A Multicenter, 6-month, Open-label Safety Study of Lubiprostone in Pediatric Subjects Aged ≥ 6 Years to < 18 Years with Functional Constipation

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PROTOCOL SIGNATURE PAGE

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PROTOCOL SCMP-0211-303

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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 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.

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Principal Investigator Signature Date

_____

Name of Principal Investigator (Printed)

_____

Institution

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ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
ALT	Alanine Transaminase (SGPT)
AST	Aspartate Transaminase (SGOT)
BID	Twice Daily
BM	Bowel Movement
BUN	Blood Urea Nitrogen
bpm	Beats Per Minute
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
CRF	Case Report Form
eCRF	Electronic Case Report Form
CS	Clinically Significant
DSMB	Data Safety Monitoring Board
EDC	Electronic Data Capture
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
IBS	Irritable Bowel Syndrome
ICD	Informed Consent Documentation
ICH	International Conference on Harmonisation
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRE	Immediately Reportable Event
IXRS	Interactive Voice/Web Response System
LAR	Legally Authorized Representative
LDH	Lactose Dehydrogenase
MAO	Monoamine Oxidase
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MCT	Medium Chain Fatty Acid Triglycerides

MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
mITT	Modified Intent-to-Treat
NCS	Non-clinically Significant
OTC	Over-the-Counter
QD	Once Daily
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis 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 Multicenter, 6-month, Open-label Safety Study of Lubiprostone in Pediatric Subjects Aged ≥ 6 Years to < 18 Years with Functional Constipation	
Study Phase	Phase 3
Short Title	6-month, open-label safety study of lubiprostone for the treatment of pediatric functional constipation in subjects aged ≥6 to <18 years
Objectives, Study Medication and Dose Regimen:	To assess the long-term safety and tolerability of oral lubiprostone 12 or 24 mcg capsules dosed twice daily (BID) when administered orally for 24 weeks in pediatric subjects with functional constipation. Evaluation of lubiprostone safety and tolerability is the primary objective in this study. A dose of 12 mcg BID will be assigned to subjects weighing <50 kg, and a dose of 24 mcg BID to subjects weighing ≥ 50 kg at time of enrollment.
Assumed No. of Sites: **Est. No. Enrolled Subjects:** **Est. No. Screened Subjects:**	Approximately 15 (United States) 150 subjects 150
Duration of Participation: **Duration of Treatment:**	Up to 25 weeks (including follow-up) 24 weeks
	Visit 1: Screening/Enrollment Visit (Clinic Visit) — Day 1 Visit 2: Telephone Assessment — Week 1 (Day 8 + 2 days) Visit 3: Interim Treatment Visit (Clinic Visit) — Week 12 Visit (Day 85 ± 3 days) Visit 4: End-of-Treatment (Clinic Visit) — Week 24 Visit (Day 169 + 3 days) Visit 5: Follow-Up (Clinic Visit) — Week 25 Visit (Day 176 + 3 days)
Inclusion Criteria:	1. Written informed consent obtained from subject and/or parent/legal guardian (and assent from subject where applicable). 2. Subject is at least 6 years of age but less than 18 years of age at the time of enrollment. 3. Subject fulfills the modified Rome III Diagnostic Criteria for Childhood Functional Constipation (Child/Adolescent; Section H3a) as follows: Must include **two or more** of the following in a child with a **developmental age of at least 4** years with insufficient criteria for diagnosis of irritable bowel syndrome (IBS)*: • Two or fewer defecations in the toilet per week • At least one episode of faecal incontinence per week • History of retentive posturing or excessive volitional stool retention • History of painful or hard bowel movements • Presence of a large faecal mass in the rectum • History of large diameter stools which may obstruct the toilet * Criteria fulfilled at least once per week for at least 2 months prior to diagnosis.

	4. If subject was previously screened for study participation in the SAG/0211PFC-1131 study, subject must have screen failed due to inclusion criterion numbers 7, 10, and/or 11 (see Section 3) for protocol SAG/0211PFC-1131; individuals who screen failed from SAG/0211PFC-1131 due to other eligibility criteria will not be considered for this protocol. 5. If subject is taking a concomitant medication (prescribed or over-the-counter) that affects gastrointestinal motility, he/she must discontinue use at the time of the Screening/Enrollment Visit (Visit 1); 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; 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 during the study if no relevant change of dose is anticipated at the time of enrollment. 6. Subject (and if necessary, parent/legal guardian) must be willing and able to use or administer recommended (rectal and/or oral) rescue medications if needed.
Exclusion Criteria:	1. Subject's constipation is known to be attributed to any of the following: a. Physical/Mental/Cognitive – any condition, other than functional constipation, that in the Investigator's opinion would interfere with meaningful study participation or evaluation. b. Anatomic – associated with a mechanical bowel obstruction (tumour, hernia, obstructive polyps, etc.), or pseudo-obstruction. c. Neurological – associated with spinal cord disorder, congenital disorder, or Guillain-Barre syndrome. d. Endocrine/Metabolic – associated with hypothyroidism, diabetes, hypercalcaemia, or hypokalaemia. e. Inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, celiac disease). f. Medication – associated with the use of medication known to cause constipation. 2. Subject is a candidate for, or undergone abdominal surgery including bowel resection, colectomy, 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 has Hirschsprung's disease. 5. Subject reports episodes of faecal incontinence that are not associated with retention of stool (e.g., non-retentive faecal incontinence as defined by the Rome III Diagnostic Criteria). 6. Subject has current evidence of untreated faecal impaction at the time of screening. 7. Subject has a medical/surgical condition that might interfere with the absorption, distribution, metabolism, or excretion of the study medication.

