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STUDY PROTOCOL

A Safety and Efficacy Evaluation of BLI400 Laxative in Constipated Adults

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A Safety and Efficacy Evaluation of BLI400 Laxative in Constipated Adults

Braintree Protocol BLI400-302

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CLINICAL PROTOCOL SUMMARY SHEET

STUDY TITLE: A Safety and Efficacy Evaluation of BLI400 Laxative in Constipated Adults

PROTOCOL: BLI400-302

VERSION DATE: 9-15-2016

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OBJECTIVE:

To evaluate a daily dose of BLI400 Laxative for safety and efficacy versus placebo in constipated adults.

STUDY DESIGN:

This will be a randomized, double-blind, parallel, multi-center study.

SUBJECTS:

Approximately 600 male or female constipated adult subjects will be randomized in this study after completing a 14 day screening period to confirm constipation status.

Approximately 30% of enrolled subjects will be elderly (greater than 65 years of age at time of randomization)

STUDY MEDICATIONS:

Group 1: BLI400 Laxative (21 grams of Lactitol Monohydrate, NF)

Group 2: Placebo (regular maltodextrin)

DURATION OF TREATMENT

Subjects will take BLI400 laxative or placebo daily for 6 months. Participation in this study will last for approximately 7 months, including the 14 day Screening Period.

PRIMARY ENDPOINT

The primary endpoint is the proportion of subjects who are weekly responders for at least 9 out of the first 12 weeks, with at least 3 of these weeks occurring during weeks 9–12. A weekly responder is a subject who has ≥ 3 complete spontaneous bowel movements (CSBMs) per week and an increase from baseline of > 1 CSBM in that week.

SECONDARY ENDPOINTS

Secondary endpoints will include but are not limited to the following:

- Weekly SBM and CSBM frequency rates during weeks 1 – 12
- Weekly stool and symptom ratings (stool consistency, stool straining, abdominal bloating, abdominal discomfort) during weeks 1 – 12
- Weekly SBM and CSBM frequency rates after week 12
- Weekly stool and symptom ratings (stool consistency, stool straining, abdominal bloating, abdominal discomfort) after week 12

Safety will be assessed using treatment emergent adverse event, laboratory, and ECG data.

1. INTRODUCTION

The present approaches to the treatment of chronic idiopathic constipation (CIC) are limited and for some patients there are significant drawbacks that have not been resolved. It would be desirable to provide a source of relief for constipation that would permit dosing adjustments to optimize efficacy and safety and that would be pleasant to consume to improve patient compliance. The treatment should not have the safety issues associated with oral phosphate laxatives, have an acceptable safety profile, and be effective in numerous types of constipation.

Braintree Laboratories, Inc. is investigating the use of a new chemical composition, BLI400 (Lactitol Monohydrate NF Powder for Reconstitution) as a treatment for adult constipation. Ample published literature with lactitol provides significant preclinical and clinical studies which support the safe and effective use of this GRAS-listed compound.

These reports indicate that the BLI400 lactitol composition has promise as a candidate for further development for the treatment of constipation, as reviewed herein.

BLI400 is a member of the pharmaceutical class of osmotic laxatives; specifically it is a non-absorbed, colonically metabolized sugar alcohol (polyol). Studies reviewed here indicate it provides relief from the symptoms of constipation by rapidly inducing a patient-controlled bowel movement. While lactitol appears to be minimally, if at all, absorbed in the small intestine, colonic microbes split lactitol into D-galactose and D-sorbitol, which are fermentable to organic acids including lactic, formic, propionic, butyric and acetic acids (as reviewed in Patil et al, 1987). The osmotic properties of the small organic molecules consistently point to their pharmacodynamic effects as dependent on water retention with the stool. Thus, BLI400 is a pro-drug of an essentially non-absorbed osmotic laxative. Lactitol is generally considered to be pharmacologically inert and is often referred to as a “prebiotic” with no specific receptor targets for its laxative action.

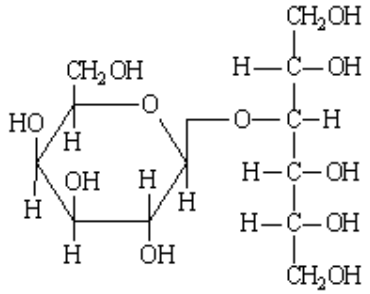
Rationale for Performing Research with the Investigational Product

Lactitol monohydrate, at a daily dose of 21 grams per day appears to be a safe and effective treatment for constipation, but it has not been studied and proven in clinical trials in the US. Lactitol appears to be a "prebiotic", a substrate for colonic bacteria which convert it into osmotically active small molecules. Extensive published and non-published literature supports its safety and efficacy, but a Phase III clinical trial is required for its registration in the US. It is envisaged there will be one, multi-site, controlled study in patients with documented constipation and that the design will be similar to other studies that have led to the approval of laxatives, such as those for MiraLAX, NDA 22-015 and consistent with FDA's recommendations for study endpoints in CIC trials.

