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STUDY PROTOCOL

A Safety and Efficacy Evaluation of BLI801 Laxative in Adults Experiencing Non-Idiopathic Constipation

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Braintree Protocol BLI801-203

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CLINICAL PROTOCOL SUMMARY SHEET

STUDY TITLE: A Safety and Efficacy Evaluation of BLI801 Laxative in Adults Experiencing Non-Idiopathic Constipation

PROTOCOL: BLI801-203

VERSION DATE: 4-27-2016

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OBJECTIVE:

To evaluate multiple doses of BLI801 Laxative for safety and efficacy versus placebo in adults experiencing opioid induced constipation.

STUDY DESIGN:

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

SUBJECTS:

Approximately 400 male or female constipated adult subjects will be randomized in this study after completing a 21 day screening period to confirm constipation status.

STUDY MEDICATIONS:

Group 1: BLI801 High Dose

Group 2: BLI801 Mid Dose

Group 3: BLI801 Low Dose

Group 4: Placebo

DURATION OF TREATMENT

Subjects will take one dose of BLI801 Laxative or placebo per day as needed for 12 weeks for relief of constipation symptoms. Participation in this study will last for approximately 15 weeks, including the 21 day Screening Period.

PRIMARY ENDPOINT

The primary endpoint is the proportion of subjects who are weekly responders for at least 9 out of 12 weeks, with at least 3 of these weeks occurring in the last 4 weeks of treatment. A weekly responder is a subject who has ≥ 3 spontaneous bowel movements (SBMs) and an increase from baseline of > 1 SBM in that week. An SBM is a bowel movement that occurs with no rescue laxative use in the previous 24 hours.

SECONDARY ENDPOINT

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

- Overall success using a ≥50% definition (weekly response in at least 6 out of 12 weeks)
- SBM and CSBM frequency rates by week
- SBM and CSBM frequency rates by month
- Stool and symptom ratings (stool consistency, stool straining, abdominal bloating, abdominal discomfort) by week
- Stool and symptom ratings (stool consistency, stool straining, abdominal bloating, abdominal discomfort) by month
- Number of study medication doses per week
- Rescue bisacodyl doses per week

Safety endpoints will include:

- Rate of treatment emergent adverse events (assessed at all visits)
- Orthostatic vital signs (assessed at all visits)
- Changes in laboratory values from Visit 1 to Visits 3, 4 and 5
    - Serum chemistry
    - Hematology
    - Urinalysis – routine urinalysis plus urine electrolytes and osmolality

1. INTRODUCTION

A relatively new bowel cleansing preparation for colonoscopy, SUPREP® Bowel Prep Kit, containing about 44 grams of sulfate salts has been approved by the United States Food and Drug Administration. The formulation depends on the osmotic activity of the sulfate anion. The formulation has been submitted to FDA as a new drug application (NDA 22-372). Based on its safety and efficacy in Phase I -III studies (1), it is believed that an acceptable laxative dose may be achieved by reducing the volume of solution administered. Patient tolerance and safety are expected to be superior to over-the-counter (OTC) stimulant laxatives which are typically associated with defecation urgency and abdominal cramping (e.g. bisacodyl). Stimulant laxatives produce a bowel movement within several hours following a single treatment. Because the sulfate anion is poorly absorbed it acts primarily as a osmotic agent, in addition sulfate containing laxatives have been reported to increase gastrointestinal transit (2,3).

Early evaluation of a reduced dose of SUPREP for laxative use and its subsequent reformulation is described below.

Preliminary Experience with the Experimental Formulation

SUPREP® Bowel Prep Kit: a sulfate based bowel preparation

Several unpublished, IRB approved, studies were carried out by an independent investigator (John Fordtran, MD, Baylor University) to determine whether mixtures of sulfate salts that omit phosphates (which are avidly absorbed) can be effective to produce colonic purgation without producing clinically significant electrolyte and fluid shifts.

