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STUDY PROTOCOL

A Pilot Evaluation of BLI4700 Bowel Preparation Administered as a One Day, Split-Dose Regimen, in Adult Subjects

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A Pilot Evaluation of BLI4700 Bowel Preparation Administered as a One Day, Split-Dose Regimen, in Adult Subjects

Braintree Protocol BLI4700-202

Version Dated 16 February 2017

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CLINICAL PROTOCOL SUMMARY SHEET

STUDY TITLE: A Pilot Evaluation of BLI4700 Bowel Preparation Administered as a One Day, Split-Dose Regimen in Adult Subjects

PROTOCOL: BLI4700-202

VERSION DATE: 16 February 2017

IND NUMBER: 124,988

STUDY PHASE: 2

OBJECTIVE: To evaluate the safety and efficacy of BLI4700 tablets administered as a one day, split-dose regimen prior to colonoscopy in adult patients.

STUDY DESIGN: This will be an open-label, multi-center study.

SUBJECTS: Up to 60 male and female adult subjects will be enrolled.

STUDY MEDICATIONS: BLI4700 tablets

DURATION: Subject participation in this study may last up to 37 days.

EFFICACY ENDPOINTS: Efficacy will be based on overall preparation success as determined by the colonoscopist. Additional efficacy measures include the proportion of excellent preparations, segmental cleansing, time to cecum, volume of intraprocedural water used to improve visualization, percent of procedures that reach the cecum.

SAFETY ENDPOINTS: Safety endpoints include:

- Adverse event reports
- Changes in serum chemistry parameters.
- Subject reported prep-related symptoms

1. INTRODUCTION

Background

Colorectal cancer (CRC) is a leading cause of cancer death. The lifetime risk of developing CRC in the US approaches 6%, and almost half of those affected will die of the disease. Despite the usefulness of screening procedures for its detection, CRC is a major cause of morbidity and mortality. In screening procedures for CRC such as sigmoidoscopy, colonoscopy, and radiography, it is important that the colon be thoroughly purged and cleansed. In particular, it is essential that as much fecal matter and fluids as possible be removed from the colon to permit adequate visualization of the intestinal mucosa.

Preliminary Experience with the Similar Bowel Preparations

Two Phase 3 studies were conducted comparing BLI800 (SUPREP) to the FDA approved preparation MoviPrep[1]. The BLI800-301 study evaluated BLI800 as a one-day preparation, completed on the day prior to colonoscopy. The BLI800-302 study utilized a two-day (or "split-dose") regimen in which half the preparation was taken the evening prior to colonoscopy, and the remaining half completed on the morning of the procedure.

The primary efficacy analysis in both Phase 3 studies supported the conclusion that BLI800 is equivalent to MoviPrep with respect to cleansing efficacy (cumulative data shown below in Table 1).

Table 1
Primary Efficacy Responder Analysis
BLI800-301/302 Studies

Responder[1]	BLI800 n (%)	MoviPrep n (%)	95% CI	p[2]	p[3]
All Patients (n)	375	376			
Success	334 (89.5%)	330 (87.8%)	-2.8, 6.3	0.410	<0.001
Fail	39 (10.5%)	46 (12.2%)			
301 Patients (n)	194	193			
Success	159 (82.4%)	155 (80.3%)	-5.7, 9.8	0.614	<0.001
Fail	34 (17.6%)	38 (19.7%)			
302 Patients (n)	181	183			
Success	175 (97.2%)	175 (95.6%)	-2.2, 5.4	0.391	<0.001
Fail	5 (2.8%)	8 (4.4%)			

(1) A successful treatment is defined as bowel cleansing graded either excellent or good by the blinded colonoscopist (grading score = 3 or 4).
(2) P-value for the difference between treatments
(3) P-value for the non-inferiority hypothesis using an equivalence margin of 15 percent

The breakdown of cleansing efficacy by study and by preparation grade is shown below in Table 2. The data indicate that a two day preparation regimen, as performed in the 302 study, produces markedly superior cleansing results over a one day preparation, as in the 301 study. In each study and overall, BLI800 achieved a greater number of excellent preparations than MoviPrep. This difference resulted in a higher Mean Preparation Score for BLI800, reaching statistical significance (p = 0.049) in the total population.

