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	Baarerstrasse 22, CH-6300, Zug, Switzerland

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PROTOCOL SIGNATURE PAGE

A Randomized, Placebo-controlled, Double-blinded, Multicenter Study of the Bioequivalence of Sprinkle and Capsule Formulations of Lubiprostone, as Compared to Placebo, in Adult Subjects with Chronic Idiopathic Constipation

PROTOCOL SCMP-0211-302

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If any contact information changes during the course of the study, written notification will be provided to the Investigator and IRB/IEC, per requirements. A protocol amendment will not be required in this case.

INVESTIGATOR AGREEMENT

I have read this protocol and discussed it with the Sponsor's representative. I agree to conduct this study in accordance with the protocol, International Conference on Harmonization (ICH) Guideline on Good Clinical Practices (GCP) and all applicable regulations.

I will use only the informed consent documentation (ICD) approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and Sponsor or its representative and will fulfil all responsibilities for submitting pertinent information to the IRB/IEC responsible for this study.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.

I agree that the Sponsor or its representatives shall have access to all original source documents, regardless of media, from which case report form (CRF) information may have been generated.

I agree that all information regarding this protocol and lubiprostone will be treated as strictly confidential. I further agree not to use the name of Sucampo AG (SAG), the name of any of its employees, the name of the drug or compound, or information relating to this protocol or any amendment hereto, in any publicity, news release, or other public announcement, written or oral, without the prior written consent of SAG

_____

Principal Investigator Signature Date

_____

Name of Principal Investigator (Printed)

_____

Institution

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ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
ALT	Alanine Transaminase (SGPT)
ANCOVA	Analysis of Covariance
AST	Aspartate Transaminase (SGOT)
BID	Twice Daily
BM	Bowel Movement
BOCF	Baseline Observation Carried Forward
BUN	Blood Urea Nitrogen
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	Confidence Interval
CIC	Chronic Idiopathic Constipa ion
CMH	Cochran-Mantel-Haenzel
CRF	Case Report Form
eCRF	Electronic Case Report Form
CS	Clinically Significant
EDC	Electronic Data Capture
FDA	Food and Drug Administration
ECG	Electrocardiogram
EOT	End-of-Treatment
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
IBS	Irritable Bowel Syndrome
ICD	Informed Consent Documentation
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRE	Immediately Reportable Event
IRT	Interactive Response Technology

ITT	Intention-to-Treat
LDH	Lactose Dehydrogenase
MAO	Monoamine Oxidase
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
mL	Milliliters
NCS	Not Clinically Significant
NDA	New Drug Application
OC	Observed Case
OIC	Opioid-induced Constipation
OTC	Over-the-Counter
PP	Per Protocol
QD	Once Daily
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical An lysis Plan
SBM	Spontaneous Bowel Movement
SNRI	Serotonin–Norepinephrine Reuptake Inhibitor
SOC	System Organ Class
SSRI	Serotonin-Specific Reuptake Inhibitor
WBC	White Blood Cell
WHO	World Health Organization

PROTOCOL SYNOPSIS

A Randomized, Placebo-controlled, Double-blinded, Multicenter Study of the Bioequivalence of Sprinkle and Capsule Formulations of Lubiprostone, as Compared to Placebo, in Adult Subjects with Chronic Idiopathic Constipation			
Study Phase:	Phase 3		
Short Title:	Evaluation of the bioequivalence of sprinkle and capsule formulations of lubiprostone, as compared to placebo, in adults with chronic idiopathic constipation (CIC)		
Objectives, Study Medication and Dose Regimen:	To evaluate the bioequivalence of sprinkle and capsule formulations of lubiprostone, as compared to placebo, when administered orally (at 24 mcg twice daily [BID]) in subjects with CIC. Dose: 0 or 24 mcg BID (48 mcg/day) All subjects will take study medication BID from Day 1 through the evening of Day 7 and will return to the clinic on the morning of Day 8 for their End-of-Treatment (EOT) visit.		
Assumed No. of Sites: **Est. No. Enrolled Subjects:** **Est. No. Screened Subjects:**	Approximately 70 (United States) Approximately 522; 1:1:1 randomizati n (placebo: 24 mcg Sprinkle: 24 mcg Capsule; 174 subjects per arm); st atified by baseline spontaneous bowel movement (SBM) frequency ate (<1.5 or ≥1.5) and site. 1,044		
Duration of Participation: **Duration of Treatment:**	Approximately 4 weeks (including screening and follow-up) 7-day treatment		
Study Schedule:	Visit 1	Screening (Clinic Visit); Note: All subjects will complete daily diaries to record bowel habits, which will be used to confirm CIC eligibility	Day -14 (-3 day window)
	Visit 2:	Randomization & Treatment Period	Morning dose on Day 1 to evening dose on Day 7
	Visit 3:	End-of- Treatment (All subjects)	Day 8 (+2 day window)
	Visit 4:	Follow-up	Day 15 (+3 days)

Treatment:	• Treatment A: Lubiprostone sprinkle plus placebo capsule; taken BID for 7 days • Treatment B: Lubiprostone capsule plus placebo sprinkle; taken BID for 7 days • Treatment C: Placebo capsule plus placebo sprinkle; taken BID for 7 days The sprinkle formulation of lubiprostone (24 mcg) is supplied in an easy-to-open and easy-to-handle oversized hard capsule and will be sprinkled onto a teaspoon of applesauce for oral administration, followed by intake of 240 milliliters (mL) of water. The capsule formulation (24 mcg) is supplied as soft-gelatin capsules and will be taken with 240 mL of water. Doses should be taken with meals.
Inclusion Criteria:	1. Subject is male or female, ≥18 years of age. 2. Subject either has medically-confirmed diagnosis of chronic constipation (per Rome III; Appendix 1), or meets the diagnosis as confirmed using the Rome III constipation module questionnaire (Appendix 2) during the Screening period. 3. Subject is able to comprehend and willing to sign an ICD approved by the IRB after explanation of the nature and objectives of the study and prior to the conduct of any study specific procedure. 4. If subject is taking concomitant medication (prescribed or over-the-counter) that affects gastrointestinal motility, he/she must discontinue use at the time of the Screening Visit (Visit 1) through the Follow up Visit (Visit 4); these medications include: a. Cholinesterase inhibitors; anti-spasmodic, anti-diarrheal, anti-constipation, or prokinetic agents; laxative agents (e.g., PEG 3350), including homeopathic remedies; b. Tricyclic antidepressants; and/or c. Any medication, at the discretion of the Investigator, known to relieve or cause constipation or constipation-related symptoms, and which the Investigator, based on the medical history of the subject, suspects to be a contributing factor to the patient's chronic constipation, or may otherwise confound the evaluation of treatment response. **Exceptions:** Treatment with anticholinergic agents, SSRIs, SNRIs, or MAO inhibitors is allowed if a stable dose has been used for at least 30 days prior to the Screening Visit and not likely to change during the study. 5. If subject is taking a fiber supplement or a concomitant medication for the indication of lowering blood pressure, usage must have been at a stable dose and schedule for at least 30 days prior to the Screening Visit and not likely to change during the study. 6. Subject daily diary is at least 70% compliant for evening/end-of-day assessments during the Screening period. 7. Subject daily diary indicates an average of less than 3 spontaneous bowel movements (SBMs) per week during the 14 days prior to randomization. 8. Subject daily diary indicates one or more of the following for at least 25% of SBMs during the 14 days prior to randomization:

	• Bristol Stool Scale Type 1 or 2; • Moderate to very severe straining associated with SBMs; and/or • Sensation of incomplete evacuation. **Note:** For subjects with no reported SBMs during the Screening Period, it is not necessary to meet criteria for bowel movement characteristics, i.e., moderate to very severe straining and incomplete evacuation.
Exclusion Criteria:	1. Subject has known or suspected anatomic or organic disorders of the large or small bowel; e.g.: a. Associated with a mechanical bowel obstruction (e.g., tumor, hernia, obstructive polyps), or pseudo-obstruction; b. Associated with large or small bowel disorder such as ulcerative colitis or Crohn's disease. 2. Subject is a candidate for, or has undergone abdominal surgery for which an impact on GI transit/motility or defecation cannot be excluded such as bowel resection, colectomy, and gastric bypass surgery (exceptions: appendectomy, cholecystectomy, benign polypectomy and inguinal hernia). 3. Subject ha any gastrointestinal (GI) condition, other than constipation affecting GI motility or defecation. 4. Subject repor weight loss, anemia, and/or rectal bleeding AND has no documentation of the results of either a flexible sigmoidoscopy or colonoscopy performed during the 6 months prior to dosing since the report of that condition or has documented evidence suggestive of a non GI related etiology as a cause of these symptoms. 5. Subj ct has a history of loss of consciousness and/or syncope; has been iagnosed with, or has current evidence of, hypotension (i.e., systol c pressure <90 mmHg and/or diastolic pressure <60 mmHg) ba ed upon orthostatic vital sign measurements taken at the time of screening; and/or has any other medical/surgical condition that might interfere with the absorption, distribution, metabolism, or excretion of the study medication. 6. Subject has taken a systemic antibiotic within 30 days prior to screening or is scheduled to take this at any time during the study. 7. Subject has an uncontrolled cardiovascular, liver or lung disease, neurologic or psychiatric disorder, or other systemic disease, which the Investigator feels is clinically significant and would limit the subject's ability to participate in the trial. 8. Subject is unable to eat or drink, take oral medications, or to hold down oral medications due to vomiting. 9. Subject has impaired renal function (i.e., serum creatinine concentration > 1.8 mg/dL) as identified at the Screening Visit, or is known to have impaired hepatic function (Child-Pugh B or C). 10. Subject has abnormalities in vital signs, electrocardiogram (ECG), or laboratory test results (hematology, urinalysis, or blood chemistry) that cannot be explained by underlying comorbidity(ies) and which, in the Investigator's opinion, are clinically significant, relevant, and should preclude the subject's participation in the trial. 11. Subject has current evidence of, or has been treated for, cancer within the past 5 years, with the exception of localized basal cell,

	squamous cell skin cancer, or *in situ* cancer which has been resected. 12. Subject (female of childbearing potential) is currently breastfeeding or plans to breastfeed, has a positive pregnancy test, refuses/unwilling to undergo pregnancy testing, and/or does not agree to use protocol-specified contraceptive for the duration of the study. 13. Subject demonstrates a potential for non-compliance with the study protocol (i.e., dosing schedule, visit schedule, or study procedures). 14. Subject has received an investigational medication within 30 days prior to the Screening Visit (Visit 1), or plans to participate in another clinical trial during the study period. 15. Subject has received AMITIZA, lubiprostone, SPI-0211, or RU-0211 at any time prior to participation in this study.
Guidance for Rescue Treatment:	If necessary, rescue medication may be used only during the Screening period to help induce a BM. In the event that no BM has occurred within a 3-day period during the Screening period, the use of recommended rescue medications may be allowed per Investigator's instructions. Recommended rescue medications include bisacodyl suppository and saline enema. Rescue medication should not be used during the 7-day treatment period (Week 1 following Randomization).
Efficacy Endpoints:	*Primary efficacy endpoint:* • Equivalence analysis of observed SBM count at Week 1 for lubiprostone sprinkle vs. lubiprostone capsule *Secondary efficacy endpoints:* • Superiority analysis of observed SBM count at Week 1 for lubiprostone sprinkle *and* lubiprostone capsule vs. matching placebo • Change from baseline in observed SBM count at Week 1 • Overall and mean change from baseline in stool consistency associated with SBMs at Week 1 • Overall and mean change from baseline in straining associated with SBMs at Week 1 • SBM frequency rate at Week 1 • Change from baseline in SBM frequency rate at Week 1
Safety Evaluations:	*Safety endpoints*: • Incidence of adverse events grouped by MedDRA System Organ Class and Preferred Term • Changes from baseline in clinical laboratory parameters (hematology, serum chemistry, urinalysis) • Changes from baseline in vital sign measurements
Sample Size Estimate Calculation:	In clinical studies of the lubiprostone capsule formulation during the CIC development program, the average observed SBM count at Week 1 for lubiprostone 24 mcg BID was 5.62 with a standard deviation of 4.24. In order to achieve the conclusion of equivalence between the sprinkle and capsule formulations of lubiprostone, the 90% confidence interval for the ratio of means has to be contained within the interval of [0.8, 1.25]. Thus, a sample size of 156 per group is required to achieve 90% power at a 10% significance level. Assuming 10% of subjects do not meet criteria for inclusion in the Per Protocol population and/or do not have observed week 1 SBM count due to early withdrawal or other reasons, 174 subjects per treatment group (a total of 522 subjects) will be required for this study.

