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16.1 Study Information

16.1.1 Final Amended Protocol and Protocol Amendment Summaries

16.1.1.1 Final Amended Protocol

SUCAMPO AG
The Science of Innovation

A Multicentre, Long-term Safety, Efficacy, and Pharmacokinetics Study of Lubiprostone in Paediatric Subjects Aged ≥ 6 Years to < 18 Years with Functional Constipation

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PROTOCOL SIGNATURE PAGE

A Multicentre, Long-term Safety, Efficacy, and Pharmacokinetics Study of Lubiprostone in Paediatric Subjects Aged ≥ 6 Years to < 18 Years with Functional Constipation

PROTOCOL SAG/0211PFC-11S1

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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

ABPI	Association of British Pharmaceutical Industry
AE	Adverse Event
ALT	Alanine Transaminase (SGPT)
AST	Aspartate Transaminase (SGOT)
BID	Twice Daily
BM	Bowel Movement
BMC	Bone Mineral Content
BMD	Bone Mineral Density
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
DXA	Dual-energy X-ray absorptiometry
EDC	Electronic Data Capture
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
HIPAA	Health Insurance Portability and Accountability Act
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 Authorised 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
PK	Pharmacokinetics
QoL	Quality of Life
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 Multicentre, Long-term Safety, Efficacy and Pharmacokinetics Study of Lubiprostone in Paediatric Subjects Aged ≥6 to <18 years with Functional Constipation			
Study Phase	Phase 3		
Short Title	Long-term safety extension study of lubiprostone for the treatment of paediatric functional constipation in subjects aged ≥6 to <18 years		
Objectives, Study Medication and Dose Regimen:	To assess the long-term safety, efficacy, and pharmacokinetics of oral lubiprostone 12 or 24 mcg capsules dosed twice daily (BID) when administered orally for 36 weeks in paediatric subjects with functional constipation. Evaluation of lubiprostone safety is the primary objective in this study. Dose assignment will be based on the dose they were receiving at the time of rolling over from the preceding, double-blind study (SAG/0211PFC-1131) into this safety extension study for those subjects who were randomised to receive lubiprostone during the preceding study. For subjects who received placebo during the preceding study, assignment of dose will be assigned based on subject body weight at the time of rollover to this extension study. All dose assignment will be handled by an Interactive Voice/Web Response system (IXRS) and will continue to maintain blinding with respect to the treatment assignment in the preceding trial.		
Assumed No. of Sites: **Est. No. Enrolled Subjects:** **Est. No. Screened Subjects:**	Approximately 130 (Northern America and Europe) 415 subjects who completed Study SAG/0211PFC-1131 NA		
Duration of Participation: **Duration of Treatment:**	Up to 42 weeks (including follow-up) 36 weeks		
Study Schedule:	Visit 9:	Enrolment (Clinic Visit)	Day 1 (coincides with SAG/0211PFC-1131 study Visit 7)
	Visit 10:	Interim Treatment Visit (Clinic Visit)	Week 1 Visit (±2 days)
	Visit 11:	Telephone Assessment	Week 4 Visit (±3 days); Month 1
	Visit 12:	Interim Treatment Visit (Clinic Visit)	Week 12 Visit (±3 days); Month 3
	Visit 13:	Telephone Assessment	Week 16 Visit (±3 days); Month 4
	Visit 14:	Interim Treatment Visit (Clinic Visit)	Week 24 Visit (±3 days); Month 6
	Visit 15:	Telephone Assessment	Week 28 Visit (±3 days); Month 7
	Visit 16:	End-of-Treatment (Clinic Visit)	Week 36 Visit (+3 days); Month 9
	Visit 17:	Follow-Up (Clinic Visit)	Week 40 Visit (+3 days); Month 10

Inclusion Criteria:	1. Written informed consent obtained from subject and/or parent/legal guardian (and assent from subject where applicable). 2. Subject must have completed the entire 12-week treatment period from the preceding study (SAG/0211PFC-1131) prior to enrolment. 3. Subject must continue to abstain from taking concomitant medication (prescribed or over-the-counter) that affects gastrointestinal motility; 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 if a stable dose has been used for at least 30 days prior to the Baseline Visit (of the preceding study SAG/0211PFC-1131) and not likely to change during the study. 4. 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. 5. If subject is taking a fibre supplement (e.g., Metamucil®, PerDiem®, Fybogel), usage must have been at a stable dose not likely to change during the study. 6. Subject and his/her parent/legal guardian must be willing and able to fill out his/her own diary.
Exclusion Criteria:	1. Subject has current evidence of untreated faecal impaction. 2. Subject has experienced an adverse event during the SAG/0211PFC-1131 study which the Investigator considers to be clinically significant and would limit the subject's ability to participate in the trial. 3. Subject has had a significant change in their medical status, newly diagnosed and 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. 4. Subject has developed abnormal laboratory test (haematology, urinalysis, or blood chemistry), which in the Investigator's opinion is clinically significant, unexplained, and would limit the subject's ability to participate in the trial. 5. 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. 6. Subject demonstrated non-compliance with study protocol (i.e., dosing schedule, visit schedule, diary completion, or study procedures) during the SAG/0211PFC-1131 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, sodium picosulfate, 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
	  ○ Height will be measured using a wall-mounted stadiometer, if available
	• For those subjects who were aged 6 to 9 or 14 to 17 at the time of enrolment into the SAG/0211PFC-1131 study, and who were qualified to participate and enrolled in the dual-energy X-ray absorptiometry (DXA) substudy:
	  ○ Percent changes from baseline in bone mineral density (BMD) and bone mineral content (BMC)
	  ○ Changes from baseline in BMD Z-scores and in height-adjusted Z-scores, as assessed by DXA for DXA Subgroup
	  ○ Changes from baseline in height and weight Z-scores for DXA Subgroup
	  ○ Incidence of clinical fractures
	
	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.