Table 2
Preparation Cleansing Score
BLI800-301/302 Studies

	All Patients		301 Patients		302 Patients	
Score	SUPREP n (%)	MoviPrep n (%)	SUPREP n (%)	MoviPrep n (%)	SUPREP n (%)	MoviPrep n (%)
4 Excellent	200 (53.6%)	168 (44.7%)	86 (44.6%)	72 (37.3%)	114 (63.3%)	96 (52.5%)
3 Good	134 (35.9%)	162 (43.1%)	73 (37.8%)	83 (43.0%)	61 (33.9%)	79 (43.2%)
2 Fair	25 (6.7%)	37 (9.8%)	22 (11.4%)	31 (16.1%)	3 (1.7%)	6 (3.3%)
1 Poor	11 (2.9%)	8 (2.1%)	9 (4.7%)	6 (3.1%)	2 (1.1%)	2 (1.1%)
Mean Score	3.41	3.31	3.24	3.15	3.59	3.47
p value	0.049		0.278		0.050	

Adverse events were also evaluated in the Phase III studies. The only treatment emergent adverse event category with a frequency greater than 3% was gastrointestinal (BLI800 = 4.5% and MoviPrep = 4.3%). The expected symptoms of nausea and vomiting were the most frequent (1.3% each) within the gastrointestinal category. There was no difference between BLI800 and MoviPrep in the frequency of any treatment-emergent adverse events, including those that were gastrointestinal in origin. No clinically significant differences between groups were seen in laboratory testing of serum chemistry and hematology. At the one month follow-up visit, no change in serum creatinine was observed for BLI800 patients.

A smaller Phase III study (n = 136) was conducted comparing the safety and efficacy of SUPREP (in the FDA approved split-dose regimen) to NuLYTELY[2]. In addition to preparation success (as defined above), the blinded colonoscopist also rated the amount of residual fluid and stool in each colon segment. As shown below in Tables 3 and 4, SUPREP was superior to NuLYTELY in overall preparation success, as well as in reducing the amount of residual stool and fluid in most colon segments (most importantly the right colon, a segment with higher miss rates for polyps and flat lesions).

Table 3
Primary Efficacy Responder Analysis
Number and Percent of Successful Preparations

Responder[1]	**SUPREP n**	**NuLYTELY n**	**95% CI**	**P**[2]
All Patients (n)	63	67		
Success	62 (98.4%)	60 (89.6%)	0.9, 16.8	**0.038**
Fail	1 (1.6%)	7 (10.4%)		

(1) A successful treatment is defined as bowel cleansing graded either excellent or good by the blinded colonoscopist (grading score = 3 or 4).
(2) P-value for the difference between treatments

Table 4
Investigator Grading of Preparations by Segment

	Residual Stool		Residual Fluid	
Symptom (score)	SUPREP (n=63)	NuLYTELY (n=67)	SUPREP (n=63)	NuLYTELY (n=67)
Cecum				
Absent	57 (91%)	45 (67%)	27 (43%)	10 (15%)
Small	6 (9%)	15 (22%)	28 (44%)	42 (63%)
Moderate	0	3 (5%)	8 (13%)	10 (15%)
Excess	0	0	0	1 (2%)
P[1]	0.010		0.004	
Ascending (Right) Colon				
Absent	57 (91%)	46 (69%)	40 (64%)	24 (36%)
Small	6 (9%)	16 (24%)	23 (36%)	29 (43%)
Moderate	0	1 (2%)	0	10 (15%)
Excess	0	0	0	0
P[1]	0.020		< 0.001	
Transverse Colon				
Absent	58 (92%)	55 (82%)	43 (68%)	33 (49%)
Small	5 (8%)	6 (9%)	20 (32%)	20 (30%)
Moderate	0	1 (2%)	0	9 (13%)
Excess	0	1 (2%)	0	1 (2%)
P[1]	0.644		0.005	
Descending Colon				
Absent	58 (92%)	56 (84%)	42 (67%)	26 (39%)
Small	5 (8%)	6 (9%)	17 (27%)	32 (48%)
Moderate	0	1 (2%)	4 (6%)	5 (8%)
Excess	0	0	0	0
P[1]	0.763		0.013	
Sigmoid Colon/Rectum				
Absent	59 (94%)	54 (81%)	40 (64%)	32 (48%)
Small	3 (5%)	7 (10%)	20 (32%)	28 (42%)
Moderate	1 (1%)	3 (5%)	3 (5%)	5 (8%)
Excess	0	2 (3%)	0	0
P[1]	0.173		0.283	

[1]P-value for difference between treatments

There were no deaths or serious adverse events for patients who received SUPREP in this study. No statistically significant differences between the preparations with respect to adverse events were detected in the elderly population or overall. The number of events expected with gastrointestinal cleansing agents (e.g. nausea, bloating and cramping) was insignificant. Differences in laboratory results were considered by investigators to be clinically insignificant.