Statistical Methodology:	For the primary efficacy variable of observed Week 1 SBM count, the 90% confidence intervals (CIs) of the treatment difference between the sprinkle and capsule formulations will be calculated and the equivalence of the two medications can be claimed if the equivalence limits are within the interval of [0.8, 1.25]. For the secondary efficacy variables to compare the sprinkle and capsule formulations of lubiprostone with the matching placebo group, analysis of covariance (ANCOVA) and the van Elteren test will be performed. Adverse events will be summarized in terms of incidence by treatment group and overall. Overall mean and changes from baseline or clinical abnormalities in clinical laboratory data and vital signs will be summarized by treatment group and overall.

SCHEDULE OF EVALUATIONS

Study Stage	Screening Period and Eligibility/ Baseline SBM Diary[1]	Randomization	End-of-Treatment	Follow-up[11]
Study Day	**-14 (-3 window)**	**1**	**8 (+2)**	**15 (+3)**
Visit Number	**1**	**2**	**3**	**4**
Assessment				
Informed Consent	X			
Inclusion/Exclusion	X	X		
Demographics	X			
Medical History	X	X		
Vital Signs[2]	X	X	X	X
12-Lead ECG	X			
Height and Weight[3]	X	X	X	X
Physical Examination[4]	X	X	X	X
Blood Chemistry, Hematology, Urinalysis	X	X	X	X
Pregnancy Test[5]	X	X		X
Bowel Habits Data Collection[6]	←	→		
Concomitant Medications[7]	←	→		
Adverse Events[8]	←	→		
Study Medication Distribution[9]		X		
Study Medication Collection[10]			X	

[1] Use of a rescue medication is permitted during the Screening period but prohibited during the 7-day treatment period;
[2] Orthostatic blood pressure and heart rate measurements (i.e., first measurement after 5 minutes in supine position, followed by a second measurement after 5 minutes in standing position) will be taken at Screening and Randomization (i.e., 0 hour/pre-dose and 1-hour post-dose); all other blood pressure and heart rate measurements (i.e., at End-of-Treatment and at the Follow-up Visit) will be taken with the subject in supine position for at least 5 minutes prior to measurement. If abnormalities in blood pressure (i.e., systolic pressure <90 mmHg and/or diastolic pressure <60 mmHg, or a decrease in orthostatic systolic and/or diastolic pressure [from supine to standing] of ≥20 mmHg) are observed at 1-hour post-dose on the day of first dose (Randomization), a repeat measurement of orthostatic blood pressure and heart rate must be taken at 2 hours post-dose. If abnormalities persist at 2 hours post-dose, subject should be discontinued immediately, and an AE of hypotension should be recorded;
[3] Height is captured at the Screening Visit only. Weight is captured at the Screening, Randomization, End-of-Treatment, and Follow-up Visits;
[4] A full physical examination will be performed at Screening, and abbreviated physical examinations will be performed at all other designated visits, reviewing only those body systems where there has been a change in health or there is new finding to report;

[5] All females of childbearing potential will have a serum pregnancy test during Screening. A urine pregnancy test will be performed at the Randomization and Follow-up visits;
[6] Details regarding bowel movements (time of occurrence and associated subject ratings of consistency and straining), as well as details regarding rescue medication administration, will be collected via an electronic diary by subject from Screening. Recue medication is allowed only during Screening, but bowel movement information will be collected through the end of treatment;
[7] Will include history of medications used within 30 days of the Screening Visit. A full history of constipation medication use should be collected, with particular focus on any constipation medications taken within the 90 days prior to screening;
[8] AEs will be recorded from the time the informed consent is signed. Those occurring prior to first dose of study drug will be considered non-treatment emergent;
[9] Observe the subject as he/she administers the first dose of study medication while in the clinic at Visit 2. One bottle of study medication and applesauce will be distributed at this visit. For all subjects, the last dose of treatment will be administered the evening before Visit 3;
[10] Subjects should return the bottle of study medication to the site at Visit 3 for drug accountability. If the study medication is not returned, the bottle should be returned to the site at the subsequent office visit (Visit 4);
[11] A follow-up clinic visit will occur approximately 7 days after the last clinic visit to review any on-going or evaluate newly occurring adverse events (AEs), to record any changes in concomitant medications, to assess the subject's condition via physical examination, and to obtain laboratory samples. This will conclude the subject's involvement in the study.

1. INTRODUCTION

1.1 Disease Overview

Constipation is generally considered as infrequent and difficult passage of stool. Medical reporting estimates that one of every 50 people in the United States suffers from constipation, making it one of the most common disorders among Americans.[1] Constipation is more likely to affect females than males and more likely to occur in older adults, showing an exponential increase after the age of 65.[2,3]. The actual occurrence of constipation is likely higher than reported, as many individuals suffer at home without seeking professional care.

Although in some instances constipation may be caused by obstruction, most constipation can be associated with factors such as a diet low in soluble and insoluble fibers, inadequate exercise, medication use (in particular, opiate analgesics, anticholinergic antidepressants, antihistamines, and vinca alkaloids), bowel disorders, neuromuscular disorders, metabolic disorders, poor abdominal pressure or muscular atony.[4] Chronic Idiopathic Constipation (CIC) is defined as the chronic presence of these symptoms. It is called idiopathic because the cause of this type of constipation is unknown and it is not caused by underlying illness or medication.

Lubiprostone has been approved to treat adults with chronic idiopathic constipation or opioid-induced constipation (24 mcg BID) and for the treatment of women with irritable bowel syndrome with constipation (8 mcg BID). Currently, the only dosage form in which lubiprostone is available is a capsule form. Sucampo has recently developed lubiprostone in a sprinkle dosage form. This study aims to evaluate the efficacy (based on bowel movement data) and safety of this lubiprostone sprinkle formulation (24 mcg dose BID, equivalent dose as approved for capsule form) in subjects with CIC.

1.2 Product Background

Lubiprostone (24-mcg capsules BID) is currently approved in the US under the trade name AMITIZA® for the treatment of adults with chronic idiopathic constipation or opioid-induced constipation. Lubiprostone (8-mcg capsules BID) is also approved for the treatment of women with irritable bowel syndrome with constipation. Lubiprostone 24-mcg BID is also approved for treatment of adult chronic idiopathic constipation in Canada and various countries within the European Union and for treatment of CIC and opioid-induced constipation (OIC) in Switzerland. Lubiprostone was approved for marketing in Japan on 29 June 2012 for the treatment of chronic constipation (excluding constipation caused by organic diseases). In several well-controlled clinical studies in adult subjects with chronic idiopathic constipation, opioid-induced constipation or irritable bowel syndrome with constipation, lubiprostone has been shown to increase the frequency of spontaneous bowel movements (SBMs), to improve stool consistency, and to reduce straining, abdominal bloating, and abdominal discomfort.[5] An open-label safety and efficacy study of 4 weeks' duration has also been conducted in paediatric functional constipation subjects aged 3-17 years who were treated with AMITIZA® 12 mcg QD, 12 mcg BID, or 24 mcg BID and improvement in SBM frequencies were reported in all dose groups.[6]

A sprinkle formulation of lubiprostone for oral administration has been developed. It is supplied in an easy-to-open and easy-to-handle oversized hard capsule and will be sprinkled onto a teaspoon of applesauce for oral administration.

1.2.1 Preclinical information

A full summary of the findings from all preclinical studies can be found in the current Investigator Brochure.

1.2.2 Clinical information

A full summary of previous clinical studies with lubiprostone, and known and potential adverse effects can be found in the current Investigator Brochure.

1.3 Rationale for Study

The availability of lubiprostone sprinkle provides an alternate dosing formulation for patients who prefer not to take capsules. The purpose of this study is to evaluate the bioequivalence of lubiprostone sprinkle and lubiprostone capsule as compared to placebo, in adults with CIC.

The dose selected for this study (24 mcg BID) is equivalent to that of the FDA approved dosage for use of lubiprostone capsules to treat patients with either CIC or non-cancer related opioid-induced constipation in adults.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

To evaluate the bioequivalence of Sprinkle and Capsule formulations of lubiprostone, as compared to placebo when administered orally (at 24 mcg twice daily [BID]) in subjects with CIC.

2.2 Endpoints

2.2.1 Efficacy

2.2.1.1 Primary Efficacy Endpoint

- Equivalence analysis of observed SBM count at Week 1 for lubiprostone sprinkle vs. lubiprostone capsule

2.2.1.2 Secondary Efficacy Endpoints

- Superiority analysis of observed SBM count at Week 1 for lubiprostone sprinkle and lubiprostone capsule vs. matching placebo
- Change from baseline in observed SBM count at Week 1
- Overall and mean change from baseline in stool consistency associated with SBMs at Week 1
- Overall and mean change from baseline in straining associated with SBMs at Week 1
- SBM frequency rate at Week 1
- Mean change from baseline in SBM frequency rate at Week 1

Details regarding BMs (time of occurrence and associated subject ratings of consistency and straining), as well as details regarding study medication and rescue medication administration (see Appendix 3), will be reported by subjects from Screening through the end of double-blinded treatment.

2.2.2 Safety Endpoints

The safety endpoints are as follows:

- Incidence of adverse events grouped by MedDRA System Organ Class and Preferred Term
- Changes from baseline in clinical laboratory parameters (hematology, serum chemistry, urinalysis)
- Changes from baseline in vital sign measurements

3. STUDY DESIGN

This is a phase 3, multicenter, double-blinded, randomized, placebo-controlled study evaluating the bioequivalence of sprinkle and capsule formulations of lubiprostone, as compared to placebo, when administered orally in subjects with CIC. Approximately 522 subjects will be randomized to study treatment in a 1:1:1 ratio to receive either lubiprostone Sprinkle 24 mcg BID, Capsule 24 mcg BID, or matching placebo BID from the morning of Day 1 through the evening of Day 7 before returning to the clinic on the morning of Day 8. The Sprinkle formulation of lubiprostone (24 mcg) is supplied in an easy-to-open and easy-to-handle oversized hard capsule and will be sprinkled onto a teaspoon of applesauce for oral administration, followed by intake of 240 mL of water. The Capsule formulation (24 mcg) is supplied as soft-gelatin capsules and will be taken with 240 mL of water. Doses should be taken with meals.

Enrollment at approximately 70 sites within the United States is anticipated. Duration of subject participation is approximately 4 weeks from the beginning of the Screening period until the Follow-up visit. A schematic representation of the study design is provided below in Figure 1.

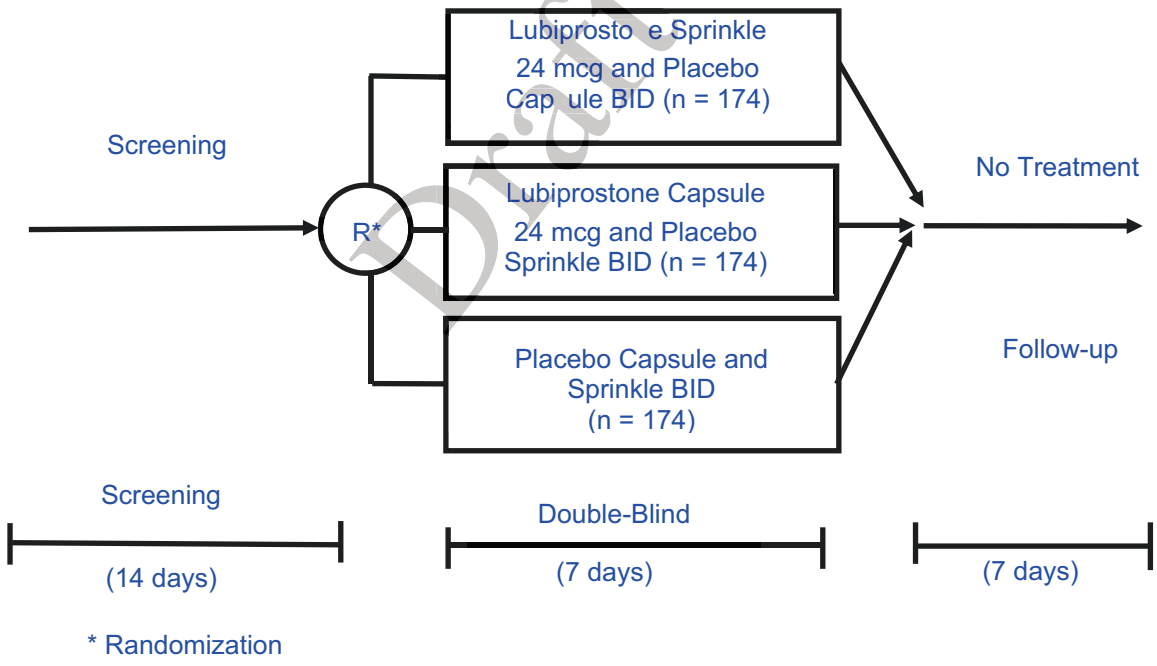


Figure 1: Study Design Flow Chart

3.1 Study Procedure Overview

A detailed description of the procedures to be performed is outlined in Section 6. The schedule of events is outlined in tabular format in the Protocol Synopsis section.

