer Drug Promotion (DCDP)
- Kendra Y. Jones, Regulatory Review Officer, review signed 11/07/2012

Office of Scientific Investigations, Division of Good Clinical Practice Compliance
- Khairy W. Malek, M.D., Ph.D., review dated 09/06/2012

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information
- Jeanne M. Delasko and Laurie Burke, electronically signed 01/14/2013

3. CMC/Device

In his initial review (dated 8/17/2012), the CMC reviewer concluded that the applicant had not provided sufficient information to assure the identity, strength, purity, and quality of the drug substance and drug product.

The following constitute the initial list of deficiencies identified in the initial CMC review with discussion on how they were resolved (see CMC review addendum electronically signed 1/17/2013):

Regarding the Drug Substance

Initial CMC review noted the following review issues:

- Inadequate specification for assuring the purity of the PEG 3350, which is not controlled for the presence of carcinogenic (b) (4) and (b) (4) Revised specification with a test and acceptance criterion of less than (b) (4) for these two carcinogenic impurities is needed.

The CMC Reviewer notes the following in his initial review of the PEG specifications:

"The Braintree specification for PEG 3350 contains a test for Residual Solvents (b) (4) by USP method <467>. The ICH Q3C recommended permitted daily exposure for (b) (4) In order to achieve the PDE limit, a residual (b) (4) limit of (b) (4) in the drug substance would be required. The Pharmacology Toxicology review team has also raised questions about the proposed limits of (b) (4) for residual (b) (4). At the proposed limit of (b) (4) a single dose of the drug product containing 210 g of PEG 3350 could result in a dose of (b) (4) of (b) (4)

The CMC reviewer also noted in his initial review that the drug substance specifications are based on the current USP/NF requirements. The Braintree specification for PEG reflects that of the manufacturer which is cross-referenced to (b) (4) The CMC reviewer concluded that the specification is acceptable except for the absence of adequate controls of (b) (4) and (b) (4) with proper test method and acceptance criterion. See Section 4 for a discussion of this issue from the Nonclinical reviewer's standpoint.

However, the applicant did not have a validated assay developed to test for (b) (4) and (b) (4) An appropriate assay was developed during the review extension period following a major amendment (based on the August 10, 2012, solicited major amendment).

On January 8, 2013 the applicant responded to the issues concerning the PEG3350 drug substance and provided the method validation summary for the assay .This method validation supports a combined limit of (b) (4) for the sum of (b) (4) and

(b) (4) for PEG3350 raw material samples. CMC Review noted that the method validation of the assay is acceptable.

On January 11, 2013, the applicant submitted batch analysis data for PEG3350 sourced from (b) (4) (6 lots) and (b) (4) (8 lots). (b) (4) therefore requested that the applicant withdraw (b) (4) as a supplier of PEG drug substance within the NDA. The applicant agreed on January 17, 2013, Braintree deleted (b) (4) as a supplier of PEG33350 via an amendment.

Material sourced from (b) (4) meets the revised specification of NMT (b) (4) Applicant did not report the individual values for (b) (4) but reported the total as (b) (4) which CMC found to be acceptable.

Both components of the drug product have been tested according to USP microbial limits and preservative effectiveness. Results met requirements and demonstrated that the formulation does not support microbial growth.

All facilities inspections have been completed and the Offices of Compliance and New Drug Quality Assessment have determined these facilities to be acceptable.

Regarding the Drug Product

Initial CMC review noted the following review issues:

- Batch analysis data for unflavored SUCLEAR Part 2 is absent. The information submitted in section 3.2.P.5.4 Batch Analysis is for the lemon-lime flavored product.
- Identity of manufacturer of the flavor packets and a copy of the flavor packet labeling are needed.
- Clarification of the purpose/use of (b) (4) is needed.
- Absence of the expiration dating period of the flavor packets.
- Absence of a batch record for the unflavored drug product.

The applicant responded to the drug product deficiencies on September 7, 2012. The above CMC issues were resolved.

Because the applicant chose to use a different cup that had a more prominent fill line (See Section 12) in order to address DMEPA's concern (see Section 12), the CMC reviewer was asked to evaluate the new cup specifications. As noted in the final CMC review, the materials of construction (b) (4) are unchanged and meet the requirements for materials in contact with food. The volume will remain the same (16 oz). On January 14, 2013, the applicant submitted revised specifications and a drawing of the new cup. From the CMC perspective, the newly proposed cup is acceptable.

In addition, the CMC reviewer recommended the following labeling revisions in the CMC review dated 8/17/2012.

- The established name of this product should be as follows: *SUCLEAR (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; and PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)*
- (b) (4) is not acceptable as a part of the established name, and it should be revised as follows: *PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution*
- On the individual component labels, the product names should be SUCLEAR Dose 1 and SUCLEAR Dose 2.
- On all labels, list ingredients in order of decreasing concentration (amount) in the formulation. Revise strengths on Dose 2 label to be consistent with Dose 1.
- Dosage strength is not correctly specified on the carton label.
- The statement, "Keep out of reach of children" should appear either on all label/labeling or none.

The applicant has made these revisions to the labeling.

Finally, with regard to establishing stability of the potassium sulfate salt, the CMC reviewer notes that storage conditions were not defined. However, since the material is an inorganic salt, the only parameter likely to change with time is (b) (4) . Sufficient information has been provided to ensure the quality of the drug substance.

Upon resolution of these issues, this NDA was recommended for approval from the ONDQA perspective.

4. Nonclinical Pharmacology/Toxicology

The Nonclinical review concludes that this application should be approved. For more details, refer to the Nonclinical reviews by Yuk-Chow Ng, Ph.D., dated 9/14/2012 and 10/04/2012.

The Sponsor did not submit any new nonclinical studies to support the current application. All nonclinical toxicology studies on the BLI850 components were submitted and reviewed previously under NDA 21-551 (HalfLytely), NDA 19-797 (NuLytely), NDA 22-372 (Suprep), and NDA 22-015 (Miralax). As noted in the Nonclinical review, the review of nonclinical studies with Suprep (containing twice the sulfate salt amount as Suclear) concluded that the animal data adequately supported the proposed use at the intended therapeutic dosage (Pharmacology/Toxicology review of NDA 22-372 by Dr. Tamal Chakraborti, dated 03/06/2009). The Nonclinical reviewer also notes that it was concluded previously that PEG-ELS did not produce any signs of

toxicity, except soft stools and diarrhea, in dogs. In addition, the safety of the PEG-ELS components in HalfLytely has been previously established through its clinical and post-marketing experience in bowel cleansing agents (Pharmacology/Toxicology review of NDA 21-551 by Dr. Tamal Chakraborti, dated 11/13/2002). Therefore, from a nonclinical standpoint, there isn't a safety concern for the proposed use of SuClear. David B. Joseph, the Pharmacology Team Leader, noted in his review dated 10/11/2012 that the Agency did not request nonclinical studies to support clinical testing or approval of this drug product in part because studies on its components have already been evaluated for other products and Suclear is a single-use product with low probability of new or unexpected toxicities.

However, as also discussed in the overview of the CMC issues, (b) (4) and (b) (4) are potential process impurities that may be present in PEG-3350. As noted in the Nonclinical review, the applicant justifies their proposed limit of (b) (4) for (b) (4) based on the recommendation in ICH Q3C under (b) (4) (b) (4) However, the Nonclinical reviewer found that this limit applies to drug products with a daily dose less than (b) (4) per day. As described in the initial Nonclinical review dated 9/14/2012, because the one day (or split dose 2-day) intake of PEG in the proposed dosing is 210 g, the limit should have been calculated based on the ICH Permissible Daily Exposure (PDE) level, which is (b) (4) based on an intake of 210 g PEG. (b) (4) is considered to have similar toxicity as observed for (b) (4) , therefore the Nonclinical reviewer concluded in his review dated 9/14/2012 that the Sponsor should be asked to set a limit of (b) (4) for the combined total amount of (b) (4) and (b) (4)

Subsequent to this review, the applicant indicated that they will be able to reduce the specified combined limit for (b) (4) and (b) (4) to (b) (4) The Nonclinical reviewer concluded in an addendum to his review dated 10/04/2012, that the proposed specified limit of (b) (4) is acceptable, based on the following reasons:

1. The PDE of (b) (4) stated in ICH Q3C is intended as a limit for a lifetime exposure of (b) (4) Because SuClear is taken only as a onetime dose, the higher limit of (b) (4) proposed by the Sponsor is deemed reasonable for this drug product.
2. The Agency for Toxic Substances and Disease Registry (ATSDR) sets a MRL (Minimal Risk Level) of (b) (4) in intermediate-duration exposure (15-364 days). This level is equivalent to (b) (4) at a 210 g PEG dose, based on a 60-kg bodyweight. Thus, the maximum (b) (4) in a 60-kg patient) at the newly proposed limit is well below the MRL.
3. The Environmental Protection Agency (EPA) has set the RD (Reference Dose) at (b) (4) which is equivalent to (b) (4) in a 210 g PEG dose, based on a 60-kg bodyweight.
4. Although SuClear in indicated for use in adults only, the safety concern related to the potential presence of (b) (4) is also relevant to pediatric patients, given that clinical studies in pediatric patients will be required after approval of this application. Thus, the limit for combined (b) (4) should provide a reasonable assurance of safety in both adult and pediatric patient populations.

As noted in the overview of the CMC review, the review clock was extended on Oct. 10, 2012, which allowed sufficient time for the applicant to develop an assay to measure (b) (4) and (b) (4) in the PEG.

5. Clinical Pharmacology/Biopharmaceutics

Based on the Clinical Pharmacology reviewer by Sandhya Apparaju, Ph.D., dated 9/18/2012, this NDA is acceptable [for approval] from a Clinical Pharmacology perspective provided an agreement can be arrived at with the sponsor regarding proposed labeling language.

Dedicated dose-ranging phase 2 studies were not conducted in support of this NDA. However, data from two earlier PD studies (005-082 and 006-181) were presented in the NDA in order to address the issue of dose-selection for the active components. In these studies, the PD parameter was derived from the final stool sample after the test dose(s) was centrifuged and analyzed for percent solids. According to this method a 5 g sample from the final stool is centrifuged at 3000 rpm for 30 minutes. The supernatant is decanted and the remaining pellet weighed. The stool percent solid is then calculated as the weight of the pellet divided by 5g: % stool solid = (pellet weight/5g)*100; This parameter, % stool solids in the final bowel movement, also dubbed by sponsor as "scatocrit" in this NDA, along with total weight of stools (g) produced was used as PD measures.

These studies were also used as evidence that the components by themselves would be inadequate bowel cleansing agents.

The phase 1 PD studies are briefly summarized below:

PD (Baylor) Study 005-082: Title - Detection of laxative ingestion by thin layer chromatography and development of an appropriate formulation for a sulfate based bowel cleansing solution.

This was a single-center, open-label, non-randomized study of various laxatives and sulfate based formulations in normal healthy males and female volunteers at least 18 years of age (n = 27). Subjects received one or more of approved bowel preparation/laxative products or new sulfate based formulations (with a minimum of one

week washout when receiving more than one treatment) and their final stool was analyzed for percent solids. After an overnight fasting, subjects were given a dose of laxative sufficient to produce diarrhea, and bowel movements and urine were collected for 24 hours. Blood samples were taken about 2 hours prior to ingestion of the dose and 2-4 hours after ingestion. Subjects were not allowed food and only water was allowed during study period. Stool and urine were analyzed for volume and electrolytes. Experimental laxatives were as follows: Bisacodyl 20 mg, Senna 34.4 – 68.8 mg, Milk of Magnesia 123- 239 mmol, NuLytely 2L, NuLytely 4L [both containing PEG3350 with Electrolytes], HalfLytely [containing 20 mg bisacodyl with 2L NuLytely], and five different experimental sulfate formulations containing varying amounts of sodium, potassium and magnesium sulfates.

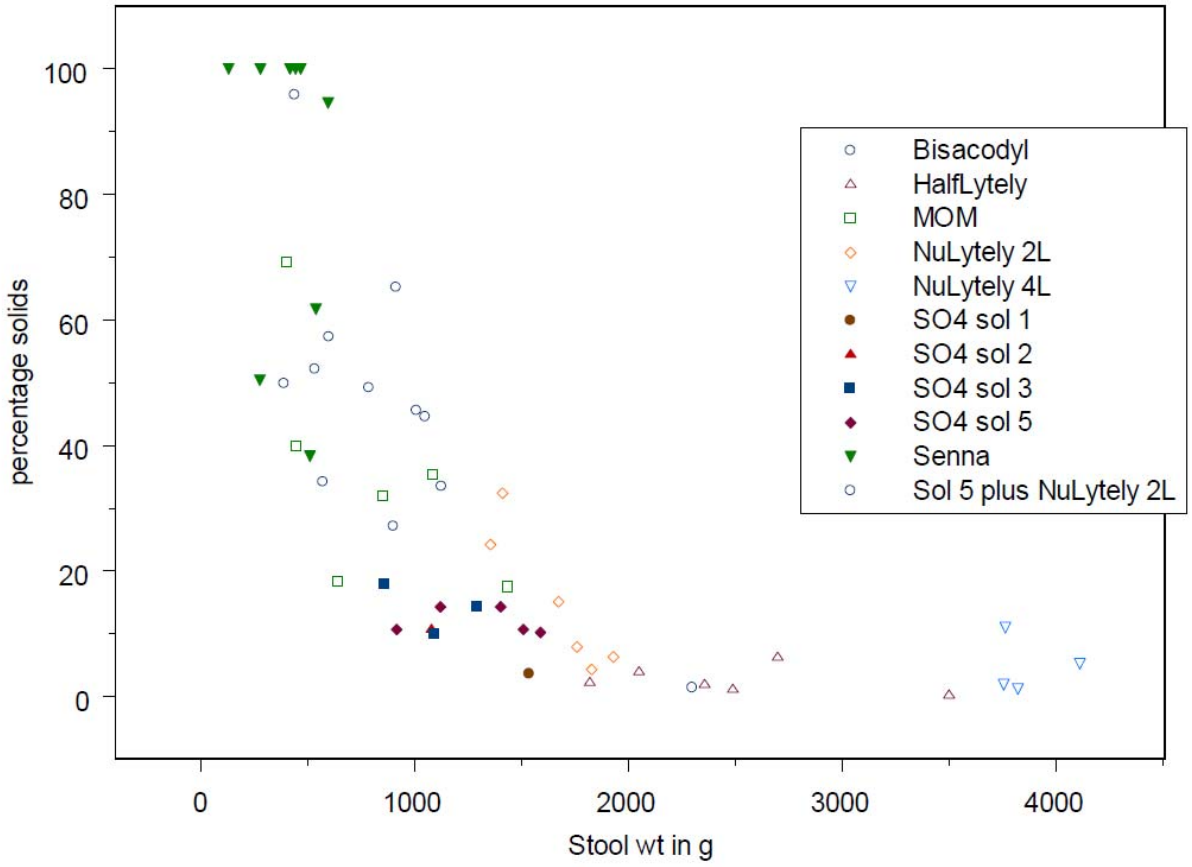
The results of the study are presented in Table 3 and Figure 1.

Table 3. Results of Study 005-082

Formulation	**Total stool weight (g)**	**Percentage solids (%) in the final bowel movement**
Senna (n = 9)	407 (150)	82.8 (25.3)
Bisacodyl 20 mg (n = 11)	757 (260)	50.4 (18.7)
Milk of Magnesia (n = 6)	813 (398)	35.3 (18.9)
NuLytely 2L (n = 6)*	1659 (231)	15 (11.2)
NuLytely 4L (n = 4)#	3861 (168)	4.8 (4.5)
HalfLytely (n = 7)#	2403 (577)	2.6 (2.2)
SO4 solution 1 (n = 1)	1536	3.6
SO4 solution 2 (n = 1)	1080	10.7
SO4 solution 3 (n = 3)	1082 (215)	14.1 (4)
*SO4 solution 4 [# 5 with 2L NuLytely] (n = 1)***	*2298*	*1.4*
SO4 solution 5 (n = 5)*	1308 (281)	12 (2.1)
*Individual components of proposed product; ** proposed combination; # FDA approved drug products		

Source: Applicant, Response to FDA Information Request (8/3/2012)

Figure 1.



Source: Clinical Pharmacology review.

