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STUDY PROTOCOL

A Safety and Efficacy Study of a Bowel Cleansing Preparation (BLI800) in Pediatric Subjects Undergoing Colonoscopy

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A Safety and Efficacy Study of a Bowel Cleansing Preparation (BLI800) in Pediatric Subjects Undergoing Colonoscopy

Braintree Protocol BLI800-502

Version Dated 4/18/16

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_____ _____
Mark v.B. Cleveland, Ph.D. Date
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Principal Investigator Signature Date

CLINICAL PROTOCOL SUMMARY SHEET

STUDY TITLE: A Safety and Efficacy Study of a Bowel Cleansing Preparation (BLI800) in Pediatric Subjects Undergoing Colonoscopy

PROTOCOL: BLI800-502

VERSION DATE: 4/18/16

IND NUMBER: 74,808

STUDY PHASE: 3

OBJECTIVE: To compare the safety, tolerance and efficacy of BLI800 to NuLYTELY as bowel preparations prior to colonoscopy in adolescent patients.

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

SUBJECTS: Approximately 300 male and female pediatric subjects will be enrolled.

STUDY MEDICATIONS:
Preparation 1: BLI800 split-dose regimen (6oz per dose)
Preparation 2: BLI800 split-dose regimen (4.5oz per dose)
Preparation 3: NuLYTELY

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

EFFICACY ENDPOINTS: Primary efficacy will be based on overall preparation success as determined by the colonoscopist. Secondary efficacy endpoints will include proportion of excellent preparations, preparation quality by colon segment and percent of procedures that reach the cecum.

SAFETY ENDPOINTS: Safety endpoints include:

- Adverse event reports, including subject reported prep-related symptoms
- Change in serum chemistry and urine parameters
- Change in vital signs

TOLERABILITY ENDPOINTS: Subject tolerance of the preparation will be graded by caregiver at the time of dosing using a scale ranging from “very badly accepted/unacceptable” to “very well accepted”.

1. INTRODUCTION

2. STUDY OBJECTIVE

The objective of this study is to compare the safety and efficacy of BLI800 versus NuLYTELY, administered prior to colonoscopy, in adolescent subjects ages 12 to 16 years.

3. STUDY PLAN

3.1. Study Design

This is a randomized, parallel, multi-center, dose-ranging, investigator-blinded, safety and efficacy study in pediatric subjects ages 12 to 16 years.

3.2.Number of Subjects

A total of 300 male or female subjects, 12 to 16 years (inclusive) who are undergoing colonoscopy will be enrolled in this study.

3.3. Duration of Study

Subject participation in this study will last up to 60 days. A screening visit (Visit 1) should be performed between 30 days to 4 days prior to colonoscopy. Subjects meeting all eligibility criteria will be randomized to receive either BLI800 solution or NuLYTELY. In addition to the screening visit, subjects will have visits on Day 2 (day of colonoscopy), Day 4, Day 9, and Day 32 (if subject requires safety follow-up from Day 9).

3.4. Study Preparations

BLI800 - SUPREP Bowel Prep Kit

SUPREP Bowel Prep Kit (Braintree Laboratories, Inc.) is a low-volume osmotic solution that is FDA approved for cleansing of the colon as preparation for colonoscopy in adults. SUPREP is orally administered in a split-dose regimen and consists of two 6 ounce doses (for dilution), each containing the following ingredients in liquid form:

Component	Grams
Na_2SO_4	17.51
$MgSO_4$	1.6
K_2SO_4	3.13
Sodium Benzoate	0.098
Flavoring agents	1.35
Artificial Sweetener	1.2

Each dose will be supplied in a 6 ounce amber plastic bottle with a Clic-Loc closure. Each bottle will have a clinical label containing a caution statement, study code, study sponsor and kit number.

BLI800 – 4.5 ounce dose

A reduced dose (3/4 of the approved SUPREP dose) will be supplied in two 6 ounce amber plastic bottles with a Clic-Loc closure. Each bottle will have a clinical label containing a caution statement, study code, study sponsor and kit number.