Physical, Chemical, and Pharmaceutical Properties and Formulation

Lactitol is a simple monosaccharide sugar alcohol, a synthetic derivative of the milk sugar lactose that was discovered in the 1920s. It is a dry, free flowing powder, readily soluble in aqueous solutions. As shown by the structure diagrams, it is an analog of the disaccharide lactulose.

Lactitol



Lactulose

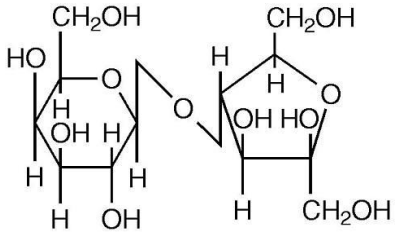


Table 1-1
Components of a Typical Single Dose of BLI400

Component	Amount (g)*
Lactitol monohydrate, NF	21

The product will be provided in multi-dose bottles with a measuring cap to deliver 10.5 grams of BLI400 powder.

Nonclinical Studies: Extensive nonclinical studies have been performed with lactitol as support for its registration and marketing in countries outside the US and are reviewed in detail in the BLI400 Investigators' Brochure. The studies have covered basic pharmacology, genotoxicity and mutagenicity, acute and chronic studies including carcinogenicity and reproductive toxicity. These studies were carried out in mice, rats, dogs and rabbits.

Pharmacology: Lactitol is not degraded by the galactosidase enzymes of the small intestine. However, colonic microflora degrade lactitol extensively in rats so that lactitol elevated the proportions of acetic acid and lowered proportions of butyric acid in the hindgut of rats. The osmotic effects of these organic acids appear to provide the pharmacodynamic basis for lactitol's laxative action. Increased output of moist feces was seen in all animals species studied in a dose-related manner. The highest doses tested caused frank diarrhea in some studies.

Metabolic Effects: In some studies, total serum cholesterol and triglycerides were reduced equally in rats fed diets containing 7% sorbitol or lactitol. By acidifying fecal contents, lactitol lowered ammonia levels in animal models of hepatic encephalopathy, perhaps as a result of production of the poorly absorbed ammonium ion that follows lowering the cecal pH. Rats fed a diet containing 5% of lactitol for two weeks displayed a significant increase of calcium absorption.

Toxicology Studies: Only weak edema ensued after lactitol application to intact skin, but erythema and edema emerged when it was applied to abraded skin. Rodents treated with lactitol had loose, frequent stools and cecal enlargement. This was often accompanied by decreased weight gain and increased water consumption. Clinical chemistry changes included changes in electrolyte levels, decreased cholesterol and alkaline phosphatase. Perhaps as compensation for the electrolyte changes that probably followed the diarrhea, adrenal weight and hypertrophy of the zona fasciculata were seen in the highest dose

groups. Renal tubular degeneration with nephrocalcinosis was occasionally seen and may follow the increased calcium absorption. Lactitol was not considered positive for mutagenicity or chromosomal damage studied in standard in vitro and in vivo assays. Life-long carcinogenicity studies have indicated that Leydig cell dysplasia occurred in rats at high lactitol doses, but this was not seen in mice dosed for 24 months or dogs dosed for 12 months. This species-specific effect in some rat strains was not considered significant to humans, since ordinary milk sugar, lactose, produces a similar effect in rodents.

Clinical Pharmacology and Safety: Since lactitol is extensively degraded to organic acids in the colon, it is little surprise that there are no published studies on its level in blood after administration. Some have estimated that only 0.6% of an oral dose of lactitol is excreted in urine. Similar to what is found in animals, lactitol is extensively metabolized in the human colon, making available a significant proportion of the metabolites for colonic absorption. Unlike in animals, lactitol does not seem to stimulate calcium absorption in humans, although in one study when 15 g of lactitol was administered along with calcium in solution to fasting volunteers, calcium absorption was diminished. Administering lactitol increases fecal Bifidobacteria levels, while other bacteria (fecal anaerobes, aerobes, Enterobacteriaceae or lactobacilli) were unaffected. After the ingestion of 25 g lactitol, xylitol, or glucose by eight healthy male volunteers the rise in plasma glucose was significantly greater 30 and 60 minutes after ingestion of glucose while no rise in plasma glucose followed ingestion of lactitol.