	8. Subject has uncontrolled cardiovascular, liver or lung disease, neurologic or psychiatric disorder, or other systemic disease, which the Investigator considers to be clinically significant and would limit the subject's ability to participate in the trial. 9. Subject has a diagnosis of impaired renal function or impaired hepatic function. 10. Subject has experienced an unexplained significant weight loss within 6 months prior to the Screening Visit (Visit 1). 11. Subject (female of childbearing potential) has a positive pregnancy test, refuses/unwilling to undergo pregnancy testing, and/or does not agree to use protocol-specified contraceptive measures for the duration of the study. 12. Subject has current evidence of, or has been treated for, cancer within the past 5 years. 13. Subject or parent/legal guardian demonstrates a potential for non-compliance with 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.
Rescue Treatment	In the event that no bowel movement (BM) has occurred within a 3-day period, the use of recommended rescue medications may be allowed per Investigator's instructions. Recommended rescue medications include bisacodyl, senna, and saline enemas.
Safety Endpoints:	The safety endpoints are as follows: • Incidence of adverse events (AEs) grouped by MedDRA System Organ Class (SOC) and Preferred Term • Changes from baseline in clinical laboratory parameters (haematology, serum chemistry, urinalysis) • Changes from baseline in physical examination • Changes from baseline in vital sign measurements, including height and weight A Data Safety Monitoring Board (DSMB) will monitor safety data on a regular basis throughout the study. Specifics, including meeting frequency and stoppage criteria, are provided in the DSMB Charter.
Sample Size Estimate Calculation	For purposes of establishing the safety profile with lubiprostone long-term exposure in pediatric functional constipation, safety data from subjects enrolled in this study will be considered together with subjects enrolled in Sucampo study SAG/0211PFC-11S1. The sample size is based on the expected attrition that would occur to have at least 100 subjects complete the full 24-week treatment period.
Statistical Methodology	Adverse events will be summarized in terms of incidence by treatment group and overall. Changes from baseline or clinical abnormalities in clinical laboratory data, physical examinations, and vital signs will be summarized by treatment group and overall.

SCHEDULE OF EVALUATIONS

Study Week(s)	0	1	12	24	25
Study Day(s)	1	8 (+ 2)	85 (± 3)	169 (+ 3)	176 (+ 3)
Visit Number	1	2	3	4	5
Visit Type	Screening/ Enrollment	Telephone Assessment	Clinic Examination	End-of-Treatment Clinic Examination	Follow-up Clinic Examination
Assessment					
Informed Consent/Assent	X				
Inclusion/Exclusion Criteria Review[1]	X				
Demographics	X				
Medical History	X				
Vital Signs, Height, and Weight[2]	X		X	X	X
Physical Examination[3]	X			X	
Blood Chemistry, Hematology, Urinalysis[4]	X		X	X	X
Urine Pregnancy Test[5]	X		X	X	X
Concomitant Medications	→	→	→	→	→
Adverse Events	→	→	→	→	→
Study Medication Distribution[6]	X		X		
Investigator Assessment of Treatment Effectiveness			X	X	
Study Treatment	→	→	→		
Study Medication Collection[6]			X	X	

[1] It is required to complete a Rome III Diagnostic Criteria Questionnaire for all screened subjects, unless a Questionnaire was completed within the most recent 30 days prior to Screening for this protocol (i.e., prior diagnosis of PFC must be verified *via* completion of a Questionnaire for all subjects) – in all cases, a copy of the Questionnaire must be maintained in the Subject's source documentation for this study;

[2] Measure predose vital signs at Visit 1, as well as measurement of heart rate and blood pressure 1 hour after the first dose of study medication. If blood pressure and/or heart rate are, according to the Investigator, clinically significantly elevated relative to predose at the 1 hour postdose measurement, additional measurements should be taken again at 2 hours and 3 hours postdose. Subjects should be asked to remain seated for at least 5 minutes prior to measurement of vital sign parameters. A wall-mounted stadiometer, where available, should be used for measurement of height. Record the time of all vital sign measurements in the source documents. Age-appropriate equipment, e.g., blood pressure cuffs, should be used for all assessments;

[3] Complete full physical examinations at Enrollment and End-of-Treatment visits;

[4] Laboratory results from subjects who screen failed on the SAG/0211PFC-1131 study may be used as the baseline assessment for this protocol, if these results are within the most recent 30 days prior to Screening for this protocol (i.e., laboratory samples do not need to be re-collected at Screening/Enrollment [Visit 1]);

[5] Female subjects of childbearing potential will have a urine pregnancy test performed at all clinic visits. Childbearing potential is defined as any subject who has reported first menses;

[6] A dose of 12 mcg BID will be assigned to subjects weighing <50 kg, and a dose of 24 mcg BID for subjects weighing ≥ 50 kg at time of enrollment. Observe the subject or parent/legal guardian as he/she administers the first dose of study medication while in the clinic at Visit 1. Over the next 1 hour, monitor subject for any adverse reactions. Three bottles of study medication will be provided at Visit 1 and then 3 bottles at Visit 3. Subjects should return the used bottles of study medication at each clinic visit 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. The subject will be instructed to take the study medication only from the newly dispensed bottles.

1. INTRODUCTION

1.1 Disease Overview

Constipation in children has similar characteristics to that of constipation in adults in that symptoms include infrequent bowel movements (BMs), hard stools, and painful passage of stools. Children may also experience faecal retention due to withholding.[1,2] There is a tendency to avoid defecation and withhold BMs due to pain experienced from the passage of large stools. This withholding of BMs can result in episodes of faecal incontinence. Functional constipation occurs in all pediatric age groups, from newborns to young adults and its severity may vary from mild and short-lived to severe and chronic with faecal impaction. It is responsible for 3–5% of pediatric outpatient visits and 25% of pediatric gastroenterology consultations.[1,2,3] Standardized diagnostic criteria for pediatric functional constipation have been defined by the Rome Committee for Functional Gastrointestinal Disorders.[3] Under Rome III, the diagnostic criteria for childhood functional constipation require that children of a developmental age of at least 4 years with insufficient criteria for diagnosis of irritable bowel syndrome (IBS) present with two or more of the following at least once per week for 2 months prior to diagnosis:

- Two or fewer defecations in the toilet per week
- At least one episode of faecal incontinence per week
- History of retentive posturing or excessive volitional stool retention
- History of painful or hard bowel movements
- Presence of a large faecal mass in the rectum
- History of large diameter stools which may obstruct the toilet