Component	Grams
Na_2SO_4	13.13
$MgSO_4$	1.2
K_2SO_4	2.35
Sodium Benzoate	0.074
Flavoring agents	1.01
Artificial Sweetener	0.9

NuLYTELY

NuLYTELY (Braintree Laboratories, Inc.) is FDA approved for cleansing of the colon as preparation for colonoscopy in pediatric patients. NuLYTELY will be provided in clinical packaging with a label containing a caution statement, study code, study sponsor, address and kit number.

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 (randomization, drug dispensing, return and accountability). Any failure to maintain blinding of the treatment to the colonoscopist will be documented as a protocol violation. Subjects and caregivers will be instructed not to discuss their study preparation with any staff member.

3.5. Subject Selection

3.5.1. Inclusion Criteria

Subjects will be admitted to the study if they are:

1. Male or female between the ages of 12 to 16 (inclusive)

2. Undergoing colonoscopy for routinely accepted indications, including (but not limited to):
   - Subjected inflammatory bowel disease (IBD) or IBD follow-up
   - Lower gastrointestinal bleeding
   - Suspected colitis (allergic or other)
   - Abdominal pain
   - Chronic diarrhea
   - Cancer surveillance
   - Anemia of unknown etiology
   - Abnormal endosonography or manometry
   - Evaluation of barium enema results

3. If female, and of child-bearing potential, subject must use an acceptable form of birth control (hormonal birth control, IUD, double-barrier method, or depot contraceptive) or remain abstinent for the duration of the study.

4. Negative pregnancy test at screening, if applicable

5. In the Investigator's judgment, caregiver is mentally competent to provide informed consent for their child 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 known or suspected ileus, impaction, severe ulcerative colitis, acute peritonitis, gastrointestinal obstruction, gastric retention (gastroparesis), bowel perforation, toxic colitis or megacolon.

2. 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.

3. Subjects with increased risk of bowel perforation, including connective tissue disorders, toxic dilation of the bowel or recent bowel surgery.

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, uncorrected dehydration, or those secondary to the use of diuretics or angiotensin converting enzyme (ACE) inhibitors.

5. Subjects with bleeding disorders and/or impaired platelet function, or neutropenia.

6. Subjects with a prior history of renal, liver or cardiac insufficiency (including congestive heart failure or other significant cardiac abnormality)

7. Subjects with estimated glomerular filtration rate (GFR) below normal range (less than 70 ml/min/1.73m^2)

8. Subjects required to take any other oral medication within 3 hours of dosing until completion of both doses.

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

10. Subjects with tendency for nausea and/or vomiting, or that have known swallowing disorders.

11. Subjects for whom intake of substances is likely to affect gastrointestinal motility or urinary flow rate.

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

13. Subjects with an abnormal ECG result at Visit 1.

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

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

16. Subjects with a history of hypersensitivity to any preparation components (BLI800: sodium sulfate, potassium sulfate, magnesium sulfate and sucralose; NuLYTELY: polyethylene glycol 3350, sodium bicarbonate, sodium chloride and potassium chloride).

17. Subjects who, in the opinion of the Investigator, should not be included in the study for any reason, including inability to follow study procedures and history of major medical/psychiatric conditions that would compromise the safety of the study.

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

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

3.6. Study Endpoints

3.6.1. Efficacy

Primary efficacy will be assessed on the basis of preparation success or failure after completion of the examination. Investigators will grade each preparation on a scale from 1 (poor) to 4 (excellent). This scale is similar to those used in numerous previous studies to support the approvals of GoLYTELY, NuLYTELY, HalfLytely with Bisacodyl Tablet Bowel Prep Kit and SUPREP Bowel Prep Kit[1]. Secondary efficacy measures are described in Section 4.9.3.

3.6.2. Safety

Safety will be assessed through the collection of treatment emergent adverse events, as well as changes in vital signs, physical examination findings and serum chemistry measures from Visit 1.

3.6.3. Tolerability

The tolerability of each dose will be assessed by caregivers using a categorical scale inclusive of the following responses: very badly accepted/unacceptable; badly, but accepted; neither good nor bad; well accepted; very well accepted.

4. STUDY PROCEDURES

Study procedures are described as follows and depicted graphically in Section 4.6, below.

