CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213135Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Memorandum

Clinical Joint Summary Review

From	Omolara Adewuni MD, Clinical Reviewer, Division of Gastroenterology (DG) Tara Altepeter, MD, Medical Team Leader, DG Jessica Lee, MD, MMSc., Division Director, DG
Subject	Joint Summary Review
NDA #	213135
Applicant	Braintree Laboratories, Inc.
Date of Submission	May 12, 2020
PDUFA Goal Date	November 12, 2020
Established/Proper name	Sodium sulfate, Magnesium sulfate, and Potassium chloride
Pharmacologic Class	Osmotic laxative
Code name	BLI4700
Dosage form	Oral tablets
Dosing Regimen	24 tablets given in split-dose regimen (12 tablets evening prior and 12 tablets morning of colonoscopy)
Proposed Indication	Cleansing of the colon in preparation for colonoscopy in adults
Recommended Action:	Approval

Executive Summary:

SUTAB (sodium sulfate, magnesium sulfate, and potassium chloride) tablets are proposed for use as a bowel cleansing agent, to be administered to adults for cleansing of the colon, prior to colonoscopy. NDA213135 was received as a Class 2 resubmission on May 12, 2020.

The original application (submitted May 15, 2019) contained reports of two randomized, assessor blinded, active control phase 3 trials (Study 301 and Study 302) designed to demonstrate non-inferiority of SUTAB against approved comparators (Moviprep and Prepopik, respectively). Detailed review of the phase 3 trial data is outlined in the multidisciplinary review that was completed with the initial submission (review dated March 13, 2020). Although the clinical efficacy and safety data supported approval, the original application received a Complete Response (CR) on March 13, 2020, due to lack of readiness for commercial manufacturing. This memo summarizes the new information contained in the resubmission to address the deficiencies outlined in the CR letter. In addition, the presentation of adverse reaction data (section 6.1 of the prescribing information) was under negotiation at the time the CR letter was issued. During this review cycle, the clinical review team worked with the Applicant to revise the presentation of the safety data, which is described in this memo below.

The application is recommended for approval.

Readiness for Commercial Manufacturing:

The original NDA for SUTAB was submitted on May 15, 2019. The review team concluded that the NDA met all conditions for approval, except for deficiencies in a drug product manufacturing facility (Braintree Laboratories, Inc., MA). Specifically, the pre-approval inspection (PAI) on October 22, 2019 identified several deficiencies that were conveyed to the drug product manufacturing facility. Based on inadequate response, the Office of Pharmaceutical Manufacturing Assessment (OPMA) made a

recommendation for "Withhold" due to lack of readiness of Braintree Laboratories, Inc, MA. for commercial manufacturing of the drug product. For additional details, please refer to the March 13, 2020 Multidisciplinary Review for NDA 213135. Due to the abovementioned deficiencies at the drug product manufacturing facility, the Office of Pharmaceutical Quality (OPQ) did not recommend the NDA for approval per 21 CFR 314.125(b)(13) until deficiencies could be satisfactorily resolved; therefore, the Agency issued a CR letter on March 13, 2020. Specifically, the CR letter stated the following: "During a recent inspection of the Braintree Laboratories, Inc., MA (FEI1000513636) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this NDA may be approved."

A resubmission of the application was received on May 12, 2020. The resubmission contained modifications to the drug product manufacturing process and in-process controls, revised drug product specification, additional drug product stability data, revised drug product container closure system, and revised drug product container/carton labels.

Because it was not possible to perform an on-site pre-approval inspection (PAI) of the manufacturing facility (Braintree Laboratories Inc., MA) due to COVID-19 imposed travel restrictions, the Office of Regulatory Affairs (ORA)/OPMA initiated the 704(a)(4) process in-lieu of an on-site inspection. The Applicant provided requested documents regarding the drug product manufacturing facility, list of equipment, manufacturing process, executed batch records and stability data. These documents were reviewed and the OPQ team concluded that the facility is acceptable. The OPQ review states, "Documents were requested and evaluated. Based on that assessment, we find the facility acceptable. Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing or facility risks for the facilities. The manufacturing facilities for NDA 213135 are found to be acceptable." Based on submitted information, OPQ now recommends the application for approval (see review by OPQ reviewers, Qin Liang, Ph.D. and Nallaperumal Chidambaram, Ph.D., finalized on October 5, 2020 for further details).

Refer also to the Integrated Quality Assessment 2 dated October 5, 2020 (application technical lead, Hitesh Shroff, Ph.D.).

Prescribing Information (PI):

During the initial review cycle, there were outstanding issues related to the presentation of the adverse reaction data in section 6.1 of the prescribing information. As described in the prior multidisciplinary review (review dated March 13, 2020), the Applicant used a symptom questionnaire on the day of colonoscopy to elicit reports of gastrointestinal (GI) specific symptoms of nausea, abdominal distension, upper abdominal pain, and vomiting. Using this questionnaire, study personnel queried each patient at Visit 2 (day of colonoscopy) regarding the presence or absence of any of these four symptoms, and also recorded the severity of each symptom as mild, moderate, or severe.

The most common treatment emergent adverse events (TEAEs) reported in the trials were largely from the questionnaire. (b) (4)

(b) (4)

As a result, the Agency agreed to limit data presented in the tables to questionnaire responses with their severity. A separate paragraph was added for other common adverse events that were spontaneously reported.

In the resubmission, the Applicant submitted the most recently discussed version of the PI that was last negotiated prior to the CR. Below is a high-level summary of the changes made by the Agency in section 6.1 (Clinical Trials Experience).

1. A paragraph was included to describe the GI adverse reactions collected using the symptom questionnaire, including the procedure for completing the questionnaire and the overall number of patients who reported at least one GI adverse reaction captured in the questionnaire.
2. Tables 1 and 2 (common adverse reactions by treatment group) were modified to present only the results of the symptom questionnaire (which also represent the most common GI AEs) capturing events occurring between initiation of ingestion of the bowel preparation through colonoscopy, instead of presenting the tables with combined AEs from solicited (questionnaire) and unsolicited (spontaneous) reports.
    a. The AE terms of nausea, stomach bloating, stomach cramping and vomiting that were used on the questionnaire were re-coded per MedDRA version 19.1 terms as nausea, abdominal distension, abdominal pain upper and vomiting; the recoded terms were used in Tables 1 and 2.
3. A paragraph was added to describe other common AEs that were reported spontaneously, but not captured in the symptom questionnaire.

Given that majority of adverse events in the trials were from the symptom questionnaire, the review team conducted an analysis of each GI symptom included in the questionnaire (nausea, abdominal distension, abdominal pain upper and vomiting) by severity. There were minor discrepancies in the numbers/percentages of events between the review team and the Applicant, which resulted in multiple information requests (June 19, 2020, July 9, 2020, September 23, 2020) and responses (July 1, 2020, July 13, October 1, 2020 respectively).

The majority of the discrepancies were due to patients who reported no AEs on the symptom questionnaire (solicited) but had a spontaneous (unsolicited) event that matched the questionnaire term. The Applicant's rationale for including these spontaneous events initially was to be conservative and capture all relevant events. The review team excluded the spontaneous reports of adverse events from the analysis for the reasons previously described, and this approach did not change the overall characterization of the safety profile of SUTAB.

The Applicant requested that the percentage of patients experiencing each of the specified GI adverse events (nausea, vomiting, abdominal distension, abdominal pain upper) be calculated as the proportion of patients in each study arm who experienced the event, rather than out of the number of patients who reported one or more events on the questionnaire. This rationale was found to be reasonable given that, in general the presentation of the common adverse events in the prescribing information is listed as a proportion of patients experiencing an AE by study arm. Of note, the severity (mild, moderate, severe) of each AE will be presented within each category as a proportion of patients who reported that AE.

Based on the multiple information requests from the review team and the Applicant's responses, the discrepancies in numbers/percentages were resolved on October 8, 2020 and confirmed by the Applicant on October 23, 2020. Below are the final AE tables for Study 1 and Study 2 that describe the gastrointestinal symptoms collected using the symptom questionnaire and will be included in the final prescribing information.

Table 1: Gastrointestinal Symptoms by Severity[a] From Symptom Questionnaire in Adult Patients Following Colon Cleansing and Prior to Colonoscopy – Study 1[b]

Symptom	SUTAB	Polyethylene glycol 3350, sodium sulfate, sodium chloride, potassium chloride, ascorbic acid and sodium ascorbate
Total Number of Patients per Treatment Arm (N)	281	271
Patients with at Least One Gastrointestinal Adverse Reaction from Symptom Questionnaire	163	124
Nausea[c] (b) (4)	(b) (4) **(48)**	(b) (4) **(26)**
Mild	(71)	(77)
Moderate	(27)	(23)
Severe	(2)	0
Abdominal Distension[c] (b) (4)	**(29)**	**(22)**
Mild	(68)	(71)
Moderate	(30)	(29)
Severe	(1)	0
Vomiting[c] (b) (4)	**(23)**	**(5)**
Mild	(48)	46)
Moderate	(52)	54)
Severe	0	0
Upper Abdominal Pain[c] (b) (4)	(b) (4) **(16)**	**(18)**
Mild	(65)	(71)
Moderate	(35)	(29)
Severe	0	0

[a] *Mild*: barely noticeable, does not influence functioning causing no limitations of usual activities; *Moderate*: makes participant uncomfortable, influences functioning causing some limitations of usual activities; *Severe*: severe discomfort, treatment needed, severe and undesirable, causing inability to carry out usual activities

[b] Study 1 was not designed to support comparative claims for SUTAB for the adverse reactions reported in this table.

[c] Percentage represents n/N for the patients who had at least one gastrointestinal adverse reaction on the symptom questionnaire.

(b) (4)

Table 2: Gastrointestinal Symptoms by Severity[a] From Symptom Questionnaire in Adult Patients Following Colon Cleansing and Prior to Colonsocopy – Study 2[b]

Symptom	SUTAB	Sodium picosulfate, magnesium oxide, and anhydrous citric acid
Total Number of Patients per Treatment Arm	190	199
Patients with at Least One Gastrointestinal Adverse Reaction from Symptom Questionnaire (N)	135	67
Nausea[c] (b) (4)	(b) (4) **(52)**	(b) (4) **(18)**
Mild	(74)	(94)
Moderate	(20)	(6)
Severe	(6)	0
Abdominal Distension[c] (b) (4)	**(34)**	**(15)**
Mild	(73)	(69)
Moderate	(27)	(31)
Severe	0	0
Vomiting[c] (b) (4)	**(16)**	**(2)**
Mild	(53)	(33)
Moderate	(47)	(67)
Severe	0	0
Upper Abdominal Pain[c] (b) (4)	**(23)**	**(13)**
Mild	(82)	(100)
Moderate	16)	0
Severe	(2)	0

[a] *Mild*: barely noticeable, does not influence functioning causing no limitations of usual activities; *Moderate*: makes participant uncomfortable, influences functioning causing some limitations of usual activities; *Severe*: severe discomfort, treatment needed, severe and undesirable, causing inability to carry out usual activities

[b] Study 2 was not designed to support comparative claims for SUTAB for the adverse reactions reported in this table.

[c] Percentage represents n/N for the patients who had at least one gastrointestinal adverse reaction on the symptom questionnaire.

An additional item revised in the final label was removal of (b) (4)

(b) (4)

Post-Marketing Commitments/Requirements:

No new safety issues were identified that require additional post-marketing requirements. The applicant received orphan designation on December 19, 2017 and is therefore exempt from PREA requirements.

Conclusion:

From the clinical perspective, the benefit-risk profile of SUTAB for the proposed indication is acceptable (See the Multidisciplinary Review and Evaluation dated March 13, 2020 for complete details on NDA 213135 including the benefit and risk analysis for SUTAB). We agree with OPQ's recommendation for approval of this NDA because the deficiencies in the manufacturing facility have been satisfactorily resolved.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA - 505(b)(2)
Application Number	213135
Priority or Standard	Standard
Submit Date	May 15, 2019
Received Date	May 15, 2019
PDUFA Goal Date	March 15, 2020
Division/Office	OND / ODEIII / DGIEP
Review Completion Date	March 13, 2020
Established/Proper Name	sodium sulfate, magnesium sulfate, and potassium chloride
(Proposed) Trade Name	SUTAB
Pharmacologic Class	Osmotic laxative
Code name	BLI4700
Applicant	Braintree Laboratories, Inc.
Dosage form	Oral tablets
Applicant proposed Dosing Regimen	24 tablets given in split-dose regimen (12 tablets evening prior and 12 tablets morning of colonoscopy)
Applicant Proposed Indication(s)/Population(s)	Cleansing of the colon in preparation for colonoscopy in adults
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	346350006 Bowel cleansing solution (product)
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	n/a
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	n/a
Recommended Dosing Regimen	n/a

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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
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DPMH = Division of Pediatric and Maternal Health
DPV = Division of Pharmacovigilance
DMPP = Division of Medical Policy Programs
TL = Team Leader

Glossary

ADaM	analysis dataset model
ADR	adenoma detection rate
AE	adverse event
API	active pharmaceutical ingredient
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenzel
CRF	case report form
CSR	Clinical Study Report
DMF	drug master file
ECG	electrocardiogram
FDA	Food and Drug Administration
GI	gastrointestinal
IND	Investigational New Drug
KDIGO	kidney disease improving global outcome
mITT	modified intent to treat
NDA	new drug application
NI	non-inferiority
NOAEL	no observable adverse effect level
PK	pharmacokinetics
PP	per-protocol
QC	quality control
SAE	serious adverse event
SAP	statistical analysis plan
SPA	Special Protocol Assessment
TBM	to-be-marketed
TEAE	treatment-emergent adverse event

1. Executive Summary

1.1. Product Introduction

SUTAB (BLI4700) is a minimally absorbed osmotic laxative for use for cleansing the bowel prior to colonoscopy (bowel preparation). It is an oral sulfate tablet formulation that is closely related to the already approved liquid-based sulfate formulation (SUPREP, NDA 022372, approved on August 5, 2010). The only difference in the active composition of SUPREP and SUTAB is the substitution of potassium sulfate for potassium chloride in SUTAB. It is administered as two doses, in a split-dose regimen. Twelve tablets are equivalent to one dose, and each dose contains 17.75 grams of sodium sulfate, 2.7 grams of magnesium sulfate, and 2.25 grams of potassium chloride as active components. Two doses are required for complete preparation. SUTAB is an osmotic laxative that produces an osmotic effect based on sodium and magnesium sulfate salts that are poorly absorbed in the gastrointestinal (GI) tract. The osmotic activity of SUTAB thus increases the water content of stool and produces a bowel movement.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This new drug application (NDA) contains results from two randomized, multicenter, single-blind (colonoscopist-blinded), active-controlled clinical trials designed to demonstrate that SUTAB is non-inferior to the chosen comparator. The first trial, BLI4700-301 (study 301), enrolled 620 patients, randomized 1:1 to receive SUTAB or MoviPrep (ascorbic acid, polyethylene glycol [PEG] 3350, potassium chloride, sodium ascorbate, sodium chloride, sodium sulfate). The second trial, BLI4700-302 (study 302), enrolled 444 patients, randomized 1:1 to receive SUTAB or Prepopik (sodium picosulfate, magnesium oxide, anhydrous citric acid). Efficacy was assessed in both trials using a colonoscopy rating scale that was negotiated with the Division early in development. The quality of the bowel cleansing was scored on this four point scale, where a score of 3 (Good) or 4 (Excellent) was considered a successful preparation; the description of both a score of 3 or 4 includes clear visualization of the entire colonic mucosa. The primary endpoint in both trials was the proportion of patients achieving a successful preparation. Scores were assessed upon withdrawal of colonoscope. In study 301, 92% of SUTAB-treated subjects achieved success, versus 89% on MoviPrep. In study 302, 92% of SUTAB-treated subjects achieved success, compared to 88% on Prepopik. In both studies, the study drug was demonstrated to be non-inferior to the comparator (non-inferiority [NI] margin of 10%). Although the 10% NI margin and choice of Prepopik as an active comparator were not agreed on with the Division in advance, the results were robust (even using a 99% CI and 5% NI margin, non-inferiority is demonstrated). Additionally, the results of sensitivity analyses were generally consistent with the primary analysis results. The efficacy data are adequate to provide substantial evidence of effectiveness.

1.3. Benefit-Risk Assessment

Colonoscopy is a commonly performed procedure, utilized to screen for colorectal cancer, as well as to diagnose and treat various conditions of the large intestine. A prerequisite for a safe and effective colonoscopy is a well prepared bowel, whereby clear visualization of the entire colonic mucosa is possible. Although there are multiple approved products for cleansing the colon prior to colonoscopy, additional options that offer greater convenience, tolerability, improved efficacy or safety would be useful and may potentially be widely used.

SUTAB is proposed under NDA 213135 for cleansing the colon in preparation for colonoscopy in adults. It is a fixed-dose combination drug product containing sodium sulfate, magnesium sulfate, and potassium chloride, administered via "split dose regimen" (one dose the night prior to colonoscopy and one dose the morning of the procedure); the osmotic load of SUTAB causes profuse watery diarrhea, resulting in bowel cleansing. SUTAB is closely related to an approved product, SUPREP, owned by the same company, which also contains sodium sulfate, magnesium sulfate, and potassium. There are minor differences between the two products (SUTAB contains potassium chloride, whereas SUPREP contains potassium sulfate), and SUTAB is administered as oral tablets, whereas SUPREP is a powder that is reconstituted with water prior to administration. The clinical safety and efficacy data contained in this NDA support approval; **however, the drug product manufacturing facility, Braintree Laboratories, Inc., was determined to be unacceptable during pre-approval inspection due to lack of readiness for commercial manufacturing of the drug product, and therefore the application will receive a complete response action during this review cycle.** In future, if the manufacturing deficiencies are adequately resolved such that the manufacturing facilities are considered ready for commercial manufacturing, and no other new review issues arise, the application should be approvable at that time based on the clinical efficacy and safety data submitted in this NDA.

This NDA contains results from two randomized, multicenter, single blind (colonoscopist blinded), active-controlled clinical trials designed to demonstrate that SUTAB is non-inferior to the chosen comparator. The first trial, BLI4700-301 (study 301), enrolled 620 patients, utilizing an approved bowel prep, MoviPrep (ascorbic acid, polyethylene glycol [PEG] 3350, potassium chloride, sodium ascorbate, sodium chloride, sodium sulfate), as the comparator. The second trial, BLI4700-302 (study 302), enrolled 444 patients, utilizing another approved bowel prep, Prepopik (sodium picosulfate, magnesium oxide, anhydrous citric acid), as the comparator. Efficacy was assessed by colonoscopy on a four point scale, where adequacy of cleansing was rated on withdrawal of colonoscope; scores of 3 (Good) or 4 (Excellent), both of which require clear visualization of the entire colonic mucosa, were considered success. The primary endpoint was the proportion of patients achieving a successful preparation. In study 301, 92% of SUTAB-treated subjects achieved success, versus 89% on MoviPrep. In study 302, 92% of SUTAB-treated subjects achieved success, compared to 88% on Prepopik. In both studies, the study drug was demonstrated to be non-inferior to the comparator (NI margin of 10%), and in fact would exclude a 5% margin if assessed utilizing the more stringent 99% CI. The results of sensitivity analyses were generally consistent with the primary analysis results. Overall, the efficacy data are sufficient to support approval.

The safety profile of SUTAB supports approval, and identified safety risks were those expected for this drug class. The safety database is adequate to characterize the safety of this single-use product. The safety events of interest in this drug class include electrolyte abnormalities, dehydration, and gastrointestinal (GI) adverse events (AEs such as nausea, vomiting, bloating and abdominal cramping), all of which were adequately assessed.

No deaths occurred and serious adverse events (SAEs) were infrequent. A total of five SAEs occurred across the two trials, none of which were considered study drug related. The most common adverse events included nausea, abdominal distention, vomiting, and abdominal pain. Other events occurring in at least 2% of patients in either arm included headache, dizziness, hypermagnesemia, and increased liver function tests. In both trials, nausea, abdominal distention, and vomiting occurred with greater frequency in SUTAB-treated subjects than comparator. However, in general, the gastrointestinal adverse events reported were mostly mild to moderate in intensity and self-limited. The increased rate of GI AEs reported did not result in major differences in the rate of discontinuations due to adverse events between the two arms in either trial. 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 abnormality was hypermagnesemia, which is expected based on the composition of the drug. No reported cases of hypermagnesemia were clinically symptomatic. While electrolyte shifts were highly prevalent, they were mostly clinically insignificant, and the majority resolved on follow-up without intervention. Specific analyses of renal safety were conducted, to assess for the potential for acute kidney injury (assessed by individual subject change from baseline in serum creatinine). Cases of clinically important increase in creatinine were infrequent, and occurred with similar frequency in SUTAB-treated patients compared to comparator; thus no new signal for potential renal injury was detected.

In summary, the results of the safety and efficacy analyses demonstrate that SUTAB is efficacious and adequately tolerated to support approval. The benefits include an effective product for bowel preparation, and a novel formulation (tablets rather than liquid), which may be preferable to some patients. The risks identified are similar to other approved products in the class. Though the rate of GI adverse events was higher in SUTAB arms than in comparators, the severity of these events did not preclude successful preparation and do not pose an approvability issue. No unique safety concerns were identified for SUTAB as compared with other approved bowel preparations used as comparators in these clinical trials.

While the clinical data support approval, the application will receive a complete response due to facilities issues. A prior facilities inspection resulted in "withhold" recommendation and FDA Form 483 was issued. The Applicant's response (received November 11, 2019) indicated they are (b) (4) **At the time of action, the drug product manufacturing facility was not yet re-inspected. Because readiness for commercial manufacturing cannot be determined, in order to assure the safety, quality, and potency of the final drug product, the application is not approvable.**

1.4. Patient Experience Data

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

x	**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		
		x	Patient reported outcome (PRO)	8.1.1, 8.2.3 and Appendix Patient preparation questionnaire results
		□	Observer reported outcome (ObsRO)	
		x	Clinician reported outcome (ClinRO)	8.1.1 and Appendix Efficacy assessment
		□	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):		
□	**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 may be performed to diagnose or treat various conditions of the large intestine. In U.S. adults, the most common indication for colonoscopy is screening, surveillance, or diagnosis of colorectal cancer. In all indications, a well-cleansed bowel is a prerequisite for a successful and safe procedure; quality of bowel preparation is of particular importance when a procedure is conducted for cancer screening and/or surveillance.

Colorectal screening by colonoscopy is established as a standard of care for early detection of colorectal cancer in subjects 50 years and older. The U.S. Multi-Society Task Force on Colorectal Cancer defines an adequate colonoscopy examination as one that allows confidence that lesions other than small (≤5 mm) polyps are generally not obscured by the residual colonic contents (Wexner et al. 2006; Mamula et al. 2009). Effective bowel cleansing is, therefore, a prerequisite for achieving a high-quality colonoscopy procedure to achieve recommended targets of an adenoma detection rate (ADR) of approximately 25% and cecal intubation rate of 90% to 95% (Rizk et al. 2015). Inadequate bowel preparation for colonoscopy can result in missed lesions, cancelled procedures, increased procedural time, increased costs, and a potential increase in adverse event (AE) rates. Lower adenoma detection rates are associated with higher rates of interval cancers (Corley 2014). In addition, studies have shown that 28% to 42% of patients with inadequate (fair) bowel preparation had an adenoma that was detected on repeat examination within 3 years, including up to 27% with advanced adenomas (Lebwohl et al. 2011; Chokshi et al. 2012; Menees et al. 2013). The American Society for Gastrointestinal Endoscopy/American College of Gastroenterology Task Force on Quality in Endoscopy recommend a minimum unadjusted cecal intubation rate of 90% to 95% for complete examination of the cecum because the medial wall of the cecum between the appendicular orifice and ileocecal wall cannot be visualized from a distance (Rex et al. 2015).

Split dosing of bowel preparations (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) has emerged as an important factor in bowel cleansing efficacy and compliance (Cohen 2010). The American College of Gastroenterology guidelines for colorectal cancer screening recommend that bowel preparations be administered in split dosing.

2.2. Analysis of Current Treatment Options

A number of products are available for use in bowel cleansing prior to colonoscopy as summarized in Table 1.

Table 1. Current Therapeutic Options

Product(s) Name NDA/ANDA #	Formulation	Year of Approval	Dosing/Administration
Colyte 18-983	Powder for oral solution (in 1 gallon): Sodium sulfate, 21.50 g (anhydrous) Sodium chloride, 5.53 g Sodium bicarbonate, 6.36 g Potassium chloride, 2.82 g PEG-3350, 227.10 g	1984	Ingestion of 1 gallon of oral solution prior to colonoscopy.
GoLYTELY 19-011	Powder for oral solution (in 1 gallon): Sodium sulfate, 21.5 g Sodium chloride, 5.53 g Sodium bicarbonate, 6.36 g Potassium chloride, 2.82 g PEG-3350, 227.1 g	1984	Ingestion of 1 gallon of solution prior to colonoscopy.
NuLYTELY 19-797	Powder for oral solution (in 4 L): Sodium chloride, 11.2 g Sodium bicarbonate, 5.72 g Potassium chloride, 1.48 g PEG-3350, 420 g	1991	Ingestion of 4 L of solution on the day prior to colonoscopy.
HalfLytely and Bisacodyl tablets bowel prep kit 21-551	One 5-mg Bisacodyl delayed release tablet HalfLytely powder for 2 L solution: PEG-3350, 210 g Sodium chloride, 5.6 g Sodium bicarbonate, 2.86 g Potassium chloride, 0.74 g	2004* 2007† 2010‡	Ingestion of one 5-mg Bisacodyl tablet; followed by 2 L HalfLytely solution in water on the day prior to colonoscopy.
OSMOPREP 21-892	Per tablet: 1.5 g total of sodium phosphate as: -Monobasic monohydrate, 1.102 g -Dibasic anhydrous, 0.398 g	2006	Ingestion of 32 tablets with 2 quarts of clear liquids as split-dose (20 tablets on the evening before, and 12 tablets on the day of colonoscopy).
MOVIPREP 21-881 (split-dose used as the comparator in MORA study)	Each pouch A contains: Sodium sulfate, 7.5 g Sodium chloride, 2.69 g Potassium chloride, 1.015 g PEG-3350, 100g Each pouch B contains: Sodium ascorbate, 5.9 g Ascorbic acid, 4.7 g	2006	Ingestion of a 2 L solution, containing contents of one pouch A and one pouch B, either as split-dose (2-day) or day-prior (1-day) regimen. Additional fluids may be needed.