One systematic review showed a worldwide prevalence of childhood constipation in the general population ranging from 0.7% to 29.6%.[4] Similar prevalence rates were reported for boys and girls. Childhood constipation continues beyond puberty in up to one third of the children followed up.[5] Children aged 2 to 4 years seem to have a higher recurrence rate and a need for prolonged medication and support than younger infants.[6] One follow-up study has noted increased risk of persistent constipation in children who developed constipation early in infancy and who have a family history of constipation.[7] Another follow-up study assessing the clinical course of severe functional constipation in early childhood found that after initial success of treatment, a relapse occurred in 15% of the children within 3 years. Symptom duration of 3 months or less before referral was significantly correlated with better outcome.[8]

Medical treatment is aimed at disimpaction of the impacted faeces and restoration of regular bowel habits, which consist of passage of soft, normal stools without discomfort. The administration of laxatives is also used to achieve a normal bowel habit of passing a soft stool without pain. Even though the traditional treatment is well established and safe, for many patients it does not provide a satisfactory improvement, prompting interest in other therapeutic strategies.[9]

1.2 Product Background

Lubiprostone (24-mcg capsules administered twice daily [BID]) is currently approved in the US under the trade name Amitiza® for the treatment of adults with chronic idiopathic constipation and opioid-induced constipation in adults with chronic, non-cancer pain, and for women with irritable bowel syndrome with constipation (8 mcg BID). Lubiprostone 24-mcg BID is also marketed for treatment of adult chronic idiopathic constipation in the United Kingdom and Switzerland as well as it is approved for this indication in some other countries of the European Union (EU). Lubiprostone was approved for marketing in Japan for the treatment of chronic constipation (excluding constipation caused by organic diseases) in the adult population. In several well-controlled clinical studies in 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) in adults, to improve stool consistency, and to reduce straining, abdominal bloating, and abdominal discomfort.[10] An open-label safety and efficacy study of 4 weeks' duration has also been conducted in pediatric functional constipation subjects aged 3-17 years who were treated with lubiprostone 12 mcg once daily (QD), 12 mcg BID, or 24 mcg BID and improvement in SBM frequencies were reported in all dose groups.[11]

1.2.1 Preclinical information

A full summary of the findings from all non-clinical studies with lubiprostone can be found in the current Investigator Brochure.

1.2.2 Clinical information

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

1.3 Rationale for Study

Even though traditional treatment of functional constipation in children is available and safe, for many patients it does not provide a satisfactory improvement, prompting interest in other therapeutic strategies. This particular study is being conducted to assess safety and tolerability of the product in the pediatric population, with the intention of combining data from this trial with safety data from two other ongoing trials of the product in this population. The doses selected for this study are based on the results obtained during the previous open-labeled study in children.[11]

Lubiprostone is currently being evaluated in two large, global Phase 3 studies, SAG/0211PFC-1131 and SAG/0211PFC-11S1. Study SCMP-0211-303 is being conducted with the intention to provide additional long-term exposure data to complement safety data from the ongoing studies. Subjects who are either AMITIZA (lubiprostone, SPI-0211, or RU-0211)-treatment-naïve, or who were screen failed due to protocol-specified inclusion criterion (i.e., inclusion criterion numbers 7, 10, and/or 11; see Section 3 of this protocol) in the ongoing lubiprostone study, SAG/0211PFC-1131, may be eligible to enroll into this open-label, long-term safety study. Individuals who screen failed from SAG/0211PFC-1131 due to other eligibility criteria will not be considered for this protocol. A dose of 12 mcg BID will be assigned to subjects weighing <50 kg, and a dose of 24 mcg BID for subjects weighing ≥ 50 kg at time of enrollment.

Lubiprostone has a well-documented safety record in clinical studies involving over 4,000 adult subjects. The safety record, along with previously observed improvement in constipation signs and symptoms in both children and adults, provides a potential treatment option in a pediatric population.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

To assess the long-term safety of oral lubiprostone 12 or 24 mcg capsules dosed twice daily (BID) when administered orally for 24 weeks in pediatric subjects with functional constipation. Evaluation of lubiprostone safety is the primary objective in this study.

2.2 Endpoints

2.2.1 Safety

The safety endpoints are as follows:

- Incidence of adverse events grouped by MedDRA System Organ Class (SOC) and Preferred Term
- Changes from baseline in clinical laboratory parameters (haematology, serum chemistry, urinalysis)
- Changes from baseline in physical examination
- Changes from baseline in vital sign measurement, including height, and weight

A DSMB will monitor safety data on a regular basis throughout the study. Specifics, including meeting frequency and stoppage criteria, are provided in the DSMB Charter.

2.2.2 Efficacy

An exploratory Investigator's assessment of treatment effectiveness will be assessed in this study.

3. STUDY DESIGN

This is a phase 3, multicenter, 6-month study to assess the safety and tolerability of oral lubiprostone for the treatment of functional constipation in children. Approximately 150 subjects who are either AMITIZA (lubiprostone, SPI-0211, or RU-0211)-treatment-naïve with a diagnosis of Pediatric Functional Constipation under Rome III, or who were screen failed due to protocol-specified inclusion criterion (i.e., inclusion criterion numbers 7, 10, and/or 11) in the ongoing lubiprostone study, SAG/0211PFC-1131, may be eligible to enroll into this open-label, long-term safety study across approximately 15 sites within the United States. If subject was previously screened for study participation in SAG/0211PFC-1131 study, the subject must have screen failed due to the following criterion for protocol SAG/0211PFC-1131:

- Subject was not taking a stable dose of fibre supplement (e.g., Metamucil®, PerDiem®, Fybogel) within 30 days prior to the Screening Visit;
- Subject daily diary indicated an average of at least 3 spontaneous bowel movements (SBMs) per week during the Screening period; and/or
- Subject did not have at least one of the following for at least 25% of SBMs during each week of the screening period (as reported in the daily diary):
  - Modified Bristol Stool Scale Type 1 or 2; and/or
  - Some to extreme straining associated with SBMs.

Individuals who screen failed from SAG/0211PFC-1131 due to other eligibility criteria will not be considered for this protocol.

A dose of 12 mcg BID will be assigned to subjects weighing <50 kg, and a dose of 24 mcg BID for subjects weighing ≥ 50 kg at time of enrollment. Duration of subject participation is approximately 25 weeks through follow-up. A schematic representation of the study design is provided below in Figure 1.