Efficacy Endpoints:	The efficacy endpoints are as follows:
	• Overall and monthly changes from baseline in BM and SBM frequency rate
	• Overall and monthly assessments of the average degree of, and changes from baseline in:
	  ○ Stool consistency of SBMs
	  ○ Straining associated with SBMs
	  ○ Abdominal pain associated with SBMs
	  ○ Constipation severity
	• Monthly SBM Response
	  ○ A monthly responder is defined as a subject who is a weekly responder for 3 of 4 weeks per month.
	  ○ A weekly responder is defined as a subject who has a frequency rate of ≥ 3 SBMs/week and an increase from baseline of ≥ 1 SBM/week for that week.
	• Overall and monthly assessment of average treatment effectiveness rating
	• Overall Health-related quality of life (PedsQL™)
	• Overall and monthly change from baseline in incontinence episodes frequency (analysis performed for subset of subjects presenting with incontinence at baseline)
	• Overall and monthly change from baseline in the production of large diameter stool (a stool that clogs the toilet) frequency
	• Overall and monthly change from baseline in frequency of faecal impaction
	• Overall and monthly change from baseline in proportion of BMs and SBMs in toilet overall
	• Overall and monthly change from baseline in frequency of retentive posturing or excessive volitional stool retention

Pharmacokinetic Evaluation:	Plasma samples will be collected for population pharmacokinetic (PK) modeling at Visit 9 as follows: • Pre-dose and 1 sample between 30 and 90 minutes after dose administration (2 samples total) A population PK analysis will be performed using the concentration-time data from the sparse PK samples in this study. The analysis may include data from other studies with lubiprostone in adults, paediatric subjects, or healthy volunteers. A separate analysis plan for the population PK analysis will be prepared prior to database lock.
Sample Size Estimate Calculation	For purposes of establishing the safety profile with lubiprostone long-term exposure in paediatric functional constipation, safety data from subjects enrolled in this study will be considered together with the 100 subjects enrolled in Sucampo study SAG/0211PFC-11S2 (subjects in this study will be below 6 years old). The sample size is based on the expected attrition that would occur and the remaining number of safety evaluable subjects at each timeframe during the study.
Statistical Methodology	Efficacy analysis will be based on modified intent-to-treat (mITT) population which includes all enrolled subjects who take at least one dose of study medication and have at least one treatment period diary entry. Categorical and discrete variables will be summarized by counts and percentage, and continuous variables will be summarized by descriptive statistics. Detailed statistical methodology will be documented in the Statistical Analysis Plan (SAP). 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. The PK profile for lubiprostone will be determined from the concentration-time data for all evaluable subjects based on the plasma concentrations lubiprostone (if measurable) and of lubiprostone's metabolite, M3. Actual post-dose sampling times relative to time of study medication administration, rather than scheduled sampling times, will be used in all PK profile computations involving sampling times.

SCHEDULE OF EVALUATIONS

Study Week(s) / Month(s)	0	1 / 0	4 / 1	12 / 3	16 / 4	24 / 6	28 / 7	36 / 9	40 / 10
Study Day(s)	1	8 (± 2)	29 (± 3)	85 (± 3)	113 (± 3)	169 (± 3)	197 (± 3)	253 (+ 3)	281 (+ 3)
Visit Number	9	10	11	12	13	14	15	16	17
Visit Type	Enrolment[1]	Clinic Examination	Telephone Assessment	Clinic Examination	Telephone Assessment	Clinic Examination	Telephone Assessment	End-of-Treatment Clinic Examination	Follow-up Clinic Examination
Assessment									
Informed Consent/Assent	X								
Inclusion/Exclusion Criteria Review	X								
Demographics	(V1)								
Medical History	(V1/V2)								
Vital Signs, Height, and Weight[2]	(V7)	X		X		X		X	X
Physical Examination[3]	(V7)	X		X		X		X	X
Pharmacokinetic Sampling[4]	X								
Blood Chemistry, Hematology, Urinalysis	(V7)	X		X		X		X	X
Pregnancy Test[5]	(V7)	X		X		X		X	X
Concomitant Medications	→	→	→	→	→	→	→	→	
Adverse Events	→	→	→	→	→	→	→	→	
BMD and BMC Assessments[6]	(V7)							X	
Study Medication Distribution[7]	X	X		X		X			
QoL Assessment	(V7)			X		X		X	
Study Treatment	→	→	→	→	→	→	→		
Study Medication Collection		X		X		X		X	
Electronic Diary[8]	→	→	→	→	→	→	→	→	→

Note: The Visit numbers in parentheses are in reference to the preceding placebo-controlled study (SAG/0211PFC-1131).