A study performed by John Fordtran compared the safety and efficacy of an optimized sulfate formulation containing a mixture of sulfate salts yielding about 44 grams of sulfate anion (SUPREP), to Fleet Phospho-soda (EZ-Prep) and NuLYTELY in normal volunteers (Baylor Study 006-181 and reference 4). The primary efficacy measure was based on total

stool output, with percentage of stool solids (as described above) serving as a secondary measurement. Five normal volunteers completed treatment with SUPREP, NuLYTELY and a Fleet Pharmaceuticals sodium phosphate preparation; EZ-Prep. SUPREP induced somewhat higher stool output compared to Fleet, yielding 2911g to Fleet's 1986g. Measurement of the quantity of solids in the final bowel movement after preparation (expressed as percent stool solids) provided an indication of bowel cleansing efficacy. Stool solids also favored SUPREP over Fleet where SUPREP samples produced an average stool solids result of 1.6%, lower than the Fleet average of 4.1% and about the same as NuLYTELY (1.1%). The Fleet preparation induced significant losses of potassium and elevation of phosphate. This increased phosphate absorption contributed to a concomitant serum calcium reduction and CaXP elevation, consistent with previous literature reports and may be due to calcium phosphate precipitation. SUPREP study subjects absorbed about 4.2g of sulfate but no other clinically significant changes in serum or urine electrolytes were observed. Urine from SUPREP volunteers was shown to have a reduced tendency to precipitate calcium phosphate compared to urine from Fleet subjects. Subject reported side effects did not show any differences between the preparations. No unexpected or serious adverse events were reported.

Studies in rats and dogs (5) demonstrated that the SUPREP formulation did not induce soft tissue calcification as occurs for the phosphate based preparations. These observations and the safety of the sulfate formulation were confirmed in studies of patients with renal and hepatic failure (6).

Two Phase 3 studies were conducted comparing SUPREP to the FDA approved preparation MoviPrep in a total of 751 patients requiring colonoscopy (1). The BLI800-301 study evaluated SUPREP as a one-day preparation, completed on the day prior to colonoscopy. The BLI800-302 study utilized a two-day (or "split-dose") regimen in which half the preparation was taken the evening prior to colonoscopy, and the remaining half completed on the morning of the procedure.

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

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

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

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

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

Adverse events were also evaluated in the Phase 3 studies. The most frequent adverse events reported by patients taking both preparations were gastrointestinal, and included the expected events of overall discomfort, abdominal pain and distension, nausea, and vomiting. No clinically significant differences between groups were seen in laboratory testing of serum chemistry and hematology. At the one month follow-up visit, no change in serum creatinine was observed for SUPREP patients.

Reduced Dose SUPREP for Laxative Use

The results described above indicated that a reduced dose of sulfate salts may safely provide relief for patients with constipation. A randomized, open-label pilot study was therefore conducted in 60 constipated patients (Braintree Study BLI801-101). SUPREP was administered at four different dose levels (1.2g, 3.7g, 6.2g and 8.7 grams of sulfate salts) as a single dose of solution to evaluate product efficacy to induce bowel movements within 3 hours of ingestion while minimizing patient discomfort and diarrhea. Since it had been reported that about 4 grams of sulfate are required to have a laxative effect (5), the 1.2g dose was chosen as a placebo dose. Patient tolerance and safety were expected to be superior to over-the-counter (OTC) stimulant laxatives (e.g. bisacodyl).

As shown in Table 2 below, most patients in the 6.2g and 8.7g groups had at least one bowel movement within 3 hours after ingesting their dose of sulfate salts. As expected, the number having a bowel movement within three hours increased with increasing dose.

Table 2
Patients with BM<3hrs

Dose	n	# with BM
10ml (1.2g)	15	6 (40%)
30 ml (3.7g)	15	8 (53%)
50 ml (6.2g)	14	12 (86%)
70 ml (8.7g)	14	10 (71%)

Table 3 shows a direct relationship between stool amount and consistency, with the 6.2g and 8.7g groups experiencing larger bowel movements of softer consistency. As expected, these groups also reported higher Bristol Stool Scores, indicating softer, looser stools.

Table 3
Mean BM Amount and Consistency

Dose	n	Stool Amount[1] Score	Stool Consistency[2] Score	Mean Bristol Stool Scale[3]
10ml (1.2g)	15	1.5	1.5	3.0
30 ml (3.7g)	14	1.8	1.8	3.8
50 ml (6.2g)	14	2.2	2.1	4.5
70 ml (8.7g)	15	2.1	2.2	5.0

[1]Amount: 1=a little; 2=some; 3=a lot
[2]Consistency: 1=hard; 2=soft; 3=liquid
[3]Bristol: 1 = separate hard lumps, like nuts – 7 = watery, no solid pieces

No significant adverse events were reported. Based on efficacy and stool form results, a dose of approximately 6.2 grams appears adequate to achieve laxation without eliciting excessive loose stools.

