NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA Efficacy Supplement – 505(b)(1)
Application Number	022372 Supplement 013
Priority or Standard	Standard
Submit Date	July 5, 2019
Received Date	July 5, 2019
PDUFA Goal Date	August 5, 2020
Division/Office	OND / OII / DG
Review Completion Date	March 27, 2020
Established/Proper Name	sodium sulfate, magnesium sulfate, and potassium sulfate
Trade Name	Suprep Bowel Prep Kit
Pharmacologic Class	(b) (4) osmotic laxative
Code Name	BLI800
Applicant	Braintree Laboratories, Inc.
Dosage Form	Solution, concentrate
Applicant Proposed Dosing Regimen	6 oz per dose, administered in 2 doses (split-dose regimen)
Applicant Proposed Indication(s)/Population(s)	Cleansing of the colon prior to colonoscopy; proposed expansion of indication to include pediatric patients 12 years of age and older
Applicant Proposed SNOMED CT Indication Disease Term for Each Proposed Indication	346350006 Bowel cleansing solution (product)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Cleansing of the colon prior to colonoscopy in adult and pediatric patients 12 years of age and older
Recommended SNOMED CT Indication Disease Term for Each Indication (if applicable)	346350006 Bowel cleansing solution (product)
Recommended Dosing Regimen	Pediatric patients 12 years of age and older: 4.5 oz per dose, administered in 2 doses (split-dose regimen) Adults: 6 oz per dose, administered in 2 doses (split-dose regimen) Must consume additional water after each dose.

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Division Director (designated signatory authority)	Jessica Lee

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OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DPMH = Division of Pediatric and Maternal Health
QAL = Quality Assured Label
TL = Team Leader
PM = Project Manager
DD = Deputy Director

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Clinical Pharmacology Team Leader	Jie (Jack) Wang, Ph.D.	OTS/OCP/DTPM	Sections: 6, 14.3	___ Authored _X_ Approved
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Clinical Team Leader	Tara Altepeter, M.D.	OII / DG	Authored Sections: 1.2, 1.3 Approved: All sections	_X_ Authored _X_ Approved
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Acting Division Director	Jessica Lee, M.D., M.M.Sc.	OII / DG	Authored Section: 13 Sections: All sections	_X_ Authored _X_ Approved
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Glossary

AE	adverse event
BLA	biologics license application
CFR	Code of Federal Regulations
CIR	cecal intubation rate
ECG	electrocardiogram
FDA	Food and Drug Administration
GI	gastrointestinal
IBD	inflammatory bowel disease
IND	investigational new drug
ITT	intention-to-treat
mITT	modified intention-to-treat
NDA	new drug application
PEG	polyethylene glycol
PK	pharmacokinetics
PMR	postmarketing requirement
SAE	serious adverse event
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Suprep is an orally administered solution containing active ingredients of sodium sulfate, potassium sulfate, and magnesium sulfate, approved in 2010 for cleansing the colon prior to colonoscopy in adults as a split-dose (2-day) regimen. The osmotically active sulfate anion is poorly absorbed in the gastrointestinal (GI) tract, retaining fluids in the colon and leading to voluminous diarrhea, resulting in cleansing of the colon.

The Applicant, Braintree Laboratories Inc, seeks with this submission to expand the indication of Suprep Bowel Prep Kit 6-oz dosing regimen currently approved in adults (referred to as Suprep for the purpose of this review), to include pediatric patients 12 to 16 years of age.

The phase 3 study investigated efficacy and safety of the two 6-oz bottles of Suprep (adult dose) or two 4.5-oz doses of Suprep (3/4 of the Suprep adult dose) administered orally as a 2-day split-dose regimen in patients 12 to 16 years of age. The first dose was given in the evening a day prior to the procedure and the second dose was given in the morning on the day of the procedure. Each 6-oz dose was diluted in 16 oz of water and 4.5-oz dose was diluted in 12 oz of water and administered orally, followed by required intake of additional water/fluids of 32oz and 24 oz, respectively, over the next 1 to 2 hours.

Active ingredients and other constituents of Suprep are shown in Table 1 below.

Table 1. Composition of Suprep Formulations

Ingredients	Suprep 6 oz (g)	Suprep 4.5 oz (g)
Na_2SO_4	17.51	13.13
$MgSO_4$	1.6	1.2
K_2SO_4	3.13	2.35
Sodium benzoate	(b) (4)	
Flavoring agents		
(b) (4)		

Source: Section 9.4.1- Treatment(s) administered, of the study protocol BLI800-502

The proposed split-dose regimen (defined as giving a portion, usually half, of the bowel preparation the evening prior to the procedure day, and the remaining portion early on the day of the procedure) is appropriate and consistent with published guidelines. Split dosing of the bowel preparations has emerged as an important factor in bowel cleansing efficacy and compliance (Cohen 2010). A meta-analysis showed that a split-dose regimen of polyethylene glycol (PEG) significantly improved the percentage of patients with satisfactory colon cleansing and patient compliance; nausea was also significantly decreased (Kilgore et al. 2011). It is also more likely to reduce the risk of dehydration associated with bowel preparations, especially in pediatric patients. The American College of Gastroenterology guidelines for colorectal cancer screening also recommend that the bowel preparations be administered via split dosing.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This application relies upon partial extrapolation of efficacy, relying upon the similarity of the anticipated response to treatment between adults and pediatric patients undergoing bowel preparation prior to colonoscopy. The efficacy of Suprep was previously established in adults in two adequate and well-controlled trials. This submission contains results from a single, controlled clinical trial conducted in pediatric patients, which demonstrated that the efficacy of Suprep (both dosages studied) was numerically greater than that of an approved comparator (NuLytely). A powered noninferiority trial was considered infeasible, as the necessary sample size would preclude completion of the trial in a reasonable timeframe, noting that colonoscopy is performed relatively infrequently in pediatric patients, as compared with adults. The results of the study are consistent with efficacy results demonstrated in adults who received split-dose administration, and when taken together with available adult data, support extending the indication down to 12 years of age. Although efficacy of both dosages studied (4.5 oz and 6 oz) was demonstrated in this small study, only the 4.5 oz dosage is recommended for approval, given that the efficacy of both doses was comparable, and the lower dose was better tolerated.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Suprep is a sulfate-based fixed-combination drug product approved for cleansing the colon in preparation for colonoscopy in adults.
This supplemental new drug application contains the results from a single controlled clinical trial, comparing safety and efficacy of Suprep (6-oz or 4.5-oz doses) to NuLytely (a polyethylene glycol based bowel preparation product approved for pediatric patients and adults); this trial was conducted to address a pediatric postmarketing requirement (PMR). The supplement proposes to expand the indication for Suprep to include adolescents (pediatric patients ages 12 and older). The Applicant initially proposed use of the 6-oz dose (in a "split-dose regimen"); however, the efficacy data for the 2 doses appear comparable, and the safety profile of the 4.5-oz dose appears more favorable. Therefore, the 4.5-oz dose is recommended for approval.

Currently, there are three bowel preparation products approved for the pediatric population, including NuLytely (large volume polyethylene glycol [PEG] based prep, used as the comparator in this program), as well as Prepopik (powder for reconstitution containing sodium picosulfate, magnesium oxide, and anhydrous citric acid) and Clenpiq (premixed solution of same composition as Prepopik). In clinical practice the most widely utilized bowel preparation remains off-label use of a combination of PEG3350 and stimulant laxatives. For this reason, a need remains for additional bowel preparation products for children that are efficacious, safe, and palatable.

The benefits of Suprep for use in adolescents are that it provides an efficacious, safe, and adequately tolerated option for bowel preparation.
The efficacy of Suprep in this population was demonstrated in a single clinical study (Study BLI800-502) in which 97 patients were randomized 1:1:1 to receive Suprep 6 oz, 4.5 oz, or NuLytely. Efficacy was assessed by an endoscopist blinded to treatment assignment.
The endoscopist rated each colon segment (proximal, mid, distal) using a 4 point scale as "excellent,""good," "fair," or "poor" after completion of the exam (during withdrawal of the endoscope) and provided a global rating of preparation quality for the entire colon (inclusive of their perception of all segments). The definitions of "excellent" or "good" included complete visualization of the mucosa. The primary endpoint was the proportion of patients achieving overall cleansing success defined by an overall cleansing assessment grade of "excellent" or "good." In this trial, successful preparation was achieved in 81%, 85%, and 59% of the patients treated with Suprep 6 oz, Suprep 4.5 oz, or NuLytely, respectively.

Overall, the safety profile of Suprep in adolescents was acceptable. Adverse events (AEs) were common, occurring in >90% of patients regardless of arm, but most were mild and related to GI effects of bowel preparation. There were no serious adverse events (SAEs) in the trial. The most common adverse events were nausea, abdominal pain, bloating, and vomiting. The reported rates of some of the more common events (nausea, bloating, headache) were lower in the 4.5 oz arm as compared to the 6 oz arm, but given the small numbers of patients per arm, the precision of these estimates is low.

Electrolyte changes were relatively common, as is expected after administration of a bowel preparation which causes profuse watery diarrhea in order to cleanse the colon. The most common electrolyte or chemistry parameter shift was increased anion gap, which occurred with greater frequency with Suprep than NuLytely. Overall, the majority of changes in electrolytes were transient and not clinically significant.
Based on numerically greater success rate with 4.5 oz than 6 oz, fewer AEs leading to discontinuation, and some differences in rates of gastrointestinal (GI) AEs that favored 4.5 oz over 6 oz, the 4.5-oz dose is recommended for approval in adolescents 12 to 16 years of age. The available evidence did not support any incremental benefit of 6 oz, and that dose may have poorer tolerability. Subgroup analyses were also conducted for efficacy and safety to evaluate if the older or highest body weight subgroup of the adolescent population (who may be adult size) may require the 6 oz dose, but there was no evidence to suggest that this is required to attain adequate efficacy.

In summary, the results of the study support approval of the 4.5-oz dose for pediatric patients 12 years of age and older. The benefits of providing an additional option for an efficacious bowel preparation product in pediatric patients appear to outweigh the identified risks, which are mainly GI AEs of mild to moderate severity and tend to be self-limited.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		x	Clinician reported outcome (ClinRO)	8.1.2 Efficacy results are scored based on ClinRO
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☒	Other: (Please specify): Tolerability of the taking Bowel Preparation.		8.2.8. Clinical Outcome Assessment Analyses Informing Safety/Tolerability
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

Colonoscopy is standard of care as a diagnostic and therapeutic procedure in the management of medical conditions involving the colon in both children and adults. Effective bowel cleansing is a prerequisite for achieving a high quality colonoscopy procedure and high completion rate—a cecal intubation rate (CIR) of 90% to 95% (Rex et al. 2015). Inadequate bowel preparation for colonoscopy can result in missed lesions, increased procedural time, increased adverse event (AE) rates, and cancelled procedures leading to requirement for a repeat procedure and increased costs (Rex et al. 2002; Wexner et al. 2006; Lebwohl et al. 2011).

Key indications for diagnostic, therapeutic, and surveillance colonoscopy in pediatric patients include evaluation of lower GI bleeding, chronic diarrhea, inflammatory bowel disease (IBD), suspected polyposis syndromes, foreign body removal, and colonic-stricture dilatation.

2.2. Analysis of Current Treatment Options

There are currently three FDA-approved bowel preparations for the pediatric population:

- NuLytely is approved for cleansing of the colon before colonoscopy in pediatric patients aged 6 months and older. The recommendation is to administer the solution orally at the rate of 25 mL/kg/hour until watery stool is clear and free of solid matter. NuLytely is administered the night before the colonoscopy as a single dose.
- Prepopik is approved for pediatric patients ages 9 years and older for cleansing of the colon as a 2-day split dose administration (preferred method), as well as a day-before (alternate method) dosing regimen, if split-dosing is inappropriate (2 doses given 6 hours apart).
- Clenpiq is approved for pediatric patients ages 9 years and older for cleansing of the colon as a 2-day split-dose administration.

For additional details please see Table 2.

Table 2. Summary of Treatment Armamentarium Relevant to Proposed Indication for the Pediatric Population

FDA-Approved Treatments	Relevant Indication	Year of Approval	Dosing/Administration	Efficacy Information*	Important Safety and Tolerability Issues	Other Comments
NuLytely	Cleansing of the colon in preparation for colonoscopy in adults and pediatric patients aged 6 months or greater	1991	NuLytely is administered the night before colonoscopy as a single dose. The solution is taken at the rate of 25 ml/kg/hour until watery stool is clear and free of solid matter.	Age 6 months to adults: 86%	Warning and Precautions section includes the risk of fluid and electrolyte abnormalities, arrhythmias, seizures, and renal impairment. Use of NuLytely in children younger than 2 years of age should be carefully monitored for occurrence of possible hypoglycemia, as this solution has no caloric substrate.	The efficacy in pediatric patients was based on the efficacy data from the published studies of similar formulations.
Prepopik**	Cleansing of the colon as a preparation for colonoscopy in adults and pediatric patients ages 9 years and older	Adults: 2012 Pediatrics: 2018	Prepopik is recommended for 2-Day split as well as Day before dosing regimens. Age 9-12 yrs.: 1 sachet X 2 Age 13-16 yrs.: 1 sachet X 2	Age 9-12 yrs: 88% Age 13-16 yrs: 81%	Warning and Precautions section includes all the safety information stated for NuLytely and additional risk of vomiting and other GI complications. Compared to adults, the AEs in pediatrics 9-16 years are higher (>5%) & include nausea, vomiting, and abdominal pain.	Limited number of overall patients in the study as well as small number of patients in 2-day split-dose regimen.
Clenpiq**	Cleansing of the colon as a preparation for colonoscopy in adults and pediatric patients ages 9 years and older	Adults: 2012 Pediatrics: 2019	Clenpiq, ready to drink oral solution, is recommended as 2-Day split dose: Adults and Pediatric patients: 1 bottle X 2	Age 9-16 yrs: 88%	Safety results were similar to those from the original trials that supported Clenpiq initial approvals. No new or unexpected safety findings were reported.	

Abbreviations: AE = adverse event; GI = gastrointestinal
* Endpoints and assessment scales differed across programs, these efficacy results cannot be directly compared across studies
** Clenpiq is a premixed oral solution (160 mL) of sodium picosulfate (10 mg), magnesium oxide (3.5 g), and anhydrous citric acid (12 g) approved on the basis of a biowaiver to the listed drug Prepopik.
Source: Compiled by the reviewer

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Suprep was approved for cleansing of the colon in preparation for colonoscopy in adults in August 2010.

The current submission contains the results of study BLI800-502 (referred to below as Study 502), which was conducted to fulfill the requirements of postmarketing requirement (PMR) 1580-3 issued under the Pediatric Research Equity Act at the time of the initial approval.

3.2. Summary of Presubmission/Submission Regulatory Activity

The development for Suprep occurred under IND 74,808. Key regulatory interactions related to the pediatric development plan are summarized below in chronological order.

3.2.1. Regulatory History Pertaining to Pediatrics

At the time of initial approval, five pediatric study requirements were issued. Table 3 shows information on the proposed PMR studies and their current status.