[1] The End-of-Treatment Visit (V7) in study SAG/0211PFC-1131 will serve as the Enrolment Visit and the corresponding assessments are designated above as "V7". Other corresponding visits from preceding study are also designated by the visit number;

[2] Measure predose vital signs at Visit 9, 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. Vital sign assessments will be performed prior to PK sampling when these assessments are collected at the same visit. 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 comprehensive physical examinations at Enrolment and End-of-Treatment visits. An abbreviated physical examination is to be performed at all other visits;

[4] PK samples will be collected predose and 1 sample between 30 and 90 minutes after dose administration (2 samples total). PK samples will be taken under non-fasting conditions. The samples will be collected via direct venipuncture. Approximately 8 mL of blood will be taken for each sample such that the total of all PK samples does not exceed 50 mL or 5 mL/kg of body weight;
[5] Urine pregnancy tests will be performed at all study visits on subjects of childbearing potential.
[6] All subjects who withdraw from the study after Visit 12 (Month 3) should complete the final visit of the treatment period (Visit 16) and therefore have a final DXA assessment performed. This will only be required for subjects that were originally part of the DXA subgroup. Any subject demonstrating a decline in 4% in BMD at any skeletal site from Screening to End of Treatment should additionally undergo a follow-up DXA assessment 6 to 12 months later;
[7] Observe the subject or parent/legal guardian as he/she administers the first dose of study medication while in the clinic at Visit 9. Over the next 1 hour, monitor subject for any adverse reactions. One bottle of study medication will be provided at Visit 9 and then 3 bottles each at Visits 10, 12 and 14. Subjects should return the used bottle of study medication at each clinic visit for collection by site for drug accountability. If the study medication is not returned, the bottle of all 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 bottle;
[8] Change eDiary mode to new treatment mode (associated with current study - SAG/0211PFC-11S1) at Visit 9.

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 paediatric 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 paediatric outpatient visits and 25% of paediatric gastroenterology consultations.[1,2,3] Standardized diagnostic criteria for paediatric 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 approved for treatment of adult chronic idiopathic constipation in the United Kingdom and Switzerland. Lubiprostone was approved for marketing in Japan on 29 June 2012 for the treatment of chronic constipation (excluding constipation caused by organic diseases) in 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 paediatric 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 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. Since lubiprostone has been shown to increase the frequency of SBMs in both adults and children, further evaluation in well controlled studies in children is needed to demonstrate use in a paediatric population. The doses selected for this study are based on the results obtained during the previous open-labeled study in children.[12] Highly statistically significant ($p<0.0001$) changes from baseline SBM frequency at Week 1 were observed overall for children treated with lubiprostone, with children treated with either lubiprostone 12 mcg BID or 24 mcg BID achieving a mean SBM frequency of > 3 SBMs following one week of treatment with lubiprostone. The greatest Week 1 improvement was observed for the lubiprostone 24 mcg BID group. Results from this study also suggested that allowance for dose escalation in some subjects initially dosed with 12 mcg BID may have provided some additional treatment benefits.

Subjects who completed the entire 12-week treatment in the preceding double-blind study (SAG/0211PFC-1131) will be eligible to enrol into this long-term safety study. Dose assignment will be based on the dose they were receiving at the time of rolling over from the previous study into this safety extension study for those subjects who were randomised to receive lubiprostone during the preceding study. For subjects who received placebo during the preceding study,

assignment of dose will be assigned based on subject body weight at the time of rollover to this extension study. All dose assignment will be handled by an Interactive Voice/Web Response system (IXRS) and will continue to maintain blinding with respect to the treatment assignment in the preceding trial.

Lubiprostone has a well-documented safety record in clinical studies involving over 3,500 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 paediatric population.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

To assess the long-term safety, efficacy, and pharmacokinetics of oral lubiprostone 12 or 24 mcg capsules dosed twice daily (BID) when administered orally for 36 weeks in paediatric 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
  - Height will be measured using a wall-mounted stadiometer, if available
- For those subjects who were aged 6 to 9 or 14 to 17 at the time of enrolment into the SAG/0211PFC-1131 study, and who were qualified to participate and enrolled in the DXA substudy:
  - Percent changes from baseline in BMD and BMC
  - Changes from baseline in BMD Z-scores and in height-adjusted Z-scores, as assessed by DXA for DXA Subgroup
  - Changes from baseline in height and weight Z-scores
  - Incidence of clinical fractures

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

The efficacy endpoints are as follows:

- Overall and monthly changes from baseline in BM and SBM frequency rate
- Overall and monthly assessments of the average degree of, and changes from baseline in:
  - Stool consistency of SBMs
  - Straining associated with SBMs
  - Abdominal pain associated with SBMs
  - Constipation severity
- Monthly SBM Response
  - A monthly responder is defined as a subject who is a weekly responder for 3 of 4 weeks per month.