Sulfate Laxative Reformulation

The sulfate solution was reformulated by Dr. Fordtran in an Investigator-sponsored study to exclude magnesium sulfate. This was evaluated in a single center study comparing sulfate salt compositions containing 43.8mM (4.2g) or 80mM (7.7g) sulfate to 10mg bisacodyl (Baylor Study 008-211). The compositions were tested in seven normal volunteers for efficacy to induce a rapid, controlled bowel movement without significant gains or losses of electrolytes. Volunteers were given a single dose in an in-patient setting during which all stool and urine were collected for 24 hours after laxative administration.

A sulfate formula containing 43.8mM sulfate induced less stool and fewer bowel movements over a 12 hour period than 10mg bisacodyl. Sulfate formulas containing 80 mM sulfate induced about the same amount of stool and bowel movements as 10mg bisacodyl, although the stools had a higher water content and tended to be more liquid. The 80 mM sulfate formulation, but not the 43.8 mM formula, had a much faster time of onset inducing a bowel movement in less than three hours in all patients. Only one bisacodyl volunteer had a bowel movement in less than three hours. No study volunteer reported incontinence in association with any of the test laxatives. Gastrointestinal symptoms were similar between the 10mg bisacodyl and the sulfate formulations and no unexpected adverse events were reported. A formulation providing a 3:1 ratio of sodium to potassium minimized sodium and potassium electrolyte absorption or loss from the laxative and was considered appropriate for further study in constipated patients at a dose of about 60mM (5.8 grams sulfate).

A pilot study of the reformulated sulfate solution (BLI801 Laxative) was conducted to evaluate a seven day treatment of the BLI801 Laxative in adult outpatients meeting ROME III constipation criteria. The intent of this multi-center study was to determine the

efficacy of the laxative as both a one day and a seven day therapy. 33 patients received BLI801 laxative and 19 received placebo (a solution of sodium chloride).

The primary endpoint of the study was the percentage of patients experiencing a bowel movement within 3 hours of the first study medication dose. The co-primary endpoint was the percentage of patients with a successful treatment week, defined as not meeting ROME III criteria at the end of the treatment week. Seventy percent of patients that received BLI801 Laxative had a bowel movement within 3 hours versus 53% of placebo patients (p=0.412). The rapid effect of BLI801 Laxative was more predictable over the treatment week, with significantly more BLI801 Laxative patients having a bowel movement within 3 hours on at least 4 out of 7 treatment days, as shown below in Table 4.

Table 4

Secondary Efficacy Responder Analysis
Percent of Patients having a BM within 3 hours of Dosing (min. 4 out of 7 days)

Responder	BLI801 n (%)	Placebo n (%)	95% CI	p
All Patients (n)	33	19		
Success	20 (60.6%)	4 (21.1%)	11.4, 62.9	0.008
Fail	13 (39.4%)	15 (78.9%)		

With respect to weekly treatment success, 69.7% of BLI801 Laxative patients no longer met the ROME III definition (6) of constipation by the end of the study versus 26.3% of placebo recipients (p<0.01). There was no evidence of tachyphylaxis.

There were no statistically significant differences between BLI801 Laxative and placebo with respect to treatment emergent adverse events. Also, there was no significant differences seen for the expected patient reported symptoms of gas and cramping (rated using a five point scale ranging from “1=None” to “5=Severely Distressing”). More patients experienced watery stools in the BLI801 group, which is expected due to its laxative effect. There were no serious adverse events during the study and no on-study deaths. Laboratory results showed no differences between BLI801 Laxative and Placebo for serum chemistry data, including sulfate.

A second Phase 2 study was conducted to evaluate two dose levels of BLI801 Laxative taken on an as needed, or "on demand" basis for 4 weeks. Patients were instructed to take up to one full dose of BLI801 Laxative if they felt they needed relief of their constipation symptoms. Sixty constipated patients meeting ROME III criteria completed the protocol. Their average age was 43 years and study participants were predominantly female (88%). Subjects in both the high and low dose group averaged 4 doses of BLI801 laxative during each treatment week. There was no difference between the two dose groups with respect to overall treatment success which was defined as $\geq$ 3 complete spontaneous bowel movements (CSBMs) during a given treatment week with an accompanying increase of at least 1 CSBM from baseline for that week for 3 out of 4 weeks of treatment. The low dose group had about 35.5% of study subjects with a successful outcome according to this definition versus 38.7% for the higher dose. When a lower success threshold was applied (2 out of 4 successful weeks), the high dose group had a success rate of 58% compared to 42% in the low dose group.

As shown in Table 5, the higher dose was associated with many more patients having a BM within three hours of dose ingestion (55%) than the lower dose (29%). This difference persisted when a more strict definition of complete, spontaneous BMs was applied.