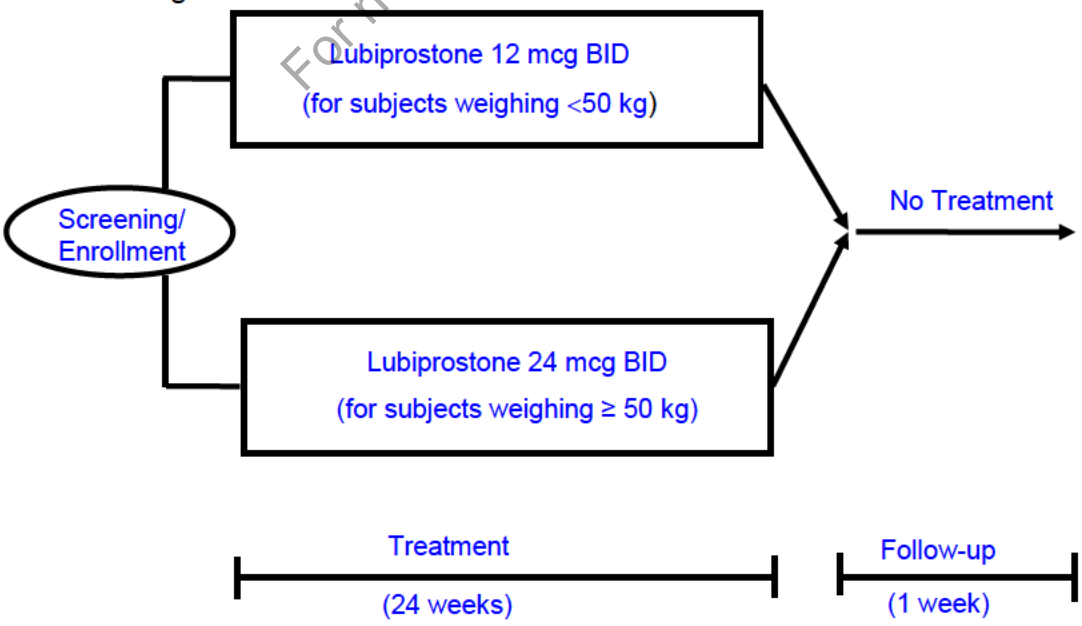

Figure 1: Study Design Flow Chart

3.1 Study Procedure Overview

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

There will be five distinct visits for this study:

- **Screening/Enrollment Visit (Visit 1; Day 1)**: This visit is considered study Day 1 and first day of study medication administration (first dose will be administered in the clinic).

- **Interim Telephone Assessment (Visit 2; Week 1)**: A telephone assessment will be performed by site personnel at Study Day 8 (+2 days). This assessment will be performed to evaluate safety.

- **Interim Treatment Clinic Examination (Visit 3; Week 12)**: A clinic visit will occur on Study Day 85 (± 3 days). Clinical and laboratory assessments will be performed to evaluate the safety of study treatment.

- **End-of-Treatment Visit (Visit 4; Week 24)**: A clinic visit will occur on Study Day 169 (+ 3 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 5; Week 25 [Day 176 + 3 days])**: A follow-up clinic visit will occur to perform post-treatment clinical and laboratory 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. Written informed consent obtained from subject and/or parent/legal guardian (and assent from subject where applicable).
2. Subject is at least 6 years of age but less than 18 years of age at the time of enrollment.
3. Subject fulfills the modified Rome III Diagnostic Criteria for Childhood Functional Constipation (Child/Adolescent; Section H3a) as follows:

   Must include **two or more** of the following in a child with a **developmental age of at least 4 years** with insufficient criteria for diagnosis of irritable bowel syndrome (IBS)*:

   - Two or fewer defecations in the toilet per week
   - At least one episode of faecal incontinence per week
   - History of retentive posturing or excessive volitional stool retention
   - History of painful or hard bowel movements
   - Presence of a large faecal mass in the rectum
   - History of large diameter stools which may obstruct the toilet

   * Criteria fulfilled at least once per week for at least 2 months prior to diagnosis.
4. If subject was previously screened for study participation in the SAG/0211PFC-1131 study, subject must have screen failed due to inclusion criterion numbers 7, 10, and/or 11 (see Section 3) for protocol SAG/0211PFC-1131; individuals who screen failed from SAG/0211PFC-1131 due to other eligibility criteria will not be considered for this protocol.
5. If subject is taking a concomitant medication (prescribed or over-the-counter) that affects gastrointestinal motility, he/she must discontinue use at the time of the Screening/Enrollment Visit (Visit 1); 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; 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 during the study if no relevant change of dose is anticipated at the time of enrollment.
6. Subject (and if necessary, parent/legal guardian) must be willing and able to use or administer recommended (rectal and/or oral) rescue medications if needed.

4.2 Exclusion Criteria

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

1. Subject's constipation is known to be attributed to any of the following:
   a. Physical/Mental/Cognitive – any condition, other than functional constipation, that in the Investigator's opinion would interfere with meaningful study participation or evaluation.
   b. Anatomic – associated with a mechanical bowel obstruction (tumour, hernia, obstructive polyps, etc.), or pseudo-obstruction.
   c. Neurological – associated with spinal cord disorder, congenital disorder, or Guillain-Barre syndrome.
   d. Endocrine/Metabolic – associated with hypothyroidism, diabetes, hypercalcaemia, or hypokalaemia.
   e. Inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, celiac disease.
   f. Medication – associated with the use of medication known to cause constipation.
2. Subject is a candidate for, or undergone abdominal surgery including bowel resection, colectomy, gastric bypass surgery (exceptions: appendectomy, cholecystectomy, benign polypectomy and inguinal hernia).
3. Subject has any gastrointestinal (GI) condition affecting GI motility or defecation.
4. Subject has Hirschsprung's disease.
5. Subject reports episodes of faecal incontinence that are not associated with retention of stool (e.g., non-retentive faecal incontinence as defined by the Rome III Diagnostic Criteria).
6. Subject has current evidence of untreated faecal impaction at the time of screening.
7. Subject has a medical/surgical condition that might interfere with the absorption, distribution, metabolism, or excretion of the study medication.
8. Subject has uncontrolled cardiovascular, liver or lung disease, neurologic or psychiatric disorder, or other systemic disease, which the Investigator considers to be clinically significant and would limit the subject's ability to participate in the trial.
9. Subject has a diagnosis of impaired renal function or impaired hepatic function.
10. Subject has experienced an unexplained significant weight loss within 6 months prior to the Screening Visit (Visit 1).
11. Subject (female of childbearing potential) has a positive pregnancy test, refuses/unwilling to undergo pregnancy testing, and/or does not agree to use protocol-specified contraceptive measures for the duration of the study.
12. Subject has current evidence of, or has been treated for, cancer within the past 5 years.
13. Subject or parent/legal guardian demonstrates a potential for non-compliance with 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 urine pregnancy tests performed at all site visits. Childbearing potential will be defined as any female subject who has reported first menses.