Table 3. Status of the PMR Studies

PMR	Study	Key Findings	Status
1580-1	Conduct a retrospective study of colonoscopy rates in the pediatric population (birth through 16 years).	Total number of colonoscopies for all pediatric patients in the United States: 2007: 53,317 2008: 53,960 2009: 58,982	Completed
1580-2	Conduct an OL dose-finding pilot study assessing the efficacy and tolerability of 2 doses of Suprep in adolescents (12 years to 16 years).	Enrolled 32 patients (mITT=29). No difference in preparation success between the 6-oz (n=16) and 4.5-oz (n=13) dose groups (81% versus 83%). No differences in AE rates were noted between the two groups.	Completed
1580-3	Conduct a R, SB, MC dose ranging study comparing the safety and efficacy of Suprep to NuLytely in adolescents (12 years to 16 years).	Enrolled 90 patients (mITT=89) No difference in preparation success between the 6-oz and 4.5-oz dose groups (81% versus 85%).	Completed. Supporting the current submission
1580-4	Conduct a R, SB, MC dose ranging study comparing the safety and efficacy of Suprep to NuLytely in children (3 years to 11 years).		Pending

PMR	Study	Key Findings	Status
1580-5	Conduct a R, SB, MC dose ranging study comparing the safety and efficacy of Suprep to NuLytely in children (from birth to 2 years).		Changed to 1580-9
1580-9	Conduct a R, SB, MC, dose ranging study comparing the safety and efficacy of Suprep to NuLytely in children (6 months to 2 years).		Pending

Abbreviations: AE, adverse events; MC = multicenter; OL = open-label; PMR = postmarketing requirement; R = randomized; SB = single-blind
Source: Compiled by the reviewer

(b) (4)

the Division agreed to a partial waiver in patients under age 6 months because a reasonable bowel preparation in this age group can be achieved with only administration of clear liquids for 24 hours.

- Suprep may offer a benefit of decreasing the total fluid intake because of the split-dose regimen and reducing the need to consume large amounts of an unpalatable liquid for infants and children.
- Studies examining the dosing, safety, and treatment effect should be feasible.
- There is no evidence from the adult studies that the product would be ineffective or unsafe in all pediatric age groups.

3.2.2. Other Relevant History

During the review of the initial NDA it was noted that there was an inadequate short-term follow up evaluation of blood chemistry including sulfate data between the day of colonoscopy and at Month 1. In the absence of such information, transient interval changes as well as the exact time course of resolution of electrolyte shifts could not be assessed. In addition, there was a lack of electrocardiogram (ECG) assessments at the maximum sulfate exposure and orthostatic vital signs data. The following postmarketing requirements were issued:

- PMR 1580-6: conduct a prospective descriptive epidemiologic study to identify adverse events associated with Suprep administration in 20,000 patients undergoing colonoscopy and 20,000 patients in an appropriate control group
- PMR 1580-7: evaluate renal and metabolic toxicity and sulfate levels in patients, including elderly patients, patients with renal impairment, and patients with hepatic impairment taking Suprep prior to colonoscopy
- PMR 1580-8: assess ECG changes to capture maximum effects of sulfate exposures in subjects taking Suprep

Key findings of the PMRs are summarized:

- PMR 1580-6:

The results showed that Suprep may have lower or similar incidence rates for TEAEs compared to other bowel preparations prescribed for administration the day before a screening colonoscopy.

- PMR 1580-7:

  The study was a randomized, active control single blind trial that evaluated renal and metabolic toxicity and sulfate levels in patients, including elderly patients, patients with renal impairment, and patients with hepatic impairment taking SUPREP prior to colonoscopy. Based on the chemistry and hematology data, the Suprep administration was shown to be comparable to GoLYTELY, with respect to the safety. No unique safety signals in the elderly, renally impaired or hepatically impaired populations were identified that required updates to the labeling.

- PMR 1580:

  The Study was conducted to assess ECG changes to capture maximum effects of sulfate exposures in subjects taking SUPREP. Thorough QT Interdisciplinary Review Team (TQT-IRT) was consulted to review the study report. The TQT-IRT noted that the timing of ECGs was acceptable to capture potential effects at Tmax (5 to 8 hours after dosing) of sulfate and delayed effects over 6 days. The TQT-IR team noted that electrolyte abnormalities could still result in QT changes, and recommended maintaining language in the label (including Warning, Section 5.2) regarding potential risk of arrythmia; however no new safety information was required to be added in the label as a result of this study.

The above PMR studies conducted to address the safety issues related to sulfate showed no additional safety concerns; no significant AEs related to the transient higher levels of sulfates were observed in adults. The above listed PMRs were considered fulfilled.

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

No specific issue for any particular site related to efficacy or safety that could drive the results were noted. Therefore, no clinical site inspections were recommended for this efficacy supplement.

The Office of Scientific Investigations conducted an inspection as a part of FDA's Bioresearch Monitoring Program, which included but was not limited to review of training records, written procedures, safety data exchange agreements, call center oversight, expedited and nonexpedited individual case safety reporting, reporting of EX-US adverse drug events, documentation of receipt date, accuracy of source data extraction, adverse drug event follow-

up procedures, and Periodic Adverse Drug Experience Report preparation and submission. The Office of Scientific Investigations classified this inspection as No Action Indicated (report finalized in DARRTS February 25, 2020).

4.2. Product Quality

Sections 3 (Dosage Forms and Strengths), 11 (Description), and 16 (How Supplied/Storage and Handling) of the labeling were reviewed by the chemistry, manufacturing, and controls team and found adequate. Since Suprep Bowel Prep Kit will be administered for the same indications and duration and at lower dosage levels than that previously approved for adults, the Applicant's request for categorical exclusion from the environmental analysis was granted. For details, see review by Dr. Hossein Khorshidi.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

This supplement includes labeling changes to comply with the Pregnancy and Lactation Labeling Rule.

The Applicant did not submit any nonclinical study report in this submission. Nonclinical studies were reviewed under the original NDA submission (pharmacology review of NDA 022372 dated March 6, 2009 by Tamal Chakraborti, PhD).

5.2. Referenced NDAs, BLAs, DMFs

Not applicable.

5.3. Toxicology

5.3.1. General Toxicology

No general toxicology studies were submitted in this supplement. General toxicology studies were reviewed under the original NDA 022372. The systemic toxicity of Suprep was tested in repeat dose toxicity studies in rats and dogs that received up to 28 days of oral administration. The sulfate salts of sodium, potassium, and magnesium contained in Suprep Bowel Prep Kit

were administered orally (gavage) to rats and dogs for up to 28 days up to a maximum daily dose of 5 g/kg/day. This is approximately 0.9 and 3 times, respectively, the recommended human dose of 44.48 g/day or 0.89 g/kg based on the body surface area. Suprep caused diarrhea; electrolyte and metabolic changes, including hypochloremia, hypokalemia, hyponatremia, and lower serum osmolality; higher urine sodium and potassium; alkaline urine; and high serum bicarbonate indicative of metabolic alkalosis. In dogs, Suprep caused emesis, excessive salivation, excessive drinking of water, abnormal excreta (soft and/or mucoid feces and/or diarrhea), and increased urine pH and sodium excretion. In rats, the target organs appeared to be the adrenal cortex (alteration of vacuolation), colon (dilated colon), jejunum (dilated), and kidney (minimal mineralization). In dogs, no significant organ toxicities were observed. These findings do not have any impact on the labeling changes to comply with the PLLR.

6. Clinical Pharmacology

6.1. Executive Summary

Suprep Bowel Prep Kit (Suprep) is an osmotic laxative initially approved in 2010 for cleansing of the colon in preparation for colonoscopy in adults. In the current submission, the Applicant proposed to expand the approved indication to include pediatric patients 12 years of age and older. The Applicant proposed the same 6 oz split-dose regimen in pediatric patients as that in adults. To support the proposed indication in pediatrics, the Applicant has provided efficacy and safety results from Study BLI800-502 in pediatric patients aged 12 to 16 years which was conducted to fulfill PMR 1580-3. Two Suprep doses at 4.5 oz (i.e., two 4.5-oz doses, equivalent to 3/4 of the approved adult dose) and 6 oz (i.e., two 6-oz doses, the approved adult dose) were studied in Study BLI800-502. The two doses (4.5 oz vs 6 oz) demonstrated similar efficacy (see section 8.1.2.5) and 4.5 oz dose was better tolerated (see section 8.2.3.5); therefore, the 4.5-oz dose is recommended for approval.

The Applicant has not conducted any new clinical pharmacology study to support this submission.

Recommendations

From a clinical pharmacology standpoint, this supplemental NDA is acceptable to support the approval of Suprep Bowel Prep Kit for cleansing of the colon in preparation for colonoscopy in pediatric patients 12 years of age and older.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Clinical Pharmacokinetics

In pediatric patients who received Suprep treatment in Study BLI800-502, the pharmacokinetics (PK) results on the day of colonoscopy showed that serum sulfate concentrations were generally higher in patients who received the 6 oz split-dose regimen than the 4.5 oz split-dose regimen. The median serum sulfate concentrations were 34% higher at the 6-oz dose than the 4.5-oz dose. Note that the sample size in Study BLI800-502 was small with limited sparse PK sample collection.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The overall efficacy and safety results from Study BLI800-502 support a recommendation of the 4.5-oz split-dose regimen for pediatric patients 12 to 16 years of age. No clear dose-response relationship for efficacy was observed between the 4.5-oz and 6-oz doses in Study BLI800-502. From a safety perspective, 4.5 oz dose demonstrated lower rates of several common GI adverse events.

Therapeutic Individualization

Dose individualization based on intrinsic or extrinsic factors is not necessary.

Outstanding Issues

There are no outstanding issues that would preclude the approval of this sNDA from a clinical pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

In pediatric patients who received Suprep treatment in Study BLI800-502, predose serum sulfate concentrations were not quantifiable in all the PK samples. Postdose serum sulfate concentrations on the day of colonoscopy (Day 2) are presented in Table 4. Except for one patient who had a concentration of 0.22 mmol/L on Day 9, all other postdose serum sulfate concentrations on Day 4 (2 days after colonoscopy), Day 9 (7 days after colonoscopy), and Day 32 (30 days after colonoscopy) were not quantifiable (<0.2 mmol/L).

The serum sulfate concentrations were not quantifiable (<0.2 mmol/L) in all the PK samples in the NuLytely treatment group. Of note, NuLytely does not contain sulfate.

Table 4. Serum Sulfate Concentrations on the Day of Colonoscopy in Pediatric Patients Aged 12 to 16 Years in Study BLI800-502

Treatment	Postdose Concentrations (mmol/L)
Suprep 4.5 oz	
N	15
Mean	0.36
Median	0.35
Range (Min-Max)	0.21-0.56
Suprep 6 oz	
N	20
Mean	0.51
Median	0.47
Range (Min-Max)	0.29-1.42

Pediatric patients received Suprep with a "split-dose" 2-day regimen at 4.5 oz (i.e., two 4.5-oz doses, equivalent to 3/4 of the approved adult dose) and 6 oz (i.e., two 6-oz doses, the approved adult dose) doses.
One PK sample for serum sulfate concentrations was collected at each study visit from each patient: predose on Day 1 (Visit 1), postdose on Day 2 (the day of colonoscopy, Visit 2), Day 4 (Visit 3), Day 9 (Visit 4), and Day 32 (Visit 5). PK samples at Visit 2 were collected between 13.8 and 25.4 hours after the first dose.
Lower Limit of Quantitation (LLQ) = 0.2 mmol/L
Source: Reviewer's analysis based on the data provided in Study BLI800-502 report

Following the 6-oz Suprep split-dose regimen, mean sulfate concentrations in pediatric patients on the day of colonoscopy appeared to be similar to that in adult subjects (mean C_{max} of 0.5 mmol/L, Clinical Pharmacology review dated April 10, 2009 in DARRTS). Note that because only a single postdose PK sample was collected from pediatric patients in Study BLI800-502, it is not feasible to accurately estimate the C_{max} in pediatric patients. Based on the review of individual PK data, except for Patient (b) (6), the postdose concentrations observed in all pediatric patients receiving the Suprep treatment were within the range of these observed in adult subjects. Patient (b) (6) was a 14-year-old female patient, received the 6-oz dosing regimen, and had a concentration of 1.42 mmol/L collected at 18.1 hours postdose. The reason for this relatively higher concentration observed in Patient (b) (6) is unknown. Of note, mild adverse events (stomach cramping, stomach bloating, and nausea) were reported for this pediatric patient.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The efficacy of Suprep for cleansing of the colon in preparation for colonoscopy has been demonstrated for the split-dose regimen at both the 4.5-oz and 6-oz doses in Study BLI800-502. See Section 8 of this multidisciplinary review for detailed efficacy results. There is no additional clinical pharmacology information to provide supportive evidence of effectiveness.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

No. We recommend the 4.5 oz split-dose regimen for pediatric patients 12 to 16 years of age, instead of the Applicant-proposed 6 oz split-dose regimen. No clear dose-response relationship for efficacy was observed between the two studied doses. From a safety perspective, 4.5 oz

dose demonstrated lower rates of several common GI adverse events, supporting its selection over 6 oz.

The efficacy results in Study BLI800-502 supported that both the 4.5-oz and 6-oz split-dose regimens are effective. The percentage of preparation success was numerically greater in both the Suprep treatment groups (84.6% at 4.5 oz; 80.6% at 6 oz) as compared to the NuLytely treatment group (59%). The sample size is small to make definitive conclusions about comparative efficacy between the two dose groups, and a clear dose-response relationship was not demonstrated. Nevertheless, noting the small sample size, the observed overall rate of preparation success was numerically higher in the 4.5-oz treatment group than the 6 oz treatment group, and the supportive analyses by "excellent only" grade also favored the 4.5 oz over the 6 oz dose. We do not recommend including an option of a dose of 6 oz because the available data did not show a preferential treatment benefit with the 6-oz dose in any particular subsets of pediatric patients.

From a safety perspective, the rates of several common AEs (including nausea, bloating/distention, and headache) were numerically greater in the 6 oz group than the 4.5 oz group, suggesting that 4.5 oz dosage may be better tolerated. See Section 8.2.3 for detailed safety results.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No, an alternative dosing regimen or management strategy for subpopulations based on intrinsic factors is not necessary. See Section 8 for subgroup analysis results based on age and body weight. Note that the effectiveness of Suprep for cleaning of the colon is not dependent on its systemic exposure; therefore, a systemic exposure-response analysis for efficacy is not needed for further assessment of optimal dosing regimens in subpopulations.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The current submission does not contain additional clinical pharmacology information to update clinically relevant food-drug or drug-drug interactions for Suprep.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 5 summarizes the key attributes of the pivotal phase 3 trial BLI800-502.

Table 5. Listing of Clinical Trials Relevant to This NDA

Controlled Study to Support Efficacy and Safety Trial Identity	Trial Design	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
BLI800-502	Phase 3, MC, R, SB, DR, AC (NuLytely approved in the United States), PG.	2-day split-dose regimen: Suprep Bowel Prep Kit administered as 2 x 6-oz or 2 x 4.5-oz dosing, each diluted with water and administered orally as split-dose regimen. First dose given in the evening before and second dose given in the morning of colonoscopy; compared with NuLytely administered as a single dose the evening before the colonoscopy. After each Suprep dose, subjects were required to take mandatory amount of water/fluids per prescribing information.	Primary: overall preparation of success defined as "Excellent" (Score = 4) and "good" (score = 3) of the colonoscopy scoring system.* Secondary: individual colon segment cleansing for proximal, mid, and distal colon.	2 days FU 7 days	97 randomized, 83 completed	Pediatric subjects ages 12 to 16 years undergoing colonoscopy for routinely accepted indications.	16 study centers in the United States

Abbreviations: AC = active control; DR = dose ranging; FU = follow-up; MC = multicenter; PG = parallel group; R = randomized; SB = single-blind (investigator)
* Each colon segment (proximal, mid, distal) used the following scale: "Excellent" described as no more than small bits of feces/fluid that can be suctioned easily; achieves clear visualization of the entire colonic mucosa, "Good" descr bed as feces and fluid requiring washing and suctioning, but still achieves clear visualization of the entire colonic mucosa.
Source: Compiled by the reviewer

7.2. Review Strategy

The Applicant submitted a single clinical study (Study 502) to support expanding the indication of colon cleansing in preparation for colonoscopy to include pediatric patients ages 12 to 16 years and fulfill the requirement for PMR 1580-3. Comparisons between doses are descriptive in nature given the small size of the study.

