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STUDY PROTOCOL

A Pilot Evaluation of BLI4900 Bowel Preparation in Adult Subjects

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A Pilot Evaluation of BLI4900 Bowel Preparation in Adult Subjects

Braintree Protocol BLI4900-201

Version Dated 8 July 2019

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CLINICAL PROTOCOL SUMMARY SHEET

STUDY TITLE: A Pilot Evaluation of BLI4900 Bowel Preparation in Adult Subjects

PROTOCOL: BLI4900-201

VERSION DATE: 8 July 2019

IND NUMBER: 134,507

STUDY PHASE: 2

OBJECTIVE: To evaluate the safety and efficacy of BLI4900 as a bowel preparation prior to colonoscopy in adult patients.

STUDY DESIGN: This will be an active-controlled, sequential cohort, open-label study.

SUBJECTS: Approximately 120 male and female adult subjects will be enrolled.

STUDY MEDICATIONS: BLI4900 Bowel Preparation
PEG-SD (polyethylene glycol 3350 plus Gatorade with bisacodyl)

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

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

SAFETY ENDPOINTS: Safety endpoints include:

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

1. INTRODUCTION

In sigmoidoscopy, colonoscopy, radiographic examination and other medical or diagnostic procedures on the colon, it is important that the colon be thoroughly purged and cleansed. In particular, it is essential that as much fecal matter as possible be removed from the colon to permit adequate visualization of the intestinal mucosa.

Large volume (e.g. 4L) orally administered compositions have been developed for use as gastrointestinal "washes" for diagnostic purposes. Such orally administered preparations are usually formulated as dilute or isotonic solutions of polyethylene glycol 3350 (PEG-3350) and electrolyte containing salts such as sodium sulfate, sodium bicarbonate, sodium chloride and potassium chloride (1). These orally administered compositions are useful in the rapid cleansing of the colon for diagnostic purposes. However, due to the large volume of poorly tasting fluid that must be ingested, patient compliance is often poor.

One attempt to answer this problem has been to reduce the volume of preparation and improve its palatability. To this end, a sulfate-based bowel preparation kit, SUPREP ® Bowel Prep Kit (sodium sulfate, potassium sulfate and magnesium sulfate) Oral Solution, was cleared by FDA in 2010. SUPREP requires the patient to consume two separate administrations of this oral sulfate solution (OSS). Each administration purges the colon of fecal material. The colon is cleansed after the second administration. Each administration is followed by 946 ml supplemental water to prevent dehydration. The total volume of fluid intake (including SUPREP) is about 3L. SUPREP was specifically formulated to prevent fluid and electrolyte disturbances, unlike the phosphate preparations (2).

Nevertheless, some physicians have adopted a bowel preparation that consists of PEG-3350 combined with a "sports drink" such as Gatorade® (PEG-SD). It combines PEG-3350 (available over-the-counter and one of the active ingredients of several FDA-approved bowel cleansing preparations), with the electrolytes and sugar found in the sports drink. It is an osmotically unbalanced formulation and its effects on fluid and electrolyte balance have not been studied. It appears that the patients' perception of this product is so acceptable that physicians recommend its use, despite evidence that it is less effective and perhaps less safe than those cleared by FDA (3,4,5).

Table 1 shows that the quantities of the electrolytes in PEG-SD are much less than in marketed bowel preparation products, which is not surprising as the sports drink was developed to replace electrolytes lost in sweat, not from diarrhea.

Table 1: Comparison of Composition (Grams) in Two Marketed Bowel Cleansing Products and PEG-SD*

	NuLYTELY	GoLYTELY	PEG-SD**
Prep Volume	4L	4L	~ 2 L
PEG	420.00	236.00	238
Na	5.95	10.37	0.865
Cl	7.52	15.04	0.804
K	0.76	1.55	0.22
HCO_3	4.16	8.32	0

*Matro et al, 2014. **PEG-SD contains 112g of sugars

Although it is unapproved by the FDA, doctors make this decision because of a variety of factors, such as cost, taste and patient requests.

For example, Matro et al (2014) randomized patients to receive PEG-SD (N = 180) or PEG-EA (N=184), which is an approved bowel preparation (MOVIPREP®), and collected clinical chemistry data at baseline and on the day of colonoscopy. Although the incidence of hyponatremia (serum sodium < 135 mmol/L) was higher in the osmotically unbalanced PEG-SD group, (3.9%) vs the PEG-EA treated group (2.2%), it did not differ statistically. For other electrolytes, small but statistically significant changes from baseline to colonoscopy occurred with PEG-SD for sodium, potassium and chloride (P = 0.001, 0.012, 0.001, respectively).