The investigation of the use of a mixture of lactitol for the treatment of constipation has been extensively studied, but the information is only available in published form. From these observations, it appears that lactitol's adverse events are limited largely to the gastrointestinal system. Symptoms such as nausea, cramps, abdominal pain, flatulence and vomiting may be expected and could lead to withdrawal from the study if not controlled. Their incidence and severity may be ameliorated in some patients by dose-adjustment. Changes in hematology, clinical chemistry or urinalysis may be seen, and their clinical significance will be assessed during the development of lactitol. In one study plasma potassium was elevated with lactitol, but the values stayed within the normal range.

Clinical Efficacy: Lactitol has been marketed since at least 1985 outside the US in Europe and other regions (where it is known as Lactitol Ex-Lax® or Importal®, for example) as a syrup or powder for the treatment of constipation in adults, including the elderly and children. As a result a substantial body of evidence has accumulated on its use in treating constipation, as evidenced by more than 19 publications since 1988, including two recent review articles (Maydeo, 2010; Faruqui and Joshi, 2012).

A minimal effective dose of 0.25 g/kg has been suggested, and most studies have found that a starting dose of 20 g of lactitol is effective and produces minimal side effects. Some studies that have allowed the subjects to make dosage increases to achieve relief of constipation symptoms and dose reductions to minimize side effects have indicated that this strategy can optimize therapy.

Maydeo (2010) presented a systematic review of six published randomized, non-randomized and open trials comparing the safety and efficacy of lactitol to those of lactulose. Overall, lactitol was comparable to lactulose in efficacy measures (normal stool consistency and number of bowel movement per week). Patients found lactitol to be more acceptable and were more compliant with it largely due to its superior palatability (73.2 % vs. 26.8 %). Lactitol was significantly better than lactulose in the frequency of adverse events (31.2 ± 0.8 % vs. 62.1 ±1.1 %, p= 0.0019). The physicians' assessment favored lactitol as compared to lactulose (61.91% vs. 47.83%). The following table is adapted from Maydeo's summary of the reviewed trials.

Parameter Evaluated	Lactitol	Lactulose
Patient's acceptance	73.2%	26.8%
Consistency of stool (normal/soft)	80.5 ± 4.5%	75.0± 8.0%
Bowel movement/week	5.9 ± 0.2	5.6 ± 0.6
Incidence of side-effects	31.2 ± 0.8	62.1 ±1.1%
Global efficacy judged by physicians	61.9%	47.8%

2. STUDY OBJECTIVE

To compare the safety and efficacy of BLI400 laxative versus placebo in constipated adults.

3. STUDY PLAN

3.1. Study Design

This is a randomized, double-blind, parallel group, multi-center study in constipated adult subjects.

3.2. Number of Subjects

Approximately 600 constipated, but otherwise healthy subjects will be randomized into this study. Approximately 30% of enrolled subjects will be elderly (greater than 65 years of age at time of randomization). A "completed" subject is defined as one who took the study treatment and completed 6 months of treatment.

3.3. Duration of Study

The day after Visit 1, subjects will begin a 14 day Screening Period to confirm their constipation status. Qualifying subjects will be randomized at Visit 2 and will begin a 6 month Treatment Period. Subjects will return for follow up clinic visits every 4 weeks during the Treatment Period.

3.4. Study Treatments

BLI400 Laxative

BLI400 laxative will be provided polyethylene bottles containing enough study medication for approximately 30 days. The bottles will be equipped with a cap that can be used to measure 10.5 grams of BLI400. Using the provided measuring cap on the bottle, subjects will be instructed to mix 2 capfuls of study medication (approximately 21 g) in 4-8 oz of juice or other beverage and take once daily, preferably in the morning. Subjects that develop persistent diarrhea or loose stools will be allowed to adjust their dose down to 10.5g (1 capful) per day.

BLI400 placebo will be provided in identical polyethylene bottles containing regular maltodextrin.

Rescue Bisacodyl

Subjects will be dispensed bisacodyl tablets at each study visit. Subjects will be instructed to take 5 – 10mg (1 -2 tablets) of bisacodyl if they are experiencing severe discomfort due to their constipation, or have not had a BM in 4 days. No more than 6 tablets (30mg) of bisacodyl should be taken in a week.