Product(s) Name NDA/ANDA #	Formulation	Year of Approval	Dosing/Administration
SUPREP 22-372	Each 6 oz bottle of oral solution: Sodium sulfate, 17.5. g Potassium sulfate, 3.13 g Magnesium sulfate, 1.6 g	2010	Ingestion of two 6 oz bottle solution diluted to 16 oz, in a 2-day split regimen. Total volume of liquid required for colon cleansing is approximately 2.8 L.
PREPOPIK 202535	Powder for reconstitution in 5 oz liquid: each of the two packets contains: Sodium picosulfate, 10 mg Magnesium oxide, 3.5 g Anydrous citric acid, 12.0 g	2012[§]	Ingestion of two 5 oz solutions (each 5 oz solution contains one packet), either as split-dose or day-prior regimen. Additional clear liquids are needed after each dose.
SUCLEAR 203595	One 6-oz oral solution (1st dose): Sodium sulfate, 17.5 g Potassium sulfate, 3.13 g Magnesium sulfate, 1.6 g + 2-L jug with powder for oral solution (2nd dose): PEG 3350, 210 g Sodium chloride, 5.6 g Sodium bicarbonate, 2.86 g Potassium chloride, 0.74 g	2013	Two doses administered as a split-dose (preferred) or day-prior regimens: 1st dose: 6 oz fluid reconstituted to 16 oz with water; 2nd dose: Dissolve powder in the jug in 2 L water. Follow up with additional water.
COLPREP 204553	Kit includes two 200 mL bottles with 22.7 g powder for oral solution, containing: Sodium sulfate, 17.5 g, Potassium sulfate, 3.13 g Magnesium sulfate, 1.6 g	2016	Ingestion of two 200 mL solution diluted to 16 oz, in a 2-day split regimen; additional fluids after each dose are required.
CLENPIQ 209589	Ready-to-drink 160 mL oral solution contains: Sodium picosulfate, 10 mg Magnesium oxide, 3.5 g Anhydrous citric acid, 12 g	2017[¶]	Ingestion of 40 oz or more of clear liquids after first dose and 32 oz or more of clear liquids after second dose as a split-dose regimen.

Product(s) Name NDA/ANDA #	Formulation	Year of Approval	Dosing/Administration
PLENVU 209381	Powder for reconstitution. Each dose to be mixed in 500 mL/ 16 oz of fluid) 1st dose contains: PEG3350, 100 g Sodium sulfate, 9 g Sodium chloride, 2 g Potassium chloride 1 g and flavorings 2nd dose (divided into 2 Sachet) contains: PEG3350, 40 g Sodium chloride, 3.2 g Potassium chloride, 1.2 g Ascorbic acid, 7.54 g Sodium ascorbate, 48.11 g	2018	Two doses administered using either "two-day" or "one-day" regimen. Dose 1 is diluted in 16 oz of fluid, and is followed by 16 oz additional clear fluid. Dose 2 is diluted in 16 oz of clear fluid, and is followed by at least 16 oz additional clear fluids. Additional fluid is encouraged.

Source: Reviewer's table, based on data available on drugs@fda, updated 2.6.20; table includes NDA approvals, but does not include the approved generics.
* Original Approval (2004): Four 4 (5mg) bisacodyl tablets and one 2 liter bottle of HalfLytely solution
† Changes in Dosage and Administration: Two (5mg) bisacodyl tablets and one 2 liter bottle of HalfLytely solution. Changes in Warnings & Precaution: Addition of ischemic colitis, seizures, risk of aspiration, renal impairment
‡ Changes in Dosage and Administration: One (5mg) bisacodyl tablets and one 2 liter HalfLytely solution. Changes in Warnings & Precaution: Addition of arrhythmias from fluid and electrolyte abnormalities
§ Pediatric indication granted for ages 9 and up in August 2018
¶ Pediatric indication granted for ages 9 and up in August 2019

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

BLI4700 (SUTAB) is a new proposed product, not previously approved or marketed in the United States. SUTAB is a sulfate-based tablet formulation closely related to the already approved SUPREP (liquid-based sulfate formulation, NDA 022372). The active ingredients in SUTAB are sodium sulfate, magnesium sulfate, and potassium chloride. The difference in the active composition of SUPREP and SUTAB is the substitution of potassium sulfate for potassium chloride in SUTAB. The clinical development program for SUTAB was conducted under IND 124988.

3.2. Combination Rule

SUTAB, similar to other prescription bowel preparation products, includes multiple active ingredients in a fixed-dose combination in order to achieve the requisite stool output necessary to cleanse the colon prior to colonoscopy; therefore, the Fixed-Combination Drug Rule (21 CRF 300.50) is applicable. The Applicant adequately addressed the combination rule by demonstrating the contribution of each active ingredient in SUTAB to either efficacy (stool output) or safety (net neutral electrolyte movement). See Appendix 15.2 Combination Rule for further details.

3.3. Summary of Presubmission/Submission Regulatory Activity

During clinical development, there were three communications between the Applicant and the Division that are summarized below:

(1) May 4, 2015: Type B meeting preliminary comments. The meeting was requested to attain agreement on study design of the proposed phase 3 studies.
At that time, the Sponsor was considering a phase 3 program consisting of (b) (4) . The Sponsor cancelled the in-person meeting after receipt of the preliminary comments.

(I) The sponsor proposed a 10% non-inferiority margin for the planned trial BLI-4700-301. The Agency noted that the 10% non-inferiority margin would be acceptable, but only for a primary endpoint that defined success on a 4 point scale, where a bowel preparation cleansing score of 4 (excellent) or 3 (good) was considered successful bowel preparation. However, the Agency also noted concerns that subjectivity of colonoscopists may influence scoring of 2 (fair) versus 3 (good); Ultimately the Agency recommended that the Sponsor redefine the primary endpoint, such that only a score of 4 (excellent) would be considered success, and recommended that the sponsor redefine the NI margin to account for this change

(II) The sponsor proposed (b) (4) The Agency did not agree and recommended assessments of adverse reactions in all patients at 24 to 48 hours after colonoscopy (Visit 3) as well as repeat testing 7 days after colonoscopy for patients with abnormal results at Visit 3. Patients with persistently abnormal laboratory results and ongoing adverse reactions should undergo repeat testing 30 days after colonoscopy and followed until resolution of laboratory abnormalities and symptoms.

(III) The Agency agreed that the sponsor could rely upon the nonclinical data presented in SUPREP (NDA 022372), and no additional nonclinical studies were needed.

(IV) (b) (4)

(2) November 9, 2015: Type C meeting preliminary comments. At this time the sponsor submitted a revised proposal for the phase 3 program, which included a plan to (b) (4) The formal meeting was cancelled by the Applicant after receipt of preliminary comments.

(I) The Agency did not agree to the Applicant's propose (b) (4)

(b) (4) The Agency therefore recommended that the Applicant use the originally proposed four-point scale, incorporating specific modifications to the definitions to improve the clarity of each score.

(II) The Agency noted that the proposed non-inferiority margin of 10% appeared reasonable, only if the sponsor utilized the Agency's proposed four-point scale (outlined in the preliminary comments) and defined success by score of "good" (3) or "excellent" (4), though statistical justification of the margin should still be submitted.

(III) Additional recommendations given to the sponsor included:

a) Perform electrocardiogram (ECG) on the day of colonoscopy, and it should be reviewed prior to start of procedure.

b) Repeat laboratory testing performed 24 to 48 hours after colonoscopy, and those with abnormal results should be retested 7 days after colonoscopy. Patients with persistently abnormal laboratory values or ongoing adverse events should undergo repeat laboratory tests 30 days after colonoscopy or followed until resolution of adverse events.

c) Include stratification factor based on presence or absence of criteria associated with suboptimal bowel preparation (i.e., body mass index [BMI] >30, diabetes mellitus Type 1 or 2, or a history of chronic constipation) in the primary efficacy analysis or a sensitivity analysis.

d) Predefine the patient population that will be used for efficacy analysis. Several sensitivity analyses should be proposed to ensure the robustness of the primary efficacy results. Missing binary data should be treated as failures for the primary efficacy analysis.

(3) May 12, 2017: Special Protocol Assessment (SPA) No Agreement responses to sponsor (based on protocols submitted March 28, 2017). At that time the proposed phase 3 studies included BLI4700-301 (revised to propose the use of MOVIPREP, (b) (4), as the active comparator), and BLI-4700-302 (proposing the use of PREPOPIK as the active comparator). The Agency did not agree with the Sponsor's SPA request. The Agency's responses to the Sponsor's questions regarding protocol BLI4700-301 and BLI4700-302 are summarized below:

(I) BLI4700-301

(i) The Division agreed with the Sponsor's choice of MoviPrep as the active comparator in BLI4700-301. However, the Division did not agree with (b) (4) Instead, the Division recommended incorporating centralized reading in a subset of the study population. The number of readings necessary to provide reassurance about quality and consistency of local readings would depend in part on the number of investigators who will perform colonoscopies at each site, as well as the agreement (or lack thereof) found between central and local assessment. Significant discrepancy between the readings would be a review issue.

(a) Colonoscopies that receive central reading should be randomly selected from both treatment groups.
(b) Obtain and store a video-recording of all study colonoscopies to ensure additional data are available, if necessary.

Additional recommendations included:

(c) Conduct laboratory assessments based on the schedule of visits the Agency recommended in the preliminary comments of the November 17, 2015 meeting.
(d) Obtain ECG on the day of the colonoscopy, in addition to that obtained at the screening visit.
(e) Detail parameters of vital signs in screening visit that would lead to exclusion of patients with abnormal physical examination and ECG from the screening visit.

(II) BLI4700-302

(i) The Agency did not agree with the Applicant's choice of PREPOPIK as the active comparator in BLI4700-302 for two reasons. First, the efficacy of PREPOPIK was numerically less than that reported for other approved products. Second, PREPOPIK itself was approved based on a non-inferiority trial in which the active control was associated with a numerically low success rate. Therefore, there were concerns that biocreep must be adequately accounted when planning a future NI trial. The Agency recommended the Sponsor select an alternate comparator. However, the Agency also noted that if the Sponsor continued to pursue PREPOPIK as the active comparator, detailed support for a conservative NI margin would need to be provided, and the assessment would need to utilize a 99% lower confidence bound for estimation of M1, given that there was only one historical trial on which to rely for PREPOPIK.
(ii) Additional comments were provided consistent with those summarized for BLI4700-301 above.

No Pre-NDA meeting was held.

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

4.1. Office of Scientific Investigations

Six clinical sites were selected for inspection. Five of six sites were assessed as No Action Indicated. A single site (site 112, Dr. Louis Korman) received a Form FDA 483 for "failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation."

Site 112 enrolled 57 subjects in study 302. The specific deficiencies included inadequate documentation of sedation medications used intraprocedurally, poor documentation of patient

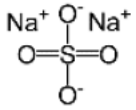
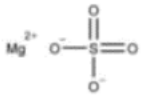
status (misclassifiying patient status such as "withdrawal of consent," "screen failure post-randomization," etc.), and inadequate control of investigational product storage area. The investigator responded to the FDA Form 483 with a corrective actions plan, which was considered by the OSI reviewer to be reasonable.

The Office of Scientific Investigations reviewer concluded that, overall, the data from studies 301 and 302 (including data from site 112) were sufficient to rely upon. For details refer to the review by Dr. Zana Marks (dated January 17, 2020).

4.2. Product Quality

SUTAB tablets contain sodium sulfate (anhydrous), magnesium sulfate (anhydrous), and potassium chloride as active ingredients as well as the following inactive ingredients: polyethylene glycol 8000 and sodium caprylate. The detailed information on Chemistry and Manufacturing Controls of each active ingredient is provided in the drug master file (DMF) from its manufacturer. These DMFs were reviewed and deemed adequate to support the drug product.

Figure 1. SUTAB Drug Master Files

DMF	Chemical Name	Structure	DMF Holder
(b) (4)	Sodium Sulfate (anhydrous)		(b) (4)
	Magnesium Sulfate (anhydrous)		
	Potassium Chloride	KCl	

Source: Reviewer-created image
Abbreviation: DMF = drug master file

SUTAB tablets are white to off-white, film coated, oblong, and biconvex with flat sides immediate release tablets. Each tablet is debossed with *S24* on one side. Each SUTAB contains 1.479 g of sodium sulfate, 0.225 g of magnesium sulfate, and 0.188 g of potassium chloride as active pharmaceutical ingredients (APIs) and the following inactive ingredients: polyethylene glycol 8000 (b) (4) and sodium caprylate (b) (4) ethylene glycol and vinyl alcohol graft copolymer. The tablets are supplied in 30cc white, round high-density polyethylene bottles with a canister containing silica gel. The bottles are sealed

with induction seal and (b) (4) cap. Each bottle contains 12 tablets.

SUTAB tablets are manufactured by Braintree Laboratories, Inc. MA. The tablets are manufactured by (b) (4) During the manufacturing process critical steps were identified and in-process controls were established. The drug product manufacturing process was reviewed by Dr. Qin Liang and was found to be acceptable. For details, refer to the Integrated Quality review dated February 16, 2020.

All active ingredients in the tablet formulation are highly soluble in water and, therefore, the drug product dissolution method for rapidly dissolving oral dosage forms was adopted from FDA guidance. The drug product dissolution method, dissolution data and dissolution specification were reviewed by Dr. Vincent Li and deemed acceptable from Biopharmaceutics perspective. For details, refer to the Integrated Quality review dated February 16, 2020.

The drug product specification includes microbial testing and limits per U.S. Pharmacopeia <61> and U.S. Pharmacopeia <62>. The drug product microbial specification was deemed acceptable.

Based on satisfactory stability studies of the drug product, 24 months of expiration dating period is granted when stored at room temperature in the proposed 30cc high density polyethylene bottle.

The claim of a categorical exclusion from the requirements of an environmental assessment is granted.

The label/labeling is satisfactory from the CMC perspective.

The Office of Pharmaceutical Manufacturing Assessment has made an “Adequate” recommendation for the manufacturing and testing facilities of all three drug substances.

At the time of the pre-approval inspection on October 22, 2019, a number of deficiencies were observed, which were conveyed to the drug product manufacturing facility, Braintree Laboratories Inc., MA. It was determined that the firm's response to address the deficiencies was inadequate, and the firm is not ready for commercial manufacturing of the drug product. Therefore, a "Withhold" recommendation has been made for the drug product manufacturing facility, Braintree Laboratories Inc., MA.

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has ***not*** made a final overall “Approval” recommendation for the facilities involved in this application. Consequently, this NDA is not recommended for approval from OPMA.

Therefore, from the Office of Pharmaceutical Quality perspective, this NDA is not recommended for approval in its present form per 21 CFR 314.125(b)(13) until above mentioned issues are satisfactorily resolved.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

From the nonclinical perspective, no approvability issues have been identified for the proposed product at the proposed dose.

No nonclinical studies have been conducted by the Applicant with BLI4700 (SUTAB; sodium sulfate, magnesium sulfate, and potassium chloride tablets). The Applicant is cross-referencing all nonclinical information submitted under NDA 022372 (SUPREP Bowel Prep Kit [liquid formulation]) to support the safety of SUTAB. NDA 022372 was approved on August 5, 2010. Further, the Applicant is relying on the FDA's finding of safety for NDA 019123 (Klor-Con) and NDA 018238 (Micro-K) to support the safety of the new API, potassium chloride.

BLI4700 is a tablet formulation using the sodium and magnesium sulfate salts that are present in the liquid formulation of SUPREP Bowel Prep Kit, but replacing one of the APIs, potassium sulfate, with potassium chloride. Further, the amount of magnesium sulfate was increased (from 3.2 g to 5.4 g in total) to account for the loss of sulfate due to the change to potassium chloride. There are no safety concerns with the new API, potassium chloride, or the increased amount of magnesium sulfate present in the BLI4700 formulation.

There are no safety concerns for the level of excipients used in SUTAB.

5.2. Referenced NDAs, BLAs, DMFs

NDA 022372: SUPREP Bowel Prep Kit; Approved August 5, 2010
NDA 019123: Klor-con (potassium chloride); Approved April 17, 1986
NDA 018238: Micro-K (potassium chloride); Approved October 17, 1980

5.3. Toxicology

5.3.1. General Toxicology Studies

SUTAB is a minimally absorbed osmotic laxative comprised of sodium sulfate, potassium chloride, and magnesium sulfate. Sulfate is considered the primary cause for osmotic diarrhea. However, the amount of magnesium (via magnesium sulfate) in SUTAB is 70% higher than in SUPREP to achieve a similar level of sulfate. Magnesium is generally considered safe. Magnesium is not well absorbed in rats or humans above a point of saturation, with the absorption decreasing with increasing ingested dose (Schuchardt and Hahn 2017). Due to the low absorption and bioavailability of magnesium, there are no safety concerns with the increased amount of magnesium sulfate present in the SUTAB formulation compared to SUPREP.

There are no safety concerns for the level of potassium chloride, present in SUTAB (2.25 mg/day). The Applicant is relying on the FDA's finding of safety of potassium chloride in Klor-Con (NDA

019123) and Micro-K (NDA 018238), which contain potassium chloride at levels higher than those in SUTAB.

5.3.2. Other Toxicology Studies

Safety Assessment of Excipients

There are no safety concerns for the level of sodium caprylate present in SUTAB ((b) (4) mg/day). The safety of sodium caprylate is supported by the levels of caprylate ester excipients present in FDA-approved drug products. Glyceryl monocaprylate ($C_{11}H_{22}O_4$; 218.29 daltons) is an ester of glycerol and caprylic acid used in approved oral products at levels up to 400 mg/dose. Upon digestion, the glyceryl monocaprylate hydrolyzes to give glycerol and caprylic acid, delivering 264 mg/dose of caprylate. By comparison, at the level of sodium caprylate present in SUTAB, patients would be exposed to (b) (4) mg/day.

There are no safety concerns for the level of PEG 8000 present in SUTAB ((b) (4) g/day). The safety of PEG 8000 is supported by the levels of lower molecular weight polyethylene glycol compounds, such as PEG 3350, that are used as active ingredients in approved bowel prep products. Pegylated products are poorly absorbed compounds, with the majority of the ingested compound excreted in feces. PEG 8000, which is a higher molecular weight than PEG 3350, is expected to have even poorer systemic absorption than the smaller molecule, PEG 3350, because gastrointestinal absorption of PEG decreases as the molar mass of the compound increases (Knop et al. 2010).

There are no safety concerns for the level of (b) (4) present in SUTAB (b) (4) mg/day). (b) (4) is (b) (4) PEG and polyvinyl alcohol. The Applicant submitted published literature in which rats and dogs were orally exposed to PEG and polyvinyl alcohol for 13 weeks (no observable adverse effect level [NOAEL]: 1,611 to 2,191 mg/kg/day) and 9 months (NOAEL: 783 to 811 mg/kg/day), respectively (see SDN 11: Response to Information Request; August 9, 2019) (b) (4) The safety margins are at least (b) (4) times and (b) (4) times, respectively, the proposed clinical dose (b) (4) mg/kg; (b) (4) mg/m^2) in a 60 kg patient (based on the daily dose of (b) (4) mg). The margins w re based human equivalent dose at the NOAEL in rat (260 mg/kg; 9,700 mg/m^2) and dog (435 mg/kg; 15,700 mg/m^2).

6. Clinical Pharmacology

6.1. Executive Summary

SUTAB (sodium sulfate, magnesium sulfate, and potassium chloride) is an osmotic laxative indicated for the cleansing of the colon as a preparation for colonoscopy in adults. The dose for colon cleansing requires administration of two bottles of SUTAB. Each bottle contains 12 tablets. Each 12-tablet dose contains sodium sulfate 17.75 grams, magnesium sulfate 2.7 grams, and potassium chloride 2.25 grams.

The proposed dosing regimen is a split-dose (2-day) regimen. A patient takes one bottle of 12 tablets in the evening before colonoscopy and one bottle the next morning on the day of colonoscopy. For each 12 tablets, a patient has to consume 48 ounces of water over 2 hours after the administration of each dose. Patient has to complete preparation and water at least 2 hours before colonoscopy.

In support of this NDA, the Applicant has conducted two phase 1 studies (BLI4700-101 and BLI4700-102), two phase 2 studies (BLI4700-201 and BLI4700-202), and two phase 3 trials (BLI4700-301 and BLI4700-302). Phase 1 and phase 2 studies were formulation optimization studies, whereas the phase 3 trials evaluated the efficacy and safety of the to-be-marketed (TBM) formulation.

The Applicant submitted the NDA application of SUTAB via 505(b)(2) regulatory pathway relying on FDA's previous nonclinical and clinical finding of SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate and magnesium sulfate oral solution, NDA 022372), for which the Applicant holds the right of reference. Potassium chloride, one of the active pharmaceutical ingredients of SUTAB, is not included in SUPREP. The Applicant relied on Klor-Con (potassium chloride, NDA 019123) and Micro-K (potassium chloride, NDA 018238) for safety of potassium chloride.

6.1.1. Recommendations

From a clinical pharmacology standpoint, this NDA is acceptable to support the approval of SUTAB for the cleansing of the colon as a preparation for colonoscopy in adults.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action

SUTAB consists of sulfate anions, which are poorly absorbed. Since there is a limited capacity for intestinal absorption of sulfate, unabsorbed sulfate in the intestine can exert a laxative action. The osmotic effect of unabsorbed sulfate thus increases the water content of stool and causes watery diarrhea.

Pharmacodynamics

The physiological consequence is increased water retention in the lumen of the colon, resulting in watery stools.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed split-dose (2-day) regimen of SUTAB consists of two doses, where each dose contains 12 tablets. Dose 1 of the split dose is to be administered the evening before the

colonoscopy, and Dose 2 is to be administered on the morning of the colonoscopy. Each 12-tablet dose consists of sodium sulfate 17.75 grams, magnesium sulfate 2.7 grams, and potassium chloride 2.25 grams.

Therapeutic Individualization

Therapeutic individualization based on intrinsic or extrinsic factor is not necessary. The effectiveness of SUTAB to cleanse the gastrointestinal tract is not dependent on the systemic exposure of sulfate, the active pharmaceutical ingredient of SUTAB. However, based on the mechanism of action, the Applicant proposed the following:

- Do not take other laxatives while taking SUTAB.
- Do not take oral medications within 1 hour of starting each dose of SUTAB.
- If taking tetracycline or fluoroquinolone antibiotics, iron, digoxin, chlorpromazine, or penicillamine, take these medications at least 2 hours before and not less than 6 hours after administration of each dose of SUTAB.

The Applicant's proposal regarding drug-drug interaction is acceptable and consistent with other colon cleansing agents' labeling.

Outstanding Issues

There are no outstanding issues that would preclude the approval of SUTAB from the Clinical Pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Sparse pharmacokinetic (PK) samples were collected for sulfate concentration in all subjects in phase 1 trials (BLI4700-101 and BLI4700-201) and phase 3 trials (BLI4700-301 and BLI4700-302). No intensive PK sampling and PK analysis was performed in any of the clinical trials. While phase 1 studies evaluated exploratory formulations, phase 3 trials BLI4700-301 and BLI4700-302 were conducted with the TBM formulation. Therefore, the PK assessment will focus on the results of the phase 3 trials with TBM formulation.

In phase 3 trials (BLI4700-301 and BLI4700-302), PK samples were collected at screening (Visit 1), on the day of colonoscopy (Visit 2, 5 to 8 hours after consuming the second dose of preparation), and post colonoscopy (Visit 3, 24 to 48 hours post colonoscopy). Less than 12% of the patients had measurable sulfate levels (the lower limit of quantitation of 0.2mM) at the screening. However, the majority of subjects (97% to 99%) had measurable sulfate levels on the day of colonoscopy after the administration of SUTAB (Table 2). The median serum sulfate concentration increased by about 2.5-fold on the day of colonoscopy compared to baseline and returned to baseline by 24 to 48 hours after colonoscopy.

Table 2. Median (Range) of Serum Sulfate Concentrations (mM) Following Split-Dose Regimen of SUTAB in Phase 3 Studies

	Study BLI4700-301			Study BLI4700-302		
PK Time	**Median**	**Range**	**n*/N† (%)**	**Median**	**Range**	**n*/N† (%)**
Visit 1: screening	0.2475	0.219,0.885	26/281 (9.3)	0.2440	0.201, 0.374	22/188 (11.7)
Visit 2: day of colonoscopy	0.62	0.217, 2.58	271/274 (98.9)	0.608	0.205, 1.71	177/183 (96.7)
Visit 3: post colonoscopy	0.287	0.201, 0.593	13/274 (4.7)	0.232	0.201, 0.288	14/188 (7.4)

Source: Table 14.3.7.4 in Study BLI4700-301 Section 14 Tables and Study BLI4700-302 Section 14 Tables
* Number of patients whose sulfate concentration was above LLOQ, 0.2mM
† Total number of patients
Abbreviation: PK = pharmacokinetic

6.3.2. Clinical Pharmacology Questions

The clinical development program for SUTAB (NDA 213135) consisted of the following six studies:

- Phase 1 formulation optimization studies evaluating pharmacodynamics and safety in healthy subjects

BLI4700-101: evaluated formulation 1
BLI4700-102: evaluated formulation 1, 2, 3, 3 (b) (4)), 4, 5, 8, 9, 10, 11, and formulation 8's variations: formulation 12 and ST24

- Phase 2 pilot studies evaluating safety and efficacy in patients undergoing colonoscopy

BLI4700-201: evaluated formulations 3, 5, 10, and 12
BLI4700-202: evaluated formulation 5

- Phase 3 clinical safety and efficacy studies using TBM formulation

BLI4700-301: MoviPrep as the active comparator
BLI4700-302: PREPOPIK as the active comparator

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The efficacy of SUTAB for the cleansing of the GI tract was demonstrated in two phase 3 trials (BLI4700-301 and BLI4700-302). In these trials, SUTAB was compared with marketed bowel cleansing products MoviPrep and Prepopik as active comparators in non-inferiority trials.