The Clinical Pharmacology reviewer commented that the Results of this PD study in totality suggest that the individual components [PEG3350 (NuLytely) 2L or oral sulfate solution #5] when administered alone did not generate the total stool weight and didn't reduce % stool solids in the final stool to an extent that were attained with the approved colon cleansing formulations. However the Clinical Pharmacology reviewer admits in he review that this study has its limitations, as currently there is no established correlation between the PD endpoints used (% stool solids and total stool weight in g) and the clinical efficacy of colon cleansing preparations.

PD Study 006-181: Title - A comparison of the safety and efficacy of BLI800 [SUPREP] oral sulfate solution to the fleet EZ-Prep and NuLytely in normal volunteers.

This was an open label study that compared the safety and efficacy of oral sulfate solution in SUPREP to Fleet EZ-Prep (Phosphosoda) and NuLytely (an approved 4L PEG lavage) in normal volunteers. SUPREP contains twice the amount of oral sulfate solutions than that proposed in the current drug product; this dose is administered as 6 oz doses and therefore pharmacodynamic information collected after the first dose will be

relevant for the current NDA. Study was conducted in 9 subjects. Patients were allowed to use multiple treatments if they underwent adequate washout period. In this study 5 patients received single treatment only while 4 others received 2 to 3 treatments. Average patient age was 23 years. All preparations were consumed in a split dose regimen; half of the dose was administered in the evening and the second half during the next morning, 12 h apart. The first half of the dose corresponds to 4 oz (125 ml) for BLI800, 45 ml for EZ-Prep and 2L for NuLytely. The second half of the dose corresponds to 4 oz for BLI800, 30 ml for EZ-Prep and 2L for NuLytely. BLI800 and EZ-Prep subjects were required to drink additional water (to allow comparisons to NuLytely 4L). Primary efficacy was assessed via quantitative measurement of stool weight. All stools were collected and weighed and subsequently analyzed for electrolyte composition. Secondary efficacy outcomes include analysis of percentage of fecal solid content of the final diarrheal sample (i.e., "scatocrit") collected during each preparation period [preparation periods are defined as Period 1: 7PM to 5 AM; Period 2: 5 AM to 12 PM]. Serum, stool and urine were also analyzed for electrolyte composition. Patient adverse events were also collected.

Results of this study are presented in Table 4.

Table 4.

Stool % solids in final bowel movement	BLI800 (oral sulfates; n=5)	EZ-Prep (n = 5)	NuLYTELY (PEG-ELS; n = 5)
Period 1 [first ½ dose]	6.4 (7.7)	16.4 (8.9)	8.5 (8.3)
Period 2 [second ½ dose]	1.6 (0.8)	4.1 (0.8)	1.1 (0.2)

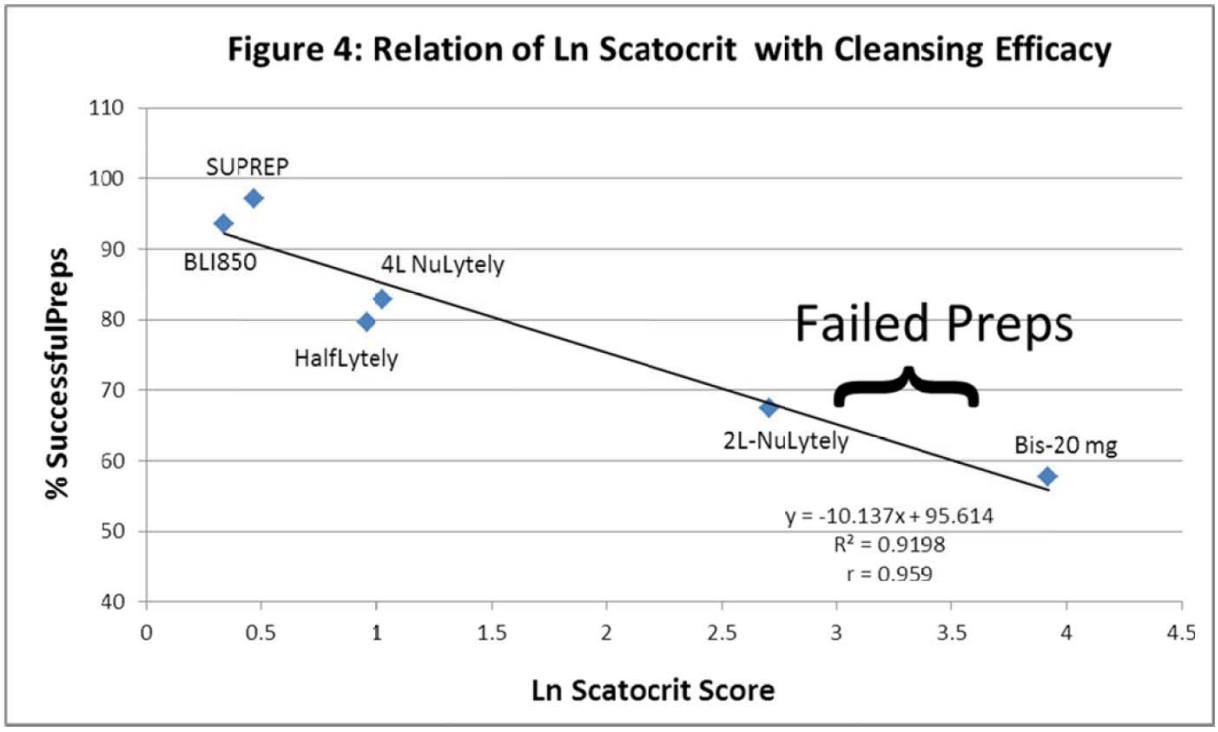
Source: Clinical pharmacology review.

The Clinical Pharmacology reviewer comments that this data suggests that % stool solids was higher for all three groups after the first period, while it decreased considerably after the second dose in the second period, thus suggestive of more complete cleansing with the second half of the dose. In addition, Period 1 data suggests that the half-doses of oral sulfate solution in BLI800 [SUPREP] and PEG3350 in NuLytely, very similar to those proposed as individual components of the proposed product (BLI850), may be inadequate within the context of the PD endpoints assessed. In this study the PD findings for half-doses of oral sulfate solution and NuLYTELY were comparable. The Clinical Pharmacology reviewer concludes that it is likely that combination of these two components may provide additional benefit with regard to % solids in final bowel movements.

The Clinical Pharmacology reviewer also discussed many of the other analyses and tabulation of data presented by the sponsor, but these are also discussed in depth within the Clinical review.

The Clinical Pharmacology review does note the findings presented in Figure 2 below.

Figure 2



Source: Applicant

The Clinical Pharmacology reviewer notes that this regression equation correlating scatocrit and cleansing response for successful and unsuccessful formulations across studies was used to arrive at a 70 % (inadequate) cleansing efficacy rate for a ½ dose of Suprep (22g), such as proposed in BLI850. Together with 2L of NuLytely - that also provides a 67% (inadequate) cleansing response – the reviewer concludes that "it may support the hypothesis that the combination will provide adequate colon cleansing as demonstrated by clinical trials of BLI850 which show 92.5% cleansing rates."

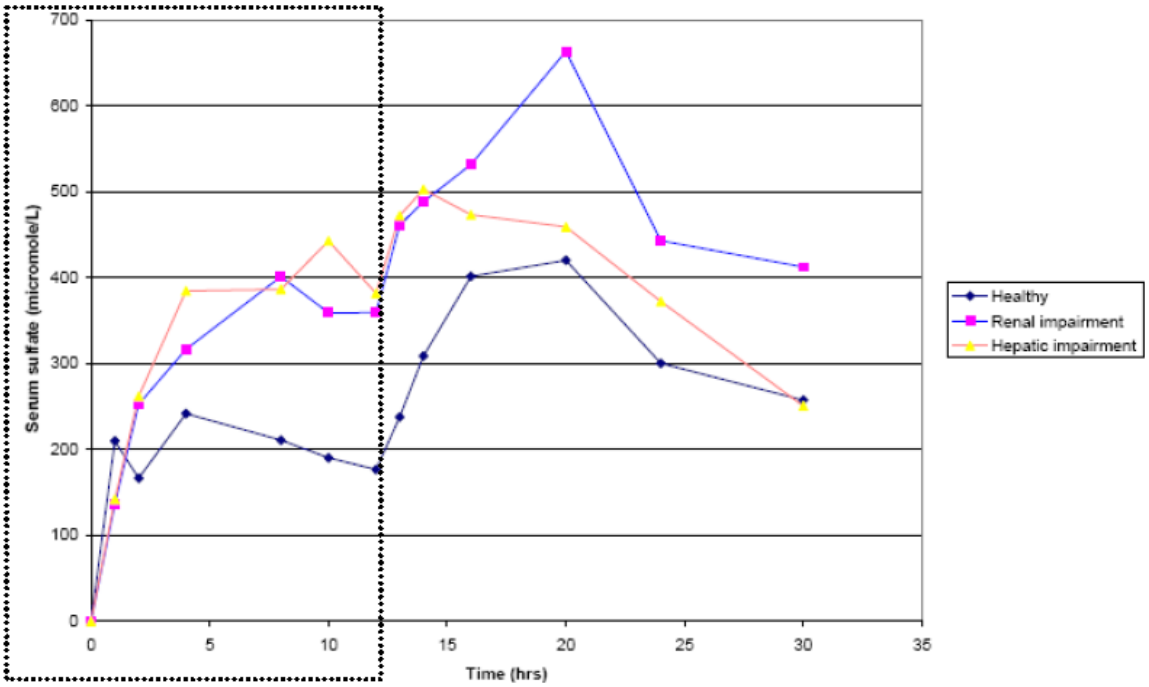
The Clinical Pharmacology reviewer concluded that the analyses provided by the applicant suggest likely correlation between the PD endpoint ('scatocrit') and the clinical efficacy outcomes and notes the following evidence:

1) the observed trend for association between PD parameters and clinical efficacy noted for the single components of approved HalfLytely or half-doses of approved NuLYTELY 4 (2L PEG-ELS).
2) the observed association between the PD parameter and clinical efficacy noted for the full dose of approved Suprep, along with higher scatocrit (PD) noted for ½ dose of Suprep.
3) the comparable efficacy of full doses of Suprep and BLI850 in randomized clinical trials (93.5% vs. 97.2%).

- Evaluation of Sulfate Exposures

As discussed in the Clinical Pharmacology review, serum sulfate levels were not evaluated in the current clinical trials supporting this NDA; however they were evaluated in Study BLI800-202 that was originally conducted for the approval of SUPREP. This was an open-label, safety and PK study in mild to moderate hepatic impairment (n = 5 with Child-Pugh (CP) A; n = 1 with CP-B), moderate renal disease (n=6; CrCl: 30 - 50 mL/min) or healthy volunteers (n =6). This study evaluated the pharmacokinetics after two 6 oz doses of the oral sulfate solution. Study was previously reviewed under NDA 22372. For this study, following oral administration of 6 oz of oral sulfate salt solution (the same amount taken in BLI850), sulfate levels rose above the basal concentrations within 1 hour of the first dose. Concentrations then peaked after the first dose at a median Tmax of 4 hours in healthy volunteers. Concentrations after the first dose did not return to baseline prior to the second dose of oral sulfates at 12 h. At the end of dosing, sulfate concentrations returned to endogenous levels within 3 days post-dose. The half-life of elimination was ~ 8.5 hours in healthy volunteers. Based on urinary excretion data, the fraction of total dose absorbed appeared to be approximately 20% following oral administration of oral sulfate salts.

Figure 3. Serum sulfate levels (dotted box contains data after only first dose excluding data after 2nd)



Considering only the 12 h data following the first dose, mean Cmax, median Tmax, AUC_{12h} values were as follows for the three groups:

Healthy volunteers:	399 umol/L at a median Tmax of 4 h; AUClast: 2404 umol.h/L
Mild/MHI:	469 umol/L at a median Tmax of 8 h; AUClast: 4057 umol.h/L
MRI:	429 umol/L at a median Tmax of 8 h; AUClast: 3757 umol.h/L

Source: Clinical Pharmacology review.

The Clinical Pharmacology reviewer concluded that the clinical implication of this increase in systemic exposure of sulfate anion is not known: while drug clearance is somewhat slower than normal in organ dysfunction, considering that the drug is for single use prior to colonoscopic procedure and that the dose of sulfates proposed is half that in SUPREP thus ruling out accumulation potential, it appears reasonable not to require dose adjustments in specific subpopulations including renal impairment. Sections 8.6 (renal impairment) and 12.3 (PK) of the proposed label have been updated to reflect the Clinical Pharmacology reviewer's recommendations.

- PEG absorption

PK of PEG3350 following the proposed drug product has not been provided in this NDA. Sponsor has primarily relied upon literature that suggests predominant fecal excretion of unabsorbed PEG following oral dosing.

- Drug-drug interactions

No specific drug-drug interaction studies have been conducted for the proposed drug product. The proposed labeling cautions regarding drugs that may increase risks due to fluid and electrolyte abnormalities and effect on absorption of concomitant drugs taken within 1h of bowel cleansing agents. The Clinical Pharmacology review concludes that the rationale as provided by sponsor addresses the absence of DDI potential between the formulation components and no further action is needed in this regard.

- Intrinsic Factors
  The Clinical Pharmacology reviewer makes the following conclusions in her review:
    - Renal Impairment: renal impairment has a potential to reduce the sulfate clearance
    - Elderly: Caution should be recommended while dosing in elderly. However, a specific dose adjustment is not necessary based on age as elderly patients constituted 25% of patient population in the two clinical trials for BLI850 and have not identified significant differences in safety and efficacy.
    - Gender: No differences in efficacy were noted for the primary endpoint between genders (~ 92.3% vs. 91.1% success rates for females and males respectively across both studies). No dosage adjustment is necessary based on gender.
    - Race: Majority of patients in clinical trials for BLI850 were Caucasian, with approximately 13% of enrolled patients belonging to other races. For BLI850, the % successful preparations were 92.1% and 88.6%, respectively for Caucasians, and non-Caucasians for both studies combined. No dosage adjustment is necessary based on race.
    - Pediatric: Safety and effectiveness in pediatric patients have not been established.

- Thorough QT study or other QT assessment

QT prolongation potential of BLI850 was not formally evaluated. Individual components of the formulation (i.e. oral sulfates and PEG3350 with electrolytes) are approved at similar and higher doses in formulations such as SUPREP, NuLytely, GoLytely and HalfLytely. No thorough QT studies were required for those approved formulations. FDA has not typically required TQT studies for osmotic laxatives since EKG changes are known to occur secondary to electrolyte and fluid shifts (see reviews for Visicol NDA 021097 and Prepopik NDA 202535).

- Phase IV Commitments

The Clinical Pharmacology review notes that the sponsor did not assess the systemic exposure to PEG3350 following the recommended dosing regimen. Assessments in this regard for evaluation of PEG3350, as well as (b) (4) and (b) (4) have been recommended by the Clinical Pharmacology reviewer for evaluation post-approval.

6. Clinical Microbiology

Not relevant to this application.

7. Clinical / Statistical- Efficacy

The Applicant submitted two adequate and well-controlled efficacy trials, BLI850-301 (Study 301) and BLI850-302 (Study 302), to support the indication of colon cleansing in preparation for colonoscopy in adults. Because the dosing regimen and the active comparator were different for Studies 301 and 302, these studies were not combined for integrated efficacy evaluation.

Table 5: Clinical trials submitted to support NDA

Trial	Location	Trial Design	Treatment Arms	# of Patients Treated[1]	# of Patients Completing Trial[2]	Trial Duration
BLI850-301 **(Study 301)** *Day-Before Regimen*	12 sites from U.S.	Phase 3, MC, R, SB, AC, PG efficacy and safety trial	BLI850 HalfLytely+ Bisacodyl Tablet Bowel Prep Kit	176 190 Total: 366	175 (99%) 187 (98%)	15 days
BLI850-302 **(Study 302)** *Split-Dose Regimen*	12 sites from U.S.	Phase 3, MC, R, SB, AC, PG efficacy and safety trial	BLI850 MoviPrep (split-dose)	186 185 Total: 371	184 (99%) 185 (100%)	15 days

MC, multi-center; R, randomized; SB, single-blind (investigator); AC, active control; PG, parallel group
[1]Treated patients consist of patients who took any amount of the study preparation (i.e., ITT patients or safety population).
[2]Completed patients consist of patients who received their study preparation fully and completed the study (i.e., patients who underwent colonoscopy)
Source: Reproduced from Dr. Jessica Lee's review. Originally adapted from the Applicant's Clinical Study Reports on Protocols BLI850-301 and BLI850-302, Tables 301-2 and 302-2, respectively.