  - A weekly responder is defined as a subject who has a frequency rate of ≥ 3 SBMs/week and an increase from baseline of ≥ 1 SBM/week for that week.
- Overall and monthly assessment of average treatment effectiveness rating
- Overall Health-related quality of life (PedsQL™)
- Overall and monthly change from baseline in incontinence episodes frequency (analysis performed for subset of subjects presenting with incontinence at baseline)
- Overall and monthly change from baseline in the production of large diameter stool (a stool that clogs the toilet) frequency
- Overall and monthly change from baseline in frequency of faecal impaction
- Overall and monthly change from baseline in proportion of BMs and SBMs in toilet overall
- Overall and monthly change from baseline in frequency of retentive posturing or excessive volitional stool retention

2.2.2.1 Patient Reported Outcomes

Hand-held electronic diaries will be utilized to collect daily responses to questions involving bowel habit symptoms, study drug administration, and rescue medication administration (see Appendix 1).

The PedsQL™ Generic Core Scales[13] will be completed by the subject or parent/legal guardian via paper questionnaires at Visit 9, Visit 12, Visit 14 and Visit 16.

2.2.3 Pharmacokinetics

Plasma samples will be collected for population PK modeling at Visit 9 as follows:

- Pre-dose and 1 sample between 30 and 90 minutes after dose administration (2 samples total)

A population PK analysis will be performed using the concentration-time data from the sparse PK samples in this study. The analysis may include data from other studies with lubiprostone in adults, paediatric subjects, or healthy volunteers. A separate analysis plan for the population pharmacokinetic analysis will be prepared prior to database lock.

3. STUDY DESIGN

This is a phase 3, multicentre, long term study to assess the safety, efficacy, and pharmacokinetics of oral lubiprostone for the treatment of functional constipation in children. Approximately 415 subjects who participated in the preceding, double-blinded study (SAG/0211PFC-1131) will be enrolled in the study across approximately 130 sites within the United States, Canada, and Europe. Dose assignment will be based on the dose they were receiving at the time of rolling over into this safety extension study for those subjects who were randomised to receive lubiprostone during the preceding study. For subjects who received placebo during the preceding study (as identified via IXRS), assignment of dose by the IXRS will be based on subject body weight at the time of rollover to this extension study. Dose assignment will only be known in subjects who were at least 50 kg in weight at the time of randomisation in the preceding study (SAG/0211PFC-1131). All dose assignments will be handled by the IXRS and will continue to maintain blinding with respect to the treatment assignment in the preceding trial. Duration of subject participation is approximately 42 weeks through follow-up. A schematic representation of the study design is provided below in Figure 1.

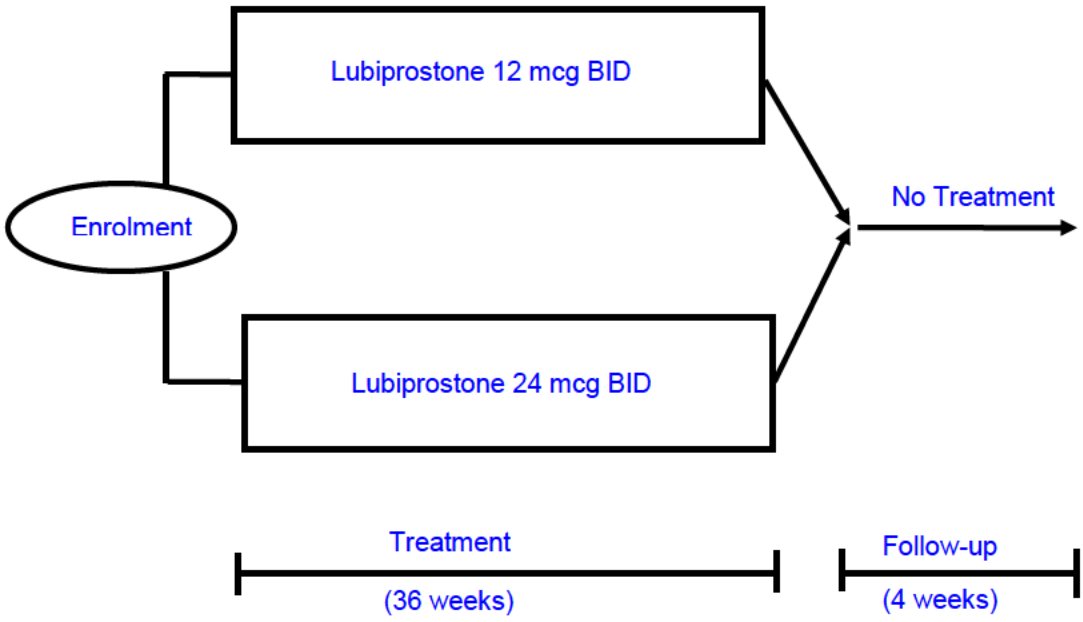


Figure 1: Study Design Flow Chart

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 four distinct visits or periods during the study:

- **Enrolment Visit (Visit 9; Day 1)**: This visit is considered study Day 1 and the visit takes place on the first day of study medication administration and will coincide with Visit 7 of the preceding study SAG/0211PFC-1131.

- **Interim Treatment Clinic Examinations (Visits 10, 12, 14; Weeks 1, 12, 24) and End-of-Treatment Visit (Week 36)**: A clinic visit will occur on Study Days 8 (±2 days), 85 (±3 days), 169 (±3 days) and 253 (±3 days). Clinical assessments will be performed to evaluate the safety of study treatment.

