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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s)	Jessica J. Lee, M.D. Helen Sile, M.D.
Review Completion Date	December 21, 2012
Established Name	Sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution
(Proposed) Trade Name	SUCLEAR
Therapeutic Class	Osmotic laxative
Applicant	Braintree Laboratories, Inc.
Formulation(s)	Oral solution, and powder for oral solution
Dosing Regimen	Day-Before or Split-Dose regimen
Indication(s)	Colon cleansing in preparation for colonoscopy
Intended Population(s)	Adults 18 years and older

Template Version: [March 6, 2009](#)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, NDA 203-595 is acceptable to support the recommendation for approval of BLI850 for cleansing of the colon in preparation for colonoscopy in adults. The clinical reviewer recommends the split-dose regimen as the preferred method of administration, since a numerically larger proportion of patients attained successful bowel cleansing on this regimen and this practice is also supported by the literature. Adequate visualization is critical for early detection of malignant lesions, and the current practice guidelines recommend the split-dose regimen due to improved quality of preparation, patient compliance, and increased adenoma and polyp detection rates.^{1,2}

1.2 Risk Benefit Assessment

Colorectal cancer (CRC) is the third most common cancer and second leading cause of death from cancer.³ The current recommendation for CRC screening is a colonoscopy beginning at age 50 with follow-up colonoscopies every 10 years in individuals with average risk for colon cancer.¹ A good-quality bowel preparation is essential for colonoscopy to be effective, as inadequate visualization can result in incomplete procedures, missed lesions, higher complication rates, and increased costs and burden to patients due to repeated procedures.² The potential benefit of products such as BLI850 is to provide adequate preparation prior to colonoscopy, permitting better visualization of polyps or malignant lesions in the colon. BLI850 will provide another option for patients who cannot tolerate ingesting a large amount of solution (e.g., 4 liters) required by older bowel preparations. This product does not contain phosphate salts or bisacodyl plus polyethylene glycol, which may result in improved safety profiles with respect to nephrotoxicity and ischemic colitis. A review of the submitted application did not reveal significant safety concerns for BLI850 as long as it is used as instructed. Fluid and electrolyte abnormalities are well-known risks associated with osmotic bowel preparations, and these risks will need to be communicated in the label similar to related products. As with other bowel preparations, patients should be

1 Rex DK, Johnson DA, Anderson JC, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2008. *Am J Gastroenterol* 2009;104:739-50.

2 Gurudu SR, Ramirez FC, Harrison ME, et al. Increased adenoma detection rate with system-wide implementation of a split-dose preparation for colonoscopy. *Gastrointest Endosc* 2012;76:603-8.

3 Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a Joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin* 2008;58:130-60.

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monitored for electrolyte disturbances and dehydration after receiving BLI850. In summary, the benefit of BLI850 for cleansing of the colon as a preparation for colonoscopy outweighs the risk of its use in an appropriate patient population.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Based on the review of this application, a REMS is not recommended at this time. There is a Medication Guide informing patients about the risks associated with BLI850, side effects that may occur, and instructions for preparation and administration.

1.4 Recommendations for Postmarket Requirements and Commitments

1) Required Pediatric Assessment

The Applicant should conduct required pediatric trials under the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b)). The deferred pediatric trials 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.

Currently, NuLYTELY is the only approved bowel preparation in the pediatric population, but its approval was based on literature reports. Therefore, appropriate community's standard of care should be identified for each age group and used as a comparator in the pediatric trials.

The following pediatric trials are recommended:

Study 1: An open-label pilot study assessing the efficacy and tolerability of BLI850 in pediatric patients ages 12-16 years, inclusive.

- Protocol submission: June 1, 2014 (assumes January 2013 approval for adults)
- Study completion: March 1, 2015
- Study report submission: June 1, 2015

Study 2: A randomized, single-blind, multicenter, dose-ranging study comparing the safety and efficacy of BLI850 (up to 3 doses) versus community standard of care in adolescents (12-16 years of age, inclusive).

- Protocol submission: September 1, 2015
- Study completion: September 1, 2016
- Study report submission: December 1, 2016

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Study 3: A randomized, single-blind, multicenter, dose-ranging study comparing the safety and efficacy of BLI850 (up to 3 doses) versus community standard of care in children (3-11 years of age, inclusive).

- Protocol submission: March 1, 2017
- Study completion: March 1, 2018
- Study report submission: June 1, 2018

Study 4: A randomized, single-blind, multicenter, dose-ranging study comparing the safety and efficacy of BLI850 (up to 3 doses) versus community standard of care in children (1-2 years of age, inclusive).

- Protocol submission: September 1, 2018
- Study completion: September 1, 2019
- Study report submission: December 1, 2019

Study 5: Assess the systemic exposure and pharmacokinetics of PEG-3350, (b) (4)

following administration of BLI850 in an adequate number of pediatric patients, encompassing all relevant age groups. Assessments listed under Study 5 may be conducted as part of the PREA required studies listed above.

- Protocol submission: September 1, 2018
- Study completion: September 1, 2019
- Study report submission: December 1, 2019

If safety data from the preceding studies in older children and adolescents support the study in children 1-2 years of age (Study 4), this reviewer recommends that this study be conducted in an in-patient setting to allow administration of the product via nasogastric tube⁴ and for close monitoring of electrolytes and adverse events. It is unlikely that very young children will be able to consume a large volume of bowel preparation orally due to palatability issues and young children are more prone to electrolyte disturbances.

A Drug Safety Board meeting was convened on June 18, 2009 to discuss the potential risks of metabolic acidosis and neuropsychiatric adverse events in children exposed to polyethylene glycol (PEG) products.⁵ Although a clear safety signal could not be confirmed based on the available data, the Board agreed that the PEG products need

4 Turner D, Levine A, Weiss B. Evidence-based recommendations for bowel cleansing before colonoscopy in children: a report from a national working group. *Endoscopy* 2010;42:1063-70.

5 Drug Safety Oversight Board Meeting, June 18, 2009

(<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm171059.htm>)

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to be better characterized for molecular components since the potential risk for adverse events might be greater with the lower molecular weight products (b) (4) and little is known about their absorption in children. Therefore, in addition to routine collection of adverse events, the Applicant should monitor for electrolyte abnormalities and record neuropsychiatric adverse events (if any), as well as obtain serum levels of PEG and its small molecular weight impurities (b) (4) during the conduct of pediatric trials.

The above outlined pediatric studies were presented at a Pediatric Review Committee (PeRC) meeting on August 1, 2012, and the Committee agreed with the plan. Discussions regarding the goal dates and details of the study requirements are ongoing at the time of this review.

2) Postmarketing requirement under 505(o)

Compared to the comparator groups, patients who received BLI850 had numerically higher rates of new-onset elevated anion gap, elevated alanine aminotransferase (ALT), elevated creatine kinase (CK), and decreased estimated creatinine clearance (eC_{Cr}). In one patient who received BLI850 in Study 302, eC_{Cr} (calculated using the Cockcroft-Gault method) decreased from 90 mL/min at baseline to 49 mL/min at Visit 2. Since the laboratory follow-up did not extend beyond the day of colonoscopy except for a small set of patients in the submitted phase 3 trials, it is not clear whether the laboratory abnormalities and renal function continued to worsen over time or returned to baseline. Therefore, this clinical reviewer recommends that the Applicant conduct a randomized, active-control, single-blind post-marketing trial to evaluate renal function and laboratory abnormalities in patients exposed to BLI850 beyond the day of colonoscopy. This trial should include a sufficient number of elderly patients and patients with renal or hepatic impairment taking BLI850 prior to colonoscopy. Laboratory values of all patients should be followed at regular intervals for at least 30 days post-treatment.

2 Introduction and Regulatory Background

Colorectal cancer (CRC) is the third most commonly diagnosed cancer diagnosed in the United States, and the second leading cause of death from cancer.³ Since CRC can be largely prevented by the detection and removal of adenomatous polyps, the current practice guidelines recommend a colonoscopy beginning at age 50 with follow-up colonoscopies every 10 years in individuals with average risk.¹ Detection of CRC at an early localized stage is associated with significantly improved survival.⁶

6 Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012;366:687-96.

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The importance of a good-quality bowel preparation in detecting polyps and adenomas is well documented. Inadequate bowel preparation can result in incomplete procedures, missed lesions, higher complication rates, and increased costs and burden to patients due to repeated procedures.² Therefore, it is important to have available safe and effective bowel preparations that are well-tolerated by patients.

More recently, split dosing of bowel preparations has emerged as an important factor in bowel cleansing efficacy and patient tolerability.⁷ Accordingly, the American College of Gastroenterology guidelines for CRC screening (2008) recommend that bowel preparations be given in split doses.

2.1 Product Information

BLI850 consists of (1) sodium sulfate, potassium sulfate and magnesium sulfate oral solution; and (2) PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution. The Applicant's proposed indication is "for cleansing of the colon in preparation for colonoscopy in adults".

The chemical properties of each ingredient of BLI850 are listed in Table 1.

Table 1: Chemical name, formula, molecular weight, density, and melting point of ingredients in BLI850

Chemical name	Formula	Molecular Weight	Density	Melting Point
Sodium Sulfate, USP	Na ₂ SO ₄	142.04	2.68 g/cm ³	844°C
Potassium Sulfate, (b) (4)	K ₂ SO ₄	174.26	2.66 g/cm ³	1067°C
Magnesium Sulfate, USP	MgSO ₄	120.37	2.66 g/cm ³	1124°C (decomposition)
Polyethylene Glycol 3350, NF	H(OCH ₂ CH ₂) _n OH	3350	1.072 g/cm ³ (20°C)	53-56°C
Sodium Chloride, USP	NaCl	58.44	2.17 g/cm ³	801°C
Sodium Bicarbonate, USP	NaHCO ₃	84.01	2.2 g/cm ³	60°C
Potassium Chloride, USP	KCl	74.55	1.984 g/cm ³	770°C

Source: Summarized from the Applicant's NDA 203-595 submission, Module 2.3S.

⁷ Cohen LB. Split dosing of bowel preparations for colonoscopy: an analysis of its efficacy, safety, and tolerability. *Gastrointest Endos* 2010;72:406-12.

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Components of BLI850:

- First component or Dose 1 (oral solution): 6-oz liquid concentrate contains sodium sulfate, USP, potassium sulfate, (b) (4) and magnesium sulfate, USP, as well as inactive ingredients listed in Table 2. The liquid concentrate must be diluted with 10 oz 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 bottle or half of the 12-oz dose of SUPREP).

Table 2: BLI850 product composition: First component or Dose 1 (Sulfate solution)

Raw material and Grade quality	Method	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)	In-house method	(b) (4)	(b) (4)
Malic Acid, FCC	FCC	(b) (4)	(b) (4)
Citric Acid, USP	USP	(b) (4)	(b) (4)
(b) (4) Flavor	(b) (4)	(b) (4)	(b) (4)
Purified Water	USP	(b) (4)	(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 the following substances: polyethylene glycol 3350 (PEG-3350), NF, sodium chloride, USP, sodium bicarbonate, USP, and potassium chloride, USP (see Table 3). PEG-3350 is the primary, osmotically active ingredient in this PEG-ELS component. The 2-L 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.

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Table 3: BLI850 product composition: Second component or Dose 2 (PEG-ELS)

Raw material and Grade quality	Method	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)	In-house method	1.00 g	flavoring agent

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

2.2 Tables of Currently Available Treatments for Proposed Indications

Several products are available for bowel cleansing for preparation for colonoscopy. The FDA-approved bowel preparation products are listed in Table 4. It should be noted that Colyte and GoLYTELY are also approved for use for bowel cleansing prior to barium enema X-ray examination.

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Table 4: Summary of FDA-approved bowel preparation products (in the order of approval)

Drug Name	NDA/ANDA #	Formulation	Treatment	Approval Date
Colyte	NDA 18-983	<u>Per 4L solution:</u> PEG-3350, 240 g Sodium Sulfate, 22.72 g (anhydrous) Sodium Chloride, 5.84 g Sodium Bicarbonate, 6.72 g Potassium Chloride, 2.98 g	Ingestion of 4L solution	October 26, 1984
GoLYTELY	NDA 19-011	<u>Per 4L solution in jug/packet:</u> PEG-3350, 236 g/227.1 g Sodium Sulfate, 22.74 g/21.5 g Sodium Chloride, 5.86 g/5.53 g Sodium Bicarbonate, 6.74 g/6.36 g Potassium Chloride, 2.97 g/2.82 g	Ingestion of 4L solution	July 13, 1984
NuLYTELY TriLyte: generic (Half dose [2L] used as the comparator arm in BLI850 Study 301)	NDA 19-797 ANDA 76-491	<u>Per 4L solution:</u> PEG-3350, 420 g Sodium Chloride, 11.2 g Sodium Bicarbonate, 5.72 g Potassium Chloride, 1.48 g	Ingestion of 4L solution	April 22, 1991 February 5, 2004 (approval of TriLyte)
Visicol	NDA 21-097	<u>Per tablet:</u> Sodium Phosphate - monobasic monohydrate, 1.102 g - dibasic anhydrous, 0.398 g	Ingestion of 40 tablets	September 21, 2000
HalfLyteLy and Bisacodyl Tablets Bowel Prep Kit (Solution only without bisacodyl same as the comparator arm in BLI850 Study 301)	NDA 21-551	<u>Per 2L solution and bisacodyl:</u> PEG-3350, 210 g Sodium Chloride, 5.6 g Sodium Bicarbonate, 2.86 g Potassium Chloride, 0.74 g One 5 mg bisacodyl delayed-release tablet	Ingestion of 2L solution and one 5mg bisacodyl tablet	May 10, 2004 [†] September 24, 2007 July 16, 2010
OsmoPrep	NDA 21-892	<u>Per tablet:</u> Sodium Phosphate - monobasic monohydrate, 1.102 g - dibasic anhydrous, 0.398 g	Ingestion of 32 tablets (gluten-free)	March 16, 2006
MoviPrep (Split-dose used as the comparator arm in BLI850 Study 302)	NDA 21-881	<u>Per 2L solution:</u> PEG 3350, 200 g Sodium Sulfate, 15 g Sodium Chloride, 5.38 g Potassium Chloride, 2.03 g Sodium Ascorbate, 11.8 g Ascorbic Acid, 9.4 g	Ingestion of a 2L solution, either as split-dose or full dose regimen	August 2, 2006
SUPREP	NDA 22-372	<u>Per 12 oz solution:</u> Sodium Sulfate, 35.02 g Potassium Sulfate, 6.26 g Magnesium Sulfate, 3.2 g Sodium Benzoate (b) (4)	Ingestion of two 6-oz bottles as split-dose regimen	August 5, 2010

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PREPOPIK	NDA 202535	<u>Per 10 oz solution (reconstituted using two packets):</u> Sodium Picosulfate, 20 mg Magnesium Oxide, 7.0 g Citric Acid, 12.0 g	Ingestion of two 5-oz solution (each 5 oz solution contains one packet), either as split-dose or full dose regimen	July 16, 2012
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[†]The initially approved dose of bisacodyl in the HalfLyte and Bisacodyl Tablets Bowel Prep Kit was 20 mg. Subsequently, the reduced dose of 10 mg was approved on September 24, 2007 due to concerns of ischemic colitis. The currently approved dose is 5 mg (approved on July 16, 2010).

Source: Adapted from Dr. Donna Griebel's Division Director Summary Review for SUPREP dated August 5, 2010.

In addition to the above list, MiraLAX (polyethylene glycol 3350) is used off label as a bowel cleansing agent, especially in pediatric population.^{8,9}

2.3 Availability of Proposed Active Ingredient in the United States

Currently, BLI850 is not approved or marketed in the U.S. or other countries around the world. However, the active ingredients of BLI850 are available in the U.S. since BLI850 is comprised of components from approved products: (1) SUPREP and (2) NuLYTELY or the PEG solution part of HalfLyte without bisacodyl.

SUPREP was approved under NDA 22-372 on August 5, 2010 for cleansing of the colon prior to colonoscopy in adults. The approved dose of SUPREP is two 6-oz bottles that are administered as a split-dose (2-day) regimen. The first dose of BLI850 consists of a half dose of the approved SUPREP (i.e., one 6-oz bottle).

NuLYTELY was approved under NDA 19-797 on April 22, 1991. The approved dose of NuLYTELY is 4L. The second dose of BLI850 consists of a half dose of the approved NuLYTELY (i.e., 2L).

2.4 Important Safety Issues With Consideration to Related Drugs

An increased risk of fluid and electrolyte abnormalities, cardiac arrhythmias, seizures, and renal impairment are associated with the use of osmotic laxative products for bowel preparation and are described in the label of similar products. The label advises that patients with impaired renal function be adequately hydrated and followed closely with laboratory tests. In addition, osmotic laxative products have been associated with colonic mucosal aphthous ulcerations and reports of more serious cases of ischemic

⁸ Hunter A, Mamula P. Bowel preparation for pediatric colonoscopy procedures. *JPGN* 2010;51:254-61.

⁹ Pashankar DS, Uc A, Bishop WP. Polyethylene glycol 3350 without electrolytes: a new safe, effective, and palatable bowel preparation for colonoscopy in children. *J Pediatr* 2004;144:358-62.

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colitis. Although these cases have not been observed during phase 3 trials, the same precautions should be applied when administering BLI850.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

BLI850 has been developed under IND 102,894.

- **July 7, 2008:** The Division received the protocols for two phase 3 trials (Studies 301 and 302).
According to the Applicant's Clinical Study Report included in this NDA submission, Study 301 was conducted from August 25, 2008 to November 21, 2008, and Study 302 was conducted from August 25, 2008 to November 14, 2008. There was no End-of-Phase 2 or pre-NDA meeting for this application.
- **January 5, 2009:** The Division received the Statistical Analysis Plan.
- **January 30, 2009:** The Division sent an advice letter to the Applicant detailing clinical and statistical comments for Studies 301 and 302. The recommendations are summarized below:
 - The Division recommended that patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency be excluded as Moviprep has the potential to induce hemolytic reactions in these patients.
 - The Division requested a rationale for selection of the control arm. The Division recommended using 4-liter polyethylene glycol plus electrolytes solution as a control comparator in one of the two active controlled studies.
 - The Division recommended that the Applicant use a non-inferiority margin delta based on the historical evidence of the efficacy of the active control. In addition, the Division requested that the Applicant provide a justification for selecting a 15% non-inferiority margin and address the 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. In addition, 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.

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- The Division requested that the Applicant submit the statistical analysis plan (SAP) for review prior to start of the trials.
- **June 9, 2009:** The Division sent an advice letter to provide statistical comments for the submitted SAP for Studies 301 and 302. The following were the written 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 was advised to propose additional sensitivity analyses, which included observed and worse case scenarios.
- **December 19, 2011:** The Division received the Applicant's NDA 203-595.

2.6 Other Relevant Background Information

Combination Rule (21 CFR 300.50):

BLI850 is a combination product consisting of two components: (1) 6-oz oral sulfate solution (containing 22.24 g sulfate salts), and (2) 2-L polyethylene glycol and electrolytes (sodium chloride, sodium bicarbonate, and potassium chloride) for solution. The first component is equivalent to a half dose of the approved SUPREP, and the second component is equivalent to a half dose of the approved NuLYTELY (or the PEG solution part of HalfLytely without bisacodyl). Since two or more drugs are combined in a single dosage form, the Combination Rule needs to be addressed under 21 CFR 300.50. To address the Combination Rule, the Applicant submitted available pharmacodynamic (PD) and clinical efficacy data to demonstrate that individual components of BLI850 would be inferior to the combination in providing adequate bowel preparation.

The Applicant used two PD markers to compare and predict colon cleansing efficacy during development of their bowel cleansing products, including HalfLytely and SUPREP. The first PD marker is total stool output, where all stools resulting from bowel cleansing are collected and weighed in grams. The second PD marker is percent (%) stool solids (or "scatocrit"), where the pellet of the last diarrheal stool is weighed and expressed as a proportion. To calculate % stool solids, 14 mL sample from the final diarrheal sample [after bowel cleansing] was centrifuged at 3.6×10^3 rpm for 20 minutes, supernatant was decanted, and the remaining pellet was weighed. The stool percent solid (i.e., the quantity of solid material at the bottom of the tube) was assessed using the following formula:

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$$\% \text{ stool solid ("scatocrit")} = (\text{pellet weight}/14) \times 100$$

The above procedure for measuring % stool solids was described in the principle investigator Dr. John Fordtran's letter included in response to FDA Information Request dated August 24, 2012.

Although there are no data that directly correlate colon cleansing efficacy with total stool output or % stool solids, a published pediatric study reported that related clinical markers such as stool frequency and stool consistency are useful at predicting adequate colon preparation.¹⁰ It should also be noted that clear stool without solid matter has been used in clinical practice and clinical trials to predict adequacy of colon cleansing in preparation for colonoscopy. Currently approved labels of GoLYTELY and NuLYTELY recommend that patients consume the product until the "rectal effluent is clear," and the label of Colyte states that "lavage is complete when fecal discharge is clear." In addition, a clinical trial comparing various cleansing methods for colonoscopy instructed patients to consume the bowel cleansing product until diarrheal fluid was clear without particulate matter.¹¹ Hence, a low % stool solids appears to a reasonable pharmacodynamic marker to predict adequacy of colon cleansing prior to colonoscopy.

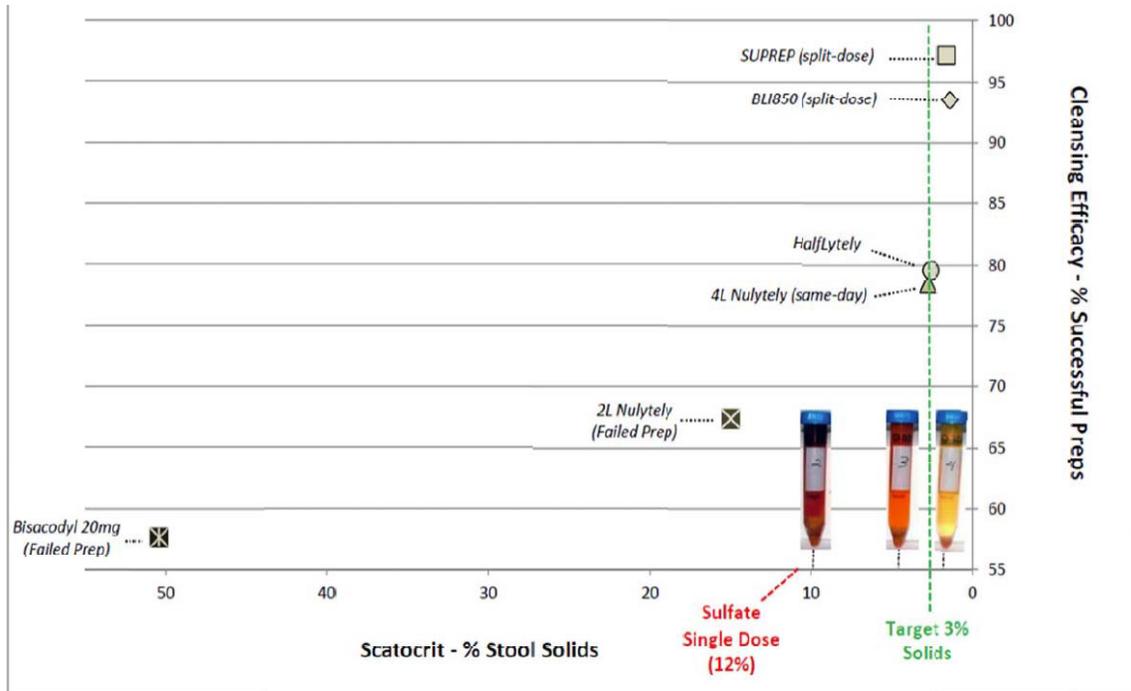
The Applicant used total stool output and % stool solids during the early phase trials in healthy volunteers to predict cleaning efficacy of products in development. The results of these two PD markers were compared to those that were obtained post-bowel cleansing with known-to-be effective (i.e., FDA-approved) and ineffective products. Based on the available data, the Applicant reports that % stool solids > 3% will likely result in failed bowel cleansing. The Applicant provided Figure 1 to support a correlation between % stool solids and colon cleansing efficacy from the clinical trials of various bowel preparation products. Although these PD markers were used as surrogate measures of colon cleansing efficacy, these are not widely used measures and their correlation to the clinical endpoints has not been validated.

10 Safder S, Demintieva Y, Rewalt M, et al. Stool consistency and stool frequency are excellent clinical markers for adequate colon preparation after polyethylene glycol 3350 cleansing protocol: a prospective clinical study in children. *Gastrointest Endos* 2008;68:1131-5.