Refer to Dr. Jessica Lee's clinical review signed 01/03/2013 for a detailed description of the clinical trials and outcomes.

Study BLI850-301 (Study 301): "Day-Before" Study

Study Design

Study 301 was a phase 3, multi-center, randomized, active-controlled, single-blind, parallel-group trial to assess efficacy and safety, The trial consisted of a screening visit (Visit 1), a colonoscopy exam visit (Visit 2), which was to occur within 15 days after visit 1, and a telephone follow-up period scheduled two weeks after Visit 2 for subjects that experienced ongoing adverse events. The trial was conducted from August 25, 2008 to November 21, 2008.

Study population consisted of male or non-pregnant female ≥18 years of age undergoing outpatient colonoscopic examination for a routinely accepted indication (routine screening, GI bleeds / anemia, IBD polypectomy, etc.). Subjects were excluded if they had known or suspected ileus, severe ulcerative colitis, gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis, or megacolon.

BLI850 was supplied as a kit containing one 6-oz bottle of sulfate solution (first dose) and one 2L bottle of polyethylene glycol 3350 and electrolytes (PEG-ELS) for solution (second dose).

Dosing instructions for BLI850 in Study 301:

1. Beginning at approximately 6 PM on the evening prior to the colonoscopy exam, subjects were instructed to dilute the 6-oz sulfate oral solution by pouring the entire contents of the bottle into the provided mixing container and then filling the container with water to the 16-oz fill line. Then, subjects were instructed to drink the entire cup of solution. Over the next 2 hours, subjects were instructed to drink one additional 16-oz glass of water.
2. At approximately 8 PM (2 hours after starting the first dose), subjects were instructed to dissolve the powder by adding water to the 2L fill line on the jug and begin drinking the 2 liters of PEG-ELS solution at a rate of one 16-oz glass every 20 minutes until the jug was empty. The subjects were recommended to drink at least one additional 16-oz glass of water on the evening prior to colonoscopy.

HalfLytely was supplied as a kit containing two 5 mg bisacodyl tablets and one 2L bottle of PEG-ELS.

Dosing instructions for HalfLytely and Bisacodyl Tablets Bowel Prep Kit in Study 301:

1. Between approximately 12 to 3 PM on the day prior to colonoscopy, subjects were instructed to take the two 5-mg bisacodyl tablets with water.
2. After waiting for a bowel movement to occur or a maximum of 6 hours after taking the bisacodyl tablets, subjects were instructed to drink the 2L of HalfLytely solution at a rate of 8 oz every 10 minutes.

All subjects in both treatment arms were instructed to consume only clear liquids from the day prior to until after completion of the colonoscopy exam.

Blinded investigators rated the quality of each colonoscopy preparation according to a 4-point rating scale as presented in Table 6.

Table 6: Colonoscopist Colon Cleansing Score

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

Source: Jessica Lee's clinical review. Originally reproduced from Applicant's Clinical Study Report for Protocol BLI850-301, Table 301-1.

As noted in Dr. Lee's clinical review, the Applicant reported that the above scoring scale was developed by the Applicant. This is despite substantial experience within the

literature of other scales to assess the effectiveness of bowel cleansing agents, such as the Ottawa Scale[5] or the Boston Bowel Preparation Scale[6].

The primary endpoint was the outcome ("success" or "failure") of the colon preparation. Successful treatment was defined as bowel cleansing grade of either excellent (a score of 4) or good (a score of 3) as evaluated by the blinded colonoscopist using the 4-point rating scale Colonoscopist Colon Cleansing Score.

Secondary endpoints included:

1. Adequacy of colon cleaning (cleaning adequate for evaluation) and need for re-preparation
2. Number of excellent preparations as rated by the blinded colonoscopist
3. Number of colonoscopic examinations in which the colonoscopist reached the cecum

Justification of Non-Inferiority Margin

The Applicant calculated a sample size of 360 subjects based on the goal of establishing non-inferiority on the primary endpoint between BLI850 and HalfLytely using a non-inferiority margin of 15%. As noted by both the Clinical and Statistical reviewers, the Division did not agree with this non-inferiority margin and recommended a lower margin of 9%. Refer to *Statistical Considerations* below for additional discussion on the choice of the non-inferiority margin.

Results

Of the 394 randomized subjects, 366 subjects administered the study medication and therefore, were included in the ITT analysis. A total of 28 subjects did not administer the study medication after randomization, as 22 subjects withdrew the consent prior to receiving the study medication and 6 subjects in the BLI850 group were found to not have met the eligibility criteria after the study medication was dispensed. The reasons for not meeting the eligibility criteria are listed below:

- 3 subjects with clinically significant laboratory abnormalities at Visit 1
- 1 subject without venous access to obtain blood samples
- 1 subject with a previous significant gastrointestinal surgery (i.e., prior colectomy)
- 1 subject involved in the conduct of the trial as a study coordinator

The primary efficacy analysis was based on the modified intent-to-treat (mITT) population, defined as all subjects who were dispensed a preparation kit, subsequently

[5] Rostom A, Jolicoeur E. Validation of a new scale for the assessment of bowel preparation quality. Gastrointest Endosc. 2004 Apr;59(4):482-6.

[6] Edwin J. Lai, MD, Audrey H. Calderwood, MD, Gheorghe Doros, PhD, Oren K. Fix, MD, MSc, and Brian C. Jacobson, MD, MPH, FASGE. The Boston Bowel Preparation Scale: A valid and reliable instrument for colonoscopy-oriented research. *Gastrointest Endosc*. 2009 March; 69(3 Pt 2): 620–625.

took any amount of the preparation, and did not withdraw prior to colonoscopy for reasons unrelated to safety or efficacy. Study population definitions are presented in Table 7.

Table 7: Definition of study populations included in the efficacy and safety analyses

Population	Study 301 N	Definition
All randomized subjects (RAND)	394	Subjects who were randomized to a preparation kit.
Intent-to-treat (ITT)	366	Subjects who were dispensed a preparation kit and subsequently took any amount of the preparation. This ITT population was used for all ***safety*** analyses.
Modified Intent-to-treat (mITT)	364	Subjects who were dispensed a preparation kit, subsequently took any amount of the preparation, and did not withdraw prior to colonoscopy for reasons unrelated to safety or efficacy. The mITT population was used for the ***primary*** efficacy endpoint analyses.
Completed subjects	362	Subjects who were dispensed a preparation kit, subsequently administered any amount of the preparation, and underwent a colonoscopy. Completed subjects were used for some of the ***secondary*** efficacy endpoint analyses.

Source: Dr. Lee's clinical review, originally summarized from the Applicant's Response to Information Request dated May 10, 2012.

Table 8: Primary efficacy analysis of Study 301 (mITT population)

Treatment Group	Responders[1] (%)	(95% CI)	[BLI850] – [HalfLytely] (95% CI)
BLI850	158/176 (89.8%)	(84%, 94%)	6.3%
HalfLytely Kit	157/188 (83.5%)	(77%, 89%)	(-0.8%, 13.4%)

[1]Responders were defined as subjects whose colon preparations were graded as either excellent or good by the colonoscopist (grading score 4 or 3).
Source: Summarized from Dr. Wen Jen Chen's Statistical review.

As shown in Table 9, BLI850 demonstrated numerically higher proportion of subjects with bowel preparations rated as "excellent" compared with HalfLytely, even when the colon cleansing grade of "good" was excluded from comparison.

Table 9: Number of subjects in Study 301 with "Excellent" colon cleaning score

	Treatment Group	
	BLI850	HalfLytely
Colon cleansing graded as "excellent"	84/176 (47.7%)	76/188 (35.6%)

Source: Dr. Lee's clinical review, originally sourced from the Applicant's Clinical Study Report for Protocol BLI850-301, Table 301-4.

The following secondary endpoints were evaluated in both Studies 301 and 302:

- Adequacy of cleansing (cleaning adequate for evaluation) and need for re-preparation
- Number of excellent preparation as graded by the blinded colonoscopist
- Number of examinations in which the colonoscopist reached the cecum

No adjustment was made for multiplicity testing of secondary endpoints. Therefore, the results of secondary endpoints are considered exploratory in nature.

To assess adequacy of cleansing, colonoscopists blinded to treatment were asked whether the cleansing was "adequate" for evaluation. They were also asked whether re-preparation was needed. Adequate cleansing was reported in 97% (170/175) of BLI850 and 98% (183/187) of HalfLytely subjects, with re-preparation required in virtually all of those with inadequate preps.

The result of the secondary endpoint of the proportion of "excellent" preps has been presented in Table 9, but is further broken down in Table 10.

Table 10: Colonoscopy assessment analysis by cleansing grade in Study 301 (mITT population)

Colon Cleansing Grade	BLI850 n = 176	HalfLytely n = 188
Excellent (4)	84 (47.7)	67 (35.6)
Good (3)	74 (42)	90 (47.9)
Fair (2)	13 (7.4)	25 (13.3)
Poor (1)	4 (2.3)	5 (2.7)
Missing	1 (0.6)	1 (0.5)
Mean ± SD[2]	3.36 ± 0.7	3.17 ± 0.8

[2]Two missing subjects (one from each treatment group) were not included in the calculation of mean scores.
Source: Modified from the Applicant's Clinical Study Report for Protocol BLI850-301, Tables 301-4 and 14.2.1.1.

For the third secondary endpoint, the cecum was reached in 97% (170/175) of BLI850 subjects and 98% (184/187) of HalfLytely subjects.

Study BLI850-302 (Study 302): "Split Dose" Study

Study Design
Like Study 301, Study 302 was a phase 3, multi-center, randomized, active-controlled, single-blind, parallel-group trial to assess efficacy and safety. The trial consisted of a screening visit (Visit 1), a colonoscopy exam visit (Visit 2), which was to occur within 15 days after visit 1, and a telephone follow-up period scheduled two weeks after Visit 2 for subjects that experienced ongoing adverse events. The trial was conducted from August 25, 2008 to November 14, 2008.

Eligibility criteria were the same as Study 301, except that Study 302 excluded subjects with phenylketonuria and known glucose-6-phosphate dehydrogenase deficiency because MoviPrep contains aspartame.

Subjects were dispensed BLI850 or MoviPrep and were provided instructions on dosing and dietary restrictions. Eligible subjects were instructed to take the first dose of the assigned bowel preparation the evening prior to their scheduled colonoscopy and begin the second dose the morning of their scheduled colonoscopy.

BLI850 was supplied as a kit containing one 6-oz bottle of sulfate solution (first dose) and one 2L bottle of PEG-ELS for solution (second dose). The compositions of the oral sulfate solution and PEG-ELS for solution were the same as Study 301.

Dosing instructions for BLI850 in Study 302:

1. Dose 1 (evening prior to colonoscopy)
    - Beginning at approximately 6 PM the evening prior to the colonoscopy exam, subjects were instructed to dilute the 6-oz sulfate oral solution by pouring the entire contents of the bottle into the provided mixing container and then filling the container with water to the 16-oz fill line. Then, subjects were instructed to drink the entire cup of solution. Over the next 2 hours, subjects were instructed to drink one additional 16-oz glass of water.
    - Subjects were recommended to drink at least one additional 16-oz glass of water on the evening prior to colonoscopy.

2. Dose 2 (morning of colonoscopy)
    - At approximately 6 AM, subjects were instructed to dissolve the powder by adding water to the 2L fill line on the jug and begin drinking the 2 liters of PEG-ELS solution at a rate of one 16-oz glass every 20 minutes until the jug was empty. The second dose would take approximately 1.5 hours to complete, and it had to be completed at least 2 hours prior to the scheduled colonoscopy exam.

All subjects in the comparator arm were instructed to follow the approved split-dose regimen of MoviPrep.

Dosing instructions for MoviPrep in Study 302:

1. Dose 1 (evening prior to colonoscopy)
    - At approximately 6 PM the evening prior to the colonoscopy exam, subjects were instructed to pour contents of pouch A and B into the 1 liter container and fill with water to the fill line. Subjects were instructed to drink the solution over one hour at a rate of 8 oz every 15 minutes until the container was empty.
    - Subjects were required to drink an additional 0.5 liters of clear liquid that evening.

2. Dose 2 (morning of colonoscopy)
    - At approximately 6 AM, subjects were instructed to prepare the second liter of solution and drink the solution over one hour at a rate of 8 oz every 15 minutes until the container was empty.
    - Subjects were required to drink an additional 0.5 liters of clear liquid that morning. The additional clear liquid had to be completed at least one hour prior to the scheduled colonoscopy exam.

Subjects in the BLI850 group were instructed to consume only clear liquids from the day prior to until after completion of the colonoscopy exam.

Subjects in the MoviPrep group were permitted to have a normal breakfast, light lunch, and clear soup and/or plain yogurt for dinner the day prior to colonoscopy. Subjects were instructed to consume only clear liquids from the time they start the MoviPrep treatment until after completion of the colonoscopy exam.

The endpoints and assessments of efficacy were the same in Study 302 and Study 301.

Results

Dropouts and discontinuations were generally similar between the two treatment arms in Study 302 (unlike Study 301). Refer to Dr. Lee's review for a more detailed presentation of the discontinued subjects.

Table 11: Primary efficacy analysis of Study 302 (mITT population)

Treatment Group	Responders[1] (%)	(95% CI)	[BLI850] – [MoviPrep] (95% CI)
BLI850	173/185 (93.5%)	(89%, 97%)	0% (-5.0%, 5.0%)
MoviPrep	173/185 (93.5%)	(89%, 97%)	

[1]Responders were defined as subjects whose colon preparations were graded as either excellent or good by the colonoscopist (grading score 4 or 3).
Source: Summarized from Dr. Wen Jen Chen's Statistical review

Table 12: Number of subjects in Study 302 with "Excellent" colon cleaning score

	Treatment Group	
	BLI850	MoviPrep
Colon cleansing graded as "excellent"	96/185 (51.9%)	95/185 (51.4%)

Source: The Applicant's Clinical Study Report for Protocol BLI850-302, Table 302-4.

The secondary endpoints in Study 302 were the same as in Study 301.

Adequacy of cleansing for evaluation was reported in 98% (181/184) of BLI850 subjects and 97% (180/185) of MoviPrep subjects. Re-preparation was needed in 1/3 of the inadequate evaluations in BLI850 and in 2/5 of the inadequate evaluations in MoviPrep.

The proportion of subjects achieving excellent preps is presented in Table 13.

Table 13: Colonoscopy assessment analysis by cleansing grade in Study 302 (mITT population)

Colon Cleansing Grade	BLI850 n = 185 (%)	MoviPrep n = 185 (%)
Excellent (4)	96 (51.9)	95 (51.4)
Good (3)	77 (41.6)	78 (42.2)
Fair (2)	10 (5.4)	10 (5.4)
Poor (1)	1 (0.5)	2 (1.1)
Missing	1 (0.5)	0
Mean ± SD[2]	3.46 ± 0.6	3.44 ± 0.7

[2]Two missing subjects (one from each treatment group) were not included in the calculation of mean scores.
Source: Modified from the Applicant's Clinical Study Report for Protocol BLI850-301, Tables 301-4 and 14.2.1.1.

The cecum was reached in 98% (181/184) of subjects who received BLI850 and in 98% (182/185) of subjects who received MoviPrep.

Statistical Considerations

The Statistics Review by Wen Jen Chen outlines a number of statistical issues related to this application that are discussed below.

Choice of Non-Inferiority Margin (NIM)

As noted by the Statistics reviewer, the justification for the non-inferiority margin of 15% submitted by the applicant is for the two active control arms (HalfLytely and MoviPrep) employed by the two studies (BLI850-301 and BLI850-302).

The Statistics reviewer noted that as per the ICH E-10 guidance, the non-inferiority margin should be based on the smallest effect size of the active control arm as shown in historical well-controlled placebo trials (conducted under the conditions similar to that of the current trials).

However, as the Statistics reviewer points out, none of the three studies (F38-15, F38-20, and F38-26) submitted by the applicant to support the non-inferiority margin of 15% was a placebo-controlled study using HalfLytely or MoviPrep as a treated arm. Details regarding the applicability of each trial to support the non-inferior margin are discussed in the Statistical review. Since all three studies provided by the applicant did not comply with the ICH E10 guidance for a non-inferiority margin selection, the Statistics reviewer concludes that the justification for the non-inferiority margin of 15% as determined by the applicant is problematic.

