NCT03261960

STUDY PROTOCOL

A Safety and Efficacy Comparison of BLI4700 Bowel Preparation versus an FDA-approved Comparator in Adult Subjects prior to Colonoscopy

DOCUMENT DATE: 07/28/2017

A Safety and Efficacy Comparison of BLI4700 Bowel Preparation versus an FDA-approved Comparator in Adult Subjects prior to Colonoscopy

Braintree Protocol BLI4700-302

Version Dated 7-28-17

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_____
Principal Investigator Name (printed)

CLINICAL PROTOCOL SUMMARY SHEET

STUDY TITLE: A Safety and Efficacy Comparison of BLI4700 Bowel Preparation versus an FDA-approved Comparator in Adult Subjects prior to Colonoscopy

PROTOCOL: BLI4700-302

VERSION DATE: 7-28-17

IND NUMBER: 124,988

STUDY PHASE: 3

OBJECTIVE: To compare the safety and efficacy of BLI4700 bowel preparation to PREPOPIK as 2-day, split-dose bowel preparations prior to colonoscopy in adult patients.

STUDY DESIGN: This will be a randomized, parallel, multi-center, single-blind study.

SUBJECTS: Approximately 400 male and female adult subjects will be enrolled and undergo colonoscopy. It is anticipated that approximately 450 subjects will be randomized to achieve 400 completed colonoscopies.

STUDY MEDICATIONS:
Treatment 1: BLI4700 bowel preparation
Treatment 2: PREPOPIK

DURATION: Subject participation in this study may last up to 60 days.

EFFICACY ENDPOINTS: Efficacy will be based on overall preparation success as determined by the blinded 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 and hematology parameters
- Subject reported prep-related symptoms
- Orthostatic heart rate and blood pressure

1. INTRODUCTION

2. STUDY OBJECTIVE

The objective of this study is to compare the safety and efficacy of BLI4700 to PREPOPIK as 2-day, split-dose bowel preparations prior to colonoscopy in adult patients.

3. STUDY PLAN

3.1. Study Design

This is a randomized, parallel, multi-center, single-blind study in adult subjects.

3.2.Number of Subjects

Approximately 450 male and female subjects who are undergoing colonoscopy for routinely accepted indications will be enrolled in this study. Enrolment will continue until approximately 400 subjects have undergone a colonoscopy.

3.3. Duration of Study

Subject participation in this study will last up to 60 days. A screening visit (Visit 1) should be performed within 30 days of the colonoscopy. Subjects meeting all eligibility criteria during the screening visit will be assigned to receive either BLI4700 or PREPOPIK using a dynamic minimization scheme. Subjects will return to the clinic for Visit 2 on the day of their colonoscopy. A follow up visit (Visit 3) will occur 24-48 hours after colonoscopy. Subjects with abnormal laboratory values and/or ongoing adverse events will have follow-up visits 7 days after colonoscopy (Visit 4) and 30 days after colonoscopy (Visit 5), if needed.

3.4. Study Preparations

BLI4700 Tablets

Subjects will consume a total of 24 tablets (two 12 tablet doses). Each 12 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.

PREPOPIK

PREPOPIK (Ferring Pharmaceuticals, Inc.) is FDA approved for cleansing of the colon as preparation for colonoscopy in adults. PREPOPIK consists of 2 packets, each holding 16.1 grams of powder for oral solution. Each packet contains 10mg sodium picosulfate, 3.5g magnesium oxide and 12g anhydrous citric acid. PREPOPIK will be provided to the subject in clinical packaging with a label containing a caution statement, study code, study sponsor and kit number. Subjects will be provided with instructions on how to complete the preparation.

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. 18 to 85 years of age (inclusive)

3. 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 until 1 month after colonoscopy.

4. Negative serum pregnancy test at screening, if applicable

5. 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, gastrointestinal obstruction, gastroparesis, gastric retention, bowel perforation, toxic colitis or megacolon.