Table 5
Day 1 Efficacy Parameters

	BLI 801 Low Dose	**BLI801 High Dose**	**p**[1]
Bowel Movement (BM) within 3 hrs	9 (29%)	17 (55%)	0.062
Complete Spontaneous BM within 3 hrs	6 (19%)	11 (36%)	0.206

1) P value is from a CMH Chi-square test, controlling for site

BLI801 Laxative was well tolerated in this study with few side effects other than loose stools and diarrhea. There were more reports of treatment emergent diarrhea in the high dose group (19% vs 0%). However, average Bristol stool ratings were similar between

the dose groups (average scores about 4) with no effect of "on demand" dosing versus daily treatment observed. Other treatment emergent adverse events were infrequent, with no significant differences detected between the two treatments.

This study supports the conclusion that BLI801 laxative solution is effective and predictable both as a one day "on demand" treatment for chronic idiopathic constipation as well as a laxative for daily use. The current study will evaluate the efficacy of BLI801 Laxative in subjects whose constipation is caused by treatment with opiate containing medications.

2. STUDY OBJECTIVE

To compare the safety and efficacy of multiple doses of BLI801 Laxative versus placebo in adults experiencing opioid induced constipation.

3. STUDY PLAN

3.1. Study Design

This is a randomized, double-blind, parallel group, multi-center, dose-ranging study in adult subjects with opioid induced constipation receiving chronic opioid therapy for non-malignant pain.

3.2. Number of Subjects

Approximately 400 subjects with opioid induced constipation will be randomized into this study. A "completed" subject is defined as one who took the study treatment and completed 12 weeks of treatment.

3.3. Duration of Study

The day after Visit 1, subjects will begin a 21 day Screening Period to confirm their constipation status. Qualifying subjects will be randomized at Visit 2 and will begin a 12 week Treatment Period. Subjects will return for follow up clinic visits every 4 weeks during the Treatment Period.

3.4. Study Treatments

BLI801 Laxative

BLI801 Laxative will be provided in tablet form and will be packed in blister packs. Each dose will consist of 6 tablets as shown below:

	Component Amounts (anhydrous equivalents)	
	Na_2SO_4	K_2SO_4
High Dose	5.54g	2.27g
Mid Dose	3.69g	1.51g
Low Dose	1.85g	0.76g
Placebo	0g	0g

A small bottle containing 6 blister packaged tablets will be provided for each potential day of dosing (30 bottles per month). The bottles will be provided in boxes, each with a clinical label containing a caution statement, study code, study sponsor and kit number. Each subject will receive a 30 day supply of tablets (1 box) at Visit 2. Placebo will be provided in identical tablets containing normal maltodextrin.

Rescue Bisacodyl

Subjects will be dispensed bisacodyl (5 mg) tablets at each study visit. Subjects will be instructed 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. During the Treatment Period, subjects should not take rescue bisacodyl unless they have taken at least 2 consecutive daily doses of study medication. 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. Use of alternative rescue methods (e.g. enemas) must be pre-approved by the Sponsor.

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).

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 between the ages of ≥ 18 and < 85 years

2. Constipated, defined by the following criteria:

    - Fewer than 3 spontaneous defecations per week and at least one of the following symptoms for the previous 4 weeks:

        - Straining during > 25% of defecations
        - Lumpy or hard stools in > 25% of defecations
        - Sensation of incomplete evacuation for > 25% of defecations

3. Receiving a stable maintenance opioid regimen consisting of a total daily dose of 30 mg to 1000 mg of oral morphine, or equianalgesic amount(s) of 1 or more other opioid therapies for a minimum of 8 weeks prior to screening for non-cancer-related pain with no anticipated change in opioid dose requirement over the proposed study period as a result of disease progression. Patients will be disqualified if their average dose of long-acting maintenance opioid dose is modified outside the protocol specified range (30mg to 1000mg) at any time during the study.

4. If female, and of child-bearing potential, is using an acceptable form of birth control (hormonal birth control, IUD, double-barrier method, depot contraceptive, sterilized, abstinent, or vasectomized spouse)