There will be four distinct visits for the study:

- **Screening Period (Visit 1; Day -14 [-3 days]):** This visit will occur up to 17 days prior to the first dose of study medication to determine subject's eligibility for participation in the study. This period includes a diary eligibility period during which subjects will record their bowel habits data prior to randomization.

- **Randomization Visit (Visit 2; Day 1):** This visit is considered Day 1, occurring after the subject has completed the screening requirements and taking place on the first day of study medication administration.

- **End-of-Treatment Visit (Visit 3; Day 8 [+2 days]):** Clinical and laboratory assessments will be performed to evaluate the safety of study treatment. This is the final visit of the treatment period and should be conducted for all subjects including subjects who discontinue early from the study.

- **Follow-up Visit (Visit 4; Day 15 [+3 days]):** A follow-up clinic visit will occur to perform post-treatment clinical and labo atory assessments. This will conclude the subject's involvement in the study.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Subjects must satisfy the following criteria before entering the study:

1. Subject is male or female, ≥18 years of age.
2. Subject either has medically-confirmed diagnosis of chronic constipation (per Rome III; Appendix 1), or meets the diagnosis as confirmed using the Rome III constipation module questionnaire (Appendix 2) during the Screening period.
3. Subject is able to comprehend and willing to sign an ICD approved by the IRB after explanation of the nature and objectives of the study and prior to the conduct of any study specific procedure.
4. If subject is taking concomitant medication (prescribed or over-the-counter) that affects gastrointestinal motility, he/she must discontinue use at the time of the Screening Visit (Visit 1) through the Follow-up Visit (Visit 4); these medications include:
   a. Cholinesterase inhibitors; anti-spasmodic, anti-diarrheal, anti-constipation, or prokinetic agents; laxative agents (e.g., PEG 3350), including homeopathic remedies;
   b. Tricyclic antidepressants; and/or
   c. Any medication, at the discretion of the Investigator, known to relieve or cause constipation or constipation-related symptoms, and which the Investigator, based on the medical history of the subject, suspects to be a contributing factor to the patient's chronic constipation, or may otherwise confound the evaluation of treatment response.

   Exceptions: Treatment with anticholinergic agents, SSRIs, SNRIs, or MAO inhibitors is allowed if a stable dose has been used for at least 30 days prior to the Screening Visit and not likely to change during the study.

5. If subject is taking a fiber supplement or a concomitant medication for the indication of lowering blood pressure, usage must have been at a stable dose and schedule for at least 30 days prior to the Screening Visit and not likely to change during the study.
6. Subject daily diary is at least 70% compliant for evening/end-of-day assessments during the Screening period.
7. Subject daily diary indicates an average of less than 3 spontaneous bowel movements (SBMs) per week during the 14 days prior to randomization.
8. Subject daily diary indicates one or more of the following for at least 25% of SBMs during the 14 days prior to randomization:
   - Bristol Stool Scale Type 1 or 2;
   - Moderate to very severe straining associated with SBMs; and/or
   - Sensation of incomplete evacuation.

Note: For subjects with no reported SBMs during the Screening Period, it is not necessary to meet criteria for bowel movement characteristics, i.e., moderate to severe straining and straining at defecation.

4.2 Exclusion Criteria

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

1. Subject has known or suspected anatomic or organic disorders of the large or small bowel; e.g.:
   a. Associated with a mechanical bowel obstruction (e.g., tumor, hernia, obstructive polyps), or pseudo-obstruction;
   b. Associated with large or small bowel disorder such as ulcerative colitis or Crohn's disease.
2. Subject is a candidate for, or has undergone abdominal surgery for which an impact on GI transit/motility or defecation cannot be excluded such as bowel resection, colectomy, and gastric bypass surgery (exceptions: appendectomy, cholecystectomy, benign polypectomy and inguinal hernia).
3. Subject has any gastrointestinal (GI) condition, other than constipation, affecting GI motility or defecation.
4. Subject reports weight loss, anemia, and/or rectal bleeding AND has no documentation of the results of either a flexible sigmoidoscopy or colonoscopy performed during the 6 months prior to dosing since the report of that condition or has documented evidence suggestive of a non GI-related etiology as a cause of these symptoms.
5. Subject has a history of loss of consciousness and/or syncope; has been diagnosed with, or has current evidence of, hypotension (i.e., systolic pressure <90 mmHg and/or diastolic pressure <60 mmHg) based upon orthostatic vital sign measurements taken at the time of screening; and/ or has any other medical/surgical condition that might interfere with the absorption, distribution, metabolism, or excretion of the study medication.
6. Subject has taken a systemic antibiotic within 30 days prior to screening or is scheduled to take this at any time during the study.
7. Subject has an uncontrolled cardiovascular, liver or lung disease, neurologic or psychiatric disorder, or other systemic disease, which the Investigator feels is clinically significant and would limit the subject's ability to participate in the trial.
8. Subject is unable to eat or drink, take oral medications, or to hold down oral medications due to vomiting.
9. Subject has impaired renal function (i.e., serum creatinine concentration > 1.8 mg/dL) as identified at the Screening Visit, or is known to have impaired hepatic function (Child-Pugh B or C).
10. Subject has abnormalities in vital signs, electrocardiogram (ECG), or laboratory test results (hematology, urinalysis, or blood chemistry) that cannot be explained by underlying comorbidity(ies) and which, in the Investigator's opinion, are clinically significant, relevant, and should preclude the subject's participation in the trial.

11. Subject has current evidence of, or has been treated for, cancer within the past 5 years, with the exception of localized basal cell, squamous cell skin cancer, or *in situ* cancer which has been resected.
12. Subject (female of childbearing potential) is currently breastfeeding or plans to breastfeed, has a positive pregnancy test, refuses/unwilling to undergo pregnancy testing, and/or does not agree to use protocol-specified contraceptive for the duration of the study.
13. Subject demonstrates a potential for non-compliance with the study protocol (i.e., dosing schedule, visit schedule, or study procedures).
14. Subject has received an investigational medication within 30 days prior to the Screening Visit (Visit 1), or plans to participate in another clinical trial during the study period.
15. Subject has received AMITIZA, lubiprostone, SPI-0211, or RU-0211 at any time prior to participation in this study.

4.3 Reproductive Potential

All female subjects of childbearing potential will have a serum pregnancy test performed at Screening and a urine pregnancy test at Randomization (Visit 2) and Follow-up. Childbearing potential will be defined as any female subject who has not undergone surgical sterilization within the last 3 months or who is not post-menopausal for at least 1 year.

4.4 Contraception Specifications

Sexually active females and their partn rs must agree to use adequate contraception during study participation.

The type of contraception being u ed by the subject shall be recorded in the source document. Adequate contraception is defined as use of any of the following:

- Oral Contraceptives– must have been used for at least 3 months prior to the Screening Visit (Visit 1);
- Intrauterine Device (IUD); or
- Double barrier method.

4.5 Withdrawal of Subjects

A subject is free to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the study site. The Investigator or Sponsor may also withdraw the subject at any time in the interest of subject safety. The primary reason for withdrawal must be recorded in the subject's source documents and on the withdrawal form in the electronic Case Report Form (eCRF).

Subject participation may be terminated prior to completion of the clinical study for any of the following reasons:

- AE;
- Lack of efficacy;

- Subject choice;
- Lost to follow-up;
- Non-compliance with study drug;
- Investigator decision;
- Sponsor request; or
- Any other reason upon agreement between the Investigator and the Sponsor.

Subjects who withdraw from the study early or who are terminated from the study should complete the End-of-Treatment and Follow-up procedures as outlined in Sections 6.1.3.1 and 6.1.4.

Attempts should be made to locate subjects who are lost to follow-up so that as much study information as possible may be obtained. Every effort should be made to retrieve dispensed study medication, electronic diaries, and obtain the general overall status of the subject at the time of withdrawal from the study. The subject's source documents should verify that at least two attempts have been made by telephone to locate the subject and that a final attempt to locate the subject has been made by certified or traceable mail.

4.6 Emergency Unblinding

As a double-blinded, placebo-controlled study, both the subjects and Investigators are blinded to the study treatment assignment. In addition, clinical research personnel, laboratory personnel, and others are blinded to the treatment assignment and will remain blinded through the completion of the study.

In the event emergency unblinding of study treatment is necessary, the Investigator shall utilize the interactive response technology (IRT) system to obtain subject dose details. The individual subject dose details should be revealed only in case of an emergency where the further treatment of the subject is dependent on knowing the study medication he or she has received. The date and time of breaking the blind as well as the reason must be recorded on the subject study medication record. The subject will be automatically discontinued from the study in the event emergency unblinding of study treatment takes place. If a blind is broken due to an adverse event, a corresponding adverse event entry must be completed in the eCRF.

It is strongly encouraged that unblinding only be completed after consultation with the study medical monitor, provided this does not compromise subject safety. If unblinding should occur (either by accident or for a medical emergency), the Investigator must promptly and immediately notify the study medical monitor, and IRB/IEC, and document the circumstances surrounding this action in a memorandum to the study file.

4.7 Stopping Rules

4.7.1 Individual Stopping Criteria

The following stopping criteria should be applied for individual subjects who experience one or more of the following spontaneously-reported adverse events:

- Loss of consciousness, hypotension (blood pressure <90 mmHg systolic and/or <60 mmHg diastolic, or a decrease of ≥20 mmHg from pre-dose), ischemic colitis, and severe hypersensitivity reactions/anaphylaxis should result in immediate discontinuation.
- Severe, treatment-related cases of diarrhea, tachycardia, chest discomfort/chest pain, and dyspnea should result in discontinuation.

4.7.2 Overall Study Stopping Criteria

The study will be stopped if at least 2 subjects experience the same treatment-related, life-threatening event.

5. STUDY AND CONCOMITANT TREATMENTS

5.1 Study Medication Formulation

Lubiprostone drug substance is white, odorless crystals or crystalline powder and is very soluble in ether and ethanol, and practically insoluble in hexane and water. Lubiprostone is available for oral administration as a multi-particulate Sprinkle formulation, or a Capsule formulation in this study. Matching placebo will be supplied for the study.

The Sprinkle formulation consists of micro-beads of multi-layer coating. The core of the beads is inactive (cellulose based material) and the drug substance is carried in one of the polymer coatings. The coated beads are filled in easy-to-open and easy-to-handle oversized hard capsules. The capsule formulation consists of a soft-gelatin capsule that is filled with lubiprostone dissolved in medium chain fatty acid triglycerides (MCT) solution.

5.2 Packaging

The lubiprostone formulations and the corresponding matching placebo will be manufactured and packaged by an independent company. An independent packaging company, not involved in the conduct or monitoring of the study, will label and distribute study medication. Study medication will be provided to the site for distribution by authorized personnel to subjects according to the randomization code.

5.3 Labelling

All study medication product will be labeled with a minimum of the following information:

- Protocol Number;
- Kit Number (if applicable);
- Dosage form (including product name and quantity in pack);
- Manufacturing information;
- Directions for use, storage conditions, expiry date (if applicable), batch number;
- The statements ‘For clinical trial use only’, and/or ‘CAUTION: New Drug - Limited by Federal (United States) Law to Investigational Use’, as applicable;
- The Sponsor's name and address;
- Subject Number (To be written by the site);
- Dispense Date (To be written by the site).

5.4 Storage and Handling

The Investigator has overall responsibility for ensuring that study medication is stored in a safe, limited-access location under the specified appropriate storage conditions. The study medication will be stored at controlled room temperature of 20 °C (68 °F) to 25 °C (77 °F); excursions between 15°C and 30°C (59°C to 86°F) are allowed. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Study medication will be distributed by the pharmacy or nominated member of the study team. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The Investigator

is responsible for ensuring that the temperature is monitored throughout the total duration of the trial and that records are maintained.