The BLI800-301 and BLI800-302 studies supported the FDA's determination that SUPREP was safe and effective in adults undergoing colonoscopy, leading to its FDA approval in August 2010.

As a condition of the SUPREP approval, FDA required Braintree Laboratories to conduct several post marketing studies in order to further demonstrate the safety of SUPREP in special populations (the elderly, and those with renal or hepatic impairment) and to look for rare occurring serious adverse events. In study BLI800-440 (PMR 1580-7), patients in special populations (renal/hepatic/elderly) took SUPREP prior to colonoscopy and were followed for 6 months. 184 patients took SUPREP in this study, which also included non-special population patients (e.g. patients undergoing screening colonoscopy). SUPREP was shown to be safe in all of these patient groups in near term and long term follow up, comparable to the GoLYTELY comparator used in the study.

Studies BLI800-430 and BLI800-431 (PMR 1580-8) evaluated the safety of SUPREP in special populations (renal/hepatic/elderly) through repeated ECG measurements. A total of 37 patients completed the study and no significant ECG changes were seen after patients took two SUPREP doses 2 hours apart (acute administration).

For study BLI800-450 (PMR 1580-6), a large retrospective review of electronic medical records and insurance claims was conducted to tabulate the rates of specific serious adverse events (e.g. cardiac events, rental failure, ischemic colitis) occurring within 3 months of patients taking SUPREP. Claims data on approximately 33,000

SUPREP patients and 266,000 control patients was analyzed, revealing no difference between groups for serious adverse events of interest.

Preliminary Development of BLI4700

The goal of the current study is to evaluate the safety and efficacy of BLI4700 given in a one day, split-dose regimen prior to colonoscopy in adult patients.

2. STUDY OBJECTIVE

The objective of this study is to evaluate the safety and efficacy of BLI4700 as a bowel preparation prior to colonoscopy in adult patients.

3. STUDY PLAN

3.1. Study Design

This is an open-label, multi-center study in adult subjects.

3.2.Number of Subjects

Up to 60 male and female subjects who are undergoing colonoscopy for routinely accepted indications will be enrolled in this study.

3.3. Duration of Study

Subject participation in this study will last up to 37 days. A screening visit (Visit 1) should be performed within 30 days of the colonoscopy. Subjects meeting all eligibility criteria will be enrolled to receive BLI4700. Subjects will return to the clinic the day of

colonoscopy (Visit 2). Subjects with clinically significant laboratory abnormalities and/or ongoing adverse events related to the study preparation may return for a follow up visit 7 days after colonoscopy.

3.4. Study Preparations

BLI4700 Tablets

Multiple BLI4700 formulations consisting of two 12 tablet doses may be evaluated in this trial. The two formulations contain the following active ingredients in solid form:

Formulation #1

Material and Grade	BLI4700 #1 (24 tablets)
Sodium Sulfate	
Potassium Bicarbonate	

Formulation #2

Material and Grade	BLI4700 #2 (24 tablets)
Sodium Sulfate, USP	
Potassium Bicarbonate	
Magnesium Chloride	

Subjects will consume a total of 24 tablets (two 12 tablet doses). Each tablet dose will be contained in a separate bottle. The bottles will have a clinical label containing a caution statement, study code, study sponsor and kit number. Subjects will be provided with instructions on how to complete the preparation.

Any additional formulations evaluated under this protocol will require a formal amendment and IRB approval prior to enrollment of subjects.

3.5. Subject Selection

3.5.1. Inclusion Criteria

Subjects will be admitted to the study if they are:

1. Male or female outpatients who are undergoing colonoscopy for a routinely accepted indication, including (but not limited to):

- Routine screening
- Polyp or neoplasm history
- Rectal bleeding
- Other gastrointestinal bleeding
- Abdominal pain
- Unknown diarrhea or constipation etiology
- Anemia of unknown etiology
- Inflammatory bowel disease
- Abnormal endosonography
- Evaluation of barium enema results
- Laser therapy

2. At least 18 years of age

3. Subjects must be scheduled for an afternoon colonoscopy (12:00PM or later)

4. If female, and of child-bearing potential, is using an acceptable form of birth control (hormonal birth control, IUD, double-barrier method, depot contraceptive, abstinent, or vasectomized spouse). Subjects practicing abstinence must agree to use an acceptable form of birth control should they become sexually active during the study. Pharmacologic methods of contraception must be stable for at least one month prior to Visit 1 and remain stable though completion of the study.