4.4 Contraception Specifications

Female subjects of child-bearing potential must agree to remain abstinent or to use adequate contraception during study participation. The type of contraception being used by the subject shall be recorded in the source document. Adequate contraception is defined as use of any of the following:

- Oral Contraceptive– must have been used for at least 3 months prior to the Screening/ Enrollment 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 institution. The Investigator or Sponsor may also withdraw the subject at any time in the interest of subject safety.

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;
- 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 (Visit 4) as outlined in Section 6.1.3.3 and the Follow-up Visit (Visit 5) as outlined in Section 6.1.4.1.

When a subject withdraws prior to completing the study, the reason for withdrawal shall be documented in the source documents and on the appropriate eCRF page. In any case where the action taken with study medication is listed as permanently withdrawn due to an adverse event, the reason selected for withdrawal in the eCRF must be “AE” (i.e., Investigator decision or other category should not be selected in such cases).

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 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

There is no need for emergency unblinding since this is an open-label study.

5. STUDY AND CONCOMITANT TREATMENTS

5.1 Study Medication Formulation

Lubiprostone drug substance is white, odourless 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 in a soft gelatin capsule formulation. Each soft gelatin capsule is filled with lubiprostone dissolved in medium chain fatty acid triglycerides (MCT) solution. Lubiprostone is the sole active ingredient. Each capsule contains 12 or 24 mcg lubiprostone.

5.2 Packaging

An independent packaging company, not involved in the conduct or monitoring of the study, will label, package, and distribute study medication. Study medication labelling will be provided in accordance with current Good Manufacturing Practice (cGMP) requirements and local regulatory specifications and requirements. The study medication will be packaged in bottles with a child-resistant cap. Each bottle will contain a 4-week supply plus a 4-day overage (64 capsules) of study medication (lubiprostone 12- or 24-mcg capsules).

5.3 Labelling

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

- Protocol Number;
- Bottle Number (if applicable);
- Dosage form (including product name);
- Manufacturing and storage 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’,
- The Sponsor's name and address;
- Any additional labeling requirements for participating countries and/or controlled substances will also be included on the label;
- Subject Number (To be written by the site);
- Subject Initials (To be written by the site, where applicable);
- 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 until it is assigned and handed over to the study subject. The medication will be stored at room temperature, defined as thermostatically-controlled to normal working environment of 20°C (68°F) to 25°C (77°F); excursions between 15ºC and 30ºC (59ºC to 86ºF) 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. The study subjects have to be advised that they store the study medication at room temperature, and that no temperature-control is needed.

No study medication stock or returned inventory may be removed from the investigational site without prior 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.

5.5 Supply and Dosing

Each bottle of study medication will contain 64 capsules, sufficient for 28 days plus a 4-day overage in the event that any capsules are lost, accidentally destroyed, or there is a delay in the completion of the scheduled clinic visit. Each treatment day should consist of two (2) doses of study medication, one (1) capsule per dose in the morning and in the evening. If a dose is missed, the subject should take the missing dose as soon as possible, but should not "double up" doses, i.e., take 2 doses at one meal.

The subject and his/her parent/legal guardian will be instructed to administer study medication with meals and at least 8 ounces (240 mL) of fluid. All doses should be taken at least 5 hours apart. The study medication will be handled by authorized personnel and dispensed under the supervision of the Investigator or designated site personnel.

Each subject will receive three 64-capsule bottle of study medication at the Enrollment Visit (Visit 1; Day 1), and three bottles at Visit 3. The first dose of study medication will be administered in the clinic at the Enrollment Visit and the Study Coordinator will record this first dose in the appropriate eCRF page.

Subject and/or parent/legal guardian should return the used bottles of study medication at each clinic visit 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. The subject will be instructed to take the study medication only from the newly dispensed bottles. The last dose of study medication in this study will be taken on the day of End-of-Treatment (Visit 4).

5.5.1 Reduction in Study Medication Dosing

A dose reduction may be initiated by the Investigator, if one of the following conditions is reported by the subject and/or parent/legal guardian to the site and **has been ongoing for three or more days**:

- **Nausea** – In cases where the subject is experiencing severe nausea, the Investigator may reduce the study medication to once daily (QD) dosing at their discretion and in consultation with the subject.
- **Diarrhea** – In cases where the subject is experiencing severe diarrhea, the Investigator may reduce the study medication to QD dosing at their discretion and in consultation with the subject.
- **Other** – In cases where the subject is experiencing some other type of AE, the Investigator may reduce the study medication to QD dosing upon consultation with and approval of the medical monitor.

Once the adverse event is reported by the subject, site personnel should follow the subject for any change in the nature of the event. If the event has not resolved after 3 days, a reduction to QD dosing may be initiated by the elimination of the morning dose of the study medication such that only the evening dose is taken once a day. Once a dose reduction occurs, the subject may resume administration of the BID dose regimen per Investigator discretion.

Note: Investigators should assess the need for reduction of the study medication at each visit.

5.5.2 Randomisation and Blinding

This study will not involve randomisation. A dose of 12 mcg BID will be assigned to subjects weighing <50 kg, and a dose of 24 mcg BID for subjects weighing ≥ 50 kg at time of enrollment.

There is no need for blinding since this is an open-label study.