If a subject does not have a bowel movement within 24 hours of taking a bisacodyl dose, a second dose should be taken. If after the second bisacodyl dose the subject does not have a BM within 24 hours, the subject should contact the site. The investigator should then consider having the subject return for an evaluation and/or discontinuing the subject from the study to seek alternative treatment.

All study medication is required to remain at room temperature 20°-25°C (68°-77°F); excursions permitted between 15°-30°C (59°-86°F).

All drug components will also have a clinical label containing a caution statement, study code, study sponsor and subject number.

Sites can view weekly summaries of subject diary data, including rescue bisacodyl use. Investigators should consider discontinuing subjects consistently taking more than 30mg of bisacodyl per week.

3.5. **Subject Selection**

3.5.1. **Inclusion Criteria**

Subjects will be admitted to the study if they are:

1. Male or female subjects at least 18 years of age

2. Constipated, defined by the following adapted ROME II definition (Drossman et al, 2000):

   A. Fewer than 3 spontaneous defecations per week and at least one of the following symptoms for at least 12 weeks (which need not be consecutive) in the preceding 12 months:

      a. Straining during > 25% of defecations

      b. Lumpy or hard stools in > 25% of defecations

      c. Sensation of incomplete evacuation for > 25% of defecations

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, sterilized, abstinent, or vasectomized spouse)

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. Report loose (mushy) or water stools in the absence of laxative use for more than 25% of BMs during the 12 weeks before Visit 1
2. Meet the Rome II criteria for Irritable Bowel Syndrome: reports abdominal discomfort or pain that has two or more of the following three features for at least 12 weeks, which need not be consecutive, in the 12 months before Visit 1:
   - Relieved with defecation
   - Onset associated with a change in frequency of stool
   - Onset associated with a change in form (appearance of stool)
3. Subjects with known or suspected ileus, gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis, toxic megacolon
4. Subjects who have had major surgery 30 days before Visit 1; appendectomy or cholecystectomy 60 days before Visit 1; abdominal, pelvic, or retroperitoneal surgery 6 months before Visit 1; bariatric surgery or surgery to remove a segment of the GI tract at any time before Visit 1
5. Subjects with hypothyroidism that is being treated and for which the dose of thyroid hormone has not been stable for at least 6 weeks at the time of Visit 1
6. Subjects taking laxatives, enemas or prokinetic agents that refuse to discontinue these treatments from Visit 1 until after completion of the study
7. Subjects who are pregnant or lactating, or intend to become pregnant during the study
8. Subjects of childbearing potential who refuse a pregnancy test
9. Subjects who are allergic to any study medication component (lactitol or maltodextrin)
10. Subjects taking narcotic analgesics or other medications known to cause constipation
11. Subjects with clinically significant cardiac abnormalities identified at the Visit 1 ECG
12. Subjects with clinically significant laboratory abnormalities, deemed as a potential safety issue by the Investigator
13. Subjects who, in the opinion of the Investigator, should not be included in the study for any reason, including inability to follow study procedures
14. Subjects who have participated in an investigational clinical, surgical, drug, or device study within the past 30 days
15. Subjects with an active history of drug or alcohol abuse
16. Subjects have been hospitalized for a psychiatric condition or have made a suicide attempt during the 2 years before Visit 1
17. Subjects who withdraw consent at any time prior to completion of Visit 1 procedures

4. STUDY PROCEDURES

Study procedures are described as follows and depicted graphically in Section 4.4, below. Acceptable deviations from the visit schedule are indicated. These variations must not be cumulative; i.e. visits should always be scheduled in relationship to Visit 2 (Day 0).

4.1. Visit 1: Screening

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 including history of constipation (ROME criteria – see inclusion #2)
- 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 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 and urine samples will be collected for testing at a central laboratory, as shown below.

  Chemistry: alkaline phosphatase, ALT, anion gap, AST, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatine kinase (CK), creatinine, eGFR, GGT, HCG, inorganic phosphate, magnesium, osmolality, potassium, sodium, uric acid. CK-MB will be tested in samples where the CK value is greater than 2.5 times the upper normal limit.

  Hematology: hematocrit, hemoglobin, platelets count, red blood cell count, white blood cell count (and differentials)

  Pharmacokinetic (PK) Sampling: lactitol

  Urinalysis: including electrolytes (sodium, potassium, magnesium, calcium), microscopic analysis, urine osmolality

  Subjects with clinically significant laboratory abnormalities, deemed as a potential safety issue by the Investigator, may be discontinued at the Investigator's discretion.