5. Negative urine pregnancy test at screening, if applicable

6. In the Investigator's judgment, subject is mentally competent to provide informed consent to participate in the study

3.5.2. Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Subjects with dysphagia or an aversion to swallowing tablets.

2. Subjects with known or suspected ileus, severe ulcerative colitis, gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis or megacolon.

3. Subjects who had previous significant gastrointestinal surgeries (e.g. colostomy, colectomy, gastric bypass, stomach stapling). Any questions regarding the

significance of a previous gastrointestinal surgery should be directed to Braintree Laboratories.

4. Subjects with uncontrolled pre-existing electrolyte abnormalities, or those with clinically significant electrolyte abnormalities based on Visit 1 laboratory results, such as hypernatremia, hyponatremia, hyperphosphatemia, hypokalemia, hypocalcemia, dehydration, or those secondary to the use of diuretics or angiotensin converting enzyme (ACE) inhibitors.

5. Subjects with a prior history of renal, liver or cardiac insufficiency (including congestive heart failure or other significant cardiac abnormality) that the investigator feels is clinically significant and should rule out the subject from participation in the study.

6. Subjects with impaired consciousness that predisposes them to pulmonary aspiration.

7. Subjects undergoing colonoscopy for foreign body removal and/or decompression.

8. Subjects who are pregnant or lactating, or intending to become pregnant during the study.

9. Subjects of childbearing potential who refuse a pregnancy test.

10. Subjects allergic to any preparation components.

11. Subjects who, in the opinion of the Investigator, should not be included in the study for any reason, including inability to follow study procedures.

12. Subjects who have participated in an investigational surgical, drug, or device study within the past 30 days.

13. Subjects who withdraw consent before completion of Visit 1 procedures.

4. STUDY PROCEDURES

Study procedures are described as follows and depicted graphically in Section 4.5, below.

4.1. Visit 1

Following the informed consent process, the subjects will sign a consent form. Subject's demographics and concomitant medications will be recorded, vital signs will be obtained (including height (visit 1 only), weight, pulse, orthostatic blood pressure), and a physical examination will be performed. Medical history will be recorded to include all ongoing conditions at Visit 1 as well as any significant conditions, defined

as:

Abdominal surgeries, Renal failure/dysfunction, Liver failure/dysfunction, Cardiac disorders (e.g. myocardial infarction, coronary artery disease tachycardia), Hypertension, Diabetes, Cancer (must indicate type of cancer), Electrolyte abnormalities

Blood samples will be collected for testing. Colonoscopies must be scheduled to allow for receipt of laboratory results prior to the day the subject is scheduled to begin preparation.

Serum Chemistry: Alkaline Phosphatase, ALT, anion gap (calculated), AST, bicarbonate, total bilirubin, blood urea nitrogen, calcium, chloride, creatinine kinase, creatinine, eGFR (calculate), GGT, magnesium, phosphorus, potassium, sodium, total protein and uric acid

A urine pregnancy test will be performed on female subjects of childbearing potential (see Section 4.7). Subjects meeting all entry criteria will be eligible for enrollment.

4.1.1. Study Drug

Eligible subjects will be provided with instructions on how to use the study preparation. Subjects will self-administer the study preparation starting the morning of their scheduled colonoscopy according to the instructions provided by the study site (full preparation instructions are included in Appendix A). Subjects will be instructed to bring the used preparation components when they return for colonoscopy.

Subjects that have clinically significant electrolyte abnormalities, in the opinion of the principle investigator, based on Visit 1 laboratory results must be discontinued from the study. Subjects must be notified and instructed to return their unopened bowel preparation to the study center. These subjects will be classified as screen failures. Returned un-used study drug kits will not be re-dispensed to another subject.

4.1.2. Dietary Restrictions

Subjects may have a light breakfast on the day before colonoscopy, followed by clear liquids until the colonoscopy is completed the following day.

Examples of acceptable clear liquids are provided below:

- Water
- Strained fruit juices (without pulp) including apple, orange, white grape, or white cranberry
- Limeade or lemonade
- Gatorade/ Powerade
- Ginger ale
- Coffee or tea (do not use any dairy or non-dairy creamer)
- Chicken broth
- Gelatin desserts without added fruit or topping

Note: Purple/Red liquids (including red/purple varieties of Gatorade/Powerade), Milk and Alcoholic beverages are not permitted.

Non-compliance with the dietary restrictions will be documented, but will not require separate reporting as a protocol violation.