11 DiPalma JA, Brady CE, Stewart DL, et al. Comparison of colon cleansing methods in preparation for colonoscopy. *Gastroenterology* 1984;86:856-60.

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Figure 1: Predictive value of % stool solids (“scatocrit”) for cleansing efficacy



Source: Applicant’s response to FDA’s Information Request dated August 3, 2012, Figure 3.

Table 5 compares the results of PD markers and cleaning efficacy of the failed preparations (e.g., bisacodyl 20 mg, 2 L NuYTELY) and the FDA-approved preparations (e.g., 4L NuLYTELY, HalfLyteLyte Kit, SUPREP).

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Table 5: 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	HalfLyte (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 RCT [‡]	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 HalfLyte 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: Applicant's response to FDA's Information Request dated August 3, 2012, Table 2.

It should be noted that one bottle of Sulfate Solution 5 (22 g SO₄) is almost identical in the amount of total sulfates as the first component of BLI850 (or 6 ounces of SUPREP). The minor difference between the two is outlined in Table 6.

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Table 6: Composition of Sulfate Solutions¹

Salt	Sulfate Solution 5 (mmol)	BLI800 ² (mmol)	BLI850 (mmol) ^{(b) (4)}
Na ₂ SO ₄			
MgSO ₄			
K ₂ SO ₄			
Total SO ₄			

¹The composition was based on one bottle of Sulfate Solution 5, one bottle of BLI800, and the first component of BLI850.

²SUPREP was known as BLI800 during development. Indicated amount of sulfates is half of the approved SUPREP solution.

Source: Adapted from the Applicant's response to FDA's Information Request dated August 24, 2012, Table 1.

In addition, 2L of NuLYTELY is equivalent to 2L of polyethylene glycol and electrolytes (sodium chloride, sodium bicarbonate, and potassium chloride) for solution used in the second component of BLI850. Although only one patient's % stool solids and stool output data are available for Solution 4 (sulfate + 2L NuLYTELY) in Table 5, this preparation is the same as BLI850. Data on the two individual components of BLI850 as well as the combined product (i.e., Solution 4) are highlighted in Table 5.

In response to FDA's Information Request dated August 24, 2012, the Applicant confirmed that the diet and liquid intake instructions for patients who participated in studies described in Table 5 were similar with respect to the pre-study and treatment period instructions. Except for those who received SUPREP, all patients whose stool output and % stool solids data are presented in Table 5 participated in the study under the same protocol (i.e., Baylor study 005-082). In Baylor study 005-082, patients were instructed to fast for at least 10 hours prior to reporting to the study site. Only water was permitted during this time and throughout the experimental period over the next 8 hours, although the amount of water intake was not standardized.

The stool output and % stool solids data for SUPREP (BLI800) were obtained from Baylor study 006-181, where patients were studied for two consecutive days. On Day 1, patients had no food or drink after midnight and were only allowed a clear liquid diet from 6 AM until one hour prior to starting the study treatment at 7 PM. During the subsequent 17-hour study period, patients receiving SUPREP drank additional 3760 mL of water. Although the amount of water intake was not the same between Baylor studies 005-082 and 006-181, it is unlikely that this difference alone would have affected the study outcome substantially to preclude cross-study comparison of PD markers.

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Data to support that the first component of BLI850 (i.e., Sulfate Solution 5 or half dose of SUPREP) alone would result in inadequate bowel cleansing.

As shown in Table 5, one bottle of Sulfate Solution 5 (or a half dose of SUPREP) resulted in high % stool solids (12%) and low stool output (1308 g), suggesting that this preparation will likely result in inferior bowel cleansing efficacy compared to other approved bowel cleansing preparations and BLI850. Upon request, the Applicant provided information on salt composition of the sulfate solutions used during drug development to demonstrate that one bottle of Sulfate Solution 5 indeed has close to an identical amount of sulfate salts as the first component of BLI850 (and one bottle of BLI800 [SUPREP]) (previously shown in Table 6).

The Applicant provided additional supportive data from a phase 1 study that one dose (i.e., a half dose) of SUPREP is inferior to two doses (i.e., a full dose) of SUPREP. In this phase 1 study (Baylor Study 006-181), % stool solids was measured in 5 patients after the first and second doses of BLI800 (SUPREP). As shown in Table 7, patients had a mean % stool solids of 6.4% after the first dose (Period 1) and 1.6% after the second dose (Period 2). It should be noted that this is not a true comparison between a half dose vs. a full dose regimen of SUPREP as these two measurements were collected from the same patients longitudinally. However, the Applicant allowed 10 hours in between the two doses to minimize the carry-over effect of the first dose. A similar trend was observed when % stool solids and stool output data were compared between Sulfate Solution 5 and SUPREP, as previously shown in Table 5. A lower % stool solids seen in the 4L NuLYTELY treatment group in Table 7 compared with that in Table 5 could be due to the product being administered as split doses.

Table 7: % Stool Solids of BLI800 and 4L NuLYTELY by Study Period

	BLI800¹	4L NuLYTELY
n	5	5
Period 1 % stool solids (SD)	6.4% (7.7)	8.5% (8.3)
Period 2 % stool solids (SD)	1.6% (0.8)	1.1% (0.2)

¹SUPREP was known as BLI800 during product development. Period 1 % stool solids was not measured for one patient in the BLI800 group.

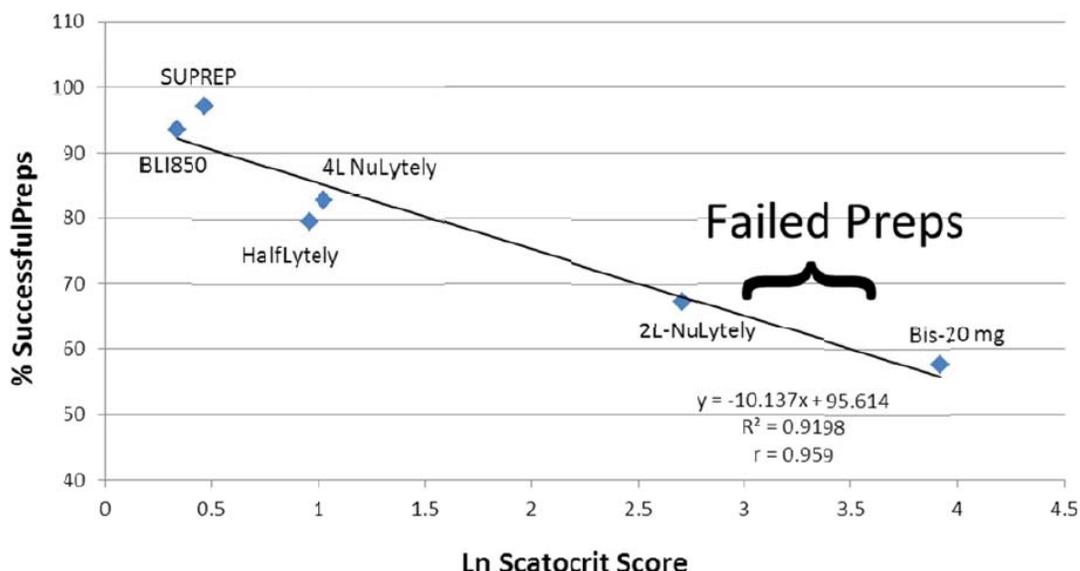
Source: Adapted from the Applicant's final study report for Baylor Study 006-181 included in the NDA 203-595 submission, Module 5.3.4.1.B, Table 12.

Although an efficacy trial was not conducted with a half dose of SUPREP (i.e., first component of BLI850), the Applicant's data presented in Table 5 and Table 7 suggest that the first component alone would likely result in inadequate bowel cleansing. To strengthen this proposal, the Applicant provided a regression equation correlating %

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stool solids and cleansing efficacy results to derive a predicted cleansing efficacy rate of less than 70% for a half dose of SUPREP (See Figure 2).

Figure 2: Relation of Ln % stool solids (“scatocrit”) with cleansing efficacy



Source: Applicant's response to FDA's Information Request dated August 3, 2012, Figure 3.

When there is evidence to suggest that a bowel preparation would be ineffective, there are ethical concerns to conducting a study to evaluate such a product. Colonoscopies are most commonly conducted for colorectal cancer screening, and adequate visualization of the colonic mucosa is essential to identifying and removing polyps and adenomas. Missed lesions due to inadequate bowel preparation can result in diagnosis of interval colon cancers between screening colonoscopies.¹² Therefore, patients who receive a half dose of SUPREP would be at an increased risk of undergoing a procedure in which a polyp or malignancy could be missed. Additionally, the procedure itself involves a rare but serious risk of bowel perforation, as well as risks associated with sedation and anesthesia. Exposure of patients to such risk, while knowing that they have undergone an inadequate bowel preparation and will require the procedure to be repeated, raises ethical concerns.

12 Chokshi RV, Hovis CE, Hollander T, et al. Prevalence of missed adenomas in patients with inadequate bowel preparation on screening colonoscopy. *Gastrointest Endosc* 2012;75:1197-203.

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Data to support that the second component of BLI850 (i.e., 2L NuLYTELY or HalfLyteLy solution without bisacodyl) alone would result in inadequate bowel cleansing.

As previously shown in Table 5, 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. There was only one patient who received Solution 4 (i.e., BLI850), but the % stool solids (1.4%) and stool output (2298 g) results were numerically closer to the approved products than products known to be ineffective. For 2L NuLYTELY, the bowel cleansing efficacy data from a clinical trial was also available to allow comparison to % stool solids and stool output results. However, the limitation of this comparison is that % stool solids and stool output data were not obtained from the same patients who underwent colonoscopy.

Table 8 summarizes clinical trial data from Study F38-15, which provided evidence that 2L NuLYTELY or bisacodyl alone is inferior to the approved product 4L NuLYTELY for bowel cleansing. The ITT population included all enrolled patients, and those who did not undergo colonoscopy due to safety or non-compliance reasons were treated as efficacy failure. It should be noted that Study F38-15 used the same scoring system to evaluate bowel cleansing efficacy (i.e., Colonoscopist colon cleansing score) as the trials included in this NDA submission. All doses in Study F38-15 were given the day prior to colonoscopy.

Table 8: Primary Efficacy Responder Analysis in Study F38-15¹

Responder ²	4L NuLYTELY n (%)	2L NuLYTELY n (%)	20 mg Bisacodyl n (%)	95% CI ³	P-value ⁴
Success	77 (82.8)	62 (67.4)	-	-27.7, -3.1	0.018
Fail	16 (17.2)	30 (32.6)			
Success	77 (82.8)	-	56 (57.7)	-37.5, -12.6	<0.001
Fail	16 (17.2)		41 (42.3)		

¹Study 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.

²Success was defined as bowel cleansing graded either "excellent" or "good" by the blinded colonoscopist.

³Confidence interval (CI) for percent success difference between treatments was calculated using a Chi-square test.

⁴P-value for difference between treatments was calculated using an exact Chi-square test.

Source: Applicant's response to FDA Clinical and Statistical Comments and Recommendations for IND 102,894, dated June 6, 2009, Table 1.

Conclusion

The pharmacodynamic and particularly the colon cleansing efficacy data discussed above have provided adequate evidence that the individual components alone in BLI850 will likely result in inadequate bowel cleansing required for a thorough colonoscopy examination. In addition, there are ethical concerns associated with

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conducting an efficacy trial using bowel preparations that are expected to be inadequate at study initiation. Based on the totality of the data presented and ethical concerns, this reviewer concludes that the Combination Rule has been adequately addressed.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This NDA was submitted in a paper format with electronic datasets. The initial electronic datasets consisted of data from all randomized patients including those who never received any treatment. An information request was sent to the Applicant to re-submit data excluding those patients who never received any treatment. In addition, multiple information requests were sent to the Applicant during the review cycle to obtain information necessary to allow a comprehensive review. Information requests sent to the Applicant are summarized below in a chronological order:

- **March 2, 2012:** Communicated the following potential review issues after a filing review:
 - It is not clear that the combination rule has been adequately addressed.
 - No clear justification of the 15% non-inferiority margin has been provided. The non-inferiority margin of 15% may not be considered acceptable.
 - A (b) (4) waiver of PREA studies may not be acceptable.

- **May 10, 2012:** Requested the Applicant to
 - Clarify elements that constituted protocol violations and to provide reasons for all protocol violations in Studies 301 and 302.
 - Explain how vomiting was documented.
 - Provide additional explanation for patients who were considered screen failures due to not meeting the criteria.
 - Clarify definitions of the different populations in Studies 301 and 302 (i.e., ITT, mITT, patients treated, patients in efficacy assessment and safety population).
 - Provide literature reference for the Colonoscopist Colon Cleansing Score used in Studies 301 and 302.
 - Provide revised tables of laboratory data, where the analysis is limited to patients without missing data only for that specific laboratory parameter.
 - Repeat laboratory analyses for the age subgroup < 65 and ≥ 65, as well as for the patients who were and were not considered high risk.

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- Provide revised laboratory datasets that include the following variables: an indicator for whether the patient was included in the ITT analysis, randomized treatment, treatment received, high-risk group, and an indicator for whether the baseline assessment was within the normal range. – *Responses received June 1, 2012.*
- **July 6, 2012:** Requested to submit a modified laboratory dataset to address reasons for missing values. – *Response received July 20, 2012.*
- **July 18, 2012:** Requested the Applicant to
 - Submit modified safety datasets that only include the ITT population (safety population). – *Modified datasets received July 24, 2012*
 - Revise specification for PEG-3350 to reflect the Agency’s proposed acceptance criterion of (b) (4) for combined (b) (4) and (b) (4) to comply with the ICH PDE limit (b) (4). – *Response received September 10, 2012.*
- **August 3, 2012:** Requested to address the Combination Rule to support that the combination product (BLI850) would be superior to each component alone (6 oz of SUPREP or 2L of NuLYTELY). – *Response received August 13, 2012.*
- **August 24, 2012:** Requested to
 - Provide information on patients’ diet and liquid intake to determine the appropriateness of comparing % stool solids resulting from different cleansing regimens.
 - Describe how “scatocrit” was measured and calculated; and specify if a different method was used in different studies.
 - Provide a table comparing the amount of each salt in Sulfate Solution 5 (used in Baylor 005-082) and BLI800. – *Responses received September 6, 2012.*
- **September 17, 2012:** Requested % stool solids (“scatocrit”) and stool output of individual patients included in Baylor studies 005-082 and 006-181. – *Response received September 19, 2012.*

3.2 Compliance with Good Clinical Practices

According to the Applicant, Studies 301 and 302 were conducted in accordance with the U.S. Code of Federal Regulations (CFR) governing the protection of human patients (21 CFR 50), IRBs (21 CFR 56), and the obligations of clinical investigators (21 CFR 312). Both studies were conducted in accordance with U.S. Title 21 CFR on Good Clinical Practices (GCPs), which is consistent with the ethical principles set forth

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in the Declaration of Helsinki, the International Conference on Harmonization, and the Food and Drug Administration.

An Office of Scientific Investigations (OSI) audit was requested for the sites listed in Table 9 due to enrollment of large number of study patients.

Table 9: List of sites inspected by the Office of Scientific Investigations

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: Dr. Khairy Malek's Clinical Inspection Summary dated September 6, 2012.

The field investigator did not find violations of federal regulations and felt that the data originated from all four audited sites were reliable and could be used in support of the NDA.

3.3 Financial Disclosures

The statements on financial disclosures (Form FDA 3454) were reviewed. A total of 24 (100%) investigators who participated in the phase 3 trials (Studies 301 and 302) certified that they had no financial arrangements as defined in 21 CFR 54.2. All investigators who participated in these trials responded to the Applicant's request to complete the Form FDA 3454.

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4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The reader is referred to Dr. Gene Holbert's CMC review dated August 17, 2012 and addendum for details. According to Dr. Holbert's initial review, the Applicant had not provided sufficient information to assure the identity, strength, purity, and quality of the drug substance and drug product as per 21 CFR 314.125(b)(1). Specifically, the proposed product did not comply with the ICH Q3C-recommended permitted daily exposure for (b) (4). Currently, the Applicant's proposed specification for (b) (4), but this calculation is based on a daily dose less than (b) (4) per day. A single dose of BLI850 (containing 210 g of PEG 3350) could result in a dose of (b) (4) which far exceeds the recommended limit. Since (b) (4) is considered to have similar toxicity as (b) (4) the Division requested that the sponsor set a limit of (b) (4) for the combined total amount of (b) (4) that could be present as impurities in PEG-3350. This request was communicated to the Applicant during a teleconference on July 16, 2012. The Applicant responded on September 10, 2012 that the specified combined limit for (b) (4) could be reduced (b) (4). This new proposed limit was considered to be acceptable by the CMC review team. However, the Applicant has not yet submitted a revised specification table incorporating this new limit and the assay that will be used to test the impurities in BLI850 at the time of this review.

4.2 Clinical Microbiology

No clinical microbiology data were submitted for review, since microbiology considerations do not apply to this bowel preparation product.

4.3 Non-clinical Pharmacology/Toxicology

Since BLI850 uses a combination of two approved and marketed products, the Applicant did not conduct any new non-clinical studies. The reader is referred to Dr. Yuk-Chow Ng's review dated September 10, 2012 for discussion of non-clinical toxicology studies that were reviewed under NDA 21-551 (HalfLytely), NDA 19-797 (NuLYTELY), and NDA 22-372 (SUPREP). Dr. Ng reported that there are no safety concerns for BLI850 from the non-clinical standpoint.

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4.4 Clinical Pharmacology

The reader is referred to Dr. Sandhya Apparaju's Clinical Pharmacology review dated September 18, 2012 for details. Dr. Apparaju considers this NDA acceptable from a clinical pharmacology perspective provided an agreement can be reached with the Applicant regarding proposed labeling language.

4.4.1 Mechanism of Action

BLI850 combines two components, an oral sulfate solution and PEG-ELS for solution. The primary mode of action is the osmotic effect of the unabsorbed sulfate salts and PEG. The osmotic effect of unabsorbed sulfate anions and the associated cations cause water to be retained within the gastrointestinal tract. Similarly, PEG is also a largely unabsorbed osmotic agent which causes water to be retained within the gastrointestinal tract. When ingested with additional fluids, the osmotic effect of the sulfate ions and PEG results in copious watery diarrhea.

4.4.2 Pharmacodynamics

No new pharmacodynamic (PD) studies were conducted in support of this NDA. The Applicant submitted data from two earlier PD studies (Study 005-082 and Study 006-181) in order to address the appropriateness of dose-selection for the active components. The two PD endpoints used were total stool output (in grams) and % stool solids (or "scatocrit"). The reader is referred to Dr. Apparaju's Clinical Pharmacology review for details on evaluation of PD studies. Her assessments are briefly summarized below.

The results of Study 005-082 suggested that the individual components (oral sulfate solution or NuLYTELY 2L) when administered alone did not generate the total stool weight and did not reduce % stool solids in the final bowel movement to an extent comparable to the approved colon cleansing formulations. Dr. Apparaju also acknowledged the limitation of the study since there is no established correlation between the PD endpoints used and the clinical efficacy of colon cleansing preparations.

The results from Study 006-181 suggested that a half dose of oral sulfate solution and a half dose of NuLYTELY had comparable PD findings, and more complete cleansing occurred after the second half of the dose. Dr. Apparaju reported that a combination of these two components may provide additional benefit with regard to % stool solids in final bowel movements. However, the combination regimen was not evaluated in the study.

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4.4.3 Pharmacokinetics

No new PK or dose-ranging studies were conducted in support of this NDA. The reader is referred to Dr. Apparaju's Clinical Pharmacology review that summarized previously reviewed PK data for oral sulfate solution that were submitted in support of the approval of SUPREP (NDA 22372). Dr. Apparaju's summary assessments and recommendations are outlined below:

- Following oral administration of 6 oz of oral sulfate solution (first dose), the sulfate concentration peaked at a median T_{max} of 4 hours in healthy volunteers. The concentration after the first dose did not return to baseline prior to the second dose of oral sulfate solution at 12 hours. At the end of two doses, the sulfate concentration returned to endogenous level within 3 days post-dose. The half-life of elimination was approximately 8.5 hours in healthy volunteers. Based on the urinary excretion data, the fraction of total dose absorbed appears to be approximately 20% following oral administration of oral sulfate salts.
- The drug clearance of the sulfate solution was slower than normal in organ dysfunction (e.g., hepatic insufficiency, renal impairment). However, BLI850 is intended for single use prior to colonoscopic procedure at a half dose of SUPREP, thus ruling out accumulation potential. Therefore, it appears reasonable not to require dose adjustments in specific subpopulations including renal impairment. Nevertheless, this information should be communicated in the labeling.

Since the Applicant did not evaluate the systemic exposure of PEG-3350 following the recommended dosing regimen, Dr. Apparaju is recommending a post-marketing pharmacokinetic study to evaluate the systemic exposure and pharmacokinetics of PEG-3350, (b) (4) and (b) (4) following oral administration of BLI850 in adult patients. The reader is referred to Dr. Apparaju's Clinical Pharmacology review addendum dated October 2, 2012 for details.

5 Sources of Clinical Data

The primary source of clinical data for this application consisted of two phase 3 trials (Studies 301 and 302).

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5.1 Tables of Studies/Clinical Trials

Table 10: Primary 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) <i>Day-Before Regimen</i>	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) <i>Split-Dose Regimen</i>	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

¹Treated patients consist of patients who took any amount of the study preparation (i.e., ITT patients or safety population).

²Completed patients consist of patients who received their study preparation fully and completed the study (i.e., patients who underwent colonoscopy)

Source: Adapted from the Applicant's Clinical Study Reports on Protocols BLI850-301 and BLI850-302, Tables 301-2 and 302-2, respectively.

5.2 Review Strategy

Clinical review of this NDA was conducted by Drs. Helen Sile and Jessica Lee. Dr. Sile was the initially assigned reviewer, but this NDA was reassigned to Dr. Lee on June 28, 2012 when Dr. Sile left the Division. Therefore, Dr. Sile began the review but it was completed by Dr. Lee.

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. The two trials were reviewed in detail and the results are discussed in this document. The reader is also referred to the Statistical Review by Dr. Wen-Jen Chen, dated October 31, 2012 for evaluation of the efficacy analyses.

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

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 BLI850-301 (Study 301: “Day-before regimen”)

Title

A Safety and Efficacy Evaluation of BLI850 vs. HalfLytely and Bisacodyl Bowel Prep Kit as Bowel Cleansing Preparations in Adult Patients.

Study Objective

To evaluate the efficacy and safety of BLI850 as compared to HalfLytely as bowel preparation before colonoscopic examination in adult patients.

Study Design

Study 301 was a phase 3, multi-center, randomized, active-controlled, single-blind, parallel-group trial to assess efficacy and safety.

Duration

The trial consisted of a screening visit (Visit 1), a colonoscopy examination visit (Visit 2), which was to occur within 15 days after visit 1, and one telephone follow-up scheduled two weeks after Visit 2 for patients who experienced ongoing adverse events. The trial was conducted from August 25, 2008 to November 21, 2008.

Protocol Amendments

There were no protocol amendments during the trial.

Study Population

Key Inclusion Criteria:

- Male or non-pregnant female \geq 18 years of age undergoing outpatient colonoscopic examination for a routinely accepted indication including:
 - Evaluation of barium enema results
 - GI bleeding

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- Anemia of unknown etiology
- Neoplastic disease surveillance
- Abnormal endosonography
- Inflammatory bowel disease
- Unknown diarrhea or constipation etiology
- Polypectomy
- Laser therapy
- Routine screening

Key Exclusion Criteria:

- Known or suspected ileus, severe ulcerative colitis, gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis, or megacolon
- Impaired consciousness that predisposes them to pulmonary aspiration
- Undergoing colonoscopy for foreign body removal or decompression
- Have clinically significant electrolyte abnormalities based on Visit 1 laboratory data
- History of previous significant gastrointestinal surgeries (e.g., colostomy, colectomy, gastric bypass)

Study Treatments

Patients were dispensed BLI850 or HalfLyte and were provided instructions on dosing and dietary restrictions.

BLI850

BLI850 was supplied as a kit containing one 6-oz bottle of sulfate solution (first dose) and one 2-L bottle of polyethylene glycol 3350 and electrolytes (PEG-ELS) for solution (second dose). The reader is referred to Table 2 and Table 3 for the composition of the oral sulfate solution and PEG-ELS for solution.

