CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203595Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA: 203595	Submission Date(s): 12/16/2011, 04/25/2012
Brand Name	SUCLEAR
Generic Name	Sodium sulfate, potassium sulfate and magnesium sulfate oral solution (Component 1); PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution (Component 2)
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Sue Chih Lee, Ph.D.
OCP Division	DCP3
OND Division	DGIEP
Sponsor	Braintree Laboratories
Relevant IND(s)	102894
Submission Type; Code	Standard
Formulation; Strength(s)	Oral solution (component 1); Powder for oral solution (component 2)
Indication	Bowel cleansing prior to colonoscopy

An optional intra-divisional level OCP briefing was held for NDA 203595 on September 11, 2012 in conference room 3300, building 51 of the FDA White Oak campus. Briefing attendees included Drs' Edward D. Bashaw, Hae Young Ahn, Sue Chih Lee, Kris Estes, Jessica Lee and Sandhya Apparaju.

Introduction: The purpose of this addendum is to finalize the post-marketing study recommendations for NDA 203595. This NDA has been deemed acceptable from a Clinical Pharmacology perspective. Please refer to Clinical Pharmacology review in DARRTS signed 09/18/2012.

Recommendation: The following pharmacokinetic study is recommended as a post-marketing commitment (PMC) for NDA 203595:

Assess the systemic exposure potential/pharmacokinetics of PEG3350, (b) (4) following oral administration of SUCLEAR to adult subjects scheduled to undergo colonoscopy.

PK assessments for SUCLEAR may be conducted as a stand-alone trial or as a sub-study in another clinical trial with this formulation. Validated analytical methods should be employed for this purpose.

Final study report including analytical methods and any relevant labeling revisions in this regard should be submitted for agency review.

Rationale: As noted in section 1.2 of the original Clinical Pharmacology review (signed in DARRTS 09/18/2012), sponsor did not assess the systemic exposure of PEG3350 following the recommended dosing regimen. Limited information from the literature has been presented in the NDA in this regard to address the systemic exposure potential of PEG3350. Information on the systemic exposure potential for (b) (4) and (b) (4) is currently unavailable in the literature. Previously published findings on PEG absorption have primarily relied upon fecal assay of PEG3350 which is often variable. The lower limit of detection for PEG3350 plasma assay was also very high in these older studies making systemic exposure determination difficult. It is our understanding that more sensitive and specific assays for systemic exposure assessment are now feasible (e.g. Pelham et al, 2006) and therefore can be developed to assess systemic uptake of this widely used (b) (4) product and to characterize/rule-out systemic exposure of smaller molecular weight byproducts.

Currently there are several FDA approved bowel cleansing preparations with PEG3350. While these agents are not intended for chronic use but for single dose administration prior to colonoscopy, there has been very little effort to definitively characterize systemic PK following these rather large PEG doses in adults. Information generated from a PK study will be useful in filling the knowledge gaps in this regard and potentially to inform future drug development efforts with these moieties.

The proposed post-marketing recommendation has been discussed with Dr. Edward D. Bashaw, the director of Division of Clinical Pharmacology 3 in OCP. The Citizen Petition dated June 3, 2012, which raised concern regarding use of PEG3350 products in pediatric patients was included in this discussion. Dr. Bashaw has concurred with this recommendation for a PMC. It should be noted that the PREA requirements as communicated to DGIEP for NDA 203595 include PK assessment of PEG3350, (b) (4) (b) (4) and (b) (4) in each pediatric age group.

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/s/

SANDHYA K APPARAJU
09/28/2012

SUE CHIH H LEE
09/28/2012

EDWARD D BASHAW
10/02/2012

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

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1 Executive Summary

1.1 Recommendation

NDA 203595 is acceptable from a Clinical Pharmacology perspective provided an agreement can be arrived with the sponsor regarding proposed labeling language.

1.2 Phase IV Commitments

The sponsor did not assess the systemic exposure to PEG3350 following the recommended dosing regimen. Assessments in this regard for evaluation of PEG3350, as well as potential metabolites of interest namely [redacted] (b) (4) and [redacted] (b) (4) will be recommended for evaluation post-approval. This may be conducted as a stand-alone pharmacokinetic study or as part of another clinical trial. Discussion is underway in this regard internally. An addendum will be entered into DARRTS once it has been determined whether the recommended assessments need to be conducted as a post-marketing commitment or as a post-marketing requirement.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The proposed drug product for oral administration, BLI850 (Tradename: SUCLEAR) is indicated for colon cleansing prior to colonoscopic procedures. It is essentially a half-dose of NuLytely plus half dose of SUPREP, both approved formulations for the same indication as BLI850. Thus as proposed BLI850 is a 2-component formulation where in, component 1 consists of an oral sulfate salt solution (Na, Mg, K sulfates) and component 2 consists of PEG3350 with electrolytes. The components are intended for administration within 2 hours of each other [redacted] (b) (4) regimen) or after an overnight gap (split-dose regimen) along with additional water consumption requirements prior to colonoscopic procedures. Both components are largely unabsorbed and have osmotic effects, where in they draw water into the stools, resulting in copious diarrhea for achieving colon cleansing. Each component has been approved at similar or higher doses in previous formulations either alone or in combination with other laxatives (HalfLytely: Bisacodyl + PEG-ELS; NuLYTELY: PEG-ELS 4L; SUPREP: Oral Sulfate Salt Solution).

In support of this NDA, the sponsor has conducted two randomized, double-blind, parallel-group, active-controlled, phase 3 clinical trials in patients undergoing colonoscopic procedures. Each study evaluated one of the two proposed dosing regimens [redacted] (b) (4) or split-dose) and each one evaluated efficacy of BLI850 in comparison to one of two approved cleansing preparations (Half-Lytely or Moviprep). The primary efficacy variable was the investigator rating of colon cleansing which was based on a four point scale ranging from poor to excellent. Please refer to clinical and statistical reviews for details.

While BLI850 is a combination of two previously approved active agents, the design of the two Phase 3 trials did not address the combination rule requirements, i.e., to

demonstrate that the combination of the two components is superior to either component alone. Pharmacodynamic (PD) evidence was used to address this issue.

Pharmacodynamic Information – dose/combination rationale: No dedicated Phase 2 dose-finding studies were conducted as part of this drug development. However information from two phase 1 PD studies (005-082 and 006-181) conducted in earlier drug development programs for similar products was submitted again in supporting the dose/combination proposed. In these PD studies, a measurement dubbed as 'scatocrit', which is essentially % stool solids in the final bowel movement, as well as total stool weight (g) were used as surrogate measures of colonic cleansing efficacy. However, these are not widely used measures as their correlation to the clinical endpoints is not known.

Data from the phase 1 PD study 005-082 in general showed that each component as proposed (i.e. 22 g of oral sulfate salts or 210 g PEG-ELS solution) alone produced PD outcomes that appear inferior to those for approved products HalfLytely or NuLytely. Data for the combination was minimal in this study (n =1) and the correlation of the PD with efficacy is not understood.

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

Data from the other phase 1 PD study 006-181 showed that PD (as evaluated by scatocrit) was inferior after a first ½ dose of each component but was substantially improved with the second ½ dose, thus suggesting that single components (1/2 doses) alone would be inadequate.

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

However due to paucity of data on PD endpoints for the proposed combination in these studies (n =1 in PD study 005-082) and more importantly due to current lack of understanding of any correlation between the PD and efficacy outcomes, PD data as available while supportive in justifying proposed combination, is not conclusive.

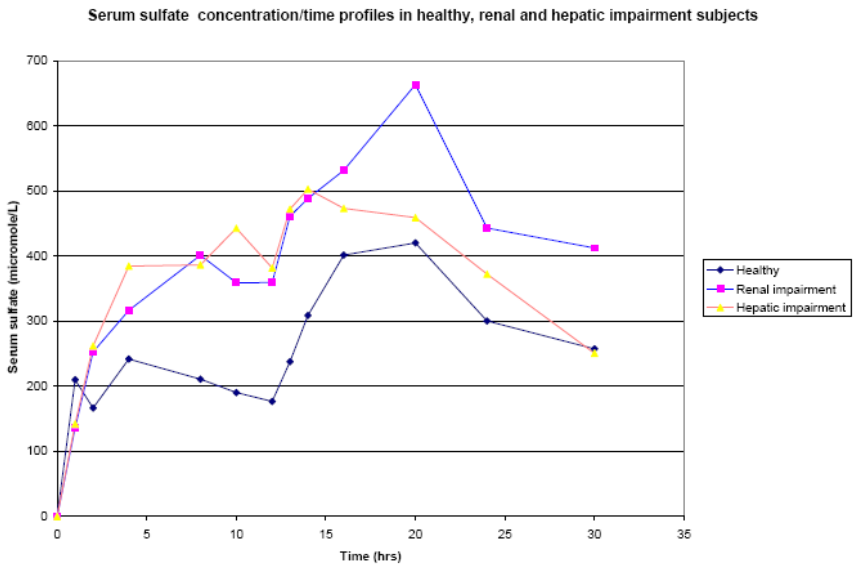
In response to a recent information request by the Clinical Division with regard to combination rule requirements, the sponsor has attempted to address the correlation of PD and efficacy outcomes, by providing available information for successful and failed bowel cleansing preparations. Data provided is a compilation from various sources and as presented, there appears to be a trend for a successful clinical outcome with a lower scatocrit value (PD endpoint) and vice versa. Nevertheless, data presented was not a rigorous attempt to validate and establish a correlation between the PD and clinical outcomes. A factorial design requirement may not always be ethically feasible as it may require dosing some patients with a potentially ineffective dose of bowel cleansing product, followed by colonoscopic procedure under anesthesia in order to assess clinical endpoints. Thus the available PD information and trends for their correlation with efficacy in totality may be helpful in justifying the proposed combination. We defer the final determination to the clinical review team (Dr. Jessica Lee, Medical Officer of DGIEP and Dr. Rob Fiorentino, Clinical TL, DGIEP).

Lab measurements for safety assessment:
In PD study 005-082, no effect on any of the analytes measured (BUN, creatinine, magnesium, protein, potassium and sodium) were noted in the data for sulfate solution #5 (similar to component 1 of BLI850). A reduction in osmolality from 295 mOsm at baseline to 288 at post-treatment was noted but clinical implication is not known. A decrease in serum osmolality from 296 to 287 was also noted in the individual who received both NuLytely 2L and SO4 solution 5.

In PD study 006-181, electrolyte measurements were taken at baseline, at 10 h after the first half of the dose (prior to second dose) and 3 h after the second half of the dose. Post-treatment sulfate levels were greater for BLI800 i.e. SUPREP (0.61 at baseline vs. 1.94 mg/L at 3 h after the second dose). With the exception of sulfate increases in serum at post-treatment, no other electrolyte losses/gains were noted. One can infer the sulfate changes with the proposed combination using the data following the first dose of BLI800 in this study (at 10 h post-first dose; from 0.6 to 1.2 mg/L). Information on when these sulfate levels returned to baseline was not available from this study.

Lab measurements from these small PD studies will not provide adequate information to ascertain safety of the proposed formulation. Please refer to the clinical and statistical reviews for an extensive discussion of the phase 3 safety data including lab measures.

Systemic exposure of sulfate and PEG3350: PK information for each active moiety has been presented in the NDA. PK of oral sulfates at twice the dose proposed in BLI850 (i.e. at 44 g) was previously evaluated in study BLI800-202 as part of drug development program for SUPREP (NDA 22-372). Information relevant to the first dose of oral sulfates (22 g) in this split-dose study will be relevant to the current NDA for component 1.



PK was not evaluated for the proposed PEG-ELS component (210 g dose) of BLI850 (SUCLEAR). Similar as well as higher doses of PEG-ELS are currently approved for the same indication as HalfLytely and NuLYTELY 4L. As suggested by the available information from the published literature in general, PEG3350 appears to undergo minimal systemic absorption following oral dosing and is primarily eliminated in feces. Absorbed portions of PEG appeared in urine.