5. Negative pregnancy test at screening (Visit 1), if applicable

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

3.5.2. **Exclusion Criteria**

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

1. Subjects with known or suspected ileus, gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis ortoxic megacolon
2. Subjects who have had major surgery within 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
3. Medical conditions associated with diarrhea, intermittent loose stools or constipation, which could confound the interpretation of the results, eg, fecal incontinence or irritable bowel syndrome. Subjects with irritable bowel syndrome (IBS) that has been previously diagnosed by a physician prior to initiation of the constipating therapy and that meets the following criteria, are excluded:
    a. Absence of a structural or biochemical explanation for the abdominal pain symptom
    b. At least 12 weeks during a period of 12 months, of abdominal discomfort or pain with at least 2 of the following 3 features:
        i. Relieved with defecation, and/or
        ii. Onset associated with a change in frequency of stool, and/or
        iii. Onset associated with a change in form of stool.
4. Subjects diagnosed with chronic constipation prior to initiation of opioid treatment
5. Subjects taking laxatives (with the exception of fiber supplements), prokinetic agents or antidiarrheal drugs and refuse to discontinue these treatments from Visit 1 until after completion of Visit 5
6. Subjects who are pregnant or nursing, or intend to become pregnant during the study
7. Subjects of childbearing potential who refuse a pregnancy test
8. Subjects who are allergic to any BLI801 component
9. Subjects taking non-opioid medications or supplements known to cause constipation
10. Subjects with an active history of drug or alcohol abuse
11. Subjects who have participated in an investigational clinical, surgical, drug, or device study within the past 30 days
12. Subjects who, in the opinion of the Investigator, should not be included in the study for any reason, including inability to follow study procedures.
13. Subjects who have had a colonoscopy within 2 weeks of Visit 1 or are scheduled to have a colonoscopy during their participation in the study.
14. 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)
- Physical examination (including height and body weight)
- Vital signs: including temperature, weight, heart rate, respiratory rate, and an assessment of orthostatic hypotension (while seated and after standing for a minimum of 2 minutes)
- A 12-lead ECG will be performed by qualified, trained site personnel. ECG output must be reviewed by a physician investigator (MD only). 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, ionized calcium, magnesium, osmolality, potassium, sodium, sulfate and 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)

  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 21 full screening days.

Subjects that are ineligible due to prohibited medication use (Exclusion Criteria 5 and 9) must be washed out for a period of 14 days prior to beginning the Screening Period. No additional procedures should be performed on these patients until after they have completed washout (laboratory testing must be repeated after washout if done at Visit 1). 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 and vital signs 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 015 will become Subject Number 015003. 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: Randomization**

Subjects will return to the study center as soon as possible after the 21 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 spontaneous bowel movements (SBMs) per week during the last 2 weeks of the 21 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 5 responses in the bowel movement diary entries per week or more during the last 2 weeks of the 21 day Screening Period.

Vital signs will be taken. Subjects will be queried for any adverse events or changes to their concomitant medications (including ongoing opioid dose). Subjects will complete the Patient Assessment of Constipation Quality of Life questionnaire (PAC-QOL, refer to Appendix A) and the Patient Assessment of Constipation Symptom questionnaire (PAC-SYM, refer to Appendix B).

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. Dispensing kits out of order is considered a protocol violation.

4.2.1. **Study Medication**

During Visit 2, subjects will be provided with instructions on how to take the study medication. A 30 day supply of study medication will be dispensed per subject. Subjects will take a daily dose of study medication (6 tablets) as needed to treat constipation symptoms. Daily dosing is not required.

Subjects will also be dispensed bisacodyl (5 mg) tablets at each study visit. Subjects will be instructed 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. Subjects should not take rescue bisacodyl unless they have taken at least 2 consecutive daily doses of study medication.

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, and the reason for taking the dose (eg, subject felt constipated, subject didn't have a BM today, etc). On days in which no dosing was reported, subjects will be prompted to answer why they felt like they did not need a dose that day.

4.3.2. **Treatment Day 1**

Starting on Treatment Day 1 (the day after randomization), subjects will take a daily dose of study medication (6 tablets) as needed to treat their symptoms of constipation.

4.3.3. **Visits 3 – 4 (Day 28 and 56)**

Subjects will return to the clinic for Visit 3 (Day 28 +/- 2 days) and Visit 4 (Day 56 +/- 2 days). Vital signs will be repeated. Study personnel will review dosing bottles (including blister packs) 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. excessive study medication or rescue bisacodyl use, reporting compliance). Subjects will complete the PAC-QOL and PAC-SYM questionnaires. Subjects will be queried for any adverse events or changes to their concomitant medications (including ongoing opioid dose). Samples for chemistry, hematology and urinalysis will be repeated as outlined in Section 4.1.

A 30 day supply of study medication along with 1 packet 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.