4.1. Visit 1

Following the informed consent process, caregivers will sign a consent form. Subjects of age to provide assent (as determined by the IRB for each center) will sign an assent form. Subject's demographics and concomitant medications will be recorded, vital signs will be obtained (including temperature, heart rate, respiratory rate, orthostatic manual blood pressure, height and weight), and a physical examination will be performed. An electrocardiogram (ECG) will be performed and subjects with an abnormal ECG will be excluded from continuing in the study. 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, Inflammatory Bowel Disease, Rectal Bleeding, Polyposis, Diabetes, Cancer (must indicate type of cancer), Electrolyte abnormalities

Blood and urine samples will be collected for testing at a central laboratory. The specific testing to be conducted is described below. Please refer to the laboratory manual for detailed instructions on sample processing. Colonoscopies must be scheduled to allow for receipt of laboratory results prior to the day the subject is scheduled to begin preparation.

> **Serum Testing:** albumin, ALT, anion gap, AST, bicarbonate, total bilirubin, blood urea nitrogen, calcium, chloride, creatine kinase (CK), creatinine, eGFR, GGT, glucose, HCG, magnesium, osmolality, osmolar gap, phosphorus, potassium, sodium, sulfate, total protein, and uric acid. CK-MB will be tested in samples where the CK value is greater than 2.5 times the upper normal limit.

Urine Testing: standard spot urinalysis (including microscopic analysis and ketones)

Investigators will be notified promptly by the central laboratory if a critical result is reported for the following tests:

Calcium	< 6.1 mg/dL (low)	> 12.9 mg/dL (high)
Creatine Kinase	> 2000 U/L	
Glucose	< 40 mg/dL (low)	> 450 mg/dL (high)
Potassium	< 2.8 mEq/L (low)	> 6.3 mEq/L (high)
Sodium	< 117 mEq/L (low)	> 160 mEq/L (high)
HCG	Positive	

Investigators should discontinue subjects with a critical value unless they feel the result is erroneous due to poor sample quality or laboratory error. In such cases the investigator must perform a redraw.

Subjects meeting all entry criteria will be eligible for randomization.

4.1.1. Randomization

Subjects that meet eligibility criteria will be randomized using an automated interactive web response system (IWRS). The randomization schedule will be implemented in the automated interactive web response (IWR) system prior to kit distribution to the site. At the time of randomization 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 two groups:

Group 1: Subjects with a baseline weight > 40 kg

Group 2: Subjects with a baseline weight ≤ 40 kg

The site personnel must only dispense a drug kit that has been assigned by the IWRS. Dispensing kits out of order is considered a protocol violation.

Subjects and caregivers will be provided with instructions on how to administer the study preparation. Subjects will be provided with a Preparation Questionnaire (see Section 4.7) to report their experience with the study preparation. Subjects will complete this questionnaire from the time the first dose of study drug is taken until the colonoscopy and will return it to the clinic at Visit 2. Subjects should complete the questionnaire themselves; however, in the event that subjects are unable to complete the questionnaire, caregivers are allowed to do so. Subject intake of food, beverages (including amounts) and medications will be recorded in a specific section of this questionnaire.

4.1.2. Study Drug

The study preparation will be administered starting on the day prior to the scheduled colonoscopy according to the instructions noted in Section 4.1.3. Caregivers/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. Caregivers/subjects must be notified and instructed to return the unopened bowel preparation to the study center. Returned un-used study drug kits will not be re-dispensed to another subject.

4.1.3. Preparation Instructions

BLI800 (6 oz dose)

DAY 1 (evening before colonoscopy)

1. Take a 6 ounce bottle of study preparation and pour the entire contents into the mixing cup provided. Fill the cup with cool water to the fill line (16 ounces) and drink the entire cup of solution.
2. Drink two **(2)** 16 ounce glasses of **WATER** over the next 1 – 2 hours. Fill the mixing cup with water up to the fill line (16 ounces) and drink the entire glass.