3. Subjects with ongoing severe, acute inflammatory bowel disease

4. Subjects who had previous significant gastrointestinal surgeries (e.g. colostomy, colectomy, gastric bypass, gastric banding, stomach stapling). Any questions regarding the significance of a previous gastrointestinal surgery should be directed to Braintree Laboratories.

5. Subjects with uncontrolled pre-existing electrolyte abnormalities, or those with clinically significant electrolyte abnormalities based on Visit 1 laboratory results.

   Subjects with Visit 1 laboratory results outside the following ranges will be excluded regardless of investigator assessment of clinical significance:

   - Serum sodium > 150 mmol/L or < 132 mmol/L
   - Serum potassium > 5.5 mmol/L or < 3.5 mmol/L
   - Serum magnesium > 2.7 mg/dL or < 1.2 mg/dL

6. Subjects taking diuretics, anti-hypertensive medications, including angiotensin converting enzyme (ACE) inhibitors and Angiotensin II receptor blockers (ARBs), or chronic NSAIDs, that have not been stable for 30 days. NSAID use for occasional pain is not exclusionary.

7. Subjects with uncontrolled hypertension (systolic blood pressure > 170 mmHg and diastolic blood pressure > 100 mmHg).

8. Subjects taking antibiotics within 7 days of colonoscopy.

9. Subjects with severe renal insufficiency (GFR < 30 mL/min/1.73m^2).

10. Subjects with known severe hepatic insufficiency (Child Pugh C)

11. Subjects with cardiac insufficiency (NYHA Functional Classifications 3 or 4).

12. Subjects with an abnormal and clinically significant physical examination or ECG finding at Visit 1.

13. Subjects undergoing insulin therapy for any indication.

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

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

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

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

    Subjects allergic to any BLI4700 components

19. Subjects using drugs of abuse, including abused prescription medications.

20. Subjects who are withdrawing from alcohol or benzodiazepines.

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

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

23. 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

At the screening visit, the following procedures will be undertaken:

- Subject is fully informed about the study and gives written agreement to study participation in the form of a signed informed consent form (refer to Section 4.1.1) and assign a subject number
- Assess eligibility (refer to inclusion/exclusion criteria)
- Review of medications
- Medical history - 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

- Physical examination
- Vital signs: including assessment of orthostatic hypotension (while seated and after standing for a minimum of 2 minutes) including height and bodyweight, pulse, respiratory rate and temperature
- A 12-lead ECG will be performed by qualified, trained site personnel. ECG output must be reviewed by a physician investigator. Any clinically significant cardiac abnormalities identified on the ECG should disqualify a subject. Data from the ECG will be collected in the eCRF.
- Blood samples will be collected for testing at a central laboratory, as shown below.

  Serum Chemistry: ALT, anion gap (calculated), AST, bicarbonate, total bilirubin, blood urea nitrogen, calcium, chloride, creatine kinase, creatinine, eGFR (calculated), GGT, magnesium, phosphorus, potassium, sodium, sulfate (Visits 1, 2 and 3 only), total protein, uric acid and osmolality. Creatine kinase results > 2.5 times the upper normal limit will trigger a test for CK-MB.

  Hematology: Basophils, HCT, HGB, Lymphocytes, MCH, MCV, MPV, Neutrophils, Platelets, RBC, WBC

  Urinalysis: dipstick analysis (Visits 1, 2 and 3 only). Urine positive for bacteria will require follow-up if the investigator believes the result is due to urinary tract infection.

Investigators will be instructed to comment on all out of range values for clinical significance. For critical values (those indicative of a potential safety concern), investigators will be contacted by the central laboratory. Critical value alert levels are listed in the laboratory manual.

A serum 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. **Informed Consent**

Following the informed consent process, study subjects will sign a current IRB approved consent form. No study procedures may be performed prior to the subject providing informed consent. The subject's original signed and personally dated Informed Consent Form (together with any subsequent IRB approved amended versions) must be retained

by the Investigator in the subject's file. A copy of the original signed and dated Informed Consent Form must be given to the subject.