5.5.3 Allocation of Subject Identification Number and 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. A dose of 12 mcg BID will be assigned to subjects weighing <50 kg, and a dose of 24 mcg BID for subjects weighing ≥ 50 kg at time of enrollment.

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 and in subject’s eCRF. See Section 5.5 for instructions about return of study medication. Study medication returned by the subjects will be stored and disposed of according to the Sponsor’s instructions. Contents of the study medication bottles must not be combined.

Designated study personnel will maintain a log of all study medications dispensed and returned. The Sponsor or designee will verify the drug accountability log during on-site monitoring visits. 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.

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 Enrollment Visit through the end of the first week following the End-of-Treatment Visit:

- Anti-spasmodics;
- Cholinesterase inhibitors;
- Anti-diarrheal medications;
- Anti-constipation medications (e.g., Linzess™/ Constella™, Relistor®, or Resolor®);
- Prokinetic agents;
- Laxative agents (e.g., PEG 3350), including homeopathic remedies;
- Tricyclic antidepressants;
- 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 during the study if no relevant change of dose is anticipated at the time of enrollment.

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 Fibre Therapy

Any fibre supplement used should be documented as a concomitant medication.

5.7.3 Rescue Medication

If necessary, rescue medication may be used to help induce a BM. The use of approved rescue medications is outlined below. Each parent/legal guardian should be educated on the protocol-specified use of rescue medications at the Screening/Enrollment Visit (Visit 1) and throughout the study.

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

a. **Rescue medication 1**: The subject or parent/legal guardian administer the clinically recommended dose of bisacodyl or senna.
b. **Rescue medication 2**: If the first rescue medication fails to induce a bowel movement, the subject or parent/legal guardian may administer a repeat dose of bisacodyl, senna, or administer a saline enema.
c. If both rescue medications fail, the subject or parent/legal guardian may contact the Investigator who may prescribe another medication at their discretion for immediate short-term use. The recommendation may include a medication from the excluded medication list **other than** any form of polyethylene glycol (PEG), Linzess™/ Constella™, Relistor®, or Resolor® (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 Concomitant Medication eCRF page.

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 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. Subjects who withdraw from the study early or who are terminated from the study should complete the End-of-Treatment (Visit 4) and the Follow-up Visit (Visit 5). All visits are outlined in this section.

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

Medical History – An updated medical history of the subject will be recorded. Particular attention should be made regarding the subject's continued status of functional constipation and related symptoms.

Inclusion/Exclusion – The subject will be assessed to determine their eligibility for the study based upon the inclusion (Section 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. The time of vital sign measurements should be recorded in the source documents. Vitals may be repeated, however all measurements taken should be recorded in the source documents. Any repeat readings at a particular timepoint should be recorded as unscheduled data points. Subjects should be asked to remain seated for at least 5 minutes prior to all measurements of vital sign parameters.

Age-appropriate equipment, e.g., blood pressure cuffs, should be used for all assessments.

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.

Laboratory Tests – Urine and blood samples will be collected and sent to a central laboratory for analysis (see Section 6.3 for details). Age-appropriate normative clinical laboratory values, based on the clinical laboratory's pediatric ranges, will be used to determine abnormal laboratory values for this study.

Pregnancy Test – All female subjects of childbearing potential will have a urine pregnancy test performed at all clinic visits. Childbearing potential will be defined as any female subject who has reported first menses.

Adverse Events – AEs will be reported by the subject and/or parent/legal guardian 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 – An updated concomitant therapy history of the subject will be recorded. The subject and/or parent/legal guardian must be reminded that prescription and laxative medications are disallowed per Section 5.7.1 of the protocol and not to change their diet or lifestyle.

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.

Investigator Assessment of Treatment Effectiveness – The Investigator's assessment of treatment effectiveness will be collected at Visit 3 and Visit 4, using the following scale:

> 0=Not at all effective, 1=A little bit effective, 2=Moderately effective, 3=Quite a bit effective, 4=Extremely effective.

6.1.2 Screening/Enrollment – Visit 1 (Study Day 1)

At this visit, a review of the inclusion and exclusion criteria will be conducted for all subjects to ensure the subject is eligible for the study. Consent/assent must be obtained before any study procedures are performed. Subjects not meeting eligibility criteria at this visit will be considered screen failures.

The following procedures will take place at this visit:

- Confirm compliance with inclusion/exclusion;
- Assign subject identification number;
- Record the demographics information;
- Perform a full physical examination;
- Collect medical history and concomitant medication information, including:
  - Documentation/Re-documentation of functional constipation diagnosis according to Rome III (see Section 4.1, Inclusion Criteria #3);
  - History of constipation treatment administered;
  - History of previously failed constipation treatments;

- Measure predose vital signs, including height and weight; measure heart rate and blood pressure 1 hour after the first dose of study medication. Subjects should be asked to remain seated for at least 5 minutes prior to measurement of vital sign parameters. If blood pressure and/or heart rate are confirmed to be clinically significantly changed (as defined in Section 6.3) at the 1 hour postdose measurement relative to predose, additional measurements should be taken again at 2 hours and 3 hours postdose. Record the time of vital sign measurements in the source documents. Age-appropriate equipment, e.g., blood pressure cuffs, should be used for all assessments;
- Collect blood and urine samples for clinical laboratory analysis (including a urine pregnancy test, if applicable). A total of about 5.5 mL of blood will be collected for clinical laboratory analysis;
- Review definition of rescue medication and instruct subject or parent/legal guardian how rescue medication administration is handled per protocol;
- Dispense 3 bottles of study medication based on subject weight, provide dosing instructions and remind the subject or parent/legal guardian to bring the bottles with any remaining study medication to the next visit;
- Observe the subject or parent/legal guardian as he/she administers the first dose of study medication while in the clinic. Over the next 1 hour, monitor subject for any adverse reactions. Ensure blood pressure and heart rate are collected at 1 hour postdose as described above; and
- Schedule the telephone visit (Visit 2; Day 8).

6.1.3 Treatment Period

The treatment period will begin on the day the first dose of study medication is administered (Enrollment Visit; Visit 1; Day 1) and will end upon administration of the last dose (End-of-Treatment; Visit 4).