Sulfate concentrations were higher in presence of renal and hepatic impairment.
The clinical relevance of decreased clearance of sulfates in presence of renal impairment is not understood, particularly in the context of the proposed single use nature of BLI850 for colon cleansing. Available information nevertheless should be communicated in the labeling. No dosage adjustment appears to be necessary based on age, gender, race, or concomitant medications.

2 Summary of CPB Findings

Relevant regulatory information: Proposed drug product is for single use administration for bowel cleansing prior to colonoscopy and contains two components administered orally on separate occasions, either in a (b) (4) or split dose regimen. The two components, broadly described are the 1) oral sulfate salts, OSS and 2) PEG3350 with electrolytes (PEG-ELS).

There are other approved drug products for the same indication containing either of these active ingredients with or without other active moieties. These include the following:

- SUPREP (NDA 22-372); Compared to the proposed product, it contains twice the amount of oral sulfates; it is also referred to as BLI800.
- HalfLytely (NDA 21-551); Compared to the proposed product, it contains the same amount of the PEG-ELS; it also contains bisacodyl as a second component.
- NuLytely (NDA 19-797); Compared to the proposed product, it contains twice the amount of PEG-ELS (420 g; 4L);
- GoLytely (NDA 19-011); Compared to the proposed product, it contains slightly higher amount of PEG3350 (236 g) and also has sodium sulfate (21.64 g) in addition to the electrolytes proposed.

Combination rule requirement: While the drug product is a combination of two approved osmotic agents, the sponsor has not specifically addressed the combination rule requirements in the NDA (e.g. via phase 3 design) in order to demonstrate that the combination is superior compared to each individual component alone for the desired clinical efficacy outcomes.

2.1 General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review? Include any relevant regulatory background.

Description: Proposed product (also referred to as BLI850) has two components:

- One 6oz bottle of oral sulfate solution for dilution with 16oz water, consisting of sodium sulfate 17.5 g, potassium sulfate 3.13 g, magnesium sulfate 1.6 g.
- One 2 liter jug of powder for reconstitution with water, containing PEG-3350 210 g, sodium bicarbonate 2.86 g, sodium chloride 5.6 g, potassium chloride 0.74 g. An optional 1g flavoring ingredient may be added.

The composition of the proposed 2-component formulation is shown below:

Material	Function	Proposed formulation (BLI850)	Suprep	Half-Lytely
Component 1 (oral sulfate solution; quantity per dose)				
Sodium Sulfate, USP	Active	17.510 g (b) (4)	35.020 g	-
Potassium sulfate (b) (4)	Active	3.130 g (b) (4)	6.260 g	-
Magnesium sulfate, USP	Active	1.600 g (b) (4)	3.200g	-
Sodium Benzoate, NF	(b) (4)	(b) (4)	(b) (4)	-
Sucralose (b) (4)	(b) (4)	(b) (4)		-
Malic acid, FCC	(b) (4)	(b) (4)		-
Citric acid, USP	(b) (4)	(b) (4)		-
(b) (4)	(b) (4)	(b) (4) (b) (4)		-
				-
				-
Purified water	(b) (4)	(b) (4)		-
Component 2 (PEG-ELS for solution; quantity per dose)				
Polyethylene Glycol 3350, NF	Active	210 g (b) (4)	-	210 g
Sodium chloride, USP	Active	5.60 g (b) (4)	-	5.60 g
Sodium bicarbonate, USP	Active	2.86 g (b) (4)	-	2.86 g
Potassium chloride, USP	Active	0.74 g (b) (4)	-	0.74 g
Flavor ingredients optional	Flavoring	1.00 g	-	1.00 g

The sodium sulfate (MW 142.04) used in the manufacture of the oral solution (part 1) is anhydrous and USP grade. It consists of large, colorless, odorless, transparent crystals or granular powder. It is freely soluble in water with a maximum solubility of 1 g/2 mL. Sodium sulfate is the dominant, osmotically active ingredient. Potassium sulfate (MW 174.26) used in the manufacturing of the oral solution is (b) (4) grade. It is a white granular powder, odorless and soluble in water (1 g in 8.3 mL). Magnesium sulfate (MW 120.37) used in the manufacturing of the oral solution is anhydrous and USP grade. It is a white crystalline solid with a water solubility of 25.5 g/100 mL at 20°C.

The polyethylene glycol used in the manufacture of component 2 is NF grade and has an average molecular weight of 3350. It is the dominant, osmotically active ingredient. It is a fine, free flowing or waxy, white/off-white powder or granules.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Drug product combines two components, an oral sulfate solution and PEG-ELS solution. The primary mode of action is the osmotic effect of the un-absorbed PEG and sulfate salts. Sulfate salts provide sulfate anions, which are poorly absorbed. The osmotic effect of unabsorbed sulfate anions and the associated cations cause water to be retained within the gastrointestinal tract. Polyethylene glycol (PEG) is also a largely unabsorbed osmotic agent which causes water to be retained within the gastrointestinal tract. The osmotic effect of the unabsorbed PEG and sulfate ions, when ingested with a large volume of water, produces a copious watery diarrhea.

Proposed indication: SUCLEAR is indicated for cleansing of the colon as a preparation for colonoscopy in adults.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

Dosing regimen: Drug product is for oral use and is proposed for use as either a 1) split-dose (2-Day) regimen, where the 6oz bottle (oral sulfate solution; diluted with water) is consumed the evening before colonoscopy, and the 2 liter bottle (PEG-ELS powder for oral solution) is consumed the next morning, to be completed at least 2 h before colonoscopy; or 2) (b) (4) (1-Day) regimen, in which both components are consumed within 2 hours of each other. Additional clear fluids (no solid food or milk) must be consumed after every dose for both dosing regimens.

Details of the dosing regimen as proposed in the labeling are as follows:

(b) (4)

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In order to support an NDA for this 2-component drug product (oral sulfate solution and PEG-ELS), the sponsor conducted two multicenter phase 3 studies (BLI850-301 and BLI850-302). Each study included an approved active comparator, and each tested one of the two proposed regimens (split-dose or (b) (4) These are under review by the Clinical Reviewer(s) for this NDA. Phase 3 study design is briefly summarized below:

- BLI850-301: Randomized, single blind, parallel, active-controlled, multi-center, phase 3 safety and efficacy trial comparing same-day dose regimen of BLI850 to the same-day dose regimen of Halflytely. This was a single dose administration study in healthy patients indicated for colonoscopy (n =366).
- BLI850-302: Randomized, single blind, parallel, active-controlled, multi-center, phase 3 safety and efficacy trial comparing split-dose regimen of BLI850 to the split-dose regimen of Moviprep. This was a

single dose administration study in healthy patients indicated for colonoscopy (n =371).

No other new trials have been conducted in addition to these two phase 3 trials. However, relevant information from sponsor's other NDA applications including that of SUPREP have been referenced in order to support dose selection (Pharmacodynamics, PD) of the components, in this NDA. While the drug product is a combination of two approved osmotic agents, the sponsor has not specifically addressed the combination rule requirements in the NDA (e.g. phase 3 design doesn't allow demonstration of the need for the combination over each component alone).

The phase 1 PD studies are briefly summarized below:

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

Design: This was a single-center, open-label, non-randomized study of various laxatives and sulfate based formulations in normal healthy males and female volunteers at least 18 years of age (n = 27). Study was conducted in adherence to GCP. Subjects received one or more of approved bowel preparation/laxative products or new sulfate based formulations (with a minimum of one week wash-out when receiving more than one treatment) and their final stool was analyzed for percent solids.

After an overnight fasting, subjects were given a dose of laxative sufficient to produce diarrhea, and bowel movements and urine were collected for 24 hours. Blood samples were taken about 2 hours prior to ingestion of the dose and 2-4 hours after ingestion. Subjects were not allowed food and only water was allowed during study period. Stool and urine were analyzed for volume and electrolytes.

Experimental laxatives were as follows: Bisacodyl 20 mg, Senna 34.4 – 68.8 mg, Milk of Magnesia 123- 239 mmol, NuLytely 2L, NuLytely 4L [both containing PEG3350 with Electrolytes], HalfLytely [containing 20 mg bisacodyl with 2L NuLytely], and five different experimental sulfate formulations containing varying amounts of sodium, potassium and magnesium sulfates. Only one individual in this study received both components together i.e. oral sulfate solution, along with 2L PEG3350, hence data on concomitant use of the two osmotic laxatives on the PD endpoints evaluated is minimal.

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

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

Active ingredients in the total dose of each preparation are as follows:

BLI800 (approved as SUPREP):

Sodium sulfate 35.02 g
Potassium sulfate 6.26 g
Magnesium sulfate 3.2 g

EZ-Prep (approved):

Monobasic sodium phosphate 36 g
Dibasic sodium phosphate 13.5 g

NuLytely (approved, 4L):

Polyethylene glycol 3350 420 g
Sodium bicarbonate 5.72 g
Sodium chloride 11.2 g
Potassium chloride 1.48 g

It should be noted that the proposed 2-component Suclear contains ½ the oral sulfate dose of Suprep or BLI800, along with ½ the PEG3350-electrolyte dose of NuLytely 4L.

Study was conducted in 9 subjects. Patients were allowed to use multiple treatments if they underwent adequate washout period. In this study 5 patients received single treatment only while 4 others received 2 to 3 treatments. Average patient age was 23 years.

Timing of administration: All preparations were consumed in a split dose regimen; half of the dose was administered in the evening and the second half during the next morning, 12 h apart. The first half of the dose corresponds to 4 oz (125 ml) for BLI800, 45 ml for EZ-Prep and 2L for NuLytely. The second half of the dose corresponds to 4 oz for BLI800, 30 ml for EZ-Prep and 2L for NuLytely. BLI800 and EZ-Prep subjects were required to drink additional water to allow direct comparisons to NuLytely 4L.

Efficacy endpoints: Primary efficacy was assessed via quantitative measurement of stool weight. All stools were collected and weighed and subsequently analyzed

for electrolyte composition. Secondary efficacy outcomes include analysis of percentage of fecal solid content of the final diarrheal sample ("Scatocrit") collected during each preparation period [preparation periods are defined as Period 1: 7PM to 5 AM; Period 2: 5 AM to 12 PM].

Serum, stool and urine were also analyzed for electrolyte composition. Patient adverse events were also collected.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Phase 3 Clinical Trials: The primary efficacy endpoint was the proportion of patients with successful colon cleansing as assessed by the colonoscopists, who were not informed about the type of preparation received. Responders were patients whose colon preparations were graded excellent (no more than small bits of adherent feces/fluid) or good (small amounts of feces or fluid not interfering with the exam) by the colonoscopist. Colon cleansing response rates were compared between the drug and active comparator.

PD studies: In the two PD studies, the final stool sample after the test dose(s) was centrifuged and analyzed for percent solids. According to this method a 5 g sample from the final stool is centrifuged at 3000 rpm for 30 minutes. The supernatant is decanted and the remaining pellet weighed. The stool percent solid is then calculated as the weight of the pellet divided by 5 g:
% stool solid = (pellet weight/5g)*100;

This parameter, % stool solids in the final bowel movement, also dubbed by sponsor as 'scatocrit' in this NDA, along with total weight of stools (g) produced was used as PD measures.

The current limitation of these measures (% stool solids in the final bowel movement and total stool weight) is that their correlation to the clinical efficacy of colon cleansing preparations (i.e. colon cleansing response rates) is not known.

Safety assessment included analysis of stool electrolytes to determine electrolyte gains or losses during the cleansing process. Blood samples were analyzed for electrolytes, albumin and hematocrit.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Active moieties (sulfates, PEG3350) in biological matrices were determined using validated analytical methods previously deemed acceptable by the agency under NDA 22372. No new PK studies/assays were conducted for this proposed NDA.

The concentrations of sulfates were determined using validated analytical methodologies during study BLI800-202. The assay and ensuing PK results were deemed acceptable by the agency during the review of NDA 22372 for SUPREP [see Clinical Pharmacology review for NDA 22372, signed 04/10/2012].