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Dosing instructions for BLI850 in Study 301:

- 1. Beginning at approximately 6 PM on the evening prior to the colonoscopy examination, patients 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 10 oz of water to the 16-oz fill line. Then, patients were instructed to drink the entire cup of solution. Over the next 2 hours, patients were instructed to drink one additional 16-oz glass of water.*
- 2. At approximately 8 PM (2 hours after starting the first dose), patients were instructed to dissolve the powder by adding water to the 2-L 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 patients were recommended to drink at least one additional 16-oz glass of water on the evening prior to colonoscopy.*

HalfLyte and Bisacodyl Tablets Bowel Prep Kit (hereafter referred to as HalfLyte)

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

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

- 1. Between approximately 12 to 3 PM on the day prior to colonoscopy, patients 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, patients were instructed to drink the 2-L solution part of HalfLyte at a rate of 8 oz every 10 minutes.*

Dietary restrictions

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

Concomitant Medications

There were no restrictions on prior and/or concomitant medications. Concomitant medications taken 7 days prior to Visit 1 until the completion of Visit 2 were recorded.

Study Procedures

Study 301 included two in-person visits and one telephone follow up.

Screening/Baseline (Visit 1): Patients participated in a one-day screening visit where eligibility criteria and medical history were reviewed and laboratory and physical examinations were performed. Eligible patients were randomly assigned to BLI850 or HalfLyte in a 1:1 ratio. Patients were instructed to take the assigned bowel preparation the day prior to their scheduled colonoscopy and complete a treatment

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questionnaire to record (1) the date and time of preparation administration, (2) vomiting episodes, and (3) any food consumption (Appendix 1: Treatment Questionnaire for Study 301) from start of the bowel preparation until return to the study site for Visit 2.

Day of Colonoscopy (Visit 2): Eligible patients were expected to return for their scheduled colonoscopy within 15 days of Visit 1.

Telephone Follow-Up: Two weeks after Visit 2, patients who had ongoing adverse events that were deemed possibly, probably, or definitely related to the study medication received a telephone follow-up. Blood samples were redrawn if patients had laboratory results at Visit 2 which were determined by the investigator to be clinically significant. It should be noted that there was no standardized definition for “clinically significant” laboratory values.

Table 11 details the study schedule of events.

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Table 11: Study Schedule of Events

Procedures	Visit 1 Screening/ Baseline	Day before colonoscopy	Visit 2 Day of colonoscopy	Telephone Follow-up 2 weeks post colonoscopy
Informed Consent	X			
Inclusion/Exclusion Criteria Review	X			
Medical History	X			
Physical Exam & Vital Signs	X		X	
Review of Concomitant Medication	X		X	
Blood Collection for Chemistry/Hematology	X		X	
Urine Pregnancy Test (if applicable) ¹	X			
Randomization ²	X			
Dispense Drug ²	X			
Instruct Patient	X			
Patient Completes Preparation		X	X (302 only)	
Patient Completes Treatment Questionnaire		X	X	
Patient Completes Symptom Scale			X	
Collect Patient Questionnaires			X	
Drug Accountability ²			X	
Perform Colonoscopy			X	
Assess Safety			X	
Assess Ongoing Adverse Events from Visit 2 that are possibly, probably, or definitely related to the study preparation				X

¹Female patients of childbearing potential must have urine pregnancy test done at screening. If tested positive, they were excluded from participating in the trial.

²To be performed by unblinded personnel only.

Source: Adapted from the Applicant's Protocols BLI850-301 and BLI850-302, Table 4.4.

Criteria for Discontinuing Patients from the Trial

1. Intercurrent illness which interferes with the visit schedule
2. Investigator's decision to withdraw the patient due to serious adverse event, protocol violation, preparation non-compliance, or inadequate preparation
3. Patient's decision to withdraw from the study

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Outcome Measurements

Efficacy

- Blinded investigators rated the quality of each colonoscopy preparation according to a 4-point rating scale (see Table 12).

Table 12: 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: Applicant's Clinical Study Report for Protocol BLI850-301, Table 301-1.

In response to FDA's Information Request dated May 10, 2012, the Applicant reported that the above scoring scale was developed by the Applicant. Although distinguishing between a score of 1 (poor) and a score of 4 (excellent) would not be difficult using this scale, the subjectivity of colonoscopists could potentially influence the middle scores, namely a score of 2 (fair) and a score of 3 (good). Therefore, it is important to assess to what extent scores of 3 (as opposed to scores of 4) contributed to the primary efficacy result.

Safety

- At Visit 2 (prior to colonoscopy), patients were instructed to rate the intensity of symptoms associated with bowel preparations using a symptom scale provided by the Applicant (Table 13). Patients used a 5-point scale for each symptom where a score of 1 = "None", 2 = "Mild", 3 = "Bothersome", 4 = "Distressing" and a score of 5 = "Severely distressing." In addition, patients were instructed to record the date and time of each vomiting episode.

Table 13: Symptom Scale completed by patients at Visit 2 prior to colonoscopy

Symptom	Scale
Stomach Cramping	1- No cramping ----- 5-Severely distressing cramping
Stomach Bloating	1- No bloating ----- 5-Severely distressing bloating
Nausea	1- No nausea ----- 5-Severely distressing nausea
Overall discomfort	1- No discomfort----- 5-Severely distressing discomfort

Source: Summarized from the Applicant's Protocol BLI850-301, Section 4.5.

- Other safety measurements included adverse events, vital signs, physical examinations, and clinical laboratory assessments.

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Endpoints

Primary Efficacy Endpoint

The primary endpoint was the outcome (“success” or “failure”) of the colon preparation. The primary efficacy variable was assessed as a binary outcome of overall preparation success or failure.

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 a 4-point rating scale “Colonoscopist Colon Cleansing Score” (see Table 12).

Failed treatment was defined as meeting any of the following criteria:

- Bowel cleansing graded as either poor (a score of 1) or fair (a score of 2) by the blinded colonoscopist using a 4-point rating scale (see Table 12)
- Any patient who did not have a colonoscopy based on the investigator's evaluation of the cleansing (e.g., insufficient fecal output) or due to study drug-related adverse events
- Any patient for whom colon cleansing was not adequate for assessment

Secondary Efficacy Endpoints

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

Statistical Analysis

The reader is referred to Dr. Wen-Jen’s Statistical review dated October 31, 2012 for detailed evaluation of the Applicant’s statistical analysis.

The Applicant calculated a sample size of 360 patients based on the goal of establishing non-inferiority between BLI850 and HalfLytely using a non-inferiority margin of 15%. However, it should be noted that the Division did not agree with this non-inferiority margin and recommended a lower margin.

The Applicant defined intent-to-treat (ITT) population as all enrolled patients who took any amount of BLI850 or HalfLytely. The Applicant stated in the Statistical Analysis Plan dated February 4, 2009 that patients who meet the following criterion would be considered non-evaluable and excluded from efficacy analyses:

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- Withdrawal from the study prior to colonoscopy for a reason unrelated to preparation safety or efficacy, such as family emergency, inability to return to the study center for Visit 2, or lack of insurance coverage for colonoscopy.

Methods of Handling Missing Data

The Applicant pre-specified that missing data would not be imputed and would remain missing. Patients without a preparation grade were evaluable for the primary endpoint if the reason they did not have a colonoscopy was due to inadequate bowel preparation, lack of effect, or as a result of adverse event(s). These patients were considered treatment failures for the primary endpoint.

Missing data for analyses using data collected at multiple time points (e.g., serum chemistry data, vital signs) were handled as follows:

- Patients with missing data for one of the two time points (Visit 1 or Visit 2) were included in the descriptive analysis for the time point that was collected. They were excluded for the time point that was not collected.
- Patients with missing data for one of the two time points (Visit 1 or Visit 2) were excluded from the change from baseline analysis.

Primary Efficacy Analysis

For the primary endpoint, the Applicant analyzed the success rate using the Cochran-Mantel-Haenszel (CMH) Chi-square test, adjusting for the effect of investigator site. The Applicant planned to present *P*-value for treatment difference together with a two-sided 95% confidence interval (CI) for the difference. The Applicant stated that a lower CI bound greater than 15% would establish non-inferiority between BLI850 and HalfLytely for a non-inferiority margin of 15%. However, it should be noted that the Division did not agree with a non-inferiority margin of 15%.

Secondary Efficacy Analyses

For the secondary efficacy endpoints, the treatment comparisons were performed in a similar manner to the primary endpoint analysis using the CMH chi-square test and two-way analysis of variance (ANOVA). No adjustment was made for multiplicity testing of secondary endpoints. Therefore, all secondary efficacy analyses are considered exploratory in nature.

Safety Analyses

The safety analyses included all patients who administered any portion of the study medication (ITT population). Descriptive analyses were performed.

Interim Analysis

No interim analysis was planned.

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5.3.2 BLI850-302 (Study 302: “Split-dose regimen”)

Title

A Safety and Efficacy Evaluation of BLI850 vs. MoviPrep as Bowel Cleansing Preparations in Adult Patients.

Study Objective

To evaluate the efficacy and safety of BLI850 as compared to MoviPrep administered as split doses for bowel preparation before colonoscopic examination in adult patients.

Study Design

Study 302 was a phase 3, multi-center, randomized, active-controlled, single-blind, parallel-group trial to assess efficacy and safety.

Duration

The trial consisted of a screening visit (Visit 1), a colonoscopy examination visit (Visit 2), which was to occur within 15 days after visit 1, and one telephone follow-up scheduled two weeks after Visit 2 for patients who experienced ongoing adverse events. The trial was conducted from August 25, 2008 to November 14, 2008.

Protocol Amendments

There were no protocol amendments during the trial.

Study Population

Key Inclusion Criteria:

- Same as Study 301

Key Exclusion Criteria:

- Same as Study 301 except for the two items below
 - Known phenylketonuria
 - Known glucose-6-phosphate dehydrogenase (G-6-PD) deficiency

Study Treatments

Patients were dispensed BLI850 or MoviPrep and were provided instructions on dosing and dietary restrictions. Eligible patients were instructed to take the first dose of the

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assigned bowel preparation the evening prior to their scheduled colonoscopy and begin the second dose the morning of their scheduled colonoscopy.

BLI850 (BLI850)

BLI850 was supplied as a kit containing one 6-oz bottle of sulfate solution (first dose) and one 2-L 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 examination, patients 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 10 oz of water to the 16-oz fill line. Then, patients were instructed to drink the entire cup of solution. Over the next 2 hours, patients were instructed to drink one additional 16-oz glass of water.*
- Patients 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, patients were instructed to dissolve the powder by adding water to the 2-L 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 examination.*

MoviPrep

All patients were instructed to follow the 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 examination, patients were instructed to pour contents of pouch A and B into the 1 liter container and fill with water to the fill line. Patients were instructed to drink the solution over one hour at a rate of 8 oz every 15 minutes until the container was empty.*
- Patients were required to drink an additional 0.5 liters of clear liquid that evening.*

2. Dose 2 (morning of colonoscopy)

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- *At approximately 6 AM, patients 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.*
- *Patients 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 examination.*

Dietary restrictions

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

Patients 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. Patients were instructed to consume only clear liquids from the time they start the MoviPrep treatment until after completion of the colonoscopy examination.

Concomitant Medications

Same as Study 301

Study Procedures

Similar to Study 301, Study 302 included two in-person visits and one telephone follow up. The only difference in the Study 302 procedure was that patients completed Dose 2 of the colon preparation on the day of colonoscopy (Visit 2). Patients in Study 302 were also instructed to complete a treatment questionnaire (Appendix 2: Treatment Questionnaire for Study 302) from start of the bowel preparation until return to the study site for Visit 2. The reader is referred to Table 11 for the study schedule of events.

Criteria for Discontinuing Patients from the Trial

Same as Study 301

Outcome Measurements

Same efficacy and safety measurements as Study 301

Endpoints

Same primary and secondary endpoints as Study 301

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Statistical Analysis

Same as Study 301

6 Review of Efficacy

Efficacy Summary

Two phase 3 clinical trials (Studies 301 and 302) were conducted to support the efficacy claim for BLI850 for cleansing of the colon in preparation for colonoscopy in adults. Studies 301 and 302 were multi-center, parallel-group, single-blind (colonoscopist only), active-controlled trials whose primary objectives were to evaluate the efficacy and safety of BLI850 compared with HalfLyte[®] and Bisacodyl Tablets Bowel Prep Kit and MoviPrep, respectively, for colon cleansing in patients undergoing colonoscopy. Study 301 evaluated the day-before regimen, whereas Study 302 evaluated the split-dose regimen.

Studies 301 and 302 had the same primary endpoint, which was the proportion of patients with successful colon cleansing as assessed by the colonoscopists. The primary efficacy variable was assessed as a binary outcome of “success” or “failure.” Successful treatment was defined as bowel cleansing grade of excellent or good (grading score 4 or 3) as evaluated by the blinded colonoscopist. Scores of “fair” or “poor” were regarded as non-responders.

Since the Applicant’s proposed non-inferiority margin of 15% was not adequately justified, it could not be used to demonstrate statistical significance. However, both trials demonstrated that BLI850 had numerically higher or same responder rates compared with the active comparator groups (Table 14 and Table 15).

Table 14: Proportion of patients with successful colon cleansing in Study 301 (Day-before regimen)

BLI850		HalfLyte [®]		Difference between treatment groups	
% (n/N)	95% CI	% (n/N)	95% CI	Difference	95% CI
90% (158/176)	(84%, 94%)	84% (157/188)	(77%, 89%)	6%	(-1%, 13%)

Table 15: Proportion of patients with successful colon cleansing in Study 302 (Split-dose regimen)

BLI850		MoviPrep		Difference between treatment groups	
% (n/N)	95% CI	% (n/N)	95% CI	Difference	95% CI
94% (173/185)	(89%, 97%)	94% (173/185)	(89%, 97%)	0%	(-5%, 5%)

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Secondary endpoint analyses evaluated (1) the adequacy of cleansing and need for re-preparation, (2) the number of excellent preparations as graded by the blinded colonoscopist, and (3) the number of examinations in which the colonoscopist reached the cecum. The results of secondary analyses supported the primary efficacy results, but they were considered exploratory since they were not adjusted for multiplicity.

When BLI850 was given as split doses over two days, it resulted in a numerically higher percentage of responders compared to when it was given as same-day regimen the day before the colonoscopy (93.5% vs. 89.8%). This finding is consistent with the current practice guidelines that advocate the split-dose regimen for more effective bowel cleansing. Therefore, the split-dose regimen should be recommended as the preferred method.

If approved, BLI850 will provide another option for patients who cannot tolerate ingesting a large amount of solution (e.g., 4 liters) required by older bowel preparations.

6.1 Indication

The proposed indication is “for cleansing of the colon in preparation for colonoscopy in adults”.

6.1.1 Methods

Two phase 3 trials, BLI850-301 (Study 301) and BLI850-302 (Study 302) form the basis of efficacy review. Studies 301 and 302 were multi-center, parallel-group, single-blind (colonoscopist only), active-controlled trials whose primary objectives were to evaluate the efficacy and safety of BLI850 compared with HalfLytely and Bisacodyl Tablets Bowel Prep Kit and Moviprep, respectively, for colon cleansing in patients undergoing colonoscopy. Study 301 evaluated the day-before regimen, whereas Study 302 evaluated the split-dose regimen. Sites and investigators did not overlap between the two studies. See Section 5.3 Discussion of Individual Studies/Clinical Trials for description of the two trials.

The definition of study populations included in the efficacy and safety analyses for Study 301 and 302 are described in Table 16.

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Table 16: Definition of study populations included in the efficacy and safety analyses

Population	Study 301 N	Study 302 N	Definition
All randomized patients (RAND)	394	386	Patients who were randomized to a preparation kit.
Intent-to-treat (ITT)	366	371	Patients 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	370	Patients 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 patients	362	370	Patients who were dispensed a preparation kit, subsequently administered any amount of the preparation, and underwent a colonoscopy. Completed patients were used for some of the secondary efficacy endpoint analyses.

Source: Summarized from the Applicant's Response to FDA's Information Request dated May 10, 2012.

6.1.2 Demographics

The study population consisted of adults who were undergoing colonoscopy for a routinely accepted indication (See inclusion criteria). Demographic and baseline characteristics were similar between treatment groups in both Studies 301 and 302.

Study 301 (Day-before regimen)

Table 17 summarizes demographics of the 366 patients enrolled in Study 301. The majority of the trial population was White (79%), with a similar racial distribution among the treatment groups. Patients ranged in age from 22 to 86 years, with a mean age of 57 years. There were similar numbers of elderly patients (≥ 65 years) in the two treatment groups. There was a slight female predominance (55%) in both treatment groups. The most common indication for a colonoscopy in both treatment groups was routine screening.

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Table 17: Demographics and indications for colonoscopy in Study 301 (ITT population)

Category	Treatment Group		Total N = 366
	BLI850 N = 176	HalfLytely N = 190	
Age (years), N			
Mean	56.8	56.9	56.9
Std deviation	13.1	12.3	12.7
Median	55	56	56
Min-Max	22-86	22-83	22-86
Age group, N (%)			
≥ 65 years old	48 (27.3)	49 (25.8)	97 (26.5)
≥ 75 years old	16 (9.1)	16 (8.4)	32 (8.7)
Sex, N (%)			
Male	79 (44.9)	86 (45.3)	165 (45.1)
Female	97 (55.1)	104 (54.7)	201 (54.9)
Race, N (%)			
White	143 (81.3)	145 (76.3)	288 (78.7)
Black	25 (14.2)	28 (14.7)	53 (14.5)
Asian	4 (2.3)	5 (2.6)	9 (2.5)
American Indian or Alaska Native	0	2 (1.1)	2 (0.5)
Weight (lbs)			
N	175	190	365
Mean	181.2	181.1	181.2
Std deviation	41.8	41.5	41.6
Median	175	178	177
Min-Max	104-340	87-320	87-340
Indication for colonoscopy, N (%)			
Routine screening	87 (49.4)	91 (47.9)	178 (48.6)
Polyp or neoplasm history	38 (21.6)	37 (19.5)	75 (20.5)
Rectal bleeding	21 (11.9)	28 (14.7)	49 (13.4)
Unknown constipation/diarrhea etiology	13 (7.4)	14 (7.4)	27 (7.4)
Abdominal or pelvic pain	4 (2.3)	8 (4.2)	12 (3.3)
Anemia of unknown etiology	3 (1.7)	5 (2.6)	8 (2.2)
GI bleeding	4 (2.3)	2 (1.1)	6 (1.6)
Inflammatory bowel disease	4 (2.3)	2 (1.1)	6 (1.6)
Rectal pain or hemorrhoids	1 (0.6)	2 (1.1)	3 (0.8)
Irritable bowel syndrome	1 (0.6)	0	1 (0.3)
Weight Loss; Fatigue	0	1 (0.5)	1 (0.3)

Source: Adapted from the Applicant's Clinical Study Report on Protocol BLI850-301, Tables 14.1.3 and 14.1.4.

In Study 301, a total of 169 patients (46%) in the ITT population were classified as high risk by the Applicant due to reported medical history of cardiac, renal or vascular problems (hypertension), or diabetes. The distribution of high risk patients was similar

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between the two treatment groups (80 patients [45%] in the BLI850 group and 89 patients [47%] in the HalfLytely group). Overall, demographics and clinical characteristics were similar between the two treatment groups in Study 301, and unlikely to have biased the outcome.

Study 302 (Split-dose regimen)

Table 18 summarizes demographics of the 371 patients enrolled in Study 302. Again, the majority of the trial population was White (86%). Patients ranged in age from 21 to 86 years, with a mean age of 57 years. The percentage of elderly patients was numerically higher by 4% in the MoviPrep group compared with the BLI850 group, but it is unlikely that this small difference affected the trial outcome. There was a slight male predominance in the BLI850 group (54%), whereas there was a female predominance (58%) in the MoviPrep group. However, it is unlikely that this small difference in gender distribution affected the trial outcome. There was no substantial difference among the two groups in indication for undergoing colonoscopy.

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BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

Table 18: Demographics and indications for colonoscopy in Study 302 (ITT population)

Category	Treatment Group		Total N = 371
	BLI850 N = 186	MoviPrep N = 185	
Age (years), N			
Mean	56.9	56.8	56.9
Std deviation	11.4	11.0	11.2
Median	55	55	55
Min-Max	21-85	23-86	21-86
Age group, N (%)			
≥ 65 years old	42 (22.6)	49 (26.5)	91 (24.5)
≥ 75 years old	13 (7.0)	10 (5.4)	23 (6.2)
Sex, N (%)			
Male	101 (54.3)	77 (41.6)	178 (48)
Female	85 (45.7)	108 (58.4)	193 (52)
Race, N (%)			
White	160 (86)	159 (85.9)	319 (86)
Black	9 (4.8)	13 (7)	22 (5.9)
Asian	2 (1.1)	3 (1.6)	5 (1.3)
American Indian or Alaska Native	1 (0.5)	2 (1.1)	3 (0.8)
Other	2 (1.1)	0	2 (0.5)
Weight (lbs)			
N	185	185	370
Mean	188.4	182.8	185.6
Std deviation	43.7	46.2	45
Median	185	174	178
Min-Max	105-300	82-451	82-451
Indication for colonoscopy, N (%)			
Routine screening	117 (62.9)	106 (57.3)	223 (60.1)
Rectal bleeding	23 (12.4)	27 (14.6)	50 (13.5)
Polyp or neoplasm history	23 (12.4)	19 (10.3)	42 (11.3)
Unknown constipation/diarrhea etiology	11 (5.9)	17 (9.2)	28 (7.5)
Anemia of unknown etiology	3 (1.6)	4 (2.2)	7 (1.9)
GI bleeding	4 (2.2)	1 (0.5)	5 (1.3)
Abdominal or pelvic pain	2 (1.1)	2 (1.1)	4 (1.1)
Family history of GI disease	2 (1.1)	2 (1.1)	4 (1.1)
Inflammatory bowel disease	0	2 (1.1)	2 (0.5)
Iron abnormal or Iron deficiency anemia	0	2 (1.1)	2 (0.5)
Change in bowel habits	1 (0.5)	0	1 (0.3)
Rectal pain or hemorrhoids	0	1 (0.5)	1 (0.3)
Diagnosis or history of diverticulitis	0	1 (0.5)	1 (0.3)
History of anal cancer	0	1 (0.5)	1 (0.3)

Source: Modified from the Applicant's Clinical Study Report on Protocol BLI850-302, Tables 14.1.3 and 14.1.4.

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BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

In Study 302, a total of 191 patients (51%) in the ITT population were classified as high risk by the Applicant due to reported medical history of cardiac, renal or vascular problems (hypertension), or diabetes. A slightly larger proportion of patients in the MoviPrep group were classified as high risk (101 patients [55%]) compared with those in the BLI850 group (90 patients [48%]), but it appears unlikely that this small difference affected the trial outcome.

6.1.3 Patient Disposition

A total of 791 patients were screened from 24 U.S. sites for enrollment into the two primary phase 3 trials. Of these 791 patients who were screened, 11 patients were screen failures and not randomized (5 patients in Study 301 and 6 patients in Study 302). Patient disposition is described separately for Study 301 and Study 302.