The protocol, statistical analysis plan, study report, and data sets were reviewed to evaluate safety and efficacy of 2 doses of Suprep administered as a split-dose regimen compared to single administration dosing regimen of NuLytely.

Primary efficacy was assessed based on colon preparation's success or failure after completion of the colonoscopy examination.

Safety was assessed through the collection of treatment-emergent adverse events, as well as changes in vital signs, physical examination findings, and serum chemistry measures from Visit 1 and follow-up visits. Review was based primarily on the clinical reviewer's independent analysis of the efficacy and safety datasets provided by the Applicant, and secondarily on the Applicant's study report. Narratives and case report forms of patients with serious adverse events (SAEs) were reviewed.

Results of the questionnaire completed by the caregivers were reviewed to evaluate tolerability of Suprep based on the responses to the questionnaire inclusive of the following responses: very badly accepted/unacceptable; badly but accepted; neither good nor bad; well accepted; very well accepted.

8. Statistical and Clinical Evaluation

The Applicant conducted a single clinical trial (Study BLI800-502) to evaluate the safety and efficacy of a bowel cleansing preparation (BLI800) in pediatric subjects undergoing colonoscopy

8.1. Review of Efficacy

8.1.1. Trial Design

A randomized, parallel-group, multicenter, dose-ranging, investigator-blinded study was conducted in the United States at 16 sites and compared the safety and efficacy of two doses (6 oz and 4.5 oz) of Suprep to NuLytely in adolescents (12 years to 16 years).

The study planned to enroll 300 patients and later reduced its sample size to approximately 100 due to difficulties in patient recruitment. The study enrolled 97 pediatric patients who were undergoing a planned colonoscopy for routine indications (including but not limited to diagnosis of possible inflammatory bowel disease, evaluation of chronic diarrhea, anemia, GI bleeding, cancer surveillance, abnormal imaging, etc.).

The study duration for each patient was up to 60 days (including the screening and follow-up period). The trial was conducted over a period of 21 months, initiated on July 13, 2016, and completed on March 27, 2018.

Laboratory parameters were performed at baseline (Visit 1), day of colonoscopy (Visit 2), 24 to 48 hours post colonoscopy (Visit 3), day 7 (Visit 4), and day 30 (Visit 5).

The active comparator (NuLytely) used in the trial is approved in the United States for the proposed indication in pediatric population.

The study design appears appropriate; the general study design is similar to that used for FDA approval of Suprep (NDA 022372) in adults. The follow-up of laboratory parameters at 24 to 48 hours and 7 days after colonoscopy appear reasonable to ascertain occurrence of any biochemical/electrolyte abnormality with the administration of bowel preparation and to assess whether the abnormality returned to the baseline.

8.1.1.1. Amendments to the Original Protocol

The sample size was reduced from 300 to approximately 100 due to difficulty in patient recruitment. On August 15, 2017, the Applicant notified the Division regarding the difficulty in enrollment and proposed reducing the study size to 100. The Applicant enrolled 97 patients, 89 patients received at least some study drug, and 83 patients completed the study. Therefore, only descriptive analysis was performed for all the efficacy endpoints as well as safety due to the smaller number of subjects in each of the three treatment groups.

The Division has traditionally accepted pediatric studies of a similar size to evaluate efficacy and safety for the other bowel preparation products.

Study Population

Inclusion Criteria

- Male or female ages 12 to 16 years (inclusive) scheduled to undergo an elective colonoscopy including but not limited to IBD or IBD follow-up, lower gastrointestinal bleeding, suspected colitis (allergic or other), abdominal pain, chronic diarrhea, cancer surveillance, anemia of unknown etiology, abnormal endosonography, or manometry evaluation of barium enema results
- Females of childbearing potential must have been using an acceptable form of birth control (hormonal birth control, intrauterine device, double-barrier method, or depot

contraceptive) or remain abstinent for the duration of the study with a negative pregnancy test at screening
- Negative pregnancy test at screening, if possible
- Caregiver mentally competent to provide informed consent for the child

Exclusion Criteria

Patients with the following conditions were excluded:

- Known or suspected ileus, fecal impaction, severe ulcerative colitis, acute peritonitis, gastrointestinal obstruction, gastric retention (gastroparesis), bowel perforation, toxic colitis, or megacolon
- Previous significant gastrointestinal surgeries (e.g., colostomy, colectomy, gastric bypass, stomach stapling)
- Increased risk of bowel perforation, including connective tissue disorders, toxic dilation of the bowel or recent bowel surgery
- Uncontrolled pre-existing electrolyte abnormalities, or those with clinically significant electrolyte abnormalities based on Visit 1 laboratory results, such as hypernatremia, hyponatremia, hyperphosphatemia, hypokalemia, hypocalcemia, uncorrected dehydration, or those secondary to the use of diuretics or angiotensin converting enzyme inhibitors
- Bleeding disorders and/or impaired platelet function, or neutropenia
- Prior history of renal, liver, or cardiac insufficiency (including congestive heart failure or other significant cardiac abnormality)
- Estimated glomerular filtration rate below normal range (less than 70 mL/min/1.73m^2)
- Required to take any other oral medication within 3 hours of dosing until completion of both doses
- Impaired consciousness that predisposed them to pulmonary aspiration
- Tendency for nausea and/or vomiting, or who had known swallowing disorders
- Intake of substances was likely to affect gastrointestinal motility or urinary flow rate
- Patients undergoing colonoscopy for foreign body removal and/or decompression
- Abnormal ECG result at Visit 1
- Pregnant or lactating, or intended to become pregnant during the study
- Childbearing potential who refused a pregnancy test
- History of hypersensitivity to any preparation components (BLI800: sodium sulfate, potassium sulfate, magnesium sulfate, and sucralose; NuLytely: polyethylene glycol 3350, sodium bicarbonate, sodium chloride, and potassium chloride)
- In the opinion of the Investigator, should not be included in the study for any reason, including inability to follow study procedures and history of major medical/psychiatric conditions that would compromise the safety of the study
- Participated in an investigational surgical, drug, or device study within the past 30 days
- Withdrew consent before completion of Visit 1 procedures

The inclusion and exclusion criteria appear reasonable.

Study Treatment

The study evaluated two doses of BLI800 (Suprep). Patients were provided the two doses as described:

- two 6-oz doses of Suprep (Suprep adult dose) supplied in 6 oz bottles or
- two 4.5-oz doses of Suprep (3/4 of the adult dose) in 6 oz bottles

The two doses of Suprep used were based on the results of an earlier pilot study (BLI800-501, conducted under PMR 1580-2) described in Section 3.2, Summary of Presubmission/Submission Regulatory Activity.

The study randomized eligible patients to one of three regimens: Suprep 6 oz or Suprep 4.5 oz (both administered as a split-dose regimen), or NuLytely prescribed as a single dose administered as prior-day preparation. Eligible patients for randomization were stratified into one of the following two groups:

- **group 1:** subjects with a baseline weight >40 kg
- **group 2:** subjects with a baseline weight <40 kg

Instructions for Taking Bowel Preparations

Following instructions were provided to the subjects for taking allotted bowel preparation. The dosing commenced in the evening of the day before colonoscopy.

<u>Suprep (6-oz dose)</u>

Two doses of Suprep were provided to the patient.

- Day 1 (evening before colonoscopy):
  - subjects were asked to take the first dose of a 6 oz bottle of study preparation and pour the entire contents into the mixing cup provided and fill the cup with cool water to the fill line (16 oz) and drink the entire cup of solution, and
  - drink two 16 oz cups of water (water in the mixing cup up to the fill line) over the next 1 to 2 hours
- Day 2 (morning of colonoscopy, at least 3 hours prior to the procedure):
  - take the second 6 oz bottle of study preparation and follow the same instruction as for the first dose.

The subjects were asked to drink the complete solution and additional water at least 2 hours before the colonoscopy.

Suprep (4.5-oz dose)

Two doses of Suprep were provided to the patient. Dosing instructions were similar to those for 6-oz dose, as noted above, except that the bottle contained their 4.5-oz dose.

- Day 1 (evening before colonoscopy):
  - subjects were asked to pour the contents of their bottle into the mixing cup provided, and fill with cool water to the fill line (12 oz) and drink the entire cup of solution and
  - drink two 12-oz cups of water (water in the mixing cup up to the fill line) over the next 1 to 2 hours
- Day 2 (morning of colonoscopy, at least 3 hours prior to the procedure):
  - subjects were asked to take the second dose and follow the same instructions as for the first dose

The subjects were asked to drink the complete solution and additional water at least 2 hours before the colonoscopy.

NuLytely

The active comparator used in the pediatric trial, NuLytely, is an FDA-approved bowel preparation (NDA 19-797) for cleansing of the colon before colonoscopy in pediatric patients aged 6 moths and older. NuLytely was supplied as a powder and reconstituted with water before its use to a volume of 4 liters. The active ingredient in NuLytely is PEG 3350 420 grams; it also contains electrolytes (sodium bicarbonate 5.72 grams, sodium chloride 11.2 grams, potassium chloride 1.48 grams, and flavoring ingredients 2 grams). For the pediatric population, the solution was administered, as per labeling instructions, at the rate of 25 mL/kg/hour until watery stool is clear and free of solid matter. It is important to note that NuLytely is administered the night before colonoscopy as a single dose and not as a split-dose regimen.

The following instructions for the single dose of NuLytely were provided to the patient.

- Day 1 (evening before colonoscopy):
  - Tear open 1 flavor pack of choice and pour into NuLytely bottle. Add lukewarm drinking water to the fill mark (4 liters) on the NuLytely bottle. Do not add any other ingredients, flavors, etc.
  - Cap bottle securely and shake it vigorously several times to dissolve powder. The bottle may be refrigerated to improve palatability. Once the solution is reconstituted it must be used within 48 hours.
  - Begin drinking solution at a rate of 25 ml/kg/hour until bowel movements run clear and free of solid matter or until you have completed the entire 4 liters of solution.

8.1.1.2. Dietary Restrictions

Subjects taking Suprep were allowed to have a light breakfast on the day before colonoscopy, followed by clear liquids until the colonoscopy was completed the following day.

Subjects taking NuLytely were permitted to have only clear liquids on the day prior to colonoscopy until completion of the colonoscopy the following day.

Clear liquids for both preparations included water; strained fruit juices (without pulp) including apple, orange, white grape, or white cranberry; limeade or lemonade; Gatorade/Powerade; Ginger Ale; coffee or tea without milk or creamer; chicken broth; and gelatin desserts without added fruit or topping. Purple/red liquids, milk, and alcoholic beverages were not permitted.

While following the labeled dietary plan for NuLytely, and modeling the adolescent Suprep dietary plan after that approved in adults is reasonable, the difference in permitted solid food could potentially bias the efficacy results because continuing solid food later into the preparatory period could result in reduced efficacy.

Procedures and Schedule

Study Procedures

There were five in-person visits during the study.

(1) Screening/Baseline (Visit 1: Day 30 to -1): eligibility criteria and medical history were reviewed. Physical examination and laboratory tests, including an ECG, were performed. Eligible patients for randomization were also stratified into one of the following two groups based on body weight:
   (I) **group 1:** subjects with a baseline weight >40 kg
   (II) **group 2:** subjects with a baseline weight <40 kg
(2) Subjects and caregivers were provided with instructions on how to administer the randomized study preparation and a preparation questionnaire to report their experience with the study preparation. The questionnaire was to be completed from the time of the first dose of study drug until the colonoscopy (Visit 2). For details see Appendix 14.4.1.
(3) Day of colonoscopy (Visit 2): subjects/caregivers were instructed to bring the used or leftover preparation components to determine compliance and return the completed preparation questionnaire. The subjects were asked about occurrence of AEs and any change in concomitant medications. Physical examination including vital signs was performed and blood and urine samples were collected for testing.
(4) Day 4 ± 1 day (Visit 3): patients returned 2 days after the colonoscopy. The subjects were asked about occurrence of AEs and any change in concomitant medications. Vital signs were repeated and blood and urine samples were collected for testing.
(5) Day 9 ± 1 day (Visit 4): Subjects returned 7 days after the colonoscopy. The subjects were asked about occurrence of AEs and any change in concomitant medications. Vital signs were repeated and blood and urine samples were collected for testing.

(6) Day 32 ± 3 days (Visit 5): subjects with persistently abnormal laboratory results and ongoing adverse events at Visit 4 were instructed to return to the study center 30 days (+/- 1 day) after colonoscopy. Additional blood and/or urine samples were collected, and symptoms assessed as indicated. Applicant and Medical Monitor were consulted to determine if additional follow-up was required.

For details of the scheduled assessment and procedures see Table 6.

Table 6. Schedule of Assessments

Procedures	Visit 1 Screening *Between 4 and 30 days prior to colonoscopy*	Day 1 *Day Before Colonoscopy*	Visit 2 Day 2 *Colonoscopy*	Visit 3 Day 4 *(+/- 1 days)*	Visit 4 Day 9 *(+/- 1 days)*	Visit 5* Day 32 *(+/- 1 days)*
Informed Consent/Assent	X					
Inclusion/Exclusion Criteria Review	X					
Medical History	X					
Physical Examination	X		X	X	X	
Vital Signs	X		X	X	X	
Review of Concomitant Medication	X		X	X	X	X
Blood Collection for Serum Chemistry Testing	X		X	X	X	X
Urine Collection for Urinalysis	X		X	X	X	X
Electrocardiogram	X					
Serum Pregnancy Test (if applicable)	X					
Randomization	X					
Dispense Drug & Questionnaires	X					
Instruct Subject	X					
Subject Takes 1st Dose of Preparation		X				
Subject Completes Preparation Questionnaire		X	X			
Subject Takes 2nd Dose of Preparation (BLI800 only)			X			
Subject Completes Symptom Scale			X			
Drug Accountability			X			
Colonoscopy performed with Intra-procedural Safety and Efficacy Grading			X			
Collect and assess adverse event data		X	X	X	X	X

* Visit 5 was performed only for subjects with ongoing adverse events or that have clinically significant lab values at Visit 4.
Source: Table 2 of the BLI800-502 study report

Prior and Concomitant Therapy

Subjects required to take any other oral medication within 3 hours of dosing were excluded. Standard medical treatment(s) taken by the subject were continued during the study.

Treatment Compliance

Study subjects were instructed to bring the used/unused preparation components when they returned for colonoscopy. The compliance was evaluated by assessing the number of used bottles in Suprep group and volume of solution remaining in the NuLytely jug.

8.1.1.3. Study Endpoints

Primary Endpoint

The blinded colonoscopist rated each colon segment (proximal, mid, distal) using the 4-point scale (Table 7) after completion of the exam (during withdrawal of the endoscope) and provided a global rating of preparation quality for the entire colon (inclusive of their perception of all segments). Preparation success was defined as overall cleansing score of "Excellent" (score=4) or "Good" (score=3). A failed preparation was defined as overall cleansing assessment of "Fair" (score=2) or "Poor" (score=1). The efficacy variable was assessed as a binary outcome of overall success or failure. The scale shown in Table 7 is similar to that used in adult studies that supported Suprep Bowel Prep Kit approval. However, some modifications were made for each cleansing Grade for this study to reduce any potential overlap between categories and ensure that a successful rating required complete visualization of the entire colonic mucosa.

Table 7. Segmental Cleansing Assessment

Score	Grade	Description
1	Poor	Large amounts of fecal residue, additional bowel preparation required
2	Fair	Enough feces even after washing and suctioning to prevent clear visualization of the entire colonic mucosa
3	Good	Feces and fluid requiring washing and suctioning, but still achieves clear visualization of the entire colonic mucosa
4	Excellent	No more than small bits of feces/fluid which can be suctioned easily; achieves clear visualization of the entire colonic mucosa

Source: Adapted from Section 4.9.1 of the study protocol

Secondary Endpoints

Secondary efficacy endpoints included proportion of patients with excellent preparation, cleansing score by segment, proportion of examinations that reach the cecum, and volume of additional water used for washing.