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *efficacy*? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Dedicated dose-ranging phase 2 studies were not conducted in support of this NDA. However, data from two earlier PD studies were presented in the NDA in order to address the issue of dose-selection for the active components:

PD study 005-082: This study explored various over-the-counter laxative products, approved bowel cleansing formulations as well as various experimental sulfate formulations on their effects on two investigational PD endpoints, namely % stool solids and total stool weight. As previously mentioned, these endpoints are not widely accepted as their correlation to the overall clinical efficacy in colon cleansing is not known.

Efficacy variables: Efficacy was determined by comparison of the percent solids of the final BM (resulting from a laxative dose) to the percent solids from the final BM of the FDA approved products (NULYTELY 4L and HalfLytely).

Study results:

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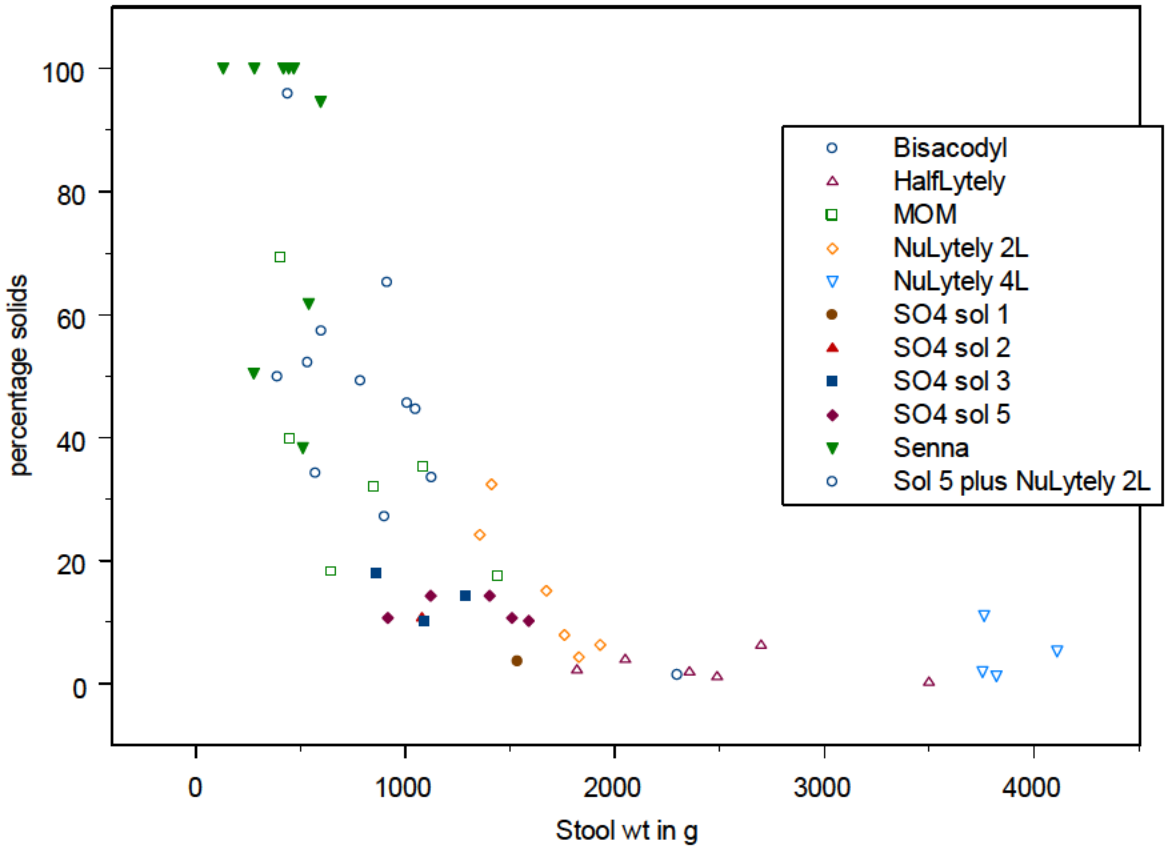
SO4 solution 3 (n = 3)	1082 (215)	14.1 (4)
*SO4 solution 4 [# 5 with 2L NuLytely] (n = 1)***	*2298*	*1.4*
SO4 solution 5 (n = 5)*	1308 (281)	12 (2.1)
*Individual components of proposed product; ** proposed combination; # FDA approved drug products		

The composition of the various sulfate solutions is briefly summarized below:

mMole	Solution 1	Solution 2	Solution 3	Solution 4 (dosed with NuLytely2L)	Solution 5

Na2SO4	(b) (4)
MgSO4	
K2SO4	
Volume ml	

A scatter plot of individual subject data is shown below suggesting a trend for decreasing % of stool solids with increasing stool weight (g):



In this study, the stool weight (g) for NuLytely 2L and the sulfate solution #5 were 1659 g and 1308 g, respectively. The corresponding % of solids in the final bowel movements for these two groups was 15 % and 12 %, respectively. These two formulations (with some modifications to the final sulfate formulation) constitute the ingredients of the proposed two-component formulation.

Compared to these two individual components, the two FDA approved formulations for colon cleansing, namely NuLytely 4L and HalfLytely provided greater total stool weight (3861 g and 2403 g) and lower % solids in the final bowel movement (4.8 % and 2.6 %).

This may suggest that individually, each of these components were less effective than the FDA approved products with regard to the PD endpoints assessed.

A single patient in this study received a dose of the oral sulfate solution #5 along with 2L NuLytely, i.e. a combination similar to the proposed 2-component formulation. Although the data in this patient is suggestive of better outcomes as demonstrated by lower % solids (1.4 %) and higher stool weight (2298 g) compared to the individual components administered separately, due to a sample size of n=1 it is difficult to conclude additive effects of the combination on the PD endpoints.

In this study, the individual components of the approved colon cleansing product HalfLytely, i.e. bisacodyl 20 mg and NuLytely (PEG-ELS) 2L resulted in lower total stool weights (757 g and 1657 g, respectively) and higher % stool solids (50 % and 15 %, respectively), compared to the combination (approved) HalfLytely formulation (2400 g total weight and 2.6% stool solids respectively). Noteworthy is that the sum total of stool weights (g) generated with the individual components of HalfLytely roughly add up to the total stool weight noted with the final approved formulation. Data thus adds support to the possibility that BLI850 that essentially replaces the bisacodyl component of HalfLytely with an oral sulfate solution #5 that had produced total stool weight and % stool solids (1300 g and 12 %) comparable to that of NuLYTELY 2L (1657 g and 15 %) may result in a final formulation that is comparable to the approved HalfLYTELY.

Reviewer's comments:
Results of this PD study in totality suggest that the individual components [PEG3350 (NuLytely) 2L or oral sulfate solution #5] when administered alone did not generate the total stool weight and didn't reduce % stool solids in the final BM to an extent that were attained with the approved colon cleansing formulations.

Nevertheless, study has its limitations as currently there is no established correlation between the PD endpoints used (% stool solids and total stool weight in g) and the clinical efficacy of colon cleansing preparations.

PD study 006-181: Efficacy endpoints: Primary efficacy was assessed via quantitative measurement of stool weight. All stools were collected and weighed and subsequently analyzed for electrolyte composition. Secondary efficacy outcomes include analysis of percentage of fecal solid content of the final diarrheal sample ("Scatocrit") collected during each preparation period [preparation periods are defined as Period 1: 7PM to 5 AM; Period 2: 5 AM to 12 PM]. Serum, stool and urine were also analyzed for electrolyte composition. Patient adverse events were also collected.

Efficacy results:

Primary efficacy: Stool output (g)

Mean stool output (g) is reported for the total dose administered. Since this dose provided twice the sulfate or PEG3350-ELS doses as those proposed in the proposed 2-component drug product, total stool output data is not relevant for the intended preparation:

Mean (SD)	BLI800 (n = 5)	EZ-Prep (n = 5)	NuLytely (n = 5)
Input (water + Prep)	3960 (554)	3035	4096 (125)
Total output	2911 (492)	1986 (294)	3021 (252)
Water output	2801 (475)	1891 (281)	2564 (253)
Retained water	+1159 (314)	+1144 (281)	+1532 (218)

The percentage of fecal solids was reported for the end of each preparation period (i.e. after half the doses of SUPREP (sulfates) and NuLytely (PEG-ELS), as those proposed in the 2-component Suclear were administered) and therefore is relevant to the current NDA preparation. However, data for the combination is still lacking.

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

Review comments: *Data suggests that % stool solids was higher for all three groups after the first period, while it decreased considerably after the second dose in the second period, thus suggestive of more complete cleansing with the second half of the dose. Period 1 data suggests that the half-doses of oral sulfate solution in BLI800 and PEG3350 in NuLytely as those proposed as individual components of the proposed product (BLI850), may be inadequate within the context of the PD endpoints assessed. In this study the PD findings for half-doses of oral sulfate solution and NuLYTELY were comparable. It is likely that combination of these two components may provide additional benefit with regard to % solids in final bowel movements. However, the combination regimen was not evaluated in this study. In addition, a correlation of % solids in stools with the cleansing efficacy of bowel preparations is not known.*

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *safety*? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

PD study 005-082: Safety assessments included measurement of serum, urine and stool electrolytes to determine electrolyte gains or losses during the cleansing process.

Serum electrolytes: No effect on any of the analytes measured (BUN, creatinine, magnesium, protein, potassium and sodium) were noted in the data for sulfate solution #5. A reduction in osmolality from 295 mOsm at baseline to 288 at post-treatment was noted but clinical implication is not known. A decrease in serum osmolality from 296 to 287 was also noted in the individual who received both NuLytely 2L and SO4 solution 5.

Stool electrolytes:

	Na^+	K^+	Mg^{+2}	Cl^-	$HCO3^-$
Bisacodyl 20 mg (n=11)	-72.8 (33)	-52.2 (21.8)		-43.7 (17.5)	-16.6 (10.4)
NuLytely 2L (n = 6)*	+11.6 (27)	-36 (19.1)		+45.9 (22.8)	+3.4 (25.7)
NuLytely 4L (n = 1)[#]	-55.5	-51.6		+14.6	-2.1
HalfLytely (n = 6)[#]	-79 (56.9)	-40.1 (22)		-51.9 (47.3)	-16.9 (12.3)

SO4 solution 3 (n = 3)	+101 (37.4)	+0.7 (11.9)	-25.2 (26.5)	-22.2 (10.3)	-14.2 (6.5)
SO4 solution 5 with 2L NuLytely (n = 1)**	+88.6	+16.4	-19.4	-29.1	-7.4
SO4 solution 5(n = 5)*	+27.8 (67)	-0.1 (11.1)	-18.1 (10.4)	-25.3 (11.5)	-21.1 (9.9)
*Individual components of proposed product; ** proposed combination; # FDA approved drug products					
A negative change in electrolytes suggests loss since the output in stools is greater than the input via ingested treatments.					

Stool electrolyte data suggests that NuLytely 2L demonstrated net loss for K alone. SO4 solution 5 demonstrated net losses in Mg, Cl and HCO3. The Mg content in the final sulfate formulation is higher than the SO4 solution 5 used in this study to compensate for potential Mg losses. In one individual who received both components, there was no net loss in K noted. Net losses were however noted for Mg, Cl and HCO3. The approved preparation HalfLytely demonstrated net losses of Na, K, Cl and HCO3 in this study, while NuLytely 4L demonstrated net loss of Na and K.

PD study 006-181: Study included serum, urine and stool analyses of various analytes. Changes (loss or gain) noted in stool or urine samples were in general not reflected as changes in serum analytes from baseline, with the exception of serum sulfate.

Serum sulfates: Measurements were taken at baseline, at 10 h after the first half of the dose (prior to second dose) and 3 h after the second half of the dose. Post-treatment sulfate levels were greater for BLI800 i.e. SUPREP (0.61 at baseline vs. 1.94 mg/L at 3 h after the second dose). With the exception of sulfate increases in serum at post-treatment, no other electrolyte losses/gains that were noted in the stool analyses were reflected as serum changes. One can infer the sulfate changes with the proposed combination using the data following the first dose of BLI800 in this study (at 10 h post-first dose; from 0.6 to 1.2 mg/L).