4.3.4. **Visit 5 – Day 84**

Subjects will return at after a full 84 days of dosing (+4 days) for their final clinic visit. Vital signs and ECG will be repeated. A physical examination will be performed (including bodyweight). Study personnel will review dosing bottles (including blister packs) 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. excessive study medication or rescue bisacodyl use, reporting compliance). Subjects will complete the PAC-QOL and PAC-SYM questionnaires. Subjects will be queried for any adverse events or changes to their concomitant medications (including ongoing opioid dose). Samples for chemistry, hematology and urinalysis will be repeated as outlined in Section 4.1.

4.3.5. **Day 98 Follow-up Telephone Call: *+/- 3 days***

At Day 98, 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 5 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** *Days: 28* *+/-2 days*	**Visit 4** *Day 56* *+/-2 days*	**Visit 5/ ET** *Day 84* *+4 days*	**Day 98** ☎ *+/- 3 days*
Informed Consent	X					
Inclusion/Exclusion Criteria Review	X					
Medical History	X					
Physical Examination	X				X	
Vital Signs	X	X	X	X	X	
Electrocardiogram	X				X	
Review of Concomitant Medication	X	X	X	X	X	X
Dispense Electronic Diary	X	X	X	X		
Blood Samples for Chemistry & Hematology Testing	X		X	X	X	
Urine Sample for Urinalysis	X		X	X	X	
Dispense Rescue Bisacodyl	X	X	X	X		
Randomize Eligible Subjects		X				
Subject to Complete PAC-QOL, PAC-SYM		X	X	X	X	
Dispense Study Drug		X	X	X		
Study Drug and Rescue Bisacodyl Accountability		X	X	X	X	
Assess Safety		X	X	X	X	X

4.5. **Pregnancy**

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

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.

4.6. **Concomitant Medications**

The use of concomitant medication will be recorded from 14 days prior to Visit 1 until the end of the study at the telephone contact on Day 98. 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 84. Any restricted laxative use during the study may result in termination of subject's participation. Subjects may not initiate treatment with any constipating medication and must remain on a qualifying dose of opioid pain medication (30mg to 1000mg).

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.

Adverse event collection will coincide with the patient providing informed consent to participate in the study and will conclude with the end of study participation at Day 98 (2 week follow-up phone call). Diarrhea should be reported as an adverse event if a patient has more than 3 watery stools per day (Bristol Stool Rating = 7). Patients with clinically significant laboratory results at Visit 5 which are classified by the Investigator as adverse events should return for a repeat blood draw. Patients 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 Phase 3 studies, adverse events associated with Oral Sodium Sulfate administered at doses consistent with colonoscopy preparation have included nausea, vomiting, abdominal cramping and bloating. These adverse reactions were transient and subsided rapidly.

In a Phase 2 study of BLI-801 laxative, the most frequently reported adverse events were abdominal pain, diarrhea, flatulence and nausea. These adverse reactions were transient and subsided rapidly.

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 a patient'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 (M-F, 8:30 am – 5:00 pm EDT)	781-843-2301
After hours or weekends	781-964-9051

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 or non-opioid constipating medications during the Screening or Treatment Period
4) Subject significantly modified their opioid medication dose
5) An adverse event requiring discontinuation (including failure to tolerate study medication).
6) The Investigator decides that the patient should be dropped from the study (e.g. serious adverse event, protocol violation, non-compliance).
7) The patient decides to withdraw from the study. Patients 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.

9. DATA ANALYSIS

9.1. Sample Size

Four hundred subjects will be randomly assigned to BLI801 Laxative (one of 3 doses) or placebo in a ratio of 1:1:1:1 (100 subjects per group). The definition of a weekly responder is based on weekly assessments of spontaneous bowel movements (SBMs).

Based on data from a previous Phase 2 study, it is anticipated that approximately 50% of subjects would be classified as responders in the BLI801 arm, with a placebo response up to 30% (based on placebo response in recent Phase 3 studies with the same endpoint) (REF). The proposed study size will have greater than 80% power to detect a difference of 20% between the active and placebo groups at a one-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 of BLI801 Laxative to placebo in patients with opioid induced 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 SBMs and an increase from baseline of > 1 SBM in that week.

The null hypothesis will be that there is no difference in the response rates between BLI801 Laxative and placebo, the alternative hypothesis being that the response rate is higher for BLI801 Laxative than for placebo.

9.3. Planned Analyses

9.3.1. Demographic and Baseline Characteristics

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)

- Constipation History (ANOVA)
- Screening spontaneous bowel movement frequency (ANOVA)
- Screening rescue bisacodyl use (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 proportion of subjects who are weekly responders for 9 out of the 12 weeks of treatment, with at least 3 of these weeks occurring in the last 4 weeks of treatment. A weekly responder is a subject who has an average of ≥ 3 SBMs/week and an average increase from baseline of > 1 SBM/week in that week. A SBM is a bowel movement that occurs with no rescue laxative use in the previous 24 hours.