Additional Efficacy Endpoints

The following additional metrics were collected:

(1) need for repreparation: if the preparation was not adequate
(2) start time of colonoscopy
(3) time of cecal intubation
(4) completion time of colonoscopy
(5) volume of water used to improve visualization

Items 2, 3, and 4 were used to calculate the total time for the procedure, and items 1 and 5 were included as the supportive efficacy endpoints.

8.1.1.4. Statistical Analysis Plan

As stated above, only descriptive analyses were performed for all the efficacy endpoints as well as safety assessments due to small number of subjects in each of the three treatment groups.

The following definitions of preparation success and failure were used:

Definition of successful preparation:

(1) Overall Cleansing Assessment by the colonoscopist of "Excellent" or "Good" and does not satisfy any of the failure criteria

Definition of failed preparation:

(1) Overall Cleansing Assessment of "Fair" or "Poor" by the colonoscopist
(2) any subject who did not have a colonoscopy based on the Investigator's assessment of the cleansing (insufficient fecal output, unclear fecal discharge, etc.) or due to preparation-related adverse events
(3) any subject for whom cleaning was not adequate for evaluation

The study populations were defined for the data analyses:

- Intention-to-treat (ITT) population: this population included all subjects randomized to treatment
- Modified intention-to-treat (mITT) population: this population consisted of all randomized subjects who took at least one dose of study medication. The mITT population served as the analysis population for all primary and secondary safety and efficacy analyses.
- Per-protocol population: the per-protocol population consisted of all subjects in the mITT population who had not violated any major entry criteria and did not deviate significantly from the protocol during the study.

The mITT population was an appropriate choice for efficacy and safety analyses, and was used in all analyses. The mITT and per-protocol populations were identical in this study.

8.1.2. Study Results

8.1.2.1. Compliance with Good Clinical Practices

The Applicant certified that the requirements of the 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act apply to one or more of the clinical trials referenced in the application/submission, which this certification accompanies. They also certified that the requirements of 42 U.S.C. 282(j), including any applicable provisions of 42 CFR part 11, have been met. In addition, the Applicant provided an Audit Certificate stating that an audit was performed in accordance with Quality Assurance policies and procedures that reflect applicable (b) (4) SOPs, International Conference on Harmonisation Good Clinical Practice, International Organization for Standardization 14155 principles, and local regulations.

8.1.2.2. Data Quality and Integrity

No data integrity concerns were observed. The submission included a complete study report, proposed labeling, appropriate case report forms, and the relevant datasets. The study report was appropriately indexed and organized to allow review.

8.1.2.3. Patient Disposition

Of the 99 patients screened, 97 were randomized (ITT population) into three treatment arms (Suprep 6 oz, Suprep 4.5 oz, and NuLytely) at 16 study sites in the United States. Eight patients did not receive any study drug (one subject in the Suprep 6-oz group, six subjects in the Suprep 4.5-oz group, and one subject in the NuLytely group). The reasons included screen failure in six of the eight patients, physician decision in one patient, and adverse event in one patient.

The mITT population (subjects who took at least one dose of study medication) included 89 patients (Suprep 6 oz=31, Suprep 4.5 oz=26, and NuLytely=32). The mITT population is used for all the efficacy and safety analyses[1].

Table 8 shows patient disposition in the mITT population. Overall, 83/89 (93%) patients completed the study. Five patients in the Suprep 6-oz group and one patient in the NuLytely group discontinued from the study. No patient discontinued in the Suprep 4.5-oz group. The common reasons for the discontinuation in the Suprep group were AE (n=2), lost to follow-up (n=1), withdrawal of consent (n=1), and others (n=1). The reason for discontinuation of the one patient in the NuLytely group was lost to follow-up.

Table 8. Patient Disposition (mITT) in Different Groups

Patient Disposition	Suprep 6 oz N (31)	Suprep 4.5 oz N (26)	NuLytely N (32)
Total number of subjects (%)			
Completed study	26 (84)	26 (100)	31 (97%)
Discontinued study	5 (16%)	0	1 (3%)
Reasons for discontinuation from the study			
Adverse event	2	0	0
Lost to follow-up	1	0	1
Withdrawal of consent	1	0	0
Others	1	0	0

Abbreviations: mITT = modified intention-to-treat
Source: Dataset ADKEYVAR and Table 3 of the BLI800-502 study report

[1] A single subject, (b) (6) was excluded from mITT population, due to incomplete data. This subject is documented to have taken "only sips" of study drug, per notes in the ADAE dataset, before deciding not to continue. While taking some study medication would normally result in inclusion in the safety population, the reviewer was unable to confirm if the patient was actually treated. The datasets were incomplete for this patient, including no documented first dose start date/time, and no date/time for the adverse effects. Given minimal available data and conflicting information as to whether or not the subject actually took the study drug, the clinical reviewer excluded this patient from both safety and efficacy analyses; hence, the mITT population contains 89 patients.

A brief summary of patients who discontinued is provided below.

Suprep 6-oz Group

The following five subjects discontinued from the study:

- Two female patients (b) (6) 6) discontinued from the study due to AE; one due to stomach cramps as well as diarrhea, and another patient due to vomiting. The drug was withdrawn in both patients and colonoscopy procedure was not performed; both patients were considered nonresponder (failure).
- One female patient (b) (6) was lost to follow-up. She reported to have TEAEs of nausea, vomiting, abdominal bloating, and stomach cramps. The patient had colonoscopy and was graded as successful.
- One male patient (b) (6) was discontinued due to other reasons. Patient was reported to have TEAEs of nausea, abdominal bloating, and stomach cramps. Patient had colonoscopy and was graded as successful.
- One female patient (b) (6) withdrew consent. However, she had a colonoscopy that was graded as failure.

NuLytely Group

- One male subject (b) (6) was lost to follow-up. He was reported to have TEAEs of nausea and vomiting; however, he had a colonoscopy that was graded as failure.

Overall, a numeric difference in discontinuations between the two dose levels was noted, favoring the 4.5 oz dose. No patient receiving Suprep 4.5 oz discontinued from the study due to AE compared to two patients receiving Suprep 6 oz. However, the small number of patients per arm limits the ability to draw a definitive conclusions.

8.1.2.4. Treatment Compliance

Overall reported compliance across treatment groups in the mITT population was 80% (subjects completing the entire preparation). Compliance in the Suprep groups was based on completing the full dose of dose 1 and 2 and returning the unused bottles. Three of the five patients did not complete the first dose, two of the five patients did not complete the second dose, and overall three patients returned one unused Suprep bottle each. Additional details for extra water intake were not provided in the application. For the NuLytely group, compliance was based on the quantity of NuLytely solution returned. The volume returned in the NuLytely group ranged from 1,300 mL to 2,000 mL. Numerically, a greater proportion of patients (84%) in the high dose (Suprep 6 oz) group achieved compliance compared to low dose (Suprep 4.5 oz) and comparator (NuLytely) groups, 77% and 75%, respectively (Table 9). Overall, noting the limitations such as not accounting for the volume of additional clear liquid taken with each dose (which is an important part of truly complying with labeled instructions for use) as well as the fact that regardless of the numerically lower rate of compliance in the 4.5oz group, that arm achieved nominally higher rate of success, the compliance data was of limited utility but did not

raise a review issue.

Table 9. Medication Compliance (mITT) in the Different Treatment Groups

	Patient Completing Entire Preparation n (%)			
Patient Compliance	**Suprep 6 oz (N=31)**	**Suprep 4.5 oz (N=26)**	**NuLytely (N=32)**	**All Subjects (N=89)**
Yes	26 (84)	20 (77)	24 (75)	70 (80)
No	4 (13)	6 (23)	8 (25)	18 (20)
X [redacted]*	1 (3)	-	-	-

Abbreviations: mITT = modified intention-to-treat
* Patient (b) (6) was not rated for drug compliance in the data set but returned one bottle of Suprep.
Source: Dataset ADMED and Table 14.1.5 of the study report BLI800-502

Additional assessment was performed to evaluate the incidence of TEAEs in these patients as well as outcome of colonoscopy.

All patients who did not complete the entire preparation in the three treatment groups were associated with ≥1 TEAEs (Table 10). The majority of the TEAEs in the Suprep groups were considered mild to moderate, whereas those reported in the NuLytely group were moderate to severe in intensity.

Nine of the 11 patients across the two Suprep groups achieved successful grading on colonoscopy despite some degree of noncompliance with study drug. The remaining two (both in Suprep 6-oz group) were discontinued from the treatment and did not undergo colonoscopy. In the NuLytely group, four of the eight patients with noncompliance achieved successful grading.

The majority of the patients considered noncompliant achieved successful grading in the two Suprep groups. Noncompliance and associated efficacy were evenly spread out across age groups and not associated with lower or higher age group. However, in the absence of details regarding exact quantity (less than the complete preparation) patients were able to take, it cannot be ascertained the minimum quantity of preparation that is needed to achieve successful grading.

Table 10. TEAEs and Outcome of Colonoscopy in Noncompliant Patients in Different Treatment Groups

Treatment Group	Pt ID/ Age (Yrs)	TEAEs/Treatment Outcome	Colonoscopy Outcome
6 oz Suprep	(b) (6) (12)	Nausea, retching, anorectal discomfort (mild) (Dose not changed)	Success
	(b) (6) (16)	Stomach cramps, diarrhea (mild) (Drug withdrawn)	Failure (Did not have colonoscopy)
	(b) (6) (15)	Nausea, stomach cramps, abdominal pain, abdominal bloating, dizziness (moderate)	Success
	(b) (6) (15)	Stomach cramps, nausea, bloating (mild) (Dose reduced)	Success
	(b) (6) (13)	Vomiting (moderate) (Drug interrupted)	Failure (Did not have colonoscopy)
4.5 oz Suprep	(b) (6) (12)	Nausea, stomach cramps, abdominal bloating (mild to moderate) (Dose not changed)	Success
	(b) (6) (15)	Vomiting, nausea (mild to moderate) (Drug interrupted)	Success
	(b) (6) (15)	Abdominal pain (mild) (Dose not changed)	Failure
	(b) (6) (15)	Abdominal pain and bloating (mild) (Dose not changed)	Success
	(b) (6) (14)	Nausea, vomiting, stomach cramps (mild to moderate) (Dose not changed)	Success
	(b) (6) (12)	Nausea, vomiting, stomach cramps (mild) (Dose not changed)	Success

Treatment Group	Pt ID/ Age (Yrs)	TEAEs/Treatment Outcome	Colonoscopy Outcome
NuLytely	(b) (6) (15)	Nausea, abdominal cramps (moderate) (Dose not changed)	Success
	(b) (6) (14)	Nausea, vomiting (moderate) (Dose not changed)	Failure
	(b) (6) (16)	Nausea, vomiting abdominal cramps, bloating (moderate) (Dose not changed)	Failure
	(b) (6) (14)	Nausea, stomach cramps, bloating (moderate to severe) (Dose not changed)	Success
	(b) (6) (15)	Nausea, abdominal cramps, bloating (mild/moderate) (Dose not changed)	Failure
	(b) (6) (11)	Nausea, vomiting, abdominal cramps (moderate) (Dose not changed)	Failure
	(b) (6) (15)	Nausea, vomiting, abdominal cramps, bloating (moderate and severe) (Dose not changed)	Success
	(b) (6) (16)	Nausea (mild) (Dose not changed)	Success

Abbreviations: TEAE, treatment-emergent adverse event
Source: Compiled by the reviewer from ADMED, ADAE and ADEFF datasets

8.1.2.5. Primary Endpoint

Table 11 shows the primary efficacy results, in the mITT population, based on the responder definition of colon preparation success (responder) defined as achieving overall cleansing grade of "Excellent" or "Good" by the colonoscopist. It is noted that the efficacy analyses include three patients (2 in the Suprep 6-oz group [Patients (b) (6) and 1 in the NuLytely group [Patient (b) (6)) in whom colonoscopy was not performed and who were appropriately considered nonresponders.

Responder rates were numerically greater in the Suprep 6 oz (81%) and Suprep 4.5 oz (85%) groups compared to the NuLytely group (59%). The responder rates within the Suprep groups were numerically higher in the 4.5-oz group (85%) compared to the Suprep 6 oz group (81%). Although the bowel cleansing success rate achieved in the Suprep groups in this pediatric population appears to be lower than that required for colorectal screening in the adult patients to perform high quality colonoscopy procedure and high completion rate (a CIR of ≥95%)[2], it may be acceptable for the pediatric population where the lesions are expected to be bigger and colorectal screening is not the aim in the vast majority of patients. In addition, the modifications to the efficacy assessment scale that occurred between the time of adult approval and initiation of the pediatric study may have resulted in lower estimates of success in the pediatric patients, because the modifications resulted in a more stringent definition of success.

The noninferiority comparison to NuLytely may not be clinically relevant in this trial. First, the efficacy in the NuLytely group was much lower than the comparator in this trial, and in fact lower than what would be considered acceptable for any new bowel preparation product being developed today. Possible reasons for the lower observed efficacy of NuLytely may be inadequate dosing as the age- or weight-based dosing regimen was not utilized, day prior (rather than the currently recommended split-dose) administration, the subjective assessment by the patient/caregiver which informs the total dose ingested (i.e., drink 25 mL/kg/hour orally until *watery stool is clear and free of solid matter* [which must be assessed by parent/caregiver at home]), and/or inability of the pediatric population to ingest the required amount of liquid bowel preparation in one sitting/time. Nevertheless, even with the small sample size the point estimate of the success rate for both doses of Suprep in adolescents was consistent with success rates in other more recently approved bowel preps indicated for this age range.[3]

[2] Maged K Rizk et al. Quality indicators common to all GI endoscopic procedures. Gastrointestinal Endoscopy, 2015 (1): 3-16.
[3] Approved prescribing information for Prepopik; recently expanded indication includes patients down to 9 years of age. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202535lbl.pdf

Table 11. Primary Efficacy: Responder Rates in the Suprep and NuLytely Groups

Responder Rates Grade (n%)	Suprep 6 oz (N=31*)	Suprep 4.5 oz (N=26)	NuLytely (N=32**)	All Subjects (N=89)
Success	25/31 (81)	22/26 (85)	19/32 (59)	66 (74)
Failure	6/31 (19)*	4/26 (15)	13/31 (41)**	23 (26)

* Includes two patients who did not have colonoscopy as failure.
** One patient who did not have colonoscopy as failure
Source: Dataset ADEFF and Table 5 of the Study Report BLI800-502

8.1.2.6. Secondary Endpoints

The following secondary efficacy endpoints were evaluated to provide supportive evidence of efficacy:

- breakdown of successful colon cleansing as good versus excellent
- individual colon segmental cleansing grading
- intraprocedural efficacy endpoints (CIR, procedure time, and irrigation water volume used during the procedure)

Breakdown of Successful Colon Cleansing (Good vs. Excellent)

Table 12 shows the proportion of patients who achieved an overall score of excellent or good. Across the three arms, a numerically greater proportion of patients achieved excellent grading (69%) in the Suprep 4.5 oz group, compared to the 6-oz group (64%) and NuLytely group (28%).