Study 301 (Day-before regimen)

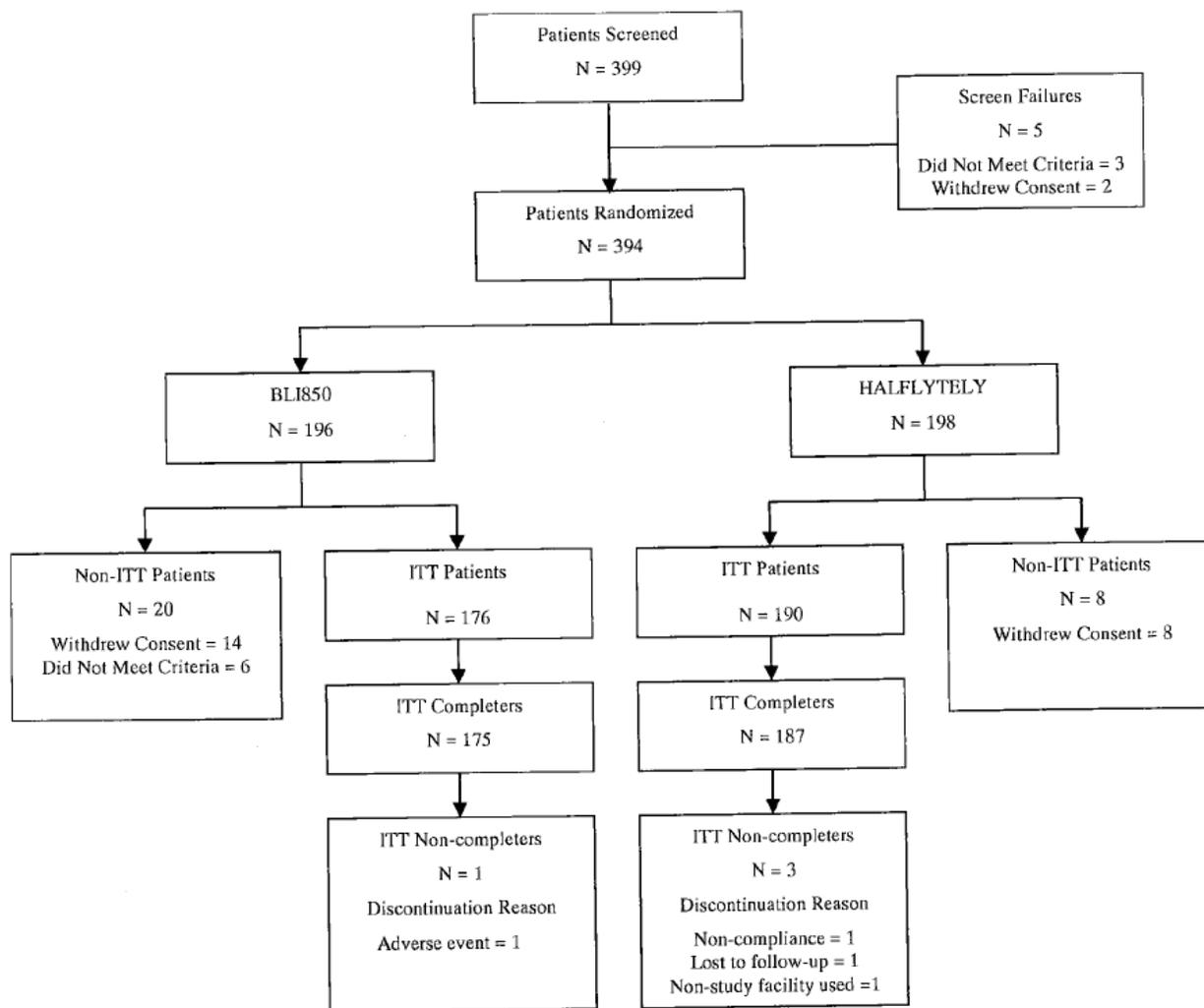
Patient disposition for Study 301 is summarized in Figure 3. A total of 399 patients were screened from 12 sites in the United States. Of the 399 patients screened, 394 were randomized into treatment groups and dispensed a study medication. Five patients were considered screen failures: 2 patients withdrew the consent and 3 patients did not meet the eligibility criteria (1 patient had ongoing uncontrolled hypertension, and 2 patients had previous significant gastrointestinal surgeries).

Of the 394 randomized patients, 366 patients administered the study medication and, therefore, were included in the ITT analysis. A total of 28 patients did not administer the study medication after randomization, as 22 patients withdrew the consent prior to receiving the study medication (14 in the BLI850 group and 8 in the HalfLyte group) and 6 patients in the BLI850 group were found to not have met the eligibility criteria after the study medication was dispensed. A larger number of patients randomized to the BLI850 group withdrew the consent compared with those randomized to the HalfLyte group, but the withdrawal of the consent occurred prior to the administration of any study medication. It is possible that patients opted to withdraw the consent once they found out that they would be receiving an experimental treatment since the study was single-blinded (colonoscopists only). These patients were not included in the ITT analysis. The reasons for 6 patients in the BLI850 group not meeting the eligibility criteria are listed below:

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

BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

Figure 3: Patient disposition for Study 301



Source: Applicant's Clinical Study Report for Protocol BLI850-301, Figure 2.

Table 19 summarizes patient disposition of the ITT population in Study 301. Of the 366 patients who administered the study medication, 362 patients completed the trial (i.e., patients who underwent a colonoscopy examination).

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BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

Table 19: Patient disposition of the ITT population in Study 301

Disposition	BLI850 n (%)	HalfLyteLy n (%)	Total n (%)
Patients treated (ITT)	176 (100)	190 (100)	366 (100)
Patients in efficacy assessment ¹ (mITT)	176 (100)	188 (98.9) ²	364 (99.5) ²
Completing patients ¹	175 (99.4)	187 (98.4)	362 (98.9)
Patients discontinued ¹	1 (0.6)	3 (1.6)	4 (1.1)
Reasons for discontinuation ³			
Adverse event	1 (100)	0	1 (25)
Non-compliance	0	1 (33.3)	1 (25)
Lost to follow-up	0	1 (33.3)	1 (25)
Non-study facility used	0	1 (33.3)	1 (25)

¹Percentages are based on the number of patients in the ITT group.

²Two patients (05040 and 10003) were not included in the efficacy analysis. One patient had the colonoscopy performed at a non-study facility due to concerns about anesthesia administration and one patient was not able to secure transportation to the study site.

³Percentages are based on the number of patients who discontinued in each treatment group.

Source: Adapted from the Applicant's Clinical Study Report for Protocol BLI850-301, Tables 301-2 and 14.1.1.

A total of 4 patients (1.1%) administered the assigned treatment but discontinued the trial prior to the colonoscopy examination for the following reasons:

- Patient 05006 took BLI850 and experienced new-onset atrial fibrillation (Patient has a history of myocardial infarction and hypertension).
- Patient 05040 took HalfLyteLy but had the colonoscopy performed at a non-study facility due to concerns about anesthesia administration.
- Patient 06027 discontinued taking HalfLyteLy because the patient did not have a bowel movement within 6 hours of taking the bisacodyl tablets.
- Patient 10003 took HalfLyteLy but could not secure transportation to the study site.

Patients 05006 and 06027 were included in the primary efficacy analysis as treatment failures. Patients 05040 and 10003 were not included in the efficacy analysis as they withdrew prior to colonoscopy for reasons unrelated to safety or efficacy.

Protocol Violations

Table 20 summarizes all protocol violations that occurred during the conduct of Study 301. There were 59 and 92 protocol violations in the BLI850 and HalfLYTELY treatment groups, respectively. However, most of the protocol deviations were considered minor and did not result in patients being excluded from the primary efficacy and safety analyses, except as noted in patient disposition. In the Statistical Analysis Plan (SAP), failure to maintain blinding of the treatment and dispensing kits out of order were to be documented as protocol violations.

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Table 20: Protocol violation summary for Study 301

Protocol violation category	BLI850 N = 59 n (%)	HalfLyteLy N = 92 n (%)	Total N = 151 n (%)
Did not return investigational product packaging	16 (27)	33 (36)	49 (32)
Patient violated food restriction	19 (32)	21 (23)	40 (26)
Physical examination incomplete	16 (27)	20 (22)	36 (24)
Preparation dose time not followed as instructed	3 (5)	8 (9)	11 (7)
Treatment Questionnaire and/or Symptom Scale incomplete or not returned	2 (3)	4 (4)	6 (4)
Laboratory testing done on different days or processing problems	1 (2)	3 (3)	4 (3)
Medical history finding (e.g., exclusion criteria violation)	1 (2)	1 (1)	2 (1)
Screening visit completed on different days	1 (2)	0 (0)	1 (1)
Patient had colonoscopy at non-study location	0 (0)	1 (1)	1 (1)
Patient participated in another investigational study within 30 days of screening	0 (0)	1 (1)	1 (1)

Source: Summarized from the Applicant's Clinical Study Report for Protocol BLI850-301, Section 16.2.20 and the Applicant's response to FDA's Information Request dated May 10, 2012, Question 2.

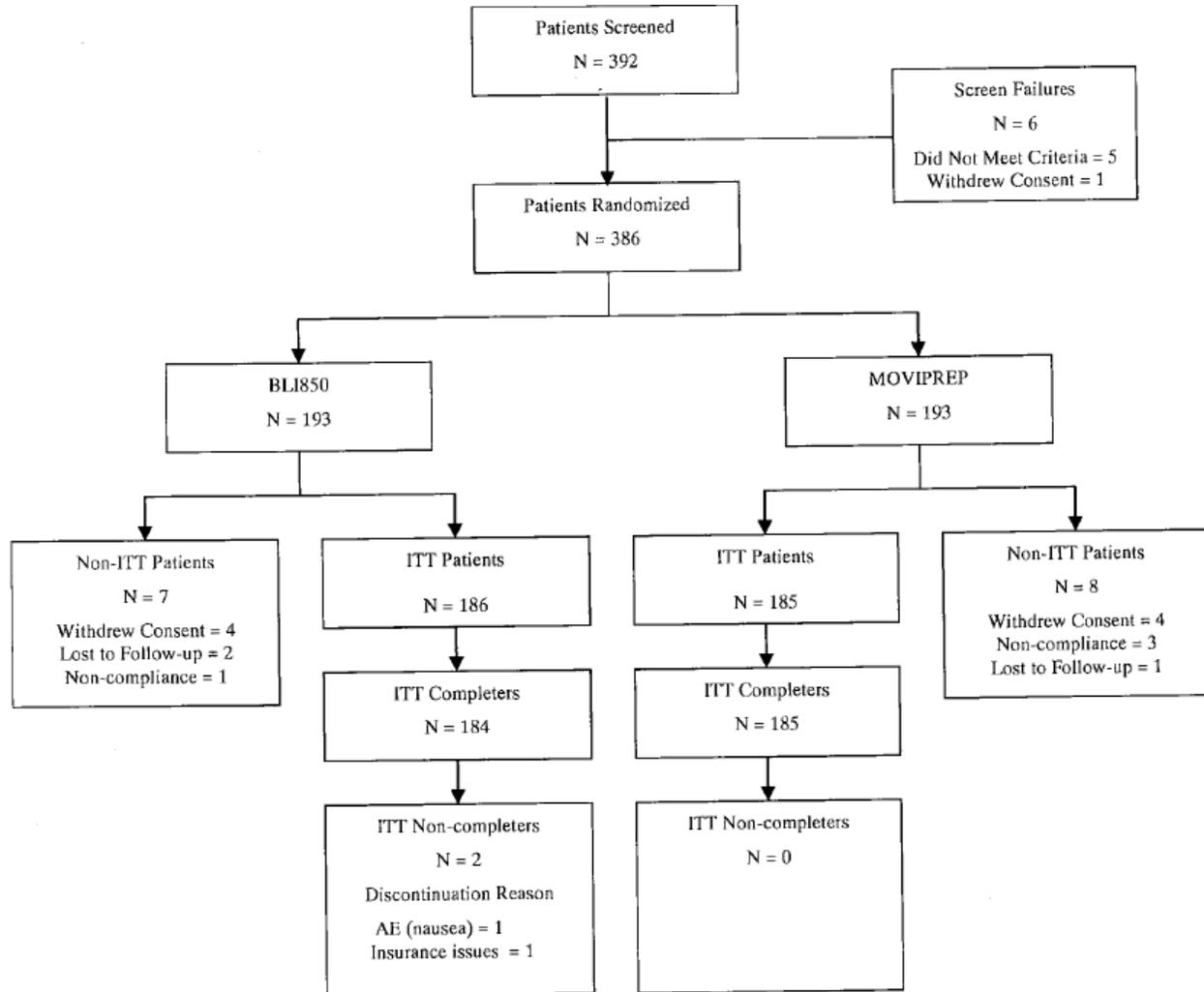
Study 302 (Split-dose regimen)

Patient disposition for Study 302 is summarized in Figure 4. A total of 392 patients were screened from 12 sites in the U.S. Of the 392 patients screened, 386 were randomized into treatment groups and dispensed a study medication. Six patients were considered screen failures: 1 patient withdrew the consent and 5 patients did not meet the eligibility criteria (one patient had a history of allergy to a component of the study medication [sucralose], and 4 patients had previous significant gastrointestinal surgeries).

Of the 386 randomized patients, 371 patients administered the study medication and were included in the ITT analysis. A total of 15 patients did not administer the study medication (8 patients withdrew the consent prior to receiving the study medication, 4 patients were non-compliant, and 3 patients were lost to follow-up).

BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

Figure 4: Patient Disposition for Study 302



Source: Applicant's Clinical Study Report for Protocol BLI850-302, Figure 2.

Table 21 summarizes patient disposition of the ITT population in Study 302. Of the 371 patients who administered the study medication, 369 patients completed the trial (i.e., patients who underwent a colonoscopy examination).

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BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

Table 21: Patient disposition of the ITT population in Study 302

Disposition	BLI850 n (%)	MoviPrep n (%)	Total n (%)
Patients treated (ITT)	186 (100)	185 (100)	371 (100)
Patients in efficacy assessment ¹ (mITT)	185 (99.5) ²	185 (100)	370 (99.7) ²
Completing patients ¹	184 (98.9)	185 (100)	369 (99.5)
Patients discontinued ¹	2 (1.1)	0	2 (0.5)
Reasons for discontinuation ³			
Adverse event	1 (50)	0	1 (50)
Lack of insurance coverage	1 (50)	0	1 (50)

¹Percentages are based on the number of patients in the ITT group.

²One patient (26002) was not included in the efficacy analysis. This patient withdrew from the trial prior to colonoscopy due to insurance issues.

³Percentages are based on the number of patients who discontinued in each treatment group.

Source: Adapted from the Applicant's Clinical Study Report for Protocol BLI850-302, Tables 302-2 and 14.1.1.

A total of 2 patients administered the assigned treatment but discontinued the trial prior to the colonoscopy examination for the following reasons:

- Patient 25063 took BLI850 and experienced moderate nausea, and decided to discontinue the study treatment and withdrew from the trial.
- Patient 26002 administered and completed taking BLI850, but withdrew from the trial prior to the colonoscopy examination as the patient was informed that colonoscopy would not be covered by her insurance.

Patient 25063 was included in the efficacy analysis as treatment failure. Patient 26002 was not included in the efficacy analysis since this patient withdrew for reasons unrelated to safety or efficacy.

Protocol Violations

Elements that constituted protocol violations were same as those in Study 301, except study treatments administered more than 2 hours outside the protocol-specified timeframes (6 PM and 6 AM) were also considered protocol violations. Table 22 lists all protocol violations that occurred during the conduct of Study 302. Most of the protocol deviations were considered minor and did not result in patients being excluded from the primary efficacy and safety analyses.

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Table 22: Protocol violation summary for Study 302

Protocol violation category	BLI850 N = n (%)	MoviPrep N = n (%)	Total N = 172 n (%)
Did not return investigational product packaging	24 (27)	31 (38)	55 (32)
Patient violated food restriction	30 (33)	10 (12)	40 (23)
Laboratory testing done on different days or processing issue	8 (9)	18 (22)	26 (15)
Physical exam incomplete	14 (16)	10 (12)	24 (14)
Preparation dose time not followed as instructed	10 (11)	11 (13)	21 (12)
Screening visit completed on different days	2 (2)	1 (1)	3 (2)
Treatment Questionnaire and/or Symptom Scale incomplete or not returned	2 (2)	1 (1)	3 (2)

Source: Summarized from the Applicant's Clinical Study Report for Protocol BLI850-302, Section 16.2.20 and the Applicant's response to FDA Information Request dated May 10, 2012, Question 2.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy analysis was based on the modified intent-to-treat (mITT) population, defined as all patients 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.

Studies 301 and 302 had the same primary endpoint, which was the proportion of patients with successful colon cleansing as assessed by the colonoscopists. The primary efficacy variable was assessed as a binary outcome of "success" or "failure." Successful treatment was defined as bowel cleansing grade of excellent or good (grading score 4 or 3) as evaluated by the colonoscopist (blinded to treatment) using a 4-point rating scale. Scores of "fair" or "poor" were regarded as non-responders (i.e., failure). See Table 12 for details on the 4-point rating scale.

It should be noted that the Division recommended to the Applicant that a non-inferiority margin of 15% was not appropriate and that a lower margin (i.e., 9%) should be used. Therefore, the Applicant's analyses using 15% as a non-inferiority margin to establish non-inferiority between BLI850 and HalfLytely are not acceptable. The reader is referred to Dr. Wen-Jen Chen's Statistical review for the evaluation of the Applicant's proposed non-inferiority margin.

Study 301 (Day-before regimen)

As shown in Table 23, the percentage of responders was numerically higher in the BLI850 group compared with the HalfLytely group. Although the Applicant's non-inferiority margin cannot be accepted to demonstrate statistical significance (See Dr. Wen-Jen Chen's Statistical review), the BLI850 group demonstrated a numerically

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higher responder rate compared with the HalfLyte group by 6.3%. In addition, the lower bound of the two-sided 95% confidence interval for the BLI850 group was higher than the HalfLyte group (84% vs. 77%).

Table 23: Primary efficacy analysis of Study 301 (mITT population)

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

¹Responders were defined as patients whose colon preparations were graded as either excellent or good by the colonoscopist (grading score 4 or 3).

Source: Adapted from Dr. Wen-Jen Chen's Statistical review dated October 31, 2012. The confidence intervals were provided by Dr. Chen.

Although the Colonoscopist Colon Cleansing score has been used in the approval of multiple bowel preparation products, there could be a fair amount of subjectivity in mid-range scores, specifically scores graded as "fair" or "good." However, a score of "good" is considered a success, whereas a score of "fair" is considered a failure. Therefore, it would be important to assess whether the efficacy result remains similar between the two treatment groups when only the bowel preparations graded as "excellent" are considered successful. As shown in Table 24, the BLI850 group continued to have numerically higher proportion of patients with successful bowel preparations compared with the HalfLyte group, even when the colon cleansing grade of "good" was excluded from comparison.

Table 24: Number of patients in Study 301 with "Excellent" colon cleaning score

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

Source: The Applicant's Clinical Study Report for Protocol BLI850-301, Table 301-4.

In summary, colon cleansing with BLI850 resulted in a numerically higher percentage of responders (i.e., patients with colon cleansing graded as "excellent" or "good") compared with the HalfLyte group. The BLI850 group continued to have numerically higher percentage of responders when only bowel preparations graded as "excellent" were considered successful.

Study 302 (Split-dose regimen)

Table 25 summarizes the result of primary efficacy analysis comparing the percentage of responders between the BLI850 and MoviPrep groups when given as split doses. The BLI850 and MoviPrep groups had numerically same percentage of successful colon cleansing. The lower bound of the two-sided 95% confidence interval for the BLI850 group was 89%, which was same as the MoviPrep group.

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Table 25: 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 patients whose colon preparations were graded as either excellent or good by the colonoscopist (grading score 4 or 3).

Source: Adapted from Dr. Wen-Jen Chen's Statistical review dated October 31, 2012. The confidence intervals were provided by Dr. Chen.

Even when the colon cleansing grade of "good" was excluded from comparison, the proportions of patients with successful preparation remained almost identical between the BLI850 and MoviPrep groups (Table 26).

Table 26: Number of patients 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.

When BLI850 was given as split doses over two days, it resulted in a numerically higher percentage of responders compared to when it was given as same-day regimen the day before the colonoscopy (93.5% vs. 89.8%). This finding is consistent with the published practice guidelines that advocate the split-dose regimen for more effective bowel cleansing.¹ Hence, the split-dose regimen should be specified as the preferred method and the day-before regimen as the alternative method.

6.1.5 Analysis of Secondary Endpoints(s)

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.

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Secondary Endpoint 1: Adequacy of cleansing and need for re-preparation

Study 301 (Day-before regimen)

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.

As shown in Table 27, the two treatment groups had similar percentages of patients who had adequate colon cleansing for evaluation. Only 4 patients in each treatment group required re-preparation due to inadequate preparation. It should be noted that although *P*-values are reported, the results of this analysis is considered exploratory since there was no adjustment for multiplicity testing of secondary endpoints.

Table 27: Adequacy of Cleansing in Study 301 (completing patients¹)

	BLI850 n = 175	HalfLytely n = 187	95% CI²	P-value³
Was cleaning adequate for evaluation? n (%)				
Yes	170 (97.1)	183 (97.9)	(-3.9, 2.5)	0.744
No	5 (2.9)	4 (2.1)		
Was re-preparation needed? ⁴ n (%)				
Yes	4 (80)	4 (100)	(-55.1, 15.1)	1.0
No	1 (20)	0		

¹362 of the 366 patients (ITT population) who received the study preparation fully completed the study (i.e., patients who underwent a colonoscopy exam).

²Confidence interval (CI) for percent difference between treatments was calculated using a Chi-square test.

³*P*-value for difference between treatments was calculated using an exact Chi-square test.

⁴The need for re-preparation was only documented for patients who did not have adequate cleansing for evaluation.

Source: Applicant's Clinical Study Report for Protocol BLI850-301, Table 14.2.3.

This secondary endpoint is particularly subjective in nature, since the definition of "adequate" cleansing can vary depending on the colonoscopist. However, it is reassuring that results were numerically similar between the two treatment groups and the majority of bowel preparations were considered adequate for evaluation by colonoscopists. Although these data lack objectivity, they are supportive of primary efficacy analysis.

Study 302 (Split-dose regimen)

As shown in Table 28, the two treatment groups had similar percentages of patients who had adequate colon cleansing for evaluation. Only 1 patient who received BLI850 and 2 patients who received MoviPrep required re-preparation due to inadequate preparation.

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Jessica Lee, MD; Helen Sile, MD

NDA 203-595

BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

Table 28: Adequacy of cleansing in Study 302 (completing patients¹)

	BLI850 n = 184	MoviPrep n = 185	95% CI²	P-value³
Was cleaning adequate for evaluation? n (%)				
Yes	181 (98.4)	180 (97.3)	(-1.9, 4.0)	0.724
No	3 (1.6)	5 (2.7)		
Was re-preparation needed? ⁴ n (%)				
Yes	1 (33.3)	2 (40)	(-75.1, 61.8)	1.0
No	2 (66.7)	3 (60)		

¹369 patients of the 371 patients (ITT population) who received the study preparation fully completed the study (i.e., patients who underwent a colonoscopy exam).

²Confidence interval (CI) for percent difference between treatments was calculated using a Chi-square test.

³P-value for difference between treatments was calculated using an exact Chi-square test.

⁴The need for re-preparation was only documented for patients who did not have adequate cleansing for evaluation.

Source: Applicant's Clinical Study Report for Protocol BLI850-302, Table 14.2.3.

Although the above secondary endpoint is subjective in nature and the analysis is exploratory, the results are supportive of the primary efficacy outcome.

Secondary Endpoint 2: Number of excellent preparations as graded by the blinded colonoscopist

Study 301 (Day-before regimen)

Table 29 compares efficacy of two treatment groups by cleansing grade. This analysis was based on the mITT population, as it also included patients who did not undergo colonoscopy for reasons unrelated to safety and efficacy. These patients were designated as missing in Table 29. Patients in the BLI850 group had a numerically higher percentage of preparations graded as excellent (48%) compared with patients who received HalfLytely (36%). Although a P-value for this comparison is reported, this analysis is considered exploratory since there was no adjustment for multiplicity testing of secondary endpoints. Only small percentages of preparations were graded as either fair (7%) or poor (2%) in both treatment groups.

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Jessica Lee, MD; Helen Sile, MD

NDA 203-595

BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

Table 29: Colonoscopy assessment analysis by cleansing grade in Study 301 (mITT population)

Colon Cleansing Grade	BLI850 n = 176	HalfLyte n = 188	P-value ¹
Excellent (4)	84 (47.7)	67 (35.6)	0.010
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	0.016

¹P-value comparing excellence preparation was calculated using the CMH Chi-square test, controlling for site; P-value for mean score was calculated using a one-way ANOVA.

²Two missing patients (one from each treatment group) were not included in the calculation of mean scores.

Source: Adapted from the Applicant's Clinical Study Report for Protocol BLI850-301, Tables 301-4 and 14.2.1.1.

Although the above secondary endpoint analysis is considered exploratory, these data strengthen the evidence that BLI850 works at least as well as the approved HalfLyte Bowel Prep Kit based on numerical comparison and may even be superior. However, none of the secondary endpoint analyses was adjusted for multiplicity, (b) (4)

Study 302 (Split-dose regimen)

Table 30 compares efficacy of two treatment groups by cleansing grade using the mITT population. Patients who received BLI850 and Moviprep had similar percentages of preparations graded as excellent, 52% and 51%, respectively. Although a P-value for this comparison is reported, this analysis is considered exploratory. Only a small percentage of preparations were graded as either fair (5%) or poor (1%) in the BLI850 treatment group.

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Jessica Lee, MD; Helen Sile, MD

NDA 203-595

BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

Table 30: Colonoscopy assessment analysis by cleansing grade in Study 302 (mITT population)

Colon Cleansing Grade	BLI850 n = 185	MoviPrep n = 185	P-value ¹
Excellent (4)	96 (51.9)	95 (51.4)	0.986
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	0.779

¹P-value comparing excellence preparation was calculated using the CMH Chi-square test, controlling for site; P-value for mean score was calculated using a one-way ANOVA.

²Two missing patients (one from each treatment group) were not included in the calculation of mean scores.

Source: Adapted from the Applicant's Clinical Study Report for Protocol BLI850-301, Tables 301-4 and 14.2.1.1.

Although the above secondary endpoint analysis was considered exploratory, these data strengthen the evidence that BLI850 works similarly to the approved MoviPrep based on numerical comparison.