No study medication stock or returned inventory may be removed from the investigational site without prior knowledge and consent by the Sponsor. All returned and unused study medication shall be returned or destroyed as instructed by the Sponsor.

The Sponsor will be permitted upon request to inspect the supplies storage and distribution procedures and records provided that the blind of the study is not compromised.

5.5 Supply and Dosing

Treatments will be blinded and double-dummy, whereby subjects will be randomized to either lubiprostone sprinkle, lubiprostone capsule, or matching placebo doses BID. Each treatment day should consist of two (2) doses of study medication, one dose in the morning and one dose in the evening with meals. The Sprinkle formulation is supplied in an easy-to-open hard capsule and will be sprinkled onto a teaspoon of applesauce for oral administration, followed by intake of 240 mL of water. The Capsule formulation will also be taken with 240 mL of water.

All doses should be taken at least 5 hours apart. The subject should record the actual time the dose was taken in the electronic diary. If taken late, the site personnel should record the actual time the dose was taken in the subject records. If the dose was missed entirely, the subject should indicate the omission in the electronic diary as instructed. The study medication will be handled by authorized personnel and dispensed under the supervision of the Investigator or designated study personnel.

Subjects should return the used bottles of study medication at Visit 3 for collection by site for drug accountability. If the study medication is not returned, all bottles of unused study medication should be returned to the site at the subsequent office visit (Visit 4). The last dose of study medication in this study will be taken the evening before Visit 3.

5.5.1 Randomization and Blinding

There will be approximately 522 subjects randomized 1:1:1 to the following treatment arms:

- Treatment A: Lubiprostone sprinkle plus placebo capsule; taken BID for 7 days
- Treatment B: Lubiprostone capsule plus placebo sprinkle; taken BID for 7 days
- Treatment C: Placebo capsule plus placebo sprinkle; taken BID for 7 days

An independent third party will generate and hold the randomization code throughout the conduct of the study. Each investigational site will randomize subjects to treatment groups using the Interactive Response Technology (IRT) system with balancing factors for baseline SBM frequency rate (<1.5 or ≥1.5) and site.

Most study personnel will remain blinded until the clinical database has been locked. To allow for the execution of clinical trial-related services, the following individuals will be unblinded during the study:

- Sponsor Quality Assurance representative
- External IRT vendor
- Sponsor Pharmacovigilance representative
- Sponsor Regulatory representative
- External clinical supply distribution vendor
- Sponsor Drug Supply Management representative

5.5.2 Allocation of Subject Identification Number Study Medication

Three-digit subject numbers ("yyy") will be allocated as subjects consent to take part in the study. Within each site, this number will be allocated to subjects according to the sequence of presentation for trial participation. The subject number will be combined with a 4-digit site number ("xxxx") to form the unique 7-digit subject identifier ("xxxx-yyy") for the study. This subject ID number will also be used as a unique identifier for the subject throughout the study for lab reports, source data, eCRFs, etc.

5.6 Compliance and Drug Accountability

It is the responsibility of the Investigator to ensure that all study medication received at the site will be inventoried and accounted for throughout the study and the result recorded in the Drug Accountability Form.

5.7 Concomitant Medications

5.7.1 Excluded Medication

The following medications are to be excluded during the course of the study and must be discontinued from the Screening period through study completion (Visit 4):

- Anti-spasmodics;
- Cholinesterase inhibitors;
- Anti-diarrheal medications;
- Anti-constipation medications (e.g., Linzess™);
- Prokinetic agents;
- Systemic antibiotics (within 30 days prior to screening or at any time during the study);
- Laxative agents (e.g., Miralax®, PEG 3350), including homeopathic remedies;
- Tricyclic antidepressants; and
- Any medications at the discretion of the Investigator known to relieve or cause constipation or constipation symptoms, and which the Investigator, based on the medical history of the subject, suspects to be a contributing factor to the patient's chronic constipation, or may otherwise confound the evaluation of treatment response.

Exceptions: Treatment with anticholinergic agents, SSRIs, SNRIs, or MAO inhibitors is allowed if a stable dose has been used for at least 30 days prior to the Screening Visit and not likely to change during the study.

These medications should be documented as concomitant medications. The Sponsor (medical monitor) must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are taken. Continued participation of the subject will be at the discretion of the Sponsor.

5.7.2 Daily Fiber Therapy

The use of a daily fiber supplement shall be permitted as long as the usage schedule and dose has been stable for at least 30 days prior to the Screening Visit. The schedule of usage and dose of the daily fiber supplement should not change during the course of the study. Any fiber supplement used should be documented as a concomitant medication.

5.7.3 Concomitant Blood Pressure Lowering Medications

The use of a concomitant medications for the indication of lowering blood pressure shall be permitted as long as the usage schedule and dose has been stable for at least 30 days prior to the Screening Visit. The schedule of usage and dose of the such medications should not change during the course of the study. Any medication used for blood pressure lowering should be documented as a concomitant medication.

5.7.4 Guidance for Rescue Medication

If necessary, rescue medication may be used only during the Screening period to help induce a BM. The use of approved rescue medications is outlined below.

In the event that no BM has occurred within a 3-day period during the Screening period, the use of rescue medications is pe mitted per the Investigator's instructions as described below.

a. **Rescue medication 1**: The subject may receive the clinically recommended dose (10 mg) of bisacodyl suppository.

b. **Rescue medication 2**: If the first rescue medication fails to induce a BM, the subject may be given a saline enema.

c. If both rescue medications fail, the subject may receive another medication at the physician's discretion for immediate short-term use. The recommendation may include a medication from the excluded medication list **other than** AMITIZA (lubiprostone) capsules or any form of polyethylene glycol (PEG) or Linzess™ (Section 5.7.1), all of which are considered prohibited rescue medications.

Should the use of rescue therapy be necessary, it will be recorded in the electronic diary by the subject, and recorded on the Rescue Medication eCRF page by site personnel.

Rescue medication use is prohibited during the treatment period (Week 1 following randomization).

6. STUDY PROCEDURES

6.1 Study Procedures by Visit

6.1.1 Completion of Study Procedures

The Schedule of Evaluations included in the protocol synopsis summarizes the frequency and timing of the entry, efficacy (diary), and safety measurements for this study. All study visits should be scheduled so that each visit occurs within the allotted timeframe. All visits should be based upon the date of the first dose of study medication.

Subjects are expected to complete all study periods: Screening, Randomization, EOT, and Follow-up. Subjects who withdraw from the study early or who are terminated from the study after receiving a dose of study medication are encouraged to complete the final visit of the treatment period (Visit 3) and the follow-up visit (Visit 4). All visits are outlined in the sections below.

The details of the procedures for the Screening Visit and subsequent visits as specified are below.

Medical History – A complete medical history of the subject will be recorded. A complete medical history will include all history within the past 90 days (and also relevant medical history earlier than 90 days). Particular attention should be made regarding the subject's history of gastrointestinal disease and related symptoms.

Inclusion/Exclusion – The subject wi be assessed to determine their eligibility for the study based upon the inclusion (Secti n 4.1) and exclusion (Section 4.2) criteria.

Height – The subject's height will be recorded in inches or centimeters.

Weight – The subject's weight will be recorded in pounds or kilograms.

Vital Signs – The subject's blood pressure, heart rate, respiratory rate, and temperature will be recorded. Where indicated in the sections below, orthostatic blood pressure and heart rate measurements should be performed. All measurements taken should be recorded in the source documents

Electrocardiogram – A 12-lead electrocardiogram will be performed to determine subject eligibility for the study.

Physical Examination – A complete physical examination of the subject will be performed by appropriate site personnel. Physical examination findings should correlate with the subject's medical history and current diagnosis.

Abbreviated Physical Examination – At certain visits, an abbreviated physical examination will be performed by appropriate site personnel. This examination reviews only those body systems where there has been a change in health or there is a new finding to report.

Laboratory Tests – Urine and blood samples will be collected and sent to a central laboratory for analysis (see Section 6.3 for details).

Pregnancy Test – All female subjects of childbearing potential will have a serum pregnancy test performed at Screening and a urine pregnancy test at Randomization and Follow-up. Childbearing potential will be defined as any female subject who has not undergone surgical sterilization within the last 3 months or who is not post-menopausal for at least 1 year.

Adverse Events – AEs will be reported by the subject from the time of informed consent through the end of the follow-up period. AEs will be followed by the Investigator as determined by Sponsor or designee. Further details on AE reporting are provided in Section 7.

Concomitant Therapy – A complete history of medications (prescribed and over-the-counter [OTC]) used within the past 30 days will be recorded, including herbal remedies and contraceptives. A full history of constipation medication use should be collected, with particular focus on any constipation medications taken within the 90 days prior to screening. The subject must be instructed to stop all disallowed prescription and laxative medications per Section 5.7.1 of the protocol. A subject who has been routinely administering a daily fiber supplement and/or concomitant blood pressure lowering medication for at least 30 days preceding the Screening Visit may remain on the supplement/medication throughout the study provided the regimen and dose does not change.

Drug Accountability – All study medication received at the site will be inventoried and accounted for throughout the study and the result recorded in the Drug Accountability Form and in subject's eCRF. Study medication supplies for each subject will be inventoried and accounted for throughout the study. Study medication administration will be documented in the source documentation, including dispensation information and capsule counts, and entered in the appropriate eCRF page.

6.1.2 Screening/Randomization

Subjects believed to meet the inclusion/exclusion criteria may be contacted and provided with information about the study. Subjects who choose to participate in the study should be scheduled for a Screening Visit.

Subjects are expected to start the screening period within the established window (Day -17 to -14). The research staff will follow an appropriate Informed Consent process as noted in Section 9.3.1. The subject must sign the informed consent and consent must be obtained before any study procedures are performed.

6.1.2.1 Screening Period – Visit 1 (Study Days -17 to -1)

Once written consent is obtained, the following will be performed by the Investigator or designee as part of the Screening Visit:

- Confirm compliance with inclusion/exclusion criteria;
- Obtain subject identification number from the IRT system;
- Record the subject's demographic information;
- Collect medical history and concomitant medication information, including:

  - Documentation of chronic idiopathic constipation (see Appendix 1 and Appendix 2);
  - History of constipation treatment administered (see Section 6.1.1 under Concomitant Therapy);
- Measure vital signs (body temperature, respiratory rate, and orthostatic blood pressure and heart rate [i.e., first measurement after 5 minutes in supine position, followed by a second measurement after 5 minutes in standing position]), including height and weight;
- Perform a full physical examination;
- Perform a 12-lead ECG;
- Collect blood and urine samples for laboratory analysis and serum pregnancy test (if applicable);
- Provide the subject with an electronic diary. The diary is to be completed daily, starting the day of the Screening Visit and continuing throughout the 7-day treatment period. Provide the subject instructions on the diary questions and instructions for completion. Diary data will be automatically transmitted from the device each night;
- Remind subject to complete the diary daily and that failure to complete at least 70% of daily evening reports during the Screening period will result in the subject being ineligible for study entry;
- Perform adverse event (AE) assessment;
- Review definition of rescue medication and instruct subject how rescue medication administration is handled per protocol and
- For subjects meeting eligibility, remind them to discontinue taking concomitant medication (prescribed or over-the-counter) that affects GI motility from Visit 1 and throughout the study.

Note: Subjects not meeting eligibility criteria at the time of the Screening Visit, or at the end of Screening (or at any time prior to randomization), will be considered screen failures.

6.1.2.2 Randomization Visit – Visit 2 (Day 1)

The treatment period will begin at randomization when the first dose of study medication is administered on the morning of Study Day 1 and will continue with BID dosing thereafter through administration of the last dose on the evening of Day 7.