DAY 2 (morning of colonoscopy)

3. **At least 3 hours prior to your procedure**:
   Take the second 6 ounce bottle of study preparation and pour the entire contents into the mixing cup provided. Fill the cup with cool water to the fill line (16 ounces) and drink the entire cup of solution.
4. Drink two **(2)** 16 ounce glasses of **WATER** over the next 1 – 2 hours. Fill the mixing cup with water up to the fill line (16 ounces) and drink the entire glass. You must complete the solution and additional water at least 2 hours before your colonoscopy.

BLI800 (4.5 oz dose)

DAY 1 (evening before colonoscopy)

1. Take a 6 ounce bottle of study preparation and pour the entire contents into the mixing cup provided. Fill the cup with cool water to the fill line (12 ounces) and drink the entire cup of solution.
2. Drink two **(2)** 12 ounce glasses of **WATER** over the next 1 – 2 hours. Fill the mixing cup with water up to the fill line (12 ounces) and drink the entire glass.

DAY 2 (morning of colonoscopy)

3. **At least 3 hours prior to your procedure**:
   Take the second 6 ounce bottle of study preparation and pour the entire contents into the mixing cup provided. Fill the cup with cool water to the fill line (12 ounces) and drink the entire cup of solution.
4. Drink two **(2)** 12 ounce glasses of **WATER** over the next 1 – 2 hours. Fill the mixing cup with water up to the fill line (12 ounces) and drink the entire glass. You must complete the solution and additional water at least 2 hours before your colonoscopy.

Early morning colonoscopies should be scheduled accordingly to allow for completion of the Day 2 preparation dosing within the specified timeframes.

NuLYTELY

DAY 1 (evening before colonoscopy)

1. Tear open 1 (one) flavor pack of choice and pour into NuLYTELY bottle. Add lukewarm drinking water to the fill mark (4 liters) on the NuLYTELY bottle. Do not add any other ingredients, flavors, etc.

2. Cap bottle securely and shake vigorously several times to dissolve powder. The bottle may be refrigerated to improve palatability. Note: once the solution is reconstituted it must be used within 48 hours.

3. Begin drinking solution at a rate of 25 ml/kg/hour until your bowel movements run clear and free of solid matter or until you have completed the entire 4 liters of solution.

Dietary Restrictions

BLI800 subjects may have a light breakfast on the day before colonoscopy, followed by clear liquids until the colonoscopy is completed the following day.

NuLYTELY subjects may only have clear liquids on the day prior to colonoscopy until completion of the colonoscopy the following day.

Examples of acceptable clear liquids for both preparations are noted 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, 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.

4.2. Visit 2 – Day of Colonoscopy

Subjects and Caregivers will return to the study center for colonoscopy following completion of the preparation. 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/Caregivers will bring back the Preparation Questionnaire. Study personnel must review the questionnaire for completeness in the presence of the subject/caregiver so that any missed responses can be captured. Any violations of the dietary restrictions must be confirmed with the subject.

Subject's vital signs (see section 4.1 for details) 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 and urine samples will be collected for laboratory testing.

Prior to the colonoscopy, subjects will complete the Symptom Scale (see Section 4.8) to report their overall experience with the preparation.

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 4.9. Additional data will be collected as outlined in Section 4.9.3.

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. Staff members will perform drug accountability by assessing the number of used BLI800 bottles and volume of remaining solution in the NuLYTELY jug.

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

4.3 Visit 3 – Day 4 (+/- 1 day)

Subjects will return to the study center 2 days (+/- 1 day) after colonoscopy. Subject's vital signs (see section 4.1 for details) will be repeated and the subject will be queried for occurrence of adverse events and changes in concomitant medications. Blood and urine samples will be collected for laboratory testing.

4.4 Visit 4 – Day 9 (+/- 1 day)

Subjects will return to the study center 7 days (+/- 1 day) after colonoscopy. Subject's vital signs (see section 4.1 for details) will be repeated and the subject will be queried for occurrence of adverse events and changes in concomitant medications. Blood and urine samples will be collected for laboratory testing.

4.5 Visit 5 – Day 32 (+/- 3 day)

Subjects with persistently abnormal laboratory results and ongoing adverse events at Visit 4 will return to the study center 30 days (+/- 1 day) after colonoscopy. Additional blood and/or urine samples will be collected and symptoms assessed as indicated. For subjects with ongoing abnormalities at Visit 5, site personnel should consult with the Sponsor and Medical Monitor to determine if additional follow up is required.