Mean Serum Analytes (SD)

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

* t test vs BLI800 p ≤0.05
1 = values from 1 study subject; 2 = values from 2 study subjects; 3 = values from 4 study subjects
4 = not established

Stool electrolytes: Summary of stool net electrolyte changes in mEq are shown for the total dose (calculated as electrolyte input from ingested preparations minus electrolyte output in stools):

+Gain/-Loss (SD)	BLI800 (sulfates; n = 5)	EZ-Prep (n = 5)	NuLytely (PEG-ELS; n = 5)
Na	-5.7 (123.9)	+58.1 (41.2)	+106.9 (48.5)
K	+8.1 (15.1)	-46.1 (12.6)	-7.2 (6.0)
Cl	-50.0 (39.1)	-14.4 (13.1)	+129.2 (31.4)
HCO3	-48.7 (25.4)	-11.3 (8.0)	+6.1 (16.4)
P	-0.27 (0.12)	+3.2 (1.4)	-0.15 (0.05)
Ca	-21.7 (7.8)	-5.2 (1.4)	-6.2 (2.0)

Mg	-13.0 (7.3)	-17.4 (7.9)	-10.7 (5.3)
SO4	+88.2 (28.6)	-3.6 (1.8)	-1.3 (0.7)

Stool net electrolyte change data suggests that when bowel cleansing treatments were administered entirely as PEG3350-ELS formulation (NuLytely), there was a marked retention of Na, and Cl. These two electrolytes on the other hand demonstrated net losses with the oral sulfate solution group (BLI800 or SUPREP). The oral sulfate group demonstrated some gain (retention) of K, while the NuLytely group demonstrated a loss of similar magnitude. HCO3 losses were noted with BLI800 which has no added HCO3, while small net gains were noted for NuLytely in this regard. SO4 demonstrated net gain (retention) following oral sulfate solutions administered as BLI800. Mg losses were noted and were similar for both BLI800 and NuLYTELY. Calcium loss was higher with BLI800 compared to NuLYTELY. Note however, that such changes were not reflected in serum data.

Electrolyte output in urine:

The gains of Na, and Cl based on stool data for the NuLYTELY group were also reflected as net increases in urinary output of these electrolytes.

The loss of Cl and HCO3 based on stool data for the BLI800 group were also reflected as net decreases in urinary output of these electrolytes.

The gain of SO4 based on stool data for the BLI800 group was also reflected as net increase in urinary output of this electrolyte.

Mean Urine Output Results
Pre and Post Treatment

Total Output (SD)		**BLI800**	**EZ-Prep**	**NuLYTELY**
N		5	5	5
Volume (ml)	Pre	1730 (835)	2161 (1027)	1502 (868)
	Post	2006 (400)	1678 (176)	1624 (356)
Na (mEq)	Pre	127.6 (121.6)	155.7 (25.0)	75.6 (18.1)
	Post	132.6 (73.9)	103.5 (38.7)	100.3 (67.2)
K (mEq)	Pre	57.7 (40.5)	58.1 (18.9)	50.2 (19.7)
	Post	45.7 (18.1)	38.3 (14.0)	27.6 (8.7)
Cl (mEq)	Pre	126.5 (111.7)	145.0 (29.5)	76.9 (25.8)
	Post	89.3 (65.5)	46.7 (12.4)	83.3 (59.9)
Bicarbonate (mEq)	Pre	6.1 (6.3)	8.8 (6.2)	3.6 (4.6)
	Post	0.7 (0.8)	0.1 (0.2)	2.6 (3.4)
PO_4 (g)	Pre	0.83 (0.49)	0.67 (0.10)	0.49 (0.16)
	Post	0.74 (0.32)	2.3 (0.67)	0.50 (0.08)
Ca (mEq)	Pre	4.9 (3.3)	5.6 (1.9)	5.3 (6.5)
	Post	5.2 (1.2)	1.8 (0.4)	4.8 (2.4)
Mg (mEq)	Pre	5.6 (3.2)	5.3 (2.0)	5.1 (4.9)
	Post	7.4 (2.3)	3.0 (1.4)	4.5 (1.0)
SO_4 (mEq)	Pre	31.0 (16.3)	24.8 (7.9)	23.0 (18.7)
	Post	97.6 (8.5)	20.2 (4.0)	16.4 (4.0)

2.2.4.3 Does this drug prolong the QT or QTc interval?

QT prolongation potential of BLI850 was not formally evaluated. Individual components of the formulation (i.e. oral sulfates and PEG3350 with electrolytes) are approved at similar and higher doses in formulations such as SUPREP, NuLytely, GoLytely and HalfLytely. No thorough QT studies were required for those approved formulations.

The proposed label notes the following under Warnings:

Cardiac Arrhythmias
"There have been rare reports of serious arrhythmias associated with the use of (b) (4) osmotic laxative products for bowel preparation. (b) (4) prescribing TRADENAME for patients at increased risk of arrhythmias (e.g., patients with a history of prolonged QT, (b) (4) arrhythmias, recent myocardial infarction, unstable angina, congestive heart failure, or cardiomyopathy). Pre-dose and post-colonoscopy ECGs (b) (4) considered in patients at increased risk of serious arrhythmias".

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Sponsor has combined ½ doses of two approved colon cleansing formulations (i.e. SUPREP and NULYTELY 4L) in this NDA and has conducted phase 3 clinical trials to evaluate the efficacy of the proposed regimens against active comparators. Thus safety and efficacy of the combination could potentially be addressed by these phase 3 trials. However, NDA lacks data to show that each ½ dose in itself would've been insufficient with respect to providing adequate cleansing (i.e. requirements of the 'combination rule'). Dose-ranging information was also not available from the approved NDAs for the single moiety preparations to help address this question.

The PD data provided in the Clinical Pharmacology database (i.e. % stool solids or scatocrit) while supportive of the premise that ½ doses of each component do not provide adequate effects, it nevertheless is limited in its scope to adequately address the combination rationale as the relevance of these PD endpoints to the clinical efficacy in colon cleansing is currently not understood. In addition, even for the PD endpoints evaluated, there was minimal information (n = 1) of the same for the combination. Since the scope of the PD endpoints is limited with respect to clinical relevance, there is currently no plan to request additional clinical pharmacology (PD) information on the combination to justify NDA proposal.

The Division had issued a formal information request to the sponsor regarding combination rule requirements. The sponsor has acknowledged in a recent teleconference that studies to correlate % stool solids (PD) to cleansing efficacy within the same patients were not conducted per se. However, available information for successful and unsuccessful bowel cleansing products as an attempt to bridge the PD to efficacy was submitted.

Information provided in general suggests a trend for better clinical efficacy outcomes with a formulation that provides lower scatocrit values as noted for various formulations that had both PD and efficacy information (e.g. bisacodyl 20 mg, PEG-ELS 2L, NuLYTELY 4L, HalfLytely, SUPREP etc). This is generally supported for the PEG-ELS component of BLI850 as PD and efficacy were available for both half-dose and full dose of this component. While PD and efficacy (from different studies) data are available for Suprep (containing twice the oral sulfate dose as BLI850), only PD information but not efficacy was available for the ½ dose of oral sulfate as proposed. Nevertheless, in totality the information available is suggestive of a trend that that formulations/doses providing lower scatocrit (PD) may result in higher colon cleansing efficacy. The correlation as provided however, is not a rigorous attempt to validate this relationship (for e.g. within the same patients). Please see medical officer review for further information in this regard. *Please also see appendix for additional details and review of the combination justification provided by sponsor.*

2.2.5 What are the PK characteristics of the drug components and what are the consequences of organ impairment on the PK?

PK of oral sulfates: Study BLI800-202 was originally conducted for the approval of SUPREP. This study evaluated the pharmacokinetics after two 6 oz doses of the oral sulfate solution. Study was previously reviewed and deemed acceptable under NDA 22372.
Since the sulfate PK data following the first dose of the oral sulfate solution in this study is applicable to the dose of OSS proposed as part 1 of this 2-component formulation, data will be presented briefly:

PK summary for oral sulfate solution (component 1 of BLI850): Following oral administration of 6 oz of oral sulfate salt solution, sulfate levels rose above the basal concentrations within 1 hour of the first dose. Concentrations then peaked after the first dose at a median Tmax of 4 hours in healthy volunteers; Concentrations after the first dose did not return to baseline prior to the second dose of oral sulfates at 12 h. At the end of dosing, sulfate concentrations returned to endogenous levels within 3 days post-dose. The half-life of elimination was ~ 8.5 hours in healthy volunteers. Based on urinary excretion data, the fraction of total dose absorbed appeared to be approximately 20 % following oral administration of oral sulfate salts.

This was an open-label, safety and PK study in mild to moderate hepatic impairment (n = 5 with Child-Pugh A; n = 1 with CP-B), moderate renal disease (n=6; Clcr: 30 - 50 mL/min) or healthy volunteers (n =6).

Volunteers received their first ½ dose of the oral sulfates in the morning and the second ½ dose 12 hours later. The total oral dose of sulfate was 29.7 g. Each dose had 6 oz of the oral sulfate solution diluted with 16 oz at the time of consumption

over a 15 minute period. Two additional 16-ounce glasses of water was consumed over the next 1-3 hours. No food was allowed from 8 PM on day -1 until 8 PM on day 1 when patients were allowed a standard dinner.

Composition of each ½ dose was as follows: Sodium sulfate 17.51 g, MgSO4 1.6 g, Potassium Sulfate 3.13, Sodium Benzoate, flavoring agents, artificial sweetener. All patients received BLI800 lot # RD841.

Blood samples were collected relative to dose 1 at pre-dose, at 1, 2, 4, 8, 10 hours thereafter and then relative to dose 2 at pre-dose, and at 1, 2, 4, 8, 12 and 18 hours post dose. Additional samples were collected before 12 noon on days 3 and 6. Serum sulfate PK was assessed after the first half dose. A validated ion chromatography method with a LLOQ of 10 ppm (104 umol/L) was used.

PK was assessed using non-compartmental PK analysis. Serum PK was calculated from baseline adjusted serum concentrations. Urinary sulfate was assessed using HPLC from samples collected for 30 hours after dose 1. Differences between PK parameters between healthy volunteers with each of the MRD and M/MHD groups were tested using ANOVA, and presented along with the corresponding geometric mean ratios with 90 % CIs. Urine sulfate parameters for cum.Ae, cum. %dose were tested using a Wilcoxon test statistic for differences between the healthy volunteers, with each of the organ impairment groups. Safety assessments include adverse events, 12 lead ECGs, vital signs, hematology, blood chemistry and urinalysis.

Results: Note that the sulfate PK presented here are for both doses of the oral sulfate solution (OSS), administered 12 h apart in this study. Thus PK exposure estimates for a single dose of OSS administered as part of the proposed 2- component drug product are expected to be lower and the decline to pre-dose concentrations is likely to be earlier than noted in this study. For e.g. AUCτ presented here is for the 24 h duration that includes a second dose at 12 h.

Serum sulfate PK [mean (SD)]: Corrected for pre-dose sulfate levels			
PK parameter	**Healthy (n = 6)**	**Mild/Mod. HI (n = 5/1)**	**Moderate RI (n = 6)**
Cmax (µmol/L)	499 (165)	560 (152)	717 (270)
AUC0-tau (µmol h/L)	8029 (3424)	10751 (2878)	12332 (4193)
Tmax (h)	16.8 (8.16)	14.2 (5)	17.5 (2.95)
T1/2 (h)	8.51 (4.57)	5.58 (2.31)	10.16 (9.32)

Baseline-corrected serum sulfate PK suggests that sulfate concentrations increased over baseline following the administration of oral sulfate solution, and this increase relative to baseline was highest in the renal impairment (RI) group compared to the normal volunteers. On average, Cmax and AUC24 in the moderate RI subgroup were 44 % and 54 % higher compared to normal volunteers (after two OSS doses administered 12 h apart). Based on individual profiles in serum, concentrations increased within 1 hour

post-dose 1. Concentrations did not decline to pre-dose levels prior to the second dose at 12 h.