On Day 1, the following procedures will be performed:

- Review the diary record to confirm that the subject meets the necessary inclusion criteria;
- Update medical history. Any new medical information should be added to the subject's baseline history (AEs will be captured on the AE page);
- Collect blood and urine samples for laboratory analysis;
- Review and record any new AEs and follow-up on any ongoing AEs;
- Measure weight;

- Update Concomitant Therapy – Concomitant medications (prescribed and OTC) used since the Screening Visit will be reviewed;
    - Measure vital signs (body temperature, respiration rate, and orthostatic blood pressure and heart rate [i.e., first measurement after 5 minutes in supine position, followed by a second measurement after 5 minutes in standing position]) at 0 hour (pre-dose) and at 1 hour post-dose. If abnormalities in blood pressure (i.e., systolic pressure <90 mmHg and/or diastolic pressure <60 mmHg, or a decrease in orthostatic systolic and/or diastolic pressure [from supine to standing] of ≥20 mmHg) are observed at 1-hour post-dose, a repeat measurement of orthostatic blood pressure and heart rate must be taken at 2 hours post-dose. If abnormalities persist at 2 hours post-dose, subject should be discontinued immediately, and an AE of hypotension should be recorded;
- Dispense study medication, providing dosing instructions (see Section 5.5) and remind the subject to bring the bottle back at the next visit;
- Observe the subject as he/she administers the first dose of study medication while in the clinic and record time of study medication administration in the electronic diary.
- If the subject is randomized, the diary must be switched to "treatment period" mode and the subject must continue completing th diary each day during the treatment period. Diary data will be automatically transmitted from the device each night. The diary will record information for the entire period prior to the next scheduled office visit;
- Remind the subject that rescue medication is prohibited during the treatment period; and
- Schedule the next clinic visit (Visit 3).

6.1.3 Treatment Period (Day 1 through Day 7)

The treatment period will begin at the Randomization Visit (Day 1), when the first dose of study medication is administered, and will end the evening before the clinic visit on Day 8.

6.1.3.1 End-of-Treatment Visit (Visit 3; Day 8 +2 days)

During this visit, the following procedures will be performed on all subjects:

- Measure vital signs and weight. Subjects should be asked to remain supine for at least 5 minutes prior to measurement of vital sign parameters;
- Collect blood and urine samples for laboratory analysis;
- Perform an abbreviated physical examination;
- Review and discuss rescue medication use;
- Review and update concomitant therapy (prescribed and OTC) used since the last visit; Review and record any new AEs and follow-up on any ongoing AEs;
- Collect the previously dispensed study medication and perform drug accountability. If the study medication is not returned, the study medication must be returned to the site at the subsequent office visit; and
- Collect the electronic diary.

6.1.4 Follow-up Period

The Follow-up period lasts until Day 15 (+3 days). AEs should be followed to assess their status and resolution during this timeframe. Any new concomitant medications should also be recorded.

At this visit the following procedures will be performed:

- Measure vital signs, including weight. Subjects should be asked to remain supine for at least 5 minutes prior to measurement of vital sign parameters;
- Perform an abbreviated physical examination;
- Collect blood and urine samples for laboratory analysis;
- Review and update concomitant therapy; and
- Review and record any new AEs.

6.1.5 Unscheduled Visit(s)

Additional visits may be scheduled, at the discretion of the Investigator, to ensure the safety and well-being of subjects who experience AE or other reactions during the course of the study warranting further evaluation. Any additional visits should be fully documented in the subject's eCRF on the Unscheduled Visit Screen(s).

6.2 Efficacy Evaluations

The subject will answer questions about their constipation, including recordation of bowel movements (BMs), associated stool consistency, bowel straining ratings, and complete/incomplete evacuation. Collection of study medication dosing (time dose taken) will also be captured. This information will be assessed as part of the daily evaluations recorded in the electronic diary.

6.2.1 Electronic Diary

The electronic diary is a hand-held device with a visual display and is designed to query the subject daily about the status of their constipation (see Appendix 3). The diary will prompt the subject to provide information each evening prior to bedtime about the constipation-related events during the preceding day.

Information from the subject diary is automatically transmitted each night to a secure study database and available for review by the site as needed. Since the diary information is being gathered for efficacy, it is important that the diary is completed each day.

The site will provide the subject with initial training regarding the diary use during the Screening Visit and the Investigator should review diary entries as needed to ensure proper compliance. The site will review the diary information at the time of the Randomisation Visit. At least 70% of the daily evening entries must be completed during the Screening period to be considered compliant with the diary. Additional information about the diary and its usage will be provided to the sites in a reference manual prepared by the diary vendor.

6.2.2 Efficacy Endpoints

The primary and secondary efficacy endpoints are provided in Section 2.2.1.

6.3 Safety Evaluations

The following safety evaluations will be performed during the study to measure the safety of the study medication:

Adverse Events: AEs will be reported by the subject from the time of informed consent through the end of the follow-up period. AEs will be followed by the Investigator as determined by Sponsor or designee. Further details on AE reporting are provided in Section 7.
Clinical Laboratory Tests: The following laboratory tests will be conducted and the appropriate Investigator shall determine the clinical significance of any out-of-range values.

- **Hematology Panel:** Hemoglobin, hematocrit, MCV, MCH, MCHC, RBC, WBC, white blood cell with absolute counts and percent differentials (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelet count.

- **Chemistry Panel:** Total cholesterol, triglycerides, glucose, total protein, albumin, alkaline phosphatase, AST, ALT, GGT, iron, LDH, total bilirubin, direct bilirubin, BUN, uric acid, creatinine, sodium, potassium chloride, bicarbonate, calcium, phosphorus, and magnesium.

- **Urinalysis:** Protein, glucose, ketones, occult blood, pH, specific gravity, color, appearance, leukocyte esterase nitrite, bilirubin, and macroscopic examination. Microscopic examination will be done if abnormalities are present. Urine samples will be collected, when possible from al subjects.

Physical Examination: Physical examinations will be conducted at various time points during the study. Any new post-treatment findings or changes, as noted by the Investigator, will be reported as an AE.

Vital Signs: Vital signs (including height and weight at designated visits) will be recorded during the study. Any post treatment clinically significant changes in vital signs shall be noted by the Investigator and reported as an AE. For example, if abnormalities in orthostatic blood pressure measurements (i.e., systolic pressure <90 mmHg and/or diastolic pressure <60 mmHg, or a decrease in orthostatic systolic and/or diastolic pressure [from supine to standing] of ≥20 mmHg) are observed at 1-hour post-dose on the day of first dose (Randomization), a repeat measurement of orthostatic blood pressure and heart rate must be taken at 2 hours post-dose. If such abnormalities persist at 2 hours post-dose, subject should be discontinued immediately, and an AE of hypotension should be recorded.

Rescue Medication Usage: All medications used emergently by the subject to relieve constipation. Rescue medication may be used only during the Screening period to help induce a BM.

7. ADVERSE AND SERIOUS ADVERSE EVENTS

As defined in ICH GCP Guideline E6,[7] an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, disease or exacerbation of a pre-existing condition temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal product. For this study, all safety information will be collected from the time of informed consent and any untoward medical occurrence after screening will be defined as an AE. Adverse events that are reported after initiation of study medication, and on or before the last day of study medication plus 7 days, will be defined as treatment-emergent AEs.

Each AE requires a complete and thorough description including date of onset, duration, intensity/severity, its relationship to the study drug and any corrective actions taken. Each AE should also be categorized as “serious” or “non-serious”.

Timely, accurate, and complete reporting and analysis of safety information from the clinical study are crucial for the protection of subjects and are mandated by regulatory agencies worldwide.

7.1 Definitions and Descriptions

7.1.1 Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that, at any dose:

- Results in death;
- Is life-threatening (the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe);
- Requires hospitalization or prolongation of existing hospitalization;
    - This criterion applies if the event requires inpatient hospitalization and results in an overnight stay in hospital or, if in the opinion of the Investigator, prolongs an existing hospitalization.
    - Hospitalizations for less than 24 hours with no admission are not considered “hospitalization”.
    - A hospitalization (including hospitalization for an elective procedure or routinely scheduled treatment or pre-planned procedures) for a pre-existing condition which has not worsened does not constitute an SAE.
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; and/or
- Is an important medical event (an event that may not fit the other criteria for a SAE as listed above, but based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes listed above). Examples of such events (per 21 CFR 312.32[8]) are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of drug dependency or drug abuse.

7.1.2 Non-serious Adverse Event

A non-serious AE is any event that does not meet the above-mentioned SAE definition.

7.1.3 Severity

The severity of each AE will be determined based upon the following criteria:

Mild: Transient symptoms, no interference with subject's daily activities. Less than 48 hours, no medical intervention/therapy required.

Moderate: Marked symptoms, moderate interference with the subject's daily activities. No or minimal medical intervention/therapy required.

Severe: Considerable interference with the subject's daily activities. Medical intervention/therapy required; hospitalization possible.

7.1.4 Relationship to Study Medication

The relationship to study medication will be determined and recorded on eCRF by an Investigator using the following criteria based on the World Health Organization (WHO) classification:

Causality	Definition
Unrelated	Concurrent illness, concurrent medication, or other known cause is clearly responsible for the adverse event OR based upon available information regarding subject history, disease process, relationship of adverse event to dosing, and drug pharmacology, a relationship between the drug and adverse event is unlikely.
Possible	The adverse event follows a reasonable sequence from the time of drug administration, but could also have been produced by the subject's clinical state or by other drugs administered to the subject. Event with a time to drug intake that makes a relationship improbable (but not impossible). Disease or other drugs provide plausible explanations
Probably	The adverse event follows a reasonable sequence from the time of drug administration, follows a known response pattern of the study treatment class, is confirmed by improvement on stopping the study treatment is the most likely of all causes. Event with reasonable time relationship to drug intake: • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Definite	The adverse event follows a reasonable sequence from the time of drug administration, follows a known response pattern of the study treatment class, is confirmed by improvement on stopping the study treatment, and there is no other reasonable cause exists.

7.1.5 Onset and Duration

The date and time the event was reported to investigator will be recorded, as well as the start date and time and resolution date and time of the event.

7.2 Recording and Reporting of Adverse Events

All AEs will be recorded in the source document and applicable eCRF(s) from the time the informed consent is signed until the end of study. AEs occurring prior to the first dose of study drug will be considered non-treatment emergent. The Investigator shall notify the Sponsor at any time when an SAE is believed to be related to the administration of study medication, even after the end of the study. At any time during the study, those events meeting the definition of an Immediately Reportable Event (IRE) must be recorded on source document, IRE Reporting Form, and applicable eCRF(s), and then reported to Sponsor or designee using the IRE Reporting Form as specified in Section 7.2.1.

All AEs, regardless of seriousness, severity or presumed relationship to study medication, must be recorded using medical terminology in the source document and in the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). Investigators must record on the source document and eCRF their opinion concerning the relationship of the AE to study therapy and the severity of the event. All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

For any subject who is discontinued from the study due to an AE, it is expected that the Investigator will follow the subject until the event resolves, the event returns to baseline (if a baseline value is available), or until such time that the Investigator does not anticipate any further improvement or worsening of the event.

7.2.1 Reporting of Immediately Reportable Events

The following events, regardless of severity or seriousness, are considered immediately reportable IREs and are to be reported via the IRE Form or IRE Pregnancy Report Form within 24 hours to the Sponsor or designee:

- All Serious Adverse events
- All pregnancies
- Events of Special Interest
  - Hepatotoxicity
  - Anaphylaxis, including anaphylactoid reaction and anaphylactic shock

Immediately Reportable Events, such as SAEs, should be recorded on the Adverse Event source document and eCRF. In addition, any IRE occurring during the clinical study must be reported within 24 hours to the Sponsor or designee using the IRE form. The initial report of an IRE must be documented on the study IRE form, signed by the Investigator and submitted by facsimile. The Investigator must provide the following information: protocol number, subject’s initials and study number AE term and associated dates, causal relationship between the event and study medication, relevant history, study medication dosing details, full description of the event, and other required data within the IRE form. All oral reports of an IRE

must be followed immediately by a facsimile of the IRE form signed by the Investigator. Investigators should not leave oral reports of IREs on any voicemail aside from the Sponsor's Medical Monitor or designee. The details of the adverse event reporting requirement are also outlined in a safety reporting plan.

The Sponsor assumes responsibility for reporting of expedited and periodic safety reports to the appropriate regulatory authorities. The Sponsor will distribute to the Investigator any safety expedited reports that occur in this study, and in other clinical studies involving lubiprostone. The Investigator may need to report SAEs to the appropriate IRB/IEC in accordance with local regulations.

All IREs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until either:

- the event resolves;
- the event stabilizes;
- 30 days after treatment exposure;
- the event returns to baseline, if a baseline value is available;
- the event can be attributed to medications other than the study medication, or to reasons other than study conduct; or
- the Investigator does not anticipate any further improvement or worsening of the event.