- **Interim Telephone Assessments (Visits 11, 13, and 15; Weeks 4, 16, and 28)**: A telephone assessment will be performed by site personnel at Study Days 29 (±3 days), 113 (±3 days), and 197 (±3 days). This assessment will be performed to evaluate the compliance of the subject with the study medication and electronic diary and to identify any adverse events (AEs) or changes in concomitant medications.

- **Follow-up Visit (Visit 17; Week 40 [Day 281 + 3 days])**: A follow-up clinic visit will occur to review any ongoing or new onset of AEs, record any changes in concomitant medications. The subject's overall condition will be assessed; and blood and urine will be collected for laboratory analyses. 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 or parent/legal guardian (and assent from subject where applicable).
2. Subject must have completed the entire 12-week treatment period during the preceding study (SAG/0211PFC-1131).
3. Subject must continue to abstain from taking concomitant medication (prescribed or over-the-counter) that affects gastrointestinal motility; 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 if a stable dose has been used for at least 30 days prior to the Baseline Visit (of the preceding study SAG/0211PFC-1131) and not likely to change during the study.
4. 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.
5. If subject is taking a fibre supplement (e.g., Metamucil®, PerDiem®, Fybogel), usage must have been at a stable dose not likely to change during the study.
6. Subject and his/her parent/legal guardian must be willing and able to fill out his/her own diary.

4.2 Exclusion Criteria

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

1. Subject has current evidence of untreated faecal impaction.
2. Subject has experienced an adverse event during the SAG/0211PFC-1131 study which the Investigator considers to be clinically significant and would limit the subject's ability to participate in the trial.
3. Subject has had a significant change in their medical status, newly diagnosed and 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.

4. Subject has developed an abnormal laboratory test (haematology, urinalysis, or blood chemistry), which in the Investigator's opinion is clinically significant and would limit the subject's ability to participate in the trial.
5. Subject (female of childbearing potential) has a positive pregnancy test, refuses/is unwilling to undergo pregnancy testing, and/or does not agree to use protocol-specified contraceptive measures for the duration of the study.
6. Subject demonstrated non-compliance with study protocol (i.e., dosing schedule, visit schedule, diary completion, or study procedures) during the SAG/0211PFC-1131 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 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. The primary reason for withdrawal must be recorded in the subject's medical record and on the withdrawal form in the electronic Case Report Form (eCRF).

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

- AE;
- Lack of efficacy;
- Subject choice;
- Lost to follow-up;
- Non-compliance;
- 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 final visit of the treatment period (Visit 16) as outlined in Section 6.1.3.4 and the Follow-up Visit (Visit 17) as outlined in Section 6.1.4.1. All subjects who withdraw from the study after Visit 12 (Month 3) should have a final DXA assessment performed. This will only be required for subjects that were originally part of the DXA subgroup.

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, electronic diaries, and obtain the general overall status of the subject at the time of withdrawal from the study. The subject’s source documents should verify that at least two attempts have been made by telephone to locate the subject and that a final attempt to locate the subject has been made by certified or traceable mail.

4.6 Emergency Unblinding

Dose assignment will only be known in subjects who were at least 50 kg in weight at the time of randomisation in the preceding study (SAG/0211PFC-1131). In the event emergency unblinding of study dose is necessary, the Investigator shall utilize the RTSM system to obtain subject dose details. The individual subject dose details should be revealed only in case of an emergency where the further treatment of the subject is dependent on knowing the actual dose he or she has received.

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

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 labeling 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 Labeling

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’, or the equivalent texts outside USA, as applicable;
- 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 provided that the blind of the study is not compromised. Due to the titration aspect of the preceding double-blinded study (SAG/0211PFC-1131), bottles will not specifically identify whether they contain lubiprostone 12 or 24 mcg so as to maintain the prior blind.

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 parent/legal guardian should record the actual time the dose was taken in the electronic diary. If the dose was missed entirely, the parent/legal guardian should indicate the omission in the electronic diary as instructed. The study medication will be handled by authorized personnel and dispensed under the supervision of the Investigator or designated site personnel.

Each subject will receive one 64-capsule bottle of study medication at the Enrolment Visit (Day 1), and three bottles each at Visits 10, 12, and 14. The first dose of study medication will be administered in the clinic at the Enrolment Visit and the Study Coordinator will record this first dose.

Subjects should return the used bottle of study medication at each clinic visit for collection by site for drug accountability. If the study medication is not returned, the bottle of all 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 bottle. The last dose of study medication in this study will be taken on the day of End of Treatment (Visit 16).

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 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. Due to the titration aspect of the preceding double-blinded study (SAG/0211PFC-1131), bottles will not specifically identify whether they contain lubiprostone 12 or 24 mcg so as to maintain the prior blind. Dose assignment will be based on the dose they were receiving at the time of rolling over from the preceding, double-blind study (SAG/0211PFC-1131) into this safety extension study for those subjects who were randomised to receive lubiprostone during the preceding study. For subjects who received placebo during the preceding study (as identified via IXRS), assignment of dose by the IXRS will be based on subject body weight at the time of rollover to this extension study. Dose assignment will only be known in subjects who were at least 50 kg in weight at the time of randomisation in the preceding study (SAG/0211PFC-1131). All dose assignments will be handled by the IXRS and will continue to maintain blinding with respect to the treatment assignment in the preceding trial.