Superiority Hypothesis:

The primary endpoint of treatment success will be based upon the difference $D=P_1-P_2$, where P_1 is the observed success fraction in the BLI801 Laxative group (experimental group) and P_2 is the observed success fraction in the placebo group (control group). The procedure tests the null hypothesis

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

versus the alternative hypothesis

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

where π_1 is the true underlying probability of successful treatment in the BLI801 Laxative group, and π_2 is the true underlying success probability in the placebo group.

We will test the null hypothesis of superiority separately for the comparisons of individual BLI801 Laxative dose levels versus placebo. We will preserve the family-wise type I error rate at 5% using the Bonferroni approach, conducting each test at the 2.5% two-sided level. If multiple comparisons are significant, we will conduct a test comparing the two dose levels of BLI800 at the two-sided 5% level. As we will only perform this test conditionally on the other tests being significant, it has no effect on the family-wise type I error rate, and so it requires no further multiplicity adjustment.

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

SBM frequency = 7 X (Number of SBMs/number of days with non-missing SBM 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 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 will include the following:

- Overall response by gender and age group (< 65, ≥ 65 years)
- Number of study medication doses taken per week (mean)
- Number of rescue bisacodyl doses taken per week (mean)
- % of subjects not meeting ROME criteria at the end of each treatment week
- Mean Time to BM after dose
- Weekly stool consistency
- Number of BMs with straining per week (mean)
- SBM frequency rates during each week (weeks 1 to 12)
- BM urgency score per week (mean)
- Bristol Stool Form score per week (mean)
- Number of BMs per week (mean)
- Number of diarrhea episodes per week (mean) – diarrhea is defined as > 3 watery stools per day

- Weekly stool straining
- Change in PAC-SYM from Baseline by Visit (total and individual scores)
- Change in PAC-QOL from Baseline by Visit (total and individual scores)

9.3.3. **Safety Analyses**

Analysis of safety will be performed using the Intent to Treat population (see Section 9.4).

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 30 days after the last application of treatment. 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 baseline 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 baseline (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 2 (pre-dose) and Visits 3 - 5 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 the primary efficacy analysis and all safety analyses.

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 secondary efficacy analyses and sensitivity analysis of the primary efficacy endpoint.

9.4.3. Per Protocol Population

The per protocol (PP) population will consist of all subjects in the mITT population who have not violated any major entry criteria and have not deviated significantly from the

protocol during the course of the study. 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 all 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 BLI801 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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2. Heizer WD, Sandler RS, Seal E, Murray SC, Busby MG, Schliebe BG, Pusek SN: Intestinal effects of sulfate in drinking water on normal human subjects. Dig Dis Sci 1997;42(5):1055-1061.

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4. Patel V, Nicar M, Emmett M, Asplin J, Maguire JA, Santa Ana CA, Fordtran JS. Intestinal and renal effects of low-volume phosphate and sulfate cathartic solutions designed for cleansing the colon: pathophysiological studies in five normal subjects. Am. J. Gastro. 2009: 2009 Apr;104(4):953-65.

5. Cocchetto DM, Levy G. Absorption of orally administered sodium sulfate in humans. J Pharm Sci. 1981; 70(3):331-3.

6. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology. 2006 Apr;130(5):1480-91. Review. Erratum in: Gastroenterology. 2006 Aug;131(2):688.

APPENDIX A

Patient Assessment of Constipation – Quality of Life (PAC-QOL) Questionnaire

PAC-QOL ®

PATIENT ASSESSMENT OF CONSTIPATION

The following questions are designed to measure the impact constipation has had on your daily life over the past 2 weeks. For each question, please check one box.

The following questions ask about your symptoms related to constipation. During the past 2 weeks, to what extent or intensity have you...	Not at all 0	A little bit 1	Moderately 2	Quite a bit 3	Extremely 4
1. felt bloated to the point of bursting?	☐	☐	☐	☐	☐
2. felt heavy because of your constipation?	☐	☐	☐	☐	☐
The next few questions ask about how constipation affects your daily life. During the past 2 weeks, how much of the time have you...	**None of the time 0**	**A little of the time 1**	**Some of the time 2**	**Most of the time 3**	**All of the time 4**
3. felt any physical discomfort?	☐	☐	☐	☐	☐
4. felt the need to have a bowel movement but not been able to?	☐	☐	☐	☐	☐
5. been embarrassed to be with other people?	☐	☐	☐	☐	☐
6. been eating less and less because of not being able to have bowel movements?	☐	☐	☐	☐	☐