7.2.1.1 Reporting of Pregnancies

Any pregnancy occurring in a female subject after the first intake of study medication, while not an AE, is considered an IRE. It mus be reported within 24 hours of the Investigator learning of the event using only an IRE Pregnancy Report Form. Any subject, who becomes pregnant, shall be removed from the clinical study. Pregnant subjects should be followed for the duration of the pregnancy and the outcome should be reported. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant up to one year of age will be required.

7.2.2 Outcome

The Investigator should follow all IREs until resolution (return to baseline status) or loss to follow-up or until no further improvement or worsening of the participant's condition is expected. Loss to follow-up implies that the Investigator site is no longer aware of the participant's whereabouts, and is unable to obtain current contact information. All attempts to contact the participant must be captured in the appropriate trial source document.

7.2.3 Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classified as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease. However, significant worsening of the symptoms should be recorded as an AE.

Endpoints and reports of events on the progression of underlying condition (such as worsening constipation and fecaloma) will be considered expected events even though these are not listed in the Investigator Brochure as expected events for study medication.

7.2.4 Clinical Laboratory Evaluations

A change in the value of a safety laboratory investigation can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to a pathological value, or a further worsening of an already pathological value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are pathological laboratory values which were not present at baseline, per Investigator discretion further clinical or laboratory investigations should be performed until the values return to within reference range or until a plausible explanation (e.g., concomitant disease) is found for the pathological laboratory values.

The Investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a laboratory parameter is clinically significant and therefore represents an AE.

7.2.5 Vital Signs

A change in the value of a vital sign measurement can represent an AE, per the Investigator's discretion. The Investigator should decide, based on their discretion, and the clinical condition of a subject, whether a change in vital signs is clinically significant and therefore represents an AE.

7.2.6 Overdose

There are no specific treatments or monitoring guidelines prescribed for subjects with lubiprostone overdose. It will be left to the discretion of the Investigator's clinical judgment on how to provide appropriate symptomatic treatment.

Any incidences of overdose with the investigational product will follow the same reporting procedures as an AE (see Section 7.2), and only where applicable, as an IRE (see Section 7.2.1).

7.3 Contacting Sponsor Regarding Safety

Any medical safety related issue regarding the conduct of the trial needs to be addressed by the Medical Monitor. The name of the individual (and corresponding telephone numbers) who should be contacted regarding safety issues are listed on the Sponsor Contact Information page in the front section of this protocol.

7.4 Coding of Adverse Events

All AEs will be coded by the Sponsor's designee using the current Medical Dictionary for Regulatory Activities (MedDRA)® terminology.

8. STATISTICAL METHODS AND DATA MANAGEMENT

The statistical analyses described in this section will be performed for the study as further outlined in the Statistical Analysis Plan (SAP), which will be finalised prior to unblinding of the database and will be included in the Clinical Study Report for this protocol. Investigators will be provided with subject treatment allocation information associated with their study participants upon finalisation of the Clinical Study Report.

8.1 Determination of Sample Size

This is a phase 3, multicentre, double-blinded, randomized, placebo-controlled study evaluating the bioequivalence of Sprinkle and Capsule formulations of lubiprostone when administered orally in subjects with chronic idiopathic constipation. Subjects will be randomized (1:1:1 ratio) to receive either lubiprostone sprinkle, lubiprostone capsule or matching placebo BID in a blinded, double-dummy fashion.

In clinical studies of the lubiprostone capsule formulation during the CIC development program, the average observed SBM count at Week 1 for lubiprostone 24 mcg BID was 5.62 with a standard deviation of 4.24. In order to achieve the conclusion of equivalence between the sprinkle and capsule formulations of lubiprostone, the 90% confidence interval for the ratio of means has to be contained within the interval of [0.8, 1.25]. Thus, a sample size of 156 per group is required to achieve 90% power at a 10% significance level.

Assuming 10% of subjects do not meet criteria for inclusion in the Per Protocol population and/or do not have observed week 1 SBM count due to early withdrawal or other reasons, 174 subjects per treatment group (a total of 522 subjects) will be required for this study.

8.2 Datasets Analysed

Four analysis populations, the modified Intent-to-Treat (mITT) population, the Per Protocol (PP) population, the Completers population, and the Safety population, will be defined as follows:

- **The mITT population** will include all randomized subjects who take at least one dose of study medication and have at least one diary entry. This dataset will be used for summarization of demographic and baseline characteristic data, and for all efficacy analyses.
- **The PP population** will consist of all mITT subjects who met all eligibility (i.e., inclusion/exclusion) criteria at study entry, did not have any major protocol violations, had an overall diary compliance of at least 70%, and had a dosing compliance within 75% to 125%. Dosing compliance will be verified by the use of diary data. Supportive efficacy analyses will be performed on this population to evaluate the impact of major protocol violations.
- **The Completers population** will consist of only those subjects who complete the entire treatment period of the study with a recorded primary endpoint and will be used for supportive efficacy analyses.

- **The Safety population** will consist of all randomized subjects who take at least one dose of double-blinded study medication. Analyses on the Safety population will be based on the actual treatment received.

8.3 Analysis of Subject Characteristics and Completion Status

Subject demographic and baseline disease characteristic data will be summarized by treatment group and overall with descriptive statistics for all randomized subjects. The summaries will include the number of subjects, mean, median, standard deviation, minimum, maximum, 95% confidence intervals (CIs) for continuous variables, and counts and percentages for each level of categorical variables. Treatment comparisons will be presented using two-sample t-test for continuous variables and Cochran-Mantel-Haenzel (CMH) test for categorical variables.

For Subject completion status, the frequencies and percentages of subjects who are randomized, treated, completed study, discontinued from study with reasons for discontinuation will be summarized by treatment group and overall. Subject accountability will be summarized by site and by treatment group and overall for randomized subjects and all study specific populations.

8.4 Analysis of Exposure to Study Medication, Rescue Medication, and Concomitant Medication

8.4.1 Analysis of Study Drug Exposure and Compliance

Exposure to study medication and study drug compliance will be summarized by treatment group and overall using descriptive statistics. The exposure to study medication is defined as the last dose date of study medica ion minus the first dose date of study medication plus 1 day. Percent compliance will be calculated as the total number of daily dose divided by the total number of expected doses. The total number of expected doses will be calculated as the total number of study medication exposure (day) times 2.

8.4.2 Analysis of Rescue Medication and Concomitant Medication

Rescue and concomitant medications will be classified by the World Health Organization (WHO) Drug dictionary, and numbers and percentages of subjects receiving each classified medication will be calculated for all medications.

8.5 Analysis of Efficacy

8.5.1 General Inferential Principles

All efficacy analyses will be conducted using the mITT and PP populations by randomized treatment group and, unless stated otherwise for equivalence analysis, all tests are two-tailed at a significance level of $\alpha = 0.10$ with 90% confidence intervals (CIs). For the superiority analysis compared Lubiprostone sprinkle and capsule formulations to the matching Placebo, all tests are two-tailed at a significance level of $\alpha = 0.05$. Analysis of covariance (ANCOVA) and the van Elteren test will be performed to compare the sprinkle and capsule formulations of lubipristone with matching placebo.

8.5.1.1 Missing Data

Only observed SBM count will be adjusted for missing data, and the missing data imputation will be performed using the following four methods:

Last Daily Observation Carried Forward (LDOCF): Subjects with any missing daily observed SBM count during the treatment week will have their daily value(s) imputed by carrying over the previous non-missing post-baseline SBM observed count, and the LDOCF method will be used for the primary efficacy analysis.

Average Daily Baseline Observation Carried Forward (BOCF): Subjects with any missing daily observed SBM count during the treatment week will have their daily value(s) imputed by the Baseline SBM observed count divided by 7.

Observed Case (OC) Analysis: All observed SBMs that occurred during Week 1 for each subject will be counted, without any missing data imputation being performed.

Regression Imputation: Subjects with missing Week 1 observed SBM count will have their value imputed using the regression equation found from regressing the Week 1 observed SBM count as the dependent variable for all subjects in the same treatment group on their baseline observed SBM count as the independent variable.

Median Imputation: The median observed SBM count for all subjects in the same treatment group will replace missing observed SBM count at Week 1.

BOCF, OC Analysis, Regression Imputation, and Median Imputation will be used as sensitivity assessments of the primary efficacy endpoint.

8.5.1.2 Multiplicity

Since no interim analyses are to be performed and the primary efficacy analysis consists of a single treatment comparison on one endpoint, no multiplicity adjustments will be made.

8.5.1.3 Multicenter Studies

Center effects will be explored as detailed in the SAP.

8.5.2 Primary Analysis of Efficacy

The primary efficacy analysis is the LDOCF SBM count at Week 1. SBM is defined as any BM that does not occur within 24 hours after rescue medication use.

For the primary efficacy variable of observed Week 1 SBM count, the 90% CIs of the treatment ratio between the sprinkle and capsule formulations will be calculated and the equivalence of the two medications can be claimed if the equivalence limits are within the interval of [0.8, 1.25].

The primary efficacy analysis will be performed in PP population.

8.5.3 Secondary Endpoints

8.5.3.1 Superiority Analysis of Observed SBM Count at Week 1 for Lubiprostone Sprinkle and Lubiprostone Capsule vs. Matching Placebo

The observed SBM count will be summarized by treatment group. ANCOVA for the observed SBM count with baseline SBM count as a covariate and the van Elteren test stratified by baseline SBM frequency rate (< 1.5 or ≥ 1.5) and pooled sites will be performed for the following comparisons:

- The sprinkle formulation of lubiprostone vs. the placebo group
- The capsule formulation of lubiprostone vs. the placebo group

8.5.3.2 Change from Baseline in Observed SBM Count at Week 1

Changes from baseline in observed SBM count will be summarized by treatment group. The 90% CIs of the treatment ratio between the sprinkle and capsule formulations will be calculated. ANCOVA for the change from baseline in observed SBM count and the van Elteren test stratified by baseline SBM frequency rate (< 1.5 or ≥ 1.5) and pooled sites will be performed for the following comparisons:

- The sprinkle formulation of lubiprostone vs. the placebo group
- The capsule formulation of lubiprostone vs. the placebo group

8.5.3.3 Overall and Mean Change from Baseline in Constipation Signs and Symptoms at Week 1

Overall and mean changes from baseline at Week 1 will be summarized based on subject reported data as to the degree of:

- Straining associated with SBMs; and
- Stool consistency of SBM.

The following rating scales will be used:

Stool consistency: Bristol Stool Form Scale (7-point scale);

Bowel straining: 0=Absent, 1=Mild, 2=Moderate, 3=Severe, 4=Very severe.

The overall mean scores, as well as changes from baseline, for the 7-day treatment will be calculated for each subject. The mean scores will be summarized using descriptive statistics for each treatment group. The 90% CIs of the treatment ratio between the sprinkle and capsule formulations will be calculated. ANCOVA and the van Elteren test will be performed to detect differences from baseline between the sprinkle and capsule formulations of lubiprostone and the matching placebo group.

8.5.3.4 SBM Frequency Rate at Week 1

SBM frequency rate at week 1 will be summarized by treatment group. The 90% CIs of the treatment ratio between the sprinkle and capsule formulations will be calculated. ANCOVA, using Week 1 SBM frequency rate as the dependent variable will be used to compare treatment groups with baseline SBM frequency rate as a covariate. The van Elteren test stratified baseline SBM frequency rate (< 1.5 or ≥ 1.5) and pooled sites will be performed to detect differences from baseline for lubiprostone sprinkle and lubiprostone capsule vs. matching placebo.

In order to adjust for early withdrawals or missing days, subjects with less than 7 days of treatment will have the Week 1 SBM frequency rates adjusted as follows:

7 × Number of SBMs / (Number of days treated).

If the number of observed days is less than 4 days, then the data will be considered insufficient and the rate will be missing for that subject. No imputation will be performed for missing data.

8.5.3.5 Mean Change from Baseline in SBM Frequency Rate at Week 1

Changes from baseline in SBM frequency rate at week 1 will be summarized by treatment group. The 90% CIs of the treatment ratio between the sprinkle and capsule formulations will be calculated. ANCOVA for the change from baseline in observed SBM count and the van Elteren test stratified by baseline SBM frequency rate (< 1.5 or ≥ 1.5) and pooled sites will be performed for the following comparisons:

- The sprinkle formulation of lubiprostone vs. the placebo group
- The capsule formulation of lubiprostone vs. the placebo group

8.5.4 Sensitivity Analysis of Primary Efficacy Endpoint

The primary analysis will be performed for the following specific population to assess the robustness of the primary analysis:

PP subjects discontinued early due to lack of efficacy after completing 3 days of treatment and PP subjects discontinued early because of taking the rescue medication during the 1-week treatment period will be included. PP subjects discontinued early for other reasons are excluded.