4.1.2. **Treatment Assignment / Blinding**

Subjects that meet all eligibility criteria will be assigned to a treatment group by a dynamic minimization scheme[7] implemented using an automated interactive web response system (IWRS). At the time of enrollment the IWRS will assign a drug kit number for site personnel to dispense to the subject. Subjects will be stratified into one of the following three groups. Subjects meeting Group 1 criteria will be assigned to Group 1 regardless of whether or not they meet the Group 2 criterion.

Group 1: Subjects 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 $\geq$ 35

Group 2: Subjects scheduled for a colonoscopy 12:00 PM or later

Group 3: Subjects not meeting Group 1 or 2 criteria

In this single-blinded study, to ensure an unbiased evaluation of the study preparations, the colonoscopist will not be allowed to perform any study drug related activities (treatment assignment, drug dispensing, return and accountability). Any failure to maintain blinding of the treatment to the colonoscopist will be documented as a

protocol violation. Subjects will be instructed not to discuss their study preparation assignment study staff members.

4.1.3. **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 evening prior to 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.

4.1.4. **Dietary Restrictions**

BLI4700

Subjects assigned to BLI4700 will take their first 12 tablet dose the evening before colonoscopy. This will be followed no less than four hours later by the second 12 tablet dose. The second 12 tablet dose should be taken 5 to 8 hours before the colonoscopy. BLI4700 subjects may have a low residue breakfast on the day before colonoscopy, followed by clear liquids until the colonoscopy is completed the following day. Examples of low residue foods will be provided in the subject preparation instructions (Appendix A).

PREPOPIK

Subjects assigned to PREPOPIK will take their PREPOPIK according to manufacturer's labeling for split-dose administration. These subjects may have clear liquids only on the day before their colonoscopy. This clear liquid diet must be followed until the subject completes their colonoscopy on 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 as a protocol violation, but will not require reporting to the IRB.

4.1.5. **Medication Restrictions**

Subjects assigned to Prepopik will be instructed to refrain from taking the following medications starting 2 hours prior to the start of Prepopik until 6 hours after completing Prepopik to avoid chelation with magnesium:

- Tetracycline
- Fluoroquinolone antibiotics
- Iron
- Digoxin (Lanoxin)
- Chlorpromazine
- Penicillamine (Cuprimine, Depen)

Subjects in both preparation groups will be educated that oral medication administered within one hour of the start of administration of the bowel preparation may be flushed from the GI tract and the medication may not be absorbed.

4.1.6. **Subject Questionnaires**

Subjects will be provided with a Preparation Questionnaire and Dietary Questionnaire to document their preparation and dietary intake (refer to Appendix A for full

questionnaires). Subjects will complete the Dietary Questionnaire starting the day before the colonoscopy. Completion of the Preparation Questionnaire will commence with Dose 1 on the day before colonoscopy and continue through the completion of the required clear liquids after Dose 2 the following day. 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 4.1.4.

Subjects that take any amount of bowel preparation (but do not have a colonoscopy performed) should still return for safety follow-up as outlined in Sections 4.2 – 4.4.

4.2. Visit 2

After completing both preparation doses, subjects will return to the study center for their 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. Due to follow-up requirements for laboratory testing within 24 – 48 hours of Visit 2 (See Section 4.3), colonoscopies may not be performed on a Friday unless the research center is open on Saturday or Sunday to collect a follow-up blood sample.

Subjects will bring back their questionnaires and study personnel will review the questionnaires for completeness so that any missed responses can be captured. Any violations of the dietary restrictions must be confirmed with the subject. Study personnel will perform drug accountability as described in Section 4.2.1.

Vital signs will be taken. A 12-lead ECG will be performed by qualified, trained site personnel. ECG output must be reviewed by a physician investigator and subjects with a clinically significant abnormal result must be discontinued prior to colonoscopy. A physical examination will be performed. Subjects will be queried for expected preparation symptoms using the Symptom Scale (see Section 4.2.2) or changes to their concomitant medications. Subjects will complete a Preference Questionnaire (See

Appendix A). Blood samples for chemistry and hematology testing will be taken as outlined in Section 4.1.