The results of phase 3 trials showed that higher proportions of patients in the BLI4700 treatment groups (92.1% to 92.4%) achieved overall preparation success compared to the active comparator groups (87.9% to 89.3%) supporting that SUTAB is non-inferior ($p<0.001$) to the approved products MoviPrep and Prepopik for overall bowel cleansing. See Section 8 of this multidisciplinary review for details of study design and efficacy results of the phase 3 trials, which support approval. A dose- or exposure-response study was not conducted to support the effectiveness of SUTAB.

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

The proposed SUTAB split-dose (2-day) regimen is acceptable for the cleansing of the gastrointestinal tract for the general targeted patient population. Various formulas (dose combinations), hydration regimens, and dosing regimens (two-day split-dose regimen versus same-day split-dose regimen) were explored in the phase 1 and phase 2 studies. Efficacy and safety were evaluated based on stool output, fluid consumption, fluid balance, percentage of diarrheal stool solid (Scatocrit[1]), and fecal electrolyte balance.

Dose (Formula) Selection and Hydration Optimization

Phase 1 studies, Study BLI4700-101 and Study BLI4700-102, have evaluated various compositions of formula (Table 3) and have identified BLI4700-8 formulation as an optimal formulation to be further evaluated in the phase 2 and 3 trials. A preset goal of diarrheal output in excess of 2.5 L, Scatocrit equal to or less than 5.0%, and minimal electrolytes movement as measured by net gastric electrolyte movement were used for selection of the optimal formulation.

Table 3. Comparison Tablet Formula (Total Dose, g) in Phase 1 Studies BLI4700-101/102

	Formula (4700-)*									
Ingredient	**1**	**2†**	**3**	**3‡**	**4**	**5**	**8**	**9**	**10**	**11**
										(b) (4)

In studies-101 and 102, the BLI4700-8 tablets produced a mean diarrheal output of about 2.8 L, and a Scatocrit of 3.6% with minimal electrolyte movement as presented in Table 4. Additional parameters, including fluid balance, adverse event safety profiles, and serum electrolyte measurements demonstrate that the formula has sufficient efficacy and safety profiles to be further evaluated in the phase 2 and/or 3 trials.

[1] Scatocrit was defined as percentage of diarrheal stool solid.

Table 4. Efficacy Summary of Tested Formula in Phase 1 Studies BLI4700-101/102

	Formula (4700-)									
Efficacy	**1**	**2***	**3**	**3†**	**4**	**5**	**8**	**9**	**10**	**11**
N	10	20	10	7	5	15	14	2	9	4
Stool output (mL) Mean (SD)	2,953.5 (295.5)	2,723.6 (457.9)	2,319.6 (242.0)	3,036.5 (568.4)	2,562.2 (482.6)	2,736.7 (359.6)	2,795.1 (351.6)	2,831.7 (6.0)	2716.2 (397.0)	2,594.5 (367.0)
Gastric fluid balance (mL) Mean (SD)	1,522.8 (1,154.7)	3,802.0 (1,398.5)	2,197.4 (684.9)	1,806.3 (1,093.1)	2,468.2 (375.8)	1,963.4 (1,091.3)	2,270.2 (1235.5)	2,631.8 (870.5)	2,429.4 (1,555.2)	1,545.6 (660.3)
Fluid balance (mL) Mean (SD)	5.3 (499.6)	248.8 (677.3)	-155.1 (488.2)	-284.2 (738.7)	24.2 (488.8)	161.6 (530.8)	-293.7 (586.9)	104.3 (198.0)	-115.1 (461.4)	-112.0 (27.6)
% solids Mean (SD)	4.9 (3.9)	2.2 (2.3)	1.6 (0.6)	1.8 (0.8)	5.5 (5.6)	1.5 (1.2)	3.6 (6.0)	1.4 (0.0)	2.0 (1.4)	2.0 (1.3)
Na (mEq) Mean (SD)	53.8 (35.5)	-16.5 (106.6)	79.3 (83.9)	51.9 (101.4)	133.5 (94.5)	164.9 (118.4)	-10.0 (103.0)	-212.1 (304.4)	-10.6 (143.4)	113.1 (128.5)
Cl (mEq) Mean (SD)	-74.6 (19.0)	-21.2 (33.5)	-4.4 (34.0)	-45.0 (57.7)	-30.1 (19.8)	-25.0 (30.0)	-4.1 (21.9)	-100.1 (41.6)	-21.1 (54.8)	-7.5 (40.5)
K (mEq) Mean (SD)	11.6 (16.7)	58.5 (20.2)	4.2 (11.1)	20.0 (16.9)	-11.7 (16.3)	8.3 (15.5)	-4.8 (16.7)	-11.6 (20.4)	-15.4 (14.2)	-31.1 (60.0)
Mg (mEq) Mean (SD)	4.0 (3.8)	-4.7‡ (6.6)	-8.8 (7.4)	Not tested	-16.1 (15.9)	-15.7 (9.1)	-6.8 (19.7)	-12.4 (9.5)	-1.3 (9.4)	22.1 (37.9)

Source: Table 6 in BLI4700-101/102 Clinical Study Report
*Inclusive of formula variants 4700-2.0, 2.1 and 2.2
(b) (4)
‡Provided magnesium values for 18 subjects
Abbreviations: mEq = milliequivalent, mL = milliliter

Formulation BLI4700-8 was subsequently further explored with minor change in excipients in phase 1 study, study 102, for further formulation optimization. Formulation 4700-8, 4700-12, and 4700-ST24 shared the same amount of active pharmaceutical ingredients with adjusted excipients for the scale-up activities in preparation for phase 3 trials (Table 5).

Table 5. Final 4700 Formulation and Variants

Ingredient (g)	BLI4700-8	BLI4700-12	BLI4700-ST24 (TBM Formulation)	Function
Sodium sulfate (Na_2SO_4)	35.5	35.5	35.5	Active ingredient
Magnesium sulfate ($MgSO_4$)	5.4	5.4	5.4	Active ingredient
Potassium chloride (KCl)	4.5	4.5	4.5	Active ingredient
Sodium caprylate			(b) (4)	Excipients (b) (4)
(b) (4)				Excipient- (b) (4)
PEG-8000				Excipient- (b) (4)

Source: 3.2.P.2 Drug Product
Abbreviation: TBM = to-be-marketed

Formula 4700-8 (and variants) produced a mean stool output of 2,745.2 mL and stool percent solids of 3.7% (Table 6). Total fluid balance was neutral. Minimal gastrointestinal electrolyte absorption or secretion was also achieved. These parameters meet the criteria of stool volumes greater than 2,500 ml with a Scatocrit below 5.0%. Of note, it is hard to make any conclusion on the pharmacodynamic effect of each formulation of BLI4700-12 and BLI4700-ST24 due to the small number of subjects (n=3) who received these formulations.

Table 6. Summary of Efficacy in Phase 1 Studies BLI4700-101/102: Total Fluid Intake, Stool Output and Fluid Balance of Formulas 4700-8, -12, -ST24, and MoviPrep

	Formula/Preparation					
Efficacy	**8**	**12**	**ST24**	**8/12/S24***	**MoviPrep**	**p-Value†**
N	14	3	3	20	9	
Input (fluid+prep) (mL) Mean (SD)	5,065.3 (1,120.8)	4,710.0 (230.0)	4,918.3 1,005.6	5,001.3 (1,046.5)	4,543.5 (892.2)	0.290
Stool output (mL) Mean (SD)	2,795.1 (351.6)	2,908.0 (49.6)	2,522.5 (607.5)	2,762.2 (404.7)	3,058.2 (-654.4)	0.177
Gastric fluid balance (mL) Mean (SD)	2,270.2 (1,235.5)	1,802.1‡ (279.6)	2,395.8 (725.2)	2,239.1 (1,106.7)	1,485.3 (-911.7)	0.102
Total urine output (mL) Mean (SD)	2,563.9 (1,303.1)	1,802.1 (430.4)	2,393.3 (779.3)	2,470.3 (1,178.0)	2,088.3 (-1,147.0)	0.448
Total fluid balance (mL) Mean (SD)	-293.7§ (586.9)	-175.5‡ (203.0)	2.5 (275.6)	-231.2 (527.6)	-603.0 (609.6)	0.128
Mean solid (%) Mean (SD)	3.6 (6.0)	1.4 (0.0)	6.4 (7.6)	3.7 (6.0)	5.6 (5.1)	0.452
Time to first bowel movement Mean (SD)	2:00 (0:43)	1:11 (0:10)	1:52 (1:07)	1:51 (0:48)	1:11¶ (0:18)	0.0913

Source: Table 14, Table 15 and Table 16 in BLI4700-101/102 Clinical Study Report
* Combined data from formulation 8, 12, and ST24
† p =8/12/12ST versus MoviPrep
‡ n=2 because subject (b) (6) was excluded from input fluid, gastric fluid balance, and total fluid balance calculations because the subject did not finish per-protocol water.
§ n=13 because subject (b) (6) was removed from balance equations due to methodological error in collecting fecal output volumes.
¶ n=5 because Dose 1 administration time was not provided for 5 of the 10 subjects (b) (6)
Abbreviation: mL = milliliter

Additional parameters, including gastric electrolyte and fluid balance, AE safety profiles, and serum electrolyte measurements demonstrate that formula 4700-8 has sufficient efficacy and

safety profiles to progress into phase 2 trials. The formula used in phase 2 trials (i.e., formula 4700-12) was based on formula 4700-8 with changes in excipients (b) (4) Final formula (TBM), 4700-ST24, had identical active ingredients to formula 4700-8 and 4700-12, but its excipients were further optimized for the scale up for phase 3 trials.

Formula 4700-12 was further evaluated in the phase 2 study 201 with various hydration regimens as presented in Table 7. The study demonstrated that formula 4700-12 had the highest success rate for bowel preparation (Table 7 and Table 8). The fluid regimen for this formula was to take 12 tablets in 15 to 20 minutes with 16 oz water, wait 60 minutes, drink one 16 ounce cup of water over 30 minutes, wait 30 minutes and drink second 16 ounce of water over 30 minutes.

Table 7. BLI4700 Tablet/Fluid Ingestion Regimens in Phase 2 Study BLI4700-201

Cohort	Formulation	Tablet Regimen	Fluid Regimen
1	4700-3	12 tablets in 15-20 minutes with 16oz water	Two 16oz glasses of water over 1-2 hours
2	4700-3	4 tablets every 15 minutes with 8oz water	Wait 30 mins, then three 8oz cups of water every 30 mins
3	4700-3	4 tablets every 30 minutes with 8oz water	Three 8oz cups of water over 2 hours
4	4700-5	12 tablets in 15-20 minutes with 16oz water	Wait 30 mins, then two 16oz cups of water over 2 hours
5	4700-5	12 tablets in 15-20 minutes with 16oz water	Wait 30 mins, then two 16oz cups of clear liquids over 2 hours
6	4700-10	12 tablets in 15-20 minutes with 16oz water	Wait 60 mins Drink one 16oz cup of water over 30 mins Wait 30 mins Drink second 16oz cup of water over 30 mins
7	4700-12	12 tablets in 15-20 minutes with 16oz water	Wait 60 mins Drink one 16oz cup of water over 30 mins Wait 30 mins Drink second 16oz cup of water over 30 mins

Source: Table 3 in BLI4700-201 Clinical Study Report

Table 8. Overall Efficacy Analysis—mITT Population of Phase 2 Study BLI4700-201

	Cohort # (Formulation [BLI4700-])							All
Efficacy	**1 (3)**	**2 (3)**	**3 (3)**	**4 (5)**	**5 (5)**	**6 (10)**	**7 (12)**	**Subjects**
N	14	11	15	12	25	17	20	114
Success, N (%)	13 (93)	10 (91)	12 (80)	11 (92)	25 (100)	16 (94)	19 (95)	106 (93)
Failure*, N (%)	1 (7)	1 (9)	3 (20)	1 (8)	0	1 (6)	1 (5)	8 (7)

Source: Table 8 in BLI4700-201 Clinical Study Report
* Four subjects did not undergo colonoscopy for safety or efficacy reasons and are included as failures.

Dosing Regimen Selection

In addition to evaluating the 2-day split dose regimen in phase 1 study BLI4700-101/102 and phase 2 study 201, the Applicant had also evaluated a same day split-dose, morning-only, regimen of BLI4700 tablet bowel preparation (formula 4700-5) in phase 2 study 202. Although

the proportion of successful preparations for colonoscopy was high (88%) with the same-day, split-dose regimen, the frequency of vomiting was higher than what has been historically seen in approved bowel cleansing products with a 2-day split-dose regimen. This observation is likely due to the shorter time between the two doses than the approved split-dose regimen for SUPREP (4 hours versus 12 hours). Therefore, the Applicant did not pursue a same-day, morning-only, split-dose regimen in the phase 3 trials.

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

There is no need for alternative dosing regimen for subpopulations based on intrinsic factors.

The Applicant did not conduct any dedicated renal or hepatic impairment study to assess the effect of intrinsic factors on SUTAB in this NDA submission. The Applicant relied on the SUPREP label for its finding on impact of renal and hepatic impairment on systemic exposure of sulfate concentration from SUTAB. Since both SUTAB and SUPREP are sulfate-based osmotic bowel cleansing preparations and the amount of sulfate in SUTAB is less than that in SUPREP, it is acceptable to rely on the SUPREP label regarding the impact of renal and hepatic impairment on the systemic absorption of sulfate. The list of active ingredients in SUPREP and SUTAB is presented in Table 9 below.

Table 9. Composition in Total Dose (mM): SUPREP vs. SUTAB

Kit	(b) (4)
SUPREP	
SUTAB	

Source: Table 2 in BLI4700-101/102 Clinical Study Report and Table 4 in the Applicant's response to information request submitted on August 16, 2019

(b) (4)

Renal Impairment

The systemic exposure (area under the curve and C_{max}) of sulfate increased in patients with moderate renal impairment after sulfate-based bowel cleansing product. However, these differences in systemic exposure are not considered clinically meaningful.

Hepatic Impairment

In patients with hepatic impairment, systemic exposure of serum sulfate was similar with that in healthy subjects. Therefore, dose adjustment for hepatic impairment is not necessary.

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

The Applicant proposed not to use SUTAB with other laxative concomitantly and to administer oral medications at least 1 hour before the start of administration of each dose of SUTAB based on the mechanism of action. The Applicant 's proposal appears to be reasonable. Based on the labels from other GI cleansing agents, we propose to add that the administration of tetracycline

and fluoroquinolone antibiotics, iron, digoxin, chlorpromazine, and penicillamine should be at least 2 hours before and not less than 6 hours after administration of each dose of SUTAB.

Additionally, based on the mechanism of action, the concurrent use of SUTAB with other stimulant laxatives may increase the risk of mucosal ulceration or ischemic colitis. Therefore, SUTAB should be avoided with use of stimulant laxatives (e.g., bisacodyl, sodium picosulfate).

Drug-Drug Interaction

The Applicant did not conduct any in vitro or in vivo drug-drug interaction studies. As SUTAB is proposed to have one time use for colon cleansing before colonoscopy, the lack of in vitro or in vivo drug-drug interaction studies is acceptable. Based on the mechanism of action, SUTAB can reduce the absorption of other coadministered drugs. Therefore, the Applicant proposed to administer oral medications at least 1 hour before the start of administration of each dose of SUTAB. According to the data from the phase 1 study, the first bowel movement may occur about 1 to 2 hours after the administration of an exploratory BLI4700 formulas (Table 6). Thus, the Applicant's proposal appears to be reasonable and consistent with other colon cleansing agents' labels.

Food-Drug Interaction

The Applicant did not conduct any food effect study. There is no anticipated food effect, as the intake of food is restricted according to the administration procedure due to the nature of the purpose of the product. The Applicant's proposed language regarding food intake is acceptable and consistent with the design of the phase 3 studies.

The Applicant's current proposed label:

- Consume a low residue breakfast on the day before colonoscopy, followed by clear liquids until the colonoscopy is completed.
- Do not drink milk or eat or drink anything colored red or purple.
- Do not drink alcohol.

The drug administration in relation to food in phase 3 studies were consistent with the proposed labeling.

Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

As there was no change from the phase 3 formulation to the TBM formulation of SUTAB, bioequivalence data were not needed.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The studies supporting the efficacy and safety SUTAB are summarized in Table 10 below.

Table 10. Clinical Efficacy and Safety StudiesStudy ID/ # of Sites

Study Design/ Population	Number of Patients Enrolled	Dose Regimen and Objectives	Study and Treatment Duration	Primary Endpoint
BLI4700-301 23 sites in US Jan 11, 2018 to July 10, 2018	Randomized, parallel, multicenter, single-blind study **Population** Adult (18-85 years) requiring colonoscopy for routinely accepted indication (screening and diagnostic) Median age: 59 years >65 years age: 31.9% >75 years age: 5.8% Female: 56.2% Caucasian: 78.4%	Screened: 634 pts Randomized (ITT): 620 pts **Safety pop: 552** • BLI4700: 281 pts • MoviPrep: 271 pts **mITT**: 548 pts **ITT:** randomized/dispensed study medication **Safety pop:** all who took any portion of study medication **mITT:** safety pop except for those that didn't undergo colonoscopy	**BLI4700:** orally administered 24 tablets in two split 12-tablet doses (p.m./a.m.) **MoviPrep:** 2 pouches in split-dose administration per manufacturer's labeling **Objective:** compare safety & efficacy of BLI4700 to MoviPrep as 2-day, split-dose bowel prep in adult patients	Treatment duration: 2 days **Study duration:** up to 60 days **Visit 1:** screening **Visit 2:** colonoscopy **Visit 3:** 24-48 hrs post colonoscopy **Visit 4:** 7 days post colonoscopy as needed **Visit 5:** 30 days post colonoscopy as needed	Overall preparation success or failure after completion of colonoscopy Success defined as "Excellent" or "Good" graded by blinded endoscopists on a 4-point scale

Table 10.
Clinical Efficacy and Safety StudiesStudy ID/ # of Sites

Study Design/ Population	Number of Patients Enrolled	Dose Regimen and Objectives	Study and Treatment Duration	Primary Endpoint
BLI4700-302 20 sites in US Aug 8, 2017 to March 26, 2018	Randomized, parallel, multicenter, investigator-blinded study in adult patients Median age: 58 years >65 years age: 28% >75 years age: 5.7% Female: 57.8% Caucasian: 92.5%	Screened: 449 pts Randomized (ITT): 445 pts **Safety pop: 389 pts** • BLI4700: 190 pts • Prepopik: 199 pts **mITT**: 388 pts	**BLI4700:** orally administered 24 tablets in two split 12-tablet doses (p.m./a.m.) **Prepopik:** 2 packets in split dose administration per manufacturer's labeling **Objective:** compare safety, tolerance, and efficacy of BLI4700 tablets to Prepopik as bowel prep prior to colonoscopy in adult patients	Treatment duration: 2 days **Study duration:** up to 60 days **Visit 1:** screening **Visit 2: c**olonoscopy **Visit 3:** 24-48 hrs post colonoscopy **Visit 4:** 7 days post colonoscopy as needed **Visit 5:** 30 days post colonoscopy as needed	Overall preparation success or failure after completion of colonoscopy Success defined as "Excellent" or "Good" graded by blinded endoscopists on a 4-point scale

Source: Reviewer's table, adapted from the Applicant's Summary of Clinical Efficacy Submission, May 15, 2019
Abbreviations: ITT = intent to treat, mITT = modified intent to treat

7.2. Review Strategy

For this NDA submission, the Applicant submitted two phase 3 clinical trials (BLI4700-301 and BLI4700-302). The studies were conducted in adult subjects requiring colonoscopy for a routinely accepted indication (screening and diagnostic) to support the indication of colon cleansing in preparation for colonoscopy in adults. Both of the studies were multicenter, randomized, parallel-group, and used active comparators. The comparators used in the two trials, MoviPrep and Prepopik, are approved in the United States.

Safety and efficacy data were evaluated by individual studies rather than pooling together, because the studies used different active comparators.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. BLI4700-301 (Study 301) and BLI4700-302 (Study 302)

Trial Design

BLI4700-301 and BLI4700-302 had similar study design, consisting of a randomized, parallel-group, multicenter, single-blind study, conducted at multiple sites within the United States. Qualifying study patients were randomized to one of two bowel preparations. The active comparator was MoviPrep in 301 and Prepopik in 302. Both preparations were administered in a split-dose (PM/AM) regimen starting the night before colonoscopy. Efficacy determinations were based on cleansing assessments made by the endoscopist using a four-point scale (1 = poor to 4 = excellent). The study included a total of six planned visits, including a screening period of between 4 and 30 days prior to colonoscopy and subsequent follow-up visits through 4 weeks post colonoscopy.

Key details of the study design are summarized below:

Visit 1: Screening

At the screening visit, informed consent was obtained, and current medications and patient eligibility were reviewed. Baseline physical exam including orthostatic hypotension and laboratory (hematology and chemistry) were also obtained. To ensure an unbiased evaluation of study preparation in this single blind study, the colonoscopist was not allowed to perform any study-related activities (treatment assignment, drug dispensing, return, and accountability). Any failure to maintain blinding of treatment to the colonoscopies was documented as a protocol violation.

Eligible patients were randomized equally to either study drug or active control. Randomization was stratified according to the following three groups. Group 1 criteria are accepted indicators for subjects who have difficulty adequately preparing for a colonoscopy.

Group 1: Patients who meet any of the following criteria:

- Prior diagnosis of constipation (historical or active)
- History of prior failed bowel preparation (inadequate examination)
- Currently taking opioid medications
- Body mass index >35

Group 2: Patients scheduled for a colonoscopy 12:00 p.m. or later
Group 3: Patients not meeting Group 1 or 2 criteria

Patients were provided with a Preparation Questionnaire to report their experience with the study preparation, including intake of food, beverages (including amounts), and medications. The questionnaire was to be completed from the time the first dose of the study drug was taken until the colonoscopy (Visit 2) and returned to the clinic at Visit 2.

Preparation instructions:

(1) Treatment:
   (I) BLI4700: first dose (12 tablets) the evening before colonoscopy, followed by the second dose (12 tablets) 5 to 8 hours before the colonoscopy. Subjects were instructed to not take dose 2 within 4 hours of taking dose 1. The total water given with each 12-tablet dose was 16 ounces, followed by two additional 16 ounces of water after each dose.
   (II) MoviPrep (Study 301): manufacturer's labeling for split-dose administration.
   (III) Prepopik (Study 302): manufacturer's labeling for split-dose administration.

(2) Dietary restrictions:
   BLI4700 subjects were allowed to have a low residue breakfast on the day before colonoscopy, followed by clear liquids until the colonoscopy was completed the following day.
   (I) Study 301: MoviPrep subjects were allowed to have a clear broth and plain yogurt dinner on the evening before colonoscopy. The meal must have been completed at least 1 hour before subjects started taking MoviPrep. Subjects were instructed to ingest only clear liquids while they took MoviPrep until after their colonoscopy.
   (II) Study 302: Prepopik subjects were allowed to have clear liquids only on the day before their colonoscopy. This clear liquid diet was followed until the subject completed their colonoscopy on the following day.

Visit 2: Colonoscopy

Visit 2 was scheduled between 4 days and 30 days from Visit 1; Visit 2 scheduled beyond 30 days from Visit 1 was considered a protocol violation requiring repeat blood draw. Patients

returned to the study center after completion of both preparation doses for the colonoscopy, vital signs, physical exam, and laboratory assessment.

At Visit 2, just prior to colonoscopy, patients were interviewed by site personnel about "expected" preparation symptoms of abdominal cramping, bloating, nausea, and vomiting. If any of the symptoms were reported, they were rated as mild, moderate, or severe. Patients were queried for these "expected" preparation symptoms using the symptom scale or changes to their concomitant medication (see Appendix 15.1.3 for subject symptom scale).

On the same day as Visit 2, the colonoscopy was performed. The colonoscopist (blinded to study drug assignment) assigned a score to each bowel segment, as well as an overall "global" score, on withdrawal of the colonoscope.

The grading scale, which was negotiated with the Division during development, is shown below.

Table 11. Rating Scale Used for Efficacy Assessment

FDA Grading Scale		
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: Table reproduced from colonoscopy grading worksheet provided to each investigator, Sponsor's response to IR received November 26, 2019

Visit 3: 24 to 48 Hours Post Colonoscopy

All patients returned to the site 24 to 48 hours following colonoscopy for follow-up, to include laboratory samples for serum chemistry and hematology, adverse events, vital signs, and 12-lead ECG.

Visits 4 and 5: Follow-up of Adverse Events and Laboratory Results

Patients with laboratory abnormalities that were not present at baseline Visit 1 and/or ongoing adverse events at Visit 3 returned for follow-up on day 7 (±2 days) and day 30 (±2 days).

Study Endpoints

Primary Endpoint

Defined as the proportion of subjects who had an overall successful preparation for the colonoscopy. Preparation success was defined as overall cleansing assessment by the colonoscopist 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), as well as subjects who did not have a colonoscopy due to intolerance or the Investigator's assessment of inadequate cleansing as well as cleansing inadequate for evaluation. For details on the colonoscopy scoring system see Table 11.