8.5.5 Subgroup Analysis

The primary efficacy analysis will also be performed in demographic subgroups including age, gender, and race to assess the consistency of treatment effect. Additional subgroup analyses based on other baseline characteristics and stratification factors may also be conducted.

8.6 Analysis of Safety

8.6.1 Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Events

Subjects with these critical events will be identified in separate listings, with the event, timing and outcome information and relevant demographic and baseline data.

8.6.2 Adverse Events

The original terms used in the eCRF by Investigators to identify AEs will be coded to MedDRA® system organ class and preferred terms. Adverse events will be summarized in terms of incidence per dose group and overall. The incidence of an AE is defined as the number of subjects who experienced at least one episode during the study. Adverse event incidence rates will be summarized by system organ class (SOC) and preferred term (as determined by the coding).

Whatever the level of classification, if a subject experiences multiple episodes of an event within the given time reference, then the event is only counted once. Further, for summaries by severity or causality, the most severe event is chosen for a subject if that subject experiences multiple episodes of the same event

AEs with onset dates between consent and prior to administration of the first dose of study medication or after the last day of treatment + 7 days will be considered non-treatment emergent, and excluded from the tabulations. Events with completely or partially missing onset dates will be included in the tabulations unless the available partial date information clearly indicates that the event happened outside of the treatment period.

P-values from Fisher's exact test or chi-square test will be presented in the AE summary tables. The test will be performed to compare incidence rates between the sprinkle and capsule formulations of lubiprostone and the matching placebo group.

8.6.3 Clinical Laboratory Tests

For clinical laboratory data, mean changes from pre-treatment to post-treatment visits will be summarized using descriptive statistics. Cross-tabulations analysis will be performed for laboratory parameters with reference normal ranges. The laboratory data will be categorized as low, within, and above the reference normal ranges. The summary tables will tabulate the number and percentage of subjects with pre-treatment values below/within/above the normal reference range versus minimum/maximum/final post-treatment values below/within/above the normal reference range. Normal reference ranges will also be provided in the summary display. Laboratory parameters that are not specified in the protocol will not be included in the analysis.

8.6.4 Physical Examinations

Subjects with a physical examination performed at the Screening, Randomization, EOT, and Follow-up Visits will be displayed in a subject listing.

8.6.5 Vital Signs

Descriptive statistics will be provided to evaluate the absolute values and changes from baseline for any vital signs (blood pressure, heart rate, respiratory rate, temperature, and weight) measured during the study.

8.7 Data Quality Assurance

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study sites, review of protocol procedures with the Investigator and associated personnel prior to the study, and periodic monitoring visits by the Sponsor or designee. Compliance will be achieved through a combination of study specific audits of investigational sites and audits at regular intervals of the Sponsor's systems for data handling, analysis, and reporting. eCRFs will be reviewed for accuracy and completeness by the Sponsor or designee during on-site monitoring visits and any discrepancies will be resolved with the Investigator or designees, as appropriate. The data will be entered into the clinical study database and verified for accuracy.

This study will be organised, performed, and reported in compliance with the Sponsor's Standard Operating Procedures, protocols and working practice documents, and the requirements of national and international GCP guidelines.

8.8 Data Collection

Original source data will be collected via source documents. Final data for this study will be collected using eCRFs. Data must be entered on to the eCRFs in English. All eCRFs must be completed in a timely manner before the Sponsor or designee performs a monitoring visit. The Principal Investigator will be required to electronically sign the eCRFs casebook for each subject. Laboratory reports must be reviewed, signed, and dated by an appropriate Investigator and filed with the source documents. Any laboratory findings out of the normal range should indicate the clinical significance (clinically significant [CS] or not-clinically significant [NCS]) of the results on both the source document and the corresponding eCRF.

The eCRFs are to be completed as soon as possible from the time of the subject's visit, with the exception of results of tests performed outside the Investigator's office, so that they always reflect the latest observations on the subjects participating in the study.

All eCRF corrections are to be made or reviewed by the Investigator or other authorized study site personnel.

Automatically generated queries will be answered by site personnel during the eCRF completion process.

The dates of the monitoring visits will be recorded by the monitor in a study site visit log to be kept at the site. The first post-initiation monitoring visit will usually be made as soon as possible after enrolment has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). Source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of AEs, administration of concomitant

medication, medication receipt/dispensing/return records, and study medication administration information. Specific items required as source documents will be reviewed with the Investigator prior to the study. Findings from this review of eCRFs and source documents will be discussed with the Investigator. The Sponsor expects that, during monitoring visits, the Investigator and study coordinator, will be available, the original source documentation, regardless of media, will be available, and a suitable environment will be provided for review of study-related documents.

9. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study will be conducted in accordance with current applicable regulations, ICH, and local ethical and legal requirements.

9.1 Sponsor's Responsibilities

9.1.1 GCP Compliance

The Sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their roles for this study in compliance with all applicable regulations and ICH GCP Guideline E6.[9]

Visits to Investigator sites will be conducted by representatives of the Sponsor to inspect study data, subjects' medical records and eCRFs in accordance with current GCP and the respective local and national government regulations and guidelines. Records and data may additionally be reviewed by auditors, interested commercial parties or by regulatory authorities.

9.1.2 Regulatory Approval

The Sponsor will ensure that Local Regulatory Authority requirements are met before the start of the study. The Sponsor (or a nominated designee) will be responsible for the preparation, submission and confirmation of receipt of any Regulatory Authority approvals required prior to release of investigational product for shipment to the study site.

9.1.3 Protocol Training and Management

All protocols and amendments will be prepared by the Sponsor. The Sponsor will ensure that the Investigator is trained on the protocol and appropriate documentation of training will be kept in the Investigator Site File. If it becomes necessary to issue a protocol amendment during the course of the study, the Sponsor will notify the Investigators and collect documented Investigator Agreement to the amendment.

9.2 Investigator's Responsibilities

9.2.1 GCP Compliance

The Investigator must undertake to perform the study in accordance with ICH GCP Guideline E6[10], and the applicable regulatory requirements. A copy of the guidelines will be available in the Investigator Site File.

It is the Investigator's responsibility to ensure that adequate time and appropriate resources are available at the study site prior to commitment to participate in this study. The Investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The Investigator will maintain a list of appropriately qualified persons to whom the Investigator has delegated significant trial-related tasks. An up-to-date copy of the *curriculum vitae* for the

Investigator, Sub-investigator(s) and essential study staff will be provided to the Sponsor (or designee) before starting the study.

If the subject has a primary care physician the Investigator should, with the subject's consent, inform them of the subject's participation in the trial.

A Coordinating Principal Investigator will be appointed to review the final Clinical Study Report for multicentre studies. Agreement with the final Clinical Study Report will be documented by the signed and dated signature of the Coordinating Principal Investigator (multicentre study), in compliance with ICH E3.[10]

9.2.2 Protocol Adherence and Investigator Agreement

The Investigator must adhere to the protocol as detailed in this document. The Investigator will be responsible for enrolling only those subjects who have met protocol eligibility criteria. The Investigators will be required to sign an Investigator Agreement to confirm acceptance and willingness to comply with the study protocol. The Investigator should accurately and regularly document all incidents of scientific misconduct or deviation from the protocol in the source documents and eCRFs or any other documents stipulated in the protocol.

It is the Investigator's responsibility to communicate with their local IRB/IEC to ensure accurate and timely information is provided at all phases during the study. In particular the appropriate approvals must be in place prior to recruitment, notification of any SAEs during the study must take place and the IRB/IEC must be informed of study completion.

9.2.3 Documentation and Retention of Records

9.2.3.1 Case Report Forms

Data for this study will be collected using electronic data capture (EDC). eCRFs will be accessible via the internet for each subject's study completion information.

The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information will be transcribed onto eCRFs which have been designed to record all observations and other data pertinent to the clinical investigation. eCRFs should be filled out completely by the Investigator or delegate as stated in the Site Delegation List.

Data must be entered into the eCRFs in English. All eCRFs must be completed in a timely manner and electronically submitted. The Principal Investigator will be required to electronically sign and date specified screens of the eCRF. Laboratory reports must be reviewed, signed, and dated by an appropriate Investigator.

The eCRFs are to be completed as soon as possible from the time of the subject's visit, with the exception of results of tests performed outside the Investigator's office, so that they always reflect the latest observations on the subjects participating in the study.

All eCRF corrections are to be made or reviewed by the Investigator or other authorized study site personnel.

Completed eCRFs will be continuously submitted in the EDC system database, and reviewed by the Sponsor to determine their acceptability. Automatically generated queries will be answered by site personnel during the eCRF completion process.

9.2.3.2 Recording, Access and Retention of Source Data

Source data to be reviewed during this study will include, but is not limited to: subject's medical file, subject diary cards, original laboratory reports, and histology and pathology reports.

All key data must be recorded in the subject's medical records.

The Investigator must permit authorised representatives of the Sponsor, the respective national, local or foreign regulatory authorities, the IRB/IEC, auditors and interested commercial parties to inspect facilities and original records relevant to this study.

The monitor (auditors, IRB/IEC or regulatory inspectors) may check the CRF entries against the source documents. The consent form will include a statement by which the subjects allow the monitor/auditor/inspector from the Sponsor or its representatives, national or local regulatory authorities or the IRB/IEC access to source data (e.g., subject's medical file, appointment books, original laboratory reports, X-rays etc.) which substantiate information recorded in the CRFs. These personnel, bound by professional secrecy, will not disclose any personal information or personal medication information.

As described in the ICH GCP Guidelines, "essential documents", including CRFs, source documents, consent forms, laboratory test results and investigational product inventory records, should be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Investigator must obtain written permission from the Sponsor prior to the destruction of any study document.

These records must be made available at reasonable times for inspection and duplication, if required, by a properly authorised representative of the US Food and Drug Administration (FDA) in accordance with the US Code of Federal Regulations, 21 CFR 312.68[11], or other national or foreign regulatory authorities in accordance with regulatory requirements.

9.2.3.3 Investigational Product Accountability

All investigational product required for completion of this study will be provided by the Sponsor. The recipient will acknowledge receipt of the investigational product indicating shipment content and condition. Damaged supplies will be replaced. Accurate records of all investigational product dispensed, used and returned will be maintained.

9.2.3.4 Retention of Bioequivalence Testing Samples

In compliance with 21 CFR 320.38[12] and as recommended in the Center for Drug Evaluation and Research (CDER) Guidance for Industry dated May 2004[13] regarding retention of relevant

reserve bioequivalence (BE) test samples, Investigators must retain samples when relevant BE testing has been performed under contract by Sponsor. Retained samples must meet 21 CFR 320.38 and 320.63[14] requirements for reserve samples of test article and reference standard including, but not limited to, the following:

- Reserve samples must be representative of the test batches provided and therefore must be randomly selected by Investigator or his/her designee from identical test article and/or reference standards provided to the investigational site.
- The retained quantity must be sufficient to permit FDA to perform all release testing identified in the application five (5) times.
- Samples must be adequately identified so that the reserve samples can be positively identified as having come from the same samples as used in the BE studies.
- When storage is a problem (or if the investigational sites ceases operations), the investigational site (not Sponsor) must arrange transfer of the reserve samples to an independent third party provided that the Sponsor has been notified in writing of the name and address of such independent third party prior to such transfer.
- Samples must be stored under conditions that maintain the samples identity, integrity, strength, quality, and purity (i.e., stored under conditions consistent with product labelling and in an area segregated from the area where the testing is conducted, and with access limited to authorized personnel).
- Samples must be retained for at least five (5) years following the date of New Drug Application (NDA) or supplemental NDA approval or if the Investigational New Drug application (IND) is discontinued at least five (5) years following the date of completion of the BE studies.
- The investigative site shall fully cooperate with FDA and its personnel regarding the collection of reserve samples and any other items in connection with the Study including, but not limited to, the Investigator or his or her designee providing a written assurance to the FDA that the reserve samples came from the same samples used in the BE studies.

9.2.3.5 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the UK Medicines and Healthcare products Regulatory Agency (MHRA) and other foreign regulatory authorities, the Sponsor or its representatives, interested commercial parties and the IRB/IEC for each study site.