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. A designated vendor will provide standardized video recording capabilities and centralized reading by an independent gastroenterologist. A subset of colonoscopies will be reviewed and graded by the central reader for the primary endpoint (overall cleansing assessment). The procedures and requirements for recording and transmitting colonoscopy videos will be outlined in a separate manual.

Endoscopists should limit the use of water flush to that necessary to achieve the cleansing required to achieve adequate visualization. Water immersion and/or exchange technique should be avoided unless it is medically indicated.

4.2.1. **Drug Accountability**

Subjects will be instructed to bring their used and unused preparation components when they return for colonoscopy to determine compliance. Failure of a subject to return preparation components does not constitute a protocol violation. In order to maintain the blinding, only the unblinded staff members will process drug returns. The unblinded staff members will perform drug accountability by assessing the number of used PREPOPIK packets and counting any remaining BLI4700 tablets. The subjects will be instructed not to discuss their study preparation with any staff member. Failure of staff members to maintain blinding of the treatment will be documented as a protocol violation.

All used and unused components of study preparation 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.

4.2.2. **Symptom Scale**

At Visit 2 (prior to sedation), study personnel will ask subjects to report their experience with the preparation for the most frequently occurring bowel preparation symptoms of

stomach cramping, stomach bloating, nausea and vomiting. Subjects reporting these symptoms will be asked to rate the intensity as mild, moderate or severe.

4.3. Visit 3: 24 – 48 Hours Post Colonoscopy

Subjects will return 24 – 48 hours following colonoscopy for follow-up. Blood samples will be collected for serum chemistry and hematology testing. Subjects will be queried for occurrence of adverse events and changes in concomitant medications. Subjects will be queried for information pertaining to the onset and treatment of serious adverse events occurring following the colonoscopy, and adverse events that were ongoing at Visit 2. Vital signs will be taken. A 12-lead ECG will be performed by qualified, trained site personnel. ECG output must be reviewed by a physician investigator. Subjects with abnormal and clinically significant ECG results at Visit 3 must return for follow up visits as outlined in Section 4.4.

Subjects that miss Visit 3 must return for follow-up Visit 4. If these subjects have no out of range laboratory values (that were not pre-existing at Visit 1) and/or ongoing adverse events at Visit 4, Day 30 follow-up may be performed via telephone (See Section 4.4.1).

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

Subjects with out of range laboratory values (that were not pre-existing at Visit 1) and/or ongoing adverse events at Visit 3 will return for follow up on Day 7 (+/- 2 days) and Day 30 (+/- 2 days). Subjects requiring follow-up for abnormal laboratory values must undergo repeat testing. Subjects returning due to ongoing adverse events should be assessed to determine if the event has resolved or is clinically stable.

4.4.1. End of Study Telephone Call

Subjects that do not have new or ongoing adverse events or abnormal laboratory results at Visit 3 that require follow up (per Section 4.4) will have an End of Study telephone call 30 days (+/-_2 days) after colonoscopy. During this call, study personnel will ask if any new adverse events have occurred since Visit 3 and if the subject has had any changes to their concomitant medications.

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**	**Visit 3** **24-48 hrs post colonoscopy**	**Visit 4** **Day 7** (+/- 2 days) *if needed*	**Visit 5** **Day 30** (+/- 2 days) *if needed*	**Day 30[4]** (+/- 2 days) *if by telephone*
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) [1]	X						
Treatment Assignment[2]	X						
Dispense Drug and Questionnaires [2]	X						
Subjects Begin Questionnaires		X					
Subjects Take Bowel Preparations		X	X				
Symptom Scale & Preference Questionnaire Completed[3]			X				
Drug Accountability[2]			X				
Colonoscopy performed with Intra-procedural Safety and Efficacy Grading			X				
Collect and assess adverse event data			X	X	X	X	X

[1] refer to Section 4.7 [2]to be performed by unblinded personnel only [3]to be completed at Visit 2 prior to sedation
[4]Day 30 follow-up may be performed by telephone for subjects with no new or ongoing AEs or lab abnormalities at Visit 3

4.6. Physician Assessments

4.6.1. Segmental Cleansing Assessment

The blinded colonoscopist will rate each colon segment (proximal, mid, distal) using the following scale, factoring in the amount of effort required during both insertion and withdrawal.