Note: If at any time during the study, the subject discontinues from the study, the subject should be withdrawn from the study and complete the End-of-Treatment (Visit 4) and the Follow-up Visit (Visit 5).

6.1.3.1 Interim Telephone Assessment – Visit 2 (Week 1/Day 8 +2 days)

During this telephone assessment, the following procedures will be performed:

- Review and update concomitant therapy;
- Review and record any new AEs and follow-up on any ongoing AEs;
- Review compliance associated with study medication;
- Review and discuss rescue medication use; and
- Schedule the next clinic visit (Visit 3, Day 85).

6.1.3.2 Interim Clinic Assessment – Visit 3 (Week 12; Day 85 ± 3 days)

During this visit, the following procedures will be performed:

- Measure vital signs, including height and weight. Subjects should be asked to remain seated for at least 5 minutes prior to measurement of vital sign parameters. Record the time of vital sign measurements in the source documents. Age-appropriate equipment, e.g., blood pressure cuffs, should be used for all assessments;
- Collect blood and urine samples for laboratory analysis. A total of about 5.5 mL of blood will be collected for clinical laboratory analysis;
- Perform a urine pregnancy test, if applicable;
- Review and update concomitant therapy;
- Review and record any new AEs and follow-up on any ongoing AEs;
- Review and discuss rescue medication use;
- Obtain Investigator's assessment of treatment effectiveness;
- Collect the previously dispensed bottles of study medication and perform drug accountability. Review study medication compliance with the subject and/or parent/legal guardian. If the study medication is not returned, all bottles of unused study medication should be returned to the site at the subsequent office visit;
- Dispense new supply of study medication (3 bottles). The subject and/or legal guardian will be instructed to take the study medication only from the newly dispensed bottles; and
- Schedule the next clinic visit (i.e., at Week 24/Study Day 169).

6.1.3.3 End-of-Treatment Visit – Visit 4 (Week 24/Day 169 +3 days)

During this visit, the following procedures will be performed:

- Measure vital signs, including height and weight. Subjects should be asked to remain seated for at least 5 minutes prior to measurement of vital sign parameters. Record the time of vital sign measurements in the source documents. Age-appropriate equipment, e.g., blood pressure cuffs, should be used for all assessments;
- Perform a full physical examination;
- Collect blood and urine samples for clinical laboratory analysis. A total of about 5.5 mL of blood will be collected for clinical laboratory analysis;
- Perform a urine pregnancy test, if applicable;
- Review and update concomitant therapy;
- Review and record any new AEs and follow-up on any ongoing AEs;
- Obtain Investigator's assessment of treatment effectiveness;
- Collect all previously dispensed bottles of study medication and perform drug accountability. Review study medication compliance with the subject and/or parent/legal guardian. If the study medication is not returned, all bottles of unused study medication must be returned to the site personnel at the subsequent office visit.

6.1.4 Follow-up Period

The follow-up period lasts for 1 week following the final dose of study medication. Any ongoing AEs will be followed until they are resolved, stabilized, or until 30 days after the end of treatment exposure. Any new concomitant medications should also be recorded.

6.1.4.1 Follow-up (Clinical Assessment) – Visit 5 (Week 25/Day 176 +3 days)

The follow-up visit is scheduled to assess all AEs since the end of treatment to determine if resolution has occurred or update the ongoing status of these events. Also, any new events should be recorded. A review of the subject's concomitant therapy should be made to determine if any changes have been made.

At this visit, the following procedures will be performed:

- Review and update concomitant therapy;
- Review and record any new AEs and follow-up on any ongoing AEs;
- Measure vital signs, including height and weight. Subjects should be asked to remain seated for at least 5 minutes prior to measurement of vital sign parameters. Record the time of vital sign measurements in the source documents. Age-appropriate equipment, e.g., blood pressure cuffs, should be used for all assessments; and
- Collect blood and urine samples for clinical laboratory analysis (including a urine pregnancy test if applicable). A total of about 5.5 mL of blood will be collected for clinical laboratory analysis.

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 AEs during the course of the study warranting further evaluation. Unscheduled visits should be fully documented in the subject's Unscheduled Visit eCRF(s).

6.2 Efficacy Evaluations

Efficacy evaluations will not be performed in this study.

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. Any study medication related AEs persisting at the end of the study will be followed until resolution by the Investigator, or until a clinically stable endpoint has been reached.

Clinical Laboratory Tests: Laboratory results from subjects who screen failed on the SAG/0211PFC-1131 study may be used as the baseline assessment for this protocol, if these results are within the most recent 30 days prior to Screening for this protocol (i.e., laboratory samples do not need to be re-collected at Screening/Enrollment [Visit 1]).

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), 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, magnesium.

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

Physical Examination: Physical examinations will be conducted at various timepoints 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 (including weight) shall be noted by the Investigator and reported as an AE. Additional guidance regarding assessment of changes in blood pressure and heart rate are provided below.

Normal blood pressure ranges will be based on the National Institutes of Health National Heart, Lung, and Blood Institute chart (Appendix 1). If, at 1 hour postdose, a change in blood pressure of greater than 15 mmHg from the predose assessment is observed, and this change is confirmed by a repeat measure, additional measurements must be taken at 2 and 3 hours postdose. If the observed change is sustained through the three post-dose measurements, it should be considered a clinically significant change, which must be reported as an adverse event.

Normal heart rate ranges will be based on the Silverman pediatric ranges (Appendix 2). If, at 1 hour postdose, a change in heart rate of greater than 20 beats per minute (bpm) from the predose assessment is observed, and this change is confirmed by a repeat measurement, additional measurements must be taken at 2 and 3 hours postdose. If the observed change is sustained through the three post-dose measurements, it should be considered a clinically significant change, which must be reported as an adverse event.

Rescue Medication Usage: All medications used emergently by the subject to relieve constipation, will be captured during their participation in the study via interview of the parent/subject at telephone and clinic visits, and will be recorded in the Concomitant Medication eCRF page.