4.1.3. Subject Questionnaires

Subjects will be provided with a Preparation Questionnaire and Dietary Questionnaire to report document their preparation and dietary intake (refer to Appendix B for full questionnaires). Subjects will complete the Dietary Questionnaire starting the day before the colonoscopy. The Preparation Questionnaires will start the morning of colonoscopy with the first dose of study drug (Dose 1) and continue through the second dose (Dose 2). The time of all food/fluid ingestion will be recorded. Site staff must review the descriptions and times recorded on the questionnaire at Visit 2 to confirm that subjects were compliant with the dietary restrictions outlined in Section 4.1.2.

4.2. Bowel Preparation Administration

On the day prior to their colonoscopy, subjects will begin following the protocol specified dietary restrictions (as outlined in Section 4.1.2) and completing their Dietary Questionnaires (refer to Appendix B). Approximately 8 hours prior to their scheduled

colonoscopy, subjects will begin consuming their bowel preparation according to the instructions provided by the study center (refer to Appendix A). Subjects will begin taking the second dose of bowel preparation 4 hours after starting the first dose.

4.3. Visit 2

After completing both preparation doses, subjects will return to the study center for their afternoon colonoscopy. Sites should attempt to schedule subjects a minimum of 4 days from date of screening to allow for receipt and review of screening lab results up to a maximum of 30 days. Visits scheduled beyond 30 days from Visit 1 will be considered a protocol violation and subjects must have a repeat blood draw.

Subjects will bring back their questionnaires and study personnel will review the questionnaires for completeness so that any missed responses can be captured. Subjects will complete a preference questionnaire. Any violations of the dietary restrictions must be confirmed with the subject.

Subject's vital signs will be repeated, a physical examination will be performed, and the subject will be queried for occurrence of adverse events and changes in concomitant medications. Blood samples will be collected for chemistry testing.

The colonoscopy will be performed by a physician according to the site's standard procedures and evaluated on a 4-point scale, as shown in Section 4.6. The colonoscopy procedure will be video recorded through the endoscope at selected research centers.

4.3.1. **Symptom Scale**

At Visit 2, subjects will complete a form asking them to report their overall experience with the preparation by checking the box that best describes the intensity of the following symptoms:

Symptom:	Scale:
Stomach Cramping	None – Severely Distressing

Stomach Bloating	None – Severely Distressing
Nausea	None – Severely Distressing

4.3.2. **Drug Accountability**

Subjects will be instructed to bring the used preparation components when they return for colonoscopy to determine compliance. Failure of a subject to return preparation components does not constitute a protocol violation. The staff members will perform drug accountability by counting any remaining BLI4700 tablets.

Returned study preparation materials must be accounted for on drug inventory log and will be returned to the Sponsor at the completion or termination of the study, unless instructed otherwise by the Sponsor.

4.4. Follow up of Adverse Events and Laboratory Results

Subjects who have ongoing adverse events related to the study preparation (except for those expected symptoms for which the subjects are prompted in their questionnaire) or abnormal laboratory values from Visit 2 blood draws that the investigator feels are clinically significant will return approximately 7 days following colonoscopy. Subjects with prior clinically significant abnormal laboratory values should undergo repeat testing. Subjects returning due to ongoing adverse events related to study preparation should be assessed to determine if the event has resolved or is clinically stable.

4.5. Tabulated Study Procedures

The following graphically depicts the flow of study procedures at each visit.

Procedures	Visit 1 Screening	Day before colonoscopy	Visit 2 Day of colonoscopy
Informed Consent	X		
Inclusion/Exclusion Criteria Review	X		
Medical History	X		
Physical Examination / Vital Signs	X		X
Review of Concomitant Medication	X		X
Blood Collection for Laboratory Testing	X		X
Urine Pregnancy Test (if applicable) [1]	X		
Dispense Drug	X		
Instruct Subject	X		
Dispense Preparation Questionnaire	X		
Subject Begins Following Dietary Restrictions		X	
Subject Takes Dose 1 of Preparation – approximately 8 hours prior to colonoscopy			X
Subject Takes Dose 2 of Preparation – 4 hours after starting Dose 1			X
Subject Completes Preparation Questionnaire			X
Subject Completes Symptom Scale and Preference Questionnaire[2]			X
Drug Accountability			X
Colonoscopy performed with Intra-procedural Safety and Efficacy Grading[3]			X
Collect and assess adverse event data[4]			X

[1] refer to Section 4.7 [2]to be dispensed and completed at Visit 2, prior to colonoscopy
[3]Colonoscopies will be recorded at selected research centers for transmission to sponsor
[4]Subjects with ongoing preparation-related AEs/clinically significant lab results may need to return on follow up Day 7

4.6 Physician Assessments

4.6.1 Segmental Cleansing Assessment

During the exam, the colonoscopist will rate each colon segment (proximal, mid, distal) using the following 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

4.6.2 Overall Cleansing Assessment

Following completion of the procedure, the colonoscopist will provide a global rating of preparation quality for the entire colon (inclusive of their perception of all segments) using the scale outlined in Section 4.6.1.