- Provide the subject an electronic diary and review instructions with the subject in detail to ensure full understanding (refer to Section 4.1.3).
- Dispense rescue bisacodyl. Subjects will be allowed to take 5 – 10mg of bisacodyl if they are experiencing severe discomfort due to their constipation, or have not had a BM in 4 days.
- Instruct subject to maintain their normal dietary habits during study participation.
- Schedule the next study visit to occur after 14 full screening days.

Subjects that are ineligible due to prohibited medication use (Exclusion Criteria 6 and 10) may be washed out for a period of 14 days (72 hour washout only for laxatives). No additional procedures should be performed on these subjects until after they have completed washout. Subjects will receive a reminder card detailing the washout period. Rescue bisacodyl will not be dispensed at this visit. When subjects return following washout, concomitant medications should be reviewed, physical exam, vital signs, ECG, blood draws and serum pregnancy test should be performed (if not done previously).

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. **Enrollment and Allocation of Subject Number**

Subjects will be enrolled into the study only when they have given their written, informed consent to participate.

Subjects enrolled at the screening visit will be assigned a subject number by site personnel. This number will consist of:

- The 3-digit Site Number;
- A 3-digit subject identifier number (this number is a sequentially allocated number). Each site will begin with 001 for the first subject screened, 002 for the second and so on. For example, the third subject screened at Site 15 will become Subject Number 15003. After a

subject completes the informed consent process, site personnel will assign a subject number.

4.1.3. **Electronic Subject Diary during Screening Period**

Subjects will be asked to use an electronic subject diary to self-report their bowel movement and rescue medication experiences each day. Subjects will be required to enter data on each bowel movement as soon as possible following completion. This data will include assessments of BM completeness, consistency, straining and urgency.

Each dosing episode of rescue medication will be entered. Instructions on how to complete the diary questions will be supplied in a separate manual.

4.2. **Visit 2**

Subjects will return to the study center as soon as possible after the 14 day Screening Period for Visit 2.

BM Entry Criteria – to be eligible for randomization, subjects must meet the following criteria related to their Screening Period BMs:

- average of fewer than 3 complete spontaneous bowel movements (CSBMs) per week during the 14 day Screening Period. A CSBM is defined as a bowel movement which has occurred with no rescue laxative use in the prior 24 hours and is accompanied by a sense of complete evacuation
- average of fewer than 6 spontaneous bowel movements (SBMs) per week during the 14 day Screening Period. An SBM is defined as a bowel movement which has occurred with no rescue laxative use in the prior 24 hours
- No more than 1 SBM with a Bristol Stool rating of 6
- No SBMs with a Bristol Stool rating of 7

Diary Compliance Criterion to be eligible for randomization, a subject must have completed an average of at least one Bowel Movement Diary entry per day for 5 or more days per week during the 14 day Screening Period

4.2.1. **Randomization**

Subjects that meet the BM and Diary Compliance 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 < 65 years of age at time of randomization
Group 2: Subjects ≥ 65 years of age at time of randomization

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.

Vital signs will be taken. Subjects will be queried for any adverse events or changes to their concomitant medications.

4.2.2. **Study Drug**

During Visit 2, subjects will be provided with instructions on how to take the study medication and rescue medication. One bottle of study drug (a 30 day supply) will be dispensed per subject along with one box of rescue bisacodyl. The study drug bottle will be weighed for drug accountability purposes. Subjects will take a daily dose of 2 capfuls of study powder until they return for Visit 3. Subjects will be instructed to return all medication (including bisacodyl) and components at Visit 3.

4.3. **Treatment Period**

4.3.1. **Electronic Subject Diary during Treatment Period**

Each day during the Treatment Period, subjects will complete their e-diary reporting. Subjects will report each bowel movement as it occurs along with related symptoms and

characteristics (consistency, straining, urgency, completeness). Subjects will also report their daily study medication and rescue medication doses (if applicable) as they occur.

4.3.2. **Treatment Day 1**

Starting the morning of Treatment Day 1 (the day after randomization), subjects will measure two (2) capfuls of study medication and ingest it mixed in a beverage of their choice. When possible, subjects should take each dose at appromiately the same time every day (preferably in the morning). Subjects that develop persistent diarrhea or loose stools should contact their study center. Subjects with persistent diarrhea or loose stools will be allowed to adjust their dose down to 10.5g (1 capful) per day.