Pre-dose (baseline) serum sulfate levels were comparable in the normal healthy volunteers and volunteers with mostly mild hepatic impairment. Baseline sulfate levels were higher in the moderate renal impairment subgroup. Sulfate concentrations were higher than baseline by 30 h post-dose 1 (which is 18 h post-dose 2) but returned to baseline for all three groups by day 3 post-dose 1. Accumulation of serum sulfate is noted with the second dose administered at 12 h.

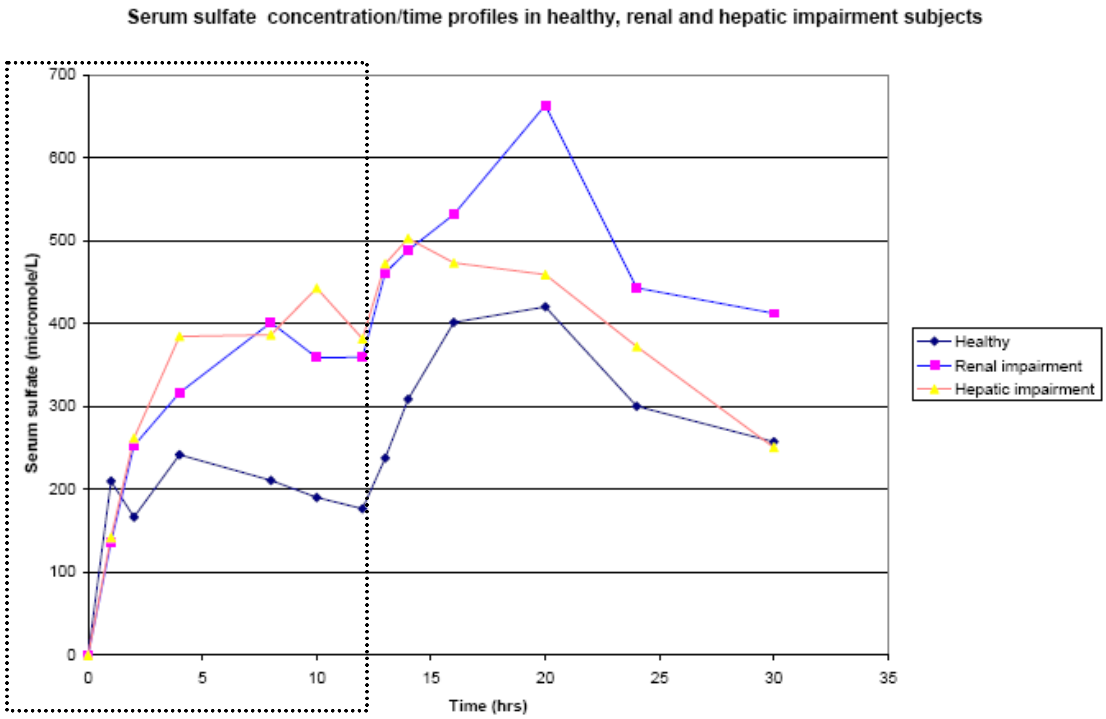
Study BLI800-202	**Normal**	**Mild/Moderate HI**	**Moderate RI**
Pre-dose 1 serum sulfate (µmol/L)	335 (115) *[range: 141 – 467]*	407 (55) *[range: 329 – 465]*	607 (192) *[range: 393 – 847]*
Pre-dose 2 sulfate (12 h; µmol/L)	*512 (139)* *[range: 325 – 637]*	*789 (146)* *[range: 620 -968]*	*966 (244)* *[range: 733 – 1379]*
30 h post-dose 1 sulfate (µmol/L)	592 (148) [range: 398 – 791]	696 (101) [range: 586 -838]	1019 (260) [range: 694 – 1431]
Day 3 post-dose (µmol/L)	366 (103) [range: 181 – 475]	392 (52) [range: 335 – 488]	618 (138) [range: 514-887]
Day 6 post-dose (µmol/L)	350 (90) [range: 214 – 462]	406 (51) [range: 354 – 479]	575 (101) [range: 503- 761]

With respect to the current NDA (203595), the information following the second dose of oral sulfate solution is not relevant. It is therefore likely that with just a single dose of oral sulfate solution as part of the two-component BLI850, serum sulfate levels may return to baseline earlier than noted in this study where two doses were administered 12 h apart.

Urinary excretion data assumes that sulfate excreted is from the oral dose ingested and therefore may overestimate % dose excreted as endogenous excretion (basal) has not been accounted for. Urinary excretion noted in this study also includes the contribution from the second dose and therefore overestimates the recovery after one dose of oral sulfate solution as proposed for the new 2-component formulation. Urinary excretion of sulfates over 30 h post-dose 1 was lowest for the renal impairment subgroup, but appears comparable for the hepatic impairment group (who had normal baseline renal function) compared to healthy volunteers.

Urinary sulfate excretion parameters [mean (SD)]			
Parameter	Healthy (n = 6)	Mild/Mod. HI (n = 5/1)	Moderate RI (n = 6)
Cum. Ae_{0-30} (mg)	6037 (3739)	6499 (1389)	5101 (1564)
Cum % Dose (0-30 h)	20.35 (12.59)	21.9 (4.69)	17.18 (5.27)
Excretion Rate (mg/h)	201.27 (124.64)	216.63 (46.3)	170.05 (52.18)
Cum. % Dose assumes all the urinary sulfate excretion is from the dose of BLI800 and doesn't take into account any basal sulfate excretion in urine during the 30 h time period post-dose			

Serum concentrations of sulfate over 12 h (first dose only) are highlighted below:



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

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

Conclusions: *Serum sulfate PK has been evaluated in this study using two doses of oral sulfate salts administered 12 h apart. The information submitted has been previously found to be acceptable by the agency when reviewed as part of NDA 22372.*

Pharmacokinetics following a single dose of OSS have been assessed using data up to 12 h following dose 1. In general, Cmax and AUC_{12h} were somewhat higher for both mild HI and moderate RI compared to healthy volunteers. Accumulation of sulfate anion noted particularly in the organ impairment populations after the second dose of oral sulfate at 12 h with SUPREP may not be a concern in the context of the proposed formulation since it only provides one dose of sulfate.

The clinical implication of this increase in systemic exposure of sulfate anion is not known. While drug clearance is somewhat slower than normal in organ dysfunction, considering that the drug is for single use prior to colonoscopic procedure and that the dose of sulfates proposed is half that in SUPREP thus ruling out accumulation potential, it appears reasonable not to require dose adjustments in specific subpopulations including renal impairment. Information should nevertheless be communicated in the labeling.

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

Di Piro et al, 1986: Absorption of polyethylene glycol after administration of a PEG-electrolyte lavage solution.
Plasma and urine samples were collected after administration of 4 L of PEG-ELS containing 240 g of PEG3350 to six healthy volunteers. PEG was not detected in any of the plasma samples and therefore it was not possible to calculate plasma PEG PK or renal clearance. The minimum detectable concentration in plasma was 10 ug/mL. PEG was detected in most urine samples after two hours; concentrations ranged from 21.3 to 1179 ug/mL. The mean total amount of PEG excreted in urine in 12 hours, Ae (12 hr), was 88.3 (20.9) mg i.e. ~ 0.04 % of total dose of PEG administered; the urinary excretion range was 54.4 to 110 mg in 12 hours post-dose. Due to limited urinary sampling (12 h), total amount excreted in urine and thus estimated % dose absorbed could be underestimated in this study.

Brady, 1986: Urinary excretion of polyethylene glycol 3350 and sulfate after gut lavage with a polyethylene glycol electrolyte lavage solution. Authors measured the urinary excretion of both polyethylene glycol and sulfate in normal subjects and inflammatory bowel patients. Mean percent polyethylene glycol load recovered in urine was minimal and similar for normal (0.06%) and inflammatory bowel (0.09%) subjects. Urinary sulfate excretion after lavage was also similar for both groups and was not different from baseline.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?
and
2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Please also refer to PK information presented under 2.2.5.

Renal impairment: Based on information available for PK of sulfate anion following administration of oral sulfate solution in study BLI800-202, it appears that renal impairment has a potential to reduce the sulfate clearance. In the study conducted for SUPREP, the exposure (Cmax and AUC) of the sulfate anion was increased by 44 % and 54 % in presence of moderate renal impairment when two doses of oral sulfate solution were consumed within 24 hours (i.e. twice the sulfate dose proposed in BLI850). The clinical significance of potential increase in the systemic exposure of sulfates due to reduced clearance in renal impairment is not understood, especially considering the single use nature of the proposed

formulation prior to colonoscopy. Furthermore, considering that only half dose of sulfates as that in SUPREP are proposed for administration in BLI850, the net increase in systemic sulfate exposure in presence of renal impairment might be even lower than that noted in study BLI800-202. However, information available in this regard should be communicated in the labeling.

Elderly: Due to a general decline in renal function with age, the observed PK effects of renal impairment may have an implication in the elderly population.

Of the 362 patients who received TRADENAME in clinical trials, 90 (25%) were 65 years of age or older, and 29 (8%) were 75 years of age or older. For the general population (unstratified by age), the primary efficacy responder rate (% successful preparations) for BLI850 for two trials combined was 98 % and was similar to the active control group. When considering only the data for the elderly, this success rate for BLI850 (combined) was 88.9 %, compared to the 85.7 % rate for the active comparators.

In phase 3 clinical trial 301, elderly patients reported a higher intensity of nausea and overall discomfort compared to active control (HalfLytely). The symptom score itself fell within none to mild. Sponsor attributes this to perhaps a larger preparation volume for BLI850 compared to HalfLytely.

Caution should be recommended while dosing in elderly. However, a specific dose adjustment is not necessary based on age as elderly patients constituted 25 % of patient population in the two clinical trials for TRADENAME and have not identified significant differences in safety and efficacy.

Gender: There were approximately similar number of males and females stratified to the BLI850 group across the two phase 3 trials. No differences in efficacy were noted for the primary endpoint between genders (~ 92.3 % vs. 91.1. % success rates for females and males respectively across both studies). No dosage adjustment is necessary based on gender.

Race: Majority of patients in clinical trials for BLI850 were Caucasian, with approximately 13 % of enrolled patients belonging to other races. For BLI850, the % successful preparations were 92.1 % and 88.6 %, respectively for Caucasians, and non-caucasians for both studies combined. No dosage adjustment is necessary based on race.

Pediatric: Safety and effectiveness in pediatric patients have not been established.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

Drug Interactions: No specific drug-drug interaction studies have been conducted for the proposed drug product. The proposed labeling notes the following under section 7.0:

(b) (4)

Potential for Altered Drug Absorption: Oral medication administered within one hour of the start of each TRADENAME dose may be flushed from the gastrointestinal tract, and the medication may not be absorbed properly.

Additionally, as the proposed drug product is a combination regimen of two approved drugs (namely oral sulfate solution of sodium, potassium, magnesium and PEG3350 with (b) (4) solution), the following information was submitted by the sponsor regarding their interaction potential:

- The 6 oz sulfate solution containing about 22 g of sulfate is diluted with 16 oz water and ingested (diarrhea usually commences within 2 hours). After 2 to 12 hours (depending on whether (b) (4) or split-dose regimens), the 2 L of PEG3350-ELS are consumed. Thus the sulfate solution and PEG solution are not ingested simultaneously.
- Both PEG3350 and sulfate are chemically and pharmacologically inert, exerting bowel-cleansing effects via passive osmotic, hydromechanical properties.
- Sulfate and PEG3350 have been safely administered together for bowel preparation as the product GoLYTELY and its generic equivalents since 1983. This product contains 236 g PEG3350 and (b) (4) sodium sulfate with other electrolytes. No evidence of interaction has been noted between these ingredients.
- Based on their lack of chemical reactivity and the fact that they are administered at separate times, as well as long history of safe co-use, no interactions between PEG3350 and the sulfate containing components of proposed product are expected or have been observed, per sponsor.