Secondary Efficacy Endpoints

These include scoring of colon cleansing by segment (proximal, mid, distal) using the four-point scale, the proportion of excellent preparation (overall and by segment), successful cleaning (good/excellent) by segment, overall adequacy of preparation, the need for re-preparation, duration of colonoscopy, the volume of intraprocedural water used to irrigate the colon for improved visualization, proportion of procedures that reached the cecum, time to cecum, polyp detection rate, adenoma detection rate, and flat lesion detection rate.

Statistical Analysis Plan

Analysis populations:

- Intent to treat population includes all subjects randomized to treatment.
- Modified intent to treat (mITT) population includes all randomized subjects who took any portion of study medication, except for those who took the study preparation but did not undergo colonoscopy for a reason other than safety or efficacy (e.g., lack of insurance coverage, unable to return to the clinic for colonoscopy). The mITT population was the analysis population for primary and secondary efficacy analyses[2].
- Safety population includes all randomized subjects who took any portion of study medication. The safety population was used for all safety analyses.
- The per-protocol (PP) population consists of all subjects in the mITT population who completed Visit 2 without a major protocol violation. This population is used for sensitivity analyses of the primary and secondary endpoints.

[2] Five patients who took preparation and were excluded from the mITT population for the following reasons:

- Site was unable to operate recording equipment, and subsequently decided not to grade the preparation cleansing.
- Investigator decided not to perform colonoscopy due to the patient's pre-existing condition of anal stenosis.
- Patient underwent colonoscopy at an unaffiliated facility and the bowel preparation was not graded.
- Site cancelled procedure after patient began preparation because the Investigator's flight was cancelled.
- Patient had a rescheduled visit and colonoscopy was not graded in error.

Primary Statistical Analyses Method

The method was a Cochran-Mantel-Haenzel (CMH) test stratified by study sites to test for non-inferiority using a 10% NI margin. The two-sided 95% confidence interval (CI) is reported for treatment difference. The NI hypothesis was rejected when the lower bound of the 95% CI was greater than the -10% NI margin. The statistical analysis plan (SAP) planned a superiority test only when the NI hypothesis was rejected at alpha level of 0.05. Nonresponder imputation is used for missing primary endpoint due to inadequate bowel preparation either due to lack of effect or as a result of adverse event(s). Subjects who took any study medication but did not have a colonoscopy due to nonpreparation reasons such as lack of insurance will be excluded from the efficacy analysis but will be part of the safety analysis. There was very little missing data in these studies and, therefore, this was not a concern.

The Applicant's SAP did not propose multiplicity adjustment on testing the secondary endpoints. There was no planned interim analysis nor any specific sensitivity analysis.

The Agency recommended independent central reading on colonoscopies in the no agreement letter to the SPAs dated May 12, 2017. The Central Reading SAP outlined procedures for independent central reading on overall cleansing for a subset of colonoscopies in the phase 3 studies. Central reading was performed on the first several colonoscopies at each site (quality control [QC] reads), as well as on a random sample at each site (random reads). If the local grade was not consistent with the central reading grade for overall cleansing success/failure, an independent adjudicator (another central reader) would determine the result.

The Central Reading SAP outlined the following analyses for both studies:

- Percent agreement for QC reads versus site reads
- Percent agreement for random reads versus site reads
- Percent agreement for total reads (QC plus random reads) versus site reads
- Percent disagreement (Local Success/Central Failure) for QC reads, random reads, or total reads

Results of additional analyses conducted to assess concordance between central and local reads are located in Appendix 15.3.1, and were generally consistent with trial results based on local reading in the mITT population.

Protocol Amendments

There was one amendment to study 301 to modify procedures for follow-up Visits 4 and 5 on April 5, 2018. No amendment was made to study 302. No changes were made to the original SAPs.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant attests that the studies were conducted in compliance with good clinical practice regulations or applicable regulations.

Financial Disclosure

Financial disclosures were reviewed; no relevant conflicts of interest were disclosed for any study investigators.

Patient Disposition

Study BLI4700-301

A total of 634 patients 18 to 85 years of age were screened, and 620 were randomized at 22 sites in the United States. The mITT population had 548 patients who received BLI4700 (278) and MoviPrep (270). The discontinuation of study rate at or after the colonoscopy was similar, about 17%, between the two treatment arms. The most common reasons for study discontinuation were lost to follow-up, subject withdrew consent and other.

Table 12. Study BLI4700-301 Patient Disposition

Subject Disposition	BLI4700 n (%)	MoviPrep n (%)	All n (%)
Subjects screened			634
Subjects randomized	314	306	620
ITT subjects	314 (100.0)	306 (100.0)	620 (100.0)
Safety subjects	281 (89.5)	271 (88.6)	552 (89.0)
mITT subjects	278 (88.5)	270 (88.2)	548 (88.4)
Completing subjects (%ITT)	263 (83.8)	252 (82.4)	515 (83.1)
Subjects discontinued (%ITT)	51 (16.2)	54 (17.6)	105 (16.9)
Reasons for discontinuation			
Adverse event	1 (2.0)	3 (5.6)	4 (3.8)
Lost to follow-up	19 (37.3)	12 (22.2)	31 (29.5)
Physician decision	2 (3.9)	1 (1.9)	3 (2.9)
Subject withdrew consent	14 (27.5)	18 (33.3)	32 (30.5)
Other	15 (29.4)	20 (37.0)	35 (33.3)

Source: Table 3 on Page 31 of Study BLI4700-301 Clinical Study Report (CSR), verified by the reviewer
Abbreviations: ITT = intent to treat, mITT = modified intent to treat

Study BLI4700-302

A total of 449 patients aged 18 to 85 years old were screened, and 445 were randomized at 20 U.S. sites. The mITT population had 388 patients, with 190 receiving BLI4700 and 198 receiving Prepopik. Study discontinuation rates were similar between treatment arms, 20% for BLI4700 and 17% for Prepopik. The most common reasons for study discontinuation in BLI4700 arm (20%) and Prepopik arm (17%) were subject withdrew consent and lost to follow-up.

Table 13. Study BLI4700-302 Patient Disposition

Subject Disposition	BLI4700 n (%)	Prepopik n (%)	All n (%)
Subjects screened			449
Subjects randomized			445
ITT subjects	220 (100)	224 (100)	444 (100)
Safety subjects	190 (86.4)	199 (88.8)	389 (87.6)
mITT subjects	190 (86.4)	198 (88.4)	388 (87.4)
Completing subjects (%ITT)	176 (80.0)	185 (82.6)	361 (81.3)
Subjects discontinued (%ITT)	44 (20.0)	39 (17.4)	83 (18.7)
Reasons for discontinuation			
Screen failure post randomization	10 (22.7)	10 (25.6)	20 (24.1)
Lost to follow-up	8 (18.2)	7 (17.9)	15 (18.1)
Physician decision	2 (4.5)	0	2 (2.4)
Subject withdrew consent	19 (43.2)	21 (53.8)	40 (48.2)
Other	5 (11.4)	1 (2.6)	6 (7.2)

Source: Table 3 on Page 31 of Study BLI4700-302 CSR, verified by the reviewer
Abbreviations: ITT = intent to treat, mITT = modified intent to treat

Protocol Violations/Deviations

The Clinical Study Reports (CSRs) did not report a summary of protocol violation/deviation but did include subject-level listings of all protocol deviations. The deviations included patients who had colonoscopy but failed to follow the dietary instruction or the instruction for the bowel cleansing drugs. There were 34 subjects who had these protocol violations in study 301 and 46 in study 302.

In addition, the Applicant confirmed that two subjects (subject IDs: (b) (6)) received treatment but did not have records that a colonoscopy was performed. These subjects were excluded from the mITT population (IR response dated July 15, 2019).

Table of Demographic Characteristics

Although demographic and baseline characteristics are typically summarized using the primary efficacy analysis population, the Applicant reported them using the safety population. Since there were very few differences between the two populations, the safety population was used to be consistent with the Applicant. For study 301, the safety population contained four more subjects than the mITT population, 522 versus 548. For study 302, the safety population contained one more subject than the mITT population, 389 versus 388.

Table 14 summarizes the subject demographics in study 301. The study population included more females (56.1%) than males (43.9%) and more subjects aged 50 years and above (82.6%). The treatment groups were similar with respect to average age (57.9 years) and mean BMI (30.2). Seventy-eight percent of patients identified as white, 16% identified as African American, and 11% identified as Hispanic or Latino.

For study 302, the patient demographics are shown in Table 15. The study population included more females (57.8%) than males (42.2%) and more older subjects aged 50 years and above

(84.8%). The treatment groups were similar with respect to average age (57.8 years) and mean BMI (29.4). The majority of the patients identified as white (92.5%), 4.9% identified as African American, and 9% identified as Hispanic or Latino.

The study population adequately represents the group likely to use the study drug. The preponderance of patients ≥50 years of age is appropriate given the current recommendations for colonoscopy screening in the United States.

Table 14. Study BLI4700-301 Demographics and Baseline Characteristics (Safety Population)

Demographics and Baseline Characteristics	BLI4700 (n=281)	MoviPrep (n=271)	All (n=552)
Age (years)			
Mean (SD)	57.5 (11.9)	58.4 (11.6)	57.9 (11.7)
Median (min, max)	59 (20, 79)	60 (19, 84)	59 (19, 84)
Age groups, n (%)			
≥50 years	229 (81.5)	227 (83.8)	456 (82.6)
<50 years	52 (19.5)	44 (16.2)	96 (17.4)
≥65 years	88 (31.3)	88 (32.5)	176 (31.9)
<65 years	193 (68.7)	183 (67.5)	376 (68.1)
Gender, n (%)			
Female	158 (56.2)	152 (56.1)	310 (56.2)
Male	123 (43.8)	119 (43.9)	242 (43.8)
Race, n (%)			
White	221 (78.6)	212 (78.2)	433 (78.4)
African American	43 (15.3)	45 (16.6)	88 (15.9)
Asian	8 (2.8)	10 (3.7)	18 (3.3)
Other	9 (3.2)	4 (1.5)	13 (2.4)
Ethnicity, n (%)			
Hispanic	27 (9.6)	31 (11.4)	58 (10.5)
Non Hispanic	254 (90.4)	240 (88.6)	494 (89.5)
BMI			
Mean (SD)	29.8 (5.9)	30.6 (6.5)	30.2 (6.2)

Source: Table 14.1.4 of Study BLI4700-301 CSR and Table 13 of IR response submitted on July 15, 2019. Verified by reviewer.
Abbreviations: BMI = body mass index

Table 15. BLI4700-302: Demographics and Baseline Characteristics (Safety Population)

Demographics and Baseline Characteristics	BLI4700 (n=190)	Prepopik (n=199)	All (n=389)
Age (years)			
Mean (SD)	58.2 (11.2)	57.3 (10.8)	57.8 (11.0)
Median (min, max)	58 (25, 83)	57 (23, 80)	58 (23, 83)
Age groups, n (%)			
≥50 years	158 (83.1)	172 (87.4)	330 (84.8)
<50 years	32 (17.9)	27 (12.6)	59 (15.2)
≥65 years	62 (32.6)	47 (23.6)	109 (28.0)
<65 years	128 (67.4)	152 (76.4)	280 (72.0)
Gender, n (%)			
Female	112 (58.9)	113 (56.8)	225 (57.8)
Male	78 (41.1)	86 (43.2)	164 (42.2)

Demographics and Baseline Characteristics	BLI4700 (n=190)	Prepopik (n=199)	All (n=389)
Race, n (%)			
White	177 (93.2)	183 (92.0)	360 (92.5)
African American	8 (4.2)	11 (5.5)	19 (4.9)
Asian	2 (1.1)	2 (1.0)	4 (1.0)
Other	3 (1.6)	3 (1.5)	6 (1.6)
Ethnicity, n (%)			
Hispanic	19 (10.0)	16 (8.0)	35 (9.0)
Non Hispanic	171 (90.0)	183 (92.0)	354 (91.0)
BMI, n(%)			
Mean (SD)	29.4 (5.8)	29.4 (5.8)	29.4 (5.8)

Source: Table 14.1.4 of Study BLI4700-302 CSR and Table 14 of IR response submitted on July 15, 2019. Verified by reviewer.
Abbreviation: BMI = body mass index

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

For both studies, the main indications for colonoscopy included age of 50 years and above (about 60%) and asymptomatic conditions (about 30%). More detailed distribution of colonoscopy indications at baseline refer to Appendix 15.3 (Table 44 and Table 45).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study 301: Compliance with administration of study drug was 85.3% across treatment arms in all randomized subjects (ITT population) in the study completing the two dosages of study drug (BLI4700=87.3%, MoviPrep=83.3%). For the safety population, the compliance rate of complete bowel preparation was 96.5% (BLI4700=97.9%, MoviPrep=95.1%).

Study 302: Compliance with administration of study drug was 85.4% across treatment arms in the randomized subjects (ITT population) in the study completing the two dosages of study drug (BLI4700=84%, MoviPrep=86.6%). For the safety population, the compliance rate of complete bowel preparation was 98.4% (BLI4700=98%, Prepopik=99%).

Data Quality and Integrity

In general, the analysis dataset model (ADaM) and Study Data Tabulation Model datasets were of sufficient quality to allow for a thorough review of the data. However, to confirm some of the demographic characteristics and the consistency of the local and central reading of the colonoscopies, ADaM efficacy datasets, ADaM data for efficacy analysis and ADZI, were requested and provided by the Applicant. These variables included location of study sites (states), BMI, and names of local and central readers.

Independent central reading was performed for a subset of colonoscopies in the phase 3 studies (27% in Study 301 and 32% in Study 302). For the primary endpoint, the interobserver agreement between the local endoscopists and central readers was high in both studies (97% in Study 301 and 92% in Study 302). For cases rated by the local endoscopist as a success, the interobserver agreement was higher (99% in Study 301 and 96% in Study 302).

Efficacy Results—Primary Endpoint

For study 301 (Table 16), the primary efficacy results showed BLI4700 is non-inferior to MoviPrep by a 10% non-inferiority margin based on an adjusted treatment difference of 3% (95% CI: -1.7, 7.8). In fact, the lower bound of the 95% CI was greater than the -10% NI margin. However, the test for superiority was not statistically significant (p-value 0.22) based on a CMH test adjusted by study sites.

Table 16. Study BLI4700-301 Efficacy Results on the Primary Endpoint (mITT)

Primary Endpoint Results	BLI4700 N=278 (%)	MoviPrep N=270 (%)	Treatment Difference*	95% CI*	p-Value†	99% CI*
Primary analysis result						
Preparation success‡ adjusted by sites	257 (92.4)	241 (89.3)	3.0	-1.7, 7.8	0.22	-3.2, 9.3
Sensitivity analysis results						
Preparation success adjusted by stratification groups	257 (92.4)	241 (89.3)	3.4	-1.4, 8.2	0.16	-2.9, 9.7
Preparation success adjusted by sites and stratification groups	257 (92.4)	241 (89.3)	3.4	-1.6, 8.4	0.18	-3.2, 9.9
Preparation success adjusted by region	257 (92.4)	241 (89.3)	3.0	-1.8, 7.8	0.22	-3.3, 9.3
Preparation success adjusted by region and stratification groups	257 (92.4)	241 (89.3)	3.3	-1.6, 8.3	0.18	-3.2, 9.8
Preparation success (unadjusted)	257 (92.4)	241 (89.3)	2.6	-1.6, 8.0	0.20	-3.2, 9.5

Source: Reviewer's analyses, confirmed by the Sponsor's IR response submitted on July 15, 2019

* Treatment difference and 95% CI are adjusted for covariates based on Cochran-Mantel-Haenzel estimates for the common risk.

† p-Value for superiority test between treatments is based on a CMH test, controlling for covariates.

‡ Preparation success is defined as bowel cleansing graded either excellent or good (grading score = 3 or 4).

Abbreviation: mITT = modified intent to treat

Table 17. Study BLI4700-302 Efficacy Results on the Primary Endpoint (mITT)

Primary Endpoint Results	BLI4700 N=190 (%)	Prepopik N=198 (%)	Treatment Difference*	95% CI*	p-Value†	99% CI*
Primary analysis result						
Preparation success‡ adjusted by sites	175 (92.1)	174 (87.9)	3.1	-2.7, 8.9	0.30	-4.5, 10.7
Sensitivity analysis results						
Preparation success adjusted by stratification groups	175 (92.1)	174 (87.9)	4.3	-1.7, 10.2	0.16	-3.5, 12.1
Preparation success adjusted by sites and stratification groups	175 (92.1)	174 (87.9)	4.1	-1.9, 10.0	0.19	-3.7, 11.9
Preparation success adjusted by region	175 (92.1)	174 (87.9)	4.3	-1.6, 10.1	0.16	-3.4, 12.0
Preparation success adjusted by region and stratification groups	175 (92.1)	174 (87.9)	3.6	-2.5, 9.6	0.25	-4.4, 11.5
Preparation success (unadjusted)	175 (92.1)	174 (87.9)	4.2	-1.7, 10.2	0.17	-3.6, 12

Source: Reviewer's analyses, confirmed by the Sponsor's IR response submitted on July 15, 2019

* Treatment difference and 95% CI or 99% CI are adjusted for covariates based on Mantel-Haenzel estimates for the common risk.

† p-Value for superiority test between treatments is based on a CMH test, controlling for covariates, at alpha level 0.05.

‡ Preparation success is defined as bowel cleansing graded either excellent or good (grading score =3 or 4).

Abbreviation: mITT = modified intent to treat

For study 302 (Table 17), the primary results showed similar overall success rates for both preparations: 92% for BLI4700 and 88% for Prepopik. The lower bound of 95% CI (-1.7, 10.2) for the difference in success rates adjusted by sites is above the -10% NI margin. Therefore, BLI4700 was non-inferior to Prepopik by a 10% NI margin. A subsequent superiority test also failed at p-value 0.30.

Note that the Agency disagreed with using Prepopik as an active comparator and recommended a comparison between the lower bound of 99% CI of the treatment difference and a NI margin for this study in the 2017 SPA no agreement letter. Regardless, the study drug was shown to be non-inferior to Prepopik, even using this more conservative 99% CI bound.

Sensitivity Analyses on the Primary Endpoint

For both studies, various sensitivity analyses on the primary endpoint were conducted using additional CMH models, different analysis populations, and different subgroup analyses. The sensitivity analyses results were consistent with the primary efficacy finding. For details on sensitivity analyses results see Appendix 15.3.1.

Most of the prespecified subgroup analyses results on the primary endpoint were similar across subgroups and consistent with the primary results. The only subgroup with a lower bound of the 95% CI (-10.8%) below -10% NI margin was the Hispanic ethnicity group and this could be attributed to the small group sizes in each arm (about 30 subjects). For details refer to Appendix 15.3.1.

Efficacy Results—Secondary and Other Relevant Endpoints

The Applicant's CSRs reported results on secondary efficacy endpoints including segment grade 'Excellent' rate and intraprocedural efficacy endpoints (Table 18 and Table 19). These secondary endpoints distributed similarly between two treatment arms in both studies. The majority of the evaluated secondary efficacy results did not show a statistically significant difference between two arms. The exceptions were segment grade 'Excellent' for proximal colon segment in study 301 (p-value=0.03) and mid-colon segment in study 301 (p-value<0.01).

Additional exploratory analyses were performed to compare the overall colon cleansing based on global assessment of the colon with the individual colon segment scores defined by the Applicant. The results for each study are discussed separately in Appendix 15.3.1. For both studies, the efficacy conclusions are similar when examining the proportion of responders in all three segments compared to the proportion of responders from the global assessment.

The following two tables (Table 18 and Table 19) summarize the Applicant's results on additional secondary and supportive endpoints. Several of these endpoints are useful in assessing the assay sensitivity of the trial (demonstrating that the chosen comparator is relevant to current practice) and clinical relevance of the reported trial results, outside of non-inferiority demonstrated. Specifically, the adenoma detection rate is considered an important

metric of quality in screening and surveillance colonoscopy, and is negatively impacted by poor quality bowel preparations. The reported ADR was above 30% in both studies (either arm), which is consistent with the published colonoscopy quality guidelines (minimum acceptable ADR for screening colonoscopy ≥25% (≥30% for men and ≥20% for women). Similarly, cecal intubation rate is expected to exceed 95% in screening colonoscopies, as was demonstrated in both trials (Rex et al. 2015). Additionally, irrigation water volume utilized was similar across arms and was lower in the SUTAB arm compared to either comparator. This is reassuring because if prep quality was poor, additional water use for irrigation would be expected, and could skew the final assessment of prep adequacy.

Table 18. Study BLI4700-301 Secondary Efficacy Results in mITT Population

Secondary Endpoints Results	BLI4700 N=278 (%)	MoviPrep N=270 (%)	p-Value*
Segment score excellent			
Proximal colon segment	174/273 (63.7)	146/265 (55.1)	0.03
Mid colon segment	192/273 (70.3)	169/266 (63.5)	0.10
Distal colon segment	183/275 (91.6)	158/267 (89.9)	0.07
Colonoscopy status†			
Attempted	276 (99.3)	267 (98.9)	0.62
Was the cecum reached? †			
Yes	271 (98.2)	261 (97.8)	0.82
Cleaning adequate for evaluation†			
Yes	268 (96.8)	255 (94.8)	0.27
Procedure duration (min)‡	n=276	n=267	
Mean (SD)	15.8 (9.6)	15.9 (8.1)	0.91
Irrigation water volume (mL)‡	n=275	n=266	
Mean (SD)	88.4 (128)	93.8 (126)	0.63
Polyp detection rate			
≥1 polyp	128 (46.0)	123 (45.6)	0.98
Adenoma detection rate			
≥1 adenoma	92 (33.1)	94 (34.8)	0.53
Flat lesion detection rate			
≥1 flat lesions	23 (8.3)	26 (9.6)	0.44

Source: Tables 8 & 9 of Study BLI4700-301 CSR
* All secondary endpoints were exploratory. None of the reported p-values was included in a family-wise Type I error control procedure.
† p-Value based on a CMH test adjusted for site
‡ p-Value based on ANOVA for continuous endpoints
Abbreviations: mITT = modified intent to treat, mL = milliliter

Table 19. Study BLI4700-302 Secondary Efficacy Results in mITT Population

Secondary Endpoint Results	BLI4700 N=190 (%)	Prepopik N=198 (%)	p-Value*
Segment score excellent			
Proximal colon segment	115/187 (61.5)	103/196 (52.6)	0.09
Mid colon segment	139/188 (73.5)	112/187 (57.1)	<0.01
Distal colon segment	126/188 (67.0)	112/197 (56.9)	0.05
Colonoscopy status†			
Attempted	187 (98.4)	197 (99.5)	0.29
Was the cecum reached? †			
Yes	186 (99.5)	196 (99.5)	0.96

Secondary Endpoint Results	BLI4700 N=190 (%)	Prepopik N=198 (%)	p-Value*
Cleaning adequate for evaluation†			
Yes	183 (97.3)	190 (96.0)	0.51
Procedure duration (min)‡			
Mean (SD)	15.5 (6.7)	15.1 (6.6)	0.98
Irrigation water volume (mL)‡			
Mean (SD)	82.5 (122)	96.2 (140)	0.82
Polyp detection rate			
≥1 polyp	85 (44.7)	77 (38.9)	0.32
Adenoma detection rate			
≥1 adenoma	60 (31.6)	62 (31.3)	0.76
Flat lesion detection rate			
≥1 flat lesions	26 (13.7)	26 (13.1)	0.60

Source: Tables 8 & 9 of Study BLI4700-301 CSR
* All secondary endpoints were exploratory. None of the reported p-values was included in a family-wise Type I error control procedure.
† p-Value based on a CMH test adjusted for site
‡ p-Value based on ANOVA for continuous endpoints
Abbreviations: mITT = modified intent to treat, mL = milliliter

8.1.3. Assessment of Efficacy Across Trials

This section is not applicable to this NDA submission. The two pivotal trials used different active comparators.

8.1.4. Integrated Assessment of Effectiveness

Based on the submission by the Applicant, BLI4700 (SUTAB) was demonstrated to be non-inferior to both MoviPrep and Prepopik. Efficacy was assessed by the proportion of patients achieving overall colon cleansing preparation success, defined by score of 3 (Good) or 4 (Excellent) on the bowel cleansing scale. For the primary endpoint, the BLI4700 arm had a lower bound of the 95% CI for the treatment difference between BLI4700 and an active comparator arm below the -10% NI margin in both trials. Even though there was not complete agreement on the 10% NI margin, it is less of a concern because the studies actually ruled out a 5% NI margin even using the more stringent 99% CI.

The findings of sensitivity analyses based on CMH test adjusted for different covariates or in various study populations (mITT, subjects with both global and segment level grades, modified PP population, and subgroups) were consistent with the primary efficacy outcome and showed that BLI4700 was non-inferior to the MoviPrep or Prepopik arm. This further supported efficacy of BLI4700 for the colon cleansing preparation.

Although the clinical trial data support approval on the basis of demonstrated efficacy and acceptable safety profile, the application will receive a Complete Response during this review cycle for reasons related to inadequate manufacturing facilities (described in more detail in Sections 1.3 and 4.2 above).

8.2. Review of Safety

8.2.1. Safety Review Approach

Two phase 3 studies (BLI4700-301 and BLI4700-302) conducted for safety and efficacy were the basis of this NDA safety review. The safety analysis was tabulated by individual studies, no pooling was done because the active comparators and associated dietary restrictions were different. BLI4700-301 will be referred to as study 301 and BLI4700-302 will be referred to as study 302 henceforth.