Secondary Endpoint 3: Number of examinations in which the colonoscopist reached the cecum

Study 301 (Day-before regimen)

In general, the ability to reach the cecum during colonoscopy is largely influenced by adequate visualization of the entire colon. Since the cecum marks the beginning of the colon, it is the last site in colon to be reached during colonoscopy. The Applicant provided an analysis of the number of examinations in which the colonoscopist reached the cecum.

As shown in Table 31, similar percentages of colonoscopies were completed in both treatment groups, but the cecum was not reached in two patients in the BLI850 treatment group. It is not possible to make an unbiased comparison to explain this small difference, since the ability to reach the cecum could also be influenced by factors unrelated to bowel preparation, such as anatomy of the patient's colon, patient's underlying disease, patient discomfort, and skills of the colonoscopist. Although P-values are reported, this secondary endpoint analysis is also considered exploratory since it was not adjusted for multiplicity.

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Jessica Lee, MD; Helen Sile, MD

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BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

Table 31: Colonoscopy completion status in Study 301 (completing patients)

	BLI850 N = 175	HalfLyte N = 187	95% CI¹	P-value²
Colonoscopy Status³ n (%)				
Completed	172 (98.3)	184 (98.4)	(-2.7, 2.5)	0.983
Not completed	3 (1.7)	3 (1.6)		
Was the cecum reached? n (%)⁴				
Yes	170 (98.8)	184 (100)	(-2.8, 0.4)	0.157
No	2 (1.2)	0		

¹Confidence interval (CI) for percent difference between treatments was calculated using a Chi-square test.

²P-value for difference between treatments was calculated using a CMH Chi-square test, controlling for site.

³Colonoscopy completion status was reported for patients in whom a colonoscopy was attempted.

⁴The percentage of patients whose cecum was reached/not reached was based on the number of patients who completed colonoscopy.

Source: Adapted from the Applicant's Clinical Study Report for Protocol BLI850-301, Table 14.2.2.

A total of 6 patients, 3 in each treatment group, could not complete their colonoscopies. According to the Applicant, 2 patients in BLI850 could not complete the examination due to excess pain (one patient refused sedatives) or discomfort, and 1 patient had fixed angulation. All 3 patients in HalfLyte group could not complete the colonoscopy examination due to poor bowel preparation. Of those who completed colonoscopy, the cecum was reached in all except for 2 patients in BLI850.

Study 302 (Split-dose regimen)

As shown in Table 32, similar percentages of colonoscopies were completed in both treatment groups, and the cecum was reached in all patients who completed the colonoscopy in both groups. It should be noted that although P-values are reported, this secondary endpoint analysis is also considered exploratory since it was not adjusted for multiplicity.

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Jessica Lee, MD; Helen Sile, MD

NDA 203-595

BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

Table 32: Colonoscopy completion status in Study 302 (completing patients)

	BLI850 n = 184	MoviPrep n = 185	95% CI¹	P-value²
Colonoscopy Status³ n (%)				
Completed	181 (98.4)	182 (98.4)	(-2.6, 2.6)	0.946
Not completed	3 (1.6)	3 (1.6)		
Was the cecum reached? n (%)⁴				
Yes	181 (100)	182 (100)	-	-
No	0	0		

¹Confidence interval (CI) for percent difference between treatments was calculated using a Chi-square test.

²P-value for difference between treatments was calculated using a CMH Chi-square test, controlling for site.

³Colonoscopy completion status was reported for patients in whom a colonoscopy was attempted.

⁴The percentage of patients whose cecum was reached/not reached was based on the number of patients who completed colonoscopy.

Source: Adapted from the Applicant's Clinical Study Report for Protocol BLI850-302, Table 14.2.2.

A total of 6 patients, 3 in each treatment group, could not complete their colonoscopies. According to the Applicant, 2 patients in BLI850 could not complete the examination due to anatomic abnormalities (i.e., obstructive lesion, multiple complex diverticula), and 1 patient had poor bowel preparation. In the MoviPrep group, 1 patient each had poor bowel preparation, tortuous colon, and "lax colon severe melanosis coli."

In summary, the three pre-specified secondary endpoints provide supportive evidence that BLI850 has similar efficacy as the comparator products. However, none of the secondary endpoint analyses was adjusted for multiplicity, (b) (4)

6.1.6 Other Endpoints

None

6.1.7 Subpopulations

The Applicant's analysis of the primary efficacy endpoint by investigator site did not reveal any significant difference or potential concern for bias. Sites with the largest number of enrolled patients were audited, and the data from these sites were deemed reliable. Below, the primary efficacy analyses for the following subgroups are reviewed: age, gender, and race.

Clinical Review

Jessica Lee, MD; Helen Sile, MD

NDA 203-595

BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

❖ Efficacy by Age

Study 301 (Day-before regimen)

Table 33 presents primary efficacy analysis by age in Study 301. Patients who were < 65 years of age or ≥ 75 years of age had higher percentages of successful bowel preparations when BLI850 was administered compared to HalfLytely. Based on this exploratory analysis, there was a trend towards BLI850 resulting in more effective bowel cleansing than HalfLytely in patients < 65 years of age (91% vs. 83%). The same size is too small to make any conclusions about differential response in patients who were ≥ 75 years of age. The efficacy results were similar between the two treatment groups in patients who were ≥ 65 years of age. Based on this exploratory analysis, BLI850 does not appear to raise efficacy concerns in the elderly population.

Table 33: Primary efficacy analysis by age in Study 301 (mITT population)

Age Group	Colonoscopy Assessment ¹	BLI850	HalfLytely	95% CI ²	P-value ³
Age < 65	Success	117/128 (91.4%)	115/139 (82.7%)	(-0.7, 16.6)	0.030
	Failure	11/128 (8.6%)	24/139 (17.3%)		
Age ≥ 65	Success	41/48 (85.4%)	42/49 (85.7%)	(-14.3, 13.7)	0.951
	Failure	7/48 (14.6%)	7/49 (14.3%)		
Age ≥ 75	Success	15/16 (93.8%)	12/16 (75%)	(-5.6, 43.1)	0.055
	Failure	1/16 (6.3%)	4/16 (25%)		

¹A successful preparation was defined as bowel cleansing graded as either “excellent” or “good” (grading score 4 or 3) and a failed preparation was defined as bowel cleansing graded as either “fair” or “poor” (grading score 2 or 1) by the blinded colonoscopist.

²Confidence interval (CI) for percent success difference between treatments was calculated using a Chi square test.

³P-value for the difference between treatments was calculated using a CMH Chi square, controlling for site
Source: Adapted from the Applicant's Clinical Study Report for Protocol BLI850-301, Table 14.2.1.4.

Study 302 (Split-dose regimen)

Table 34 presents primary efficacy analysis by age in Study 302. In general, elderly patients (both ≥ 65 and ≥ 75 years of age) had a numerically higher percentage of successful bowel preparations when BLI850 was administered as split doses compared to MoviPrep. The efficacy results were similar between the two treatment groups in patients who were < 65 years of age. Based on these exploratory data, there does not appear to be efficacy concerns with the use of BLI850 in the elderly patients.

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Jessica Lee, MD; Helen Sile, MD

NDA 203-595

BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

Table 34: Primary efficacy analysis by age in Study 302 (mITT population)

Age Group	Colonoscopy Assessment ¹	BLI850	MoviPrep	95% CI ²	P-value ³
Age < 65	Success	134/143 (93.7%)	131/136 (96.3%)	(-7.7, 2.5)	0.208
	Failure	9/143 (6.3%)	5/136 (3.7%)		
Age ≥ 65	Success	39/42 (92.9%)	42/49 (85.7%)	(-5.4, 19.7)	0.318
	Failure	3/42 (7.1%)	7/49 (14.3%)		
Age ≥ 75	Success	12/13 (92.3%)	8/10 (80%)	(-16.4, 41)	0.281
	Failure	1/13 (7.7%)	2/10 (20%)		

¹A successful preparation was defined as bowel cleansing graded as either “excellent” or “good” (grading score 4 or 3) and a failed preparation was defined as bowel cleansing graded as either “fair” or “poor” (grading score 2 or 1) by the blinded colonoscopist.

²Confidence interval (CI) for percent success difference between treatments was calculated using a Chi square test.

³P-value for the difference between treatments was calculated using a CMH Chi square, controlling for site.

Source: Adapted from the Applicant's Clinical Study Report for Protocol BLI850-302, Table 14.2.1.4.

In summary, the claimed treatment effect appears to be consistent in the elderly population based on Studies 301 and 302. In general, patients receiving split doses of BLI850 had numerically higher percentages of successful bowel preparations than those who received the entire dose of BLI850 the day before colonoscopy.

❖ Efficacy by Gender

Study 301 (Day-before regimen)

Table 35 presents primary efficacy analysis by gender in Study 301. Both males and females had numerically higher percentages of successful bowel preparations when BLI850 was administered compared to HalfLytely, but the difference is not large enough to be clinically meaningful.

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Jessica Lee, MD; Helen Sile, MD

NDA 203-595

BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

Table 35: Primary efficacy analysis by gender in Study 301 (mITT population)

Gender	Colonoscopy Assessment ¹	BLI850	HalfLyte ^{ly}	95% CI ²	P-value ³
Males	Success	69/79 (87.3%)	66/84 (78.6%)	(-2.7, 20.2)	0.211
	Failure	10/79 (12.7%)	18/84 (21.4%)		
Females	Success	89/97 (91.8%)	91/104 (87.5%)	(-4.1, 12.6)	0.283
	Failure	8/97 (8.2%)	13/104 (12.5%)		

¹A successful preparation was defined as bowel cleansing graded as either “excellent” or “good” (grading score 4 or 3) and a failed preparation was defined as bowel cleansing graded as either “fair” or “poor” (grading score 2 or 1) by the blinded colonoscopist.

²Confidence interval (CI) for percent success difference between treatments was calculated using a Chi square test.

³P-value for the difference between treatments was calculated using a CMH Chi square, controlling for site

Source: Adapted from the Applicant’s Clinical Study Report for Protocol BLI850-301, Table 14.2.1.2.

Study 302 (Split-dose regimen)

Table 36 presents primary efficacy analysis of colonoscopy assessment by gender in Study 302. Males and females had similar percentages of successful bowel preparations when BLI850 or Moviprep was administered as split doses.

Table 36: Primary efficacy analysis by gender in Study 302 (mITT population)

Gender	Colonoscopy Assessment ¹	BLI850	MoviPrep	95% CI ²	P-value ³
Males	Success	95/101 (94.1%)	73/77 (94.8%)	(-7.5, 6.0)	0.780
	Failure	6/101 (5.9%)	4/77 (5.2%)		
Females	Success	78/84 (92.9%)	100/108 (92.6%)	(-7.1, 7.7)	0.987
	Failure	6/84 (7.1%)	8/108 (7.4%)		

¹A successful preparation was defined as bowel cleansing graded as either “excellent” or “good” (grading score 4 or 3) and a failed preparation was defined as bowel cleansing graded as either “fair” or “poor” (grading score 2 or 1) by the blinded colonoscopist.

²Confidence interval (CI) for percent success difference between treatments was calculated using a Chi square test.

³P-value for the difference between treatments was calculated using a CMH Chi square, controlling for site

Source: Adapted from the Applicant’s Clinical Study Report for Protocol BLI850-302, Table 14.2.1.2.

In summary, there appears to be consistent treatment effect across both genders in Studies 301 and 302.

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Jessica Lee, MD; Helen Sile, MD

NDA 203-595

BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

❖ Efficacy by Race

Study 301 (Day-before regimen)

Table 37 presents primary efficacy analysis by race in Study 301. White patients had a higher percentage of successful bowel preparations after administration of BLI850 compared to HalfLytely (91% vs. 84%). Among the non-White patients, the difference among two treatment groups was only marginal, but the BLI850 group still had a numerically higher percentage of successful preparations. Although the failure rates were generally higher among non-Whites in both treatment groups, non-Whites consisted of a small sample size of heterogeneous population. Therefore, it is not possible to make a generalizable conclusion about the influence of race on the effectiveness of bowel preparations.

Table 37: Primary efficacy analysis by race in Study 301 (mITT population)

Race	Colonoscopy Assessment ¹	BLI850	HalfLytely	95% CI ²	P-value ³
White	Success	134/147 (91.2%)	129/153 (84.3%)	(-0.5, 14.2)	0.042
	Failure	13/147 (8.8%)	24/153 (15.7%)		
Non-White	Success	24/29 (82.8%)	28/35 (80%)	(-16.3, 21.9)	0.433
	Failure	5/29 (17.2%)	7/35 (20%)		

¹A successful preparation was defined as bowel cleansing graded as either "excellent" or "good" (grading score 4 or 3) and a failed preparation was defined as bowel cleansing graded as either "fair" or "poor" (grading score 2 or 1) by the blinded colonoscopist.

²Confidence interval (CI) for percent success difference between treatments was calculated using a Chi square test.

³P-value for the difference between treatments was calculated using a CMH Chi square, controlling for site

Source: Adapted from the Applicant's Clinical Study Report for Protocol BLI850-301, Table 14.2.1.3.

Study 302 (Split-dose regimen)

Table 38 presents primary efficacy analysis by race in Study 302. Both Whites and non-Whites had numerically similar percentages of successful bowel preparations in the two treatment groups.

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Jessica Lee, MD; Helen Sile, MD

NDA 203-595

BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

Table 38: Primary efficacy analysis by race in Study 302 (MITT population)

Race	Colonoscopy Assessment ¹	BLI850	MoviPrep	95% CI ²	P-value ³
White	Success	158/170 (92.9%)	156/167 (93.4%)	(-5.9, 4.9)	0.826
	Failure	12/170 (7.1%)	11/167 (6.6%)		
Non-White	Success	15/15 (100%)	17/18 (94.4%)	(-5, 16.1)	0.564
	Failure	0	1/18 (5.6%)		

¹A successful preparation was defined as bowel cleansing graded as either "excellent" or "good" (grading score 4 or 3) and a failed preparation was defined as bowel cleansing graded as either "fair" or "poor" (grading score 2 or 1) by the blinded colonoscopist.

²Confidence interval (CI) for percent success difference between treatments was calculated using a Chi square test.

³P-value for the difference between treatments was calculated using a CMH Chi square, controlling for site

Source: Adapted from the Applicant's Clinical Study Report for Protocol BLI850-302, Table 14.2.1.3.

In summary, BLI850 has shown numerically similar or higher rates of successful bowel preparations compared with its comparators (HalfLyte or MoviPrep) across Whites and non-Whites in Studies 301 and 302.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

As shown in Table 39, BLI850 given as split doses resulted in a slightly higher percentage of successful bowel preparations (93.5% in Study 302) compared to when it was given as a day-before regimen (89.8% in Study 301). This finding is consistent with the current practice guidelines that recommend the split-dose regimen to achieve more effective bowel cleansing. Accordingly, this reviewer recommends that the split-dose regimen be specified as the preferred method of administration.

Table 39: Efficacy comparison between Day-before and Split-dose regimens of BLI850

	Study 301: Day-Before Regimen		Study 302: Split-Dose Regimen	
	BLI850	HalfLyte	BLI850	MoviPrep
% Success ¹ (95% CI)	89.8% (84%, 94%)	83.5% (77%, 89%)	93.5% (89%, 97%)	93.5% (89%, 97%)

¹A successful preparation was defined as bowel cleansing graded as either "excellent" or "good" (grading score 4 or 3) and a failed preparation was defined as bowel cleansing graded as either "fair" or "poor" (grading score 2 or 1) by the blinded colonoscopist.

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Jessica Lee, MD; Helen Sile, MD

NDA 203-595

BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Bowel cleansing treatment in preparation for colonoscopy is usually given as a single dose (either as same day or split-dose regimen), and the effect is seen at the time of colonoscopy examination. The effect of the preparation is not expected to persist beyond the procedure once patients are allowed to resume a normal diet. Therefore, discussion of persistence of efficacy and/or tolerance effects is not applicable for this application.

6.1.10 Additional Efficacy Issues/Analyses

❖ Treatment Compliance

Treatment compliance was evaluated in all patients who returned to the study site at Visit 2 (day of colonoscopy) after they had administered the colon preparation as instructed. A compliant patient was defined as a patient who reported taking the entire study medication or returned no more than 4 oz of the study medication.

Study 301 (Day-before regimen)

As shown in Table 40, a numerically larger proportion of patients in the HalfLyte treatment group completed the entire preparation compared to patients in the BLI850 group (94% vs. 87%). The difference seen in this exploratory analysis may be due to a larger volume of medication that must be consumed with BLI850 since the sulfate solution must be consumed in addition to 2L of PEG-ELS, whereas the HalfLyte regimen only requires bisacodyl tablets in addition to 2L of PEG-ELS.

Table 40: Medication compliance in Study 301 (ITT population)

Medication Compliance	Treatment		P-value ¹
	BLI850 N = 176	HalfLyte N = 190	
Did patient complete entire preparation? ² n (%)			
Yes	153 (86.9)	178 (93.7)	0.033
No	23 (13.1)	12 (6.3)	

¹P-value for difference between treatments was calculated using an exact Chi-square test.

²Patients with ≤4 ounces of returned solution were considered to have completed the entire preparation.

Source: Adapted from the Applicant's Clinical Study Report for Protocol BLI850-301, Table 14.1.5.

Study 302 (Split-dose regimen)

A numerically larger proportion of patients in the MoviPrep treatment group (98%) completed the entire preparation compared to patients treated with BLI850 (90%).

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BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

Again, the difference may be due to a larger volume of medication that must be consumed with BLI850 (16 oz of sulfate solution and 2 L of PEG-ELS) compared with MoviPrep (2L of MoviPrep). The comparison between two treatment groups is summarized in Table 41. The overall completion rate appears acceptable for BLI850, even though it was not as good as MoviPrep. Despite lower completion rate in patients receiving BLI850 compared with those receiving MoviPrep, the results of primary outcome were numerically the same between the two treatment groups.

Table 41: Medication compliance in Study 302 (ITT population)

Medication Compliance	Treatment		P-value ¹
	BLI850 N = 186	MoviPrep N = 185	
Did patient complete entire preparation? ² n (%)			
Yes	168 (90.3)	181 (97.8)	0.003
No	18 (9.7)	4 (2.2)	

¹P-value for difference between treatments was calculated using an exact Chi-square test.

²Patients with ≤ 4 ounces of returned solution were considered to have completed the entire preparation.

Source: Adapted from the Applicant's Clinical Study Report for Protocol BLI-850-302, Table 14.1.5.

In general, a numerically larger proportion of patients were able to complete the bowel preparation when given as split doses rather than as a single day dose. Since it may be difficult for some patients to consume both doses in one day and inability to complete both doses prior to colonoscopy could affect the colon cleansing outcome, the split-dose regimen should be specified as the preferred method. However, it is also important to have available the option to take the bowel preparation as a single day dose (i.e., day-before regimen) as an alternative, since some patients may be traveling long distance prior to colonoscopy or the procedure may occur early in the morning.

7 Review of Safety

Safety Summary

The same two phase 3 trials that were used to evaluate efficacy (i.e., Studies 301 and 302) were used to evaluate safety. Safety data from these two trials were evaluated separately, since they differed in dosing regimens and active comparators. The safety analysis included both the spontaneously-reported adverse events and queried symptoms that targeted expected adverse reactions from bowel preparation products, such as overall discomfort, stomach cramping, stomach bloating, nausea, and vomiting. The most common adverse reactions that occurred at a rate of $\geq 1\%$ in both studies are summarized in Table 42.

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Jessica Lee, MD; Helen Sile, MD

NDA 203-595

BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

Table 42: Adverse reactions observed in at least 1% of patients in Studies 301 and 302

Symptom	Study 301: Day-Before Regimen		Study 302: Split-Dose Regimen	
	BLI850 N=176 n (%)	HalfLyteLy N=190 n (%)	BLI850 N=186 n (%)	MoviPrep N=185 n (%)
Overall discomfort	122 (69.3)	108 (56.8)	116 (62.4)	121 (65.4)
Abdominal distension	92 (52.3)	85 (44.7)	96 (51.6)	112 (60.5)
Abdominal pain	71 (40.3)	78 (41.1)	70 (37.6)	79 (42.7)
Nausea	74 (42.0)	75 (39.5)	86 (46.2)	72 (38.9)
Vomiting	19 (10.8)	15 (7.9)	26 (14.0)	13 (7.0)
Retching	2 (1.1)	1 (0.5)	0	2 (1.1)
Headache	1 (0.6)	3 (1.6)	3 (1.6)	2 (1.1)

No unexpected major safety signals were seen in either trial, and the most common adverse reactions were expected symptoms resulting from the consumption of a bowel preparation product. In both trials, a numerically larger proportion of BLI850-treated patients experienced nausea and vomiting compared with the active comparator-treated patients. A numerically larger proportion of patients who received the day-before regimen of BLI850 experienced overall discomfort, abdominal distension, and abdominal pain than those who received the split-dose regimen. However, a slightly larger proportion of patients who received the split-dose regimen of BLI850 experienced nausea and vomiting compared with those who received the day-before regimen.

Compared to the comparator groups, patients who received BLI850 had numerically higher rates of new-onset elevated anion gap, elevated alanine aminotransferase (ALT), elevated creatine kinase (CK), and decreased estimated creatinine clearance (eC_{Cr}). In one patient who received BLI850 in Study 302, eC_{Cr} (calculated using the Cockcroft-Gault method) decreased from 90 mL/min at baseline to 49 mL/min at Visit 2. Since the laboratory follow-up did not extend beyond the day of colonoscopy except for a small set of patients, it was not possible to determine whether laboratory abnormalities and decreased renal function continued to worsen over time or returned to baseline for the majority of patients. Therefore, this reviewer recommends a post-marketing study to evaluate renal function and laboratory abnormalities in patients beyond the day of colonoscopy.

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7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The two clinical trials that were used to evaluate efficacy (i.e., Studies 301 and 302) were also used to evaluate safety. See Table 10 for details of the study design. The safety analyses included all patients who administered any amount of the study medication (i.e., ITT population).

7.1.2 Categorization of Adverse Events

An adverse event (AE) was defined as any untoward medical event that occurred in a patient who administered a study medication, and included any unfavorable and unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product. All AEs were coded using the Medical Dictionary of Regulatory Activities (MedDRA) (Version 13.0) and were classified by the MedDRA body system and preferred term (PT).

All spontaneously reported, elicited, and observed AEs were to be documented on the CRF. Data collection for AEs began from the signing of the informed consent form. Treatment emergent adverse events were categorized as AEs with an onset on or after the date of first dose of study drug administration and within 14 days post the date of last dose of study drug administration. All safety analyses, except for serious adverse event analyses, were performed on treatment emergent AEs. Serious adverse event (SAE) collection continued until 30 days after completion of the colonoscopy procedure. Approximately two weeks after Visit 2, a telephone follow-up was performed for ongoing adverse events that were considered possibly, probably, or definitely related to the study drug based on assessment during Visit 2. Patients who had clinically significant laboratory results that were categorized by the investigator as adverse events at Visit 2 were expected to return in approximately 2 weeks for re-evaluation of laboratory tests. Therefore, not all abnormal laboratory results were repeated after Visit 2.

The intensity of adverse events was rated by the investigators according to the following definitions:

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

The causal relationship of each adverse event was also specified as “unrelated”, “possible”, “probable”, or “definite”.

In addition to collection of spontaneously reported adverse events, patients were instructed to complete a symptom scale questionnaire (Table 13) during Visit 2. This questionnaire targeted expected adverse symptoms associated with administration of bowel preparations, such as stomach cramping, stomach bloating, nausea, and overall discomfort. The Applicant included in the adverse event dataset if patients reported a score of 5 (“severely distressing”) for stomach cramping, stomach bloating or nausea. Vomiting was recorded separately by the patient 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 patients reported the same AE spontaneously as well as in the queried symptom scale questionnaire, it is difficult to retrospectively discriminate each AE that was spontaneously reported only from those that were also collected through the symptom scale questionnaire. 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 patient. In addition, all spontaneously reported and queried symptoms, regardless of severity, were included in the AE dataset. This approach was also applied during the safety evaluation of SUPREP. The reader is referred to Dr. Jasmine Gatti’s Clinical review for NDA 22-372, dated August 7, 2009, for details.

The clinical reviewer compared verbatim terms with the Applicant’s coded/preferred term to ensure consistency in coding. In general, the coding was appropriate, but the following adjustments were made prior to re-analysis:

- Combined “abdominal pain”, “abdominal pain upper”, and “abdominal tenderness” and categorized as “abdominal pain.”
- Combined “vomiting” and “vomiting projectile” as “vomiting.”