Rationale as provided by sponsor addresses the absence of DDI potential between the formulation components and no further action is needed in this regard.

Additionally, there were 107 patients in the two phase 3 studies taking narrow therapeutic index drugs. Comparison of adverse events for these NTI patients per sponsor revealed no differences between BLI850 and the control preparations.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

There are no unresolved issues related to dose/dosing regimen from a Clinical Pharmacology perspective. The efficacy and safety of the proposed combination BLI850 has been evaluated in two phase 3 clinical trials. A factorial-design study evaluating each active moiety against the combination has not been part of this drug development program and may not be ethical. Clinical review discipline is looking into whether the sponsor has adequately addressed the combination.

2.5 General Biopharmaceutics

2.5.2 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The effect of food on bioavailability of the drug has not been evaluated. The proposed product is intended for local action in the gut for colonic cleansing prior to a scheduled colonoscopy. The general instructions are to avoid consumption of solid food or milk (clear liquids only) during dosing.

2.6 Analytical Section

No new studies were conducted in support of this NDA. PK information generated from previously reviewed NDA has been summarized and therefore analytical methodologies that were previously deemed acceptable by the agency during those NDA reviews were not reviewed again. Please refer to Clinical Pharmacology review for NDA 22372 for further details of the analytical methodology employed.

3 Detailed Labeling Recommendations

Reviewer recommendations are shown in bold font for additions and strikethrough for deletions; note to sponsor is shown in blue font.

7.1 Drugs That May Increase Risks Due to Fluid and Electrolyte Abnormalities

(b) (4) **(note to sponsor: include examples of these medications),** (b) (4) increase the risk for fluid and electrolyte disturbances or may increase the risk of (b) (4) seizure, arrhythmias, and prolonged QT in the setting of

fluid and electrolyte abnormalities. Consider additional patient evaluations as appropriate [see Warnings and Precautions (5)] in patients taking these concomitant medications.

8.5 Geriatric Use

Of the 362 patients who received TRADENAME in clinical trials, 90 (25%) were 65 years of age or older, and 29 (8%) were 75 years of age or older. No overall differences in safety or effectiveness (b) (4) were observed between (b) (4) and younger (b) (4) **However, due to a potential for increased sensitivity to most medications in elderly patients and due to a general decline in renal function with age, caution is recommended when using TRADENAME in patients above 65 years of age.**

8.6 Renal Impairment

Safety of TRADENAME in presence of renal impairment has not been adequately evaluated. Due to increased risk of electrolyte abnormalities in this population and a potential for reduced clearance of active drugs in this setting, caution is recommended when using TRADENAME in patients with renal impairment *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3)].*

12.3 Pharmacokinetics

(b) (4) **Oral sulfates: Following oral administration of oral sulfate solution, approximately 20 % of dose undergoes systemic absorption, with the remainder of the dose excreted in feces. Renal elimination appears to be the predominant route of clearance for absorbed sulfate.** After administration of TRADENAME (only the 6 oz bottle of sulfate salts) to six healthy volunteers, the time at which serum sulfate reached its highest point (Tmax) was approximately **4 hours after the first dose of sulfates.** (b) (4)-Serum sulfate levels declined with a half-life of 8.5 hours. [Note to BLI: PK information for the first dose of sulfates should be presented as feasible since the second dose at 12 h in study BLI800-202 is not relevant to this NDA]

PEG3350: The pharmacokinetics of PEG3350 following TRADENAME were not assessed.- (b) (4) **Available** pharmacokinetic **information for** (b) (4)- (b) (4) PEG 3350 (b) (4) **suggests** (b) (4) that it is poorly absorbed, primarily excreted in feces, and, to the extent it is absorbed it is eliminated in urine.

Pharmacokinetic Studies in Patients with Hepatic Impairment or Renal Impairment:

The disposition of sulfate after ingestion of two 6oz bottles of the TRADENAME sulfate solution was studied in patients (N=6) with mild-moderate hepatic impairment [Child-Pugh grades A **(n = 5)** and B **(n =1)**] and in patients (N=6) with moderate renal impairment (creatinine clearance of 30 to 49 mL/min). **Following administration of two doses of sulfates 12 h apart,** the renal impairment group had the highest serum

sulfate [redacted], followed by the hepatic impairment group, and then by healthy subjects. [redacted] Renal impairment resulted in [redacted] higher mean [redacted] than healthy subjects. The mean sulfate levels of all three groups returned to their respective baseline levels by Day 6 after dose initiation. Urinary excretion of sulfate over 30 hours, [redacted] was similar between hepatic patients and normal volunteers, but was approximately 16% lower in moderate renal impairment patients than in healthy volunteers.

PK of PEG3350 in organ impairment patients at the recommended dose was not assessed.

4 Appendices

4.1 Individual Study Reviews

Combination requirement (sponsor response and justification) review:

An information request was sent to the sponsor on August 3, 2012 with the following:

In order to evaluate whether the Combination Rule (21 CFR 300.50) is adequately addressed within the NDA, provide the following:

1. **Demonstration that the combination product (i.e., BLI850) would be superior to each component alone (i.e., 6 ounces of SuPrep or 2 liters of Nulytely)**

2. **Provide clinically relevant data and/or literature to demonstrate that each component of BLI850 by itself will result in inadequate bowel cleansing prep**

   For each of the above, provide the data that support the use of "scatocrit" as a clinically relevant measure to predict bowel cleaning efficacy.

In this regard, sponsor submitted response to the agency highlighting the following as evidence to demonstrate (using available information) that individual components of BLI850 would be inferior to the combination in providing adequate bowel preparation:

Item 1: The table below shows that the FDA approved bowel preparations (Fleet Phospho Soda, HalfLytely and NuLYTELY) resulted in stool output volumes ranging from about 2400g to 3800g and achieved a percent stool solids of approximately 3% or less. In addition, the table shows the stool volume and scatocrit results for two known failing preparations (20mg bisacodyl, and 2L NuLYTELY), which resulted in total stool volumes much less than 2400ml and scatocrits greatly in excess of 3%. Table also shows the stool volume and scatocrit results for a 22g sulfate formulation (Solution 5: equal to one half the SUPREP cleansing dose) and for a complete BLI850 formulation (Solution 4: containing both the 22 gram sulfate dose and the 2L NuLYTELY dose).

Baylor Study 005-082
Mean Stool Volume Output (g) and Percent Solids
Selected Laxatives[1]

	Bisacodyl 20mg	**2L NuLYTELY**	**4L NuLYTELY**	**HalfLytely**	**Fleet Prep**	**BLI850** (Soln 4)	**Soln 5** (22g SO_4)
n	11	6	4	7	5	1	5
Output (g) (SD)	757 (260)	1659 (231)	3861 (168)	2403 (577)	2403 (269)	2298	1308 (281)
% Solids (SD)	50.4 (18.7)	15.0 (11.2)	2.8[2] (2.1)	2.6 (2.2)	NA	1.4	12.0 (2.1)

[1]All laxatives and solutions from Baylor 005-022 study except Fleet Prep from Baylor 001-022
[2]Excludes one outlier result

Reviewer comments: Data above has previously been presented in the NDA. Information pertaining to scatocrit and stool output in particular, is suggestive that the ½ doses of sulfate solution (22 g) and PEG-ELS (2L) provide lower stool volume and higher stool solids compared to the approved formulations (HalfLytely, Fleet Prep, and NuLytely 4L).

Item 2: Based on data above, neither 20mg bisacodyl nor 2L NuLYTELY when used alone would be expected to provide sufficient cleansing for colonoscopy. This was demonstrated in a previous controlled clinical study in patients requiring colonoscopy (Study F38-15, NDA 203595, Module 1, Tab 1.4, pg 10) where 20mg bisacodyl alone and 2L NuLYTELY alone resulted in 58% and 67% successful preparations, respectively, compared to 83% successful preparations for the approved 4L NuLYTELY group. These were statistically significant differences and the study concluded that both the 20mg bisacodyl and the 2L NuLYTELY, when used alone, were not acceptable for bowel cleansing prior to colonoscopy. Subsequent clinical studies in the HalfLytely application (NDA 21-551) demonstrated that the combination of bisacodyl with the 2L NuLYTELY did produce acceptable and equivalent bowel cleansing relative to approved 4L NuLYTELY. Data is also shown in the table below for Suprep (BLI800) which contains twice the amount of sulfates (44 g) as that proposed in BLI850. Suprep has been shown to provide low scatocrit values (1.6 %) in study 006-181 and high clinical efficacy rates (97.2 % in phase 3). In comparison the scatocrit value for ½ dose of sulfate (22 g), one of the two components of proposed BLI850 per study 005-082 was higher (12 %).

The clinically relevant cleansing efficacy data along with the PD measures of total stool output and scatocrit are summarized for various formulations in the table below.

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

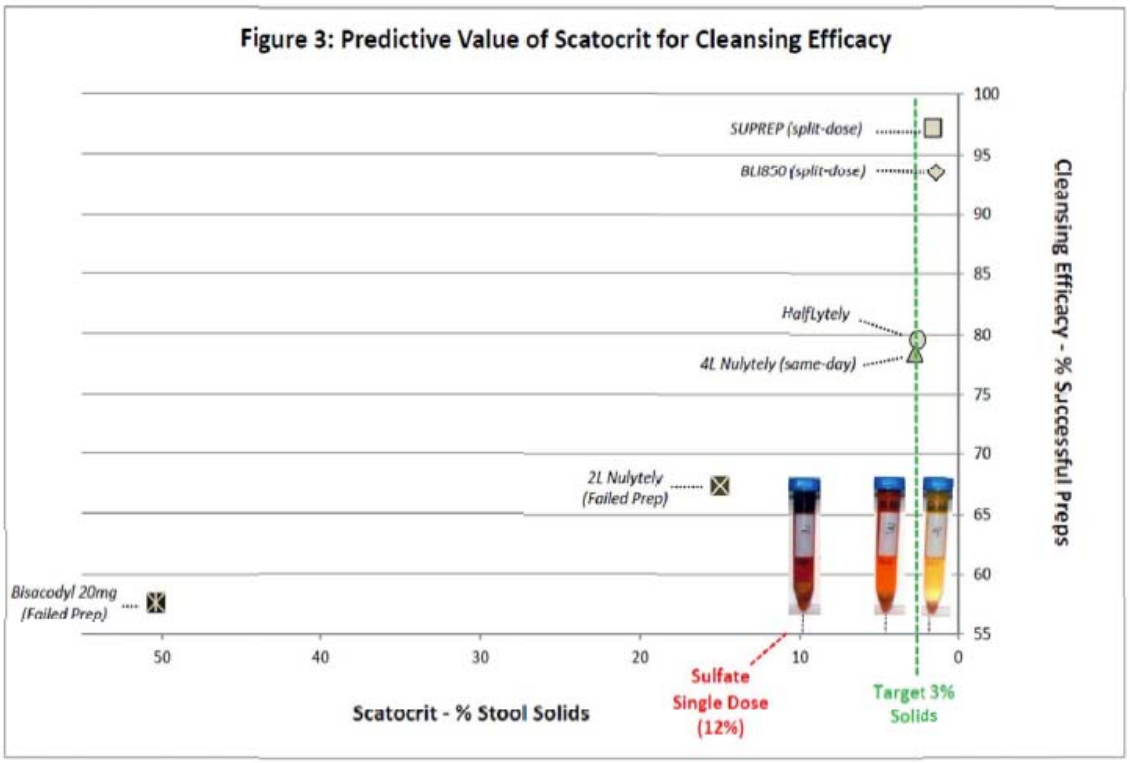
*20 mg bisacodyl and 2L NuLYTELY were statistically inferior to 4L NuLYTELY in Study F38-15