4.3.3. **Visits 3 – 7 (Days 28, 56, 84, 112 and 140)**

Subjects will return to the clinic every 4 weeks (+/- 2 days) for Visits 3 – 7. Vital signs (see section 4.1 for details) will be taken. Study personnel will weigh returned study medication bottles and count rescue bisacodyl tablets for accountability purposes and for consistency with the electronic diary reporting. Study personnel must discuss any electronic diary reporting irregularities (e.g. missed study medication or excessive rescue bisacodyl use, reporting compliance). Subjects will be queried for any adverse events or changes to their concomitant medications. Samples for chemistry, hematology, PK and urinalysis will be repeated as outlined in Section 4.1 (Note: serum pregnancy testing will be conducted at Visits 1, 5 and 8 only).

Subjects suspected by the Investigator of having developed lactic acidosis, characterized by abnormally low bicarbonate with abnormally high anion gap (deemed clinically significant by the investigator), should return for a redraw to test for lactate. Subjects with high lactate levels believed to be caused by the study medication should be discontinued.

A 30 day supply of study medication (1 bottle) along with 1 box of rescue bisacodyl will be dispensed at each visit. Unused product will not be redispensed. No rescue medication will be redispensed. Subjects will be instructed to bring all medication (including bisacodyl) and components at each follow up visit.

Subjects that develop persistent diarrhea or loose stools should contact their study center. Subjects with persistent diarrhea or loose stools will be allowed to adjust their dose down to 10.5g (1 capful) per day.

At Visit 7 (Day 140), 2 bottles of study medication will be dispensed so that subjects have a sufficient supply to reach Visit 8 (Day 180).

4.3.4. **Visit 8 – Day 180 (or Early Term)**

Subjects will return at after a approximately 180 days of dosing (+4 days) for their final clinic visit. 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. A physical examination will be performed. Study personnel will weigh study medication bottles and count rescue bisacodyl tablets for accountability purposes and for consistency with the electronic diary reporting. Study personnel must discuss any electronic diary reporting irregularities (e.g. missed study medication or excessive rescue bisacodyl use, reporting compliance). Subjects will be queried for any adverse events or changes to their concomitant medications. Samples for chemistry, hematology ,urinalysis and PK will be repeated as outlined in Section 4.1. Subjects suspected by the Investigator of having developed lactic acidosis (as described in Section 4.3.3) should return for a redraw to test for lactate.

4.3.5. **Day 194 Follow-up Telephone Call: *+/- 3 days***

At Day 194, approximately 2 weeks after the last study visit or early term visit, site personnel will contact subjects by telephone to query if any new adverse events have occurred and if any adverse events ongoing at Visit 8 have resolved. Subjects will also be asked about the status of their concomitant medications.

4.4. **Tabulated Study Procedures**

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

Procedures	**Visit 1** **Screening**	**Visit 2** *Day 0*	**Visits** **3 - 7** *Days: 28, 56, 84, 112, 140* *+/-2 days*	**Visit 8/** **ET** *Day 180* *+4 days*	**Day 194** ☎ *+/- 3 days*
Informed Consent	X				
Inclusion/Exclusion Criteria Review	X				
Medical History	X				
Physical Examination	X			X	
Vital Signs	X	X	X	X	
Electrocardiogram	X			X	
Review of Concomitant Medication	X	X	X	X	X
Dispense Electronic Diary	X	X	X		
Review Diary Compliance		X	X		
Blood Samples for Chemistry & Hematology Testing[2]	X		X	X	
Pharmacokinetics (PK) Sample	X		X	X	
Urine Sample for Urinalysis	X		X	X	
Dispense Rescue Bisacodyl	X	X	X		
Randomize Eligible Subjects		X			
Dispense Study Drug[1]		X	X		
Study Drug and Rescue Bisacodyl Accountability		X	X	X	
Assess Safety		X	X	X	X

[1]*Two bottles of study medication will be dispensed at Visit 7 (Day 140)*
[2]*Serum pregnancy testing will be performed at Visit 1 (Screening), Visit 5 (Day 84) and Visit 8 (Day 180) only*

4.5. **Pregnancy**

Subjects who are female and of childbearing potential must have a serum pregnancy test done at Visit 1. A positive result will rule out the participation of the subject in the study. Additional serum pregnancy tests will be performed at Visits 5 and 8. 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.

Female study subjects must be surgically sterilized or using oral contraceptives, depot contraceptives, double-barrier method, intrauterine device, or testifies that she is monogamous with a vasectomized partner. Subjects practicing abstinence must agree to use an acceptable form of birth control should they become sexually active during the study.

Women with a history of bilateral tubal ligation are not considered of childbearing potential and are not required to have a pregnancy test at screening.

Oral contraceptives, hormone implants, and injections are only considered effective if started at least 1 month before 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 amenorrhea.