In addition, there were four other Applicant-conducted studies using different formulations during development, which were reviewed as part of the justification for combination rule (refer to Section 15.1). Two open-label phase 1 clinical studies (BLI4700-101 and BLI4700-102) were conducted to explore the effect of various BLI4700 formulations on fecal output volume and solids content. There were two open-label phase 2 studies (BLI4700-201 and BLI4700-202) with BLI4700 tablets using a split-dose regimen in adult patients requiring colonoscopy. A final formulation was carried forward to the phase 3 studies. The phase 1 and 2 open-label studies were not relied upon in the safety analyses because of the varying methods of symptom collection and different formulations of BLI4700 tablets that did not progress to phase 3.

8.2.2. Review of the Safety Database

Overall Exposure

Overall, 941 patients were randomized and took study preparation in the BLI4700 phase 3 studies, including 471 who took the SUTAB (BLI4700 tablet preparation). See Table 20 below. Patients were exposed to study drug for the total duration of the dosing period, which was 12 hours for all the bowel preparations.

Table 20. Patient Population in BLI4700-301/302

Patient Population	Study BLI4700-301	Study BLI4700-302
Screened patients	634	449
Randomized	620	445
ITT patients*	620	444
BLI4700	314	220
MoviPrep	306	
Prepopik		224
Safety population†	552	389
BLI4700	281	190
MoviPrep	271	
Prepopik		199

Patient Population	Study BLI4700-301	Study BLI4700-302
mITT‡	548	388
BLI4700	278	190
MoviPrep	270	
Prepopik		198

Source: Reviewer's table, adapted from Applicant's BLI4700-301 and BLI4700-302 Report Body, submitted May 15, 2019)
* Population that included all patients randomized to treatment
† All patients who took any portion of study medications
‡ All patients in the safety population, except those who took the study preparation but did not undergo colonoscopy for a reason other than safety or efficacy
Abbreviations: ITT = intent to treat, mITT = modified intent to treat

One patient was enrolled in study 302 twice; the patient's original colonoscopy was cancelled due to a hurricane, although bowel preparation had already been taken at the time. The patient was re-enrolled and took a second bowel preparation 1 week later. The patient was excluded from all safety and efficacy analyses.

Exclusion of patients prior to taking study preparation or considered screen failures prior to randomization was primarily due to meeting the exclusion criteria of uncontrolled blood pressure (BP); abnormal physical exam, ECG findings, or screening laboratory results; or at the investigator's discretion.

Adequacy of the Safety Database

The size of the overall clinical study and the safety population is comparable to the typical study size for a new bowel preparation, and it was considered adequate to characterize the safety profile of SUTAB split-dose regimen.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data quality and submission organization were adequate to permit substantive review.

Clinical Safety Assessment Plan (Including Laboratory Assessment)

Table 21 summarizes the schedule of evaluation during the clinical studies. For bowel preparation products, key safety issues to evaluate include potential negative effects on fluid status (dehydration) and electrolyte changes. Thus, the schedule of assessment appears appropriate to capture these potential adverse events of interest. Specifically, physical examination and orthostatic measurements were conducted at screening, day of colonoscopy, and 24 to 48 hours after colonoscopy, which are optimal timepoints to assess clinically apparent signs of dehydration and laboratory parameters of interest. In addition, the same assessments were conducted at 7 days and 30 days (±2 days) post colonoscopy for patients with abnormal laboratory tests and/or ongoing adverse events at 24-48 hours. Follow-up for all patients with abnormal laboratory tests at 7 days is of particular interest to assess for resolution or worsening of acute kidney injury due to hypovolemia that might not be fully evident at 24 to 48 hours. The submitted laboratory data had few missing values, which resulted in adequate characterization of the safety profile.

Table 21. 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 *(24-48 hrs post colonoscopy)*	Visit 4[3] Day 7 *(+/- 1 days)*	Visit 5[3] Day 30 *(+/- 1 days)*	Day 30[3]
Informed Consent	X						
Inclusion/Exclusion Criteria Review	X						
Medical History	X						
Physical Examination	X		X				
Vital Signs (including ECG)	X		X	X	X	X	
Review of Concomitant Medication	X		X	X	X	X	X
Blood Collection for Laboratory Testing	X		X	X	X	X	
Urine Collection for Laboratory Testing	X		X	X			
Serum Pregnancy Test (if applicable)	X						
Treatment Assignment[1]	X						
Dispense Drug and Questionnaires [1]	X						
Subjects Begin Questionnaires		X					
Subjects Take Bowel Preparations		X	X				
Symptom Scale & Preference Questionnaire Completed[2]			X				
Drug Accountability[1]			X				
Colonoscopy performed with Intra-procedural Safety and Efficacy Grading			X				
Collect and assess adverse event data			X	X	X	X	X

[1]performed by unblinded personnel only [2]to be completed at Visit 2 prior to sedation
[3]Visits 4 and 5 were required clinic visits if new or ongoing AEs or lab abnormalities were seen at Visit 3. For subjects that did not meet this criteria, only a follow-up telephone call at Day 30 was required.

Source: Applicant's clinical study report body (BLI4700-301: page 19/73, BLI4700-302: page 19/71)

Categorization of Adverse Events

An AE was defined according to a standard definition, as any unfavorable or unintended signs, symptoms, or disease, regardless of causality. Laboratory abnormalities, vital signs, and physical examination findings were documented as AEs if considered clinically significant by the Investigator. Patients were queried for any problems they experienced during and after preparation by site personnel.

In addition, site personnel systemically collected what were described as "expected preparation symptoms" of abdominal cramping, bloating, nausea, and vomiting via patient interview using symptom scale (see Appendix 15.1.3), at Visit 2 (after completing entire preparation).

Any symptom on the symptom scale rated as mild, moderate, or severe was reported as an adverse event. Colonoscopy and biopsy findings were not considered as adverse events unless considered by the Investigator to be related to the preparation or colonoscopy procedure. Any blood pressure result that was deemed clinically significant and not present at Visit 1 (screening) was reported as an adverse event. In addition, any 30 mm Hg change in systolic or diastolic blood pressure from Visit 1 was reported as an adverse event.

Treatment-emergent adverse events (TEAEs) were defined as any AE that occurred after first dose of study drug; worsening of a pre-existing condition in the same time period was also considered a TEAE.

The following standard rating tables for severity and relatedness to study treatment are from the Applicant's submission.

Table 22. Applicant's Severity Standard Rating Criteria

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

Source: Applicant's protocol submission of BLI4700-301: page 69/110, BLI4700-302: page 28/64)

Table 23. Applicant's Relatedness Standard Rating Criteria

Categories of Attribution	Description
UNRELATED	There is *no* evidence of any causal relationship
POSSIBLE	There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of *other factors may have contributed* to the event (e.g., the subject's clinical condition, other concomitant events).
PROBABLE	There *is evidence* to suggest a causal relationship, and the influence of other factors is *unlikely*.
DEFINITE	There is *clear* evidence to suggest a causal relationship, and other possible contributing factors can be *ruled out.*

Source: Applicant's protocol submission of BLI4700-301: page 69/110, BLI4700-302: page 28/64)

Serious adverse events (SAEs) were any untoward medical occurrence that occurred subsequent to signing of informed consent until the follow-up visit and is described according to standard SAE definitions in 21 CFR 312.32.

To detect potential safety signals, the clinical reviewer recoded some adverse events by grouping similar conditions together. See table below.

Table 24. Reviewer- and Applicant-Created AE Coding

New Code	Previous Code
Abdominal pain	Abdominal pain and abdominal pain upper, abdominal cramping
Abdominal distension	Abdominal distension, bloating (recoding done by Applicant)
Blood pressure increased	Blood pressure increased, blood pressure diastolic increased, blood pressure systolic increased, essential hypertension and hypertension
Blood pressure decreased	Blood pressure decreased, blood pressure systolic decreased, blood pressure diastolic decreased, hypotension and orthostatic hypotension

New Code	Previous Code
Liver function test increased	Liver function test increased, ALT increased, AST increased, bilirubin increased
Hypokalemia	Hypokalemia, potassium decreased

Source: Reviewer-created table
Abbreviations: AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase

8.2.4. Safety Results

Deaths

No deaths occurred in either of the phase 3 studies.

Serious Adverse Events

There were five serious adverse events in four patients who took bowel preparation in the SUTAB phase 3 studies, none was in the SUTAB group. List of serious adverse events is listed below.

Table 25. Serious Adverse Events in Phase 3 Studies

Study No.	Subject ID	Study Drug	Preferred Term (AE)	Action Taken	Outcome	Relatedness
BLI4700-301	(b) (6)	MoviPrep	Right wrist fracture	Does not changed	Recovered /resolved	Unrelated
		MoviPrep	Acute pyelonephritis *Escherichia* sepsis	Dose not changed	Recovered /resolved	Unrelated
		MoviPrep	Acute upper gastrointestinal hemorrhage	Dose not taken, started after randomization before study drug	Recovered /resolved	Unrelated
BLI4700-302	(b) (6)	Prepopik	Cholelithiasis	Dose not changed	Recovered /resolved	Unrelated

Source: Reviewer's analysis of ADAE dataset, SAE in safety population
Abbreviation: AE = adverse event

None of the serious adverse events were related to SUTAB or the active comparator.

Dropouts and/or Discontinuations Due to Adverse Effects

The rate of discontinuation was similar between the two studies in the ITT population.

In study 301, 54/306 (17.6%) patients in the MoviPrep group discontinued at or after screening compared to 51/314 (16.2%) in the SUTAB group. Four of these discontinuations were due to adverse events and are listed below:

- MoviPrep (b) (6): 58M, Acute Upper Gastrointestinal Hemorrhage
- MoviPrep (b) (6): 23M, Crohn's flare hospitalization requiring colonoscopy before study date
- MoviPrep (b) (6)): 29F, Vomiting, "patient was intolerant to prep drug" per investigator
- SUTAB (b) (6)): 73F, Syncope

In study 302, 39/224 (17.4%) patients in the Prepopik group discontinued at or after screening, compared to 44/224 (22.7%) in the SUTAB group. No discontinuation in the Prepopik group was due to adverse events. There was one AE that resulted in drug interruption ((b) (6)) and one AE that resulted in drug withdrawal ((b) (6)) in the SUTAB group.

Overall, the rates of discontinuation in the ITT population was similar in all patients treated with SUTAB (95/534; 17.8%), MoviPrep (54/306; 17.6%) and Prepopik (39/224; 17.4%).

Below are patient information from adverse events that could be related to the bowel preparations:

(1) Patient (b) (6): Adverse event (Vomiting), MoviPrep
Screened: (b) (6), AE: (b) (6) Discontinued: (b) (6)
29 year-old female Hispanic patient who had an adverse event reported by the investigator as vomiting: patient was intolerant to prep drug on (b) (6) and was discontinued from the study due to the AE. Patient had past medical history significant for abdominal surgeries, renal failure/dysfunction, hypertension, diabetes according to the case report form. The relationship to study drug was definite, severity moderate, and drug was interrupted with an outcome of recovered/resolved. Because the patient recovered/resolved upon discontinuation of the study drug, the review team agrees with the investigator's assessment.

(2) Patient (b) (6): Adverse event (Syncope), SUTAB
Screened: (b) (6), No colonoscopy, AE: (b) (6)
73 year-old white female with past medical history of osteopenia and on calcium/Vitamin D who had onset of syncope on (b) (6) after screening and before patient ever received the study drug, thus it was considered to be unrelated to study drug. This AE was categorized as severe in intensity, and outcome was reported as recovered/resolved by the investigator. The AE occurred before the patient received the study drug, and her screening ECG on (b) (6) showed heart rate of 49 and long PR of 216 that is consistent with bradycardia and possibly first degree heart block. As such, the patient's syncope was probably related to the bradycardia and possible heart block.

In summary, there were very few adverse events leading to study drug discontinuation, and the data do not suggest that SUTAB was poorly tolerated as compared to either active comparator.

Severe Adverse Events

Generally, the reported AEs were mild to moderate in severity. This section describes AEs that were reported to be "severe" in intensity but did not meet SAE criteria.

In study 301, six patients reported 27 events that were graded as "severe" in intensity, but did not meet SAE criteria, which are shown below in Table 26.

Table 26. Severe Intensity AEs That Did Not Meet SAE Criteria

	BLI4700-301 (N=552)		BLI4700-302 (N=389)	
AEs Graded as "SEVERE" Intensity	BLI4700 N=281 (%)	MoviPrep N=271 (%)	BLI4700 N=190 (%)	Prepopik N=199 (%)
Abdominal pain	2 (0.7)	0	1 (0.5)	1 (0.5)
Abdominal distension	2 (0.7)	0	0	0
Blood creatinine increased	1 (0.4)	0	0	0
Blood creatine phosphokinase increased	0	0	1 (0.5)	0
Blood glucose increased	1 (0.4)	0	0	0
Chills	1 (0.4)	0	0	0
Constipation	1 (0.4)	0	0	0
Dizziness	1 (0.4)	0	0	0
Dysuria	1 (0.4)	0	0	0
Hematocrit decreased	1 (0.4)	0	0	0
Hemoglobin decreased	1 (0.4)	0	0	0
Hot flush	1 (0.4)	0	0	0
Joint dislocation	1 (0.4)	0	0	0
Mean cell hemoglobin decreased	1 (0.4)	0	0	0
Mean cell volume decreased	1 (0.4	0	0	0
Nausea	4 (1.4)	1 (0.4)	6 (3.1)	0
Ovarian cyst	1 (0.4)	0	0	0
Liver function test increased	0	0	1 (0.5)	0
Pain in jaw	1 (0.4)	0	0	0
Protein total increased	1 (0.4)	0	0	0
Upper respiratory tract infection	0	1 (0.4)	0	0
Vomiting	4 (1.4)	0	0	0

Source: Reviewer' s table created from ADAE dataset, AE's rated "severe" in intensity excluding SAEs
Abbreviations: AE = adverse event, SAE = serious adverse event

There were too few events of any specific type to draw conclusions regarding associations with the study drug or either of the active comparators. In addition, severe intensity adverse events that might be expected to be related to the study drug (such nausea, vomiting, dizziness, abdominal pain) generally occurred at low frequency in both groups.

The most frequently occurring AEs of severe intensity were nausea and vomiting, though it was reassuring that in only one case did this result in need to discontinue study drug.

Treatment-Emergent Adverse Events and Adverse Reactions

Table 27 highlights the most common adverse events, seen in at least 2% of patients in either group in each of the phase 3 studies.

In addition to gathering verbatim adverse events, the Applicant elicited adverse event reports at Visit 2 (prior to sedation). During the visit, study personnel asked patients to report their experience with the preparation for the most frequently occurring bowel preparation symptoms of stomach cramping, stomach bloating, nausea, and vomiting using a subject symptom scale (see Appendix 15.1.3). Patients reporting these symptoms were asked to rate the intensity as mild, moderate, or severe. Ratings of severity were based on patient's interpretation and unrelated to the severity definitions used to classify adverse events. The analysis presented in Table 27 below includes both spontaneously reported and solicited adverse events.

Table 27. Common Adverse Events in >2% Patients by Treatment Group

	BLI4700-301 (N=552)		BLI4700-302 (N=389)	
TEAEs	BLI4700 N=281 (%)	MoviPrep N=271 (%)	BLI4700 N=190 (%)	Prepopik N=199 (%)
Nausea	136 (48)	72 (27)	100 (53)	36 (18)
Abdominal distension	83 (30)	60 (22)	64 (34)	31 (16)
Vomiting	66 (24)	17 (6)	32 (17)	3 (2)
Abdominal pain	49 (17)	51 (19)	44 (23)	27 (14)
Blood pressure increased	18 (6)	20 (7)	5 (3)	10 (5)
Blood pressure decreased	16 (6)	20 (7)	9 (5)	8 (4)
Headache	6 (2)	4 (2)	3 (2)	6 (3)
Dizziness	1 (0.4)	4 (2)	1 (1)	1 (1)
Hypermagnesemia	1 (0.4)	0	4 (2)	4 (2)
Liver function test increased	1 (0.4)	2 (1)	5 (3)	2 (1)
Anemia	0	4 (2)	1 (1)	2 (1)

Source: Reviewer's analysis of ADAE dataset for study 301 and 302, using recoded AE terms summarized in Table 24
Abbreviation: TEAE = treatment-emergent adverse event

In study 301, 65.8% (185/281) of patients reported at least one TEAE in the SUTAB group compared to 56.8% (154/271) in the MoviPrep group. However, 74.7% (142/190) of patients reported at least one TEAE in the SUTAB group compared to 45.7% (91/199) in the Prepopik group for study 302. The majority of these TEAEs occurred at low frequency with one event per preferred term and at rates generally <1%.

The common adverse events profiles that were considered probably or definitely related to the study drugs were in the gastrointestinal category and were events typically associated with bowel preparations. Other notable events that were considered probably or definitely related were dizziness or headache. However, these occurred at low frequency and similar rates between the bowel preparations.

The Applicant initially did not include adverse events that were solicited by the study personnel because they were not spontaneously provided by the patients. However, review of the solicited AEs increased incidence of common TEAE rates by >10-fold. The overall rates were comparable to those seen in SUPREP (oral based formulation of SUTAB, tablet formulation) where the solicited "expected" adverse events were factored into the overall safety evaluation of common adverse events. Because all reported adverse events are relevant to characterize the safety profile, the revised analysis (as shown in Table 27 above) was proposed by the

Agency to inform the product labeling. Please refer also to section 11.1 (labeling) for further discussion of this issue.

The events listed in Table 27 were included in labeling, with the exception of the blood pressure changes and anemia. These issues were clarified with the Applicant via Information Requests during the review cycle[3].

Regarding anemia, the event was reported to reach the 2% cutoff in only one of two studies. Further details of these patients (all four of whom received MoviPrep) revealed that these events did not have reasonable likelihood of being related to study drug. Of the four patients, two had a past medical history of anemia, and one patient had below normal hemoglobin/hematocrit at screening. Given that three of the four patients with anemia had reasonable explanation for anemia outside of study drug administration, this does not appear to represent a signal of drug-related adverse event. In all four cases the anemia was mild. Further, the mechanism of action of the drug does not have biologic plausibility to induce anemia. Therefore, this term was excluded from the label as a common AE.

Regarding blood pressure, similar proportions of patients reported increased versus decreased blood pressure. In the case where drug administration had an effect on blood pressure, such a change would be expected to be observed primarily only in one direction. Based on mechanism of action, and known fluid shifts and dehydration that may occur after inducing copious diarrhea, hypotension was of greater clinical concern and further analysis was conducted.

Blood pressure decreases were explored by time of onset. Given the single-use nature of the product, it is mostly likely that drug-related hypotension, if occurring, would be present on the day of colonoscopy prior to procedure. This is shortly after completion of bowel preparation when patients are required to remain NPO and prior to any IV fluids that may be administered intraprocedurally with sedation. As seen in Table 28 below, the number of patients who experienced early blood pressure decrease on day of colonoscopy (study day 2) and 24 hours post-colonoscopy (study day 3), was small and the proportions were similar across treatment arms. Therefore, it was concluded that low blood pressure related to study drug administration did not appear to represent a common TEAE that warrants inclusion in labeling.

Table 28. Patients With Blood Pressure Decrease at Study Day 2, 3, and 4

	301		302		Total	
Day	BLI4700 N=281 (%)	MoviPrep N=271 (%)	BLI4700 N=190 (%)	Prepopik N=191 (%)	Total BLI4700 N=471 (%)	Total N=933 (%)
Study Day 2	4 (1.4)	5 (1.8)	3 (1.6)	3 (1.6)	7 (1.5)	15 (1.6)
Study Day 3	6 (2.1)	4 (1.5)	2 (1.0)	1 (0.5)	8 (1.7)	13 (1.4)
Study Day 4	2 (0.7)	2 (0.7)	1 (0.5)	0	3 (0.6)	5 (0.5)

Source: Applicant's Information Response, January 22, 2020

Further, most of the low blood pressure reported events were unrelated and transient when analyzed by each patient listing. The majority of the events were considered to be mild except

[3] Refer to Applicant's response to IR received Jan 21, 2020.

for two events of moderate severity on day 9 and day 11 (one in MoviPrep and the other in SUTAB). Based on the timing, these events are unlikely to be due to acute fluid shifts nor single administration of the product several days prior.

Hypertension was also evaluated in further detail. The evaluation of BP increase over time showed that most reported cases were a one-time increase that was transient and resolved without intervention. There did not appear to be a consistent trend over time of increasing BP or persistence of increased BP. Given the single-use nature of the product, this does not appear to be a clinically important finding.

Overall, the totality of evidence supports not including blood pressure changes in the prescribing information given that blood pressure changes were not related to a particular time point (especially not in the acute time point following ingestion of the study drug). Most of the events were mild in severity and unrelated to the study drug, and the events had similar frequencies between study drug and the active comparators.

Adverse events related to abnormal laboratory test results that investigators considered clinically significant to report as AEs were analyzed (Table 29 below).

Table 29. Electrolyte Abnormalities Reported as TEAEs

	BLI4700-301 (N=552)		BLI4700-302 (N=389)	
Preferred Term	**BLI4700 N=281 (%)**	**MoviPrep N=271 (%)**	**BLI4700 N=190 (%)**	**Prepopik N=199 (%)**
Blood creatinine increased	2 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood magnesium decreased	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
Blood magnesium increased	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood osmolarity increased	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)
Hyperkalaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Hypermagnesaemia*	0 (0.0%)	0 (0.0%)	4 (2.1%)	4 (2%)
Hyperosmolar state	1(0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypokalaemia	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hyponatraemia	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)

Source: Table 3 of Laboratory Analysis performed by Clinical Data Scientist, (b) (6) dated October 4, 2018
* Hypermagnesaemia was the only specific electrolyte derangement reported in >2%.
Abbreviation: TEAE = treatment-emergent adverse event

The only specific electrolyte derangement reported in >2% was hypermagnesemia, which is an expected laboratory finding given the composition of the drug product, and this was reported in only study 302.

Summary of patients with hypermagnesemia that worsened from baseline was further analyzed. Table below is the shift analyses of the magnitude of the hypermagnesemia.

Table 30. Shift Analysis of Hypermagnesemia That Worsened From Baseline by Severity

	Shift From Baseline Magnesium	
Study	Below LLN to Grade 0: Magnesium Normal	Normal to Grade 1: Hypermagnesemia: Mg > ULN to ≤3 mg/dL
BLI4700-301 (N=552)		
BLI4700, N=281 (%)	2 (0.7)	72 (25.6)
MoviPrep, N=271 (%)	2 (0.7)	19 (7.0)
BLI4700-302 (N=389)		
BLI4700, N=190 (%)	1 (0.5)	58 (30.5)
Prepopik, N=199 (%)	0	105 (52.8)

Source: Reviewer's table from ADLB datasets for Study 301 and 302
Abbreviations: dL = deciliter, LLN = lower limit of normal, Mg = magnesium, ULN = upper limit of normal

All the patients who had shifts of magnesium that worsened from baseline were no greater than 3 mg/dL (defined as Common Terminology Criteria for Adverse Event severity grade 1), and there were no reports of clinical symptoms associated with hypermagnesemia.

In summary, the overall incidence of TEAEs was greater in the SUTAB treatment group compared to the active comparators. Generally, common TEAEs were mild, transient in nature, and related to gastrointestinal disorders. A greater incidence of nausea, abdominal distension, and vomiting was observed in the SUTAB group compared to the active comparators.

Laboratory Findings

Changes in chemistry parameters are a specific safety issue of interest for bowel preparation products. The study drug is designed to produce copious watery diarrhea; therefore, electrolyte abnormalities, evidence of dehydration, and prerenal acute kidney injury were assessed systematically.

Laboratory assessment was conducted at screening (Visit 1), day of colonoscopy (Visit 2), and 24 to 48 hours after colonoscopy (Visit 3) in all patients. Visit 4 (7 ±2 days post colonoscopy) and Visit 5 (30 days ±2 days post colonoscopy) follow-up occurred only in patients who have abnormal laboratory tests or ongoing adverse events at visit 3.

Safety laboratory parameters of interest (Na, HCO3, Ca, Mg, K, creatinine, osmolality) were assessed for abnormal values postdose (shift analysis) and for changes that persisted post colonoscopy (persistence analysis). Laboratory data for both clinical studies (301 and 302) were assessed at Visit 1, Visit 2, Visit 3, Visit 4, and Visit 5 where appropriate.

Shift Analysis

This analysis was conducted for patients who had normal baseline values at Visit 1 and had abnormal values at Visit 2, 3, 4 or 5. The shift analysis evaluates the presence of abnormal laboratory values during post colonoscopy visit by comparing to Visit 1.

The proportion and percentage (%) of patients who had normal values at baseline (Visit 1) and demonstrates a shift to abnormal value at later visits are summarized below for study 301 and 302.