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

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

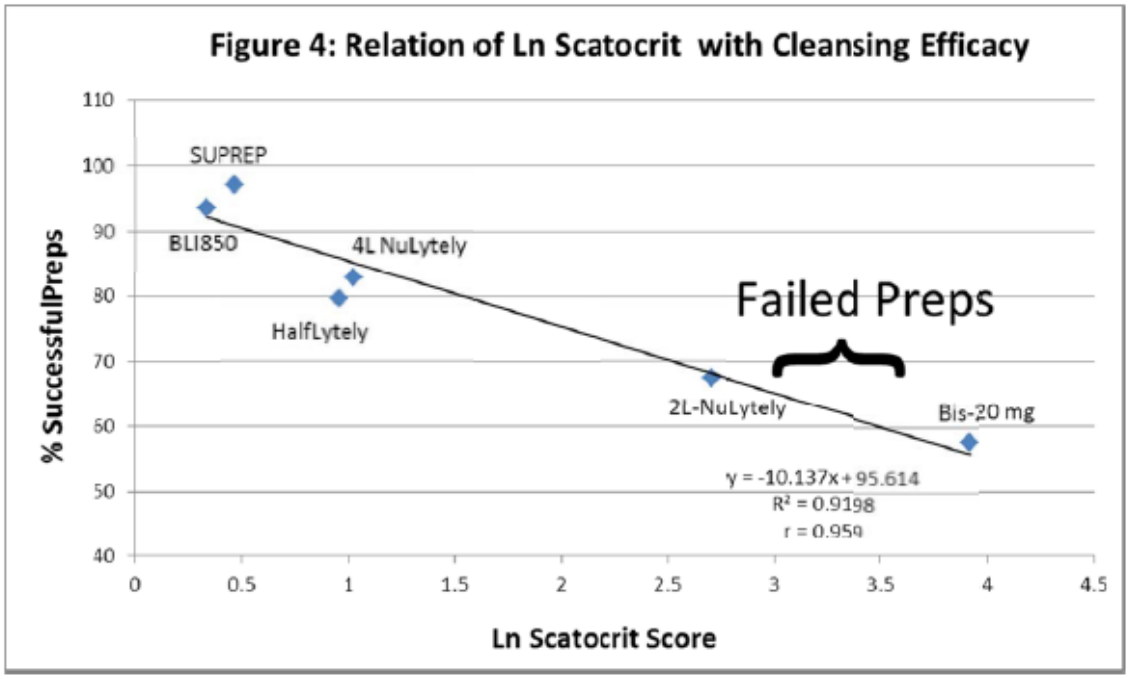
Reviewer comments: Clinical efficacy data from randomized clinical trials are available for individual components (or half doses) and for the final formulations of HalfLytely and NuLytely 4L. Data suggests that each component of HalfLytely (Bisacodyl 20 mg and PEG-ELS 2L) provided inferior cleansing efficacy compared to the final combination (57.4 % & 67. 4 % vs. 79.6 %) and that this trend was also apparent in the PD measures for these individual and combination doses. Similarly for NuLytely, the ½ dose (2L) appears to produce inferior cleansing efficacy, compared to the full dose, 4L (67.4 % vs. 82. 8%) which was again reflected in the PD measures evaluated (stool output 1650 vs. 3861 g; and scatocrit 15 % vs. 2.8 %). Data available for Suprep suggest a low scatocrit value (1.6 %) and a high clinical efficacy (97 %). While scatocrit information is available for ½ dose Suprep (oral sulfate salts) and is higher (12 %) similar to that of 2L NuLytely (15 %), clinical efficacy information is not available for this ½ dose.

Sponsor has provided the following plot to suggest relationship between scatocrit (% stool solids in final BM) and clinical cleansing efficacy of bowel prep products:



Per sponsor the above figure shows that the approved preparations 4L NuLYTELY, HalfLytely and SUPREP (containing two doses of 22grams sulfate salts) all demonstrated acceptable cleansing efficacy with scatocrit results less than 3%. In contrast, 2L NuLYTELY and 20mg bisacodyl each had unacceptable clinical cleansing results (as reported in the F38-15 study) and scatocrit scores well above 3%. However, the combination of 2L NuLYTELY with a 22 gram dose of sulfate salts (BLI850 or Solution 4) resulted in a scatocrit less than 3% as well as excellent cleansing efficacy, demonstrated in Phase III studies reported in this NDA.

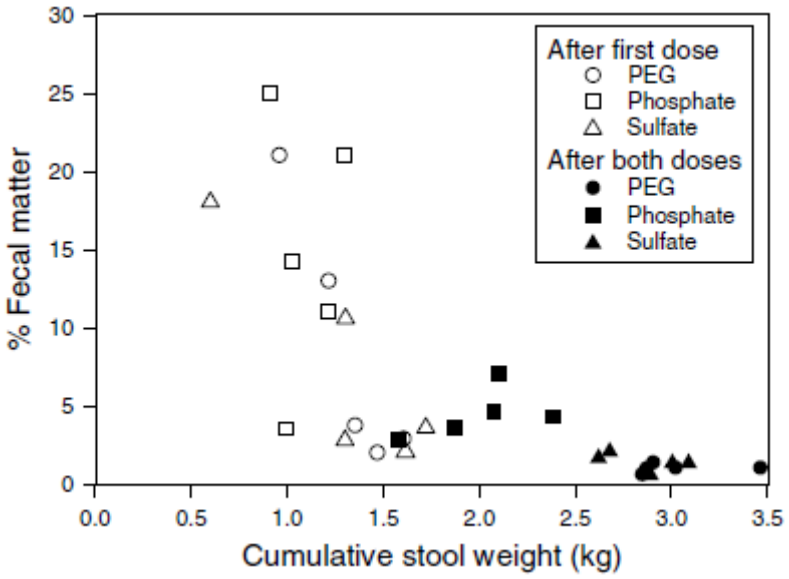
Item 3: Sponsor has also attempted a correlation between % scatocrit and clinical cleansing efficacy for the various approved and unapproved formulations ($r2 = 0.9198$). Based on the observed relationship ($Y = -10.137x + 95.164$), sponsor has predicted that for the ½ dose of Suprep (sulfate solution 22 g), the clinical cleansing efficacy (based on observed scatocrit of 12 %; ln value of 2.4) would be 70 %, similar to the unsuccessful preparations including NuLYTELY 2L, which also had a similar scatocrit value of 15 %.



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

Item 4: Publication by Patel et al, 2009: Intestinal and Renal Effects of Low-Volume Phosphate and Sulfate Cathartic Solutions Designed for Cleansing the Colon: Pathophysiological Studies in Five Normal Subjects.
Viralkumar Patel, MD1 , Michael Nicar, PhD1 , Michael Emmett, MD1 , John Asplin , MD2 , John A. Maguire , PhD3 , Carol A. Santa Ana , BS1 and John S. Fordtran, MD1

In this study, 4L of PEG-ELS, and equimolar doses of sulfate solution and phosphate solution were administered as split doses in healthy volunteers. Increasing diarrheal stool weight was associated with a reduction in percent visible insoluble fecal matter in centrifuged stool. After the first dose, average percent fecal matter in diarrheal fluid was 8.5 ± 3.7 % with PEG, 7.4 ± 3.0 % with sulfate, and 15.0 ± 3.8 % with phosphate (P = 0.112). After both doses, average percent fecal matter in diarrheal fluid was 1.1 ± 0.1 % with PEG, 1.5 ± 0.2 % with sulfate, and 4.5 ± 0.7 % with phosphate (P = < 0.001).



Summary: Sponsor concludes that above data confirms that stool volume and scatocrit are closely related to cleansing success in clinical studies and that the individual BLI850 components alone will be insufficient for adequate colon cleansing.

Reviewer conclusions: The available information for various approved and unsuccessful bowel cleansing preparations suggests a relationship between the PD endpoint and efficacy. It should be noted however that the data presented is not a rigorous exercise that could establish and validate a correlation between the PD and efficacy outcomes. The final determination regarding combination requirements is deferred to the clinical review team.

Overall three aspects of the justification provided suggest likely correlation between the PD endpoint ('scatocrit') and the clinical efficacy outcomes: 1) the observed trend for association between PD parameters and clinical efficacy noted for the single components of approved HalfLytely or half-doses of approved NuLYTELY 4L, 2) the observed association between the PD parameter and clinical efficacy noted for the full dose of approved Suprep, along with higher scatocrit (PD) noted for ½ dose of Suprep and 3) the comparable efficacy of full doses of Suprep and BLI850 in randomized clinical trials (93.5 % vs. 97.2 %).

4.2 Cover Sheet and OCP Filing Memo

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**203595**	**Brand Name**	
OCP Division (I, II, III, IV, V)	**DCPIII**	**Generic Name**	**Na, K, Mg sulfates (component 1); PEG-3350 with electrolytes (component 2)**
Medical Division	**DGIEP**	**Drug Class**	**Osmotic agents**
OCP Reviewer	**Sandhya Apparaju**	**Indication(s)**	**Bowel cleansing prior to colonoscopy**
OCP Team Leader	**Sue Chih Lee**	**Dosage Form**	**Oral solution**
Pharmacometrics Reviewer	**N/A**	**Dosing Regimen**	**Single dose prior to scheduled colonoscopy administered either as a split-dose (2-day) regimen or as a (b) (4) (1-day) regimen**
Date of Submission	**12/16/2011**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**09/07/2012**	**Sponsor**	**Braintree Laboratories**
Medical Division Due Date	**09/14/2012**	**Priority Classification**	**Standard**
PDUFA Due Date	**10/19/2012**		

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**			PK of oral sulfates from Study BLI800-202
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:	**X**			Phase 3 S & E data for elderly
renal impairment:	**X**			BLI800-202
hepatic impairment:	**X**			BLI800-202
PD -				
Phase 2:	**X**			Studies 005-082 and 006-181
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**X**			Waiver requested
Literature References	**X**			**PEG PK**
Total Number of Studies	**5**			

On **initial** review of the NDA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Clinical and to be marketed formulations are the same per CMC reviewer. Moreover, for oral solutions, BE studies are generally waived based on 21 CFR 320.22(b)(3)(iii)
2	Has the applicant provided metabolism and drug-drug interaction information?	X			No specific DDI studies; however label cautions regarding drug that may increase risks due to fluid and electrolyte abnormalities and effect on absorption of concomitant drugs taken within 1h of bowel cleansing agents. Sponsor will be asked to address

					interaction potential between the two components of the formulation (OSS and PEG-ELS)
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			Submitted for the oral sulfate assay
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?			X	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			Electronic datasets have been included.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			Additional information for PEG3350 will be requested.
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			Information from PD studies to support the combination and doses
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Pediatric waiver requested citing that drug doesn't represent a meaningful benefit over existing therapies such as NuLytely.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the	X			Pending review it appears there is

	pharmacokinetics and exposure-response in the clinical pharmacology section of the label?				information on PK in the label.
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

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

/s/

SANDHYA K APPARAJU
09/18/2012

SUE CHIH H LEE
09/18/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 203595

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**203595**	**Brand Name**	**(b) (4)**
OCP Division (I, II, III, IV, V)	**DCPIII**	**Generic Name**	**Na, K, Mg sulfates (component 1); PEG-3350 with electrolytes (component 2)**
Medical Division	**DGIEP**	**Drug Class**	**Osmotic agents**
OCP Reviewer	**Sandhya Apparaju**	**Indication(s)**	**Bowel cleansing prior to colonoscopy**
OCP Team Leader	**Sue Chih Lee**	**Dosage Form**	**Oral solution**
Pharmacometrics Reviewer	**N/A**	**Dosing Regimen**	**Single dose prior to scheduled colonoscopy administered either as a split-dose (2-day) regimen or as a (b) (4) (1-day) regimen**
Date of Submission	**12/16/2011**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**09/07/2012**	**Sponsor**	**Braintree Laboratories**
Medical Division Due Date	**09/14/2012**	**Priority Classification**	**Standard**
PDUFA Due Date	**10/19/2012**		

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**			PK of oral sulfates from Study BLI800-202
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				