4.6 Tabulated Study Procedures

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

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

[1] Includes assessments of height (Visit 1 only), oral temperature, heart rate, respiratory rate, manual blood pressure and weight
[2] refer to Section 4.10
[3]to be dispensed and completed at Visit 2, prior to colonoscopy
[4]Visit 5 will be performed only for subjects with ongoing adverse events or that have clinically significant lab values at Visit 4

4.7 Subject Preparation Questionnaire

A Preparation Questionnaire will be completed by the subject from the time the preparation is started until the subject completes the preparation. This questionnaire must be returned to a member of site staff at Visit 2. The questionnaire will prompt subjects for dosing and completion times for the study preparation and additional water (including water amount), and will contain questions about their bowel movement experiences during the preparation.

The section of the questionnaire entitled Dietary Compliance should be completed from the morning the subject starts their study preparation (i.e. day before the colonoscopy) until their procedure the following day. The subject will be instructed to record all food and beverages consumed during this two day period, keeping in mind the dietary restrictions outlined above in Section 4.1.3.

The section of the questionnaire entitled Dosing Tolerability should be completed by the caregiver after the subject completes each dose of preparation (NuLYTELY subjects will only have one questionnaire). Caregivers will be asked to rate subject tolerability using the following categories:

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

4.8 Subject Symptom Scale

This questionnaire will be completed by the subject at Visit 2, prior to colonoscopy. Subjects will rate their overall experience of stomach cramping, stomach bloating and

nausea on a 5 point scale, with 1 = no symptoms and 5 = severely distressing symptoms.

4.9 Physician Assessments

4.9.1 Segmental Cleansing Assessment

The blinded colonoscopist will rate each colon segment (proximal, mid, distal) using the following scale. This assessment will be performed during the withdrawal portion of the examination.

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

4.9.2 Overall Cleansing Assessment

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 4.9.1. This assessment will be performed upon completion of the examination (withdrawal of the endoscope).

4.9.3 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. Volume of water used to improve visualization

4.10 Pregnancy

All female subjects 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 use oral contraceptives, depot contraceptives, double-barrier method, intrauterine device, or testify that she is monogamous, 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.

Oral contraceptives, hormone implants, and injections should be stable for at least 1 month before colonoscopy, until 1 month after colonoscopy.

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.

4.11 Concomitant Medications

The use of concomitant medication (defined as prescription, over the counter and homeopathic medications) will be recorded from 14 days prior to screening until completion of Visit 5 (Day 32), including sedation medications and 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. Site personnel should review the preparation questionnaire section related to adverse events and discuss any documented events with subjects/caregivers.

In addition, any symptom on the symptom scale rated as 2 (mild) to 5 (severely distressing) must be reported as an adverse event. Reports of vomiting (of any severity) must be documented as adverse events. If multiple episodes of vomiting are reported on the Treatment Questionnaire, these should be represented as one adverse event on the case report form with severity reflecting the most severe episode.

Any abnormal anion gap laboratory finding must be reported as an adverse event and followed until resolution. 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 to participate in the study and will conclude with the completion of Visit 4. For subjects requiring Visit 5, adverse events will be collected until completion of Visit 5.

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 Adverse Events in Prior Clinical Studies

BLI800

In Phase 3 clinical trials of adult subjects, 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. In a pilot study in adolescents (Study BLI800-501), the incidences of nausea, vomiting, abdominal pain and bloating were similar to those seen in adults. Most subjects reported no symptoms or rated them as mild.

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 the subject took their preparation. Pre-scheduled surgeries, or examination findings not related to the preparation 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:

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. Exemptions must be faxed to Braintree using the designated form and approved before any action is taken. 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:

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

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

9 DATA ANALYSIS

9.1 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 4.9.2) 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.