The Statistics reviewer further points out that in bowel cleansing preparation trials, placebo controlled studies might never have been performed for most regimens, given both ethical reasons and that the success rate for placebo is likely to be close to 0%.

Regardless, a margin of 15% remains statistically unjustified and has not been considered statistically acceptable as a non-inferiority margin for evaluation of investigational bowel preparations. In addition, the Statistics review notes that a margin of 10% has been employed for approval of OsmoPrep (NDA 21-892). Accordingly, from statistical perspective, the non-inferiority margin of 15%. It should be noted that an advice letter sent by the Agency (on June 6, 2009) commented that a margin of 15% has not been justified statistically and has not been considered statistically acceptable as a non-inferiority margin for evaluation of investigational bowel preparation.

The Statistical reviewer concluded that the lack of an agreed upon NIM does not preclude a more general conclusion within the (b) (4)

In order to judge if the test drug BLI850 has efficacy superior to placebo, the Statistics reviewer calculated the two-sided 95% confidence interval on the success rate of BLI850 (P_{BLI850}) using the ITT patient population. From a statistical perspective, BLI850 can be considered effective if the lower bound of the CIs in the table exceed any expectation for a placebo response rate. Based on the Statistical Reviewer's tabulation of the 95%CI in the treatment arm of Study 301 and 302 (Table 14 & Table 15), it is apparent that BLI850 would have been, in all likelihood, superior to a placebo.

Table 14. Study 301: 95% two-sided confidence intervals on P_{BLI850}

Patient Population	BLI850 No. Success	BLI850 Success Rate (n/N)	95% Confidence Interval on P_{BLI850}
Intent-to-Treat Population	158	0.90 (158/176)	(0.84, 0.94)

Source: Statistics Review

Table 15. Study 302: 95% two-sided confidence intervals on P_{PLI850}

Patient Population	PLI850 No. Success	PLI850 Success Rate (n/N)	95% Confidence Interval on P_{PLI850}
Intent-to-Treat Population	173	0.940 (173/185)	(0.890, 0.970)

Source: Statistics Review

As noted by the Statistics reviewer, since the definition of the per-protocol population was not given in the study report and no variable for the per-protocol population was provided in the original data set submitted by the sponsor, the two-sided 95% confidence interval on the success rate of BLI 850 is shown only for the ITT population.

Finally, since a non-inferiority margin was not pre-specified for the secondary endpoint, "Was cleansing adequate for evaluation," the Statistics reviewer concluded that the results from the secondary endpoints cannot be validly assessed, are exploratory in nature (b) (4)

Single-Blinding

The Statistical review correctly notes that this is a single blinded study and patients knew which drug was used for their bowel preparation, opening the possibility for the investigators to be informed of the bowl preparation used by patients. Furthermore, the ratings of "fair" (enough feces or fluid to prevent a completely reliable exam) and "good" (small amounts of feces or fluid not interfering with exam) in bowel cleansing quality are not completely distinguishable and might be assessed subjectively. Accordingly, as long as the investigator realized which drug was used by the patient, the assessment on the successful bowel preparation (scored as "good" by investigators) could be biased in favor of the study drug.

The Statistical reviewer also states that in order to avoid the potential for biased assessments in this single blinded trial the applicant could have included another lower dose arm (2 liters of PEG-ELS) in this trial. However, he deferred the practical and ethical considerations of this approach to DGIEP. Incorporating a "lower dose" arm would raise ethical concerns (as discussed further in my review) since these trials enroll patients who are undergoing colorectal screening and ineffective bowel cleansing could result in missed lesions or lead to repeat procedures. Also, a third arm also would not entirely prevent bias if the patient is aware of what regimen they received.

Lack of Objective Endpoint

The statistical reviewer also suggested that due to the "ambiguous definitions of grade 2 and grade 3 scoring," the bowel preparation quality might not have been assessed objectively. This could have resulted in the investigators assigning similar scores to the bowel preparations for the two treatment groups and increasing the likelihood of a biased conclusion favoring non-inferiority for the two drugs is increased.

As I understand his concern, if it is somewhat uncertain which grade should be selected for a given subject and if the selection is to some extent arbitrary (i.e., investigators routinely can't decide between a 2 or 3 but end up choosing 3 anyway) the net effect in a non-inferiority trial would be to bias the trial towards a successful outcome.

I agree with this possibility and should be considered for the design of future trials. It also highlights the importance of achieving "excellent" bowel cleansing as this possibly would be the least ambiguous choice among all grades.

Combination Rule (21 CFR 300.50)

With respect to the combination rule, Dr. Lee discusses in her review the likelihood that each of the two components of BLI850 would be adequate bowel cleansing agents by themselves. She also addresses the same pharmacodynamic data as discussed in Dr. Sandhya Apparaju's clinical pharmacology review (see Section 5). In addition to Dr. Apparaju's review, Dr. Lee presents two summary figures from the sponsor's response to the 8/3/2012 FDA Information request. Both Table 16 and Figure 4 present the data that associates the PD assessment of "scatocrit" with cleansing efficacy data observed in the Applicant's previous clinical trials.

Table 16: Comparison of % stool solids ("scatocrit"), colon cleaning efficacy, and total stool output following bowel preparations

	Failed Preparations*			Approved Preparations			
	Bisacodyl 20mg	2L NuLYTELY	Sulfate Soln 5 (1 bottle, 22g SO4)	4L NuLYTELY	HalfLytely (20mg bis)	SUPREP	Solution 4 (Sulfate + 2L NuLYTELY)
n	11	6	5	4	7	5	1
Scatocrit - % Solids (SD)	**50.4%** (18.7)	**15.0%** (11.2)	**12.0%** (2.1)	**2.8%**† (2.1)	**2.6%**† (2.2)	**1.6%** (0.8)	**1.4%**
Cleansing Efficacy from Braintree RCTs‡	**57.7%** (unacceptable) (n=97)	**67.4%** (unacceptable) (n=92)	NA	**82.8%** (n=93)	**79.6%** (n=74)	**97.2%** (n=180)	**93.5%** (n=186)
Stool Output (g) (SD)	757 (260)	1659 (231)	1308 (281)	3861 (168)	2403 (577)	2911 (492)	2298
Reference (cleansing)	*Study F38-15 NDA 203595 Module 1 Tab 1.4, p10*	*Study F38-15 NDA 203595 Module 1 Tab 1.4, p10*		*Study F38-15 NDA 203595 Module 1 Tab 1.4, p10*	*Study F38-20 NDA 203595 Module 1 Tab 1.4, p11*	*Study BLI800-302 NDA 22-372 Mod. 5, Vol. 6.1 Tab 5.3.5.1B, p31*	*Study BLI850-302 NDA 203595 Mod. 5, Vol. 5.1 Tab 5.3.5.1B, p33*

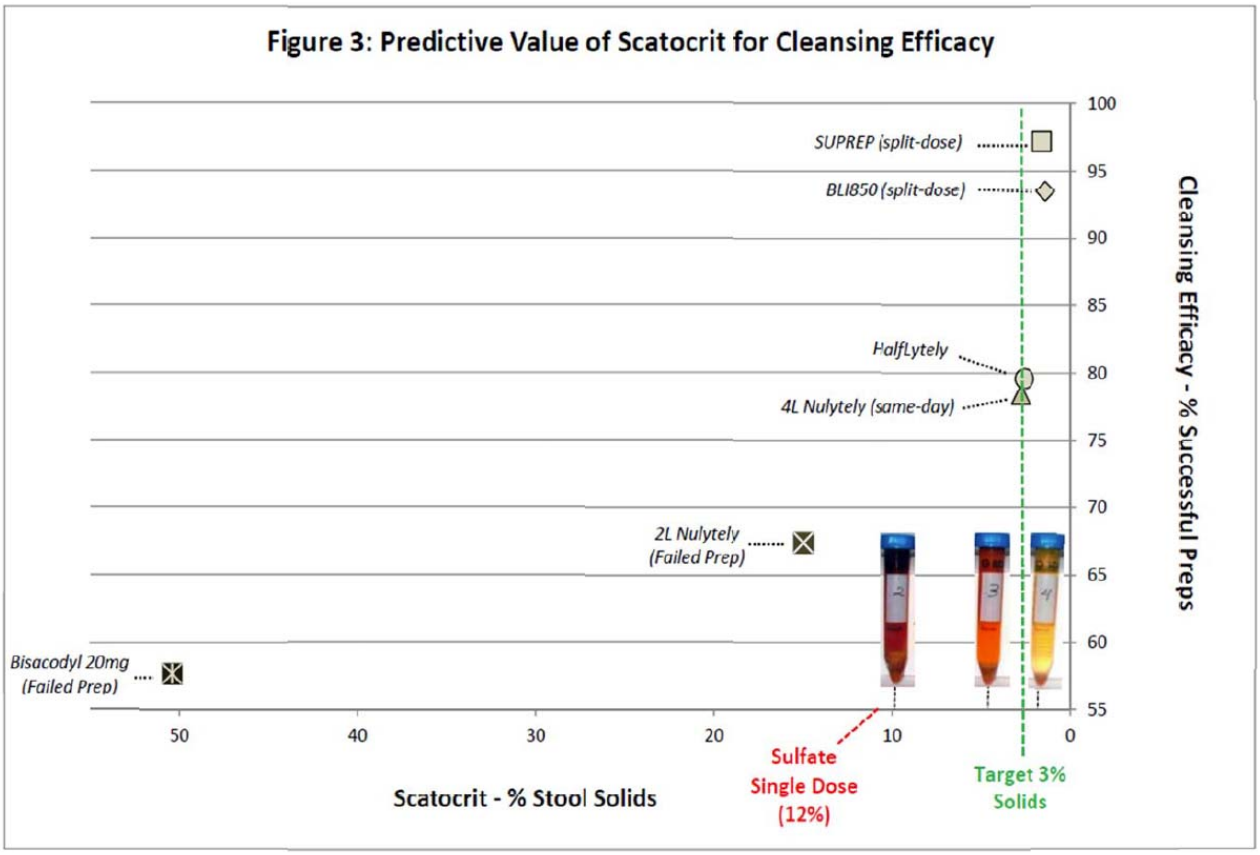
*20 mg bisacodyl and 2L NuLYTELY were statistically inferior to 4L NuLYTELY in Study F38-15

‡Percent successful preparations (cleansing rated as Excellent or Good by blinded colonoscopist) reported in randomized, controlled clinical studies

†One patient in the HalfLytely group did not have their percent solids measured; One NuLYTELY outlier result was excluded

RED BOXES highlight the components and combination formulation of BLI850.
Source: Modified from Dr. Lee's clinical review. Originally sourced from applicant's response to FDA's Information Request dated August 3, 2012, Table 2.

Figure 4. Predictive value of scatocrit for Cleansing Efficacy.



Source: Applicant

Dr. Lee provides the following summary arguments regarding the data submitted to address the combination rule:

1. Data to support that the sulfate salt solution, or first component of BLI850, would result in inadequate bowel cleansing.
    a. A phase 1 study (Study 006-181, discussed in Section 5) showed that one dose (i.e., a half dose) of SUPREP is inferior to two doses (i.e., a full dose) of SUPREP: subjects had a mean % stool solids of 6.4% after the first dose and 1.6% after the second dose (see Table 4).
    b. This data, in conjunction with that presented in Table 16 suggested to Dr. Lee that the first component of SUPREP alone, which is the same dose of sulfate salts as in BLI850, would likely result in inadequate bowel cleansing. (Although, Dr. Lee admits that an efficacy trial was never conducted with a half dose of SUPREP)
    c. Dr. Lee also cites the regression equation correlating % stool solids and cleansing efficacy results to arrive at a predicted cleansing efficacy rate of less than 70% for a half dose of SUPREP (See Figure 2).
    d. As noted by the Applicant and presented in Table 16, approved bowel cleansing preparations including SUPREP, HalfLytely (with 20mg

bisacodyl) and 4L NuLytely all had successful bowel cleansing rates of ≥80%.

e. Because there is evidence to suggest that the sulfate salt solution in BLI850 would be ineffective, there are ethical concerns to conducting a study to evaluate such a product.

2. Data to support that the PEG-ELS component of BLI850 alone would result in inadequate bowel cleansing.
   a. Dr. Lee points out that there was a study (F38-15) conducted by the Applicant that compared 2L NuLytely to the approved 4L NuLytely and presents this data in her review (Table 17):

Table 17: Primary Efficacy Responder Analysis in Study F38-15[1]

Responder[2]	2L NuLYTELY n (%)	4L NuLYTELY n (%)	95% CI[3]	*P*-value[4]
Success	62 (67.4)	77 (82.8)	-27.7, -3.1	0.018
Fail	30 (32.6)	16 (17.2)		

[1]Study F38-15 was included as a supportive study in NDA 21-551, which was submitted to support the approval of HalfLytely and Bisacodyl Tablets Bowel Prep Kit.
[2]Success was defined as bowel cleansing graded either "excellent" or "good" by the blinded colonoscopist.
[3]Confidence interval (CI) for percent success difference between treatments was calculated using a Chi-square test.
[4]*P*-value for difference between treatments was calculated using an exact Chi-square test.
Source: Dr. Lee's clinical review. Originally sourced from the Applicant's response to FDA Clinical and Statistical Comments and Recommendations for IND 102,894, dated June 6, 2009, Table 1.

   b. As noted previously in Table 16, 2L NuLYTELY resulted in higher % stool solids (15%) and lower stool output (1659 g) compared to the approved preparations, such as 4L NuLYTELY, HalfLytely and SUPREP.

Dr. Lee provides the following summary conclusions:

> "Above pharmacodynamic and particularly the colon cleansing efficacy data have provided adequate evidence that individual component alone in BLI850 will likely result in inadequate bowel cleansing required for a thorough colonoscopy examination. In addition, there are ethical concerns associated with conducting an efficacy trial using bowel preparations that are expected to be inadequate at study initiation. Based on totality of the data presented and ethical concerns, this reviewer concludes that the Combination Rule has been adequately addressed."

8. Safety

As for efficacy, the safety data from Studies 301 and 302 were reviewed individually, focusing on clinically significant electrolyte abnormalities and changes in renal function that could occur during and after bowel preparation administration.

Subjects were evaluated with physical examination, vital signs, and laboratory testing at baseline and Visit 2 (on the day of colonoscopy). Orthostatic vitals were not evaluated. Safety data from Studies 301 and 302 were evaluated separately, since these trials had different dosing regimens and active comparators. Study 301 compared BLI850 to HalfLytely and Bisacodyl Tablets Bowel Prep Kit (hereafter referred to as HalfLytely) and both were administered as day-before (one-day) dosing. However, Study 302 compared BLI850 to MoviPrep, both of which were administered as split-dose regimen.

Adverse Events

In addition to the usual method of collecting adverse events, subjects were instructed to complete a symptom scale during Visit 2. This questionnaire targeted expected reactions associated with bowel preparations, such as stomach cramping, bloating, nausea, and overall discomfort. If they reported a score of 5 ("severely distressing") for stomach cramping, stomach bloating or nausea, these events were included in the adverse event dataset. Vomiting was recorded separately by the subject on a treatment questionnaire and included as an adverse event, regardless of severity. This method combines both spontaneous reports of AEs as well as queried AEs based on expected symptoms after administration of a bowel cleansing preparation. Since it is possible that some subjects reported the same AE spontaneously as well as when queried through a symptom scale, it is difficult to retrospectively discriminate each AE that was spontaneously reported from those that were also collected through the symptom scale. Therefore, this reviewer combined both types of AEs (spontaneously reported and queried) in the safety analysis as long as the same AE was counted only once for each subject. All elicited symptoms, regardless of severity, were included in the AE dataset. This approach was also applied during the safety evaluation of SUPREP.

In Study 301, the most common adverse events included discomfort, abdominal distension, abdominal pain, nausea, and vomiting, all of which were expected reactions associated with bowel preparations and were queried from subjects. In general, BLI850 group had numerically higher rates of adverse events than the HalfLytely group.