Regarding the efficacy of PEG-SD, properly powered studies such as that of Matro et al conclude that PEG-SD is inferior in the rate of preparations considered "excellent" by the endoscopist. Patients consuming the PEG-SD also drink additional fluids and are usually instructed to receive a de-bulking laxative such as OTC bisacodyl prior to the PEG-SD consumption. Bisacodyl is a poorly absorbed stimulant laxative that acts to stimulate peristalsis in the colon resulting in stool evacuation.

1.1. Clinical Experience with the BLI4900 Active Ingredients

1.1.1. ***PEG-3350***

1.1.2. ***Sulfate Salts***

It is the purpose of the current investigation described here to further evaluate the BLI4900 formulation for safety and efficacy compared to PEG-SD in a population undergoing colonoscopy.

Version dated 8-JULY-2019

2. STUDY OBJECTIVE

The objective of this study is to evaluate the safety and efficacy of BLI4900 as a bowel preparation prior to colonoscopy in adult patients.

3. STUDY PLAN

3.1. Study Design

This is an open-label, active-controlled, sequential-cohort study in adult patients undergoing colonoscopy.

3.2. Number of Subjects

Approximately 120 male and female subjects who are undergoing colonoscopy for routinely accepted indications will be enrolled in this study at up to 4 study centers.

3.3. Duration of Study

Subject participation in this study will last up to 37 days. A screening visit (Visit 1) should be performed within 30 days of the colonoscopy. Subjects meeting all eligibility criteria will be enrolled to receive BLI4900. Subjects will return to the clinic the day of colonoscopy (Visit 2). Subjects with clinically significant laboratory abnormalities and/or ongoing adverse events related to the study preparation may return for a follow up visit 7 days after colonoscopy.

3.4. Study Preparations

BLI4900: *(First 20 subjects)*

The BLI4900 formulation ingredients being evaluated in this trial are described in Appendix A. Subjects will reconstitute each one-liter dose with water and consume the preparation according to the split-dose (PM/AM) instructions outlined in Appendix B, along with additional water. The bottles will have a clinical label containing a caution statement, study code, study sponsor and kit number. Any modifications to the BLI4900 formulation evaluated under this protocol will require a formal amendment and IRB approval prior to enrollment of subjects.

PEG-SD Control: *(Second 20 subjects)*
Subjects who receive PEG-SD will receive two 5 mg pills of OTC bisacodyl laxative, two 32 ounce bottles of Lemon Lime flavored sports drink (Gatorade G Series; PepsiCo, Inc., Chicago, IL, USA), and two 119 g bottles of Polyethylene glycol 3350. Subjects will take the bisacodyl at approximately 3PM on the day prior to colonoscopy and reconstitute the PEG-SD preparation and consume it according to the split-dose (PM/AM) instructions outlined in Appendix B, along with additional water.

BLI4900-5: *(Approximately 40 subjects)*

The BLI4900-5 formulation ingredients are described in Appendix A. Subjects will reconstitute each one-liter dose with water and consume the preparation according to the split-dose (PM/AM) instructions outlined in Appendix B, along with additional water. The bottles will have a clinical label containing a caution statement, study code, study sponsor and kit number. Any modifications to the BLI4900 formulation evaluated under this protocol will require a formal amendment and IRB approval prior to enrollment of subjects.

BLI4900-6 (Approximately 40 subjects)
The BLI4900-6 formulation ingredients are described in Appendix A. Subjects will reconstitute each one-liter dose with water and consume the preparation according to the split-dose (PM/AM) instructions outlined in Appendix B, along with additional water. The bottles will have a clinical label containing a caution statement, study code, study sponsor and kit number. Any modifications to the BLI4900 formulation evaluated under this protocol will require a formal amendment and IRB approval prior to enrollment of subjects.

3.5. Subject Selection

3.5.1. *Inclusion Criteria*

Subjects will be admitted to the study if they are:

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

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

2. 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 though completion of the study.

4. Negative urine 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 known or suspected ileus, severe ulcerative colitis, gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis or megacolon.

2. Subjects with ongoing severe, acute inflammatory bowel disease

3. 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.

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

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

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

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

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

9. Subjects undergoing insulin therapy for any indication.

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

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

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

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

14. Subjects allergic to any preparation components (refer to Appendix A).

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

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

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

18. Subjects who have regularly used laxatives or colon motility altering drugs in the last month (i.e. more than 2-3 times per week) and/or laxative use within 72 hours prior to administration of the preparation

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
- Blood samples will be collected for local laboratory testing, 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, total protein, uric acid and osmolality.