Table 12. Secondary Outcome: Proportion of Patients With Excellent and Good Preparations

	Proportion of Patients in Different Treatment Group n (%)		
Colonoscopic Preparation Grading	Suprep 6 oz (N=31*)	Suprep 4.5 oz (N=26)	NuLytely (N=32**)
Excellent	20 (64)	18 (69)	9 (28)
Good	5 (16)	4 (15)	10 (31)
Fair and poor	4 (13)	4 (15)	12 (37)

* Assessments of the two patients who did not have colonoscopy (Patients (b) (6) in the Suprep 6-oz group are not included in the table.
** Assessment of the one patient who did not have colonoscopy (Patient (b) (6)) in the NuLytely group is not included in the table.
Source: Dataset ADEFF and Table 7 of the study report BLI800-502

Individual Colon Segmental Cleansing Grading

Table 13 shows the results of segmental cleansing, including breakdown of excellent versus good scores in the proximal, mid, and distal colon segments in the mITT population.

Table 13. Segmental Cleansing Assessment (mITT)

Segment Grade n (%)	Suprep 6 oz* (N=31)	Suprep 4.5 oz (N=26)	NuLytely** (N=32)
Proximal colon segment grades			
Overall success***	25 (80)	21 (80)	19 (63)
Excellent	19 (61)	18 (69)	10 (31)
Good	6 (19)	3 (11)	9 (32)
Fair and poor	3 (10)	5 (19)	9 (32)

Segment Grade n (%)	Suprep 6 oz* (N=31)	Suprep 4.5 oz (N=26)	NuLytely** (N=32)
Mid colon segment grades			
Overall success	25 (80)	22 (85)	21 (72)
Excellent	20 (64)	21 (81)	13 (45)
Good	5 (16)	1 (4)	8 (27)
Fair and poor	4 (13)	4 (15)	8 (27)
Distal colon segment grades			
Overall success	23 (74)	23 (88)	19 (62)
Excellent	18 (58)	16 (61)	7 (23)
Good	5 (16)	7 (27)	12 (39)
Fair and poor	6 (19)	3 (11)	12 (39)

Abbreviations: mITT = modified intention-to-treat
* Suprep 6 oz: two patients (b) (6) did not have colonoscopy and one patient (b) (6) did not have proximal colon assessment/grading
** NuLytely: one patient (b) (6)) did not have colonoscopy. Three patients (Patients (b) (6) did not have proximal colon assessment/grading, and two patients (Patients (b) (6) did not have mid colon assessment/grading
*** Overall success: includes Excellent and Good grades
Source: ADEFF datasets and Table 8 of the study protocol BLI800-502

Overall, evaluating cleansing success by segment demonstrates similar trends to those observed for the overall colon cleansing success (primary endpoint). In each segment, the 4.5 oz dose performed as well, or better, than the 6 oz dose or Nulytely, in achieving overall success in the segment. In further support of the selection of the 4.5 oz dose, when considering "excellent only" scores, by segment, the 4.5 oz dose again achieved the numerically highest rate of excellent scores in each segment.

In adults, some reports indicate that it may be more difficult to achieve adequate cleansing in the proximal colon. Thus, looking specifically for adequate cleansing in the proximal colon is of interest. In this case, small numbers of patients per group limit conclusions that can be drawn. In the 4.5 oz group the rate of success in proximal colon was slightly lower than mid and distal, but this trend was not seen in the other two arms. This is not considered to be a meaningful difference given the size of each group.

The results of the comparison of the two Suprep dose groups should be interpreted with caution due to the limitations of the study that includes a small number of patients in the two treatment groups. Nevertheless, segmental cleansing scores appear to support the choice of 4.5-oz dose for adolescent patients.

Intraprocedural Efficacy Endpoints (CIR, Procedure Time, and Irrigation Water Volume Used During the Procedure)

Table 14 shows supportive intraprocedural endpoints that include cecal intubation rates, duration of the procedure, and volume of water used during the colonoscopy for washing to get clear visualization of the mucosal details.

Table 14. Intraprocedural Efficacy Endpoints Based on Colonoscopies Performed

Efficacy Parameters	Suprep 6 oz* (N=29)	Suprep 4.5 oz (N=26)	NuLytely** (N=31)
Proportion of patients in whom caecum reached n (%)			
Yes	28 (97)	25 (96)	28 (90)
No	1 (3)	1 (4)	3 (10)
Procedure duration (min)			
Mean	21.7	23.8	25.6
SD	7.58	13.75	13.36
Irrigation water volume (mL)[2]			
Mean	79.1	48.1	114
SD	140.49	74.36	156.81

* Includes number of patients who had colonoscopy
** Includes number of patients who had colonoscopy
Source: Table 9 of the study report BLI800-502

- Cecal intubation rate*:* CIR was numerically higher in the two Suprep groups compared to the NuLytely group. However, it is important to note that CIR was higher than the responder rate (the primary efficacy endpoint), which may suggest possibility of completing the procedure with additional washing and suctioning in the clinical practice setting even when the colon is not successfully clean. For the bowel cleansing evaluation, CIR evaluation is informative and supportive that the assessment of the ascending colon was performed and ability of the colonoscopist to complete the exam.
- Procedure duration: the duration of procedures was comparable between the three treatment groups.
- Irrigation water volume: the volume (mL) of water used for irrigation during the colonoscopy was numerically lower in the Suprep groups compared to the NuLytely group. Within the Suprep groups lower volume of water was used in the Suprep 4.5 oz group (48 mL) compared to the Suprep 6 oz group (79 mL).

In summary, high CIR in the Suprep 6-oz and 4.5-oz groups (97% and 96%, respectively) compared to NuLytely (90%) appears to be supportive of better cleansing in the Suprep groups, and is reassuring that colonoscopy can be completed with the degree of cleansing that was achieved with Suprep. However, the data on procedure time and water used during the endoscopy are difficult to interpret due to wide range of variability.

8.1.2.7. Subgroup Analyses by Age and Weight To Support Dose Selection

Subgroup analyses were performed to evaluate whether the dose should be the same or different in the older adolescent patients compared to those 12 to 14 years of age. Additional analyses were performed in two ways, by age brackets and weight-based bands.

Age Based Analysis

Table 15 shows efficacy based on age groups of 12 to 14 years and 15 to 16 years.

Table 15. Efficacy Based on Age Subgroups

	Success n/N (%)	
Age Groups	**Suprep 6 oz**	**Suprep 4.5 oz**
12 to 14 years	9/12 (75)	8/10 (80)
15 and 16 years	16/19 (84)	14/16 (87)

Source: Compiled from the ADEFF dataset

In both age cohorts, the proportion of patients with successful preparation were similar or slightly greater, in the 4.5-oz dose group, compared to the 6 oz group. This supports selection of the 4.5 oz dose, as there is not strong evidence to suggest that older patients require the higher dose to achieve adequate efficacy. The results of the comparison of the two Suprep dose groups should be interpreted with caution due to small number of patients in the two sub-groups.

Based on Body Weight

Table 16 shows efficacy results based on body weight less than or equal to 120 lbs compared to more than 120 lbs.

Table 16. Efficacy Based on Body Weight

	Success n/N (%)	
Weight Groups	**Suprep 6 oz**	**Suprep 4.5 oz**
≤120 lbs	5/8 (63)	6/7 (86)
>120 lbs	20/23 (87)	16/19 (84)

Source: Compiled by the reviewer from the ADEFF and AD Weight datasets.

Among patients with greater body weight (those weighing more than 120 lbs), the proportion of patients achieving success was numerically similar in both dose groups. These data do not suggest that a higher dose is needed to achieve adequate success in patients with greater body weight.

As there were many patients with body weight above 150 lbs, efficacy analysis with cut-off at 150 lbs was also performed (Table 17). The results are consistent with the analysis done using 120 lbs cut-off. Again, there is not strong evidence to suggest that 6 oz dose is required in heavier patients to achieve adequate success.

Table 17. Efficacy Analyses With Cut-Off at 150 lbs

	Success n/N (%)	
Weight Groups	**Suprep 6 oz**	**Suprep 4.5 oz**
≤150 lbs	19/23 (82)	14/16 (87)
>150 lbs	6/8 (75)	8/10 (80)

Source: Compiled by the reviewer from the ADEFF and AD Weight datasets

In summary, the subgroup efficacy analyses based on age as well as body weight did not suggest better efficacy of the 6-oz dosing regimen compared to the 4.5-oz dosing regimen for any age or body weight group. It is important to note the limitations and interpretation of the subgroup analyses results due to small number of patients in each group. Safety analyses also

support the approval of the 4.5 oz dose in adolescents 12 years of age and older, refer to Section 8.2.4, Safety Analyses by Demographic Subgroups.

8.1.2.8. Integrated Assessment of Effectiveness

In summary, the point estimates for rate of success in Suprep treated patients (81%, 6 oz; 85%, 4.5 oz) were acceptable and generally support that efficacy was demonstrated in this small, underpowered pediatric study. Numerically a higher proportion of patients in the 4.5 oz group achieved overall success compared to 6 oz or Nulytely. The additional analyses of secondary endpoints (including "excellent only" overall score, and successful cleaning by individual segments) were performed to clarify if the 6-oz dose was more efficacious than the 4.5-oz dose, to aid in dose selection. As described above, the two doses generally performed fairly similarly, and there was no clear evidence to support that the higher dose is necessary. Subgroup analyses were conducted to ensure that a subset of the adolescent population (such as the oldest or highest body weight adolescent patients) did not have decreased or unacceptably low efficacy with the lower dose. There was no evidence to suggest convincingly that the 6-oz dose performed better than the 4.5-oz dose in this limited subset. Thus, from an efficacy perspective, selection of the 4.5-oz dose appears appropriate for patients 12 years to 16 years of age. Additional safety considerations that are relevant to dose selection are discussed in Section 8.2 below.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review was based on independent analysis of the Applicant's datasets and study report for Study BLI800-502; 89 patients (mITT) received at least 1 dose of study drug(s) in the 3 treatment arms.

Bowel cleansing is achieved by inducing copious watery diarrhea. Excessive diarrhea and/or inadequate intake of oral fluids during preparation can often lead to fluid shifts that may result in clinical symptoms of dehydration such as dizziness, syncope/presyncope, orthostatic changes, electrolyte imbalance, and increased serum creatinine. Therefore, the Warning and Precautions section of the Suprep Bowel Prep Kit labeling for adults includes class labeling for the risk of fluid and electrolytes abnormalities, arrhythmias, seizures, and renal impairment. Other common adverse reactions (≥3%) specific to Suprep reported in adults include overall discomfort, abdominal fullness, nausea, abdominal cramping, and vomiting. Pediatric patients have higher body water content, metabolic rates, and increased body surface area to mass index. All of these factors contribute to the patients' higher turnover of fluids and solutes, the proportionally greater volume of water needed as compared to adults to maintain their fluid equilibrium, and their increased susceptibility to volume depletion and associated symptoms. Therefore, TEAEs associated with fluid shifts were evaluated for any increased potential safety signal in pediatric patients. In addition, sulfate levels were assessed.

Suprep Bowel Prep Kit has a higher total sulfate content compared to other approved bowel

preparations. Following initial approval of Suprep in adults, the Applicant completed two PMR studies in adults to evaluate the possibility of systemic absorption of sulfate ions and associated toxicity (refer to section 3.2.2 for a description of these PMRs and the high level results). Although no significant AEs related to the transient higher levels of sulfates were observed in those trials in adults, the sulfate levels were assessed in this study in pediatric patients. Table 4 in Section 6.3.1 above describes the results of the sulfate measurements in the pediatric study. Sulfate levels were, on average, similar to those observed in adults after ingestion of Suprep, and did not appear to pose a safety concern.

The PMR studies conducted to address the safety issues related to sulfate showed no additional safety concerns and PMRs were considered fulfilled.

8.2.2. Adequacy of the Safety Database

The overall safety database for one-time administration of bowel preparations with respect to number of patients treated appears adequate to evaluate safety of Suprep for the pediatric population aged 12 to 16 years. The sample size of the trial is comparable to the typical trial size for a new bowel preparation in the pediatric population. Although only a single trial was submitted with this supplement, the size of the safety population appears adequate to characterize the safety profile of Suprep split-dose regimen compared to NuLytely.

8.2.2.1. Extent of Exposure

Fifty-seven patients were exposed to treatment with Suprep, which included 31 patients exposed to the 6 oz dose, and 26 patients who received the 4.5 oz dose (Table 8). There were 32 patients exposed to NuLytely. Given the intended use is one-time administration, the extent of exposure is considered acceptable.

8.2.2.2. Demographics of the Safety Database

The baseline demographic parameters were similar between the treatment groups in the randomized (ITT) population (Table 18). The majority of the patients enrolled were white and of non-Hispanic or Latino ethnicity (87% to 96%). The racial distribution among the treatment groups was similar. Numerically, a higher proportion of female patients received the high dose of Suprep (6 oz), and a higher proportion of male patients received the low dose of Suprep (4.5 oz). The proportion of male and female patients were similar in the comparator group. The mean age across study groups was about 14 years; up to 60% of patients in each treatment group were in the age group of 15 to 16 years. The demographics are reasonable to represent the intended pediatric population.

Table 18. Demographic Characteristics of the mITT Population

	Treatment Groups (BLI 800) (N=57)		
Demographic Parameters	**Treatment Arm #1 (6 oz) (N=31) n (%)**	**Treatment Arm #2 (4.5 oz) (N=26) n (%)**	**Control Group (NuLytely) (N=32) n (%)**
Sex			
Male	39	62	53
Female	61	38	47
Age			
Mean years (SD)	14.5 (1.1)	14.5 (1.4)	14.3 (1.4)
Age 12-14	12 (38)	10 (38)	14 (44)
Age 15-16	19 (62)	16 (62)	18 (56)
Weight (lbs)			
Mean (SD)	142 (49)	148 (50)	136 (41)
Race			
White	87	85	62
Black or African American	6	15	28
Asian	0		3
Other*	6		6
Ethnicity			
Hispanic or Latino	13	4	9
Not Hispanic or Latino	87	96	91

Abbreviations: mITT = modified intention-to-treat
*American Indian, Mixed
Source: Dataset ADKEYVAR and Table 4 of the study report BLI800-502

8.2.2.3. Categorization of Adverse Events

The Applicant's proposal for recording, coding, and categorizing AEs met established standards. The Applicant provided appropriate definitions of adverse events and SAEs in the study protocol.

The Applicant provided the following guidelines for defining AE:

Any symptom and untoward medical occurrence associated with the use of a drug, whether or not considered drug related. The AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product.

Documentation of the AEs was started at the time the patient provided informed consent to participate in the study and concluded with the completion of Visit 4; for patients requiring Visit 5, AEs were collected until completion of Visit 5.

Subjects were instructed to promptly report AEs to the Investigator. The Investigator recorded date/time of report, date/time of onset, description and severity of the AE, action(s) taken regarding treatment of the AE, action(s) taken regarding study participation, duration of AE, and the Investigator's assessment of relationship of AE to study preparation. The relationship of each AE was categorized as unrelated, possible, probable, and definite as per predefined

criteria described in the study protocol. In addition, the investigator assigned a severity grading for each AE as 1 to 5 (mild, moderate, severe, life threatening, and fatal, respectively).

Serious AEs were defined in accordance with 21 CFR 312.32. The Investigator notified the Applicant immediately or no later than 24 hours after getting the information of the event and made a decision regarding continuing study participation. The Investigator was responsible for providing the patient with appropriate medical therapy, and all patients experiencing SAEs were followed until clinically stable.

See Section 8.1.1, Trial Design for the schedules of the procedures and assessments in the protocol for Study BLI800-502. Schedule of testing and panel of laboratory tests were acceptable.

8.2.3. Safety Results

8.2.3.1. Rates of Adverse Events

Table 19 summarizes TEAEs reported in the three treatment groups. The proportion of patients who developed severe AEs were similar in both Suprep groups.