PAC-QOL

Patient Assessment of Constipation – Quality of Life (PAC-QOL) Questionnaire

The next few questions ask about how constipation affects your daily life. During the past 2 weeks, to what extent or intensity have you...	Not at all 0	A little bit 1	Moderately 2	Quite a bit 3	Extremely 4
7. had to be careful about what you eat?	☐	☐	☐	☐	☐
8. had a decreased appetite?	☐	☐	☐	☐	☐
9. been worried about not being able to choose what you eat (for example, at a friend's house)?	☐	☐	☐	☐	☐
10. been embarrassed about staying in the bathroom for so long when you were away from home?	☐	☐	☐	☐	☐
11. been embarrassed about having to go to the bathroom so often when you were away from home?	☐	☐	☐	☐	☐
12. been worried about having to change your daily routine (for example, traveling, being away from home)?	☐	☐	☐	☐	☐

The next few questions ask about your feelings related to constipation. During the past 2 weeks, how much of the time have you...	None of the time 0	A little of the time 1	Some of the time 2	Most of the time 3	All of the time 4
13. felt irritable because of your condition?	☐	☐	☐	☐	☐
14. been upset by your condition?	☐	☐	☐	☐	☐
15. felt obsessed by your condition?	☐	☐	☐	☐	☐
16. felt stressed by your condition?	☐	☐	☐	☐	☐
17. felt less self-confident because of your condition?	☐	☐	☐	☐	☐
18. felt in control of your situation?	☐	☐	☐	☐	☐

PAC-QOL

Patient Assessment of Constipation – Quality of Life (PAC-QOL) Questionnaire

The next questions ask about your feelings related to constipation. During the past 2 weeks, to what extent or intensity have you...	Not at all 0	A little bit 1	Moderately 2	Quite a bit 3	Extremely 4
19. been worried about not knowing when you are going to be able to have a bowel movement?	☐	☐	☐	☐	☐
20. been worried about not being able to have a bowel movement?	☐	☐	☐	☐	☐
21. been more and more bothered by not being able to have a bowel movement?	☐	☐	☐	☐	☐
The next questions ask about your life with constipation. During the past 2 weeks, how much of the time have you...	**None of the time 0**	**A little of the time 1**	**Some of the time 2**	**Most of the time 3**	**All of the time 4**
22. been worried that your condition will get worse?	☐	☐	☐	☐	☐
23. felt that your body was not working properly?	☐	☐	☐	☐	☐
24. had fewer bowel movements than you would like?	☐	☐	☐	☐	☐
The next questions ask about your degree of satisfaction related to constipation. During the past 2 weeks, to what extent or intensity have you been...	**Not at all 0**	**A little bit 1**	**Moderately 2**	**Quite a bit 3**	**Extremely 4**
25. satisfied with how often you have a bowel movement?	☐	☐	☐	☐	☐
26. satisfied with the regularity of your bowel movements?	☐	☐	☐	☐	☐
27. satisfied with the time it takes for food to pass through the intestines?	☐	☐	☐	☐	☐
28. satisfied with your treatment?	☐	☐	☐	☐	☐

PAC-QOL

APPENDIX B

Patient Assessment of Constipation – Symptom (PAC-SYM) Questionnaire

Patient Assessment of Constipation-Symptom Questionnaire (PAC-SYM)

This questionnaire asks you about your constipation symptoms in the past two weeks. Answer each question according to your symptoms, as accurately as possible.

Please indicate how severe your symptoms have been during the past two weeks. If you have not had the symptom during the past two weeks, check 0. If the symptom seemed mild, check 1. If the symptom seemed moderate, check 2. If the symptom seemed severe, check 3. If the symptom seemed very severe, check 4. Please be sure to answer every question.

How severe have each of these symptoms been in the last two weeks?	Absent 0	Mild 1	Moderate 2	Severe 3	Very Severe 4
1. discomfort in your abdomen					
2. pain in your abdomen					
3. bloating in your abdomen					
4. stomach cramps					
5. painful bowel movements					
6. rectal burning during or after a bowel movement					
7. rectal bleeding or tearing during or after a bowel movement					
8. incomplete bowel movement, like you didn't "finish"					
9. bowel movements that were too hard					
10. bowel movements that were too small					
11. straining or squeezing to try to pass bowel movements					
12. feeling like you had to pass a bowel movement but you couldn't (false alarm)					