Table 31. Shift Analysis for Selected Laboratory Parameters

Laboratory Parameters	High/Low	Visit	Study 301		Study 302	
			BLI4700 (%)	MoviPrep (%)	BLI4700	Prepopik
Bicarbonate (mEq/L)	Low	Visit 2	5/243 (2.1)	12/238 (5)	2/158 (1.3)	2/166 (1.2)
		Visit 3	0 (0.0)	4/238 (1.7)	3/158 (1.9)	0 (0.0)
		Visit 4	0 (0.0)	1/238 (0.4)	1/158 (0.6)	0 (0.0)
		Visit 5	1/243 (0.4)	1/238 (0.4)	0 (0.0)	1/166 (0.6)
Calcium (mg/dL)	Low	Visit 2	13/242 (5.4)	9/236 (3.8)	7/159 (4.4)	7/164 (4.3)
		Visit 3	9/242 (3.7)	10/236 (4.2)	3/159 (1.9)	8/164 (4.9)
		Visit 4	3/242 (1.2)	4/236 (1.7)	0 (0.0)	2/164 (1.2)
		Visit 5	2/242 (0.8)	6/236 (2.5)	2/159 (1.3)	3/164 (1.8)
Creatinine (mg/dL)	High	Visit 2	2/238 (0.8)	4/232 (1.7)	0 (0.0)	3/163 (1.8)
		Visit 3	2/238 (0.8)	6/232 (2.6)	2/153 (1.3)	4/163 (2.5)
		Visit 4	4/238 (1.7)	3/232 (1.3)	2/153 (1.3)	2/163 (1.2)
		Visit 5	5/238 (2.1)	3/232 (1.3)	1/153 (0.7)	2/163 (1.2)
Magnesium (mg/dL)	High	Visit 2	63/232 (27.2)	10/216 (4.6)	49/148 (33.1)	87/148 (58.8)
		Visit 3	3/232 (1.3)	0 (0.0)	3/148 (2)	10/148 (6.8)
		Visit 4	6/232 (2.6)	6/216 (2.8)	1/148 (0.7)	2/148 (1.4)
		Visit 5	3/232 (1.3)	4/216 (1.9)	2/148 (1.4)	2/148 (1.4)
Osmolality (mOsm/kg)	High	Visit 2	14/44 (31.8)	23/54 (42.6)	14/32 (43.8)	11/39 (28.2)
		Visit 3	20/44 (45.5)	24/54 (44.4)	13/32 (40.6)	19/39 (48.7)
		Visit 4	9/44 (20.5)	15/54 (27.8)	11/32 (34.4)	10/39 (25.6)
		Visit 5	8/44 (18.2)	10/54 (18.5)	10/32 (31.2)	15/39 (38.5)
Potassium (mmol/L)	High	Visit 2	5/241 (2.1)	4/236 (1.7)	2/156 (1.3)	0 (0.0)
		Visit 3	5/241 (2.1)	1/236 (0.4)	1/156 (0.6)	4/164 (2.4)
		Visit 4	6/241 (2.5)	4/236 (1.7)	2/156 (1.3)	0 (0.0)
		Visit 5	4/241 (1.7)	1/236 (0.4)	2/156 (1.3)	3/164 (1.8)
Potassium (mmol/L)	Low	Visit 2	5/241 (2.1)	1/236 (0.4)	1/156 (0.6)	7/164 (4.3)
		Visit 3	6/241 (2.5)	4/236 (1.7)	4/156 (2.6)	2/164 (1.2)
		Visit 4	4/241 (1.7)	2/236 (0.8)	2/156 (1.3)	1/164 (0.6)
		Visit 5	2/241 (0.8)	0 (0.0)	2/156 (1.3)	0 (0.0)
Sodium (mmol/L)	High	Visit 2	7/242 (2.9)	2/234 (0.9)	1/158 (0.6)	1/166 (0.6)
		Visit 3	1/242 (0.4)	1/234 (0.4)	0 (0.0)	1/166 (0.6)
		Visit 4	0 (0.0)	0 (0.0)	0 (0.0)	1/166 (0.6)
		Visit 5	2/242 (0.8)	0 (0.0)	0 (0.0)	3/166 (1.8)
Sodium (mmol/L)	Low	Visit 2	1/242 (0.4)	3/234 (1.3)	1/158 (0.6)	7/166 (4.2)
		Visit 3	2/242 (0.8)	0 (0.0)	0 (0.0)	3/166 (1.8)
		Visit 4	0 (0.0)	1/234 (0.4)	0 (0.0)	2/166 (1.2)
		Visit 5	1/242 (0.4)	0 (0.0)	3/158 (1.9)	0 (0.0)

Source: Edited from Table 1 of Laboratory Analysis performed by Clinical Data Scientist, [redacted] (b) (6) dated October 4, 2019
Abbreviations: dL = deciliter, mEq = milliequivalent, mmol = millimole, mOsm = milliosmole

The results of the shift analysis suggest that a few patients had a shift outside normal range at Visit 2, which occurred postdose on the day of colonoscopy. The proportion of patients with a shift outside the normal range in each laboratory parameter was fairly similar between SUTAB and the active comparators, except for magnesium increase at Visit 2, which was probably due to the inclusion of magnesium in the SUTAB formulation. Refer to Table 30 above. The magnitude of these changes were small.

SUTAB is designed to produce copious watery diarrhea, thus resulting in electrolyte abnormalities. Overall, the proportion and magnitude of such changes documented was not of clinical concern. None of these electrolyte abnormalities were reported as SAEs, and <1% were reported in the common TEAEs—none of which were reported to be clinically significant.

Overall, there were no differences in laboratory shift changes that favored either SUTAB or the active comparators consistently (except from the hypermagnesemia as stated above). As a result, it was concluded that the shifts in electrolytes that occurred did not have an important impact on SUTAB safety.

Persistence Analysis

Persistence analysis was conducted to confirm whether or not the majority of electrolyte derangements identified at Visit 2 resolved/normalized with time. The criteria for conducting persistence analysis were two different laboratory parameters. The first of which was if the proportion of patients with abnormal shift at Visit 2 on study drug exceeded that for the comparator by ≥2%. The second was if the proportion of patients who had a reported AE that was associated with the laboratory abnormality on treatment exceeded that for the comparator by ≥1%. Based on these criteria, additional analyses of the shift from baseline were conducted for key laboratory parameters of interest including bicarbonate, calcium, creatinine, glomerular filtration rate, magnesium, osmolality, potassium and sodium. The vast majority of noted changes in electrolytes resolved without intervention. The exception was a small number of patients who had high osmolality in all bowel preparation treatment groups and high magnesium in BLI4700 treatment groups as listed below:

- High magnesium:

301: Visit 2 (63/232: 27.2%), Visit 3 (3/63: 4.8%)
302: Visit 2 (49/148: 33.1%), Visit 3 (3/49: 6.1%)

- High osmolality:

301: Visit 2 (14/44: 31.8%), Visit 3 (8/14: 57.1%);
302: Visit 2 (14/32: 43.8%0, Visit 3 (8/14:57.1%)

The few events of laboratory abnormalities that persisted to the Day 28 visit were further investigated by assessing the laboratory trends in the provided datasets with any associated adverse events, and none were deemed to be clinically significant.

Acute Renal Injury

Bowel preparation products have the potential to cause dehydration that could lead to renal injury. Screening for this injury was done by assessing rise in serum creatinine. A low number of patients had abnormal elevated creatinine post colonoscopy (See Table 31 above), and this did not occur more frequently with study drug when compared to comparators. Visit 3, Visit 4, and Visit 5 (if needed) were considered the most relevant timepoints, as acute renal injury from

prerenal etiology may not peak for 48 hours post exposure (and therefore may not be evident at the Visit 2).

Bowel preparation products will be used most commonly in older adults who could have a baseline mild to moderate renal impairment. As such, a patient with a pre-existing mild to moderate renal impairment might be at increased risk of acute kidney injury, so further analysis was conducted. Acute kidney injury analysis was done by utilizing the kidney disease improving global outcome (KDIGO) criteria (Acute Kidney Injury Work Group 2012) of rise in serum creatinine of ≥0.3 mg/dL from baseline within 48 hours or rise in serum creatinine to ≥1.5X from baseline within 7 days after colonoscopy.

The table below (Table 32) summarizes the data on a small number of patients with elevated creatinine at the end of Visit 3, 4**,** or 5 post colonoscopy compared to baseline who met the criteria for acute kidney injury based on the KDIGO criteria. Reassuringly, there were only a very small number of patients who met the criteria (three in total across the two studies) and, thus, no conclusions regarding differential safety across treatment arms can be drawn.

Table 32. Shift Analysis for Acute Kidney Injury: Patients meeting KDIGO Criteria for Acute Kidney Injury in Studies BLI4700-301 and BLI4700-302[*]

	Creatinine Values				
Patient Number	Cr at Baseline (Visit 1)	Cr Before Colonoscopy (Visit 2)	Cr at 24-48 Hours Post Colonoscopy (Visit 3)	Cr at 7 days ±2 Days Post Colonoscopy (Visit 4)	Cr at 30 Days ±2 Days Post Colonoscopy (Visit 5)
BLI4700301-(b) (6) 66M	1.33	1.48	2.02	1.53	
BLI4700301-(b) (6) 53F	0.75	0.81	1.09	0.6	1.43
BLI4700302-(b) (6) 67F	1.04	1.04	1.56	1.2	Patient declined Visit 5 because of living too far

Source: Reviewer's analysis of ADLB datasets for studies 301 and 302
Upper limit of normal creatinine for most patients was 1.44 mg/dL per Applicant's IR response on January 6, 2020[*] Based on KDIGO criteria rise in serum creatinine of ≥0.3 mg/dL from baseline within 48 hours or rise in serum creatinine to ≥1.5X from baseline within 7 days after colonoscopy.
Abbreviation: Cr = creatinine

Persistent Renal Injury at End of Study

In addition to the above analysis of those who met the KGIDO criteria for possible acute kidney injury, additional analysis was conducted to evaluate patients with post-treatment rise in creatinine (which may have been of smaller magnitude than the above analysis) to determine whether or not these changes resolved, stabilized, or worsened over the duration of available follow-up. While the majority of patients normalized or were trending toward baseline, Table 33 below shows the patients with elevated serum creatinine that remained above baseline at Visit 5 or end of study visit.

Table 33. Persistent Renal Injury Analysis in SUTAB-Treated Patients in BLI4700-301 and BLI4700-302

	Cases of Normal Baseline Serum Creatinine to Grade 1 Creatinine CTCAE Shift (Cr > ULN to 1.5x ULN)				
Patient Number	Cr at Baseline (Visit 1)	Cr Before Colonoscopy (Visit 2)	Cr at 24-48 Hours Post Colonoscopy (Visit 3)	Cr at 7 days ±2 Days Post Colonoscopy (Visit 4)	Cr at 30 days ±2 days Post Colonoscopy (Visit 5)
BLI4700301-(b) (6) 53M	0.88	1.03	1.00	1.03	1.33
BLI4700301-(b) (6) 76M	1.44	1.28	1.36	1.69	1.41
BLI4700301-(b) (6) 53F	0.75	0.81	1.09	0.6	1.43
BLI4700301-(b) (6) 67M	1.4	1.42	1.55	Day 7 or 30 not documented	
BLI4700302-(b) (6) 82M	1.33	1.24	1.29	1.52	1.52

Source: Reviewer's analysis of ADLB datasets for studies 301 and 201
Upper limit of normal creatinine for most patients for most patients: 1.44 mg/dL per Applicant's IR response on January 6, 2020
Abbreviation: Cr = creatinine, CTCAE = common terminology criteria for adverse event, ULN = upper limit of normal

Additional details on these patients were provided by the Applicant on January 6, 2020 in response to the Agency's information request, as summarized below:

(1) **BLI4700301-(b) (6):** This patient's creatinine rose from 0.88 mg/dL at baseline to 1.33 mg/dL. However, it was not coded as an adverse event because the patient's creatinine was slightly above normal limit of 1.12 mg/dL, which the investigator did not consider to be clinically significant. No post-study creatinine result was collected per the Applicant. Given that the elevated creatinine continued to trend upwards even after the study was over and it did not return back to baseline without further information, this patient should be considered an adverse event of acute kidney injury. Additionally, causal relationship to study drug cannot be excluded.

(2) **BLI4700301(b) (6):** The patient's baseline creatinine was 1.40 mg/dL, which was the upper limit of normal (1.44 mg/dL), and the patient returned to baseline creatinine by Visit 5 at 1.41 mg/dL.

(3) **BLI4700301-(b) (6):** The patient's creatinine rose from a baseline of 0.75 mg/dL at Visit 2 and 3, then decreased to 0.6 mg/dL. At Visit 5 (26 days after preparation), the patient's creatinine value increased to 1.43 mg/dL, above the upper limit (1.12 mg/dL). The investigator considered the event to be clinically significant with a possible relationship to the study drug. A repeat creatinine assessment on day 47 after bowel preparation exposure showed creatinine had returned to baseline of 0.74 mg/dL. Although it is less likely that the 12-hour exposure of SUTAB could have caused renal injury 26 days later, the Applicant's

assessment of the adverse event's possible relatedness to the study drug appears reasonable.

(4) **BLI4700302-** (b) (6) **:** The patient's creatinine decreased from 1.33 mg/dL to 1.24 mg/dL and 1.29 mg/dL at Visits 2 and 3, respectively, and then increased 1.52 mg/dL at Visit 4 (Day 7 post preparation) and 1.52 mg/dL (Day 30 post preparation). The investigator did not consider this to be an adverse event and did not obtain post-study creatinine because the upper limit of normal is 1.44 mg/dL, and 1.52 mg/dL is only slightly above normal.

(5) **BLI4700301-** (b) (6) **:** The patient's baseline creatinine rose from 1.40 mg/dL to 1.55 mg/dL at Visit 3. Four months later, his creatinine had risen to 3.48 mg/dL, of which the principal investigator considered to be clinically significant and documented as possibly related. The patient also reported to have been hospitalized and treated for septic shock, acute kidney injury, hyponatremia, pulmonary edema, and Barrett's esophagus at the time. The final creatinine reported was 1.45 mg/dL which was close to baseline levels. This patient thus most likely did not have acute kidney injury related to bowel preparation but rather related to his septic shock.

In conclusion, the renal safety analyses did not identify a signal for acute renal injury or worsening or pre-existing mild chronic kidney disease in the safety population. The label will therefore include a general language about the noted infrequent increase in creatinine that occurred in similar rates for both SUTAB and the active comparators.

Vital Signs

Mean changes from baseline in heart rate at each visit were small in magnitude and similar between groups. Overall, mean changes of blood pressure were similar between groups. There was one case of hypotension in each arm of bowel preparation for study 302, and some preferred terms of blood pressure decreased/increased were reported in the TEAE listing. However, none were described as an SAE. Most of the events were mild in intensity and none led to discontinuation or withdrawal. Hypotension is an expected adverse event in the context of acute volume depletion and dehydration that can occur when patients are exposed to bowel preparation products. In addition, there were some cases of elevated blood pressure/hypertension noted in the TEAE listings. However, none were reported to be severe in intensity, and most did not occur in the acute setting where patient had an increased sodium load and osmolality. The current submission has not provided a new safety signal to suggest a higher rate of hypotension or hypertension from SUTAB compared to the active comparators.

Electrocardiograms

In general, adverse events related to cardiac rhythm disturbance/potential arrythmias were low in both studies 301 and 302, and none were considered clinically significant. There were no clinically significant differences between the SUTAB groups and active comparators.

QT

The mean change from baseline in heart rate, PR interval, QRS duration, and QT/QTc intervals were evaluated, with emphasis on the day of colonoscopy visit. Changes from baseline were small, and values were similar between treatment groups.

8.2.5. Safety Analyses by Demographic Subgroups

The results of safety analyses by demographic subgroups are described in this section.

Rates of any TEAEs were evaluated by sex, race and age subgroups as shown in Table 34 below. Because SAES and AEs leading to discontinuation were very infrequent, the focus of the safety assessment by demographic subgroup is on overall rates of AEs reported.

Table 34. Any TEAEs by Sex, Age and Race Subgroup

	BLI4700-301			BLI4700-302		
Any TEAEs	**BLI4700 N=281 (%)**	**MoviPrep N=271 (%)**	**Treatment Difference**	**BLI4700 N=190 (%)**	**Prepopik N=199 (%)**	**Treatment Difference**
Sex						
Male	66/123 (53.7)	58/119 (48.7)	5%	43/78 (55.1)	30/86 (34.9)	20.2%
Female	119/158 (75.3)	96/152 (63.2)	12.1%	99/112 (88.4)	61/113 (54.0)	34.4%
Age group						
<65	126/193 (65.3)	105/183 (57.4)	7.9%	103/128 (80.5)	72/152 (47.4)	33.1%
≥65	59/88 (67.0)	49/88 (55.7)	11.3%	39/62 (62.9)	19/47 (40.4)	22.5%
≥75	7/14 (50.0)	8/18 (44.4)	5.6%	6/11 (54.5)	6/11 (54.5)	0%
Race						
White	145/221 (65.6)	128/212 (60.4)	5.2%	131/177 (74.0)	83/183 (45.4)	28.6%
Black or African American	29/43 (67.4)	22/45 (48.9)	18.5%	8/8 (100.0)	6/11 (54.5)	45.5%
Asian	5/8 (62.5)	3/10 (30.0)	32.5%	0/2 (0)	1/2 (50.0)	-50.0%
Other	6/9 (66.7)	1/4 (25.0)	41.7%	3/3 (100.0)	1/3 (33.3)	66.7%

Source: Reviewer's table adapted from Applicant's Section 14 Table of Analysis
Abbreviation: TEAE = treatment-emergent adverse event

When considering potential differences in safety profile by sex, we note that female patients—who were adequately represented—appeared to be more sensitive to adverse events on SUTAB in both studies, though the reason for this noted difference in AE rates is unclear. One possibility explored was if differences in weight may have led to larger relative dose administered to females as compared to males. The difference in mean body weight by sex was ~21 lbs; mean body weight (SD) in female patients was 175 (40) lbs and in male patients was 206 (41) lbs. Mean change from baseline in body weight (SD) from screening to colonoscopy visit was numerically similar in both sexes (F -1.9 [3.7] lbs , M -1.8 [10] lbs), which represents a greater relative percentage change of body weight in females compared to males. This potentially signals greater fluid loss/dehydration occurring in females as compared to males. The most commonly reported AEs were gastrointestinal, as was noted in the population overall, and consistent with the expected AEs for a bowel cleansing agent. Given the very low numbers of AEs leading to study drug discontinuation, and low numbers of SAEs, these findings were not considered to represent a unique safety concern for female patients warranting specific labeling.

When considering potential differences in safety profile by age, we note that within the SUTAB treatment group, patients ≥65 years of age comprised 150/471 (31.8%) of the safety population in the combined phase 3 studies, providing adequate representation of the geriatric population. Overall, the study drug appeared similarly tolerated in older versus younger patients.

Regarding racial subgroups, black patients reported more TEAEs on SUTAB than comparator in both studies, though the numbers of patients are low, making it difficult to draw definitive conclusions.

Across the phase 3 program SAEs occurred so infrequently (five events in four patients across the two studies) that no conclusions could be drawn regarding differential rate of SAE by demographic subgroup. Only one of the five serious adverse events occurred in a patient >65 years old, who had syncope that was probably due to underlying bradycardia and first degree block. Overall, there was no trend in the clinical studies for any of the demographic subgroup regarding incidence of serious TEAEs, study drug withdrawals, or trial discontinuations.

8.2.6. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

SUTAB is not marketed in the United States or other countries.

Expectations on Safety in the Postmarket Setting

No additional postmarketing studies on safety are planned at this time because review of this NDA has not identified any specific safety concern warranting targeted postmarketing studies outside of routine pharmacovigilance.

8.2.7. Integrated Assessment of Safety

The safety profile of SUTAB is similar to other approved bowel preparations. The most common TEAEs included abdominal pain, abdominal distension, nausea, vomiting, headache, hypermagnesemia, dizziness, and increased liver function. There was no death reported, and the few (four) SAEs were all unrelated to SUTAB or the active comparators. No new or unexpected safety findings were uncovered. The safety data submitted with this application supports approval.

8.3. Conclusions and Recommendations

In summary, two adequate and well controlled active-controlled trials demonstrated SUTAB to be non-inferior to the approved comparator (MoviPrep, Prepopik). The efficacy results were consistent in sensitivity analyses. The safety profile as summarized above was consistent with what is known about the drug class. No new or unexpected safety signals were identified. The clinical safety and efficacy data support approval. The recommended Complete Response action is on the basis of manufacturing/facilities issues, as outlined in Section 4 above.

9. Advisory Committee Meeting and Other External Consultations

Not applicable

10. Pediatrics

The Applicant received orphan drug designation for pediatric population on December 19, 2017. Therefore, they are exempt from required pediatric studies under the Pediatric Research Equity Act. No new pediatric information was contained within this NDA application.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

The following is a summary of high-level changes to the U.S. prescribing information that were negotiated during the review cycle and the outstanding issues that precluded reaching agreement on final PI during this review cycle. Further negotiation will be continued at the time of resubmission.

Section 2:

- Low-residue diet was clarified based on Applicant's examples in the protocol questionnaire.

Section 6.1:

- (b) (4)
- A high level summary of relevant changes in electrolytes and renal function was also included.

Section 12.3:

- PK information was incorporated based on the results of SUTAB clinical studies. This update included PK information in patients with renal and hepatic impairment.

Section 14:

- Efficacy results were incorporated based on the results of primary efficacy analysis from the BLI4700-301 and BLI4700-302 studies.
- Efficacy results as summarized using the more conservative 99% CI bound, (b) (4) due to disagreement with the Applicant's choice of Prepopik as the active comparator for Study 302 during clinical development.

12. Risk Evaluation and Mitigation Strategies

Risks will be communicated via labeling. No additional risk mitigation was deemed necessary.

13. Postmarketing Requirements and Commitment

As noted above, the Applicant received orphan designation and did not propose any pediatric studies within the NDA submission. (b) (4)

(b) (4)

14. Division Associate Director (Clinical) / Designated Signatory Authority Comments

I concur with the recommendation of the review team to issue a Complete Response letter for NDA 213135. SUTAB (sodium sulfate, magnesium sulfate, and potassium chloride) is an osmotic laxative proposed for cleansing of the colon in preparation for colonoscopy in adults. SUTAB is a tablet formulation that is closely related to the already approved liquid-based sulfate formulation (SUPREP); only difference is that SUTAB includes potassium chloride instead of potassium sulfate in SUPREP. It is administered as two doses, in a split-dose regimen (12 tablets per dose).

As discussed in detail in this multi-disciplinary review, the benefits of SUTAB outweigh the risks for the indication sought. The submission included two adequate and well-controlled non-inferiority trials, and both trials achieved statistical significance. The primary endpoint was the proportion of patients achieving a successful preparation, defined as a score of 3 (Good) or 4 (Excellent) that achieves clear visualization of the entire colonic mucosa. The results of sensitivity analyses support the primary efficacy results. The most common adverse reactions observed in clinical trials include nausea, abdominal distension, vomiting and abdominal pain, and are comparable to those associated with other bowel cleansing agents. Product labeling and a Medication Guide will be sufficient to communicate the potential risks to healthcare providers and patients, respectively; a REMS will not be required. The Applicant conducted several postmarketing studies required under 505(o) to assess the potential serious risks of a closely related product SUPREP; no new PMR studies will be required. SUTAB has an orphan drug designation and, therefore, the Applicant is exempt from Pediatric Research Equity Act requirements.

Although the efficacy and safety data contained in this NDA support approval, the drug product manufacturing facility, Braintree Laboratories, Inc., was determined to be unacceptable to support the approval of NDA 213135. The pre-approval inspection identified several deficiencies that were conveyed to the drug product manufacturing facility. Based on inadequate response, the Office of Pharmaceutical Manufacturing Assessment recommended "Withhold" recommendation due to lack of readiness of Braintree Laboratories, Inc. for commercial manufacturing of the drug product. Accordingly, the OPQ determined that the NDA is not recommended for approval. Since the Applicant does not have an alternative drug product manufacturing facility for this NDA, an approval action of this application cannot be taken until the Applicant satisfactorily resolves the deficiencies observed during the inspection of the drug product manufacturing facility.

The agreement on final product labeling could not be reached during this review cycle; further negotiation will be continued at the time of resubmission. Negotiation regarding a potential postmarketing commitment study (b) (5), if and when the application may be approvable.

15. Appendices

15.1. Clinical Appendices

15.1.1. Clinician-Reported Outcome Tools Used for Efficacy Assessment

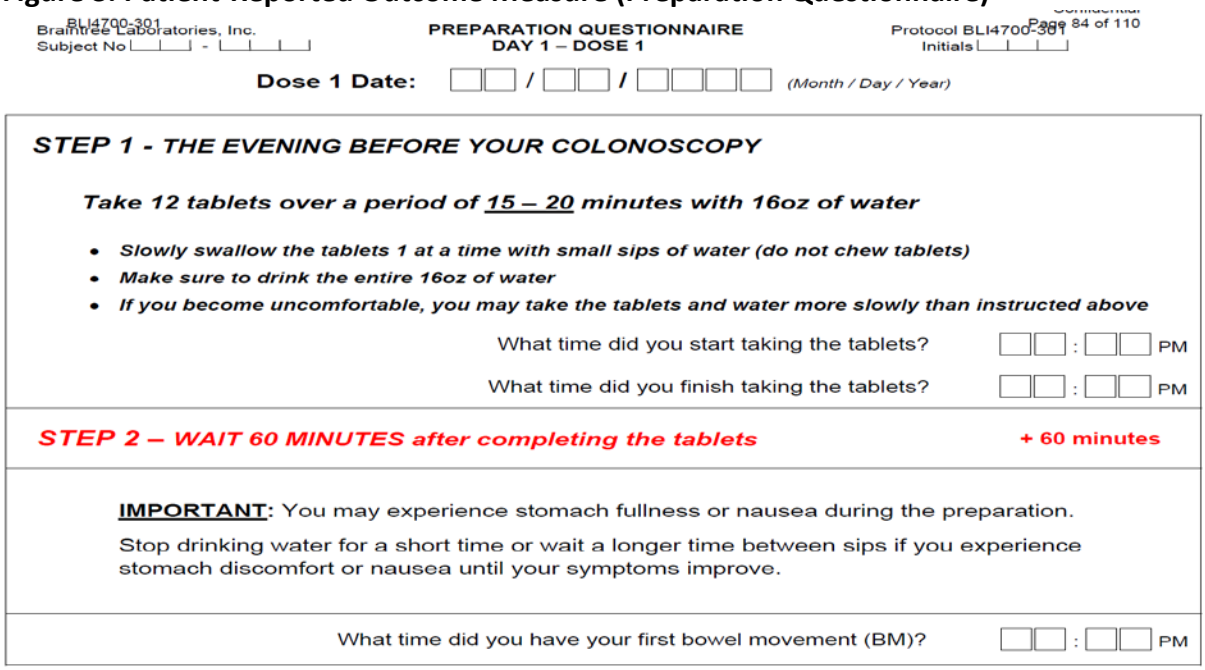
Figure 2. Bowel Cleansing Scale Agreed With Agency During Clinical Development

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: Clinical trial protocol for BLI4700-301 (pg 66/110) and BLI4700-302 (pg 25/64)

15.1.2. Patient-Reported Outcome Measure

Figure 3. Patient-Reported Outcome Measure (Preparation Questionnaire)



BLI4700-301 Confidential
Braintree Laboratories, Inc. PREPARATION QUESTIONNAIRE Protocol BLI4700-301 Page 84 of 110
Subject No ___ - ___ DAY 1 – DOSE 1 Initials ___

Dose 1 Date: ☐☐ / ☐☐ / ☐☐☐☐ *(Month / Day / Year)*

STEP 1 - THE EVENING BEFORE YOUR COLONOSCOPY

Take 12 tablets over a period of 15 – 20 minutes with 16oz of water

- ***Slowly swallow the tablets 1 at a time with small sips of water (do not chew tablets)***
- ***Make sure to drink the entire 16oz of water***
- ***If you become uncomfortable, you may take the tablets and water more slowly than instructed above***

What time did you start taking the tablets? ☐☐ : ☐☐ PM

What time did you finish taking the tablets? ☐☐ : ☐☐ PM

STEP 2 – WAIT 60 MINUTES after completing the tablets **+ 60 minutes**

IMPORTANT: You may experience stomach fullness or nausea during the preparation.