Table 19. Treatment-Emergent Adverse Events in Safety Population, Study BLI800-502

	Suprep 6 oz (N=31)		Suprep 4.5 oz (N=26)		NuLytely (N=32)	
Treatment-Emergent Adverse Events	**N**	**%**	**N**	**%**	**N**	**%**
Patients with any TEAEs	29	94	24	92	29	91
Patients with severe TEAEs	2	6	1	4	4	12
Patients with serious TEAEs	0	0	0	0	0	0
Patients with TEAEs leading to death	0	0	0	0	0	0
Patients with TEAEs leading to treatment discontinuation	3	10	1	4	1	3

Abbreviations: TEAE = treatment-emergent adverse event
Source: Data set ADAE of the Study BLI800-502

8.2.3.2. Dropouts and/or Drug Discontinuations Due To Adverse Events

The number and proportion of patients who had their dosing interrupted or reduced due to TEAEs are shown in Table 19. Numerically, a higher proportion of subjects in Suprep 6-oz group 3/31 (10%) discontinued/interrupted dosing compared to Suprep 4.5 1/26 (4%) and NuLytely group 1/32 (3%). A brief summary of patients who discontinued dosing due to TEAEs or in whom the dose was reduced is provided below.

Suprep 6 oz

- Dosing was discontinued in three patients:
  - Patient (b) (6) developed TEAE of stomach cramps and diarrhea, which were considered as mild. The drug administration was withdrawn and relationship of TEAE with drug administration was considered possible. The TEAEs were

reported to last 1 month. No medical or surgical intervention was required. Patient did not have colonoscopy and was considered as failure.

  - Patient (b) (6): developed TEAE of abdominal cramps (which was considered severe), as well as nausea, bloating, back pain, and dizziness, which were considered of moderate severity. The drug administration was interrupted and relationship of TEAEs with drug administration was considered probable. The TEAE recovered/resolved within 1 day. No medical or surgical intervention was required. Colonoscopy performed in this patient was considered as success.
  - Patient (b) (6): developed TEAE of vomiting, which was considered of moderate severity. The drug administration was interrupted and relationship of TEAE with drug administration was considered definite. The TEAE recovered/resolved within 1 day. No medical or surgical intervention was required. Patient did not have colonoscopy and was considered as failure.
  -

- The dose was reduced in two patients. The protocol did not specify a standard approach to dose-reduction in patients having difficulty tolerating their prescribed dose.
  - Patient (b) (6): developed TEAE of nausea and stomach cramps, which were considered of mild severity. The drug dose was reduced and the relationship of TEAE with drug administration was considered probable. The TEAE recovered/resolved within 1 day. No medical or surgical intervention was required. Patient had colonoscopy and was considered as success.
  - Patient (b) (6) developed TEAE of nausea, which was considered of mild severity. The drug dose was reduced and the relationship of TEAE with drug administration was considered definite. The TEAE recovered/resolved within 1 day. No medical or surgical intervention was required. Patient had colonoscopy and was considered as success.

Suprep 4.5 oz

- Patient (b) (6): developed TEAE of vomiting, which was considered moderate in severity. The drug administration was interrupted and relationship of TEAEs with drug administration was considered definite. The TEAE recovered/resolved within 1 day. No medical or surgical intervention was required. Patient had colonoscopy and was considered as success.

NuLytely

- Patient (b) (6): developed TEAE of nausea and stomach cramps, which were considered severe, and vomiting, which was considered moderate in severity. The drug administration was interrupted and relationship of TEAEs of nausea and vomiting and drug administration was considered probable. No medical or surgical intervention was required. Patient had colonoscopy and was considered as success.

Most of the patients who discontinued treatment due to AEs were related to the bowel preparation and included nausea, vomiting, abdominal cramps. In view of more patients

discontinuing the study treatment (n=3) and reducing the dose (n=2) in the Suprep high dose (6 oz) group compared to the Suprep low dose (4.5 oz) or NuLytely (n=1 each) groups, it is possible that discontinuation may be related to larger volume (adult dose) of bowel preparation administered in pediatric patients ages 12 to 16 years. However, most of these patients achieved successful colon cleansing.

8.2.3.3. Deaths

No death was reported in any of the treatment groups.

8.2.3.4. Serious Adverse Events

No SAE was reported in any of the treatment groups.

8.2.3.5. Common Adverse Events

There were 122 TEAEs in 29/31 (94%) patients in the Suprep 6-oz group, 76 TEAEs in 24/26 (92%) patients in the 4.5-oz group, and 98 TEAEs in 29/32 (91%) patients in the NuLytely group (Table 20). For the purpose of this review, the related preferred terms were combined to define the TEAEs (see Table 21).

Table 20. Number (%) of Subjects With TEAEs by SOC and PT (mITT)

System Organ Class Preferred Term	Suprep 6 oz (N=31) n (%)	Suprep 4.5 oz (N=26) n (%)	NuLytely (N=32) n (%)
Number of patients with any TEAEs	29 (94)	24 (92)	29 (91)
Gastrointestinal disorders	29 (94)	23 (88)	29 (91)
Nausea	23 (74)	16 (61)	27 (84)
Abdominal pain	22 (71)	18 (69)	20 (62)
Abdominal bloating	21 (68)	9 (35)	17 (53)
Vomiting	6 (19)	6 (23)	12 (37)
Rectal pain	2 (6)	-	1 (3)
Retching, gagging	2 (6)	-	-
Esophageal acid reflux	2 (6)	1 (4)	1 (3)
Others	3 (10)	1 (4)	2 (6)
General disorders and administration site conditions			
Fever	2 (6)	2 (8)	0
Immune system disorders			
Seasonal allergy	0	1 (4)	0
Infections and infestations			
Sinus infection, cold sores, urinary tract infection	0	2 (8)	1(6)
Injury, poisoning, and procedural complications			
Fractured metatarsals, procedural dizziness, knee injury	1 (3)	2 (8)	1 (3)
Investigations			
Urine leucocyte esterase positive	2 (6)	1 (4)	1 (3)
Urine white blood cells increased, bacteria present	1 (3)	1 (4)	0
Blood glucose decreased	1 (3)	0	
Elevated ALT/SGPT/AST (highest 45 U/L)	0	0	1(3)
Urinary protein increased	0	0	1 (3)
H. pylori positive	0	0	1 (3)

System Organ Class Preferred Term	Suprep 6 oz (N=31) n (%)	Suprep 4.5 oz (N=26) n (%)	NuLytely (N=32) n (%)
Musculoskeletal and connective tissue disorders			
Back pain	2 (6)	0	0
Nervous system disorders			
Headache	5 (16)	1(4)	0
Dizziness	2 (6)	0	0
Respiratory, thoracic, and mediastinal disorders			
Sore throat	3 (10)	1 (4)	0
Difficulty breathing	1 (3)		0
Skin and subcutaneous tissue disorders			
Facial rash	0	1 (4)	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; mITT = modified intention-to-treat; PT = preferred term; SGPT = serum glutamic pyruvic transaminase; SOC = system organ class; TEAE = treatment-emergent adverse event
Note: some of these patients had ≥1 symptoms
Source: ADAE.XPT data set of the study BLI800-502

Table 21. Combined Terms and PTs for TEAEs

TEAEs (Combined Term)	Included Preferred Term
Abdominal pain	Abdominal pain, abdominal cramps, abdominal pain aggravated, abdominal lower, lower abdominal tenderness, periumbilical pain, stomach ache, stomach cramps
Abdominal bloating	Abdominal bloating, bloating, gas
Nausea	Nausea, nausea aggravated
Retching	Retching, gagging
Rectal pain	Rectal pain, anorectal discomfort, burning rectal, rectal tenesmus
Esophageal acid reflux	Esophageal acid reflux, esophagitis, stomach ulcer
Others	Mouth ulcers, diarrhea, ulcerative colitis aggravated, blood in stool, rectal bleeding, stomach upset
Fever	Fever, malaise
Urine leucocyte esterase positive	Urine leucocyte esterase positive, bacteria urine identified
Back pain	Back pain, back pain aggravated, myalgia aggravated
Headache	Headache aggravated, migraine type headache
Dizziness	Dizziness, dizziness on standing
Sore throat	Sore throat, throat pain, throat burning sensation

Abbreviations: PT = preferred term; TEAE = treatment-emergent adverse event
Source: Compiled by reviewer

Overall, the proportion of patients who reported any TEAEs were comparable in the three treatment groups (Table 20). As expected, GI events were the most common and experienced by approximately 90% of the patients; a succinct summary of GI related TEAEs is provided below.

Nausea, abdominal pain, abdominal bloating, and vomiting were the most frequent GI events in all treatment groups. Numerically, a higher proportion of patients reported abdominal pain in both the Suprep groups, whereas a higher proportion of patients reported nausea and vomiting in the NuLytely group. Within the Suprep groups, numerically a higher proportion of patients in the Suprep 6 oz group, compared to Suprep 4.5 oz, reported overall GI disorders (94% vs 88%), as well as common AEs associated with ingestion of bowel preparations such as, nausea (74% vs

61%), abdominal bloating (68% vs 35%), headache (16% vs 4%) and retching (6% vs 0%); other common adverse events were similar- abdominal pain (71% vs 69%) and esophageal acid reflux (6% vs 4%). However, numerically a higher proportion of patients in Suprep 4.5 oz group, compared to the 6 oz group, reported vomiting (23% vs 19%); it is noted that the number of patients were same (n=6) in the two groups.

Numbers of TEAEs related to the other system organ class/preferred term were small, and no safety signal was identified related to the study drug administration.

8.2.3.6. Significant Adverse Events

Significant TEAEs (AEs graded by the investigator as "severe" in intensity) were reported in 2/31 (6%) and 2/26 (8%) patients in the high dose (6 oz) and low dose (4.5 oz) groups, respectively, compared to 4/32 (12%) patients in the NuLytely group (Table 19). A brief narrative of patients who reported severe TEAEs in the 3 treatment groups is provided below.

Suprep 6 oz

- Patient (b) (6): developed TEAE of abdominal cramps, which was considered severe. The drug administration was interrupted and relationship of TEAE with drug administration was considered probable (also see TEAEs leading to treatment discontinuation in Section 8.2.3.2). The TEAE recovered/resolved within 1 day. No medical or surgical intervention was required.
- Patient (b) (6): developed TEAE of lower abdominal pain, which was considered severe. The drug administration was not changed and relationship with the drug administration was considered definite. The AE recovered/resolved within one day. No medical or surgical intervention was required.

Suprep 4.5 oz

- Patient (b) (6): developed TEAE of nausea, which was considered severe. The drug administration not changed and relationship of TEAE with drug administration was considered probable. The TEAE recovered/resolved within 1 day. No medical or surgical intervention was required. Patients continued in the study.
- Patient (b) (6): developed TEAE of allergy to nuts, which was considered severe. The drug administration interrupted and relationship with the drug administration was considered unrelated. The AE recovered/resolved within one day. No medical or surgical intervention was required. Patient was discontinued from the study.

NuLytely

- Patient (b) (6): developed TEAE of nausea, which was considered severe. The drug dose was not changed and relationship of TEAE and drug administration was considered definite. The TEAE recovered/resolved within 1 day. No medical or surgical intervention was required.

- Patient (b) (6): developed TEAE of stomach cramps, which was considered severe. The drug dose was not changed and relationship of TEAE and drug administration was considered definite. The TEAE recovered/resolved the same day. No medical or surgical intervention was required.
- Patient (b) (6): developed TEAEs of nausea, vomiting, and stomach cramps, which were considered severe. The drug dose was interrupted and relationship of TEAE and drug administration was considered definite. The TEAEs recovered/resolved in 2 days. No medical or surgical intervention was required.
- Patient (b) (6): developed TEAE of nausea which was considered severe. The drug dose was not changed and relationship of TEAE and drug administration was considered probable. The TEAE recovered/resolved the same day. No medical or surgical intervention was required.

Numerically, a higher proportion (12%) of patients in the NuLytely group had severe TEAEs compared to the Suprep high and low dose groups (6% and 8%, respectively). Overall, GI-related severe TEAEs included nausea, vomiting, and abdominal pain/cramps. However, due to the small number of patients in each treatment group it is difficult to draw definitive conclusion regarding higher incidence of severe TEAEs related to the NuLytely group. These events (type and duration) reflect known adverse events associated with bowel preparation, and reassuringly all resolved promptly with discontinuation of medication and did not require further intervention.

For exploratory purposes, the commonly reported TEAEs in adolescents were compared to the TEAEs observed during the adult trial (Study 302). The most common GI- and CNS-related TEAEs reported in pediatric patients (Study BLI800-502) and adult patients (study 301) are described based on the labeling information and medical officer's safety review of the approved NDA for adults (Table 22).

Table 22. Proportion of Patients With Key TEAEs Related to the SOC of Gastrointestinal and Nervous System Disorders

System Organ Class Preferred Term	Suprep 6 oz (N=31) n (%)	Suprep 4.5 oz (N=26) n (%)	Suprep Adult Study* (N=190) n (%)
Number of patients with any TEAEs	29 (94)	24 (92)	132 (69)
Gastrointestinal disorders	29 (94)	23 (88)	119(62)
Overall discomfort	-	-	(54)
Nausea	23 (74)	16 (61)	69(36)
Abdominal pain	22 (71)	18 (69)	69(36)
Abdominal bloating/distension	21 (68)	9 (35)	77(40)
Vomiting	6 (19)	6 (23)	16(8)
Rectal pain	2 (6)	-	-
Retching, gagging	2 (6)	-	-
Esophageal acid reflux	2 (6)	1 (4)	-
Others	3 (10)	1 (4)	
Nervous system disorders			
Headache	5 (16)	1 (4)	1(0.5)
Dizziness	2 (6)	0	0

Abbreviations: SOC = system organ class; TEAE = treatment-emergent adverse event
* Split-day dosing regimen
Source: Labeling information of Suprep and Tables 31-32 of the Medical officer NDA review

Although there are limitations to cross-study comparisons, the purpose of the above comparison is to give an overall picture of how the safety profile in pediatric patients 12 and older may compare with the described safety profile in adults. Generally, a higher proportion of pediatric patients appeared to report GI-related TEAEs including nausea, vomiting, abdominal pain, and abdominal distension. Numerically, a higher proportion of pediatric patients also reported TEAEs of headache and dizziness. This may potentially represent a greater sensitivity to the effect of the study drug in younger patients.

8.2.3.7. Adverse Events of Special Interest

There were no specific adverse events of special interest that were specified in the protocol. In general, electrolyte changes and fluid shifts are the main safety concerns of interest for bowel preparation products

8.2.3.8. Laboratory Findings and Additional Safety Assessments:

Shift table analyses for changes in the serum electrolytes, osmolality, blood urea nitrogen, and creatinine were performed to evaluate safety. The evaluation included any change from baseline at Visit 2 (at colonoscopy) and follow-up Visit 3 (48 to 72 hours) after the Suprep dosing. Additional follow-up evaluation was performed to assess resolution of the abnormal levels. No clinically meaningful changes were observed during the study for the majority of the laboratory tests, including for sodium, potassium, bicarbonate, calcium, and magnesium (detailed analysis not shown).[4] Greater numbers of patients demonstrated shifts in serum osmolality, anion gap, creatinine, and glucose. Further details of the analyses of these parameters are shown below. Additionally, sulfate levels were evaluated; no safety concern related to transient elevations of serum sulfate was identified.

Osmolality

Table 23 shows patients with normal baseline values that were reported to have high osmolality in the three treatment groups at follow-up Visits 2, 3, and 4. The patients in each treatment group are summarized below.

[4] Refer to Tables 13 and 14 of the Clinical Study Report BLI800-502. The key results were verified by the Clinical Data Science team.