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 and after each segment has been rated, the blinded 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 blinded 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. Impact of preparation quality on surveillance interval
6. Volume of water used to improve visualization (investigator's will need to specify cases where a water immersion technique was utilized)

4.7. Pregnancy

Subjects that are female and of childbearing potential must have a serum 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 1 month after colonoscopy.

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 amenorrhea.

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 of the study, including sedation medications and intravenous fluids administered during colonoscopy. Laxatives should not be used within 72 hours of beginning the study preparation.

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. Any symptom on the symptom scale rated as mild, moderate or severe 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 and conclude 30 days after preparation exposure.

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

BLI4700

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.

PREPOPIK

In Phase 3 clinical trials, the most frequent adverse events reported by patients taking PREPOPIK (reported by >1% of patients) included nausea, vomiting and headache[4].

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 providing informed consent to participate in the study and will conclude 30 days after preparation exposure. Pre-scheduled or elective surgeries (that do not represent a worsening of a pre-existing condition) 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 satisfactory resolution occurs.

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:

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

Neither an Investigator nor Braintree Laboratories will modify the protocol without first obtaining the concurrence of the other and the IRB. 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 discontinued 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.

8.3 Safety Interim Monitoring – Study Stopping Rule

Adverse event data will be monitored on an ongoing basis. Adverse event terms from the study that are listed in the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) under the system organ classes (SOCs) of Cardiac Disorders, Renal and Urinary Disorders and Metabolism and Nutrition Disorders will be reviewed as part of the study stopping rule.

Braintree Laboratories will consider stopping the study if ≥ 2 subjects develop the same adverse reaction (based on the MedDRA preferred term) listed in the Cardiac, Renal and Urinary, and Metabolism and Nutrition SOCs of Grade 3, or if a single subject develops one of the listed adverse reactions of Grade 4 or higher.

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. For statistical analyses, the following definition of preparation success and failure will be used:

Definition of successful preparation:

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 (subject report of 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

Unevaluable Subjects:

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 (e.g. lack of insurance, inability to return for colonoscopy) will not be included in the efficacy analyses. All treated subjects will be included in the safety analysis.

Success rate will be analyzed using CMH Chi-square adjusting for the effect of investigator site. The formal hypothesis test result (p-value) for treatment difference will be presented together with a two-sided 95% confidence interval for the difference.

Null Hypothesis H0: $P1-P2 \leq D0$ versus Alternative Hypothesis H1: $P1-P2 > D0$,

where P1 is the success probability in the BLI4700 group, P2 is the success probability in the PREPOPIK group (reference or control group), and D0 is the acceptable margin of equivalence, which we set equal to −10%.

If necessary, we will pool the smallest centers into a "small-centers" stratum until each treatment arm in the smallest stratum has at least ten subjects.

If the test for non-inferiority is statistically significant, we will conduct a test of the superiority hypothesis:

Null Hypothesis H0: P1−P2<=0 versus Alternative Hypothesis H1: P1−P2>0.

The two hypothesis tests are hierarchically structured so that the second test will be conducted only if the first test rejects the hypothesis of inferiority. Thus there is no need to correct the alpha levels of the tests for multiplicity.

Sensitivity analyses will be performed for the primary endpoint based on stratification groups outlined in Section 4.1.2.

Additional efficacy endpoints will include:

- Cleansing score by segment
- 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

Secondary endpoints will be analyzed in a manner similar to the primary analysis using the CMH test adjusting for site effects for count (percentage) outcomes and two-way ANOVA with terms for treatment, site, and their interaction for continuous responses. No adjustment will be made for multiplicity in testing the secondary endpoints. P values will be presented for hypothesis tests, and two-sided 95% confidence intervals for estimates of treatment effects.