4.6.3 Additional Efficacy Measures

In addition, the following data will be collected:

1. Adequacy of preparation according to the colonoscopist. If the preparation was not adequate, the need for re-preparation will be recorded.
2. Start time of colonoscopy.
3. Time of cecal intubation.
4. Completion time of colonoscopy.
5. Volume of water used to improve visualization.

4.7. Pregnancy

Subjects that are female and of childbearing potential must have a urine pregnancy test done at screening. A positive result will rule out the participation of the subject in the study.

Female study subjects must be surgically sterilized or use oral contraceptives, depot contraceptives, double-barrier method, intrauterine device, or testify that she is monogamous with a vasectomized partner, or practices abstinence and will continue to do so during the duration of study. Subjects practicing abstinence must agree to use an acceptable form of birth control should they become sexually active during the study. Women who are post-menopausal (as defined in this section), or have had a partial or total hysterectomy or tubal ligation are not considered of child bearing potential.

Oral contraceptives, hormone implants, and injections should be stable for at least 1 month before the study, until completion of the study. Subjects are not allowed to change their birth control method during the course of the study.

Menopausal status is defined when menses have been absent for 12 months in a woman of appropriate age (usually 45 to 55 years) who has no other suspected or identified cause of amenorrheas.

If a subject becomes pregnant during the study, the subject must be removed from the study and followed until one month after the end of the pregnancy. A pregnancy will not be recorded as an adverse event.

4.8. Concomitant Medications

The use of concomitant medication will be recorded from 7 days prior to screening until completion the study, including intravenous fluids administered during colonoscopy.

5. ADVERSE EVENTS

5.1. Adverse Event Definition and Reporting

An Adverse Event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product. Subjects will be queried for any problems they experienced during and after preparation by site personnel. Symptoms on the symptom scale rated as 2 (mild) to 5 (severely distressing) must be reported as an adverse event. Colonoscopy and biopsy findings are not considered adverse events unless considered by the investigator to be related to the preparation or colonoscopy procedure.

Adverse event collection will commence at the time the patient provides informed consent. Subjects that have an ongoing treatment emergent adverse event or clinically significant abnormal laboratory value will be followed up approximately one week after colonoscopy.

Subjects will be instructed to promptly report adverse events to the Investigator. The Investigator will record date/time of report, date/time of onset, description of the adverse event, severity of adverse event, action(s) taken regarding treatment of the event, action(s) taken regarding study participation, duration of adverse event, and the Investigator's assessment of relationship of adverse event to study preparation.

The Investigator should assess the severity of each adverse event using the following categories:

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

The Investigator should assess the relationship to study drug for each adverse event using the following categories:

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*.

5.2 Expected Adverse Events

Because BLI4700 tablets contain the same active ingredient (sodium sulfate) as SUPREP, a similar adverse event profile is expected. In Phase 3 clinical trials, the most frequent adverse events reported by patients taking SUPREP (reported by >3% of patients) included overall discomfort, abdominal pain and distension, nausea, and vomiting.

6. SERIOUS ADVERSE REACTIONS AND DISCONTINUATION OF STUDY

A Serious Adverse Event (SAE) is any untoward medical occurrence that results in at least one of the following outcomes:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect
- Requires medical or surgical intervention to prevent permanent impairment or damage

SAE collection will coincide with the patient beginning the study preparation and will conclude 30 days after colonoscopy. Pre-scheduled or elective surgeries will not be considered serious adverse events. Should a serious and/or unexpected adverse event occur, the Investigator will notify Braintree Laboratories immediately or no later than 24 hours after gaining knowledge of the event. The Investigator will make a decision regarding continuing study participation, and may request input from Braintree Laboratories. The Investigator will be responsible for recommending or providing the patient with appropriate medical therapy. All patients experiencing serious adverse events will be followed until clinically stable.

Braintree Laboratories must be kept apprised of all follow-up information related to serious adverse events. In addition, Investigators must comply with the SAE reporting requirements of the Institutional Review Board with oversight of the study.