Table 23. Proportion of Patients With High Osmolality at Follow-Up*

Visit	Suprep 6 oz n/N (%)	Suprep 4.5 oz n/N (%)	NuLytely n/N (%)
2 (Day 2)	3/16 (19)	2/11 (18)	4/17 (23)
3 (Day 4)	6/16 (37)	2/11 (18)	5/17 (29)
4 (Day 9)	5/16 (31)	3/11 (27)	6/17 (35)

*Represents patients with normal osmolality at baseline
Source: Compiled from Study BLI800-502 datasets ADLB

Compared to baseline, a small increase (difference from baseline varied between 3 and 13 mOsm/kg) in the serum osmolality was observed in some patients, at Visit 2; the increase was comparable across the treatment groups. One patient in the NuLytely reported a clinically meaningful fall in the standing blood pressure >10 mm of Hg. They reported a fall of systolic blood pressure of 15 mm from baseline of 123 mm of Hg at Visit 2. The small increase in osmolality trended towards normal on follow-up visits in most of the patients and appear unlikely to be of any safety concern. However, high osmolality was reported in some patients at Visits 3 and 4 for the first time. This may be a chance finding but is considered less likely to be study drug–related, as changes in fluid status that might affect osmolality would be most likely to be present immediately after catharsis (for details see Appendix 14.4.2).

Anion Gap

Table 24 shows patients with normal baseline anion gap who reported to have high anion gap at Visits 2, 3, and 4. Patients with high baseline anion gap and missing values are not included in this assessment. The patients in each treatment group are summarized below.

Table 24. Proportion of Patients With High Anion-Gap at Follow-Up*

Visit	Suprep 6 oz n/N (%)	Suprep 4.5 oz n/N (%)	NuLytely n/N (%)
2	4/19 (21)	8/21 (37)	2/25 (8)
3	1/19 (6)	0	0
4	0	0	0

*Represents patients with normal anion-gap at baseline
Source: Compiled from Study BLI800-502 datasets ADLB

Numerically, a higher proportion of patients in the two Suprep dose groups were reported to have a transient and reversible increase in the anion gap compared to the NuLytely group. None of the patients had other signs and symptoms of dehydration or a postural hypotension (a decrease of >10 mm of Hg systolic blood pressure from baseline). All values in the two Suprep groups noted at Visit 2 returned to normal within 2 days on the next visit (Visit 3). A single patient had first occurrence of high anion gap noted at Visit 3 (Suprep 6oz arm), which also was documented to resolve by the subsequent follow-up visit. The change from the upper limit of normal was small (4 to 15) and unlikely to be clinically meaningful and of additional safety concern in the absence of signs and symptoms of dehydration (for details see Appendix 14.4.3).

Creatinine

Evaluation of patients shifting from normal to 1.5 times the upper limit of normal/baseline (considered a marker of potential acute kidney injury) for serum creatinine was conducted. A

single patient who received the 4.5-oz dose of Suprep met this criterion. Details of this case are summarized below.

A 12-year-old patient (b) (6) reported nausea, vomiting, and stomach cramping but no dizziness or postural hypotension on Visit 2 (day of colonoscopy); all symptoms resolved on the same day. He also had a minimal increase of anion gap of 6 mEq/L from his baseline to 8 mEq/L at Visit 2, which returned to 7 mEq/L (normal value: 3–11 mEq/L) on the next visit (Day 9). In addition, patient was reported to have a serum creatinine of 0.81 mg/dL at Visit 4 (Day 9), an increase of serum creatinine (1.5 times baseline) from baseline of 0.53 mg/dL. As the high value of 0.81 mg/dL was within the normal limit of 1.00 mg/dL, no further follow-up testing was performed. As per labeling, patients are encouraged to take additional liquids to prevent electrolyte abnormalities. The reports of transient minimal changes in the anion gap and creatinine are considered unlikely to suggest a new safety risk.

Glucose

A decrease in blood glucose is expected in patients undergoing preparation for colonoscopy since they are fasting overnight. Only one patient each in Suprep and NuLytely groups reported low glucose values; the low glucose in the Suprep group did not reach a level of safety concern. However, one patient in the NuLytely group reported a level of 39 mg/dL on Visit 3 (Day 4), 2 days after the day of colonoscopy. Reported AEs in this patient included nausea and bloating on the day of preparation, which resolved. Follow-up glucose was within normal limits.

Sulfate

No safety concern related to the sulfate was identified, see Section 6.3.1.

Vital Signs

The vital signs reported at Visit 1 (screening), Visit 2 (day of colonoscopy), and follow-up Visits 3 and 4 (Days 4 and 9) are summarized in Appendix-14.4.4 The vital signs reported on Day 32 (Visit 5) are not shown due to low number of patients followed up to this visit. No clinically relevant postural changes in heart rate, systolic/diastolic blood pressure, and temperature were reported in any of the treatment groups.

8.2.4. Safety Analyses by Demographic Subgroups

Additional safety analyses were performed for the subgroups that were evaluated for efficacy based on age and weight (Section 8.1.2, Study Results). The safety was focused on the most common TEAEs related to the administration of bowel preparations such as nausea, vomiting, stomach cramps, abdominal pain, and abdominal bloating (Table 25, Table 26, Table 27, Table 28). Additionally, the proportion of patients who discontinued and/or were noncompliant were also assessed. The tables reflect the number of patients with each event, and one patient may have had more than one TEAE.

Table 25 shows comparison of TEAEs between the 6-oz and 4.5-oz dosing regimens in patients aged 12 to 14 years. A higher proportion of patients in the 6-oz dose group reported nausea, stomach cramps, and abdominal bloating compared to those in the 4.5-oz dose group.

Table 25. Safety Based on Age Group Up to 14 Years

	Patients with TEAEs n/N (%)	
TEAEs	**6 oz**	**4.5 oz**
Nausea	10/12 (83)	7/10 (70)
Vomiting	4/12 (33)	4/10 (40)
Stomach cramps	8/12 (66)	6/10 (60)
Abdominal pain	1/12 (8)	1/10 (10)
Abdominal bloating	9/12 (75)	2/10 (20)
Discontinuation and/or noncompliance	2/12 (16)	3/10 (30)

Abbreviations: TEAE = treatment-emergent adverse event
Source: Compiled by the reviewer

Table 26 shows a comparison of TEAEs between the 6-oz and 4.5-oz dosing regimens in patients aged 15 and 16 years. A higher proportion of patients in the 6-oz dose group reported nausea, vomiting, abdominal pain, and bloating compared to those in the 4.5-oz dose group.

Table 26. Safety Based on Age Group of 15 Years and 16 Years

	Patients with TEAEs n/N(%)	
TEAEs	**6 oz**	**4.5 oz**
Nausea	13/19 (68)	9/16 (56)
Vomiting	3/19 (16)	2/16 (12)
Stomach cramps	12/19 (63)	10/16 (62)
Abdominal pain	3/19 (16)	2/16 (10)
Abdominal bloating	11/19 (58)	7/16 (44)
Discontinuation and/or noncompliance	4/19 (21)	3/16(19)

Abbreviations: TEAE = treatment-emergent adverse event
Source: Compiled by the reviewer

Table 27 shows a comparison of TEAEs between the 6-oz and 4.5-oz dosing regimens in patients weighing more than 120 lbs. A higher proportion of patients in the 6-oz dose group reported nausea, stomach cramps, and abdominal bloating compared to those in the 4.5-oz dose group.

Table 27. Safety Based on Body Weight >120 lbs

	Patients with TEAEs n/N(%)	
TEAEs	**6 oz**	**4.5 oz**
Nausea	18/23 (78)	12/19 (63)
Vomiting	4/23 (17)	4/19 (21)
Stomach cramps	17/23 (74)	13/19 (68)
Abdominal pain	4/23 (17)	3/19 (16)
Abdominal bloating	16/23 (69)	8/19 (42)
Discontinuation and/or noncompliance	5/23 (22)	5/19 (26)

Abbreviations: TEAE = treatment-emergent adverse event
Source: Compiled by the reviewer

Table 28 shows a comparison of TEAEs between the 6-oz and 4.5-oz dosing regimens in patients weighing equal to or less than 120 lbs. A higher proportion of patients in the 6-oz dose group reported vomiting, abdominal pain, and abdominal bloating compared to those in the 4.5-oz dose group. A higher proportion of patients in the 4.5-oz group reported nausea and stomach cramps.

Table 28. Safety Based on Body Weight ≤120 lbs

	Patients with TEAEs n/N(%)	
TEAEs	**6 oz**	**4.5 oz**
Nausea	4/8 (50)	4/7 (57)
Vomiting	3/8 (37)	2/7 (28)
Stomach cramps	3/8 (37)	3/7 (43)
Abdominal pain	1/8 (12)	0/7 (0)
Abdominal bloating	4/8 (50)	1/7 (14)
Discontinuation and/or noncompliance	1/8 (12)	0/7(0)

Abbreviations: TEAE = treatment-emergent adverse event
Source: Compiled by the reviewer

In summary, the subgroup safety analyses showed that the patients in the two age groups as well as two weight groups reported numerically higher TEAEs with 6-oz dosing regimen compared to 4.5-oz dosing regimen. Discontinuation or noncompliance were similar for the two dosing regimens. The results support selection of the 4.5 oz dose in pediatric patients as it appears to be better tolerated.

8.2.5. Integrated Assessment of Safety

A total of 89 patients, who received at least a part of the study treatment, were included for the safety assessment of Suprep bowel preparation compared to the approved NuLytely bowel preparation. The number of pediatric patients in this clinical development program appears reasonable to evaluate safety in pediatric patients, in addition to available supportive safety data from a well-controlled trial in adults and available postmarketing experience.

The majority of patients experienced ≥1 TEAE during the trial. There were 122 TEAEs in 29/31 (94%) patients in the Suprep high dose (6 oz) group, 76 TEAEs in 24/26 (92%) patients in the Suprep low dose (4.5 oz) group, and 98 TEAEs in 29/32 (91%) patients in the NuLytely group. The majority of these TEAEs were considered mild and moderate.

The most common TEAEs were similar in the three treatment groups and included nausea, vomiting, abdominal pain, and abdominal bloating. These events are expected with administration of bowel cleansing agents. However, a higher proportion of patients in Suprep high dose (6 oz) group reported nausea, abdominal pain, abdominal bloating, retching, and esophageal reflux, compared to Suprep low dose (4.5 oz) and NuLytely groups; a higher proportion of patients in Suprep low dose group reported vomiting. Subgroup safety analyses, based on the age groups (12 to 14 years versus 15 and 16 years) and weight-based groups (>120 lbs versus less or equal to 120 lbs) were performed for TEAEs that are commonly associated with bowel preparations (nausea, vomiting, and abdominal bloating/pain). The dosing regimen of 6 oz was observed to be associated with a numerically higher rate of several of these TEAEs compared to the 4.5-oz dosing regimen in majority of the subgroups. Although most of the observed TEAEs in pediatric patients were similar to those reported in the adult split-dose trial, a higher incidence of overall GI-related TEAEs (including nausea, vomiting, abdominal pain, and abdominal distension) as well as headache and dizziness were reported in the pediatric patients. Review of the laboratory safety data did not identify any new safety signals. The mean sulfate concentrations on the day of colonoscopy appeared to be similar to

that in adult patients (mean C_{max} of 0.5 mmol/L) except in one patient (b) (6) who was a 14-year-old female and received the 6-oz dosing regimen; the sulfate concentration was 1.42 mmol/L at 18.1 hours postdose. The reason for this relatively higher concentration observed in this patient is unknown. Overall the sulfate levels reported in the pediatric study were consistent with those reported in adult patients (<~0.50 mmol/L) and do not generate a safety concern. For additional details see Section 6.3.1.

In summary, the available data are sufficient to characterize the safety profile of Suprep and demonstrated an acceptable benefit risk profile for use in the pediatric patients. However, in view of the numerically higher TEAEs reported in the Suprep high dose (6 oz) group compared to the Suprep low dose (4.5 oz) group and similar efficacy between the two Suprep doses, the 4.5-oz dose is recommended for approval.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

The tolerability of each dose was assessed by caregivers using a categorical scale based on the following responses in the questionnaire: very badly accepted/unacceptable; badly but accepted; neither good nor bad; well accepted; very well accepted (for details see Appendix 14.4.1).

Table 29 shows patient responses for the first and second dose of Suprep compared to single dose of NuLytely.

Table 29. Preparation Tolerability by Dose

Parameter	Suprep 6 oz (n=31)	Suprep 4.5 oz (n=26)	NuLytely (n=32)
First dose tolerability (n%)			
Very badly accepted/unacceptable	2 (7)	2 (7)	9 (29)
Badly but accepted	13 (46)	14 (54)	14 (45)
Neither good nor bad	7(25)	4 (15)	4 (13)
Well accepted	3 (11)	2 (8)	2 (6)
Very well accepted	3 (11)	4 (15)	2 (6)
Second dose tolerability (n%)			
Very badly accepted/unacceptable	2 (7)	5 (19)	NA
Badly but accepted	10 (38)	11 (42)	NA
Neither good nor bad	8 (3)	4 (15)	NA
Well accepted	3 (11)	2 (8)	NA
Very well accepted	3 (11)	4 (15)	NA

Source: Table 14.3.8 of the Study Report BLI800-502

Numerically, a higher proportion of patients in the NuLytely group (29%) responded as unacceptable compared to the 6 oz and 4.5 oz Suprep groups (7% each). Within the Suprep groups (i.e., 6 and 4.5 oz), the proportion of patients for each response were comparable. Due to the limited number of patients in each of the five responses, the results should be interpreted with caution.

8.2.7. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable.

Expectations on Safety in the Postmarket Setting

The demonstrated safety profile in trial BLI800-502 was consistent with the safety profile demonstrated in adults. No additional post-approval studies for safety will be required.

8.2.8. Integrated Assessment of Safety

Not applicable.

8.3. Conclusions and Recommendations

Table 30 summarizes the efficacy and safety of the two Suprep dosing regimens. Patients in the Suprep 4.5-oz dose group showed numerically better efficacy and safety profile compared to the Suprep 6-oz dose. Several subgroup efficacy and safety analyses performed based on the age (12 to 14 years and 15 to 16 years) and body weight (≤120 lbs and >120 lbs) do not support labeling the higher 6-oz dosing regimen in older adolescents or those with higher body weight. It is acknowledged that a change of grading by one category (from fair to good or vice versa) even in one to two patients may change the differences in efficacy between the two Suprep dosing groups.

Table 30. Overall Comparison of Efficacy and Safety of the Two Suprep Doses

Parameter	6 oz	4.5 oz	In Favor
Discontinued (%)	16	0	4.5 oz
Medication compliance (%)	84	77	6 oz
Primary efficacy	81	85	4.5 oz
Secondary efficacy (%)			
Excellent	64	69	4.5 oz
Good	16	15	
Segmental cleansing grades			
Proximal colon segment grade [n (%)]			
Overall success**	25 (80)	21 (80)	
Excellent	19 (61)	18 (69)	4.5 oz
Good	6 (19)	3 (11)	
Mid colon cleansing grade [n (%)]			
Overall success	25 (80)	22 (85)	
Excellent	20 (64)	21 (81)	4.5 oz
Good	5 (16)	1 (4)	
Distal colon cleansing grade [n(%)]			
Overall success	23 (74)	23 (88)	
Excellent	18 (58)	16 (61)	4.5 oz
Good	5 (16)	7 (27)	

Parameter	6 oz	4.5 oz	In Favor
Safety	94	92	
Gastrointestinal disorders	29 (94)	23 (88)	4.5 oz
Nausea	23 (74)	16 (61)	4.5 oz
Abdominal pain	22 (71)	18 (69)	4.5 oz
Abdominal bloating/distension	21 (68)	9 (35)	4.5 oz
Vomiting	6 (19)	6 (23)	6 oz
Rectal pain	2 (6)	-	4.5 oz
Retching, gagging	2 (6)	-	4.5 oz
Esophageal acid reflux	2 (6)	1 (4)	
Others	3 (10)	1 (4)	
Nervous system disorders			
Headache	5 (16)	1 (4)	4.5 oz
Dizziness	2 (6)	0	4.5 oz

Source: Compiled by the reviewer

Overall, a more favorable benefit/risk profile is observed in the Suprep 4.5-oz group compared to the 6-oz dose. Therefore, the Suprep 4.5-oz dose is recommended for approval.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was not needed for this NDA supplement.