Most study personnel will remain blinded to doses assigned to subjects weighing less than 50 kg until the clinical database has been locked. To allow for the execution of clinical trial–related services, the following individuals will be unblinded during the study:

- External RTSM vendor
- Sponsor Quality Assurance representative
- Sponsor Pharmacovigilance representative
- External clinical supply distribution vendor

- External third party unblinded biostatistician (e.g., DSMB statistician)
- DSMB members
- Bioanalytical laboratory and third-party pharmacokinetic analyst
- Sponsor Drug Supply Management representative

Emergency unblinding by the Investigator of a subject's assigned treatment is addressed in Section 4.6 of this protocol.

5.5.3 Allocation of Study Medication

Subjects will keep the unique 7-digit subject identifier ("xxxx-yyy") that was assigned in the preceding double-blind study (SAG/0211PFC-1131). This subject ID number will also be used as a unique identifier for the subject throughout the study for lab reports, diary, study medication labels, eCRFs, etc.

5.6 Compliance and Drug Accountability

It is the responsibility of the Investigator to ensure that all study medication received at the site will be inventoried and accounted for throughout the study and the result recorded in the Drug Accountability Form 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. Study medication dosing will also be recorded by the subject or parent/legal guardian in the electronic diaries.

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 Enrolment 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 if a stable dose has been used for at least 30 days prior to the Baseline Visit (of the preceding study SAG/0211PFC-1131) and not likely to change during the study.

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

5.7.2 Daily Fibre Therapy

The use of a daily fibre supplement shall be permitted as long as the usage schedule and dose has been stable for at least 30 days prior to the Baseline Visit (of the preceding study SAG/0211PFC-1131). The schedule of usage and dose of the daily fibre supplement should not change during the course of the study. 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 Enrolment Visit (Visit 9) 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, senna, or sodium picosulfate.
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, sodium picosulphate, 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 the electronic diary by the subject or parent/legal guardian, and recorded on the Rescue 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 summarises the frequency and timing of the entry, efficacy 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 final visit of the treatment period (Visit 16) and the follow-up visit (Visit 17). All subjects who withdraw from the study after Visit 12 (Month 3) should have a final DXA assessment performed. This will only be required for subjects that were originally part of the DXA subgroup. All visits are outlined in this section.

The details of the procedures for the Enrolment 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 using a wall-mounted stadiometer, where available, in inches or centimeters. Alternate methods and further guidance will be provided in a study manual.

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. Vital sign assessments will be performed prior to PK sampling when these assessments are collected at the same visit.

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.

Abbreviated Physical Examination – An abbreviated physical examination of the subjects will be performed by appropriate site personnel. This examination reviews only those body systems where there has been a change in health or there is new finding to report.

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

Pharmacokinetic Evaluations – Sample collections for the determination of lubiprostone and metabolite M3 concentrations will be performed in all subjects.

Bone Growth Assessments – For those subjects who were aged 6 to 9 or 14 to 17 at the time of enrolment into the SAG/0211PFC-1131 study, and who were qualified to participate and enrolled in the DXA substudy, BMD and BMC measurement using DXA will be performed at Month 9 (Visit 16). All subjects who withdraw from the study after Visit 12 (Month 3) should complete the final visit of the treatment period (Visit 16) and therefore have a final DXA assessment performed. This will only be required for subjects that were originally part of the DXA subgroup. Analysis of scans will be performed by a central reader.

Any subject demonstrating a decline in 4% in BMD at any skeletal site from Screening to End of Treatment should additionally undergo a follow-up DXA assessment 6 to 12 months later.

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

Concomitant Therapy – An updated concomitant therapy history of the subject will be recorded. The subject 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. A subject, who has been routinely administering a daily fiber supplement during the preceding double-blind study (SAG/0211PFC-1131), may remain on the supplement throughout the study provided the regimen and dose does not change. Similarly, treatment with anticholinergic agents, SSRIs, SNRIs, or MAO inhibitors is allowed if a stable dose has been used for at least 30 days prior to the Screening Visit and not likely to change during the study.

Electronic Diary – The electronic diary dispensed to the subject or parent/legal guardian in the previous blinded study (SAG/0211PFC-1131) will continue to be used. If necessary the subject or parent/legal guardian will receive another demonstration and set of instructions for use. At enrolment (Visit 9), ensure that the electronic diary is set to capture treatment-related responses associated with this long-term safety study. The daily diary will record information throughout the study. Information from the electronic diary will be automatically transmitted from the device each night to a secure study database and will be available for review by the site as needed. The parent/legal guardian and, for certain diary questions, the subject must complete the diary each evening per the instructions. Additionally, the occurrence of bowel movements and use of rescue medications can be recorded in real-time throughout the day, with the opportunity to review any episodic entries at the time of the evening report. A maximum recall period of 24 hours will be allowed for entry of study-related event data in the diary.

6.1.2 Enrolment Period – Visit 9 (Study Day 1)

At this visit, a review of the inclusion and exclusion criteria will be conducted for all subjects to ensure the subject remains eligible for the study. Consent/assent must be obtained before any study procedures are performed.