Stop drinking water for a short time or wait a longer time between sips if you experience stomach discomfort or nausea until your symptoms improve.

What time did you have your first bowel movement (BM)? ☐☐ : ☐☐ PM

STEP 3 – Slowly drink 16oz of water over 30 minutes

What time did you start drinking the water? ☐☐ : ☐☐ PM

What time did you finish drinking the water? ☐☐ : ☐☐ PM

STEP 4 – WAIT 30 MINUTES + 30 minutes

STEP 5 – Slowly drink 16oz of water over 30 minutes

What time did you start drinking the water? ☐☐ : ☐☐ PM

What time did you finish drinking the water? ☐☐ : ☐☐ PM

If you did not complete the tablets and additional water, please explain below:

_____

****Water recorded on this sheet does not need to be included on the Diet Questionnaire****

Braintree Laboratories, Inc. **PREPARATION QUESTIONNAIRE** Protocol BLI4700-301
Subject No ☐☐☐ - ☐☐☐☐ **DAY 2 – DOSE 2** Initials ☐☐☐

Dose 2 Date: ☐☐ / ☐☐ / ☐☐☐☐ *(Month / Day / Year)*

STEP 1 – 5 to 8 HOURS BEFORE YOUR COLONOSCOPY

– No sooner than 4 hours from starting Dose 1

Take 12 tablets over a period of 15 – 20 minutes with 16oz of water

- ***Slowly swallow the tablets 1 at a time with small sips of water (do not chew tablets)***
- ***Make sure to drink the entire 16oz of water***
- ***If you become uncomfortable, you may take the tablets and water more slowly than instructed above***

What time did you start taking the tablets? ☐☐ : ☐☐ AM

What time did you finish taking the tablets? ☐☐ : ☐☐ AM

STEP 2 – WAIT 60 MINUTES after completing the tablets + 60 minutes

IMPORTANT: You may experience stomach fullness or nausea during the preparation.

Stop drinking water for a short time or wait a longer time between sips if you experience stomach discomfort or nausea until your symptoms improve.

What time did you have your first bowel movement (BM) after Dose 2? ☐☐ : ☐☐ AM

Braintree Laboratories, Inc. **PREPARATION QUESTIONNAIRE** Protocol BLI4700-301
Subject No ☐☐☐ - ☐☐☐☐ **DAY 2 – DOSE 2** Initials ☐☐☐

STEP 3 – Slowly drink 16oz of water over 30 minutes

What time did you start drinking the water? ☐☐ : ☐☐ AM

What time did you finish drinking the water? ☐☐ : ☐☐ AM

STEP 4 – WAIT 30 MINUTES + 30 minutes

STEP 5 – Slowly drink 16oz of water over 30 minutes

What time did you start drinking the water? ☐☐ : ☐☐ AM

What time did you finish drinking the water? ☐☐ : ☐☐ AM

If you did not complete the tablets and additional water, please explain below:

_____

All tablets and water must be completed at least 2 hours before the colonoscopy.
Do not drink anything within 2 hours of your colonoscopy.

****Water recorded on this sheet does not need to be included on the Diet Questionnaire****

Source: Clinical trial protocol for BLI4700-301 (pg 84-87/110) and BLI4700-302 (pg 61–64/64)

Figure 4. Patient-Reported Outcome Measure (Dietary Questionnaire)

BLI4700 DIETARY QUESTIONNAIRE

Record what you eat and drink starting on Preparation Day 1

Refer to the Patient Instructions for examples of allowable low residue breakfast items on Preparation Day 1 and acceptable clear liquids

***DO NOT INCLUDE THE WATER YOU DRANK WITH EACH DOSE ***

Day	Time	Description
1	☐☐ : ☐☐ ☐ AM ☐ PM	
1	☐☐ : ☐☐ ☐ AM ☐ PM	
1	☐☐ : ☐☐ ☐ AM ☐ PM	
1	☐☐ : ☐☐ ☐ AM ☐ PM	
1	☐☐ : ☐☐ ☐ AM ☐ PM	
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1	☐☐ : ☐☐ ☐ AM ☐ PM	
2	☐☐ : ☐☐ ☐ AM ☐ PM	
2	☐☐ : ☐☐ ☐ AM ☐ PM	
2	☐☐ : ☐☐ ☐ AM ☐ PM	
2	☐☐ : ☐☐ ☐ AM ☐ PM	

Subject Signature________________________ **Date** ☐☐ / ☐☐ / ☐☐
Month Day Year

Source: Clinical trial protocol for BLI4700-301 (pg 88/110)

15.1.3. Symptom Scale (At Visit Prior to Colonoscopy)

Figure 5. Subject Symptom Scale

Subject Symptom Scale (AS3)

Question	Data Formatting
Info_AS3_101 [.InfoTag]	
Info_AS3_201 [.InfoTag]	
Stomach Cramping [AS3.OCRAMP]	[ ] Text (3) [[Blank]]=[] [YES]=[YES] [NO]=[NO]
If YES, note intensity [AS3.CRAMPINT] [conditional on: Enable "If YES, note intensity (CRAMPINT)" when "Stomach Cramping (OCRAMP)" Equal To "YES"]	[ ] Text (12) [[Blank]]=[] [1 = Mild]=[1 = Mild] [2 = Moderate]=[2 = Moderate] [3 = Severe]=[3 = Severe]
Stomach Bloating [AS3.OBLOAT]	[ ] Text (3) [[Blank]]=[] [YES]=[YES] [NO]=[NO]
If YES, note intensity [AS3.BLOATINT] [conditional on: Enable "If YES, note intensity (BLOATINT)" when "Stomach Bloating (OBLOAT)" Equal To "YES"]	[ ] Text (12) [[Blank]]=[] [1 = Mild]=[1 = Mild] [2 = Moderate]=[2 = Moderate] [3 = Severe]=[3 = Severe]
Nausea [AS3.ONAUSEA]	[ ] Text (3)
	[[Blank]]=[] [YES]=[YES] [NO]=[NO]
If YES, note intensity [AS3.NAUSEINT] [conditional on: Enable "If YES, note intensity (NAUSEINT)" when "Nausea (ONAUSEA)" Equal To "YES"]	[ ] Text (12) [[Blank]]=[] [1 = Mild]=[1 = Mild] [2 = Moderate]=[2 = Moderate] [3 = Severe]=[3 = Severe]
Vomiting [AS3.OVOMIT]	[ ] Text (3) [[Blank]]=[] [YES]=[YES] [NO]=[NO]
If YES, note intensity [AS3.VOMITINT] [conditional on: Enable "If YES, note intensity (VOMITINT)" when "Vomiting (OVOMIT)" Equal To "YES"]	[ ] Text (12) [[Blank]]=[] [1 = Mild]=[1 = Mild] [2 = Moderate]=[2 = Moderate] [3 = Severe]=[3 = Severe]

Source: Sample Case Report Form (pg 120-121/140)

15.2. Combination Rule

SUTAB, similar to other prescription bowel preparations, includes multiple active ingredients in a fixed-combination in order to achieve the requisite stool output necessary to cleanse the intestinal mucosa prior to colonoscopy, therefore, the Fixed-Combination Drug Rule (21 CRF 300.50) is applicable.

The Applicant has submitted the studies conducted during the development program of SUTAB to support the contribution of each of the components of the active ingredients in the final SUTAB formulation.

Refer to Table 35 below for a comparison of the components of these two related products.

Table 35. Active Ingredients in SUPREP and SUTAB (BLI4700)

Ingredient (g)	SUPREP	BLI4700
Na_2SO_4	35.0	35.5
$MgSO_4$	3.2	5.4
K_2SO_4	6.26	0
KCl	0	4.5

Source: NDA 213135 (SUTAB) Information Response, submitted August 16, 2019, page 3/6

The active ingredients are mostly the same in the approved SUPREP (liquid-based) and SUTAB (tablet-based) but are present in different amounts (Na_2SO4 and $MgSO4$). There is also a change from potassium sulfate in SUPREP to potassium chloride in SUTAB. Furthermore, the active ingredients of SUTAB have been used alone or in combination in previously approved bowel preparations.

The basic principle is that the poorly absorbed sulfate anion and magnesium cation are the osmotically active agents in SUTAB, which act to induce secretion of water into the colonic lumen, resulting in diarrhea and thus colon cleansing. Similar to SUPREP, sodium sulfate is the primary contributor of sulfate (and sodium) in the SUPREP formulation and magnesium sulfate contributes a smaller amount of sulfate and magnesium cation.

The Applicant states that various formulations in the phase 1 studies were explored, (b) (4) able 36 below shows the composition of four SUPREP formulations, which used different amounts of sulfate and magnesium, before formula 8 was selected as the formulation to use in subsequent clinical studies.

Table 36. Comparison of Total Dose Tablet Formula (g)

(b) (4)

*From Table 4 in Clinical Study Report BLI4700-101/102
Source: NDA213135 Information Response, submitted August 16, 2019, page 4/6

The effect of these four different formulation on stool output was assessed by the Applicant as can be seen in Table 37 below.

Table 37. BLI4700 Stool Output Results

Formula (4700-)	3	4	5	8
N	10	5	15	14
Stool Output (ml) (SD)	2319.6 (242.0)	2562.2 (482.6)	2736.7 (359.6)	2795.1 (351.6)

Source: NDA 213135 (SUTAB) Information Response, submitted August 16, 2019, page 4/6

(b) (4)

The Applicant assessed for the effect of sodium movement in vivo as shown in Table 38 below.

Table 38. BLI4700 Electrolyte Movement

Formula (4700-)	3	4	5	8
N	10	5	15	14
Na (mEq) (SD)	79.3 (83.9)	133.5 (94.5)	164.9 (118.4)	-10.0 (103.0)
Cl (mEq) (SD)	-4.4 (34.0)	-30.1 (19.8)	-25.0 (30.0)	-4.1 (21.9)
K (mEq) (SD)	4.2 (11.1)	-11.7 (16.3)	8.3 (15.5)	-4.8 (16.7)
Mg (mEq) (SD)	-8.8 (7.4)	-16.1 (15.9)	-15.7 (9.1)	-6.8 (19.7)

Source: NDA 213135 (SUTAB) Information Response, submitted August 16, 2019, page 5/6

Study volunteers absorbed more sodium from formulas 4 and 5, indicating that the sodium content was too high, while it was approximately neutral for formula 8 (b) (4) . Of note is that magnesium movement was also generally small across formulations.

The Applicant also states that potassium chloride was included in formula 8 (b) (4)

According to the Applicant, SUPREP (without chloride content) exhibited large chloride losses in vivo, while SUTAB (with chloride content) resulted in close to neutral chloride movement as shown in Table 38 above. Based on the data presented above, formula 8 (addition of potassium chloride) as compared to formula 4 (no chloride) resulted in reduction of net chloride movement. Further, formula 8 had less net K movement, as compared to formula 4 ((b) (4)

(b) (4) thus supporting that the addition of KCL improved the profile by reducing net shifts in potassium and chloride.

15.3. Statistical Appendices on Efficacy

15.3.1. Results on Sensitivity Analyses on the Primary Endpoint

The additional Cochran-Mantel-Haenzel (CMH) models included an unadjusted CMH test, a CMH test adjusted for randomization stratification group, a CMH test adjusted for stratification group and site, and a CMH test controlling for region (i.e., state). Note that due to low enrollment in certain states, the following states were pooled (subject numbers in parentheses): BLI4700-301— (b) (4), (b) (6) BLI4700-302— (b) (4), (b) (6) The Applicant's IR responses confirmed these sensitivity analyses results in the modified intent to treat (mITT) population. The sensitivity analyses results (Table 16 and Table 17) were similar to the primary result.

In addition, we conducted exploratory analysis using logistic regression (full model included arm, site, randomization group, age group [at least 65 years], sex, race, and asymptomatic at baseline), and backward selection method identified that randomization group and age group (<65 versus ≥65 years) were two factors significantly associated with the primary outcome for study 301. The sensitivity analysis using a CMH test controlling for age group shown similar results as the primary results.

Analogously, our sensitivity analyses results in a modified per-protocol (PP) population were also consistent with the primary efficacy finding. The results were not shown in this review. The modified PP populations excluded subjects who did not follow dietary instruction or treatment instruction (e.g., took the two dosages on a wrong schedule or only part of the drug) based on the protocol violation listings. Study 301 modified PP population excluded 6 noncompliant subjects on diet and 26 subjects not following dosage instruction from the mITT population. The modified PP population of study 302 did not include 46 subjects with 12 diet violations and 34 treatment noncompliances.

Note that the statistical analysis plan (SAP) stated that the PP population will be used for sensitivity analyses of the primary and secondary endpoints. However, the Clinical Study Reports (CSRs) did not include efficacy analyses results based on PP populations.

We analyzed the primary endpoint in about 30% mITT subjects who had central readings on the overall cleansing using adjudicated reading results. Table 39 illustrates that the results in subjects with central readings were similar to the primary efficacy findings. For this subset of mITT population, the lower bound of the 95% CI of treatment difference in overall cleansing success was -6.6% in study 301 which showed BLI4700 was non-inferior to MoviPrep. Study 302 had a -10.6% lower bound, close to the -10% non-inferiority (NI) margin, which could attribute to chance due to small sample size of subjects with central readings.

Table 39. Primary Endpoint Results in mITT Subjects With Central Readings

Overall Cleansing Success Rates	BLI4700-301	BLI4700-302
BLI4700		
N=88 (%)	85 (96.6)	
N=57(%)		49 (86.0)
Active comparator		
MoviPrep N=60 (%)	58 (96.7)	
Prepopik N=66 (%)		56 (84.8)
Treatment difference* (95% CI)	-0.4 (-6.6, 5.8)	2.2 (-10.6, 15.1)
p-Value	0.90	0.74

Source: Reviewer's analyses
* Treatment difference and 95% CI are adjusted for covariates based on Mantel-Haenzel estimates for the common risk.
Abbreviation: mITT = modified intent to treat

Overall Colon Score vs. Segment Colon Score

Additional exploratory analyses were performed to compare the overall colon cleansing based on global assessment of the colon with the individual colon segment scores defined by the Applicant. The results for each study are discussed separately. For both studies, the efficacy conclusions are similar when examining the proportion of responders in all three segments compared to the proportion of responders from the global assessment.

Study 301

These analyses included 538 of out 548 mITT patients. Ten patients who were missing either the global score or any of the segment scores were excluded from the analysis. The Kendall's tau coefficient between global score and segment scores was high (global versus proximal segment score: 0.85; global versus distal segment score: 0.83; global versus mid segment score: 0.80).

The proportion of patients who were responders in all three segments was compared to the proportion of overall responders. The results are displayed in Table 40 below. Of the patients in the analysis, 475 patients (88.3%) were both responders in all three segments and overall responders and 40 patients (7.4%) were neither responders in all three segments nor overall responders. There were 23 patients (4.3%) who were overall responders but not responders for all three segments. However, these 23 patients were responders in 2 of the 3 segments, i.e., 2 segments had a score of good or excellent.

Table 40. Study BLI4700-301 Comparison of Overall Responders and Responders for All Colon Segments

	Responder for All Segments N (%)		
Overall Responder	No	Yes	Total
No	40 (7.4%)	0	40 (7.4%)
Yes	23(4.3%)	475 (88.3%)	498 (92.6%)
Total	63 (11.7%)	475 (88.3%)	538

Source: Reviewer's analysis

Study 302

These analyses included 383 of out 388 mITT patients. Five patients who were missing the either the global score or any of the segment scores were excluded from the analyses. The Kendall's tau coefficient between global score and segment scores was high (global versus proximal score is 0.80, global versus distal segment score: 0.78; global versus mid segment score: 0.79).

The proportion of patients who were responders in all three segments was compared to the proportion of overall responders. The results are displayed in Table 41 below. Of the patients in the analysis, 337 patients (88.0%) were both responders in all 3 segments and overall responders, and 33 patients (8.6%) were not responders in all 3 segments and were not overall responders. There were 12 patients (3.1%) who were overall responders but not responders for all 3 segments. However, as with Study 301, all 12 patients were responders for 2 of out 3 segments. Additionally, one subject (0.3%) was not an overall responder but was considered as responder by all three segments.

Table 41. Study BLI4700-302 Comparison of Overall Responders and Responders for All Colon Segments

	Responder for All Segments		
Overall Responder	**No**	**Yes**	**Total**
No	33 (8.6%)	1 (0.3%)	34 (8.9%)
Yes	12 (3.1%)	337 (88.0%)	349 (91.1%)
Total	45 (11.7%)	338 (88.3%)	383

Source: Reviewer's analysis

Table 42. Study BLI4700-301 Subgroup Analyses Results on Primary Efficacy Endpoint*

Overall Cleansing Success Rates by Subgroups	BLI4700 N (%)	MoviPrep N (%)	95% CI†	p-Value†
Age				
<65	179 (94.2)	166 (90.7)	-1.9, 8.9	0.21
≥65	78 (88.6)	75 (86.2)	-7.4, 12.3	0.78
Gender				
Female	146 (93.0)	132 (87.4)	-1.1, 12.2	0.15
Male	111 (91.7)	109 (91.6)	-6.9, 7.1	0.96
Ethnicity				
Hispanic/Latino	26 (96.3)	31 (100.0)	-10.8, 3.4	0.37
Non-Hispanic/Latino	231 (92.0)	210 (87.9)	-1.2, 9.5	0.12
Race				
White	198 (90.8)	187 (88.2)	-3.2, 8.4	0.46
African-American	42 (97.7)	41 (91.1)	-2.9, 16.0	0.30

Overall Cleansing Success Rates by Subgroups	BLI4700 N (%)	MoviPrep N (%)	95% CI†	p-Value†
Stratification groups				
Group 1				
History of constipation Opioid use Failed colonoscopy BMI >35	103/115 (89.6)	86/104 (82.7)	-2.3, 16.0	0.12
Group 2				
PM colonoscopy	47/49 (95.9)	45/49 (91.8)	-5.4, 13.5	0.22
Group 3				
All other subjects	107/114 (93.9)	110/117 (94.0)	-6.3, 6.0	0.61

Source: Table 10 of Study BLI4700-301 CSR and Table 12 of IR response dated July 15, 2019. Verified by reviewer.
* Primary efficacy endpoint is the preparation success defined as bowel cleansing graded either excellent or good (grading score =3 or 4).
† p-Value and CI for percent success difference between treatments are based on CMH test adjusted for site.
Abbreviation: BMI = body mass index

Table 43. Study BLI4700-302 Subgroup Analyses Results on Primary Efficacy Endpoint*

Overall Cleansing Success Rates by Subgroups	BLI4700 N (%)	Prepopik N (%)	95% CI†	p-Value†
Age				
<65	119 (93.0)	134 (88.2)	-2.0, 11.6	0.26
≥65	56 (90.3)	40 (87.0)	-8.8, 15.6	0.79
Gender				
Female	103 (92.0)	103 (91.2)	-6.5, 8.1	0.81
Male	72 (92.3)	71 (83.5)	-1.1, 18.6	0.33
Ethnicity				
Hispanic/Latino	17 (89.5)	12 (75.0)	-10.8, 40	0.34
Non-Hispanic/Latino	171 (92.4)	162 (89.0)	-2.6, 9.4	0.51
Race				
White	164 (92.7)	160 (87.4)	-0.9, 11.4	0.21
African-American	6 (75.0)	9 (90.0)	-50.3, 20.3	0.16
Stratification groups				
Group 1				
History of constipation Opioid use Failed colonoscopy BMI >35	50/55 (90.9)	49/58 (84.5)	-5.6, 18.4	0.27
Group 2				
PM colonoscopy	29/29 (100.0)	29/32 (90.6)	-0.7, 19.5	0.36
Group 3				
All other subjects	96/108 (90.6)	96/106 (88.9)	-6.5, 9.8	0.53

Source: Table 10 of Study BLI4700-302 CSR and Table 12 of IR response dated July 15, 2019. Verified by reviewer.
* Primary efficacy endpoint is the preparation success defined as bowel cleansing graded either excellent or good (grading score =3 or 4).
† p-Value and CI for percent success difference between treatments are based on CMH test adjusted for site.
Abbreviation: BMI = body mass index

Table 44. Study BLI4700-301 Patient Baseline Characteristics (Indication for Colonoscopy)

Indication for Colonoscopy	BLI4700 N=281 (%)	MoviPrep N=271 (%)	All Subjects N=552 (%)
Unknown diarrhea or constipation etiology	40 (14.2)	39 (14.4)	79 (14.3)
Asymptomatic	108 (38.4)	108 (39.9)	216 (39.1)
Age ≥50 years	180 (64.1)	176 (64.9)	356 (64.5)
Family history of CRC	44 (15.7)	34 (12.5)	78 (14.1)
African American age ≥45 years	27 (9.6)	32 (11.8)	59 (10.7)
Personal history of adenoma	50 (17.8)	61 (22.5)	111 (20.1)
Personal history of colon cancer	3 (1.1)	0	3 (0.5)
Ulcerative colitis or Crohn's	3 (1.1)	4 (1.5)	7 (1.3)
GI or rectal bleeding	31 (11.0)	27 (10.0)	58 (10.5)
Abdominal pain	30 (10.7)	25 (9.2)	55 (10.0)
Other	36 (12.8)	30 (11.1)	66 (12.0)
Anemia of unknown etiology	2 (0.7)	3 (1.1)	5 (0.9)

Source: Table 15 of Sponsor's IR response dated July 15, 2019. Verified by Reviewer.
Abbreviations: CRC = colorectal cancer, GI = gastrointestinal

Table 45. Study BLI4700-302 Patient Baseline Characteristics (Indication for Colonoscopy)

Indication for Colonoscopy	BLI4700 N=190 (%)	Prepopik N=199 (%)	All Subjects N=389 (%)
Unknown diarrhea or constipation etiology	13 (6.8)	22 (11.1)	35 (9.0)
Asymptomatic	57 (30.0)	48 (24.1)	105 (27.0)
Age ≥50 years	107 (56.3)	115 (57.8)	222 (57.1)
Family history of CRC	28 (14.7)	27 (13.6)	55 (14.1)
African American age ≥45 years	3 (1.6)	4 (2.0)	7 (1.8)
Personal history of adenoma	36 (18.9)	37 (18.6)	73 (18.8)
Personal history of colon cancer	0	2 (1.0)	2 (0.5)
Ulcerative colitis or Crohn's	12 (6.3)	6 (3.0)	18 (4.6)
GI or rectal bleeding	17 (8.9)	12 (6.0)	29 (7.5)
Abdominal pain	12 (6.3)	12 (6.0)	24 (6.2)
Other	21 (11.1)	20 (10.1)	41 (10.5)

Source: Table 16 of Sponsor's IR response dated July 15, 2019. Verified by Reviewer.
Abbreviations: CRC = colorectal cancer, GI = gastrointestinal

15.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

15.4.1. Bioanalytical Method Validation and Performant Results

Inorganic sulfate levels in human serum were quantified using a validated kit-based turbidimetric method with QuantiChromTM Sulfate Assay Kit (DSFT-200) (method validation number #177900). The method validation results are summarized in Table 46.

The bioanalytical method was adequately validated and met the acceptance criteria suggested in the FDA Bioanalytical Method Validation Guidance. The bioanalysis performance results in phase 3 clinical studies are summarized in Table 47.

Inorganic sulfate human serum samples from study 301 and study 302 were not analyzed as incurred repeats. Although incurred sample reanalysis is regarded as one of the methods validating incorporated bioanalytical process, data reproducibility of proposed bioanalytical method is sufficiently supported by other stability results.

All samples from study 301 and study 302 were analyzed within the established long-term stability window.