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- Recoded “stomach cramping” in the Symptom Scale as “abdominal pain”. Most frequently used verbatim term for “abdominal pain” in the AE dataset was “stomach cramping.”
- Recoded “stomach bloating” in the Symptom Scale as “abdominal distension.” Frequently used verbatim terms for “abdominal distension” in the AE dataset included “bloating”, “stomach bloating”, and “fullness.”
- In Study 302, patient 31027 who received MoviPrep had two separate AE entries for “abdominal pain upper” and “abdominal tenderness.” These two AEs were combined as one AE and coded as “abdominal pain.”

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

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 a day-before (one-day) regimen. However, Study 302 compared BLI850 to MoviPrep, both of which were administered as split doses.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The two dosing regimens studied and the duration of trials were acceptable to assess general safety of the product, although a longer safety monitoring to assess persistent laboratory and renal function abnormalities would have allowed a more complete safety evaluation. Only one in-person follow-up assessment was required in Studies 301 and 302, which occurred on the day of colonoscopy examination. Given the potential for electrolyte abnormalities and persistent decline in renal function, it is important to monitor patients who have undergone bowel cleansing beyond the day of colonoscopy, especially those who are at risk or those who developed new laboratory abnormalities after taking bowel preparation.

7.2.2 Explorations for Dose Response

In the current application, all patients in the BLI850 group received the same dose (sulfate solution and PEG-ELS for solution), either in one day (on the day before the

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colonoscopy examination) or as split doses over two days. There was no exploration for dose response.

7.2.3 Special Animal and/or In Vitro Testing

None

7.2.4 Routine Clinical Testing

Patients 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.

7.2.5 Metabolic, Clearance, and Interaction Workup

No specific studies were conducted under this NDA to assess metabolic, clearance, and interactions, as BLI850 consists of components from two approved products. The reader is referred to the Clinical Pharmacology review by Dr. Sandhya Apparaju (dated September 18, 2012) for a summary of previously reviewed data.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Studies 301 and 302 were acceptable to assess general safety of the product, although a longer safety monitoring to assess persistent laboratory and renal function abnormalities would have allowed a more complete safety evaluation. These two trials did not reveal any new safety signals relevant to the class of osmotic bowel cleaning preparation products.

7.3 Major Safety Results

7.3.1 Deaths

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

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7.3.2 Nonfatal Serious Adverse Events

In Study 302, there was one patient who received BLI850 who experienced a non-fatal SAE. Details of the event are summarized below:

- **Patient 25029:** A 59-year old Hispanic male took BLI850 on [REDACTED] (b) (6). The patient underwent colonoscopy on [REDACTED] (b) (6) 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. The patient was discharged on [REDACTED] (b) (6) with improved abdominal pain that later resolved completely on [REDACTED] (b) (6). No information on medical history or concomitant medications was provided. Only findings in colonoscopy included a small polyp that was removed and internal hemorrhoids. The investigator concluded that this SAE was not related to BLI850 treatment.

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. However, the presence of associated febrile symptoms and the patient’s clinical improvement on antibiotic treatment suggest that this AE was not related to the study medication.

7.3.3 Dropouts and/or Discontinuations

In Study 301, one patient (0.6%) in the BLI850 treatment group discontinued due to adverse event. This patient (05006) was a 71-year old male who experienced new-onset atrial fibrillation and was withdrawn prior to undergoing colonoscopy by the investigator. He was subsequently referred to a cardiologist for evaluation. According to the investigator, atrial fibrillation was considered unrelated to the study treatment since the patient had pre-existing risk factors, including a long-standing history of hypertension and a history of myocardial infection. In follow-up, the investigator noted that the patient was being treated with coumadin and Plavix for atrial fibrillation.

In Study 302, one patient (0.5%) in the BLI850 treatment group discontinued due to adverse event. This patient (25063) was a 52-year old female who experienced moderate nausea while drinking BLI850. She discontinued from the trial prior to her scheduled colonoscopy. Her nausea resolved by Visit 2.

The reader is referred to 6.1.3 Patient Disposition for details on patients who dropped out or discontinued due to reasons other than adverse events.

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7.3.4 Significant Adverse Events

In Study 301, a total of 5 patients in the BLI850 treatment group and 1 patient in the HalfLyte group experienced adverse events that were reported as “severe” based on the Applicant’s AE dataset. The patient IDs and their AEs that were classified as “severe” are listed below:

- Patient 1004 (BLI850) – abdominal distension, nausea
- Patient 1005 (BLI850) – headache
- Patient 3059 (BLI850) – abdominal distension
- Patient 5007 (HalfLyte) – abdominal distension
- Patient 9050 (BLI850) – abdominal pain, nausea, vomiting
- Patient 12001 (BLI850) – nausea

All of the above AEs resolved except for headache in Patient 1005, which was reported to be unrelated to the study treatment.

In Study 302, two patients each in the BLI850 treatment group and the MoviPrep treatment group categorized their AEs as “severe”:

- Patient 25002 (BLI850) –nausea, vomiting
- Patient 25014 (MoviPrep) – nausea
- Patient 25029 (BLI850) – abdominal pain (also reported under nonfatal SAE)
- Patient 27023 (MoviPrep) – abdominal pain

Although the above events were considered “severe”, only one event led to an intervention (Patient 25029 was hospitalized).

7.3.5 Submission Specific Primary Safety Concerns

A review of safety information did not raise any submission-specific safety concerns, including significant electrolyte disturbances. The adverse events were consistent with those previously described and labeled in other approved osmotic bowel cleansing preparations.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

As discussed in Section 7.1.2 Categorization of Adverse Events, the clinical reviewer-conducted safety analysis included both the spontaneously-reported AEs and

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queried symptoms from the symptom scale regardless of severity. Since bowel preparation studies are single dose studies without multiple follow-ups, there is a role for targeted AE collection based on expected adverse events that represent potential tolerability issues. This approach is consistent with the analysis the Division requested from the Applicant during the review of SUPREP NDA. Unless stated otherwise, all spontaneously-reported AEs and elicited symptoms of all severity (mild, bothersome, distressing, and severely distressing) are considered adverse events in this section.

Study 301 (Day-before regimen)

Of the 366 safety population, 289 (79%) experienced at least one adverse event in Study 301. At least one adverse event was reported by 146 patients (83%) in the BLI850 group and 143 patients (75%) in the HalfLyte group.

The highest number of AEs was reported in the MedDRA body system “gastrointestinal disorders”: 134 patients (76%) in the BLI850 group and 132 patients (69%) in the HalfLyte group.

As shown in Table 43, 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 patients. In general, BLI850 group had numerically higher rates of common adverse events than the HalfLyte group. However, the adverse event rates were similar for symptoms that are not commonly associated with the administration of bowel preparations.

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Table 43: 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 patients 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)

¹Patients were counted once within each body system and preferred term.

²One case of “abdominal pain upper” from each treatment was re-categorized as “abdominal pain.”

³One case of “projectile vomiting” from the BLI850 group was re-categorized as “vomiting.”

Source: Clinical reviewer’s analysis using the Applicant’s AESY (adverse event plus symptoms) dataset for Study 301 submitted in response to FDA’s 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 44 compares symptom events collected using a symptom scale questionnaire. The mean scores of stomach bloating, nausea and overall discomfort were slightly higher in patients 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). The largest 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.

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Table 44: 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. patients 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

¹Symptom scores were as follows: 1=none; 2=mild; 3=bothersome; 4=distressing; 5=severely distressing.

²P-value for difference between treatments was calculated using ANOVA.

Source: Adapted from the Applicant's Clinical Study Report for Protocol BLI850-301, Tables 301-9 and 14.3.8.

Table 45 compares the number of vomiting episodes between the two treatment groups. Overall, more patients vomited after receiving BLI850 (11%) compared with those who received HalfLyteLy (8%). However, more elderly patients vomited after receiving HalfLyteLy. A larger proportion of female patients vomited in the BLI850 group, but the reason for this difference is not clear. A numerically higher proportion of non-White patients vomited in the BLI850 group, but the sample size is too small to make a generalizable conclusion about this observation.

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Table 45: Patients with vomiting events of any severity in Study 301 (ITT population)

Vomiting	BLI850 N = 176 n (%) ¹	HalfLytely N = 190 n (%) ¹
All patients	19 (10.8)	15 (7.9)
Age < 65	18 (14.1)	13 (9.2)
Age ≥ 65	1 (2.1)	2 (4.1)
Age ≥ 75	0	1 (6.3)
Males	5 (6.3)	6 (7)
Females	14 (14.4)	9 (8.7)
White	13 (8.8)	11 (7.1)
Non-White	6 (20.7)	4 (11.4)

¹Percents are calculated using the total number of patients in the respective age, gender, or race category within each treatment.

Source: Adapted from the Applicant's Clinical Study Report for Protocol BLI850-301, Table 14.3.10.

Study 302 (Split-dose regimen)

Of the 371 safety population, 302 (81%) experienced at least one adverse event in Study 302. At least one adverse event was reported by 155 patients (83%) in the BLI850 group and 147 patients (80%) in the MoviPrep group.

As in Study 301, the highest number of AEs was reported in the MedDRA body system "gastrointestinal disorders": 137 patients (74%) in the BLI850 group and 138 patients (75%) in the MoviPrep group.

Table 46 is a comprehensive list of all treatment-emergent adverse events (TEAEs) that also include the queried symptoms reported by patients who received the split-dose regimen of BLI850 or MoviPrep. The most common adverse events were the expected reactions associated with bowel preparations that were queried from patients, including overall discomfort, abdominal distention, abdominal pain, nausea, and vomiting. Although the proportion of patients experiencing overall discomfort, abdominal distention, and abdominal pain were numerically higher in the MoviPrep group, a larger number of patients experienced nausea and vomiting in the BLI850 group. In fact, the percentage of vomiting in the BLI850 group (14%) doubled that of the MoviPrep group (7%). Surprisingly, a larger proportion of patients experienced

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vomiting in the split-dose regimen (14%) than in the day-before regimen (11%) for BLI850.

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Table 46: Treatment emergent adverse events and symptom scores by MedDRA Body System and Preferred Term for Study 302 (ITT population)

Body System/Preferred Term¹	BLI850 N = 186 n (%)	MoviPrep N = 185 n (%)
Number of patients 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)

¹Patients were counted once within each body system and preferred term.

²One 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-

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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: Clinical 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.

Table 47 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. Again, the mean scores were generally low for both groups. The largest difference was seen between the two groups for “stomach bloating.”

Table 47: 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

¹Symptom scores were as follows: 1=none; 2=mild; 3=bothersome; 4=distressing; 5=severely distressing.

²P-value for difference between treatments was calculated using ANOVA.

Source: Adapted from the Applicant’s Clinical Study Report for Protocol BLI850-302, Tables 302-10 and 14.3.8.

Table 48 compares the number of vomiting episodes between the two treatment groups in the split-dose regimen. A numerically larger proportion of patients vomited after receiving BLI850 (14%) compared to those who received MoviPrep (7%). This difference was most pronounced in patients < 65 years of age. No patient with age ≥ 75 reported vomiting from either treatment group. Overall, twice as many patients experienced vomiting in the BLI850 group than in the MoviPrep group, and all subgroups showed consistently higher vomiting episodes in the BLI850 group.

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Table 48: Patients with vomiting events of any severity in Study 302 (ITT population)

Vomiting	BLI850 N = 186 n (%) ¹	MoviPrep N = 185 n (%) ¹
All patients	26 (14)	13 (7)
Age < 65	23 (16)	12 (8.8)
Age ≥ 65	3 (7.1)	1 (2)
Age ≥ 75	0	0
Males	10 (9.9)	0
Females	16 (18.8)	13 (12)
White	22 (12.9)	9 (5.4)
Non-White	4 (26.7)	4 (22.2)

¹Percents are calculated using the total number of patients in the respective age or gender category within each treatment.

Source: Adapted from the Applicant's Clinical Study Report for Protocol BLI850-302, Table 14.3.10.

In both studies, there were more BLI850-treated patients (11% in Study 301, 14% in Study 302) who experienced vomiting episodes than the active comparator-treated patients (8% HalfLyte, 7% MoviPrep). As shown in Table 49, vomiting episodes classified as "moderate" or "severe" were numerically higher in the BLI850 group than in the comparator groups. This difference does not appear to be due to the number of geriatric or high risk patients in the BLI850 group. This observation raises some concerns as to whether patients will encounter more tolerability issues with BLI850 than existing products.

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Table 49: 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 (%)
Elderly (≥65 years old)	1 (5.3)	2 (13.3)	3 (11.5)	1 (7.7)
High risk ²	9 (47.7)	7 (46.7)	10 (38.5)	7 (53.8)
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)

¹The method of determining symptom severity is described in Section 7.1.2 Categorization of Adverse Events.

²High risk was defined as patients with reported medical history of cardiac, renal or vascular problems (hypertension), or diabetes.

Source: Clinical reviewer'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.

7.4.2 Laboratory Findings

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)

Table 50 lists the Applicant-provided normal ranges for laboratory results in Studies 301 and 302. These ranges were used to define normal and abnormal results.

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Table 50: 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 provided by the Applicant
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 provided by the Applicant
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

Source: Applicant's NDA 203-595 submission, Module 2, Section 2.7, Tables 2.7.4-11 and 2.7.4-12.

Patients who had clinically significant electrolyte abnormalities based on the judgment of the principal investigator at baseline (i.e., Visit 1) were discontinued from the trial. These patients were notified and instructed to return their unopened study drug to the site and were classified as screen failures. Blood samples for serum chemistry and hematology testing were collected prior to colonoscopy examination at Visit 2.

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Blood samples were redrawn if patients had laboratory results at Visit 2 which were determined by the investigator to be clinically significant. It should be noted that there was no standardized definition for “clinically significant” laboratory values. Only one patient in Study 301 (in the HalfLyte group) and 5 patients 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. Therefore, the follow-up laboratory data are limited in Studies 301 and 302.

In Study 301, one patient with an abnormal creatine kinase (CK) level at Visit 2 (baseline = 88 U/L; Visit 2 = 1381 U/L) had a follow-up laboratory testing 2 days afterwards (follow-up = 538 U/L). Although CK did not normalize in 2 days, there was a substantial decrease in the level. Table 51 summarizes laboratory measurements of patients who underwent repeat testing due to clinically significant laboratory results (investigator-determined) at Visit 2.

Table 51: Laboratory values for patients with redraw due to abnormal Visit 2 values (Study 302)

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

Source: Replicated from Dr. Bradley McEvoy's Safety Statistical review dated September 12, 2012, Table 4.

The reader is referred to Dr. Bradley McEvoy's Safety Statistical review dated September 12, 2012 for detailed analyses on laboratory parameters, including shift analysis. Except for the evidence of hemoconcentration, there were no clinically meaningful changes in hematology parameters. Clinical reviewer's analysis will focus

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on patients who had **normal baseline but developed abnormal laboratory values on the day of colonoscopy (Visit 2).**

❖ Electrolytes

Table 52, summarized from Dr. McEvoy's review, presents the proportion of patients with normal baseline who developed abnormal electrolyte values on the day of colonoscopy (Visit 2). The direction of abnormality is also indicated.

Table 52: Proportion of patients 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.

In general, no clinically concerning electrolyte abnormalities were noted. The following section details the mean change in laboratory parameters that were found to be abnormal in > 1% of the patients in at least one of the treatment groups. As noted previously, the following section will only focus on patients with **normal baseline who developed abnormal laboratory values on the day of colonoscopy.** The reader is referred to Dr. McEvoy's review for detailed laboratory analysis that includes all patients.

Anion gap (normal baseline to high):

The normal range of anion gap was not available as it was not calculated by the central laboratory that processed the electrolytes. Therefore, anion gap was calculated using the following formula:

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$$\text{Anion gap} = [\text{sodium (mEq/L)}] - [\text{chloride (mEq/L)}] + [\text{bicarbonate (mEq/L)}]$$

A commonly accepted normal range was used (i.e., 12 ± 4 mEq/L).¹³

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 HalfLyte 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 HalfLyte group.

In Study 302, the mean change in anion gap was +5.0 mEq/L in 17 patients with new-onset high anion gap in the BLI850 group and +4.7 mEq/L in 12 patients in the MoviPrep group. Patients with a normal baseline who developed a high anion gap had anion gap values 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 a numerically larger number of patients who received BLI850 developed new-onset high anion gap, the mean change was not substantially different between the two groups.

Bicarbonate (normal baseline to low):

In Study 301, the mean change in bicarbonate was -4.0 mEq/L in 4 patients with new-onset low bicarbonate (< 20 mEq/L) in the BLI850 group and -5.0 mEq/L in 5 patients in the HalfLyte group. All 4 patients with a normal baseline who developed a low bicarbonate at Visit 2 had a bicarbonate level of 19 mEq/L in the BLI850 group; the bicarbonate levels ranged from 18 to 19 mEq/L at Visit 2 in the HalfLyte group.

In Study 302, the mean change in bicarbonate was -5.0 mEq/L in 6 patients with new-onset low bicarbonate in the BLI850 group, and -4.9 mEq/L in 20 patients in the MoviPrep group. Patients with a normal baseline who developed a low bicarbonate had bicarbonate levels ranging from 17 to 19 mEq/L at Visit 2 in the BLI850 group and 13 to 19 mEq/L in the MoviPrep group. A slightly larger proportion of patients had new-onset low bicarbonate in the split-dose regimen (4%) compared with the day-before regimen (3%), which may be due to a larger amount of diarrheal output that is expected from colon cleansing over 2 days.

High anion gap metabolic acidosis:

Elevations of the anion gap usually indicate accumulation of acid in the serum and are generally accompanied by an equivalent decrease in bicarbonate concentration (known as anion gap acidosis).¹⁰ Table 53 lists the causes of high anion gap acidosis.

13 Reddy P, Mooradian AD. Clinical utility of anion gap in deciphering acid-base disorders. *Int J Clin Pract* 2009; 63:1516-25.

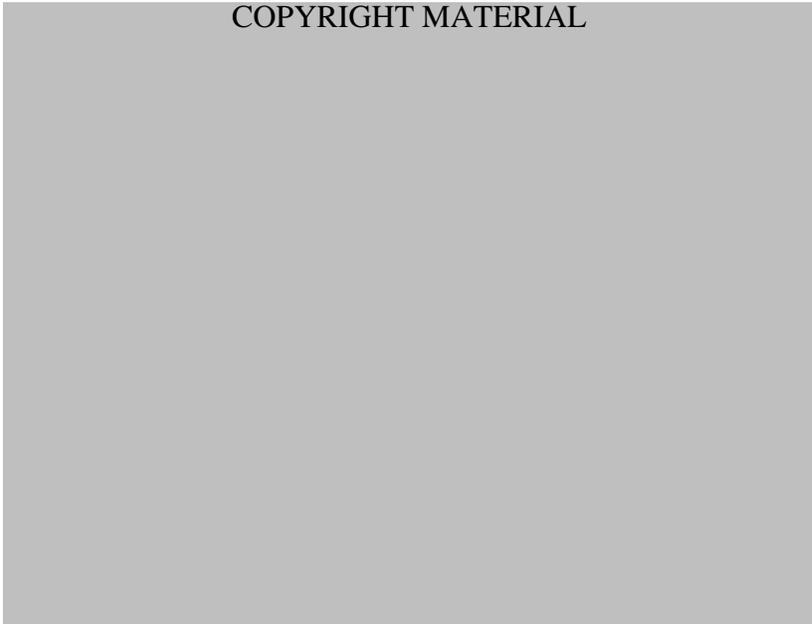
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Source: Reddy P et al. Clinical utility of anion gap in deciphering acid-base disorders. *Int J Clin Pract* 2009; 63:1516-25, Table 3.

When endogenously generated organic acids (e.g., ketoacids, lactic acids, renal failure and rhabdomyolysis) or exogenous acids (e.g., salicylates, paraldehyde, formic acid from methanol, glycolic acid from ethylene glycol) are added to the serum, they combine with bicarbonate (HCO_3^-), release CO_2 and H_2O , and add unmeasured anions, thereby increasing the anion gap. Normochloremia is a feature of high anion gap acidosis since the pre-existing Cl^- concentration remains unchanged when the new acid anion is added to the blood.¹⁰

BLI850 and the comparator products contain polyethylene glycol that has (b) (4) and (b) (4) as impurities, and it is possible that the impurities could contribute to high anion gap metabolic acidosis if sufficient amount is absorbed. Currently, little is known about the absorption of these impurities following administration of a large dose of polyethylene glycol for bowel preparation. Therefore, the clinical reviewer assessed how many patients presenting with new-onset low bicarbonate (< 20 mEq/L) also had an evidence of elevated anion gap (> 16 mEq/L). It is important to interpret the data cautiously since minor elevations in the anion gap (between 16 and 22 mEq/L) are less helpful in diagnosing metabolic acidosis.¹² In Study 301, none of the patients in the BLI850 group with new-onset low bicarbonate also had high anion gap, whereas 2 of 5 patients in the HalfLyte group with new-onset low bicarbonate had elevated anion gap (Table 54). These patients had normochloremia.

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In Study 302, three of 6 patients in the BLI850 group and 7 of 20 patients in the MoviPrep group with new-onset low bicarbonate also had increased anion gap (Table 54). All of these patients remained normochloremic.

Table 54: Patients with normal baseline who developed low bicarbonate and elevated anion gap at Visit 2 (Studies 301 and 302)

Study	Treatment	Patient ID	Bicarbonate Shift (mEq/L)	Anion Gap Shift (mEq/L)
301	HalfLytely	2017	20 → 18	14 → 19
		3051	26 → 19	11 → 17
302	BLI850	22026	22 → 19	12 → 17
		28002	24 → 19	14 → 18
		28010	28 → 17	9 → 18
	MoviPrep	25007	22 → 19	13 → 22
		25031	21 → 17	16 → 21
		25047	22 → 18	14 → 17
		27018	26 → 19	14 → 18
		29002	24 → 18	14 → 18
		29008	22 → 18	15 → 17
		30020	23 → 13	14 → 19

Source: Clinical reviewer's collection of relevant information from the Applicant's laboratory datasets from Studies 301 and 302.

As shown in Table 54, it does not appear that patients who were exposed to BLI850 are at an increased risk of developing high anion gap metabolic acidosis compared to those who were exposed to the comparator products. The elevation in anion gap was minor (between 16 and 22 mEq/L) in all patients, but the assessment only extended to the immediate post-treatment period.

Calcium (normal baseline to high):

No patient in either study experienced hypocalcemia. Only hypercalcemia was observed in both studies.

In Study 301, the mean change in calcium was +0.5 mg/dL in 12 patients with new-onset hypercalcemia (> 10.2 mg/dL) in the BLI850 group and +0.6 mg/dL in 5 patients in the HalfLytely group. Patients with a normal baseline who developed hypercalcemia had calcium levels ranging from 10.3 to 10.7 mg/dL at Visit 2 in the BLI850 group and 10.3 to 10.6 mg/dL in the HalfLytely group.

In Study 302, the mean change in calcium was +0.5 mg/dL in 6 patients with new-onset hypercalcemia in the BLI850 group and +0.7 mg/dL in 7 patients in the MoviPrep group. Patients with a normal baseline who developed hypercalcemia had calcium levels ranging from 10.3 to 10.6 mg/dL at Visit 2 in both treatment groups.

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Although hypercalcemia can result in vomiting, only 3 patients with a laboratory evidence of hypercalcemia experienced vomiting in the phase 3 trials (2 from the BLI850 group and 1 from the MoviPrep group). In general, the calcium levels were only mildly elevated, and it is unlikely that mild hypercalcemia resulted in clinically significant sequelae in these trials.

Osmolality (normal baseline to high):

High osmolality is expected from bowel cleansing due to hemoconcentration. The BLI850 group had fewer patients with new-onset high osmolality compared to the comparator groups.

Phosphate (normal baseline to low or high):

Both hypo- and hyperphosphatemia were observed in patients exposed to BLI850. Therefore, it is not possible to link the direction of phosphate's abnormality with the use of BLI850 based on the laboratory data obtained from the phase 3 trials.

Potassium (normal baseline to low):

Hypokalemia is a known electrolyte abnormality associated with the use of bowel preparations since they result in copious diarrhea. In Study 301, the mean change in potassium was -0.5 mEq/L in 5 patients with new-onset hypokalemia (< 3.6 mEq/L) in the BLI850 group and -0.5 mEq/L in 4 patients in the HalfLytely group. Patients 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 mean change was also -0.5 mEq/L in 6 patients with new-onset hypokalemia in the BLI850 group and -0.6 mEq/L in 7 patients in the MoviPrep group. Patients 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.

The lowest potassium level among patients with new-onset hypokalemia was 3.0 mEq/L, which was observed in one patient who received BLI850 in Study 301. Most of the remaining abnormal values were just below the lower limit of normal, and no patient experienced clinical sequelae relating to hypokalemia.