Table 18: Treatment emergent adverse events and symptom scores by MedDRA Body System and Preferred Term for Study 301 (ITT population)

Body System/Preferred Term[1]	BLI-850 N = 176 n (%)	HalfLytely N = 190 n (%)
Number of subjects with at least one event	146 (83.0)	143 (75.3)
Number of events	389	371
Cardiac Disorders	1 (0.6)	1 (0.5)
Atrial fibrillation	1 (0.6)	0
Bradycardia	0	1 (0.5)
Gastrointestinal Disorders	134 (76.1)	132 (69.5)
Abdominal distension	92 (52.3)	85 (44.7)
Abdominal pain[2]	71 (40.3)	78 (41.1)
Glossitis	1 (0.6)	0
Hematemesis	1 (0.6)	0
Nausea	74 (42.0)	75 (39.5)
Retching	2 (1.1)	1 (0.5)
Vomiting	19 (10.8)	15 (7.9)
General Disorders	122 (69.3)	108 (56.8)
Discomfort[3]	122 (69.3)	108 (56.8)
Nervous System Disorders	3 (1.7)	3 (1.6)
Headache	1 (0.6)	3 (1.6)
Syncope vasovagal	1 (0.6)	0
Tremor	1 (0.6)	0
Respiratory, Thoracic and Mediastinal Disorders	0	1 (0.5)
pharyngeal edema	0	1 (0.5)
Skin and Subcutaneous Tissue Disorders	1 (0.6)	1 (0.5)
Rash	1 (0.6)	0
Urticaria	0	1 (0.5)

[1]Subjects were counted once within each body system and preferred term.
[2]One case of "abdominal pain upper" from each treatment was re-categorized as "abdominal pain."
[3]One case of "projectile vomiting" from the BLI850 group was re-categorized as "vomiting."
Source: Dr. Lee's clinical review. Dr. Lee's analysis using the Applicant's AESY (adverse event plus symptoms) dataset for Study 301 submitted in response to Information Request dated July 18, 2012; also referenced the Applicant's Clinical Study Report on Protocol BLI850-301, Table 14.3.1, that included TEAEs only.

Table 19 compares symptom events collected using a symptom scale. The mean scores of stomach bloating, nausea and overall discomfort were slightly higher in subjects who received BLI850 preparation compared with those who received HalfLytely. However, the mean scores for both treatments were generally low, most ranging between 1 (no symptoms) and 2 (mild). A small but statistically significant difference was seen between the two groups for "overall discomfort," which may be due to a larger amount of solution that must be consumed with BLI850.

Table 19: Mean symptom score comparison between BLI850 and HalfLytely in Study 301 (ITT population)

Symptom[1]	BLI850 N = 176	HalfLytely N = 190	*P*-value[2]
No. subjects completed	174	186	
Stomach cramping			
Mean ± SD	1.50 ± 0.7	1.55 ± 0.8	0.393
Stomach bloating			
Mean ± SD	1.74 ± 0.9	1.62 ± 0.8	0.177
Nausea			
Mean ± SD	1.70 ± 1.0	1.65 ± 1.0	0.818
Overall Discomfort			
Mean ± SD	2.06 ± 1.0	1.76 ± 0.8	0.032

[1]Symptom scores were as follows: 1=none; 2=mild; 3=bothersome; 4=distressing; 5=severely distressing.
[2]*P*-value for difference between treatments was calculated using ANOVA.
Source: Dr. Lee's clinical review. Adapted from the Applicant's Clinical Study Report for Protocol BLI850-301, Tables 301-9 and 14.3.8.

In Study 302, the most common adverse events were the expected reactions associated with bowel preparations that were queried from subjects, including discomfort, abdominal distention, abdominal pain, nausea, and vomiting. Although the proportion of subjects experiencing discomfort, abdominal distention, and abdominal pain were higher in the MoviPrep, nausea and vomiting were higher in the BLI850 group.

Table 20: Treatment emergent adverse events and symptom scores by MedDRA Body System and Preferred Term for Study 302 (ITT population)

Body System/Preferred Term[1]	BLI850 N = 186 n (%)	MoviPrep N = 185 n (%)
Number of subjects with at least one TEAE	155 (83.3)	147 (79.5)
Number of events	416	408
Cardiac Disorders	0	1 (0.5)
Bradycardia	0	1 (0.5)
Gastrointestinal Disorders	137 (73.7)	138 (74.6)
Abdominal distension	96 (51.6)	112 (60.5)
Abdominal pain[2]	70 (37.6)	79 (42.7)
Dyspepsia	1 (0.5)	0
Nausea	86 (46.2)	72 (38.9)
Retching	0	2 (1.1)
Vomiting	26 (14.0)	13 (7.0)
General Disorders and Administration Site Conditions	116 (62.4)	121 (65.4)
Discomfort	116 (62.4)	121 (65.4)
Pyrexia	2 (1.1)	0
Injury, Poisoning and Procedural Complications	1 (0.5)	0
Excoriation	1 (0.5)	0
Investigations	5 (2.7)	2 (1.1)
Blood creatine phosphokinase increased	1 (0.5)	0
Blood creatinine increased	1 (0.5)	0
Blood phosphorus decreased	1 (0.5)	0
Blood phosphorus increased	1 (0.5)	0
Blood sodium decreased	0	1 (0.5)
Hepatic enzyme increased	1 (0.5)	0
Heart rate decreased	0	1 (0.5)
Musculoskeletal and Connective Tissue disorders	1 (0.5)	0
Muscle spasms	1 (0.5)	0
Neoplasms Benign, Malignant and Unspecified	0	1 (0.5)
Seborrheic keratosis	0	1 (0.5)
Nervous System Disorders	3 (1.6)	2 (1.1)
Headache	3 (1.6)	2 (1.1)
Psychiatric Disorders	1 (0.5)	0
Anxiety	1 (0.5)	0
Respiratory, Thoracic and Mediastinal Disorders	1 (0.5)	0
Wheezing	1 (0.5)	0
Skin and Subcutaneous Tissue Disorders	2 (1.1)	1 (0.5)
Erythema	1 (0.5)	0
Rash macular	1 (0.5)	0
Urticaria	0	1 (0.5)
Vascular Disorders	0	1 (0.5)
Hypotension	0	1 (0.5)

[1]Subjects were counted once within each body system and preferred term.
[2]One case and two cases of "abdominal pain upper" from BLI850 and MoviPrep, respectively, were re-categorized as "abdominal pain." One case of "abdominal tenderness" from each treatment was re-categorized as "abdominal pain." One case in MoviPrep had two separate AE entries for "abdominal pain upper" and "abdominal tenderness", which was re-categorized as one case of "abdominal pain."
Source: Reproduced from Dr. Lee's Clinical Review. Reviewer's analysis using the Applicant's AESY2 (adverse event plus symptoms) dataset for Study 302 submitted in response to Information Request dated July 18, 2012; also referenced the Applicant's Clinical Study Report on Protocol BLI850-302, Table 14.3.1, that included TEAEs only.

As noted in Table 20, the percentage of vomiting in the BLI850 group (14%) doubled that of MoviPrep (7%). A larger proportion of subjects experienced vomiting in the split-dose regimen (14%) than in the day-before regimen (11%) for BLI850.

As presented in Table 21, Dr. Lee performed an analysis of vomiting severity as rated by the investigators.

Table 21: Demographic and clinical characteristics of patients who experienced vomiting during Studies 301 and 302

	Study 301: Day-Before Regimen		Study 302: Split-Dose Regimen	
	BLI850 N=19 n (%)	HalfLytely N=15 n (%)	BLI850 N=26 n (%)	MoviPrep N=13 n (%)
Vomiting severity[1]				
Mild	10 (52.6)	10 (66.7)	15 (57.7)	9 (69.2)
Moderate	8 (42.1)	5 (33.3)	10 (38.5)	4 (30.8)
Severe	1 (5.3)	0 (0)	1 (3.8)	0 (0)

[1] Symptom severity was rated by the investigator and is described in Section 7.1.2 of Dr. Lee's clinical review.

Source: Dr. Lee's clinical review. Dr. Lee's analysis using the Applicant's AESY and AESY2 (adverse event plus symptoms) datasets for Studies 301 and 302, respectively, submitted in response to Information Request dated July 18, 2012.

An analysis by the Safety Stats reviewer did not suggest that subjects who vomited had more significant electrolyte shifts; however the small number of subjects who actually reported vomiting was relatively small.

Table 22 compares queried symptoms collected using a symptom scale in Study 302. Except for nausea, the mean scores of other queried symptoms (stomach cramping, stomach bloating, and overall discomfort) were slightly higher in the MoviPrep group. The mean scores were generally low for both groups however a statistically significant difference was seen between the two groups for "stomach bloating."

Table 22: Mean symptom score comparison between BLI850 and MoviPrep in Study 302 (ITT population)

Symptom[1]	BLI850 N = 186	MoviPrep N = 185	*P*-value[2]
Stomach cramping	n = 186	n = 182	
Mean ± SD	1.46 ± 0.7	1.56 ± 0.8	0.330
Stomach bloating	n = 185	n = 183	
Mean ± SD	1.66 ± 0.7	1.79 ± 0.8	0.025
Nausea	n = 186	n = 182	
Mean ± SD	1.73 ± 0.9	1.54 ± 0.8	0.472
Overall Discomfort	n = 186	n = 183	
Mean ± SD	1.87 ± 0.9	1.9 ± 0.8	0.239

[1]Symptom scores were as follows: 1=none; 2=mild; 3=bothersome; 4=distressing; 5=severely distressing.
[2]*P*-value for difference between treatments was calculated using ANOVA.
Source: Dr. Lee's clinical review. Adapted from the Applicant's Clinical Study Report for Protocol BLI850-302, Tables 302-10 and 14.3.8.

Deaths
There were no deaths reported from start of the trial until 30 days after the colonoscopy examination in both Studies 301 and 302.

Nonfatal Serious Adverse Events
There was one patient who received BLI850 in Study 302 who experienced a non-fatal SAE. The patient underwent colonoscopy and was admitted to the hospital later that evening with complaints of severe abdominal pain. The patient also presented with "febrile symptoms," which resolved the same day following antibiotic treatment. As noted by Dr. Lee, since this SAE occurred after colonoscopy, it is difficult to determine whether this event was due to the study medication, the colonoscopy procedure itself, or unrelated to either. I agree with her conclusion that this AE was not related to the study medication.

Laboratory Analyses
In Studies 301 and 302, laboratory tests were obtained at baseline (Visit 1) and on the day of colonoscopy (Visit 2). Visit 2 occurred within 15 days of Visit 1. The following laboratory tests were obtained:

- Chemistry: albumin, alkaline phosphatase, ALT, amylase, AST, bicarbonate, blood urea nitrogen, calcium, chloride, creatine kinase (CK), creatinine, direct bilirubin, GGT, glucose, magnesium, osmolality, phosphorus, potassium, sodium, total bilirubin, total protein and uric acid

- Hematology: hematocrit, hemoglobin, platelets count, red blood cell count, white blood cell count (and differentials)

- Urine pregnancy test for women (Visit 1 only)

Blood samples were redrawn if subjects had laboratory results at Visit 2 which were determined by the investigator to be clinically significant. Dr. Lee notes in her review that only one subject in Study 301 (in the HalfLytely group) and 5 subjects in Study 302 (3 in the BLI850 group and 2 in the MoviPrep group) had labs redrawn after Visit 2 to follow up abnormal chemistry laboratory results - and therefore, the follow-up laboratory data are limited in Studies 301 and 302.

Table 23 presents subjects who had laboratory redraw data for Study 302; the single subject who had a redraw for abnormal CK in Study 301 is discussed further below.

Table 23. Laboratory values for subjects with redraw due to abnormal visit 2 values (Trial 302)

Subject ID	Treatment	Laboratory Parameter	Normal Range	Visit 1	Visit 2 (date)	Redraw (date)
30017	BLI-850				(9/25/08)	(10/9/08)
		Phosphate	2.4-4.9	2.8	1.8	2.9
31021	MoviPrep				(9/30/08)	(10/16/08)
		Creatinine	0.5-1.0	1.1	1.2	1.0
31004	BLI-850				(9/3/08)	(9/17/08)
		Creatinine	0.6-1.4	1.2	2.1	1.2
30028†	BLI-850				(10/3/08)	(10/10/08)
		ALP	40-135	64	160	93
		ALT	0-47	28	327	47
		AST	0-37	27	98	21
		Gamma GT	0-33	21	61	38
31027†	MoviPrep				(9/29/08)	(10/21/08)
		ALT	0-47	116	114	84
		AST	0-37	103	143	60
		Gamma GT	0-33	144	157	78

†-Liver functions tests with visit 2 values outside the normal range are presented

Source: Safety Stats review, Table 4

Normal ranges for laboratory test results in studies 301 and 302 are presented in Table 32 in the Appendix.

Table 24, summarized from Dr. McEvoy's review, presents proportion of subjects with normal baseline who developed abnormal electrolyte values on the day of colonoscopy (Visit 2). The direction of abnormality is also indicated.

Table 24: Proportion of subjects with normal baseline who developed abnormal electrolyte values at Visit 2 in Studies 301 and 302

Laboratory Parameter	Study 301		Study 302	
	BLI850 n/N (%)	HalfLytely n/N (%)	BLI850 n/N (%)	MoviPrep n/N (%)
Anion Gap (high)	5/155 (3.2)	8/170 (4.7)	17/166 (10.2)	12/155 (7.7)
Bicarbonate (low)	4/156 (2.6)	5/167 (3.0)	6/170 (3.5)	20/161 (12.4)
Calcium (high)	12/139 (8.6)	5/139 (3.6)	6/141 (4.3)	7/144 (4.9)
Chloride (low)	1/157 (0.6)	0/171 (0.0)	1/173 (0.6)	0/163 (0.0)
Magnesium (low)	1/158 (0.6)	1/169 (0.6)	0/169 (0.0)	1/163 (0.6)
Magnesium (high)	0/158 (0.0)	0/169 (0.0)	0/169 (0.0)	1/163 (0.6)
Osmolality (high)	3/139 (2.2)	8/153 (5.2)	6/151 (4.0)	12/145 (8.3)
Phosphate (low)	0/155 (0.0)	0/168 (0.0)	5/171 (2.9)	2/160 (1.3)
Phosphate (high)	2/155 (1.3)	2/168 (1.2)	1/171 (0.6)	2/160 (1.3)
Potassium (low)	5/144 (3.5)	4/160 (2.5)	6/162 (3.7)	7/159 (4.4)
Glucose (low)	0/146 (0.0)	1/156 (0.6)	3/160 (1.9)	3/150 (2.0)
Glucose (high)	10/146 (6.8)	4/156 (2.6)	3/160 (1.9)	5/150 (3.3)
Sodium (low)	0/157 (0.0)	0/169 (0.0)	1/169 (0.6)	1/163 (0.6)
Sodium (high)	1/157 (0.6)	0/169 (0.0)	0/169 (0.0)	0/163 (0.0)

Source: Adapted from Dr. Bradley McEvoy's Safety Statistical review dated September 12, 2012, Tables 28 and 33.

Electrolytes

As presented in Dr. Lee's review, in Study 301, the mean change in anion gap was +5.6 mEq/L in 5 patients with new-onset high anion gap (> 16 mEq/L) in the BLI850 group and +4.6 mEq/L in 8 patients in the HalfLytely group. Patients with a normal baseline who developed a high anion gap had anion gap values ranging from 17 to 20 mEq/L (mean 18.0 mEq/L) at Visit 2 in the BLI850 group and 17 to 19 mEq/L (mean 17.5 mEq/L) in the HalfLytely group.

As also presented in Dr. Lee's review, in Study 302, subjects with a normal baseline who developed a high anion gap had anion gap values (>16 mEq/L) ranging from 17 to 21 mEq/L (mean 18.0 mEq/L) at Visit 2 in the BLI850 group and 17 to 24 mEq/L (mean 18.9 mEq/L) in the MoviPrep group. Although more subjects with BLI850 developed increased anion gap, the mean change was not substantially different between the two groups. Overall, in all subjects, Dr. Lee notes that there was no a significant change in anion gap between BLI850 and MoviPrep study arms in Study 302.

Table 25 presents the bicarbonate and anion gap shifts in subjects who had normal bicarbonate at baseline (≥ 20meq/L) and low bicarbonate (<20meq/L) at Visit 2 (day of colonscopy.) Notable is the fairly minor shifts in bicarbonate and anion gap.

Table 25. STUDY 301: Subjects with normal serum bicarbonate at baseline that shifted to low (<20 mEq/L) at visit 2, with concomitant changes in anion gap.