9.2.3.6 Financial Disclosure

The Investigator will be required to disclose any financial arrangement whereby the value of the compensation for conducting the study could be influenced by the outcome of the study. The following information will be collected: any significant payments from the Sponsor such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in lubiprostone; any significant equity interest in Sucampo Pharmaceuticals, Inc., or Takeda Pharmaceutical Company Limited as defined in 21 CFR 54 2(b).[15]

In consideration of participation in the study, the Sponsor will pay the Investigator or nominated payee the sums set out in the payment schedule attached to the Investigator Agreement.

9.3 Ethical Considerations

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, the note for Guidance on Good Clinical Practice (Committee for Proprietary Medicinal Products /ICH/135/95)[16], and with applicable local regulatory requirements. These documents set forth that the informed consent of the subjects is an essential precondition for participation in the clinical study.

9.3.1 Informed Consent

It is the responsibility of the Investigator to obtain written Informed Consent from subjects. All consent documentation must be in accordance with applicable regulations and GCP. Each subject is requested to sign the IRB/IEC approved Subject Informed Consent Form after the subject has received and read the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences and the subject's rights and responsibilities. A copy of the informed consent documentation (Consent Form or Subject Information) must be given to the subject.

Informed consent documentation will be appro ed in the local language. If translation is required into other languages, they must be certified and approved by the IRB/IEC for use. Signed consent forms must remain in each subject's study file and must be available for verification by Study Monitors at any time

The Principal Investigator wil provide the Sponsor with a copy of the IRB/IEC approved consent forms, and a copy of the IRB/IEC's written approval, prior to the start of the study. Additionally, if the IRB/IEC required modification of the sample Subject Information and Consent document provided by the Sponsor, the documentation supporting this requirement must be provided to the Sponsor.

The Sponsor reserves the right to delay initiation of the study at a site where the informed consent forms do not meet the standards of applicable regulations and ICH GCP.

9.3.2 Institutional Review Board or Independent Ethics Committee approval

It is the responsibility of the Investigator to submit this protocol, the informed consent document (approved by the Sponsor or its designate), relevant supporting information and all types of subject recruitment information to the IRB/IEC for review, and all must be approved prior to site initiation. Prior to implementing changes in the study, the Sponsor and the IRB/IEC must also approve any revised informed consent documents and amendments to the protocol.

On the approval letter, the trial (title, protocol number and version), the documents reviewed (protocol, informed consent material, [and amendments, if applicable]) and the date of review and actions taken should be clearly stated.

Investigational product supplies will not be released and the subject recruitment will not begin until this written approval has been received by the Sponsor.

The Investigator is responsible for keeping the IRB/IEC appraised of the progress of the study and of any changes made to the protocol, but in any case at least once a year. The Investigator must also keep the local IRB/IEC informed of any serious and significant adverse events.

9.4 Confidentiality

All US-based investigational sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). An investigational site that is not a Covered Entity as defined by HIPAA, must provide documentation of this fact to the Sponsor.

Data collected during this study may be used to support the development, registration or marketing of lubiprostone.

After subjects have consented to take part in the study their medical records and the data collected during the study will be reviewed by the Sponsor and/or its representatives. These records and data may, in addition, be reviewed by the following: independent auditors who validate the data on behalf of the Sponsor; third parties with whom the Sponsor may develop, register or market lubiprostone; national or local regulatory authorities and the IRB(s)/IEC(s) which gave its/their approval for this study to proceed.

Although subjects will be known by a unique number, their age and month and year of birth will also be collected and used to assist the Sponsor to verify the accuracy of the data, for example, that the laboratory results a e assigned to the correct subject. The results of this study containing the unique number, ge, month and year of birth and relevant medical information including ethnicity may be recorded and transferred to and used in other countries throughout the world, which m y not a ford the same level of protection that applies within the European Union. The purpose of any such transfer would be to support regulatory submissions made by the Sponsor in order to market lubiprostone in other countries.

9.5 Publication Policy

Sucampo abides by the clinical trial registration and results submission requirements to ClinicalTrials.gov described in Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801).

10. APPENDICES

APPENDIX 1 ROME III DIAGNOSTIC CRITERIA FOR FUNCTIONAL CONSTIPATION

Diagnostic Criteria*

1. Must include two or more of the following:
    a. Straining during at least 25% of defecations
    b. Lumpy or hard stools (Bristol Stool Form Scale 1-2) in at least 25% of defecations
    c. Sensation of incomplete evacuation for at least 25% of defecations
    d. Sensation of anorectal obstruction/blockage for at least 25% of defecations
    e. Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
    f. Fewer than 3 defecations per w ek
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis*

APPENDIX 2 ROME III CONSTIPATION MODULE QUESTIONNAIRE

Constipation Module		
1. In the last 3 months, how often did you have discomfort or pain anywhere in your abdomen?	⓪ Never → ① Less than one day a month ② One day a month ③ Two to three days a month ④ One day a week ⑤ More than one day a week ⑥ Every day	*Skip to question 9*
2. For women: Did this discomfort or pain occur only during your menstrual bleeding and not at other times?	⓪ No ① Yes ② Does not apply because I have had the change in life (menopause) or I am a male	
3. Have you had this discomfort or pain 6 months or longer?	⓪ No ① Yes	
4. How often did this discomfort or pain get better or stop after you had a bowel movement?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
5. When this discomfort or pain started, did you have more frequent bowel movements?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
6. When this discomfort or pain started, did you have less frequent bowel movements?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
7. When this discomfort or pain started, were your stools (bowel movements) looser?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
8. When this discomfort or pain started, how often did you have harder stools?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
9. In the last 3 months, how often did you have fewer than three bowel movements (0-2) a week?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
10. In the last 3 months, how often did you have hard or lumpy stools?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	

11. In the last 3 months, how often did you strain during bowel movements?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
12. In the last 3 months, how often did you have a feeling of incomplete emptying after bowel movements?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
13. In the last 3 months, how often did you have a sensation that the stool could not be passed, (i.e., blocked), when having a bowel movement?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
14. In the last 3 months, how often did you press on or around your bottom or remove stool in order to complete a bowel movement?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
15. In the last 3 months, how often did you have difficulty relaxing or letting go to allow the stool to come out during a bowel movement?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
16. Did any of the symptoms of constipation listed in questions 9-15 above begin more than 6 months ago?	⓪ No ① Yes	
17. In the last 3 months, how often did you have loose, mushy or watery stools?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	

C3. Functional Constipation

Diagnostic criteria*

1. Must include two or more of the following:

a) Straining during at least 25% of defecations

At least often. (question 11>1)

b) Lumpy or hard stools at least 25% of defecations

At least often. (question 10>1)

c) Sensation of incomplete evacuation at least 25% of defecations

At least sometimes. (question 12>0)

d) Sensation of anorectal obstruction/blockage at least 25% of defecations

At least sometimes. (question 13>0)

e) Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)

At least sometimes. (question 14>0)

f) Fewer than three defecations per week

At least often. (question 9>1)

2. Loose stools are rarely present without the use of laxatives.
   Loose stools occur never or rarely (question 17=0)
3. Insufficient criteria for IBS
   Diagnostic criteria for IBS not met

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Yes. (question 16=1)

Diagnostic Criteria for IBS (Exclusion Criteria for Constipation)*

Recurrent abdominal pain or discomfort** at least 3 days/month in last 3 months associated with two or more of criteria #1 - #3 below:

Pain or discomfort at least 2-3 days/month (question 1>2)

For women, does pain occur only during menstrual bleeding? (question 2=0 or 2)

1. Improvement with defecatio

   Pain or discomfort gets better after BM at least sometimes (question 4>0)
2. Onset associated with a change in frequency of stool

   Onset of pain or discomfort associated with more stools at least sometimes (question 5>0), OR Onset of pain or discomfort associated with fewer stools at least sometimes (question 6>0)
3. Onset associated with a change in form (appearance) of stool

   Onset of pain or discomfort associated with looser stools at least sometimes (question 7>0), OR Onset of pain or discomfort associated with harder stools at least sometimes (question 8>0)

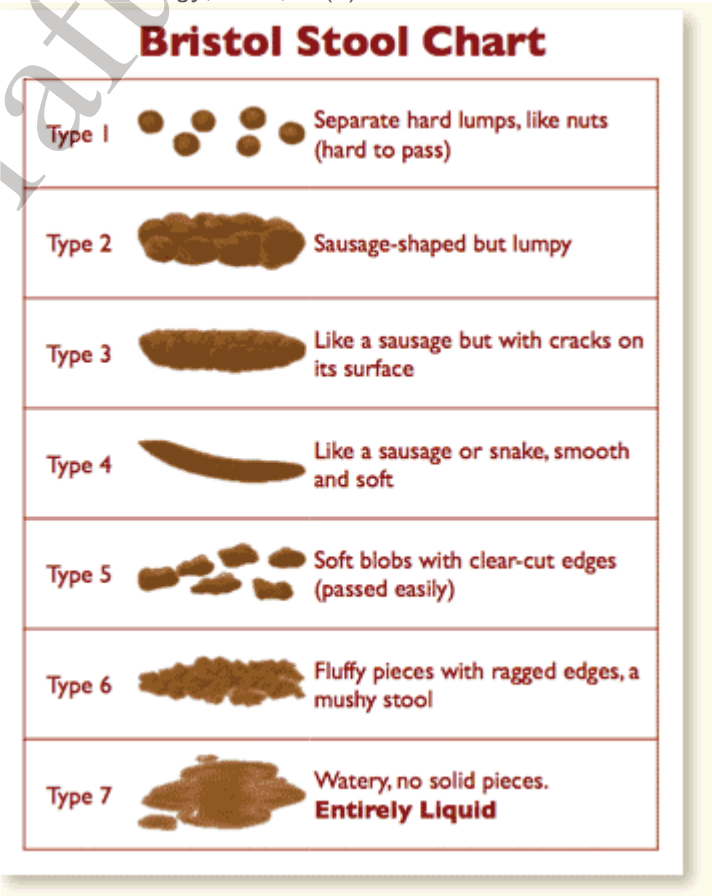
* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Yes. (question 3=1)

APPENDIX 3 SUBJECT BOWEL HABITS DIARY

The electronic diary will be completed each evening by the subject. The diary will be set up so that it may be completed each evening with responses based upon the last day.

Item/Instruction Text	Response Options
INSTRUCTIONS DAILY ASSESSMENTS The following questions will be assessed as part of the subject's daily diary. Subject will record their answers to these assessments for the entire duration of the study. Diaries are to be completed from the beginning of the screening period through the end of the double-blinded treatment period. Please note that the questions may be asked in an order different from what is presented below.	
STUDY MEDICATION Did you take your Morning Dose of STUDY MEDICATION today?	Yes No
What time did you take the Morning of STU Y MEDICATION Dose?	Morning Dose – xx:xx AM
STUDY MEDICATION Did you take your Evening Dose of STUDY MEDICATION today?	Yes No, not yet No, not taking tonight
What time did you take the Evening Dose of STUDY MEDICATION today?	Evening Dose – xx:xx PM
RESCUE MEDICATION Over the last day: Did you take a RESCUE MEDICATION to help you have a bowel movement?	Yes No
[If YES] Please indicate the OTHER RESCUE MEDICATION you used?	Bisacodyl Saline enema Other
[X will be equal to the other medicine selected in prior item response.] Did you take this RESCUE MEDICATION today or yesterday?	Today Yesterday

X Please record the time of this dose of RESCUE MEDICATION.	[spinner xx:xx]
BOWEL MOVEMENTS Confirm you would like to report a Bowel Movement you had today or yesterday: Today's Date: DD MON YYYY Yesterday's Date: DD MON YYYY	Yes No
Did this bowel movement occur today or yesterday? - *Will be asked for each bowel movement*	Today Yesterday
Please record the time of this bowel movement. - *Will be asked for each bowel movement*	[spinner xx:xx]
On the following screen, read the description and look at the picture to see which picture best matches the **consistency** of your bowel movement. - *Will be asked for each bowel movement*	Lewis SJ, Heaton KW, *Scandinavian Journal of Gastroenterology*, 1997; 32(9):920–924.[17] 

What was the degree of **straining** associated with this bowel movement? - *Will be asked for each bowel movement*	0 - None 1 - Mild 2 - Moderate 3 - Severe 4 – Very severe
Did you feel like you completely emptied your bowels with this bowel movement? - *Will be asked for each bowel movement*	Yes No

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11. 21 CFR 312.68 – Inspection o Investigator's Records and Reports.
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