Investigators will be instructed to comment on all out of range values for clinical significance.

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

4.1.1. *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. *Bowel Preparation Assignment*

Eligible subjects will be provided with instructions on how to use the study preparation. The first 20 subjects will receive BLI4900. The second 20 subjects will receive PEG-SD. A third group (approximately 40 subjects) will receive BLI4900-5. A fourth group (approximately 40 subjects) will receive BLI4900-6.

Subjects will self-administer the study preparation starting on the day prior to their scheduled colonoscopy according to the instructions provided by the study site (full preparation instructions are included in Appendix B). 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. Returned un-used study drug kits will not be re-dispensed to another subject.

4.1.3. *Dietary Restrictions*

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 acceptable low residue items are found in the preparation instructions.

Examples of acceptable clear liquids are provided below:

- Water
- Strained fruit juices (without pulp) including apple, orange, white grape, etc.
- 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.

4.1.4. ***Subject Questionnaires***

Subjects will be provided with a Preparation Questionnaire and Dietary Questionnaire to document their preparation and dietary intake (refer to Appendix C for full questionnaires), and to note any episodes of vomiting that may occur during the preparation. Subjects will complete these questionnaires starting on the morning they are scheduled to take their first dose of each preparation (Preparation Day 1) until they return to the study center the following day (Preparation Day 2). The time of 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 4.1.3.

4.2. Bowel Preparation Administration

On the day prior to their appointment, subjects will begin following the protocol specified dietary restrictions (as outlined in Section 4.1.3) and completing their Preparation and Dietary Questionnaires (refer to Appendix C). In the evening, subjects will begin consuming their bowel preparation according to the instructions provided by the study center (refer to Appendix B). Subjects will take the second dose of bowel preparation the following morning (5 – 8 hours prior to colonoscopy).

4.3. Visit 2

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

Vital signs (excluding height) will be repeated, a physical examination will be performed, and subjects will be queried for occurrence of adverse events and changes in concomitant medications. Blood samples will be collected for chemistry testing.

The colonoscopy will be performed by a physician according to the site's standard procedures and evaluated on a 4-point scale, as shown in Section 4.6. Sites with recording capabilities will record the colonoscopy procedure.

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.

4.3.1. *Symptom Scale*

At Visit 2 (prior to sedation), subjects will report their experience with the preparation on the Symptom Scale for the most frequently occurring bowel preparation symptoms of stomach cramping, stomach bloating, and nausea. These symptoms will be rated by the subjects using the following categories “None”, “Mild”, “Bothersome”, “Distressing” and “Severely Distressing”.

4.3.2. *Drug Accountability*

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

Returned study preparation materials 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.

4.4. Follow up of Adverse Events and Laboratory Results

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

4.5. Tabulated Study Procedures

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

Procedures	**Visit 1 Screening**	**Day before colonoscopy**	**Visit 2 Day of colonoscopy**
Informed Consent	X		
Inclusion/Exclusion Criteria Review	X		
Medical History	X		
Physical Examination / Vital Signs	X		X
Review of Concomitant Medication	X		X
Blood Collection for Laboratory Testing	X		X
Urine Pregnancy Test (if applicable) [1]	X		
Dispense Drug	X		
Instruct Subject	X		
Dispense Preparation Questionnaire	X		
Subject Takes the 1st Dose of Preparation		X	
Subject Completes Preparation Questionnaire		X	X
Subject Takes the 2nd Dose of Preparation			X
Symptom Scale & Preference Questionnaire Completed[2]			X
Drug Accountability			X
Colonoscopy performed with Intra-procedural Safety and Efficacy Grading[3]			X
Collect and assess adverse event data[4]			X

[1] refer to Section 4.7
[2]to be completed at Visit 2, prior to sedation
[3]Colonoscopies may be recorded (if site has recording capability) for transmission to sponsor
[4]Subjects with ongoing preparation-related AEs/clinically significant lab results may need to return on follow up Day 7

4.6 Physician Assessments

4.6.1. *Segmental Cleansing Assessment*

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

4.6.3. *Additional Efficacy Measures*

In addition, the following data will be collected:

1. Adequacy of preparation according to the colonoscopist. If the preparation was not adequate, the need for re-preparation will be recorded.
2. Start time of colonoscopy
3. Time of cecal intubation
4. Completion time of colonoscopy
5. 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 urine pregnancy test done at screening. A positive result will rule out the participation of the subject in the study.