Subject	Treatment	Bicarbonate at Baseline (mEq/L) (nl: 20-31 mEq/L)	Bicarbonate at Visit 2 (mEq/L) (nl: 20-31 mEq/L)	Anion Gap(mEq/L): Visit 1→Visit 2 (nl: 8-16mEq/L)
2017	HalfLytely	20	18	14→19
6043	HalfLytely	25	18	15→16
6050	HalfLytely	20	18	11→14
3011	HalfLytely	22	19	14→16
3051	HalfLytely	26	19	11→17
11010	BLI-850	23	19	12→13
2022	BLI-850	23	19	11→15
3048	BLI-850	21	19	10→15

Source: Robert Fiorentino, CDTL

Table 26 presents the same analysis as above, but for Study 302. The shifts in bicarbonate, together with the changes in anion gap, do not suggest that a significant metabolic acidosis is occurring in these subjects. However, it remains unclear to me if expected loss of bicarbonate secondary to bowel cleansing agents would make anion gap calculations problematic without assessing other electrolytes (potassium) or taking into consideration fluid status.

Table 26. STUDY 302: Subjects with normal serum bicarbonate at baseline that shifted to low at visit 2, with concomitant changes in anion gap.

Subject	Treatment	Bicarbonate at Baseline (nl: 20-31 mEq/L)	Bicarbonate at Visit 2 (nl: 20-31 mEq/L)	Anion Gap at Visit 1→Visit 2 (nl: 8-16)
25057	BLI-850	21	17	16→16
28010	BLI-850	28	17	9→18
25015	BLI-850	20	18	15→16
22026	BLI-850	22	19	12→17
28002	BLI-850	24	19	14→18
31020	BLI-850	24	19	12→15
30020	MoviPrep	23	13	14→19
25031	MoviPrep	21	17	16→21
25060	MoviPrep	26	17	9→14
31002	MoviPrep	22	17	14→16
31027	MoviPrep	21	17	15→15
21003	MoviPrep	26	18	12→16
25047	MoviPrep	22	18	14→17
29002	MoviPrep	24	18	14→18
29008	MoviPrep	22	18	15→17
21015	MoviPrep	22	19	15→14
22028	MoviPrep	26	19	12→15
23029	MoviPrep	20	19	13→14
24001	MoviPrep	21	19	17→14
24004	MoviPrep	23	19	13→15
24008	MoviPrep	25	19	11→16
25007	MoviPrep	22	19	13→22
25043	MoviPrep	26	19	9→15
25065	MoviPrep	20	19	13→16
27018	MoviPrep	26	19	14→18
30006	MoviPrep	22	19	11→12

Source: Robert Fiorentino, CDTL

Some evidence that the observed metabolic changes are probably "normal" compensatory shifts is found in the Safety Stats review where the changes observed in the MoviPrep arm in Study 302 are evaluated: "The statistically significant differences between groups for chloride and bicarbonate were driven by a mean increase and decrease, respectively, from baseline in the MoviPrep group [Section 3.3.4.2.1, page 22]." In the MoviPrep arm in Study 302, mean bicarbonate change from baseline was -1.69mmol, and mean change in chloride was +1.58mmol. This may suggest that decreases in serum bicarbonate were in general compensated for by increases in chloride anion (i.e., as in hyperchloremic metabolic acidosis), as expected, in most subjects. However it is uncertain how the universal presence of diarrhea in study subjects (with loss of bicarbonate) influences the interpretation of changes in anion gap (and serum bicarbonate).

As summarized in the Safety Stats review, in Study 301, compared to HalfLytely, BLI-850 had a numerically greater percentage of subjects who switched from normal at

baseline to above the normal range on the day of the colonoscopy (visit 2) for calcium (8.6% vs. 3.6%). In these subjects, the mean change in calcium was +0.5 mg/dL (n=12) with values ranging from 10.3 to 10.7 mg/dL in the BLI850 group and +0.6 mg/dL (n=5) with values ranging from 10.3 to 10.6 mg/dL, in the HalfLytely group. For comparison, although there were not differences in the number of subjects with abnormal calcium in Study 302, the mean change in calcium in subjects above the normal range was +0.5 mg/dL (n=6, (values ranging from 10.3 to 10.6 mg/dL) in the BLI850 group and +0.7 mg/dL (n=7, values ranging from 10.3 to 10.6 mg/dL [same as BLI850]) in the MoviPrep group. No subject in either study experienced hypocalcemia, however, it should be noted that, overall, subjects in both studies and arms had very small *decreases* in serum calcium of <1mg/dL. In my view the changes in calcium do not suggest a clinically relevant safety signal by themselves.

In Study 301, the proportion of subjects who had potassium levels below the normal range at visit 2 (and normal at baseline) were 3.5% (5/144) in BLI850 and 2.5% (4/160) in Halflytely. According to an analysis presented in Jessica Lee's clinical review, subjects with a normal baseline who developed hypokalemia had potassium levels ranging from 3.0 to 3.5 mEq/L at Visit 2 in the BLI850 group and 3.2 to 3.4 mEq/L in the HalfLytely group.

In Study 302, the proportion of subjects who had a potassium level below the normal range at visit 2 (normal at baseline) were 3.7% (6/162) in BLI850 and 4.4% (7/159) in MoviPrep. According to an analysis presented in Jessica Lee's clinical review subjects with a normal baseline who developed hypokalemia had potassium levels ranging from 3.2 to 3.5 mEq/L at Visit 2 in the BLI850 group and 3.3 to 3.5 mEq/L in the MoviPrep group. As noted in Dr. Lee's analysis, hypokalemia is a known electrolyte abnormality associated with the use of bowel preparations that result in copious diarrhea. The lowest potassium level that was observed in the BLI850 group was 3.0 mEq/L in one patient from Study 301, and most of the remaining abnormal values were just under the lower limit of normal (i.e., 3.5 mEq/L).

Both the Clinical and Safety Stats reviewer noted a statistically significant difference in Study 301 between groups for serum glucose, where the proportion of subjects above the normal range at visit 2 (normal at baseline) was 6.8% (10/146) in BLI850 and 2.6% (4/156) in Halfytely. Dr. Lee calculated that the mean change was +81.4 mg/dL (range +12 to +144) in these 10 BLI850 subjects. The reason for this change is not clear and is not anticipated to be due to bowel cleansing agents generally taken in a fasting state. For comparison, in Study 302 the proportion of subjects above normal glucose range at visit 2 (normal at baseline) was 1.9% (3/160) in BLI850 and 3.3% (5/150) in MoviPrep.

Renal Function

As presented in Table 27, there were only a few subjects who developed serum creatinine values that were above normal range at Visit 2 (normal range depends on gender, F: 0.5 - 1.0 mg/dL; M: 0.6 - 1.4 mg/dL). As noted in Dr. Lee's review, in Study 301 the mean

change +0.3 mg/dL in patients with new-onset high creatinine in both the BLI850 group and the HalfLytely group. Patients with a normal baseline who developed a high creatinine had creatinine levels ranging from 0.9 to 1.1 mg/dL at Visit 2 in the BLI850 group and 1.0 to 1.4 mg/dL in the HalfLytely group.

In Study 302, two patients in the BLI850 group developed new-onset high creatinine (increased by 0.1 mg/dL to 1.5 mg/dL in one patient and by 0.9 mg/dL to 2.1 mg/dL in another patient). One patient in the MoviPrep group had an increase in creatinine by 0.1 mg/dL to 1.5 mg/dL. Increases in creatinine levels were minimal in most patients who developed new-onset abnormality. However, as noted by Dr. Lee, creatinine is not as sensitive at detecting early changes in renal function as estimated creatinine clearance (eCcr) or estimated glomerular filtration rate (eGFR).

Table 27. Proportion of subjects with normal baseline who developed abnormal renal function values at Visit 2 in Studies 301 and 302

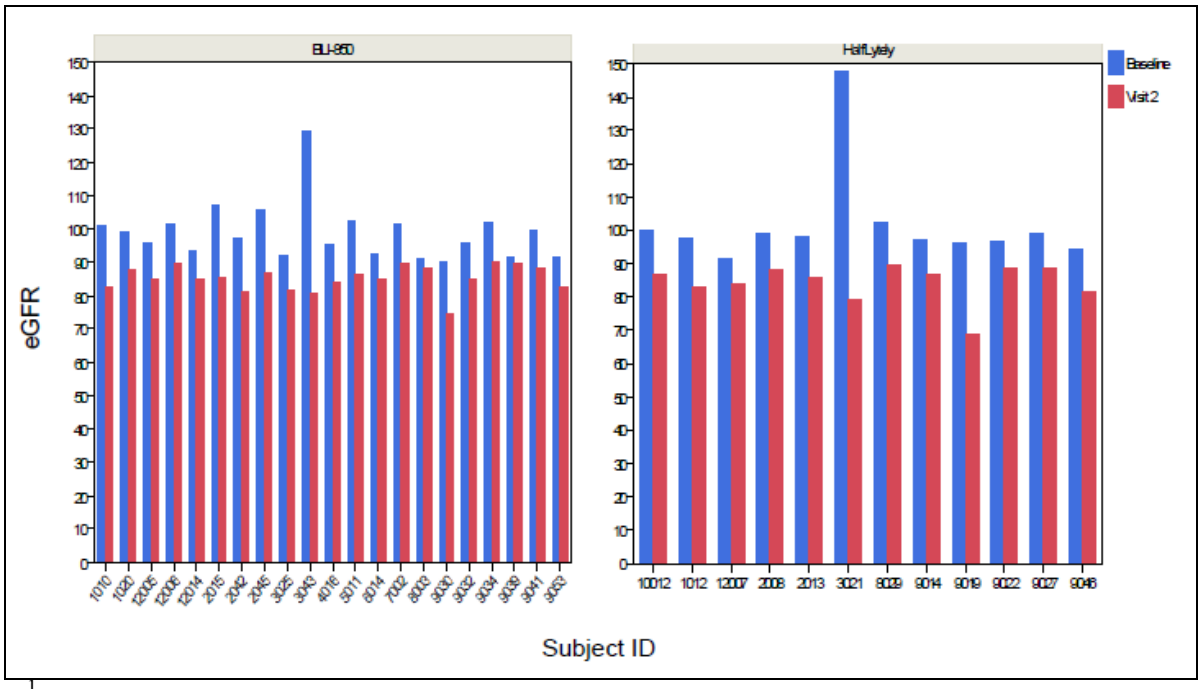
Laboratory Parameter	Study 301		Study 302	
	BLI850 n/N (%)	HalfLytely n/N (%)	BLI850 n/N (%)	MoviPrep n/N (%)
Creatinine (high)	3/145 (2.1)	4/155 (2.6)	2/167 (1.2)	1/153 (0.7)
eC_{Cr} CG (low)	21/84 (25.0)	12/88 (13.6)	9/101 (8.9)	9/85 (10.6)
eGFR MDRD (low)	12/45 (26.7)	21/63 (33.3)	20/59 (33.9)	17/54 (31.5)
eGFR CKD-EPI (low)	14/46 (30.4)	28/67 (41.8)	20/61 (32.8)	15/56 (26.8)

eC_{cr}, estimated creatinine clearance; CG, Cockcroft-Gault; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.
Source: Adapted from Dr. Bradley McEvoy's Safety Statistical review dated September 12, 2012, Tables 14 and 22.

No subject who developed BUN level *above* normal range at Visit 2 in Study 301 and only one subject each in BLI850 and MoviPrep in Study 302 developed BUN levels that were above normal range (27 mg/dL and 32 mg/dL, respectively).

In Study 301, the mean change in estimated creatinine clearance (Cockcroft-Gault) for subjects below the normal value at visit 2 was -13.7 mL/min (range of change -2.1 to -48.8 mL/min) among 21 subjects in the BLI850 group and -17.4 mL/min (range of change -7.6 to -68.5 mL/min) among 12 subjects in the HalfLytely group. The individual changes for these subjects are presented in Figure 5.

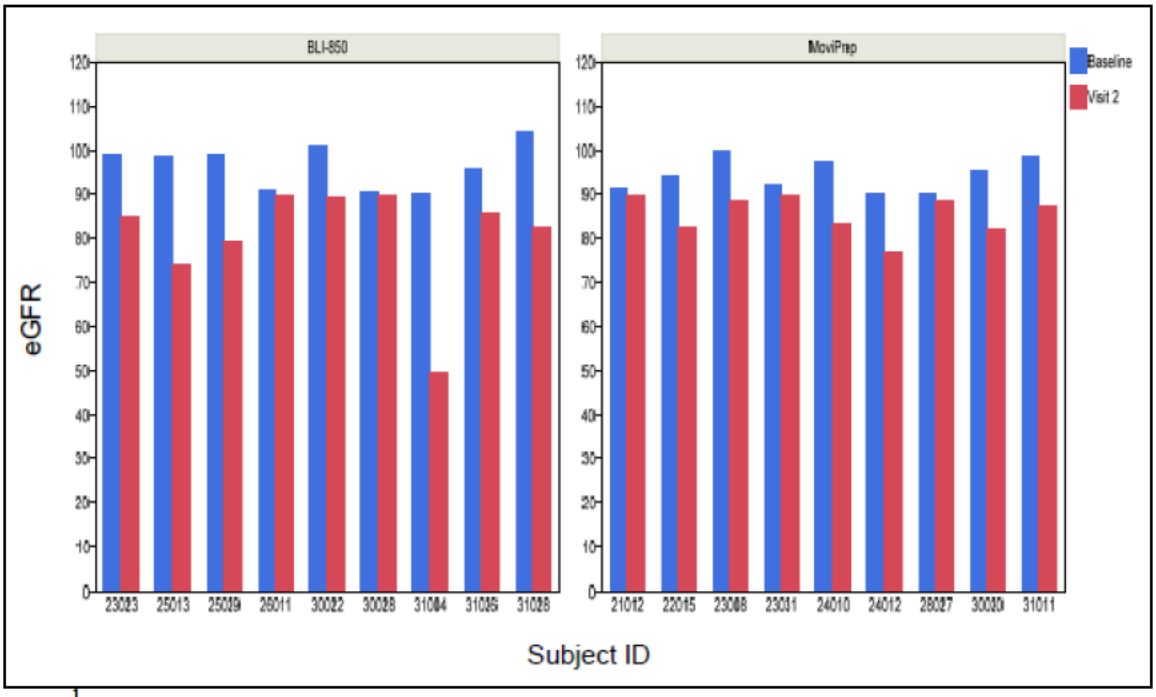
Figure 5: Subjects with baseline normal eGFR[1] who developed abnormally low eGFR (< 90 mL/min) at Visit 2 in Study 301



[1] eGFR was calculated using the Cockcroft-Gault method.
Source: Clinical reviewer's analysis of the Applicant's laboratory dataset.

In Study 302, the mean change in estimated creatinine clearance (Cockcroft-Gault) for those subjects below normal range was -16.0 mL/min (range of change -0.7 to -40.7 mL/min) among 9 subjects in the BLI850 group and -8.9 mL/min (range of change -1.5 to -13.9 mL/min) among 9 subjects in the HalfLytely group. The individual changes for these subjects are presented in Figure 6.

Figure 6: Subjects with baseline normal eGFR[1] who developed abnormally low eGFR (< 90 mL/min) at Visit 2 in Study 302



[1]eGFR was calculated using the Cockcroft-Gault method.
Source: Clinical reviewer's analysis of the Applicant's laboratory dataset.

Liver function tests

Table 28: Proportion of subjects with normal baseline who developed abnormal liver and biliary enzyme values at Visit 2 in Studies 301 and 302

Laboratory Parameter	Study 301		Study 302	
	BLI850 n/N (%)	HalfLytely n/N (%)	BLI850 n/N (%)	MoviPrep n/N (%)
Albumin (high)	7/152 (4.6)	9/164 (5.5)	12/164 (7.3)	6/159 (3.8)
AST (high)	9/151 (6.0)	7/161 (4.3)	13/161 (8.1)	14/154 (9.1)
ALT (high)	8/148 (5.4)	5/161 (3.1)	10/162 (6.2)	5/150 (3.3)
Gamma GT (high)	2/126 (1.6)	5/140 (3.6)	4/149 (2.7)	3/134 (2.2)
Total bilirubin (high)	12/157 (7.6)	17/170 (10.0)	19/170 (11.2)	6/162 (3.7)
Direct bilirubin (high)	14/157 (8.9)	18/167 (10.8)	16/169 (9.5)	10/163 (6.1)

Source: Adapted from Dr. Bradley McEvoy's Safety Statistical review dated September 12, 2012, Tables 28 and 33.