Table 46. Summary of Method Validation of Inorganic Sulfate in Human Serum Using QuantiChromTM Sulfate Assay Kit (DSFT-200)

Method Validation Details	Plan #177900
Type of assay	Kit-based turbidimetric
Biological matrix	Human serum
Sample aliquot volume	300µL
Reference standard	Sodium sulfate, Lot BA0209
Calibrated range (mM)	0.2-2.0 in 100% matrix
Defined LLOQ (mM)	0.2
Linearity (r^2)	0.98690
Acceptance criteria for standard and QCs	±15.0% (±20.0% at LLOQ)
Intra-run accuracy (% RE)	-4.86 to 8.74
Intra-run precision (% CV)	1.60 to 8.03
Inter-run accuracy (% RE)	-5.00 to 8.67
Inter-run precision (% CV)	3.67 to 13.9
Bench-top stability in human serum	22 hours at ambient temperature
Freeze/thaw stability	4-cycles freeze (-70°C)/thaw (ambient temperature) cycles
Processed sample stability	up to 60 minutes at room temperature
Solution stability (-20°C) in water	109 days at -20°C (500mM) 107 days at -20°C (10.0mM)
Solution stability (room temperature) in water	6 hours at room temperature (500mM and 10.0mM)
Long term storage stability	693 days -70°C stability
Recovery	6 out of 6 normal lots passed the criteria

Source: Validation of a Method for the Determination of Inorganic Sulfate in Human Serum Using QuantiChromTM Sulfate Assay Kit (DSFT-200) for Turbidimetric Sulfate Quantitation: (b) (4) Job Number 177900 (Lot: 001)
Abbreviations: CV = coefficient of variance, LLOQ = lower limit of quantification, QC = quality control, RE = relative error

Table 47. Summary of Bioanalysis Performance Results for Studies BLI4700-301/302

Results	Study BLI4700-301	Study BLI4700-302
Sample receipt, storage, and analysis dates		
Total number of samples received	1,699 samples and 4 duplicate samples	1,235 samples
Total number of samples analyzed	1,692 samples and 4 duplicate samples 6 samples did not have sufficient volume	1,233 samples 20 samples did not have sufficient volume 2 samples were received in unsatisfactory condition
Storage temperature	-70°C	-70°C
First date of sample collection	Jan 25, 2017	Aug 8, 2017
Experimental completion date	Sep 11, 2018	Aug 31, 2018
Maximum storage stability for samples*	442 days at -70°C	332 days at -70°C
Maximum freeze/thaw cycles for samples	2 cycles	3 cycles
Standard curve		
Inter-run accuracy (%RE)	-4.6-3.0%	-6.4-3.0%
Inter-run precision (%CV)	≤4.27%	≤3.64%
Quality controls		
Inter-run accuracy (%RE)	-2.0-0.625%	-2.67-1.25%
Inter-run precision (%CV)	≤10.4%	≤12.0%
Incurred sample reanalysis	Inorganic sulfate human serum samples from clinical Study BLI4700-301 and Study BLI4700-302 were not analyzed as incurred repeats.	
Reference standard		
Standard name	Sodium sulfate	
Lot number	SLBV7518	
Purity	99.8%	
Expiry date	Feb 4, 2023	

Source: Sample Analysis Report for the Determination of Inorganic Sulfate in Human Serum (Sponsor Study Number: BLI4700-301) and Sample Analysis Report for the Determination of Inorganic Sulfate in Human Serum (Sponsor Study Number: BLI4700-302)
* The number of days based on the individual sample collection and analysis
%RE: percent relative error, %RE =100 × (mean observed concentration – nominal concentration)/nominal concentration
%CV: percent coefficient of variation, %CV =100 × (standard deviation/mean)

15.4.2. Individual Clinical Pharmacology Study Reviews

Clinical Pharmacology studies supporting SUTAB development program are summarize in Table 48. None of these studies was conducted using the final, to-be-marketed (TBM) formulation.

Table 48. Summary of Clinical Pharmacology Studies Supporting the NDA

Study	Formulation	Goal	Clinical Pharmacology Data/Information
BLI4700-101/102	1, 2, 3, 3 ((b) (4)), 4, 5, 8, 9, 10, 11, 12, ST24	Formulation optimization	PK: baseline and predose, 4, 6 hours postdose of each dosing PD: stool output, Scatocrit
BLI4700-201	3, 5, 10, 12	Pilot efficacy and safety	PD: stool output, Scatocrit
BLI4700-202	5	Pilot efficacy and safety	PD: stool output, Scatocrit

Source: Reviewer-created table
Abbreviations: PD = pharmacodynamic, PK = pharmacokinetic

1. PROTOCOL NUMBER: BLI4700-101/102

TITLE: Evaluating an Investigational Bowel Cleansing Preparation BLI4700: Effects on Symptoms, Gastric Balance, Blood Chemistry, Fecal Physical and Chemical Properties and Breath Gases in Healthy Male Volunteers.

OBJECTIVES: The primary objective of this study was to develop a tablet-based preparation that would produce stool output and clarity sufficient for further development as a bowel preparation.

STUDY DESIGN: This was a phase 1, single-center, nonrandomized, open-label, sequential study in healthy male adults (18 to 50 years old) treated with a split-dose of 4700 tablets over a 2-day period to evaluate the safety, electrolyte and fluid balance, and stool output parameters of different formulas of the 4700 bowel preparation tablets formulas.

Treatments:
Study 101: 4700-1 and MOVIPREP (reference therapy),
Study 102: 4700-1, -2, -3, -3 ((b) (4)), -4, -5, -8, -9, -10, -11 -12, -ST24 and SUPREP (reference therapy)

Table 49. Comparison Tablet Formula (Total Dose, g) of Study BLI4700-101/102

	Formula (4700-)*									
Ingredient	**1**	**2†**	**3**	**3‡**	**4**	**5**	**8**	**9**	**10**	**11**
(b) (4)										

Table 50. Comparison Tablet Formula (Total Dose, g) of BLI4700-8 and Its Variants (-12 and -ST24)

Ingredient	**BLI4700-8**	**BLI4700-12**	**BLI4700-ST24 (To-Be-Marketed)**
Sodium sulfate(Na_2SO_4)	(b) (4)		35.5
Magnesium sulfate ($MgSO_4$)			5.4
Potassium chloride (KCl)			4.5
Sodium caprylate			(b) (4)
(b) (4)			
PEG-8000			

Source: 3.2.P.2 Drug Product

Hydration Regimen: With respect to formula 4700-8 and its variants, two dosing regimens, Regimens 2 and 4 were evaluated. Regimens 2 and 4 are identical with the sole difference being a clarification with respect to timing of the pill and per-protocol water consumption. However, the Applicant did not analyze the effect of Regimen 2 versus 4 on efficacy.

- Regimen 2: Subjects were instructed to take 12 tablets, 1 or 2 tablets at a time, as quickly as comfortably possible, along with 16 oz of water to help swallow the pills. The entire dose together with the 16 oz of water was consumed over approximately 20 minutes. Following completion of the dose, subjects drank 2 additional servings of exactly 16 oz of water over the next hour at a rate of approximately 8 oz of water every 15 minutes.

  Formula 4700-8: n=10
  Formula 4700-12: n=5
- Regimen 4 (Modified Instructions and Hydration): Subjects were instructed to swallow the tablets slowly, one at a time, with small sips of water and not to chew the tablets. The entire dose together with the 16 oz of water was to be consumed over approximately 20 minutes if possible, but no more than 30 minutes. If the subject was uncomfortable, they may take the tablets and water more slowly. Beginning 60 minutes after completion of the dose, they slowly drank an additional 16 oz of water over 30 minutes. After waiting an additional 30 minutes, they slowly drank an additional 16 oz of water over 30 minutes.

  Formula 4700-8: n=5
  Formula 4700-ST24: n=5

Study Population: The study included healthy males ages 18 to 50 in good health. A total of 123 study subjects were enrolled.

EFFICACY RESULTS: Twenty (20) study subjects who successfully completed the formula 4700-8 or one of the variants (-12 or -ST24) were included in the efficacy analysis. Five (5) subjects who vomited or regurgitated during preparation were not included in the efficacy analysis: time to first bowel movement, Scatocrit, fecal volume and fecal electrolyte balance.
Formula 4700-8 (and variants) produced a mean stool output of 2,745.2 mL and stool percent solids of 3.7% as presented in Table 52. Total fluid balance was neutral. Due to the inclusion of other electrolytes and counterions in the formula, minimal gastrointestinal electrolyte absorption or secretion was also achieved.

Table 51. Efficacy Summary of Tested Formula in Study 101

	Formula (4700-)									
Efficacy	**1**	**2***	**3**	**3†**	**4**	**5**	**8**	**9**	**10**	**11**
N	10	20	10	7	5	15	14	2	9	4
Stool output (mL) Mean (SD)	2,953.5 (295.5)	2,723.6 (457.9)	2,319.6 (242.0)	3,036.5 (568.4)	2,562.2 (482.6)	2,736.7 (359.6)	2,795.1 (351.6)	2,831.7 (6.0)	2,716.2 (397.0)	2,594.5 (367.0)
Gastric fluid balance (mL) Mean (SD)	1,522.8 (1,154.7)	3,802.0 (1,398.5)	2,197.4 (684.9)	1,806.3 (1,093.1)	2,468.2 (375.8)	1,963.4 (1,091.3)	2,270.2 (1,235.5)	2,631.8 (870.5)	2,429.4 (1,555.2)	1,545.6 (660.3)
Fluid balance (mL) Mean (SD)	5.3 (499.6)	248.8 (677.3)	-155.1 (488.2)	-284.2 (738.7)	24.2 (488.8)	161.6 (530.8)	-293.7 (586.9)	104.3 (198.0)	-115.1 (461.4)	-112.0 (27.6)
% solids Mean (SD)	4.9 (3.9)	2.2 (2.3)	1.6 (0.6)	1.8 (0.8)	5.5 (5.6)	1.5 (1.2)	3.6 (6.0)	1.4 (0.0)	2.0 (1.4)	2.0 (1.3)
Na (mEq) Mean (SD)	53.8 (35.5)	-16.5 (106.6)	79.3 (83.9)	51.9 (101.4)	133.5 (94.5)	164.9 (118.4)	-10.0 (103.0)	-212.1 (304.4)	-10.6 (143.4)	113.1 (128.5)
Cl (mEq) Mean (SD)	-74.6 (19.0)	-21.2 (33.5)	-4.4 (34.0)	-45.0 (57.7)	-30.1 (19.8)	-25.0 (30.0)	-4.1 (21.9)	-100.1 (41.6)	-21.1 (54.8)	-7.5 (40.5)
K (mEq) Mean (SD)	11.6 (16.7)	58.5 (20.2)	4.2 (11.1)	20.0 (16.9)	-11.7 (16.3)	8.3 (15.5)	-4.8 (16.7)	-11.6 (20.4)	-15.4 (14.2)	-31.1 (60.0)
Mg (mEq) Mean(SD)	4.0 (3.8)	-4.7‡ (6.6)	-8.8 (7.4)	Not tested	-16.1 (15.9)	-15.7 (9.1)	-6.8 (19.7)	-12.4 (9.5)	-1.3 (9.4)	22.1 (37.9)

Source: Table 6 in BLI4700-101/102 Clinical Study Report
*Inclusive of formula variants 4700-2.0, 2.1 and 2.2
(b) (4)
magnesium values for 18 subjects
Abbreviations: Cl = chlorine, K = potassium, mEq = milliequivalent, Mg = magnesium, mL = milliliter, Na = sodium

Table 52. Summary of Efficacy: Total Fluid Intake, Stool Output and Fluid Balance of Formulas 4700-8, -12, -ST24, and MoviPrep

Efficacy	Formula/Preparation					
	8	12	ST24	8/12/ST24	MoviPrep	p-Value*
N	14	3	3	20	9	
Input (fluid+prep) (mL) Mean (SD)	5,065.3 (1,120.8)	4,710.0 (230.0)	4,918.3 1,005.6	5,001.3 (1046.5)	4,543.5 (892.2)	0.290
Stool output (mL) Mean (SD)	2,795.1 (351.6)	2,908.0 (49.6)	2,522.5 (607.5)	2,762.2 (404.7)	3,058.2 (-654.4)	0.177
Gastric fluid balance (mL) Mean (SD)	2,270.2 (1,235.5)	1,802.1† (279.6)	2,395.8 (725.2)	2,239.1 (1,106.7)	1,485.3 (-911.7)	0.102
Total urine output (mL) Mean (SD)	2,563.9 (1,303.1)	1,802.1 (430.4)	2,393.3 (779.3)	2,470.3 (1,178.0)	2,088.3 (-1,147.0)	0.448
Total fluid balance (mL) Mean (SD)	-293.7‡ (586.9)	-175.5† (203.0)	2.5 (275.6)	-231.2 (527.6)	-603.0 (609.6)	0.128
Mean solid (%) Mean (SD)	3.6 (6.0)	1.4 (0.0)	6.4 (7.6)	3.7 (6.0)	5.6 (5.1)	0.452
Time to first bowel movement Mean (SD)	2:00 (0:43)	1:11 (0:10)	1:52 (1:07)	1:51 (0:48)	1:11§ (0:18)	0.0913

Source: Table 14, Table 15 and Table 16 in BLI4700-101/102 Clinical Study Report
* p =8/12/12ST versus MoviPrep
† n=2 because subject (b) (6) was excluded from input fluid, gastric fluid balance and total fluid balance calculations because the subject did not finish per-protocol water.
‡ n=13 because subject (b) (6) removed from balance equations due to methodological error in collecting fecal output volumes
§ n=5 because Dose 1 administration time was not provided for 5 of the 10 subjects (b) (6)

SAFETY RESULTS: No serious adverse events were reported in this study. One episode of nausea was reported as moderate and probably related to the study medication. All adverse events resolved by the end of the trial.

The most frequent adverse events reported were solicited reports of nausea, vomiting, and abdominal bloating. Review of serum electrolytes demonstrate that there were small increases in mean potassium, sodium, magnesium, phosphate, and anion gap and decreases in bicarbonate, calcium, and chloride.

Serum sulfate levels increased during the dosing period for formula 4700-8 and its variants. This is expected as the formulation contains significant amounts of sulfate to promote diarrheal production. However, the increase in serum sulfate is within the trends of historical data for other preparations with high sulfate composition, such as SUPREP.

Reviewer's Conclusion: The criteria for the decision of final formula was to yield stool volumes greater than 2,500 mL with a Scatocrit below 5.0%. Based on the pharmacodynamic results and predefined criteria, formula 4700-8 was identified as the optimal formulation to proceed to phase 2 studies.

2. PROTOCOL NUMBER: BLI4700-201

TITLE: A Pilot Evaluation of BLI4700 Bowel Preparation in Adult Subjects.

OBJECTIVES: The purpose of this study was to evaluate the safety, tolerance, and efficacy of different BLI4700 tablet formulations as bowel preparations prior to colonoscopy in adult subjects.

STUDY DESIGN: This was an open-label, multicenter study in adult subjects requiring colonoscopy.

Treatments: BLI4700-3, -5, -10, -12. Each formulation consisted of a total of 24 tablets (two 12-tablet doses). The selection of formulation regimens was based on results from phase 1 studies of BLI4700.

Table 53. BLI4700 Formulation Summary (Amount in 24 Tablets)

Ingredient (g)	Version 1 (4700-3)	Version 2 (4700-5)	Version 4 (4700-10)	Version 5 (4700-12)
Sodium sulfate	(b) (4)			(b) (4)
Potassium chloride	(b) (4)			
Magnesium sulfate	(b) (4)			

Source: Table 3 in BLI4700-201 Clinical Study Report

Dose and Dosing Regimen: The BLI4700 study preparation was administered in a 2-day "split dose" regimen with one dose given the evening before and the other dose given the morning of the colonoscopy, consistent with SUPREP labeling for adults. Subjects were provided with instructions on how rapidly to ingest the tablets and additional fluids.

Table 54. BLI4700 Tablet/Fluid Ingestion Regimens

Cohort	Formulation	Tablet Regimen	Fluid Regimen
1	4700-3	12 tablets in 15-20 minutes with 16oz water	Two 16oz glasses of water over 1-2 hours
2	4700-3	4 tablets every 15 minutes with 8oz water	Wait 30 mins, then three 8oz cups of water every 30 mins
3	4700-3	4 tablets every 30 minutes with 8oz water	Three 8oz cups of water over 2 hours
4	4700-5	12 tablets in 15-20 minutes with 16oz water	Wait 30 mins, then two 16oz cups of water over 2 hours
5	4700-5	12 tablets in 15-20 minutes with 16oz water	Wait 30 mins, then two 16oz cups of clear liquids over 2 hours
6	4700-10	12 tablets in 15-20 minutes with 16oz water	Wait 60 mins Drink one 16oz cup of water over 30 mins Wait 30 mins Drink second 16oz cup of water over 30 mins

Cohort	Formulation	Tablet Regimen	Fluid Regimen
7	4700-12	12 tablets in 15-20 minutes with 16oz water	Wait 60 mins Drink one 16oz cup of water over 30 mins Wait 30 mins Drink second 16oz cup of water over 30 mins

Source: Table 3 in BLI4700-201 Clinical Study Report

Study Population: One hundred and fourteen (114) adult subjects undergoing colonoscopy for routinely accepted indications, without standard contraindications for bowel preparation.

EFFICACY RESULTS: Primary efficacy was assessed on the basis of a binary outcome of overall preparation success for colonoscopy preparation where overall assessment of success was determined based on the colonoscopist scores of "Excellent" or "Good."

Preparation success was similar throughout all cohorts (Table 55), with the exception of Cohort 3, in which the tablets were administered over a longer period of time (1 hour). This indicates that there is little effect of the preparation regimen on cleansing efficacy except when tablet ingestion is delayed. In Cohort 7, the formulation (Formula 12) to progress into phase 3, overall cleansing success was 95%. These success rates are comparable with historical rates seen with SUPREP and MoviPrep.

Table 55. Overall Efficacy Analysis Success/Failure—mITT Population

	Cohort # (Formulation [BLI4700-])							All
Efficacy	1 (3)	2 (3)	3 (3)	4 (5)	5 (5)	6 (10)	7 (12)	Subjects
N	14	11	15	12	25	17	20	114
Success	13 (93)	10 (91)	12 (80)	11 (92)	25 (100)	16 (94)	19 (95)	106 (93)
Failure*	1 (7)	1 (9)	3 (20)	1 (8)	0	1 (6)	1 (5)	8 (7)

Source: Table 8 in BLI4700-201 Clinical Study Report
* Four subjects did not undergo colonoscopy for safety or efficacy reasons and are included as failures.
Abbreviation: mITT = modified intent to treat

SAFETY RESULTS: One hundred and fourteen subjects were enrolled and took the BLI4700 tablet preparation. Solicited preparation symptoms (stomach cramping, bloating, nausea, and vomiting) were the most frequently reported adverse events and occurred at rates comparable with other bowel preparations (Table 56). Gastrointestinal (GI) adverse events was more frequent than non-GI adverse events. Non-GI events occurred at low frequencies. No clinically significant changes were seen in serum chemistry values or vital sign measurements across formulations. There were no clear differences observed between the formulations and regimens with respect to adverse effects and patient tolerance. The majority of adverse events were mild to moderate in severity while five events were considered severe. All severe adverse events (urethral stricture, elevated liver function tests, bradycardia [n=2], and hypotension) were considered unrelated to the study drug.

Table 56. Subjects With Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in Study BLI4700-201 (Safety Population, n=114)

System Organ Class Preferred Term	Cohorts 1-3 4700-3 N=40 (%)	Cohorts 4&5 4700-5 N=37 (%)	Cohort 6 4700-10 N=17 (%)	Cohort 7 4700-12 N=20 (%)
Number of subjects with any event	30 (75.0)	24 (64.9)	12 (70.6)	15 (75.0)

System Organ Class Preferred Term	Cohorts 1-3 4700-3 N=40 (%)	Cohorts 4&5 4700-5 N=37 (%)	Cohort 6 4700-10 N=17 (%)	Cohort 7 4700-12 N=20 (%)
Total number of events	58	56	21	36
Cardiac disorders	2 (5.0)	1 (2.7)	0	0
Bradycardia	1 (2.5)	0	0	0
Sinus arrhythmia	0	1 (2.7)	0	0
Sinus bradycardia	1 (2.5)	0	0	0
Gastrointestinal disorders	28 (70.0)	24 (64.9)	12 (70.6)	14 (70.0)
Abdominal distension	11 (27.5)	18 (48.6)	6 (35.3)	8 (40.0)
Abdominal pain	9 (22.5)	12 (32.4)	3 (17.6)	4 (20.0)
Nausea	19 (47.5)	18 (48.6)	9 (52.9)	13 (65.0)
Vomiting	10 (25.0)	6 (16.2)	3 (17.6)	4 (20.0)
General disorders and administrative site conditions	0	0	0	1 (5.0)
Chills	0	0	0	1 (5.0)
Investigations	1 (2.5)	0	0	0
Liver function test increased	1 (2.5)	0	0	0
Metabolism and nutrition disorders	1 (2.5)	0	0	0
Hyperglycaemia	1 (2.5)	0	0	0
Nervous system disorders	1 (2.5)	1 (2.7)	0	2 (10.0)
Dizziness	0	1 (2.7)	0	0
Headache	1 (2.5)	0	0	1 (5.0)
Presyncope	0	0	0	1 (5.0)
Vascular disorders	2 (5.0)	0	0	0
Hypotension	2 (5.0)	0	0	0

Source: Table 14 in BLI4700-201 Clinical Study Report

Reviewer's Conclusion: BLI4700 tablets were well-tolerated and achieved successful preparation in the majority of subjects (93%). A total of 114 subjects took the preparation, including 20 who took the final formulation (4700-12).The preparation success rate was high (>91%) across all cohorts except cohort 3 (80%), in which it took 1 hour to administer one dose (12 tablets). This suggested that delayed drug administration may affect the cleansing efficacy of preparation. Safety profiles were comparable between cohorts. Overall cleansing success rate of Formula 12 which was eventually used in phase 3 trials was 95%.

3. PROTOCOL NUMBER: BLI4700-202

TITLE: A Pilot Evaluation of BLI4700 Bowel Preparation in Adult Subjects.

OBJECTIVES: The purpose of this study was to evaluate the safety, tolerance, and efficacy of a BLI4700 tablet formulation as a bowel preparation prior to colonoscopy in adult subjects.

STUDY DESIGN: This was an open-label, multicenter study in adult subjects requiring colonoscopy. Patients were provided with BLI4700 tablets to be administered as a same day "split dose" regimen, with both doses of study preparation taken on the morning of colonoscopy as two separate a.m. doses.

Treatments: Although multiple formulation candidates (BLI4700-4 and -5, Table 56) were identified in the phase 1 trials, only BLI4700 #2 containing (b) (4) was evaluated in this study (Table 57).

Table 57. BLI4700 Formulation Summary (Amount in 24 Tablets)

Material (g)	BLI4700 #2 (Formulation 5)
	(b) (4)

Source: Table 2 in BLI4700-202 Clinical Study Report

Dose and Dosing Regimen: Subjects were required to consume a total of 24 tablets (two 12 tablet doses). For each of the 2 doses, patients swallowed 12 tablets over 15 to 20 minutes with 16 ounces of water. After waiting for 30 minutes, patients had 2 additional cups of 16 ounces of water over a period of 2 hours.

The second dose was to be consumed 4 hours after starting the first dose.

Study Population: Seventeen (17) adult subjects undergoing colonoscopy for routinely accepted indications, without standard contraindications for bowel preparation.

EFFICACY RESULTS: Primary efficacy was assessed on the basis of preparation success for colonoscopy where overall assessment of success was determined based on the colonoscopist scores of "Excellent" or "Good."

Preparation success rate was high (88%) as presented in Table 58. The two subjects who were considered failures did not undergo colonoscopy. Subject (b) (6) reported no bowel movements after taking the preparation, which may be due to intolerance (vomiting) of the preparation. One subject did not take all of dose 2, and it was not clear how much preparation was taken. Therefore, the site investigator decided not to go through colonoscopy.

Table 58. Primary Outcome: Overall Preparation Efficacy (n=17)

Assessment	N (%)
Success	15 (88.2)
Failure	2 (11.8)

Source: Table 7 in BLI4700-202 Clinical Study Report

SAFETY RESULTS: Seventeen subjects took BLI4700 tablets in this study. Observed adverse events were abdominal cramping, bloating, nausea, and vomiting (Table 59). The frequency of vomiting in the study was higher than typically seen with two-day split-dose preparations, likely due to the limited time between doses in this morning regimen. There were also no clinically significant changes from baseline in serum chemistry values. There were no serious or unexpected adverse events.

Table 59. Subjects With Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in Study BLI4700-202 (ITT Population, n=17)

System Organ Class Preferred Term	N=17 (%)
Number of subjects with any event	14 (82.4)

System Organ Class Preferred Term	N=17 (%)
Total number of events	29
Gastrointestinal disorders	14 (82.4)
Abdominal distension	10 (58.8)
Abdominal pain	1 (5.9)
Abdominal pain upper	4 (23.5)
Nausea	8 (47.1)
Vomiting	6 (35.3)

Source: Table 10 in BLI4700-202 Clinical Study Report
Abbreviation: ITT = intent to treat

Reviewer's Conclusion: The rate of successful preparation for colonoscopy was high (88%) in this study with same day split-dose on the morning of the colonoscopy. Approximately 82% of the subjects experienced adverse GI events. There was no non-GI adverse events reported. However, the rate of vomiting was higher than typically seen with 2-day, split-dose bowel preparations which is likely the result of both doses being taken within about 4 hours on the same day. Based on the safety findings in this study, the Applicant did not incorporate the morning-only dosing regimen in the phase 3 clinical trials.

15.5. Financial Disclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: March 31, 2019

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable check box.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attached listing(1.3.4)for Protocol BLI-4700-201	See attached listing(1.3.4)for Protocol BLI-4700-302
	See attached listing(1.3.4)for Protocol BLI-4700-202	
	See attached listing(1.3.4)for Protocol BLI-4700-301	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
John McGowan, MPH	Vice President, Clinical Affairs
FIRM/ORGANIZATION	
Braintree Laboratories, Inc.	
SIGNATURE	DATE *(mm/dd/yyyy)*
John McGowan Digitally signed by John McGowan DN: cn=John McGowan, o=Braintree Laboratories, Inc., ou=VP, Clinical Research, email=jmcgowan@braintreelabs.com, c=US Date: 2019.01.24 09:12:23 -05'00'	

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Covered Clinical Study (Name and/or Number): BLI4700-201, BLI4700-202, BLI4700-301, BLI4700-302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 43		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.6. References

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