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

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

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

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

4.8. Concomitant Medications

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

5. ADVERSE EVENTS

5.1. Adverse Event Definition and Reporting

An Adverse Event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product. Any symptom on the Symptom Scale rated as “Mild” or more severe must be reported as an adverse event. Any reports of vomiting on the Preparation Questionnaire must be reported as adverse event (multiple episodes of vomiting should be reported as a single adverse event in the Case Report Form). Colonoscopy and biopsy findings are not considered adverse events unless considered by the investigator to be related to the preparation or colonoscopy procedure.

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

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

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

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

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

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

5.2 Expected Adverse Events

Because BLI4900 contains the same active ingredients as approved bowel preparations (PEG3350 and sulfates), a similar adverse event profile is expected. In Phase 3 clinical trials of SUPREP (which includes sodium and magnesium sulfate), the most frequent adverse events reported by ≥ 3% of patients included overall discomfort, abdominal pain and distension, nausea, and vomiting. The most frequently reported adverse events occurring in ≥ 3% of patients taking NuLYTELY (which contains PEG3350) are nausea, abdominal fullness and bloating.

PEG-SD contains the same active ingredient as BLI4900 (PEG3350), therefore a similar adverse event profile is expected. In addition, the preparation includes the commonly used OTC laxative bisacodyl. There have been rare cases of hyponatremia and ischemic colitis reported with versions of the PEG-SD combination (3,4,5).

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 colonoscopy. Pre-scheduled surgeries 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 clinically stable.

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

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

Contact Telephone Numbers:

During Business hours

(M-F, 8:30 am – 5:00 pm EDT)

After hours or weekends

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

7. INSTITUTIONAL REVIEW BOARD (IRB) AND INFORMED CONSENT

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

8. MANAGEMENT OF INTERCURRENT EVENTS

8.1. Modification of Protocol

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 dropped from the study for any of the following reasons:

- An adverse event requiring discontinuation (including failure to tolerate study medication).
- Female participants who become pregnant during the study period.
- Major protocol deviation from the study design by the subject that is observed or suspected by the Investigator
- Subject chooses to withdraw from the study, for whatever reason.

- Subject is lost to follow-up.
- The Sponsor initiates an early discontinuation of the study.
- The subject is withdrawn at the discretion of the Investigator.

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

9. DATA ANALYSIS

9.1. Study Endpoints - Efficacy

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

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 (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 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 (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.

Additional efficacy endpoints will include:

- Cleansing score by segment
- Number (%) of excellent preparations overall and by segment
- Adequacy of cleansing and need for re-preparation
- Duration of colonoscopy

- Volume of intraprocedural water needed to irrigate the colon
- Number (%) of procedures that reached the cecum

9.2. Study Endpoints - Safety

Adverse Events:

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

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

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

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

Vitals Signs and Physical Examination:

Vital signs and physical examination data will be summarized with descriptive statistics.

Laboratory Data:

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

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

9.3. Sample Size

Approximately 120 subjects will be enrolled and treated in the study. This size was chosen because of the pilot nature of this study.

10. DRUG INVENTORY AND DISPOSITION

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

11. STUDY MONITORING

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

12. DOCUMENTS AND NOTIFICATIONS

12.1. Informed Consent

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

12.2. Institutional Review Board

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

12.3. Amendments to the Protocol

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

12.4. Data Records

Braintree Laboratories will provide data collection forms for each subject. Subject medical records will be reviewed to verify all other data points, including potential adverse events. Copies of subjects' laboratory reports, colonoscopy and pathology reports (if applicable) will be collected for Braintree Laboratories after subject identifiers have been redacted by site staff. Colonoscopies will be recorded (if site has recording capability) and transmitted to Braintree Laboratories. The Investigator should retain copies of the subject consent forms and other study documents for a period of two years following the date of approval of a New Drug Application

or supplement for BLI4900, or, if the application is not approved, for two years after the drug investigation program is discontinued. The study investigator will notify Braintree Laboratories of their intent to dispose of the study records and allow Braintree to take possession of such records. Study records will be made available at reasonable times for inspection and copying if requested by a properly authorized employee of Braintree Laboratories, authorized Braintree Laboratories designee or the Department of Health and Human Services in accordance with federal regulations.

13. PUBLICATION AND AGREEMENT

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

14. INVESTIGATORS AGREEMENT

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

15. REFERENCES

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4 - Schoenfeld P. Safety of MiraLAX/Gatorade Bowel Preparation Has Not Been Established in Appropriately-Designed Studies. Clin Gastroenterol Hepatol. 2013;11(5):582.

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7 - Smyth HF Jr, Carpenter CP, Weil CS. The toxicology of the polyethylene glycols. J Am Pharm Assoc. 1955;44(1):27-30.

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