7. ADVERSE AND SERIOUS ADVERSE EVENTS

As defined in ICH GCP Guideline E6,[12] 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 (investigation) 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 enrollment will be defined as an AE. Adverse events that are reported after initiation of study medication 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[13]) 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. Any ongoing AEs will be followed until they are resolved, stabilized, or until 30 days after the end of treatment exposure. 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 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;
- the event returns to baseline, if a baseline value is available;
- the event can be attributed to other than the study medication, or to other than study conduct;
- the Investigator does not anticipate any further improvement or worsening of the event.

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.

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 within 24 hours to the Sponsor or designee:

- All Serious Adverse events;
- All pregnancies; and
- Events of Special Interest (list all 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 report to the Investigator any new safety events occurring in other studies. The Investigator may need to report SAEs to the appropriate IRB/IEC in accordance with local regulations.

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 must be reported within 24 hours of the Investigator learning of the event using 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 classed 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.

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, as discussed in Section 6.3 for blood pressure and heart rate. The Investigator should decide, based on the criteria in Section 6.3, or per their discretion (for other vital sign measurements), 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 Section7.2), 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 names of the individuals (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 version of the Medical Dictionary for Regulatory Activities (MedDRA)® terminology that is being used for the SAG/0211PFC-1131 study.

7.5 Monitoring of Safety Data

A Data Safety Monitoring Board (DSMB) will monitor safety data on a regular basis throughout the study. Specific details, including meeting frequency and stoppage criteria, are provided in the DSMB Charter.

8. STATISTICAL METHODS AND DATA MANAGEMENT

The statistical analyses described in this section will be performed for the core study as further outlined in the SAP, which will be finalised prior to database lock and will be included in the Clinical Study Report for this protocol. A dose of 12 mcg BID will be assigned to subjects weighing <50 kg, and a dose of 24 mcg BID for subjects weighing ≥ 50 kg at time of enrollment.

8.1 Determination of Sample Size

The sample size is based on the expected attrition that would occur to have at least 100 subjects complete the full 24-week treatment period.

8.2 Dataset Analyzed

The Safety population will be analysed and is defined as follows:

- **The Safety population** will consist of all enrolled subjects who take at least one dose of study medication.

8.3 Analysis of Subject Characteristics and Completion Status

Subject demographic data will be summarized by treatment group and overall with descriptive statistics. The summaries will include mean, median, standard deviation, minimum and maximum for continuous variables, and counts and percentages for each level of categorical variables.

8.4 Analysis of Exposure to Study Medication and Concomitant Medication

Assessments of actual exposure to study medication will be made based on drug accountability as recorded in the eCRF. Results will be summarized by descriptive statistics.

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

8.5 Analysis of Safety

8.5.1 Deaths, Serious Adverse Events, and Adverse Terminations

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

8.5.2 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 after administration of the first dose of study medication or prior to the last day of treatment + 7 days will be considered treatment-emergent. 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 at the SOC and "At Least One Event" level between the two treatment groups.

8.5.3 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, but they will be provided in the individual subject listings.

8.5.4 Physical Examinations

Subjects with changes from normal at baseline to abnormal during the treatment period in any organ system will be identified and listed. Shift tables, which indicate incidence rates of changes from (normal, abnormal) at baseline to (normal, abnormal) values at each visit, will be presented.

8.5.5 Vital Signs

Descriptive statistics will be provided to evaluate the changes from baseline for any vital signs, including height and weight, measured during the study.

8.5.6 Subgroup and Exploratory Analyses

Analyses of any under-represented subgroups such as males and non-whites will be performed. Details pertaining to these analyses will be specified in the SAP.

8.6 Analysis of Efficacy

8.6.1 General Inferential Principles

Only exploratory efficacy will be assessed for this study.

8.6.1.1 Missing Data

Missing data will not be imputed for this study.

8.6.1.2 Multiplicity

No multiplicity adjustments will be needed.

8.6.1.3 Multicenter Studies

No center effects will be explored in this study since center is not a stratification factor.

8.6.2 Exploratory Endpoint – Investigator's Assessment of Treatment Effectiveness

The Investigator's assessment of treatment effectiveness will be collected at Visit 3 and Visit 4, using the following scale:

> 0=Not at all effective, 1=A little bit effective, 2=Moderately effective, 3=Quite a bit effective, 4=Extremely effective.

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 electronic case report forms (eCRFs). Data must be entered onto the eCRFs in English. All eCRFs must be completed in a timely manner before the Sponsor or designee performs a monitoring visit. The 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. 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.[12]

Visits to Investigator sites will be conducted by representatives of the Sponsor to inspect study data, subjects' medical records and CRFs 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 Management

All protocols and amendments will be prepared by the Sponsor. 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[12], 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 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.[14]

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 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 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, original laboratory reports, 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 however 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[15] 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 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.

9.2.3.5 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 of other sorts 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 Pharmaceuticals as defined in 21 CFR 54 2(b).[16]

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)[17], 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, or if under the age of consent, from their Legally Authorised Representative (LAR; e.g., parent/legal guardian). Assent should be obtained, in accordance with applicable requirements, from minor subjects. Age-appropriate express consent should be obtained in accordance with applicable requirements. All consent and assent documentation must be in accordance with applicable regulations and GCP. Each subject or subject's LAR, where applicable, 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 and the Consent/Assent Form, as applicable) must be given to the subject or the subject's LAR.

Informed consent documentation will be approved 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 will 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 are assigned to the correct subject. The results of this study containing the unique number, age, 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 may not afford 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 PEDIATRIC BLOOD PRESSURE LEVELS

Blood Pressure Levels for Boys by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90

Blood Pressure Levels for Boys by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for boys with height percentiles given in Table 3 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.

Blood Pressure Levels for Girls by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88

Blood Pressure Levels for Girls by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for girls with height percentiles given in Table 4 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.

APPENDIX 2 PEDIATRIC HEART RATE RANGES

Normal Heart Rate Values for Age of Pediatric Patients*

Age	*Heart Rate (bpm)*
Newborn	90-180
1-5 months	100-180
6-11 months	100-150
1 year	100-150
2-3 years	65-150
4-5 years	65-140
6-9 years	65-120
10-12 years	65-120
13 + years	55-110

* Adapted from Silverman BK. Practical information In: Textbook of Pediatric Emergency Medicine 2006.[24]

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