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 analyzed 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. Individual tables will be provided for treatment-emergent adverse events, treatment-emergent adverse events by relationship to study drug, and treatment-emergent adverse events by severity. The difference in adverse events between study populations will be tested by the Fisher's exact test together with a 95% confidence interval for the treatment effect estimate.

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) and treatment group differences will be tested using ANOVA. In addition, shift tables will be presented to describe changes in lab parameter values between screening and post-treatment time points using normal range categories (low, normal, high).

Symptom Scale Data:

Symptom Scale data for individual symptoms for Overall Experience (stomach cramping, stomach bloating, nausea and vomiting) will be presented categorically by severity and tested by Chi-Square test.

9.3. Sample Size

Approximately four hundred (400) subjects will be randomly assigned via the minimization scheme to one of two preparations in a ratio of 1:1 (200 subjects per group) and undergo colonoscopy. Based on prior studies using a similar grading system, the success rate for PREPOPIK is expected to be no greater than 90%[4]. Assuming a similar success rate for BLI4700, a two-sided asymptotic 95% confidence interval for the difference in success rates between groups (BLI4700 – PREPOPIK) will result in a lower CI bound greater than -10%, with probability 90%. This result would establish the non-inferiority of BLI4700 to PREPOPIK for a non-inferiority margin of 10%.

Our sample-size calculations for equivalence tests with a binary outcome use the method of Chow et al[5]. If the PREPOPIK success rate is 90% and the BLI4700 success rate is also 90%, the sample size needed is n=310 (total across both study groups) for a non-inferiority margin of 10% and a target power of 90% with confidence 95%. Thus with n=400 subjects we will attain 80% power even with a dropout rate in excess of 20%.

In randomized studies, the purpose of the stratification is to eliminate the stratification factor from the error term, thereby potentially reducing variability[6]. Moreover, because the trial will use stratification in the design, for consistency we will employ a stratified test in the analysis. The CMH analysis on risk differences, by eliminating center effects, essentially renders the analysis equivalent to that of a single-center study. The sample-size calculation described above assumes a single stratum that is free of between-stratum variability and therefore effectively models the stratified analysis that we will conduct.

9.4. Study Populations

The following populations have been defined for data analyses.

9.4.1. Intention-to-Treat (ITT) Population

This population includes all subjects assigned to treatment and will be used for sensitivity analysis of the primary efficacy endpoint.

9.4.2. Modified Intention-to-Treat (mITT) Population

This population consists of all enrolled subjects that took any portion of the study preparation. This population will be utilized for primary and secondary efficacy analyses and all safety analyses.

9.4.3. Per-Protocol Population

The per protocol (PP) population will consist of all subjects in the mITT population who consumed the entire bowel preparation solution and/or tablets and who have not violated the study eligibility criteria and have not deviated significantly from the protocol during the course of the study. This population will be utilized for the primary and secondary efficacy analyses. Any efficacy analyses from this population will be considered as supportive to the ITT and mITT analyses. Reasons for exclusion from the PP population will be defined prospectively in the statistical analysis plan and prior to unblinding of the data.

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

Site personnel will be required to enter study data into electronic case report forms (eCRFs) provided by Braintree Laboratories. Subject medical records will be reviewed to verify study data points, including potential adverse events, and to

ensure correctness and consistency with the CRF entries. 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. The Investigator should retain copies of paper and electronic data, patient consent/assent 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. These records will be made available at reasonable times for inspection and copying if requested by a properly authorized employee of Braintree Laboratories or the Department of Health and Human Services in accordance with federal regulations.

13. PUBLICATION AND AGREEMENT

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

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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.

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5 – Chow S, Shao J, Wang H. 2008. Sample Size Calculations in Clinical Research. 2nd Ed. Chapman & Hall/CRC Biostatistics Series. P. 91.

6 – Fleiss JL. 1986. The Design and Analysis of Clinical Experiments. John Wiley & Sons.

7 – Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31:103–115.

16. APPENDICES

Appendix A – Preparation Instructions and Subject Questionnaires