9.1. Pediatrics

This application contains results of a study conducted to fulfill a PMR issued under Pediatric Research Equity Act (PMR 1580-3) at the time of initial approval. The contents of this submission are adequate to consider the PMR fulfilled. Pediatric dosing and labeling considerations were made in consultation with Division of Pediatrics and Maternal health colleagues. Please refer to review by Dr. Erica Radden for additional details.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Prescribing Information

The following is a summary of high-level changes made to the label with approval of this supplement. These were discussed among the review team members during the review cycle as well with the Applicant.

Section 2 DOSAGE AND ADMINISTRATION

- Added a separate section for pediatric patients 12 years of age and older to provide instructions for administration of the 4.5 oz dose including necessary additional water and dietary instructions.

Section 3 DOSAGE FORMS AND STRENGTHS

- Modified to include information on Suprep Bowel Prep Kit (for adults) as well as a new, separate Suprep Bowel Prep Kit (for pediatric patients 12 years of age and older) to align with planned container/carton and differentiate which kit will be dispensed.

Section 6: Clinical Studies Experience

- Updated to describe the pediatric population studied using the mITT population.
- Most common (>10%) TEAEs reported in the to-be-marketed dose arm (4.5 oz), for the pediatric patients, during the clinical trial were added (nausea, abdominal pain, abdominal bloating, and vomiting).
- Adult laboratory shift data (Table 2) were simplified, to be consistent with more recently approved products' labels; data are now limited to shifts which were most prevalent (at least 10% in either arm) and where there was at least 2% difference between arms.

Section 8.4: Pediatric Use

- The safety and effectiveness of Suprep Bowel Prep Kit for cleansing of the colon as a preparation for colonoscopy in pediatric patients 12 years of age and older was added based on the efficacy and safety analyses of the Study BLI800-502.
- Rationale for not approving the 6 oz dose (no additional treatment benefit observed, more frequent GI adverse reactions) was added.

Section 14: Clinical Studies

- Details of the clinical study (BLI800-502) design, key demographic attributes, and efficacy results were added.
- Study population and demographics were described based on mITT population that was used throughout this review.
- Efficacy results are presented only for the to-be-marketed 4.5 oz dose and comparator; (b) (4)

Section 16: How Supplied/Storage and Handling

- Updated to note that there are two kits (Suprep bowel prep kit for adults, and Suprep bowel prep kit for pediatric patients 12 years and older).
- Availability of a mixing container with a 12-oz fill line for the 4.5-oz dosing regimen was included for the pediatric patients 12 years of age and older.

11. Risk Evaluation and Mitigation Strategies

Risks will be communicated in prescribing information and medication guide; no risk evaluation and mitigation strategies are necessary.

12. Postmarketing Requirements and Commitment

No additional postmarketing requirements or commitments are deemed necessary at this time.

13. Signatory Comments (Acting Division Director, Division of Gastroenterology)

I concur with the recommendation of the review team to approve supplemental NDA 022372/S-013 for Suprep Bowel Prep Kit (sodium sulfate, magnesium sulfate, and potassium sulfate) to expand the indication to include pediatric patients 12 years of age and older. Suprep Bowel Prep Kit, an osmotic laxative, was approved in 2010 for cleansing of the colon prior to colonoscopy in adults as a split-dose (two-day) regimen. The recommended dosage is two 6-ounce doses in adults and two 4.5-ounce doses in pediatric patients 12 years of age and older.

I agree with the review team that data submitted in this sNDA are adequate to support a conclusion that the effectiveness of Suprep Bowel Prep Kit has been established in the intended pediatric population. Efficacy of Suprep Bowel Prep Kit in pediatric patients 12 years of age and older is supported, in part, by extrapolation of efficacy from an adequate and well-controlled trials in adults, relying upon the similarity of the anticipated response to treatment between adults and pediatric patients undergoing bowel preparation prior to colonoscopy. This sNDA submission included results from a dose-ranging, controlled clinical trial conducted in 89 pediatric patients, which demonstrated that the efficacy of Suprep Bowel Prep Kit (both 4.5-ounce and 6-ounce doses) was numerically greater than that of an approved comparator (NuLytely). The two 6-ounce doses did not demonstrate additional treatment benefit and more patients reported gastrointestinal adverse reactions compared to the two 4.5-ounce doses; therefore, the 4.5-ounce dosage is recommended for pediatric patients 12 years of age and older.

The safety profile of SUPREP Bowel Prep Kit (two 4.5-ounce doses) in this pediatric population was similar to that seen in adults; no new safety signals were identified. The most common adverse reactions reported in pediatric patients include nausea, abdominal pain, abdominal bloating, and vomiting. The existing Prescribing Information and Medication Guide incorporating pediatric information will be sufficient to communicate the potential risks to healthcare providers and patients, respectively; a REMS will not be required. Of note, following approval of Suprep Bowel Prep Kit in adults the Applicant conducted several PMR studies that addressed the safety concerns related to sulfates. No additional post-marketing studies will be required.

In order to maintain the same proprietary name (Suprep Bowel Prep Kit) but minimize potential medication errors that could result from prescribing or dispensing incorrect dosage of the product, the Applicant agreed to include the descriptor “For pediatric patients 12 years of age and older” and add the descriptor “For Adults” on the container label and carton labeling of the 4.5-ounce product and existing 6-ounce product, respectively.

14. Appendices

14.1. References

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14.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): BLI800-502

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 26		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR		

54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 26		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14.3. OCP Appendices (Technical Documents Supporting OCP Recommendations)

14.3.1. Bioanalytical Method Report

Serum inorganic sulfate concentrations were determined using a QuantiChrom Sulfate Assay Kit (DSFT-200) by (b) (4)

Briefly, human serum samples were deproteinated with a trichloroacetic acid reagent by mixing and then centrifuging at 12,000 rpm for 5 minutes. Serum inorganic sulfate concentrations were then measured using a QuantiChrom Sulfate Assay Kit (DSFT-200) with turbidimetric methodology. The assay method had a lower quantification limit of 0.2 mmol/L using 300 µL of serum. Assay validation calibration standard curve consisted of 7 levels ranged from 0.2 to 2 mmol/L in human serum and was calculated using a weighted ($1/y^2$) linear fit. Precision (% CV) for the calibration standards were <15.0% (<20.0% at the lower limit of quantitation), and the accuracy (% Bias) ranged from -12.5% to 13.8%. Stability in human serum was demonstrated to be 22 hours at room temperature and 693 days at -70°C. Stability was demonstrated up to four freeze-thaw cycles. Dilution integrity was demonstrated for a 5-fold dilution. No matrix interference was noted.

Calibration standard curve for this pediatric study BLI800-502 consisted of 7 levels ranged from 0.2 to 2 mmol/L in human serum. Quality control samples at 3 different concentrations (0.3, 0.6, and 1.6 mmol/L) were prepared, and the accuracy and the precision were within the acceptable limit. Precision (% CV) for the calibration standards for this study ranged from 0.96%

to 4.85%, and the precision for the quality controls ranged from 7.02% to 13.1%. Accuracy (% Bias) ranged from -0.8% to 1.07% for calibration standards, and -3.67% to -2.5% for quality controls.

The bioanalytical method used to determine serum sulfate concentrations in this submission is considered acceptable.

14.4. Clinical

14.4.1. Tolerability Questionnaire

Caregivers were asked to rate subject tolerability using the following categories:

- very badly accepted/unacceptable: subject showed great displeasure, compromising use of formulation
- badly but accepted: subject showed displeasure with dosing but could be coaxed to take complete dose
- neither good nor bad: subject showed no apparent displeasure and with little effort was coaxed to take complete dose
- well accepted: subject appeared to enjoy the formulation and with little coaxing ingested most of dose
- very well accepted: subject appeared eager and ingested most of dose without special coaxing.

14.4.2. Changes in Osmolality

The patients who reported changes in the osmolality in the three treatment groups also had other common treatment-emergent adverse events (TEAEs) such as nausea, vomiting, abdominal pain, stomach cramps, and abdominal bloating. However, no postural hypotension was reported in these patients. Therefore the transient mild changes in the osmolality do not appear to be clinically significant. The reported changes in osmolality in each treatment group are summarized below:

6-oz Group

From normal baseline to high osmolality during follow-up:

Visit 2 (Day 2): three patients were reported to have high osmolality in the range of 296 to 302 mOsm/kg from normal baseline (<295 mOsm/kg). Change from baseline was 9 to 12 mOsm/kg.

Visit 3 (Day 4): six patients were reported to have high osmolality in the range of 296 to 301 mOsm/kg. The change from baseline was 4 to 11 mOsm/kg. Two of the six patients were who had high osmolality at Visit 2 and 4 were new patients who were reported to have high osmolality at Visit 3 (Day 4) but not at Visit 2 (Day 2).

Visit 4 (Day 9): five patients were reported to have high osmolality in the range of 296 to 303 mOsm/kg. The change from baseline was 3 to 13 mOsm/kg. There was one new patient (b) (6) who reported high osmolality for the first time at Visit 4 (Day 9), which is considered unlikely to be related to bowel prep administration. Four other patients had reported high osmolality at previous visits randomly. One patient (b) (6)) had reported high osmolality at both the previous visits, one patient (b) (6) had reported high osmolality at Visit 1 but not at Visit 3, two patients (b) (6) had reported high osmolality at Visit 3 but not Visit 2.

4.5-oz Group

From normal baseline to high during follow-up:

Visit 2 (Day 2): two patients (b) (6) were reported to have high osmolality of 297 and 300 mOsm/kg. The change from baseline was 7 and 6 mOsm/kg respectively.

Visit 3 (Day 4): two patients were reported to have high osmolality of 299 and 300 mOsm/kg. The change from baseline was 4 and 6 mOsm/kg respectively. At Visit 3, one new patient (b) (6) was reported to have high osmolality and the second patient had earlier reported to have high osmolality at Visit 2 (b) (6).

Visit 4 (Day 9): three patients were reported to have high osmolality of 296 to 302 mOsm/kg for the first time at Visit 4; their osmolality was within normal limits at previous visits (Visits 2 and 3). The change from baseline was in the range of 2 to 11.

NuLytely Group

From normal baseline to high:

Visit 2 (Day 2): four patients were reported to have high osmolality in the range of 296 to 300 mOsm/kg. The change from baseline was in the range of 1 to 12 mOsm/kg.

Visit 3 (Day 4): five patients were reported to have high osmolality in the range of 296 to 297 mOsm/kg. The change from baseline was in the range of 3 to 7 mOsm/kg. Four of these five patients reported high osmolality for the first time at this visit, they were reported to have normal osmolality at Visit 2. One patient (b) (6) was reported to have high osmolality at Visit 2 as well.

Visit 4 (Day 9): six patients were reported to have high osmolality in the range of 296 to 302 mOsm/kg. The change from baseline was in the range of 2 to 14 mOsm/kg. One patient (b) (6) had high osmolality at all the visits, two patients (b) (6) had high osmolality at Visit 3 but not at Visit 2, and one patient (b) (6) had high osmolality at Visit 2 but not Visit 3. There were two patients (b) (6) who were reported to have high osmolality at Visit 4 for the first time.

14.4.3. Changes in Anion Gap

Suprep 6 oz

From normal baseline to high:

Visit 2 (day 2): four patients were reported to have high anion gap from the normal baseline at Visit 2 and one patient at Visit 3. The changes trended to normal on the follow-up visits. In majority of the patients the change from upper limit of normal (11) was in the range of 3 to 5.

Suprep 4.5 oz

From normal baseline to high:

Visit 2 (day 2): eight patients were reported to have high anion gap from the normal baseline at Visit 2. The changes trended to normal on the follow-up visit. In the majority of patients the change from upper limit of normal (11) was in the range of 3 to 6 except in one patient where the difference was 11 (from baseline of 4 to 15).

NuLytely

From normal baseline to high:

Visit 2 (day 2): two patients were reported to have high anion gap from the normal baseline at Visit 2. The changes trended to normal on the follow-up visit. The change from upper limit of normal (11) was 2 and 5, respectively.

14.4.4. Vital Signs (Mean [SD]) at Screening and Follow-Up Visits

Table 31. Vital Signs (Mean [SD]) at Screening and Follow-Up Visits

Sign (units)	Visit	BLI800 6 oz. (N=31)	BLI800 4.5 oz. (N=26)	NuLYTELY (N=32)
Temperature	V1 (Screening)	98.15(0.6)	98.28(0.6)	98.29(0.4)
	V2 (Day 2)	97.98(0.5)	98.02(0.6)	98.01(0.6)
	V3 (Day 4)	98.09(0.4)	98.15(0.8)	98.23(0.7)
	V4 (Day 9)	98.04(0.4)	97.98(0.6)	98.01(0.7)
Heart Rate (bpm)	V1 (Screening)	78.4(12.2)	76.4(12.0)	77.2(11.9)
	V2 (Day 2)	86.4(15.3)	77.9(13.1)	78.3(9.9)
	V3 (Day 4)	80.4(10.1)	77.6(11.7)	81.8(13.6)
	V4 (Day 9)	82.2(14.1)	77.0(11.0)	82.9(14.0)
Sitting Systolic Blood Pressure (mmHg)	V1 (Screening)	111.4(10.0)	115.0(9.9)	107.1(9.0)
	V2 (Day 2)	114.6(9.5)	115.7(13.9)	115.6(11.0)
	V3 (Day 4)	110.3(9.0)	112.8(9.8)	114.8(10.4)
	V4 (Day 9)	111.7(12.1)	114.0(11.8)	113.5(11.6)
Standing Systolic Blood Pressure (mmHg)	V1 (Screening)	112.2(9.9)	115.7(9.5)	110.0(11.8)
	V2 (Day 2)	113.9(10.3)	116.2(10.9)	115.2(10.6)
	V3 (Day 4)	112.6(10.0)	113.4(8.5)	112.5(9.7)
	V4 (Day 9)	116.1(12.5)	116.0(12.2)	116.4(14.4)
Sitting Diastolic Blood Pressure (mmHg)	V1 (Screening)	68.5(7.0)	70.0(7.5)	67.7(6.8)
	V2 (Day 2)	70.5(6.5)	72.6(9.4)	67.2(7.5)
	V3 (Day 4)	67.3(6.5)	69.1(6.3)	67.8(9.2)
	V4 (Day 9)	67.3(7.4)	70.2(9.4)	68.9(8.1)
Standing Diastolic Blood Pressure (mmHg)	V1 (Screening)	71.7(6.8)	74.0(7.9)	68.8(7.5)
	V2 (Day 2)	72.4(7.8)	72.3(6.3)	68.2(9.9)
	V3 (Day 4)	70.6(6.7)	72.0(6.3)	66.5(8.7)
	V4 (Day 9)	72.1(7.0)	72.7(8.6)	69.7(9.1)
Respiratory Rate	V1 (Screening)	17.0(1.9)	16.4(1.9)	15.9(3.0)
	V2 (Day 2)	16.8(2.6)	17.2(1.7)	16.9(3.6)
	V3 (Day 4)	16.8(2.2)	16.7(2.4)	16.7(3.3)
	V4 (Day 9)	17.2(3.4)	16.2(2.4)	16.3(2.4)

Abbreviations: bpm = beats per minute
Source: Table 16 of the study report BLI800-502

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/s/

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