Note: This visit will coincide with Visit 7 from the preceding study (SAG/0211PFC-1131). The following procedures that are recorded as part of Visit 7 from SAG/0211PFC-1131 will also be recorded to this visit and therefore do not need to be repeated:

- Completion of PedsQL™ questionnaire by subject or parent/legal guardian prior to conducting other visit procedures;
- 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. A wall-mounted stadiometer, where available, should be used for measurement of height. Age-appropriate equipment, e.g., blood pressure cuffs, should be used for all assessments;
- 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 full physical examination;
- Measurement of BMD and BMC via DXA of lumbar spine and total body (less head), if available, for DXA Subgroup (Subjects 6 to 9 and 14 to 17 years of age). This will only be required for subjects that were originally part of the DXA subgroup; and
- Urine Pregnancy Test – All female subjects of childbearing potential will have a urine dipstick pregnancy test to determine their pregnancy status prior to the dispensing of study medication.

As part of this visit, the following procedures will take place:

- Update medical history. Any new medical information should be added to the subject's baseline history (AEs will be captured on the AE page);
- Collect PK samples – Pre-dose and 1 sample between 30 and 90 minutes after dose administration (2 samples total). PK samples will be taken under non-fasting conditions. The samples will be collected via direct venepuncture. Approximately 8 mL of blood will be taken for each sample (16 mL in total) such that the total of all PK samples does not exceed 50 mL or 5 mL/kg of body weight;
- Review and record any new AEs and follow-up on any ongoing AEs;
- Update Concomitant Therapy – Concomitant medications (prescribed and over-the-counter [OTC]) used since the last visit will be reviewed. The subject or parent/legal

guardian should again be instructed not to use any prescription or OTC laxatives unless prescribed by the Investigator;

- Review and discuss rescue medication use and remind subject or parent/legal guardian to record rescue medication use in electronic diary;
- The electronic diary dispensed to the subject or parent/legal guardian in the previous blinded study (SAG/0211PFC-1131) will continue to be used. If necessary the subject or parent/legal guardian will receive another demonstration and set of instructions for use. Ensure that the electronic diary is set to capture treatment-related responses associated with this long-term safety study;
- Dispense first bottle of study medication, provide dosing instructions and remind the subject or parent/legal guardian to bring the bottle with any remaining study medication to every 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;
- Schedule the next clinic visit (Visit 10/Study Day 8).

6.1.3 Treatment Period

The treatment period will begin at the Enrolment Visit on the day the first dose of study medication is administered (Study Day 1) and will end upon administration of the last dose.

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 final visit of the treatment period (Visit 16) and the Follow-up Visit (Visit 17). All subjects who withdraw from the study after Visit 12 (Month 3) should have a final DXA assessment performed. The DXA assessment will only be required for subjects that were originally part of the DXA subgroup.

6.1.3.1 Interim Clinic Assessment – Visit 10 (Week 1/Day 8 ± 2 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. A wall-mounted stadiometer, where available, should be used for measurement of height. Age-appropriate equipment, e.g., blood pressure cuffs, should be used for all assessments;
- Perform an abbreviated physical examination;
- Collect blood and urine samples for laboratory analysis (including a pregnancy test, if applicable). A total of about 5.5 mL of blood will be collected for clinical laboratory analysis;
- Review and update concomitant therapy;
- Review and record any new AEs and follow-up on any ongoing AEs;

- Review and discuss rescue medication use and remind subject or parent/legal guardian to record rescue medication use in electronic diary;
- Review compliance associated with completion of the electronic diary;
- Collect the previously dispensed bottle 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, the bottle of all 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;
- Confirm the next telephone contact (i.e., at Study Day 29).

6.1.3.2 Interim Telephone Assessments – Visits 11, 13 and 15 (Week 4/Day 29 ±3 days, Week16/Day 113 ±3 days, and Week 28/Day 197 ±3 days)

During these telephone assessments, 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 remind subject or parent/legal guardian to record rescue medication use in electronic diary;
- Review compliance associated with completion of the electronic diary;
- Confirm the next scheduled clinic visit.

6.1.3.3 Interim Clinic Assessment – Visits 12 and 14 (Week 12/Day 85 ±3 days and Week 24/Day 169 ±3 days)

During these visits, the following procedures will be performed:

- Completion of PedsQL™ questionnaire by subject or parent/legal guardian prior to conducting other visit procedures;
- 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. A wall-mounted stadiometer, where available, should be used for measurement of height. Age-appropriate equipment, e.g., blood pressure cuffs, should be used for all assessments;
- Perform an abbreviated physical examination;
- 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 and update concomitant therapy;
- Review and discuss rescue medication use and remind subject or parent/legal guardian to record rescue medication use in electronic diary;

- Review and record any new AEs and follow-up on any ongoing AEs;
- Review compliance associated with completion of the electronic diary;
- Collect the previously dispensed bottle of study medication and perform drug accountability. Review study medication compliance with the subject or parent/legal guardian. If the study medication is not returned, the bottle of all unused study medication should be returned to the site at the subsequent office visit;
- Dispense new supply of study medication (3 bottles). The subject will be instructed to take the study medication from the newly dispensed bottles;
- Schedule the next telephone contact.