Glucose (normal baseline to low or high):

In most groups, patients experienced both hypo- and hyperglycemia. However, only hyperglycemia was observed in patients exposed to BLI850 in Study 301. The mean change was +81.4 mg/dL in 10 patients with new-onset hyperglycemia (> 141 mg/dL), three of whom had a history of diabetes mellitus.

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❖ Renal Function

Table 55, summarized from Dr. McEvoy's review, presents the proportion of patients with a normal baseline who developed abnormal renal function on the day of colonoscopy (Visit 2). The direction of abnormality is also indicated. For the calculation of estimated creatinine clearance (eC_{Cr}) and estimated glomerular filtration rate (eGFR), a value of < 90 mL/min (or 90 mL/min/1.73 m² depending on the method used) was considered abnormal. Since there are benefits and limitations to the three common methods used to predict renal function (i.e., Cockcroft-Gault, Modification of Diet in Renal Disease [MDRD], Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]),^{14,15} all three calculations are presented in this review. See Appendix 3: Formulas used to calculate eC_{Cr} and eGFR for the calculation methods.

Table 55: Proportion of patients with normal baseline who developed abnormal renal function 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. Refer to Dr. McEvoy's Addendum to original statistical safety review dated November 5, 2012 for revised values of eGFR MDRD.

Creatinine (normal baseline to high):

As shown in Table 55, there were only few patients who developed new-onset high creatinine at Visit 2. In Study 301, the mean change was marginal at +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. It should be noted that the upper limit normal of creatinine differs based on gender (Refer to Table 50).

14 Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999;130:461-70.

15 Levey AS, Stevens, LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604-12.

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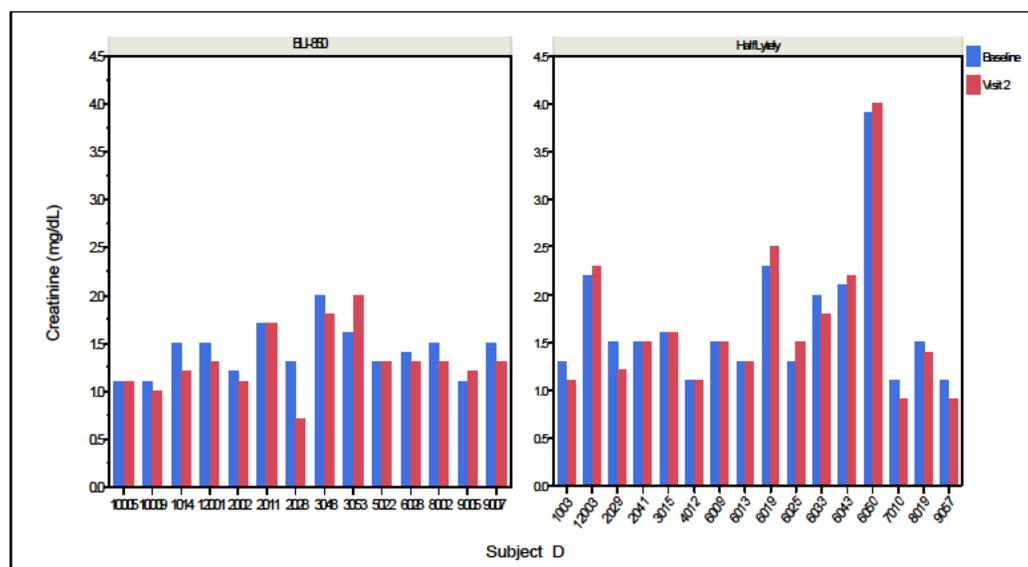
In Study 302, two patients in the BLI850 group developed new-onset high creatinine (increased by 0.1 mg/dL to 1.5 mg/dL in one patient and by 0.9 mg/dL to 2.1 mg/dL in another patient). One patient in the MoviPrep group had an increase in creatinine by 0.1 mg/dL to 1.5 mg/dL. Increases in creatinine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

It should be noted that there was no patient who developed a BUN level above the normal range at Visit 2 in Study 301 (all patients reported to have abnormal BUN levels in Dr. McEvoy's review had levels below the normal range at Visit 2); and only one patient each in the BLI850 and MoviPrep groups in Study 302 developed BUN levels that were above the normal range (27 mg/dL and 32 mg/dL, respectively).

Creatinine (high baseline):

Figure 5 and Figure 6 illustrate the trend of creatinine in patients with a high baseline creatinine in Studies 301 and 302, respectively. In the BLI850 group in Study 301, the creatinine level further increased in 2 patients, remained the same in 3 patients, and decreased in 9 patients (4 of 9 with normal creatinine at Visit 2). In the HalfLyte group, the creatinine level further increased in 5 patients, remained the same in 5 patients, and decreased in 6 patients (3 of 6 with normal creatinine at Visit 2).

Figure 5: Trend of creatinine in patients with elevated baseline (Study 301)



Source: Clinical reviewer's analysis using the Applicant's laboratory datasets from Study 301.

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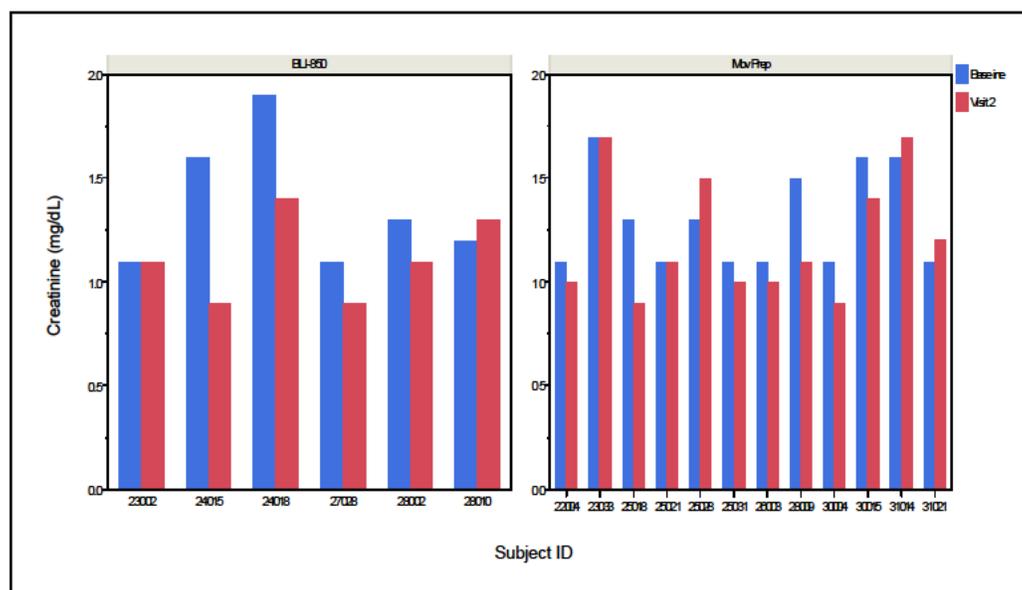
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In the BLI850 group in Study 302, the creatinine level further increased in one patient, remained the same in one patient, and decreased in 4 patients (2 of 4 with normal creatinine at Visit 2). In the Moviprep group, the creatinine level further increased in 3 patients, remained the same in 2 patients, and decreased in 7 patients (5 of 7 with normal creatinine at Visit 2).

Figure 6: Trend of creatinine in patients with elevated baseline (Study 302)



Source: Clinical reviewer's analysis using the Applicant's laboratory dataset from Study 302.

Based on the short term data, patients with a high baseline creatinine who received BLI850 do not appear to have a larger increase in creatinine compared with those who received the comparator products.

Estimated creatinine clearance rate (eC_{Cr}) based on the Cockcroft-Gault calculation (normal baseline to low):

The Cockcroft-Gault calculation was used to estimate creatinine clearance (eC_{Cr}) since it remains the most widely used method to predict renal function. In Study 301, the mean change in eC_{Cr} was -13.7 mL/min (range of change -2.1 to -48.8 mL/min) in 21 patients with new-onset low eC_{Cr} (< 90 mL/min) in the BLI850 group and -17.4 mL/min (range of change -7.6 to -68.5 mL/min) in 12 patients in the HalfLyte group. Although most changes in eC_{Cr} were small, some patients had a large decline in eC_{Cr} immediately after treatment. Patients with a normal baseline who developed a low eC_{Cr} had eC_{Cr} values ranging from 74.5 to 89.8 mL/min at Visit 2 in the BLI850 group and 69.1 to 89.4 mL/min in the HalfLyte group.

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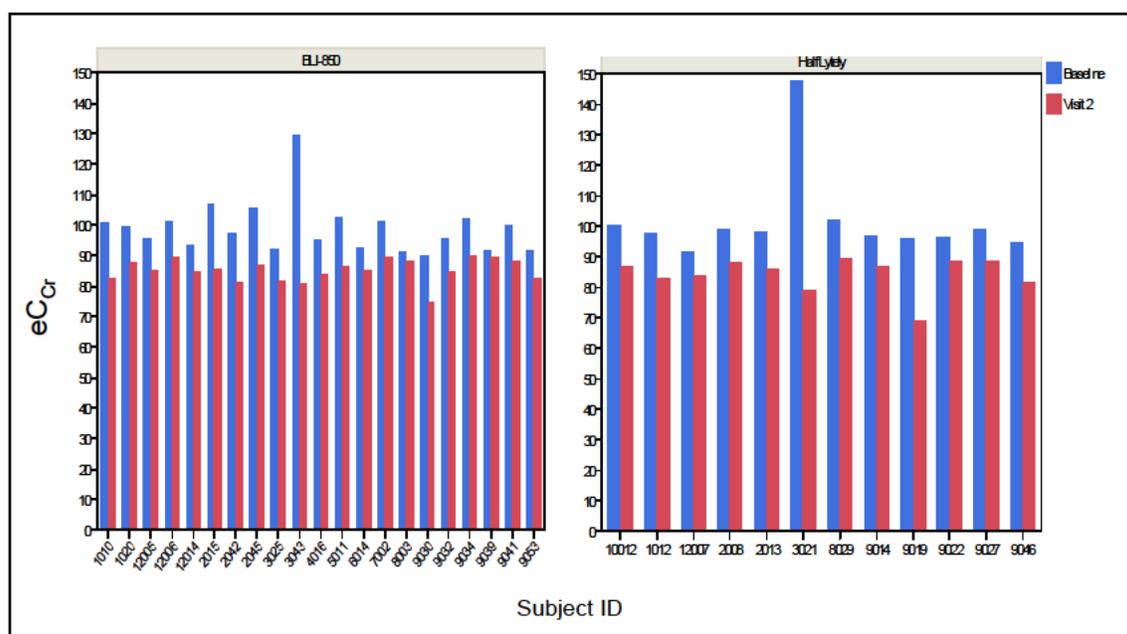
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Figure 7 compares eC_{Cr} values at baseline and Visit 2 for patients with new-onset low eC_{Cr} at Visit 2 in Study 301. Since the follow-up was limited to the day of colonoscopy, it is not possible to determine whether the majority of these patients had normalization of eC_{Cr} shortly thereafter or experienced further decline in renal function.

Figure 7: Patients with baseline normal eC_{Cr} (Cockcroft-Gault method) who developed abnormally low eC_{Cr} (< 90 mL/min) at Visit 2 (Study 301)



Source: Clinical reviewer's analysis using the information provided by Dr. Bradley McEvoy, who calculated eC_{Cr} using the Applicant's datasets on demographics and laboratory results.

In Study 302, the mean change in eC_{Cr} was -16.0 mL/min (range of change -0.7 to -40.7 mL/min) in 9 patients with new-onset low eC_{Cr} in the BLI850 group and -8.9 mL/min (range of change -1.5 to -13.9 mL/min) in 9 patients in the HalfLyely group. Patients with a normal baseline who developed a low eC_{Cr} had eC_{Cr} values ranging from 49.5 to 89.9 mL/min at Visit 2 in the BLI850 group and 76.9 to 89.9 mL/min in the MoviPrep group. In general, the amount of decrease in eC_{Cr} was less pronounced in Study 302 than in Study 301. However, one patient in BLI850 had a significant decline in renal function as evidenced by a decrease in eC_{Cr} from 90.5 to 49.5 mL/min on Visit 2. This patient also had an increase in creatinine value from 1.2 mg/dL at baseline to 2.1 mg/dL at Visit 2. Figure 8 compares eC_{Cr} values at baseline and Visit 2 for patients with new-onset low eC_{Cr} at Visit 2 in Study 302.

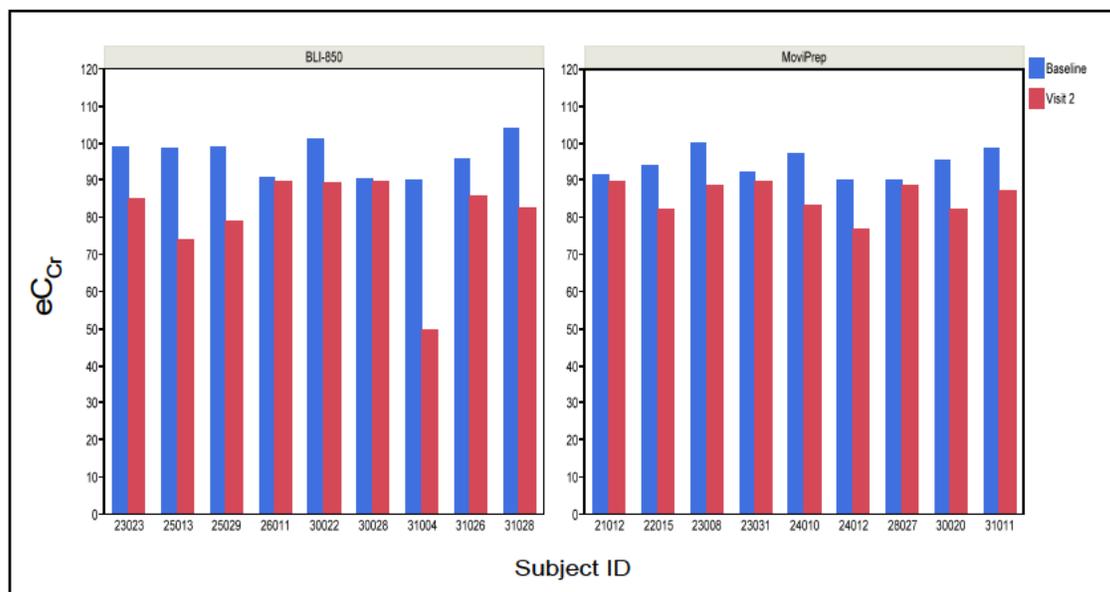
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Figure 8: Patients with baseline normal eC_{Cr} (Cockcroft-Gault method) who developed abnormally low eC_{Cr} (< 90 mL/min) at Visit 2 (Study 302)



Source: Clinical reviewer's analysis using the information provided by Dr. Bradley McEvoy, who calculated eC_{Cr} using the Applicant's datasets on demographics and laboratory results.

eGFR based on the Modification of Diet in Renal Disease (MDRD) calculation (normal baseline to low):

Since the MDRD calculation is becoming more widely accepted, the estimated glomerular filtration rate (eGFR) using this method was also explored in this review.

In Study 301, the mean change in eGFR was -14.2 mL/min/ 1.73 m² (range in change -10.3 to -24.3 mL/min/ 1.73 m²) in 12 patients with new-onset low eGFR (< 90 mL/min/ 1.73 m²) in the BLI850 group and -19.2 mL/min/ 1.73 m² (range in change -10.7 to -48.3 mL/min/ 1.73 m²) in 21 patients in the HalfLyte group. Although most changes in eGFR were small, some patients had a large decline in eGFR immediately after treatment. Patients with a normal baseline who developed a low eGFR based on the MDRD calculation had eGFR values ranging from 67.9 to 88.5 mL/min/ 1.73 m² at Visit 2 in the BLI850 group and 46.3 to 89.7 mL/min/ 1.73 m² in the HalfLyte group. Figure 9 compares eGFR values at baseline and Visit 2 for patients with new-onset low eGFR at Visit 2 in Study 301.

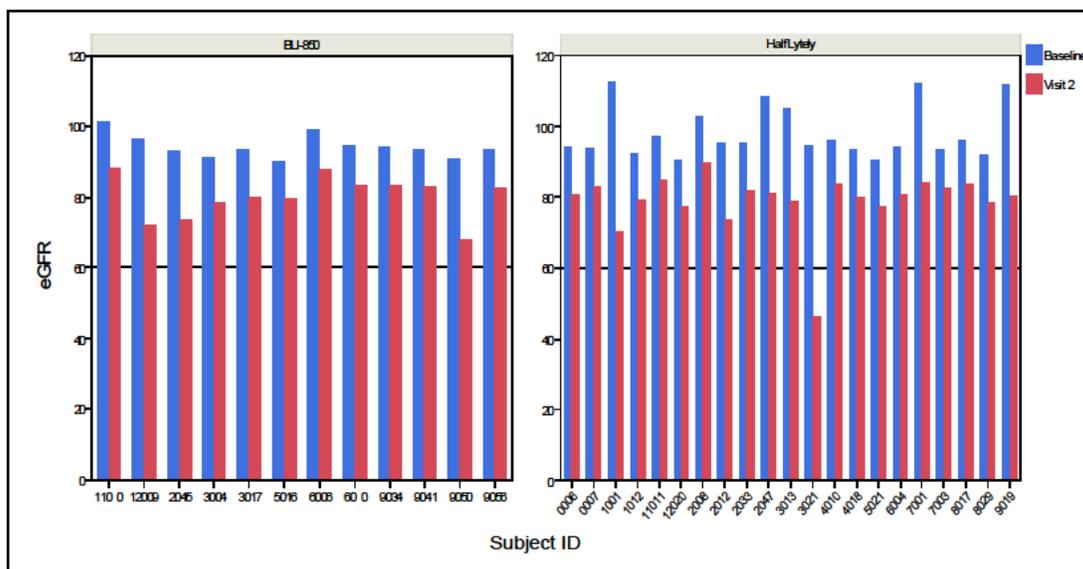
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Figure 9: Patients with baseline normal eGFR (MDRD method) who developed abnormally low eGFR (< 90 mL/min) at Visit 2 (Study 301)



Source: Clinical reviewer's analysis using the information provided by Dr. Bradley McEvoy, who calculated eGFR using the Applicant's datasets on demographics and laboratory results.

In Study 302, the mean change in eGFR was $-16.6 \text{ mL/min/1.73 m}^2$ (range in change -10.6 to $-30.5 \text{ mL/min/1.73 m}^2$) in 20 patients with new-onset low eGFR in the BLI850 group and $-15.0 \text{ mL/min/1.73 m}^2$ (range in change -8.9 to $-34.1 \text{ mL/min/1.73 m}^2$) in 17 patients in the HalfLyely group. Patients with a normal baseline who developed a low eGFR based on the MDRD calculation had eGFR values ranging from 67.7 to 89.3 mL/min/1.73 m^2 at Visit 2 in the BLI850 group and 67.1 to 89.5 mL/min/1.73 m^2 in the MoviPrep group. Figure 10 compares eGFR values at baseline and Visit 2 for patients with new-onset low eGFR at Visit 2 in Study 302.

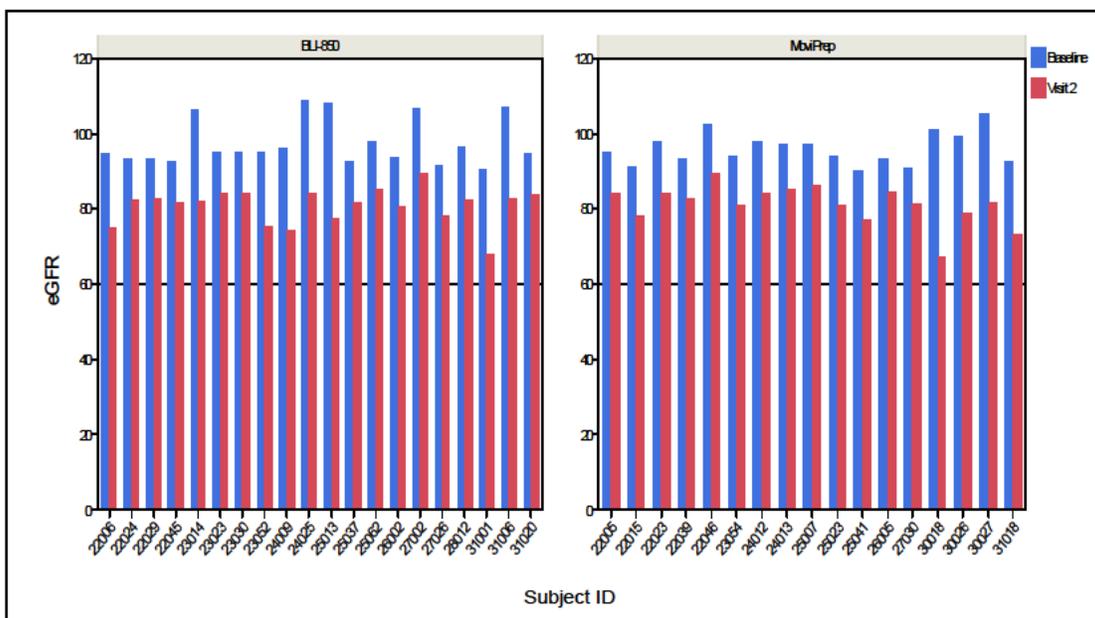
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Figure 10: Patients with baseline normal eGFR (MDRD method) who developed abnormally low eGFR (< 90 mL/min) at Visit 2 (Study 302)



Source: Clinical reviewer's analysis using the information provided by Dr. Bradley McEvoy, who calculated eGFR using the Applicant's datasets on demographics and laboratory results.

A limitation of these phase 3 trials is that laboratory and renal function follow-up did not extend beyond the day of colonoscopy. Based on available data, it is not clear whether the majority of these patients continued to have declining renal function or returned to their baseline. Therefore, this reviewer recommends that the Applicant conduct a post-marketing study to evaluate longitudinally renal function and laboratory abnormalities in patients taking BLI850 in preparation for colonoscopy, including elderly and those with renal impairment. These patients should be followed at regular intervals for at least 30 days post-treatment to better understand the long-term effect of BLI850 on renal function and laboratory abnormalities.

❖ Transaminases and Biliary Enzymes

Table 56, summarized from Dr. McEvoy's review, presents the proportion of patients with a normal baseline who developed abnormal liver or biliary enzymes on the day of colonoscopy (Visit 2). The direction of abnormality is also indicated.

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Table 56: Proportion of patients with normal baseline who developed abnormal liver or biliary enzymes at Visit 2 (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.

Albumin (normal baseline to high):

Although there were patients with new-onset abnormal albumin at Visit 2, all of them had elevated values and none had low albumin values that could potentially suggest compromised liver function. In Study 301, similar proportions of patients had hyperalbuminemia in the two treatment groups. In Study 302, a larger proportion of patients who received BLI850 had hyperalbuminemia compared with those who received MoviPrep. Hyperalbuminemia is most likely due to hemoconcentration, suggesting that BLI850 may be more dehydrating than MoviPrep.

AST (normal baseline to high):

In general, the BLI850 group had a slightly higher proportion of patients with elevated transaminases. In Study 301, the mean change in AST was +18.5 U/L in 9 patients with new-onset elevated AST in the BLI850 group, and +39.9 U/L in 7 patients in the HalfLyteLy group. 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.

In Study 302, the mean change in AST was +21.7 U/L in 13 patients with new-onset elevated AST in the BLI850 group and +16.3 U/L in 14 patients in the MoviPrep group. 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. 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 dysfunction.

ALT (normal baseline to high):

In Study 301, the mean change in ALT was +17.0 U/L in 8 patients with new-onset elevated ALT in the BLI850 group and +138.4 U/L in 5 patients in the HalfLyteLy group. The high mean ALT value in the HalfLyteLy group is due to one patient (Patient 9057)

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whose value increased from 26 to 680 U/L. There was no follow-up laboratory data on this patient. 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 HalfLyte group.

In Study 302, the mean change in ALT was +50.9 U/L in 10 patients with new-onset ALT in the BLI850 group and +27.4 U/L in 5 patients in the MoviPrep group. One patient (Patient 30028) in the BLI850 group had a large increase in ALT from 28 to 327 U/L, but the repeat laboratory testing 7 days after Visit 2 revealed normalization of ALT to 47 U/L. 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.

There were two patients with elevated AST and/or ALT values that were greater than 3 times the upper limit normal (one patient from the HalfLyte group in Study 301 and one patient from the BLI850 group in Study 302). However, neither of these patients had elevated total bilirubin values. There were no cases meeting the Hy's Law¹⁶ in these phase 3 trials.

Gamma glutamyl transpeptidase (GGT) levels were only elevated in a few patients, and the proportions of patients with abnormal values were similar across treatment groups.