4.6. **Concomitant Medications**

The use of concomitant medication will be recorded from 7 days prior to Visit 1 until the end of the study at the telephone contact on Day 194. Subjects enrolled in this study will not be permitted to take any laxatives (other than the sponsor supplied rescue bisacodyl), whether prescription or over-the-counter, from Visit 1 until after completion of Treatment Day 180. Any restricted laxative use during the study may result in termination of subject's participation. Subjects may not initiate treatment with any constipating medication.

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 (inluding a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product.

Adverse event collection will coincide with the subjects providing informed consent to participate in the study and will conclude with the end of study participation at Day 194 (2 week follow-up phone call). Diarrhea should be reported as an adverse event if a subject has more than 3 watery stools per day (Bristol Stool Rating = 7). Subjects with clinically significant laboratory results at Visit 8 which are classified by the Investigator as adverse events should return for a repeat blood draw. Subjects will be instructed to report promptly 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 treatment.

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
5	Fatal	Causes death of the participant

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 patient'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*.

In published Phase 3 studies, adverse events associated with BLI400 administered at doses required for effective treatment of constipation included flatulence, nausea, vomiting, abdominal cramping or pain and bloating. These adverse reactions were transient and subsided rapidly upon dose adjustment or cessation.

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 subject providing informed consent to participate in the study and will conclude 30 days after a subjects's last dose of study medication. Should a serious and/or unexpected adverse event occur, the Investigator must notify Braintree Laboratories immediately. The Investigator will make a decision regarding continuing the subject's study participation, and may request input from Braintree Laboratories. The Investigator will be responsible for recommending or providing the subject with appropriate medical therapy. All subjects experiencing serious adverse events will be followed until satisfactory resolution occurs. Braintree Laboratories must be kept apprised of all follow-ups relative 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 [redacted]
(M-F, 8:30 am – 5:00 pm EDT)

After hours or weekends [redacted]

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 AND INFORMED CONSENT

Institutional Review Board (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:

1) Subject did not meet BM Entry Criteria.
2) Subject did not meet Diary Compliance Criterion.
3) Subject took prohibited laxatives during the Screening or Treatment Period
4) An adverse event requiring discontinuation (including failure to tolerate study medication).
5) The Investigator decides that the subject should be dropped from the study (e.g. serious adverse event, protocol violation, non-compliance).
6) The subject decides to withdraw from the study. Subjects are free to withdraw their consent and discontinue participation in the study at any time.

Braintree Laboratories should be contacted if possible prior to discontinuation of any subject. If a subject is discontinued from the study, Braintree Laboratories must be notified with an explanation for all discontinuances.

9. DATA ANALYSIS

9.1. Sample Size

Six hundred subjects will be randomly assigned to BLI400 (21 g/day dose) or placebo in a ratio of 1:1 (300 BLI400, 300 placebo). The definition of a weekly responder is based on weekly assessments of complete spontaneous bowel movements (CSBMs).

Based on data from a previous laxative study (Lembo et al, 2011) utilizing this primary efficacy variable (percent of subjects who are responders), it is anticipated that approximately 20% of subjects would be classified as responders in the BLI400 arm, with a placebo response up to 10%. The proposed study size will have approximately 90% power to detect a difference of 10% between the active and placebo groups at a two-sided significance level of 0.05.

9.2. Null and Alternative Hypotheses

The primary objective of this study is to compare the safety and efficacy BLI400 Laxative to placebo in subjects with constipation. To establish this, the primary comparison of interest will be on the overall responder percentage based on 12 weeks of treatment. A weekly responder is a subject who has ≥ 3 CSBMs and an increase from baseline of > 1 CSBM in that week.

The null hypothesis will be that there is no difference in the response rates between BLI400 Laxative and placebo; the alternative hypothesis is that the response rate is higher for BLI400 laxative than for placebo.

9.3. Planned Analyses

Data analysis will be performed after all subjects have completed the study. No interim analyses are planned.

9.3.1. Demographic and Baseline Characteristics

An analysis of baseline comparability of the following demographic and baseline characteristics for the treatment groups will be performed.