Any serious and/or unexpected adverse events that occur during the study will be reported to Braintree Laboratories as follows:

Contact Telephone Numbers:

During Business hours
(M-F, 8:30 am – 5:00 pm EDT)
After hours or weekends

Braintree Laboratories and its medical monitor will review the report and determine whether an FDA Form 3500A will also be completed and sent to FDA.

7. INSTITUTIONAL REVIEW BOARD (IRB) AND INFORMED CONSENT

IRB review and approval of the study protocol and Informed Consent Form will be obtained prior to initiation of the study. Amendments to the study protocol and consent form generated during the course of the study will also require IRB approval.

8. MANAGEMENT OF INTERCURRENT EVENTS

8.1. Modification of Protocol

Investigators may request an exemption from Braintree Laboratories to enroll a subject with questionable eligibility or to continue a subject with a protocol violation. Note that eligibility criteria exemptions may require pre-approval from the Institutional Review Board. Investigators that continually violate the protocol or commit a serious violation may be subject to termination from the study. The study may be halted if at any time an Investigator or Braintree Laboratories deems the incidence or severity of adverse events to be unacceptable.

8.2. Subjects Discontinued from the Study

Subjects may be dropped from the study for any of the following reasons:

- An adverse event requiring discontinuation (including failure to tolerate study medication).
- Female participants who become pregnant during the study period.
- Major protocol deviation from the study design by the subject that is observed or suspected by the Investigator
- Subject chooses to withdraw from the study, for whatever reason.
- Subject is lost to follow-up.
- The Sponsor initiates an early discontinuation of the study.
- The subject is withdrawn at the discretion of the Investigator.

Braintree should be contacted if possible prior to discontinuation of any subject.

9. DATA ANALYSIS

9.1. Study Endpoints - Efficacy

Primary efficacy will be assessed on the basis of a binary outcome of overall preparation success or failure. The following definition of preparation success and failure will be used:

<u>Definition of successful preparation:</u>

1. Overall Cleansing Assessment by the colonoscopist (Section 4.6.2) of "Excellent" or "Good" and does not satisfy any of the following failure criteria.

Definition of failed preparation:

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

3. Any subject for whom cleaning was not adequate for evaluation.

Inevaluable Patients:

Subjects who were dispensed a kit but withdrew from the study prior to taking any preparation (including subjects who were disqualified subsequent to Visit 1 based on screening laboratory results) are excluded from the efficacy and safety analyses. Any subject who completely or partially took study preparation but did not have a colonoscopy due to non-preparation related reasons will not be included in the efficacy analyses. All treated subjects will be included in the safety analysis.

Additional efficacy endpoints will include:

- Number (%) of excellent preparations overall and by segment
- Adequacy of cleaning and need for re-preparation
- Duration of colonoscopy
- Volume of intraprocedural water needed to irrigate the colon
- Number (%) of procedures that reached the cecum
- Time to cecum

9.2. Study Endpoints - Safety

Adverse Events:

All subjects who took preparation in any amount will be included in the safety analysis. All adverse events will be summarized based on the principle of treatment emergence. A sign or symptom will be regarded as treatment-emergent if it was present prior to the first dose and subsequently worsened in severity, or was not present prior to the first dose but subsequently appeared.

In order to define treatment emergence for events with missing start or stop dates the following additional criteria will be used:

- if both the onset and resolution dates for a particular event are missing, then the event is considered treatment-emergent;
- if the onset date for an event is missing and the resolution date falls after the initiation of the first dose, then the event is considered treatment-emergent;

- if the onset date for an event falls after the initiation of the first dose and the resolution date is missing or present, then the event is considered treatment-emergent; and
- if the onset date for an event falls before the initiation of the first dose and the stop date is missing or present, then the event is not considered treatment-emergent.

Adverse events will be collected using MedDRA category designations for body system and preferred term. The number and percent of subjects who experienced each adverse event will be presented in a tabular form.

Vitals Signs and Physical Examination:
Vital signs and physical examination data will be summarized with descriptive statistics.

Laboratory Data:
Results of laboratory tests for the change from baseline (Screening) will be summarized with descriptive statistics.

Symptom Questionnaire Data:
Symptom questionnaire data for individual symptoms for Overall Experience (Stomach Cramping, Stomach Bloating and Nausea) will be presented.

9.3. Sample Size

Up to 60 subjects may be enrolled and treated in the study. This size was chosen because of the pilot nature of this study.