As per Dr. Lee's clinical review, in Study 301, the mean change in AST for those subjects above normal range at Visit 2 (and normal at baseline) was +18.5 U/L (range of change +6 to +33) in the BLI850 group and +39.9 U/L (range of change +5 to 204) in the HalfLytely group. In other terms, patients with a normal baseline who developed a high AST had AST values ranging from 38 to 68 U/L at Visit 2 in the BLI850 group and 39 to 221 U/L in the HalfLytely group.

Similarly, in Study 302, the mean change in AST for those above normal range was +21.7 U/L (range of change +7 to +71) in the BLI850 group and +16.3 U/L (range of change +4 to +28) in the MoviPrep group. In other terms, patients with a normal baseline who developed a high AST had AST values ranging from 38 to 98 U/L at Visit 2 in the BLI850 group and 38 to 60 U/L in the MoviPrep group. Dr. Lee noted that since AST is found in multiple organs (e.g., heart, skeletal muscle, kidneys, brain) in addition to liver, its value alone is less informative in determining potential hepatic injury or dysfunction compared to ALT and bilirubin.

In Study 301, the mean change in ALT in those subjects above normal range at visit 2 (and normal at baseline) was +17.0 U/L (range of change +1 to +40) in the BLI850 group and +138.4 U/L (range of change +7 to +654) in the HalfLytely group. In other terms, patients with a normal baseline who developed a high ALT had ALT values ranging from 48 to 72 U/L at Visit 2 in the BLI850 group and 51 to 680 U/L in the HalfLytely group. The high mean ALT value in HalfLytely is due to one subject (9057) whose value increased from 26 to 680. In Study 302, the mean change in ALT in those subjects above normal range at visit 2 was +50.9 U/L (range of change +8 to +299) in the BLI850 group and +27.4 U/L (range of change +8 to +76) in the MoviPrep group. In other terms, patients with a normal baseline who developed a high ALT had ALT values ranging from 48 to 327 U/L at Visit 2 in the BLI850 group and 52 to 118 U/L in the MoviPrep group. One subject (30028) in the BLI850 group had a large increase in the ALT value from 28 to 327. There were two subjects with elevated AST and ALT values that were greater than 3 times upper limit normal (one subject from the HalfLytely group and one subject from the BLI850 group in Study 302). However, neither of these subjects had elevated total bilirubin values. "Hy's Law" was not met in these subjects (subjects with any elevated AT of >3xULN, ALP <2xULN, and associated with an increase in bilirubin ≥2xULN)[7].

In Study 301, the mean change in total bilirubin for those subjects above normal range at visit 2 (and normal at baseline) was +0.5mg/dL (range +0.2 to +0.8) in the BLI850 group and +0.7mg/dL (range +0.2 to +1.5) in the HalfLytely group. In Study 302, the mean change in total bilirubin for those subject above normal range at visit 2 (and normal at baseline) was at +0.7mg/dL (range +0.2 to +1.3) in the BLI850 group and +0.5mg/dL (range +0.4 to +0.7) in the MoviPrep group. Of the 19 subjects with elevated total bilirubin in BLI850, 14 (74%) subjects also had elevated direct bilirubin. In general, the changes in total bilirubin values were small, and Dr. Lee concludes in her review that these are likely due to fasting and/or dehydration resulting from colon cleansing and comments that patients with Gilbert syndrome, which occurs in approximately 5% of the population, can present with unconjugated hyperbilirubinemia in the setting of fasting or dehydration.

[7] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Creatine Kinase

Table 29: Proportion of subjects with normal baseline who developed abnormal creatine kinase (CK) levels at Visit 2 in Studies 301 and 302

Laboratory Parameter	Study 301		Study 302	
	BLI850 n/N (%)	HalfLytely n/N (%)	BLI850 n/N (%)	MoviPrep n/N (%)
Creatine kinase (high)	10/138 (7.2)	6/151 (4.0)	10/147 (6.8)	7/143 (4.9)

Source: Adapted from Dr. Bradley McEvoy's Safety Statistical review dated September 12, 2012, Tables 28 and 33.

In Study 301, the mean change in CK in subjects with abnormal high values at visit 2 (and normal at baseline) was +124.7U/L (range of change +25 to +413) in the BLI850 group and +279.7U/L (range of change +38 to +1293) in the HalfLytely group. In other terms, patients with a normal baseline who developed a high CK had CK values ranging from 190 to 525 U/L at Visit 2 in the BLI850 group and 184 to 1381 U/L in the HalfLytely group. It should be noted that the upper limit normal of CK differs based on gender.One subject in Study 301, Subject 9031 (HalfLytely group) had a redraw due to an abnormal CK value at Visit 2 (baseline =88; visit 2 =1381 (09/24/2008); redraw =538 (09/26/2008).

In Study 302, the mean change in CK subjects with abnormal high values at visit 2 (and normal at baseline) was +131.4U/L (range of change +30 to +473) in the BLI850 group and +347.3U/L (range of change +11 to +2018) in the MoviPrep group. In other terms, patients with a normal baseline who developed a high CK had CK values ranging from 196 to 591 U/L at Visit 2 in the BLI850 group and 175 to 2127 U/L in the MoviPrep group. No subjects in Study 302 with abnormal CK at Visit 2 had a subsequent redraw.

Dr. Lee notes in her review that none of the subjects in Studies 301 and 302 experienced clinical sequelae associated with elevated CK, but long-term data are not available.

The causes of elevated CK in these trials, including observations made in similar trials of bowel cleansing agents, remains unclear.

9. Advisory Committee Meeting

No Advisory Committee was held to discuss this NDA.

10. Pediatrics

The Applicant is required to conduct pediatric studies under the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b)). DGIEP concurred with PMHS recommendations that a (b) (4) pediatric waiver should be denied. However, a partial waiver

for patients less than one year is now considered reasonable since bowel preparation can be accomplished by administration of clear fluids in infants pre-colonoscopy for a minimum of 24 hours. Note that previous PREA studies for recent bowel preparations (b) (4) have been waived in children < 6 months of age but current DGIEP opinion on this matter is that studies should be waived in children < 1year of age.

Deferred pediatric studies are recommended to be conducted in a step-wise approach with the initial trials being conducted in older patients before younger cohorts are studied. Pediatric clinical trials should be waived in children younger than 1 year of age, since (1) a full colonoscopy is rarely performed in this age group (flexible sigmoidoscopy is more commonly performed) and (2) a successful bowel preparation can be achieved with administration of clear liquids with or without suppositories or enemas. Since the only approved bowel preparation in the pediatric population is NuLYTELY, which is not used widely in the U.S. and whose approval appears to have been based on published literature, the appropriate community's standard of care should be identified for each age group and used as a comparator in these pediatric trials.

The following pediatric studies were presented to the Pediatric Review Committee (PeRC) on August 1, 2012, and the Committee members agreed with the plan, however the timelines have been modified after discussion with the applicant. Specifically, the applicant has requested that the Suclear timelines occur after similar PREA timelines for SUPREP PREA PMRs.

PREA Required Studies

Study 1: An open-label pilot study assessing the efficacy and tolerability of Suclear in pediatric patients 12-16 years of age, inclusive. This study will include PK assessments.

Final Protocol Submission:	06/14
Study Completion:	03/15
Final Report Submission:	06/15

Study 2: A randomized, single-blind, multicenter, dose-ranging study comparing the safety and efficacy of Suclear (up to 3 doses) versus community standard of care in pediatric patients 12-16 years of age, inclusive.

Final Protocol Submission:	09/15
Study Completion:	09/16
Final Report Submission:	12/16

Study 3: A randomized, single-blind, multicenter, dose-ranging study comparing the safety and efficacy of Suclear (up to 3 doses) versus community standard of care in pediatric patients 3-11 years of age, inclusive.

Final Protocol Submission:	03/17
Study Completion:	03/18
Final Report Submission:	06/18

Study 4: A randomized, single-blind, multicenter, dose-ranging study comparing the safety and efficacy of Suclear (up to 3 doses) versus community standard of care in pediatric patients 1-2 years of age, inclusive.

Final Protocol Submission:	09/18
Study Completion:	09/19
Final Report Submission:	12/19

Study 5: Assess the systemic exposure and pharmacokinetics of PEG 3350, (b) (4) following oral administration of Suclear in an adequate number of pediatric patients, encompassing all relevant age groups. These assessments may be conducted as part of the PREA required studies listed above.

Final Protocol Submission:	09/18
Study Completion:	09/19
Final Report Submission:	12/19

PMHS Consult

PMHS was consulted to assist with the development of the pediatric plan and to provide comments on whether any safety considerations with regard to PEG3350 would impact our assessment of the pediatric plan or acceptability of a waiver.

PMHS review notes that case reports of metabolic acidosis and neuropsychiatric adverse events associated with the use of PEG products prompted a Drug Safety Oversight Board (DSB) on June 18, 2009. The presentation to the board included a description of the adverse events, along with a safety review of the published literature, information on practice guidelines, and a review of the non-clinical and pharmacokinetic data on PEG.

PMHS review noted that the minutes of the DSB meeting did not mention the use of PEG products for bowel preparation but focused primarily on the use of OTC MiraLax (used for the management of constipation). It is not clear if the potential safety concerns discussed for Miralax would be relevant for PEG-containing bowel prep regimens. However, because the potential exposure of pediatric patients to PEG (b) (4)

[redacted] (b) (4) from PEG-containing bowel prep regimens remain unknown, such assessments should be evaluated in the pediatric studies required for SUCLEAR.

11. Other Relevant Regulatory Issues

21 CFR 300.50: "Combination Rule"

In light of the development history of bowel prep regimens, requiring a "full" factorial study can raise serious ethical concerns, particularly given of the negative impact on a patient who undergoes an inadequate bowel preparation for colonoscopy. Further, such full factorial studies likely would be impractical in many cases, as the clinical contribution of the increased intake of clear liquids used as part of the bowel prep regimen and taken outside of the co-packaged kits, would require factorial studies impractical or unfeasible by their design.

Colon cancer screening with colonoscopy is performed to detect not only cancer, but pre-malignant lesions, i.e., adenomatous polyps. Detection and removal of these lesions has been shown to prevent future development of colon cancer.[8] Adequate visualization of the colonic mucosa is key to identification and removal of these lesions. Lesions missed during colonoscopy can result in the development of interval colon cancers between screening endoscopies. These malignant tumors arise from lesions that were likely missed in the prior screening examination[9,10]. In addition, a subtype of polyps, serrated polyps, are flat, which makes them particularly challenging to visualize. Without an adequate bowel preparation there is a higher likelihood that such lesions could be missed. Therefore, a patient subjected to a bowel preparation suspected to be inadequate at study initiation (such as in a multi-arm factorial study) would place that patient at increased risk of undergoing a procedure in which a polyp or malignancy is missed. Additionally, certain concerns are raised by the colonoscopy procedure itself which usually requires sedation; both the procedure and sedation are associated with risks of serious adverse events. Exposing a patient to such risk, while knowing that that patient likely will have undergone an inadequate bowel preparation, raises serious ethical concerns.

In order to determine whether a full factorial study would be ethical in light of the concerns raised above, the Division has previously done work examining the lower bounds of the 95% confidence intervals for the proportion of successful preps (excellent + good) for various recently approved bowel preparations. Based on a review of approved bowel prep regimens, it appeared that in order to conclude that a bowel prep agent was

[8] Jemal et al, Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev. 2010;19(8):1893-907

[9] Leung et al, Ongoing colorectal cancer risk despite surveillance colonoscopy: the Polyp Prevention Trial Continued Follow-up Study. Gastrointestinal Endoscopy, Vol. 71, No 1:2010, 111-117.

[10] Cohen, Lawrence, Split-dosing of bowel preparations for colonoscopy: an analysis of its efficacy, safety, and tolerability, Gastrointestinal Endoscopy Vol. 72, No. 2:2010, 406-412.

not potentially inferior to approved products; the lower bound of the 95%CI should be no less than 70% for a same day prep administration schedule, and no less than 80% for a split dose administration schedule. Refer to recently approved NDA 202535 (Prepopik) for a detailed overview of this review[11].

Both Drs. Lee (Clinical) and Apparaju (Clinical Pharmacology) have concluded that there is sufficient evidence, based on what is known about both components of BLI850 from clinical and pharmacodynamic data, to conclude that the sulfate salt solution and PEG-ELS solution would be inadequate bowel cleansing agents if taken alone. I agree with their conclusion.

It's important to note that the sulfate salt solution in BLI850 is only one half that of the approved SUPREP bowel cleansing agent, 22.24g vs. 44.46g (for LBI850 patients take one 6 oz bottle and for SUPREP they take 2). There is no clinical efficacy data on the sulfate salt solution in BLI850 because there was implicitly no expectation that it would be adequate by itself as a bowel cleansing agent. Evidence for this comes from pharmacodynamic data presented extensively in Drs. Lee's and Apparaju's reviews and summarized in Sections 5 & 7 of my review. The Applicant has provided evidence that the ability of a bowel cleansing agent to reduce the volume of solids in the stool is a predictive marker for adequate bowel cleansing. Although by no means a surrogate, the relationship between achieving <3% stools solids and having a successful bowel cleansing seems fairly consistent. This relationship, despite comparisons across different studies that use different measures of success and different treatment protocols, is also intuitively expected given that the mechanism of these agents is to cleanse the bowel using mechanical, bulk expulsion of solid matter from the colon. I also note that the reduction in stool solids/scatocrit is fairly consistent across individual subjects treated with each agent, despite the small numbers, as is presented in Table 33 and Table 34 in the Appendix. It is not surprising that a relationship between having clear stools and have better cleansed colons should exist.

In contrast, the other component of BLI850, 2L PEG-ELS, has evidence from clinical trials that it is ineffective as a bowel cleansing agent by itself. In fact, previous studies of approved "low volume" bowel preps have only used 2L PEG-ELS in combination with stimulant laxatives (Such as bisacodyl in HalfLytely) because of the expectation that 2L PEG-ELS may be ineffective compared to larger volume (4L PEG-ELS) regimens. As shown in Table 17, the applicant has presented data in which 2L PEG-ELS was shown to be inferior to 4L PEG-ELS (67% vs. 83%, p=0.018). In addition, the success rate of 2L PEG-ELS is likely to be inferior to other approved products based on the fact that the treatment effect is less than 70%, which is typically the lower bound of effectiveness determined for approvability as described above.

In conclusion, I agree with the Clinical and Clinical Pharmacology reviewers that there is sufficient evidence for the Division to conclude with reasonable assurance that the components of BLI850 are inferior bowel cleansing agents by themselves, and that it

[11] http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202535_prepopik_toc.cfm

would be unethical to study them alone in a factorial study design in studies enrolling patients undergoing screening or diagnostic colonoscopies.

OSI Inspections

The DGIEP review team identified four sites for inspection, two for each protocol, based on evaluation of site specific efficacy. Four clinical investigator sites, two for each protocol, were inspected for this application. All inspections were classified as No Action Indicated (NAI). No violations were noted and no Form FDA 483 was issued. The data generated at the four inspected sites appear reliable and can be used in support of the NDA.

Table 30. OSI Inspection Results

Name of CI	Protocol # and # of Subjects and Site #	Inspection Date	Final Classification
Bal Raj Bhandari, M.D. 608 Grammont St., Monroe, LA 71201	BLI850-301 49 Subjects Site #2	July 9-12, 2012	NAI
Michael Schwartz, D.O. 875 Military Trail, Ste. 210 Jupiter, FL 33458	BLI850-301 58 Subjects Site #9	July 2-12, 2012	NAI
Steven Duckor, M.D. 2617 E. Chapman Ave Orange, CA 92869	BLI850-302 61 Subjects Site #23	July 5-10, 2012	NAI
Dennis Riff, M.D. 1211 W. La Palma Ave Anaheim, CA 92801	BLI850-302 65 Subjects Site #25	June 29-July 9, 2012	NAI

Key to Classifications
NAI = No deviation from regulations.
Source: OSI Review

12. Labeling

- Proprietary name

The original tradename proposed by the sponsor, (b) (4) was found to be unacceptable following review by the Division of Drug Marketing, Advertising and Communications (DDMAC). A subsequently revised tradename proposal, (b) (4) was also deemed to be unacceptable by DDMAC. Ultimately, the sponsor re-submitted a tradename, "SUCLEAR," which was found to be acceptable by DDMAC.

- Physician labeling

The following major revisions were made to the proposed label:

Dosage and Administration
Split-Dose has been noted as the Preferred regimen with Day-before as an alternative for patients for whom the Split-Dosing is inappropriate. Dosing instructions, specifically the timing of dose 1 and dose 2 were modified to better reflect the clinical trials experience.