- Age (ANOVA)
- Gender (CMH Chi square)

- Race/ethnicity (CMH Chi square)
- Weight (ANOVA)
- Screening Period Constipation Status (ANOVA)

9.3.2. **Efficacy Analyses**

Primary Efficacy Endpoint

The primary efficacy endpoint will be assessed on the basis of a binary outcome of overall treatment success or failure. The primary efficacy endpoint will be the proportion of subjects who are weekly responders for 9 out of the first 12 weeks of treatment, with at least 3 of these weeks occurring during weeks 9–12 of treatment. A weekly responder is a subject who has ≥ 3 CSBMs and an increase from baseline of > 1 CSBM in that week. A CSBM is a bowel movement that occurs with no rescue laxative use in the previous 24 hours and that is accompanied by a sense of complete evacuation.

The following equation will be used to calculate the weekly CSBM frequency:

CSBM frequency = 7 x (Number of CSBMs/number of days with non-missing CSBM assessments)

If a subject has fewer than four days of data observed for a week, then that subject's data should be considered missing for that entire week and the subject considered a non-responder.

The primary efficacy endpoint will be analyzed using the CMH test controlling for the effect of study center. The presence of a treatment-by-center interaction will be investigated by the Breslow-Day test of homogeneity of the odds ratio. The strategy for pooling centers will be based on geographical considerations, with low enrolling centers pooled by geographic region. Details of any pooling performed will be documented prior to database lock and unblinding of the study.

No bowel movements that occur within 24 hours of a rescue bisacodyl (or other prohibited laxative) dose will be included in primary or secondary efficacy analyses.

Secondary Endpoints

Secondary endpoints will include the following:

- Overall response by gender and age group (< 65, ≥ 65 years, ≥ 75 years)
- Number of study medication doses taken per week
- Number of rescue doses taken per week (includes bisacodyl and other non-study laxative)
- % of subjects not meeting ROME criteria at the end of each treatment week
- BM Frequency per week (SBM and CSBM)
- BM Frequency per month (SBM and CSBM)
- BM Symptom Ratings per week (straining, consistency, urgency, Bristol score)
- BM Symptom Ratings per month (straining, consistency, urgency, Bristol score)
- Number of diarrhea episodes per week (diarrhea is defined as > 3 watery stools per day)

9.3.3. **Safety Analyses**

Analysis of safety will be performed using the modified Intent-to-Treat population (see Section 9.4). Safety analyses may also be presented by age, gender and racial subgroup.

Adverse Events

Adverse Events will be coded using the MedDRA classification to provide a preferred term and primary system organ class for each event. Proportions of subjects with adverse events will be presented by treatment group. Tables of AEs will be presented by system organ class and preferred term, and include overall totals for AEs within each system organ class. Counting will be done by subject and not by event. A table of counts and percentages will also be made of those subjects with SAEs or AEs which led to withdrawal from the study.

Treatment-emergent AEs are defined as adverse events that had an onset day and time on or after the day and time of the first dose of study drug up to 14 days after the last dose of

study medication. Adverse Events having missing onset dates will be considered as treatment-emergent.

The difference in adverse event rates between study groups will be tested by Chi-Square or Fisher's exact test with 95% confidence intervals. Adverse events will be presented for the overall Treatment Period.

Laboratory Parameters

Summary statistics (i.e., mean, minimum, maximum, standard deviation, and number of subjects) will be presented for each treatment group for each laboratory parameter at each visit. When calculating the summary statistics only, the last observation within a visit window will be used if there are multiple observations. Changes from Visit 1 (Screening) will be presented in a similar format. An additional listing will be provided of those subjects who have clinically significant laboratory values. The data will also be presented as shift tables, and clinically significant abnormalities will be examined.

Results of laboratory tests for the change from Visit 1 (Screening) and group differences will be tested using ANOVA.

Vital Signs

Summary statistics (i.e., mean, minimum, maximum, standard deviation, and number of subjects) will be presented for each treatment group for each vital sign at each visit. When calculating the summary statistics only, the last observation within a visit window will be used if there are multiple observations. The data will also be presented as shift tables and clinically significant abnormalities will be examined.

ECG variables will be tabulated and presented for data collected at each visit. Data will be tabulated and summarized with descriptive statistics (N, mean, SD, CV%, SEM, minimum, and maximum) for each of the ECG variables. The differences in ECG variables between Visit 1 (Screening) and Visit 8 will be tested using ANOVA.

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 randomized 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 randomized subjects that took at least one dose of study medication. 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 have not violated the study eligibility criteria and have not deviated significantly from the protocol during the course of the study. 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 the 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 the Investigator 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

The Investigator and Braintree Laboratories will discuss any amendments to the study protocol. If an agreement is reached regarding the need for the amendment, it will be produced in writing by Braintree Laboratories and will be made a formal part of the protocol only after approval by an Institutional Review Board.

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. 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 BLI400 laxative, 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**

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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