Total and direct bilirubin (normal to high):

Although there were fewer patients with elevated total and direct bilirubin levels in the BLI850 group compared with those in the HalfLyte group, the opposite trend was observed when the BLI850 group was compared to the MoviPrep group. In Study 301, the mean change in total bilirubin was +0.5 mg/dL in 12 patients with new-onset total hyperbilirubinemia in the BLI850 group and +0.7 mg/dL in 17 patients in the HalfLyte group. Although 8 of 12 (67%) patients with total hyperbilirubinemia in the BLI850 group also had direct hyperbilirubinemia, the maximum value of direct bilirubin was only 0.3 mg/dL among those who had direct hyperbilirubinemia in the BLI850 group.

In Study 302, the mean change in total bilirubin was slightly higher at +0.7 mg/dL in 19 patients with new-onset total hyperbilirubinemia in the BLI850 group and +0.5 mg/dL in 6 patients in the MoviPrep group. Of the 19 patients with total hyperbilirubinemia in BLI850, 14 (74%) patients also had direct hyperbilirubinemia. However, the absolute values of direct bilirubin were generally low (i.e., one patient with 0.5 mg/dL, but mostly

¹⁶ Hy's Law cases have the following three components: (1) ≥ 3 xULN of ALT or AST than the (non-hepatotoxic) control drug or placebo, (2) serum total bilirubin >2 xULN without initial findings of cholestasis (elevated serum alkaline phosphatase, and (3) no other reason can be found to explain the combination of increased transaminase(s) and total bilirubin. Information obtained from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

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0.3 mg/dL). In general, the changes in total bilirubin were small, and these were not associated with clinically significant abnormalities in transaminases. Mild hyperbilirubinemia observed in the phase 3 trials are likely due to fasting and/or dehydration resulting from colon cleansing. In addition, patients with Gilbert syndrome, which occurs in approximately 5% of the population, can present with unconjugated hyperbilirubinemia in the setting of fasting.¹⁷

❖ Others

Creatine kinase (CK) and uric acid levels were also measured in Studies 301 and 302.

Table 57: Proportion of patients with normal baseline who developed abnormal creatine kinase (CK) and uric acid levels at Visit 2 (Studies 301 and 302)

Laboratory Parameter	Study 301		Study 302	
	BLI850 n/N (%)	HalfLyte 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)
Uric acid (high)	8/143 (5.6)	11/160 (6.9)	7/163 (4.3)	4/154 (2.6)

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

Creatine kinase (normal baseline to high):

In both trials, a larger number of patients in the BLI850 group had new-onset high levels of creatine kinase (CK) than in the comparator groups. None of these CK elevations were associated with cardiac symptoms. In Study 301, the mean change in CK was +124.7 U/L in 10 patients with new-onset elevated CK in the BLI850 group and +279.7 U/L in 6 patients in the HalfLyte group. 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 HalfLyte group. It should be noted that the upper limit normal of CK differs based on gender (Refer to Table 50).

In Study 302, the mean change in CK was +131.4 U/L in 10 patients with new-onset elevated CK in the BLI850 group and +347.3 U/L in 7 patients in the MoviPrep group. The comparator groups had one outlier each. When these two outliers were excluded, the mean change in CK decreased to +77.0 U/L and +68.8 U/L for the HalfLyte and MoviPrep groups, respectively. It should be noted that one patient (Patient 9031) in the HalfLyte group in Study 301 with elevated CK at Visit 2 underwent repeat testing (baseline = 88 U/L and Visit 2 = 1381 U/L) as it was deemed clinically significant by the investigator. The CK level decreased substantially from 1381 U/L to 538 U/L in 2 days.

17 Felsher BF, Rickard D, Redeker AG. The reciprocal relation between caloric intake and the degree of hyperbilirubinemia in Gilbert's syndrome. N Eng J Med 1970;283:170-2.

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No other patients with new-onset elevated CK underwent repeat testing from both studies. 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.

A review of other Visit 2 laboratory values in patients who experienced new-onset elevated CK after administration of BLI850 did not reveal consistent co-abnormalities. Laboratory values that were most commonly found to be also abnormal in patients with new-onset elevated CK were transaminases, bilirubin, and eGFR, but most were not new-onset abnormalities.

Elevated CK levels can be seen in muscle injury, such as rhabdomyolysis, myocardial infarction, myositis, and myocarditis. In addition, patients with acute renal failure and hypothyroidism, as well as those using statin medications could have elevated CK levels.¹⁸ None of the patients in Studies 301 and 302 experienced clinical symptoms associated with elevated CK, but long-term data are not available. No patients in either Study 301 or Study 302 experienced vomiting that was categorized as moderate or severe.

Based on the Applicant's submitted dataset on concomitant medications, no patient in Study 301 with new-onset elevated CK was being treated with statin medications or had a medical history that could explain elevated CK. In Study 302, two of 10 patients with new-onset elevated CK in the BLI850 group were on concomitant simvastatin and 2 patients had hypothyroidism (one of the patients with hypothyroidism was also on concomitant simvastatin); one of 7 patients with new-onset elevated CK in the MoviPrep group had hypothyroidism. It is possible that vigorous exercise could have contributed to elevated CK, but information regarding exercise is not available for the enrolled patients.

It should be noted that a fair number of patients had elevated baseline CK levels in all treatment groups from both studies (11-15%). Furthermore, as shown in Table 58, CK levels changed in both directions from baseline to Visit 2. A larger proportion of patients receiving BLI850 in Study 301 had CK level increased from baseline to Visit 2, as compared with those receiving HalfLyte. However, the proportions of patients with increased CK from baseline to Visit 2 were similar between the two treatment groups in Study 302.

18 Cervellin G, Comelli I, Lippi G. Rhabdomyolysis: historical background, clinical, diagnostic and therapeutic features. *Clin Chem Lab Med* 2010;48:749-56.

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Table 58: Direction of change in creatine kinase levels from baseline to Visit 2 (Studies 301 and 302)

	Study 301		Study 302	
	BLI850 N=159 n (%)	HalfLyte N=170 n (%)	BLI850 N=173 n (%)	MoviPrep N=164 n (%)
Baseline CK < Visit 2 CK	99 (62.3)	79 (46.5)	82 (47.4)	77 (47.0)
Baseline CK > Visit 2 CK	59 (37.1)	90 (52.9)	88 (50.9)	83 (50.6)
Baseline CK = Visit 2 CK	1 (0.6)	1 (0.6)	3	4

Source: Clinical reviewer's analysis using the Applicant's laboratory datasets from Studies 301 and 302.

In summary, it is not clear from available data to what extent the increase in CK levels was related to the administration of a bowel preparation or due to other unrelated factors.

Uric acid (normal baseline to high):

As shown in Table 57, some patients experienced new-onset elevated uric acid at Visit 2. In Study 301, the mean increase in uric acid was +1.2 g/dL in 8 patients with new-onset elevated uric acid in the BLI850 group and +1.3 g/dL in 11 patients in the HalfLyte group. Patients with a normal baseline who developed a high uric acid had uric acid values ranging from 6.7 to 10.0 g/dL at Visit 2 in the BLI850 group and 4.0 to 8.0 g/dL in the HalfLyte group. It should be noted that the normal range of uric acid differs based on gender (Refer to Table 50).

In Study 302, the mean increase was +1.2 g/dL in 7 patients with new-onset elevated uric acid in the BLI850 group and +1.7 g/dL in 4 patients in the MoviPrep group. Patients with a normal baseline who developed a high uric acid had uric acid values ranging from 6.5 to 9.7 g/dL at Visit 2 in the BLI850 group and 6.7 to 9.5 g/dL in the MoviPrep group.

The most likely reasons for mildly elevated uric acid levels in these patients include fasting and high dietary intake of fructose, which is a common practice when undergoing bowel cleansing preparation.

7.4.3 Vital Signs

In Studies 301 and 302, weight, height, temperature, pulse, and blood pressure were measured at Visits 1 and 2. There were no clinically or statistically significant abnormalities or changes. Table 59 summarizes changes in weight and vital signs between baseline and Visit 2 in Studies 301 and 302. In general, the mean weight loss was slightly higher in the BLI850 group than the comparator group in both trials.

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Volume contraction that resulted in weight loss may explain a slight increase in pulse rate and decrease in systolic pressure in patients who received BLI850 in Study 301. However, such associated vital sign changes were not observed in Study 302.

Table 59: Summary changes in weight and vital signs between baseline and Visit 2 in Studies 301 and 302

Vital sign	Study 301		Study 302	
	BLI850	HalfLyteLy	BLI850	MoviPrep
Mean change in weight (lbs)	-1.94	-1.73	-2.81	-2.28
Median change in weight (lb)	-1.00	-1.00	-3.00	-2.00
Range in weight change	-12 to +7	-11 to +7	-15 to +9	-19 to +13
Mean change in pulse (bpm)	+0.63	+2.31	+2.95	+3.48
Mean change in systolic BP (mm/Hg)	-1.92	-0.01	+4.84	+9.26

Source: Applicant's Clinical Study Reports for Protocol BLI850-301 and BLI850-302, Table 14.3.5.1 from both protocols.

7.4.4 Electrocardiograms (ECGs)

No ECG evaluations were performed in Studies 301 and 302.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies or clinical trials were conducted.

7.4.6 Immunogenicity

Since BLI-850 is not a protein, immunogenicity data were not collected.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable since the total dose received was the same for patients in the BLI850 treatment group in Studies 301 and 302.

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7.5.2 Time Dependency for Adverse Events

BLI850 is expected to be dosed once prior to a colonoscopy examination, either as a day-before dosing regimen or a split-dose (2-day) regimen. Therefore, time dependency for adverse events was not evaluated in this application.

7.5.3 Drug-Demographic Interactions

❖ Adverse Events by Age

Table 60 summarizes common adverse events in elderly patients in Studies 301 and 302. In Study 301, a total of 73 (75%) elderly patients ≥ 65 years old experienced at least one adverse event, 40 (83%) in the BLI850 group and 33 (67%) in the HalfLyteLy group. In Study 302, a total of 72 (79%) elderly patients ≥ 65 years old experienced at least one adverse event, 33 (79%) in the BLI850 group and 39 (80%) in the MoviPrep group. Adverse event subgroup analysis did not reveal any elderly-specific safety signals.

Table 60: Common adverse events in elderly patients (≥ 65 years old) in Studies 301 and 302 (occurring in >1 patient in any given treatment group)

Symptom	Study 301: Day-Before Regimen		Study 302: Split-Dose Regimen	
	BLI850 N=48 n (%)	HalfLyteLy N=49 n (%)	BLI850 N=42 n (%)	MoviPrep N=49 n (%)
Overall discomfort	33 (68.8)	23 (46.9)	22 (52.4)	30 (61.2)
Abdominal distension	26 (54.2)	17 (34.7)	21 (50.0)	34 (69.4)
Abdominal pain	21 (43.8)	19 (38.8)	14 (33.3)	22 (44.9)
Nausea	18 (37.5)	11 (22.4)	13 (31.0)	19 (38.8)
Vomiting	1 (2.1)	2 (4.1)	3 (7.1)	1 (2.0)

Source: Clinical reviewer'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.

❖ Adverse Events by Gender

Table 61 and Table 62 summarize subgroup analyses of common adverse events by males and females, respectively. A larger proportion of female patients experienced adverse events across all categories compared with male patients.

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Table 61: Common adverse events in male patients in Studies 301 and 302 (occurring in >1 patient in any given treatment group)

Symptom	Study 301: Day-Before Regimen		Study 302: Split-Dose Regimen	
	BLI850 N=79 n (%)	HalfLyteLy N=86 n (%)	BLI850 N=101 n (%)	MoviPrep N=77 n (%)
Overall discomfort	51 (64.4)	37 (43.0)	56 (55.4)	41 (53.2)
Abdominal distension	32 (40.5)	31 (36.0)	51 (50.5)	37 (48.1)
Abdominal pain	31 (39.2)	25 (29.1)	36 (35.6)	26 (33.8)
Nausea	25 (31.6)	21 (24.4)	37 (36.6)	18 (23.4)
Vomiting	5 (6.3)	6 (7.0)	10 (9.9)	0 (0)

Source: Clinical reviewer'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.

Table 62: Common adverse events in female patients in Studies 301 and 302 (occurring in >1 patient in any given treatment group)

Symptom	Study 301: Day-Before Regimen		Study 302: Split-Dose Regimen	
	BLI850 N=97 n (%)	HalfLyteLy N=104 n (%)	BLI850 N=85 n (%)	MoviPrep N=108 n (%)
Overall discomfort	71 (73.2)	71 (68.3)	60 (70.6)	80 (74.1)
Abdominal distension	60 (61.9)	54 (51.9)	45 (52.9)	75 (69.4)
Abdominal pain	40 (41.2)	53 (51.0)	34 (40.0)	53 (49.1)
Nausea	49 (50.5)	54 (51.9)	49 (57.6)	54 (50.0)
Vomiting	14 (14.4)	9 (8.7)	16 (18.8)	13 (12.0)
Retching	2 (2.1)	0 (0)	0 (0)	2 (1.9)
Headache	1 (1.0)	2 (1.9)	3 (3.5)	1 (0.9)

Source: Clinical reviewer'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.

7.5.4 Drug-Disease Interactions

A total of 169 patients in Study 301 and 191 patients in Study 302 were classified as high risk patients by the Applicant due to reported medical history of cardiac, renal or vascular problems (hypertension), or diabetes. Table 63 presents subgroup analysis of adverse events for high risk patients. This analysis did not reveal any safety signals

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that are specific to high risk patients, but a major limitation of this analysis is that all high risk patients were grouped together regardless of disease etiology.

Table 63: Common adverse events in high risk patients¹ in Studies 301 and 302 (occurring in > 1 patient in any given treatment group)

Symptom	Study 301: Day-Before Regimen		Study 302: Split-Dose Regimen	
	BLI850 N=80 n (%)	HalfLyteLy N=89 n (%)	BLI850 N=90 n (%)	MoviPrep N=101 n (%)
Overall discomfort	50 (62.5)	51 (57.3)	53 (58.9)	70 (69.3)
Abdominal distension	43 (53.8)	40 (44.9)	50 (55.6)	68 (67.3)
Abdominal pain	28 (35.0)	34 (38.2)	29 (32.2)	49 (48.5)
Nausea	34 (42.5)	29 (32.6)	38 (42.2)	41 (40.6)
Vomiting	9 (11.3)	7 (7.9)	10 (11.1)	7 (6.9)
Headache	0 (0)	2 (2.2)	1 (1.1)	1 (1.0)

¹High risk patients were defined as patients with reported medical history of cardiac, renal or vascular problems (hypertension), or diabetes.

Source: Clinical reviewer'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.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were performed with BLI850.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies were not performed.

7.6.2 Human Reproduction and Pregnancy Data

No formal studies with BLI850 have been conducted in pregnant women, and no pregnancies occurred during Studies 301 and 302.

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7.6.3 Pediatrics and Assessment of Effects on Growth

BLI-850 was not evaluated in the pediatric population, and there was no assessment of effects on growth. The Applicant will be required to perform a pediatric study under PREA. See Section 1.4 Recommendations for Postmarket Requirements and Commitments for details.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no cases of overdose reported during the phase 3 trials. If patients were to overdose on BLI850, they will likely experience profuse diarrhea and dehydration. These patients should be rehydrated and monitored closely. There is no known potential for abuse, withdrawal or rebound with BLI850.

7.7 Additional Submissions / Safety Issues

The Applicant's 120-day safety report was received on April 16, 2012. Since BLI850 is comprised of two components that are commercially available but in a smaller quantity or containing only a portion of the approved product, the Applicant submitted the post-marketing adverse events for SUPREP and HalfLyte that they received from May 10, 2011 to February 28, 2012 (cumulative data since the submission of last annual report). As shown in Table 64, the most common adverse events are GI-related, which are expected from bowel cleansing preparations. The adverse event rates were low at 0.04% and 0.01% for SUPREP and HalfLyte, respectively. The Applicant reported that they received one 15-day report for a case of aspiration. The report involved an inpatient (age and sex unknown) who aspirated while taking the first dose of SUPREP. No additional information was provided.

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Table 64: Postmarketing Adverse Event Summary for SUPREP and HalfLyately and Bisacodyl Tablet Bowel Prep Kit (May 10, 2011 - February 28, 2012)

	Approved Product	
	SUPREP	HalfLyately and Bisacodyl Tablet Bowel Prep Kit
Allergic reaction	6	4
Anaphylactic reaction	0	0
Aspiration	1	0
Brain	1	0
Cardiac	0	0
Death	0	0
Edema	1	0
Gastrointestinal	188	39
Mallory-Weiss Tear	0	0
Miscellaneous	21	4
Perforation	0	0
Total number of AEs	218	47
Distribution, units	583,453	462,450

Source: Modified from the Applicant's 120-day Safety Update received April 16, 2012, Tables 1 and 2.

Although submitted safety data provide supportive information, this information is not directly applicable to the current submission since BLI850 contains only a portion of the two approved products that is administered together in a sequential manner.

8 Postmarket Experience

BLI850 is not marketed in the U.S. or worldwide.

9 Appendices

Appendix 1: Treatment Questionnaire for Study 301

Braintree Laboratories, Inc.
Subject No [] [] [] [] - [] [] [] []

SOURCE DOCUMENT

Protocol BLI850-301
Initials [] [] [] []

TREATMENT QUESTIONNAIRE

Date of **DOSE 1** dose: [] [] [] [] [] [] **20** [] []
DD MMM YY

- What time did you start the first preparation dose? [] [] : [] [] AM PM
- What time did you complete the first preparation dose? [] [] : [] [] AM PM

Date of **DOSE 2** dose: [] [] [] [] [] [] **20** [] []
DD MMM YY

- What time did you start the second preparation dose? [] [] : [] [] AM PM
- What time did you complete the second preparation dose? [] [] : [] [] AM PM

****Remember Dose 1 and Dose 2 should be completed on the evening prior to your colonoscopy****

If your preparation caused you to vomit, please note date and time of each episode:

Date [] [] [] [] [] [] **20** [] [] Time [] [] : [] [] AM PM
DD MMM YY

Date [] [] [] [] [] [] **20** [] [] Time [] [] : [] [] AM PM
DD MMM YY

Date [] [] [] [] [] [] **20** [] [] Time [] [] : [] [] AM PM
DD MMM YY

Date [] [] [] [] [] [] **20** [] [] Time [] [] : [] [] AM PM
DD MMM YY

Clinical Review

Jessica Lee, MD; Helen Sile, MD

NDA 203-595

BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

Appendix 3: Formulas used to calculate eC_{Cr} and eGFR

Cockcroft-Gault:

$$\frac{(140 - \text{Age}) \times \text{Body Weight (in kg)} \times [0.85 \text{ if female}]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

Modification of Diet in Renal Disease (MDRD):

$$186 \times \text{Serum Creatinine (in mg/dL)}^{-1.154} \times \text{Age}^{-0.203} \times [1.212 \text{ if Black}] \times [0.742 \text{ if Female}]$$

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI):

- *For women with serum creatinine ≤ 0.7:*
(Serum Creatinine/0.7)^{-0.329} × (0.993)^{Age} × [166 if Black; x 144 if White or other]
- *For women with a serum creatinine > 0.7:*
(Serum Creatinine/0.7)^{-1.209} × (0.993)^{Age} × [166 if Black; x 144 if White or other]
- *For men with serum creatinine ≤ 0.9:*
(Serum Creatinine/0.9)^{-0.411} × (0.993)^{Age} × [163 if Black; x 141 if White or other]
- *For men with a serum creatinine > 0.9:*
(Serum Creatinine/0.7)^{-1.209} × (0.993)^{Age} × [163 if Black; x 141 if White or other]

9.1 Literature Review/References

The Applicant's literature search provided for this review was appropriate. The following references were used for this review:

Cervellin G, Comelli I, Lippi G. Rhabdomyolysis: historical background, clinical, diagnostic and therapeutic features. *Clin Chem Lab Med* 2010;48:749-56.

Chokshi RV, Hovis CE, Hollander T, et al. Prevalence of missed adenomas in patients with inadequate bowel preparation on screening colonoscopy. *Gastrointest Endosc* 2012;75:1197-203.

Cohen LB. Split dosing of bowel preparations for colonoscopy: an analysis of its efficacy, safety, and tolerability. *Gastrointest Endosc* 2010;72:406-12.

Clinical Review

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NDA 203-595

BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

DiPalma JA, Brady CE, Stewart DL, et al. Comparison of colon cleansing methods in preparation for colonoscopy. *Gastroenterology* 1984;86:856-60.

Felsher BF, Rickard D, Redeker AG. The reciprocal relation between caloric intake and the degree of hyperbilirubinemia in Gilbert's syndrome. *N Eng J Med* 1970;283:170-2.

Gurudu SR, Ramirez FC, Harrison ME, et al. Increased adenoma detection rate with system-wide implementation of a split-dose preparation for colonoscopy. *Gastrointest Endosc* 2012;76:603-8.

Hunter A, Mamula P. Bowel preparation for pediatric colonoscopy procedures. *JPGN* 2010;51:254-61.

Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999;130:461-70.

Levey AS, Stevens, LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604-12.

Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a Joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin* 2008;58:130-60.

Pashankar DS, Uc A, Bishop WP. Polyethylene glycol 3350 without electrolytes: a new safe, effective, and palatable bowel preparation for colonoscopy in children. *J Pediatr* 2004;144:358-62.

Reddy P, Mooradian AD. Clinical utility of anion gap in deciphering acid-base disorders. *Int J Clin Pract* 2009; 63:1516-25.

Rex DK, Johnson DA, Anderson JC, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2008. *Am J Gastroenterol* 2009;104:739-50.

Safder S, Demintieva Y, Rewalt M, et al. Stool consistency and stool frequency are excellent clinical markers for adequate colon preparation after polyethylene glycol 3350 cleansing protocol: a prospective clinical study in children. *Gastrointest Endosc* 2008;68:1131-5.

Turner D, Levine A, Weiss B. Evidence-based recommendations for bowel cleansing before colonoscopy in children: a report from a national working group. *Endoscopy* 2010;42:1063-70.

Clinical Review

Jessica Lee, MD; Helen Sile, MD

NDA 203-595

BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012;366:687-96.

9.2 Labeling Recommendations

Discussions regarding labeling recommendations are ongoing at the time of this review.

The initially proposed proprietary name [REDACTED] (b) (4) was found to be unacceptable by the Office of Medication Error Prevention and Risk Management. The reader is referred to Dr. Anne Tobenkin's review dated May 3, 2012 for details. A subsequently proposed proprietary name [REDACTED] (b) (4) was also deemed unacceptable. Finally, a revised proprietary name "Suclear" was considered acceptable, based on the review by Dr. Teresa McMillan dated September 17, 2012. A letter was sent on September 17, 2012 notifying the Applicant that the proprietary name was granted.

The proposed dosing regimens are acceptable, but this reviewer recommends specifying the split-dose regimen as the preferred method.

General labeling recommendations include:

- Both efficacy and safety results should be presented separately for each phase 3 trial since the two trials had different dosing regimens and active comparators.
- Adverse event data should include both spontaneously reported events as well as queried symptoms, regardless of severity.
- The split-dose regimen should be specified as the preferred regimen, and the day-before regimen should be specified as the alternative regimen.

For final labeling agreements, see the approved product label for SUCLEAR.

9.3 Advisory Committee Meeting

No advisory committee (AC) meeting was convened to discuss this application.

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

/s/

JESSICA J LEE
12/21/2012

HELEN SILE
01/01/2013

ROBERT FIORENTINO
01/03/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1: BLI850-301 Indication: for cleansing of the colon in preparation for colonoscopy Pivotal Study #2: BLI850-302 Indication: for cleansing of the colon in preparation for colonoscopy				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			single blind, active controlled trials
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.		X		No agreement reached on the non-inferiority margin used by the Sponsor but the Sponsor has submitted some explanation for the 15% non-inferiority margin
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	All study sites for study 301 and 302 were in the USA
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			This product has not been previously marketed but the Sponsor did provide some data on Suprep and Halflytely (related products)
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	Number to be exposed not discussed or agreed upon with the division. However, the Sponsor performed safety analyses focused on elderly patients ≥ 65 yrs old

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			Sponsor has evaluated patients who have renal insufficiency (study BLI800-202)
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			There were no deaths.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The Sponsor is requesting a waiver for pediatric population (b) (4) The justification the Sponsor provided is study BLI800-400.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	Phase 3 trials (301 and 302) were conducted in the USA
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?		X		
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Helen Sile	February 17, 2012
Reviewing Medical Officer	Date

Robert P. Fiorentino	February 17, 2012
Clinical Team Leader	Date

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

/s/

HELEN SILE
02/17/2012

ROBERT FIORENTINO
02/26/2012