10. DRUG INVENTORY AND DISPOSITION

At the conclusion of the study, all drug materials will be accounted for. Federal law requires that, at the conclusion of the study, all drug materials must be returned to the study sponsor or destroyed according to local regulations.

11. STUDY MONITORING

A Braintree Laboratories Study Monitor or qualified designee will visit each study center prior to the commencement of the study and periodically during the course of the study in accordance with federal guidelines governing the sponsorship of studies.

12. DOCUMENTS AND NOTIFICATIONS

12.1. Informed Consent

Written informed consent will be obtained from the subjects by study personnel and will be kept on file at the study center. Documentation of the consent process should be noted in the study source documents.

12.2. Institutional Review Board

Peer review and approval of the protocol by an appropriate Institutional Review Board is required prior to commencement of enrollment. Amendments to the approved protocol must also be submitted to the Institutional Review Board and approved prior to their implementation.

12.3. Amendments to the Protocol

If Braintree Laboratories determines that there is need for an amendment, it will be produced in writing by Braintree Laboratories and will be made a formal part of the protocol following its submission and approval from the IRB.

12.4. Data Records

Braintree Laboratories will provide data collection forms for each subject. Subject medical records will be reviewed to verify all other data points, including potential adverse events. Copies of subjects' laboratory reports, colonoscopy and pathology

reports (if applicable) will be collected for Braintree Laboratories after subject identifiers have been redacted by site staff. Colonoscopies at selected research centers will be recorded and transmitted to Braintree Laboratories. The Investigator should retain copies of the subject consent forms and other study documents for a period of two years following the date of approval of a New Drug Application or supplement for BLI4700, or, if the application is not approved, for two years after the drug investigation program is discontinued. The study investigator will notify Braintree Laboratories of their intent to dispose of the study records and allow Braintree to take possession of such records. Study records will be made available at reasonable times for inspection and copying if requested by a properly authorized employee of Braintree Laboratories, authorized Braintree Laboratories designee or the Department of Health and Human Services in accordance with federal regulations.

13. PUBLICATION AND AGREEMENT

The results of this study will be published if mutually agreed by Braintree Laboratories and the Investigator and at a mutually agreed upon date. Investigator agrees to submit to Braintree Laboratories, within sixty (60) days of the proposed submission date, any proposed publication or presentation for prior review. Braintree Laboratories will, within thirty (30) days after receipt, advise if there is any proprietary or patentable information, which should not be disclosed at the present time. Investigator shall not release any such proposed publication or presentation, if so notified by Braintree Laboratories.

14. INVESTIGATORS AGREEMENT

I agree to perform the protocol according to Federal Regulations and as detailed in this document to the best of my ability. I recognize that if I fail to do so my participation in this study may be terminated. I also agree to the publication provisions stated in Section 13, above. My signature on the cover page of this protocol serves as documentation of my acceptance of the terms noted above.

15. REFERENCES

1 - Di Palma JA, Rodriguez R, McGowan J, Cleveland MvB. A randomized clinical study evaluating the safety and efficacy of a new, reduced-volume, oral sulfate colon-cleansing preparation for colonoscopy.Am J Gastroenterol. 2009;104:2275-2284.

2 - Rex DK, Di Palma JA, Rodriguez R, McGowan J, Cleveland M. A randomized clinical study comparing reduced-volume oral sulfate solution with standard 4-liter sulfate-free electrolyte lavage solution as preparation for colonoscopy.Gastrointest Endosc. 2010;72:328-336.

3 - Markowitz GS, Stokes MB, Radhakrishnan J, D'Agati VD. Acute phosphate nephropathy following oral sodium phosphate bowel purgative: an underrecognized cause of chronic renal failure J Am Soc Nephrol.2005; 16(11):3389-96.

4 - Davis GR, Santa Ana CA, Morawski SG, Fordtran JS. Development of a lavage solution associated with minimal water and electrolyte absorption or secretion. Gastroenterology. 1980 May;78(5 Pt 1):991-5.

5 - DiPalma JA, Marshall JB. Comparison of a new sulfate-free polyethylene glycol electrolyte lavage solution versus a standard solution for colonoscopy cleansing. Gastrointestinal Endoscopy.1990;36:285-289.

6 - DiPalma JA, Wolff BG, Meagher A, Cleveland MvB. Comparison of reduced volume versus four liters sulfate-free electrolyte lavage solutions for colonoscopy colon cleansing. Amer. J. Gastro.2003;98:2187-2191.

APPENDIX A: PREPARATION INSTRUCTIONS

APPENDIX B: PATIENT QUESTIONNAIRES