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fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:	**X**			Phase 3 S & E data for elderly
renal impairment:	**X**			BLI800-202
hepatic impairment:	**X**			BLI800-202
PD -				
Phase 2:	**X**			Studies 005-082 and 006-181
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**X**			Waiver requested
Literature References	**X**			**PEG PK**
Total Number of Studies	**5**			

On **initial** review of the NDA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Clinical and to be marketed formulations are the same per CMC reviewer. Moreover, for oral solutions, BE studies are generally waived based on 21 CFR 320.22(b)(3)(iii)
2	Has the applicant provided metabolism and drug-drug interaction information?	X			No specific DDI studies; however label cautions regarding drug that may increase risks due to fluid and electrolyte abnormalities and effect on absorption of concomitant drugs taken within 1h of

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					bowel cleansing agents. Sponsor will be asked to address interaction potential between the two components of the formulation (OSS and PEG-ELS)
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			Oral sulfate PK is available; there is not much information for the PEG3350 component; literature in this regard has been submitted to show minimal absorption; sponsor will be asked to submit details on PK reference by Pelham et al (2008) in this regard.
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			Submitted for the oral sulfate assay
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?			X	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			Electronic datasets have been included.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			Additional information for PEG3350 will be requested.
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects)	X			Information from PD studies to support the combination and doses

	analyses conducted and submitted as described in the Exposure-Response guidance?				
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Pediatric waiver requested citing that drug doesn't represent a meaningful benefit over existing therapies such as NuLyte.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			Pending review it appears there is information on PK in the label.
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? YES

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

Please communicate the following comments to the sponsor:

1. **Address the drug-drug interaction potential between the components of the formulation (i.e. oral sulfates and PEG-ELS).**
2. **Provide complete study report including datasets and analytical validation/assay reports for the following published study titled: "Clinical trial: Single- and multiple-dose pharmacokinetics of polyethylene glycol (PEG-3350) in healthy young and elderly subjects", R.W. Pelham et al, Alimentary Pharmacology & Therapeutics, 2008 [Braintree trial]**

Sandhya Apparaju
Reviewing Clinical Pharmacologist Date

Sue Chih Lee
Team Leader/Supervisor Date

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Relevant IND No.: 102894 (product also referred to as BLI850)

Description: Proposed product has two components:

- One 6oz bottle of oral sulfate solution for dilution with 16oz water, consisting of sodium sulfate 17.5 g, potassium sulfate 3.13 g, magnesium sulfate 1.6 g.
- One 2 liter jug of powder for reconstitution with water, containing PEG-3350 210 g, sodium bicarbonate 2.86 g, sodium chloride 5.6 g, potassium chloride 0.74 g. An optional 1g flavoring ingredient may be added.

[Approved drugs with proposed active ingredients include Suprep (NDA 22-372; ref for oral sulfate solution; also referred to as BLI800); HalfLytely (NDA 21-551, ref for the PEG-ELS solution); NuLytely (NDA 19-797; also ref for PEG-ELS solution); Miralax (NDA 22-015; also ref for the PEG component)]

Dosing regimen: Drug product is proposed for use as either a 1) split-dose (2-Day) regimen, where the 6oz bottle (diluted with water) is consumed the evening before colonscopy, and the 2 liter bottle is consumed the next morning, to be completed at least 2 h before colonoscopy; or 2) (b) (4) (1-Day) regimen, in which both components are consumed within 2 hours of each other

Based on earlier approved products, it appears that (b) (4) combines two osmotic laxatives, an oral sulfate solution. The oral sulfate solution (one 6oz bottle to provide 22 g of sulfates) is at one-half the dose of that approved as SuPrep (two 6oz bottles to provide 44 g sulfates), and a PEG-ELS solution, at the same dose as the PEG-ELS component in HalfLytely (minus the Bisacodyl) or at half the PEG-ELS component approved in NuLytely.

Thus essentially (b) (4) = ½ SuPrep + HalfLytely (minus Bisacodyl)

Material	Function	(b) (4)	SuPrep	Half-Lytely
Component 1 (oral sulfate solution; quantity per dose)				
Sodium Sulfate, USP	Active	17.510 g (b) (4)	35.020 g	-
Potassium sulfate, (b) (4)	Active	3.130 g (b) (4)	6.260 g	-
Magnesium sulfate, USP	Active	1.600 g (b) (4) (b) (4)	3.200g	-
Sodium Benzoate, NF		(b) (4)	(b) (4)	-
Sucralose (b) (4)				-
Malic acid, FCC				-
Citric acid, USP				-
(b) (4)				-
			(b) (4)	-

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[redacted] (b) (4)			-	
			-	
Component 2 (PEG-ELS for solution; quantity per dose)				
Polyethylene Glycol 3350, NF	Active	210 g (b) (4)	-	210 g
Sodium chloride, USP	Active	5.60 g (b) (4)	-	5.60 g
Sodium bicarbonate, USP	Active	2.86 g (b) (4)	-	2.86 g
Potassium chloride, USP	Active	0.74 g (b) (4)	-	0.74 g
Flavor ingredients optional	Flavoring	1.00 g	-	1.00 g

New clinical trials: Two multicenter phase 3 studies (BLI850 301 and BLI850 302) were conducted in support of (b) (4) Each study included an active comparator, and each tested one of the two proposed regimens.

Clinical Pharmacology contents of the NDA:

Table 2.7.4-10
Pharmacokinetics and Pharmacodynamics Studies with BLI850

Study Identifier	Location of Study Report	Study Design And Type of Control	Test Product(s); Dosage Regimen; Route of Administration	No. of Subjects	Population
Baylor 001-022	NDA 22-372 Module 5 Vol. 2.1 Tab 5.3.4.1A	Open-label, unrandomized, active control	Sulfate formulas Phospho-soda Split-dose; oral	5	Healthy subjects
Baylor 005-082	CTD Module 5 Vol. 3.1 5.3.4.1A	Open-label, unrandomized, active control	BLI850 Sulfate formulas Laxatives NuLYTELY HalfLytely	27	Healthy subjects
Baylor 006-181	Module 5 Vol. 3.1 Tab 5.3.4.1B	Open-label, unrandomized, active control	BLI800 Phospho-soda NuLYTELY Split-dose; oral	9	Healthy subjects
BLI800-101	NDA 22-372 Module 5 Volume 2.1 Tab 5.3.4.1D	Open-label, randomized, active control	Sulfate formula Phospho-soda Same-day and split-dose; oral	19	Healthy subjects
BLI800-202	CTD Module 5 Volume 2.1 Tab 5.3.3.1A	Unblinded, no control	BLI800 Split-dose; oral	18	Patients with mild-moderate hepatic or renal insufficiency and healthy subjects

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Pharmacokinetics:

Sulfates: Study BLI800-202: Originally submitted to SuPrep NDA 22372; evaluated the pharmacokinetics of sulfates in healthy volunteers and in patients with renal or hepatic impairment. Study employed twice the dose of oral sulfate solution than that proposed for (b) (4) (see table above). Study has been resubmitted in Module 5 of this NDA for ease of review.

Analytical methodology (ion chromatography for serum and fecal sulfate) validation report has been included in module 4 section 4.2.2.1A.

PEG-ELS: This component of (b) (4) consists of 2 L of the same solution that is found in Braintree's NuLytely and Half Lytely. Thus, it is one-half the volume, with half the ingredients as the 4L PEG-ELs that is NuLytely. As described in the NDA for HalfLytely (NDA 21551), there was no net secretion or absorption of electrolytes associated with the use of this solution – the electrolyte components were effectively not absorbed. In a study by Brady et al (1986) measured urinary excretion as a measure of absorption of PEGs in ten IBD patients receiving an oral preparation of PEG-ELS in preparation for colonoscopy and in normal subjects. Average load of PEG-3350 was 168 g in IBD patients and 522 g in normal subjects. In comparison, the dose of PEG-3350 in the current formulation is 210 g (same as in HalfLytely). This study showed that urinary excretion of orally administered PEG-3350 was minimal in both populations. DiPiro et al (1986) also found that there was no detectable PEG-3350 in plasma during or after PEG-ELS preparation.

In the clinical pharmacology review for NDA 21551 (HalfLytely) reviewer notes that "no new PK information has been submitted". Reviewer also notes that "PEG 3350 has been shown to exhibit; 1) no sign of in vivo metabolism and/or fermentation to hydrogen or methane by colonic flora, 2) no detectable plasma levels after administration of PEG-3350, and 3) a minimum of urinary excretion, 0.06 ± 0.01% in normal controls and 0.08 ± 0.02 % in patients with inflammatory bowel disease". This information appears to be from the above referenced publications.

There is a pending PMC for NDA 21551 which includes request for PK in a subset of patients.

Pharmacodynamics and dose/combination rationale: Sponsor notes that studies have been conducted to examine PD of oral sulfate solutions and the PEG-ELS components of BLI850. Both components increase the volume of stool, reduce its consistency and reduce its solid contents. When used separately at a dose of 6 ounces of oral sulfates (22 g) or 2L of PEG-ELS, the amount of stool produced is about one half that which is required to provide adequate bowel cleansing. When the two components are used in a sequential manner, the fecal output is similar to that produced with currently marketed colon cleansing preparations (pending review).

Baylor study 005-082: Included in Module 5, volume 3.1., Tab 5.5.4.1A. This study examined half doses of Suprep and NuLytely which are relevant to this NDA. Study compared several laxatives and bowel cleansing agents including bisacodyl, senna, milk of magnesia, NuLytely 92L), NuLytely (4L), HalfLytely bowel prep kit with bisacodyl and four sulfate formulations (~

22 g) in 27 healthy volunteers. Sponsor notes that one volunteer received sulfate solution followed by 2L of NuLytely in this study. The amount of stool solids (%) in the final diarrheal movement was measured. According to the sponsor, stool output of 2400 g or greater with percent solids of < 3 % is consistent with adequate cleansing.

Baylor study 006-181: originally submitted in the SuPrep NDA and resubmitted in this NDA. Data comparing Suprep to marketed products is included. Since stool data were analyzed following each of the two 22 gm doses of sulfate salts, and similarly for each of the 2L NuLytely doses, sponsor notes that data are relevant to this application. Data is shown to support that combining the individual doses would provide sufficient stool to cleanse the colon.

Together with phase 3 clinical trials BLI850 301 and 302, the Baylor studies 005-082 and 006-181 are used by the sponsor to support the dose and effectiveness of (b) (4)

Drug Interactions: The two components (oral sulfate solution and PEG-ELS solution) have been previously approved in other NDAs and labels have noted caution with respect to drugs that may increase risks of fluid and electrolyte abnormalities and for potential altered drug absorption of oral medications taken within 1h of these laxatives.

There is no information on concomitant dosing of the two components. The recommended regimen for (b) (4) is to administer the components with at least a 2 h or overnight gap. The mechanism of action of each osmotic laxative component involves induction of copious watery diarrhea thus may avoid residual drug content in colon before the other component is administered.

Sponsor also notes that in phase 3 studies, 107 patients received narrow therapeutic index drugs such as warfarin, depakote, dilantin, lanoxin, lithium, synthroid, tegretol and theophylline. Comparison of AEs revealed no differences between BLI850 and its comparators.

Specific populations: Sulfate pharmacokinetics have been evaluated in renal and hepatic impairment populations in study BLI800-202.

Clinical vs. TBM: Clinical trials of (b) (4) have employed the proposed 2-component formulation. This was verified by the CMC reviewer Dr. Gene Holbert. In addition, the formulation components are solutions for oral administration with low or no systemic bioavailability. According to the BA/BE guidance, in vivo BE studies are waived for solutions on the assumption that the release of drug substance from the drug product is self-evident and that solutions do not contain any excipient that significantly affects drug absorption [21 CFR 320.22(b)(3)(iii)].

Filability: NDA is filable from a Clinical Pharmacology perspective.

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

/s/

SANDHYA K APPARAJU
02/07/2012

SUE CHIH H LEE
02/07/2012