Superiority Hypothesis:

The primary endpoint of treatment success will be based upon the difference $D=P_1-P_2$, where P_1 is the observed success fraction in the BLI800 group (experimental group) and P_2 is the observed success fraction in the NuLYTELY group (control group). The procedure tests the null hypothesis

$$H_0: \pi_1-\pi_2=0$$

versus the alternative hypothesis

$$H_1: \pi_1-\pi_2 \neq 0,$$

where π_1 is the true underlying probability of successful treatment in the BLI800 group, and π_2 is the true underlying success probability in the NuLYTELY group.

We will test the null hypothesis of superiority separately for the comparisons of full-dose BLI800 vs. NuLYTELY and 4.5-ounce BLI800 vs. NuLYTELY. We will preserve the family-wise type I error rate at 5% using the Holm-Bonferroni approach, which involves comparing the smaller of the two P values to 0.025 and, if that is significant, the larger of the two P values to 0.05. If both comparisons are significant, we will conduct a test comparing the two dose levels of BLI800 at the two-sided 5% level. As we will only perform this test conditionally on the other tests being significant, it has no effect on the family-wise type I error rate, and so it requires no further multiplicity adjustment.

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.

Secondary efficacy endpoints will include proportion of excellent preparations, cleansing score by segment, proportion of examinations that reach the cecum, and volume of additional water used for washing.

9.2 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 Questionnaire Data:

Symptom questionnaire data for individual symptoms for Overall Experience (Stomach Cramping, Stomach Bloating and Nausea) will be presented categorically by severity and tested by Chi-Square test.

9.3 Tolerability

Tolerability data will be presented categorically and tested by Chi-Square test.

9.4 Sample Size

The primary aim of the study is to show that BLI800 is superior to NuLYTELY in the proportion of subjects with successful colon cleansing. Based on prior studies in adult subjects, the proportion of subjects experiencing successful cleansing is expected to be approximately 95% in the BLI800 group and 77% in the NuLYTELY group. We will test the hypothesis of superiority separately for the two BLI800 dose groups: BLI800 full dose vs. NuLYTELY, and BLI800 4.5 ounce dose vs. NuLYTELY. To control the family-wise type I error rate at 5%, we will perform a Holm-Bonferroni adjustment, testing the hypothesis for the smaller of the two P values at the two-sided 2.5% level and, if significant, testing the hypothesis for the larger of the two P values at the two-sided 5% level. Assuming similar rates in the adolescent population and a one-sided alpha of 0.0125, with 81 subjects per group (243 total), the study will have 80% power to reject the null hypothesis of equivalence. 100 subjects will be enrolled in each preparation group to account for dropouts.

9.5. Study Populations

The following populations have been defined for data analyses.

9.5.1.Intention-to-Treat (ITT) Population

This population includes all subjects randomized to treatment. Safety and efficacy analyses using the ITT population will be used to support the primary study analyses using the modified ITT population.

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

This population consists of all randomized subjects that took at least one dose of study medication. The mITT population will serve as the analysis population for all primary and secondary safety and efficacy analyses. Safety and efficacy analyses using the mITT population will be used to support the primary study analyses using the per-protocol population.

9.5.3. Per Protocol Population

The per-protocol (PP) population will consist of all subjects in the mITT population who have not violated any major entry criteria and have not deviated significantly from the protocol during the course of the study. Reasons for exclusion from the PP population will be defined prospectively in the statistical analysis plan and prior to unblinding of the data. Safety and efficacy analyses using the per-population will be used to support the primary study analyses using the per-protocol population.

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 a parent/guardian by study personnel and will be kept on file at the study center (and assent for children of appropriate

age). 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 appropriate electronic case report forms for each subject. Subject medical records will be reviewed to verify all other data points, including potential adverse events, and to ensure consistency with the report forms. Copies will be made and retained by the Investigator as well as identical copies for Braintree Laboratories' files. 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 the report forms, 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 BLI800, 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

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 – Bitoun A, Ponchon T, Barthet M, Coffins B, Dugue C, Halphen M: Results of a prospective randomized multicenter controlled trial comparing a new 2-L ascorbic acid plus polyethylene glycol and electrolyte solution vs. sodium phosphate solution in patients undergoing elective colonoscopy. Aliment Pharmacol Ther.;24:1631-1642, 2006.