Adverse Reactions
Table 1 in the label has been extensively revised to incorporate both unsolicited and queried adverse events into the same table.

Table 2 in the label has been revised and expanded to provide a wider range of laboratory parameters.

Pharmacokinetics
Data regarding the exposure to sulfates was added (and derived from studies that supported the SUPREP NDA [NDA #22-372]).

- Carton and immediate container labels

DEMPA noted in their review (09/14/2012) the potential for incorrect filling of the mixing cup by the patient or caregiver:

> *The mixing cup is used for mixing and administration. The cup is opaque and at the top of the cup the following statements appear between two horizontal lines: "16-oz. Fill Line"* (b) (4) *Although, there are arrows which point to a fill line that appear above each statement and under the lid of the cup, the arrows, the statements, the fill line, and the lid of the cup are all opaque and thus hard to read because there is insufficient color contrast. Additionally, the placement of these statements between the horizontal lines is confusing because it is difficult to tell if the bottom line is the fill line or the top line is the fill line. To add to the confusion a small opaque fill line appears right below the upper horizontal line. This design could confuse the user and lead them to fill the cup to the incorrect water level. The cup statements and fill line should be more prominent and provide a better contrast against the background.*

To understand the potential clinical impact of a patient under-filling to the wrong line (the lower "mold" line), the applicant was asked to provide the change in volume and osmolarity of the fluid from an under-filled cup. As presented in Table 31, under-filling to the "mold" line would represent a change in volume of 74mL (2.5oz) and an increase in osmolarity of approximately 172 mOsm/L.

Table 31. Fill Cup Parameters

BLI850 Calculated Osmolarity
(mOsm = mEq/Vol)

OSS Component (one 6oz bottle)			
	Vol (L)	ΔVol (mL)	Calc (mOsm/L)
Rim	0.597	+113	770.8
Fill Line	0.484	0	950.9
Mold	0.410	-74	1122.4

Source: Applicant

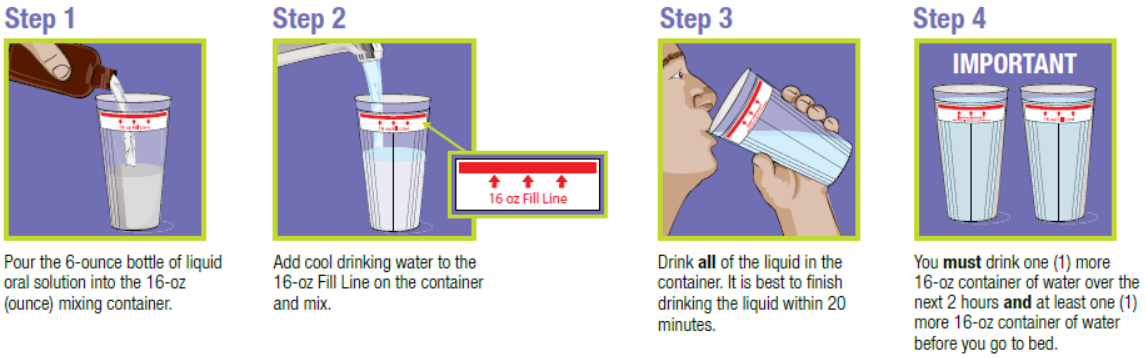
The clinical meaningful of this difference is unclear however the review team, however there was speculation that increased fluid concentration might lead to decreased palatability or tolerability.

The review team also noted that the patient Instructions for Use did not clearly represent the actual fill cup accurately and that the actual Fill Line displayed was difficult to see and misleading.

Figure 7. Patient IFU: Original Fill Cup Illustrations

The applicant was asked to revise the patient IFU in a manner that clearly and accurately represented the actual Fill Cup. Applicant submitted a revised Patient IFU with new fill cup instructions as shown in Figure 8.

Figure 8. Revised Patient IFU



The above graphical representation of the cup was deemed to be acceptable.

Minor editorial revisions to the final labeling have been incorporated into the approval letter.

- Medication guide

A Medication Guide has been submitted by the Applicant, was revised by the review team and was agreed upon with the applicant.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

  This new drug appears to meet statutory standards required under 21 CFR 314.105 and should be approved.

- **Risk Benefit Assessment**

  The benefit of SUCLEAR for preparation for colonoscopy has been established in the clinical trials.

  With respect to whether or not the "combination rule" under 21 CFR 300.50 has been adequately addressed, there have not been clinical trials submitted to this NDA to establish the relative contribution of the component products to the efficacy of this new drug. However, there is sufficient evidence in my view to conclude that the components would be ineffective if used alone and that it would be unethical to conduct a clinical trial investigating their use as a bowel cleansing agent. The applicability of and adequacy of the data to support 21 CFR 300.50 has been addressed in Section 11 of my review, *Other Relevant Regulatory Issues*.

As discussed previously in this review, the importance of a high-quality bowel preparation for the detection of colorectal polyps has been demonstrated in several studies (external to this application). Current clinical treatment and diagnostic guidelines stress that the timing of bowel preparation before colonoscopy, including the use of split-dose regimens, is of paramount importance and can improve the quality of bowel cleansing. It is interesting to note, despite the caveats of cross-study comparisons, that SUCLEAR did have a slight numerically greater rate of successful bowel cleansing when used as a 2-day split-dose regimen (94%, 173/185) compared to SUCLEAR when used as a (b) (4) (day before) regimen (90%, 158/176).

The Dosage & Administration section of the label should indicate that the split-dose regimen should be the preferred regimen, with the (b) (4) regimen reserved only for those patients for whom split-dosing would be inappropriate (similar as to what was done for Prepopik NDA 202535).

In addition, there did not appear to be major differences in the safety profile of the two regimens that would preclude approval of either. Curiously however, the rate of vomiting in the SUCLEAR arm was slightly numerically higher in split-dose regimen (SUCLEAR: 14% vs. MoviPrep: 7%) than the Day-Before regimen (SUCLEAR: 11% vs. HalfLytely: 8%). The explanation for this is not clear (particularly since the same-day regimen involved ingesting the same amount of fluid over a shorter duration). Although there were minor differences in the magnitude of electrolyte shifts between the two dosing regimens, serious or clinically significant shifts associated with SUCLEAR did not appear to have been identified by the review team that would preclude approval of either SUCLEAR regimen.

There was a trend toward a relatively higher proportion of subjects with elevated total bilirubin in the SUCLEAR arm of the split-dose study as well as a relatively higher proportion of SUCLEAR subjects, compared to controls, who had elevated serum creatine kinase in both studies. The changes in the serum levels were, however, not large enough to preclude approval, but could warrant further evaluation in post-market studies.

Data reflecting observed changes in serum electrolytes and other parameters have been incorporated into the label.

Overall, the NDA contained an adequate assessment of the safety of the proposed treatment regimen to support approval; however follow-up out to 30 days could have provided valuable information about the incidence and duration of laboratory abnormalities, as well as renal injury.

As noted previously, I do not recommend a Thorough QT study for this product given that such a study would be impractical for this osmotic bowel prep agent (e.g. the administration of supratherapeutic dosing to healthy

subjects that would be likely to result in clinically significant electrolyte shifts, dehydration and subject intolerance). There is ample evidence that QT prolongation can be expected from significant shifts in electrolytes and the risks of arrhythmias are already described in the label.

Based on the data from the clinical trials submitted to the NDA and what is known about pharmacologically related products (osmotic bowel cleansing agents), no unacceptable risks were identified with this product. Warnings and Precautions (Section 5) of the label should contain all of the key elements of recently approved bowel cleansing agents and describe the risks similarly. The most recent agreed upon label appears to conform to warnings and precautions presented in the labels of other recently approved bowel preparation.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

  A Medication Guide is recommended for SUCLEAR. A proposed Medication Guide has been submitted by the applicant and was reviewed by DMPP. DMPP comments were forwarded to the applicant for revision of the proposed MedGuide.

- **Recommendation for other Postmarketing Requirements and Commitments**

  PREA PMRs will be required in accordance with the proposal outlined previously in my review for pediatric patients >12 months of age. I recommend dose ranging studies in pediatric patients to evaluate the most appropriate dose (or formulations) across age or weight groups. The agreed upon pediatric studies have been presented in Section 10 of my review.

  I recommend that the Division consider a PMR to evaluate renal dysfunction and laboratory changes associated with SUCLEAR out to 30 days. I also recommend a PMR to evaluate the absorption and pharmacokinetics of PEG3350, (b) (4)

  The following represents FDAAA PMRs were negotiated with the applicant at the time of finalization of my review:

PMR #1 An adequate randomized, active control, single-blind trial to evaluate renal dysfunction and laboratory abnormalities in adult patients, including elderly patients, patients with renal impairment, and patients with hepatic impairment taking Suclear prior to colonoscopy. Serial laboratory and clinical assessments should be done at regular pre-specified intervals for at least 30 days post-treatment.

Final Protocol Submission:	06/14
Trial Completion:	06/16
Final Report Submission:	12/16

PMR #2 Assess the systemic exposure and pharmacokinetics of PEG3350, (b) (4) following oral administration of Suclear to adult patients. These assessments may be conducted as part of 1998-6 (above).

Final Protocol Submission:	06/14
Trial Completion:	06/16
Final Report Submission:	12/16

- **Recommended Comments to Applicant**

  As noted previously, minor editorial revisions to the final labeling have been incorporated into the approval letter.

14. Appendix

Normal Laboratory Ranges

Table 32 lists the Applicant-provided normal ranges for laboratory results in Studies 301 and 302. These ranges were used to define normal and abnormal results.

Table 32: Normal Ranges for laboratory test results in studies 301 and 302

Test	Normal Range
Serum Chemistry	
Sodium	134 - 146 mEq/L
Potassium	3.6 - 5.2 mEq/L
Calcium	8.4 - 10.2 mg/dL
Chloride	95 - 113 mEq/L
Uric acid	F: 2.2 - 6.4 mg/dL; M: 3.1 - 8.8 mg/dL
Total protein	6.1 - 7.9 g/dL
Albumin	3.7 - 4.9 g/dL
Total bilirubin	0.0 - 1.1 mg/dL
ALT/SGPT	0 - 47 U/L
AST/SGOT	0 - 37 U/L
Alkaline phosphatase	40 -135 U/L
Blood urea nitrogen	9 - 24 mg/dL
Amylase	28 - 100 U/L
Creatinine	F: 0.5 -1.0 mg/dL; M: 0.6 - 1.4 mg/dL
Glucose	70 - 141 mg/dL
Magnesium	1.4 - 2.1 mEq/L
Osmolality	275 - 295
Phosphate	2.4 - 4.9 mg/dL
GFR	no range available
Direct Bilirubin	0.0 - 0.2 mg/dL
Creatine Kinase	F: 24 - 170 U/L; M: 24 -195 U/L
GGT	F: 0 - 33 U/L; M: 0 - 51 U/L
Bicarbonate	20 - 31 mEq/L
Anion Gap	No range available
Serum Hematology	
WBC count	3.50 - 11.10 (1000/MCL)
Platelet count	150 - 400 (1000/MCL)
Hemoglobin	F: 11.5 - 15.5 g/dL; M: 13.2 - 17.0 g/dL
Hematocrit	F: 35.0 - 47.0 %; M: 40.0 - 54.0 %
Lymphocytes	19.0 - 48.0 %
Neutrophils	40.0 -74.0 %
Monocytes	3.4 - 9.0 %
Eosinophils	0.0 - 7.0 %
Basophils	0.0 - 1.5 %
RBC	F: 3.80 - 5.40 (MILL/MCL); M: 4.20 - 5.80 (MILL/MCL)

AST = aspartate aminotransferase (formerly known as SGOT = serum glutamic-oxaloacetic transaminase); ALT = alanine aminotransferase (formerly known as SGPT = serum glutamic-pyruvic transaminase); WBC = white blood cells; GGT = gamma-glutamyl transferase
M = Male; F = Female
Summarized from the Applicant's NDA 203-595 submission, Module 2, Section 2.7, Tables 2.7.4-11 and 2.7.4-12.

Individual PD Data (Studies 006-181 and 005-082)

Table 33. Baylor Study 006-181: Summary of Scatocrit Information by Subject

STUDY	Subject #	Prep Received	Stool Output (g)	Scatocrit (% solids)
006-181	3210	BLI800	1606	2.9
006-181	3212	BLI800	1781	1.1
006-181	3214	BLI800	1262	0.7
006-181	3215	BLI800	2019	1.8
006-181	3216	BLI800	1364	1.4
006-181	3230	BLI800	1372	2.1
006-181	3232	BLI800	1703	1.4
006-181	3211	EZ-Prep	1090	4.3
006-181	3217	EZ-Prep	1161	4.6
006-181	3218	EZ-Prep	927	5
006-181	3223	EZ-Prep	654	3.6
006-181	3226	EZ-Prep	592	2.9
006-181	3235	EZ-Prep	1074	7.1
006-181	3220	NuLYTELY	1405	1.1
006-181	3222	NuLYTELY	1852	1.1
006-181	3224	NuLYTELY	1637	0.7
006-181	3225	NuLYTELY	2050	1.1
006-181	3227	NuLYTELY	1551	1.4

Source: Applicant

Table 34. Baylor Study 005-082: Summary of Scatocrit Information by Subject

STUDY	Subject #-Initials	Prep Received	Stool Output (g)	Scatocrit (% solids)
005-082	3131 (b) (6)	Bisacodyl (20mg)	1050	44.6
005-082	3135	Bisacodyl (20mg)	901	27.14
005-082	3140	Bisacodyl (20mg)	914	65.24
005-082	3142	Bisacodyl (20mg)	601	57.28
005-082	3157	Bisacodyl (20mg)	787	49.16
005-082	3163	Bisacodyl (20mg)	536	52.22
005-082	3164	Bisacodyl (20mg)	1126	33.52
005-082	3169	Bisacodyl (20mg)	440	95.86
005-082	3172	Bisacodyl (20mg)	391	49.9
005-082	3174	Bisacodyl (20mg)	1010	45.64
005-082	3176	Bisacodyl (20mg)	572	34.22
005-082	3134	Halflytely	1915	.
005-082	3137	Halflytely	1819	2.22
005-082	3139	Halflytely	2697	6.24
005-082	3184	Halflytely	2049	3.88
005-082	3185	Halflytely	2488	1.06
005-082	3191	Halflytely	2355	1.86
005-082	3192	Halflytely	3498	0.18
005-082	3146	Milk of Magnesia	406	69.22
005-082	3148	Milk of Magnesia	646	18.22
005-082	3150	Milk of Magnesia	1086	35.28
005-082	3152	Milk of Magnesia	852	31.9
005-082	3167	Milk of Magnesia	1439	17.38
005-082	3171	Milk of Magnesia	449	39.82
005-082	3133	Nulytely 2L	1355	24.2
005-082	3136	Nulytely 2L	1673	15.1
005-082	3138	Nulytely 2L	1411	32.4
005-082	3145	Nulytely 2L	1828	4.32
005-082	3162	Nulytely 2L	1930	6.32
005-082	3177	Nulytely 2L	1759	7.88
005-082	3143	Nulytely 4L	3754	1.88
005-082	3193	Nulytely 4L	3761	11.04
005-082	3194	Nulytely 4L	4110	5.16
005-082	3195	Nulytely 4L	3820	1.16
005-082	3153	Senna	277	50.36
005-082	3154	Senna	419	100
005-082	3165	Senna	597	94.56
005-082	3166	Senna	444	100
005-082	3168	Senna	131	100
005-082	3170	Senna	468	99.96
005-082	3173	Senna	512	38.26
005-082	3175	Senna	539	61.66
005-082	3179	Senna	280	100.14
005-082	3199	Sulfate Solution 1	1536	3.6
005-082	3200	Sulfate Solution 2	1080	10.7
005-082	3201	Sulfate Solution 3	1291	14.3
005-082	3202	Sulfate Solution 3	861	17.9
005-082	3203	Sulfate Solution 3	1093	10
005-082	3204	Sulfate Solution 4	2298	1.4
005-082	3205	Sulfate Solution 5	1402	14.3
005-082	3206	Sulfate Solution 5	1589	10.2
005-082	3207	Sulfate Solution 5	917	10.7
005-082	3208	Sulfate Solution 5	1509	10.7
005-082	3209	Sulfate Solution 5	1121	14.3

Source: Applicant

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/s/

ROBERT FIORENTINO
01/18/2013