6.1.3.4 End-of-Treatment Visit – Visit 16 (Week 36/Day 253 +3 days)

During this visit, the following procedures will be performed:

- Completion of PedsQL™ questionnaire by subject or parent/legal guardian prior to conducting other visit procedures;
- 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. A wall-mounted stadiometer, where available, should be used for measurement of height. 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 (including a urine pregnancy test if applicable). A total of about 5.5 mL of blood will be collected for clinical laboratory analysis;
- Measurement of BMD and BMC via DXA of lumbar spine and total body (less head), if available for those subjects enrolled in DXA subgroup only;
- Review and update concomitant therapy;
- Review and record any new AEs and follow-up on any ongoing AEs;
- Review compliance associated with completion of the electronic diary;
- Collect the previously dispensed bottle 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, the bottle of all unused study medication must be returned to the site at the subsequent office visit.

6.1.4 Follow-up Period

The follow-up period lasts for 4 weeks following the final dose of study medication. AEs should be followed to assess their status and resolution during this timeframe. Any new concomitant medications should also be recorded.

6.1.4.1 Follow-up (Clinical Assessment) – Visit 17 (Week 40/Day 281 +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;
- Vital signs including height and weight;
- Abbreviated physical examination;
- 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; and
- Collect electronic diary.

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. Any additional visits should be fully documented in the subject's eCRF on the Unscheduled Visit Screen(s).

6.2 Efficacy Evaluations

The parent/legal guardian and, in some cases, the subject him/herself will answer questions about the subject's constipation, including recordation of bowel movements (BMs), associated stool consistency and bowel straining ratings, as well as evaluations of abdominal pain, constipation severity, and treatment effectiveness. This information will be assessed as part of the daily and weekly evaluations recorded in the electronic diary. Additionally, subjects will complete the PedsQL™ questionnaire at all clinic visits (except Visits 10 and 17), with responses recorded on paper at specified clinic visits.

6.2.1 Electronic Diary

The electronic diary is a hand-held device with a visual display. It is designed to query the parent/legal guardian daily about the status of their child's constipation (see Appendix 1). The diary will prompt the parent/legal guardian and, in some cases, the subject to provide information each evening prior to bedtime about the constipation-related events during the preceding day or week. Additionally, the occurrence of bowel movements and use of rescue medications can be recorded in real-time throughout the day, with the opportunity to review any episodic entries at the time of the evening report. A maximum recall period of 24 hours will be allowed for entry of study-related event data in the diary.

Information from the subject diary is automatically transmitted each night to a secure study database and available for review by the site as needed. Since the diary information is being gathered for efficacy, it is important that the diary is completed each day. Additional information about the electronic diary and its usage will be provided to the sites in a reference manual prepared by the diary vendor.

6.2.2 Efficacy Endpoints

The efficacy endpoints are provided in Section 2.2.1.

6.3 Safety Evaluations

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

Adverse Events: AEs will be reported by the subject from the time of informed consent through the end of the follow-up period. AEs will be followed by the Investigator as determined by Sponsor or designee. Further details on AE reporting are provided in Section 7. Any study medication related AEs persisting at the end of the study will be followed until resolution, or until a clinically stable endpoint has been reached.

In this study, faecal impaction and bone fractures will be captured as AEs. The events of faecal impaction will be used for the analysis of the fecal impaction frequency during the study (see Section 8.6.2.5).

Clinical Laboratory Tests: The following laboratory tests will be conducted and the appropriate Investigator shall determine the clinical significance of any out-of-range values.

- **Hematology Panel:** Hemoglobin, hematocrit, MCV, MCH, MCHC, RBC, WBC, white blood cell with absolute counts and percent differentials (neutrophils, lymphocytes, monocytes, eosinophils, basophils), 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 macroscopic 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 2). 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 3). 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.

Bone Growth Assessments: BMD and BMC assessments will be performed during the study for those subjects enrolled in DXA Subgroup only.

Any subject demonstrating a decline in 4% in BMD at any skeletal site from Screening to End of Treatment should additionally undergo a follow-up DXA assessment 6 to 12 months later.

6.3.1 Pharmacokinetic Evaluation

Plasma samples will be collected from all subjects and analysed to determine levels of lubiprostone (if measurable) and metabolite M3. These concentration-time data will be used in a population PK analysis. PK samples will be taken under non-fasting conditions. The samples will be collected via direct venepuncture. Approximately 8 mL of blood will be taken for each sample such that the total of all PK samples does not exceed 50 mL or 5 mL/kg of body weight.

7. ADVERSE AND SERIOUS ADVERSE EVENTS

As defined in ICH GCP Guideline E6,[14] 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 enrolment will be defined as an AE. Adverse events that are reported after initiation of study medication will be defined as treatment-emergent AEs.

In this study, faecal impaction and bone fractures will be captured as AEs. The events of faecal impaction will be used for the analysis of the faecal impaction frequency during the study (see Section 8.6.2.5).

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[15]) 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).
    - Chest pain/chest discomfort
    - Dyspnea/shortness of breath/difficulty breathing
    - Hepatotoxicity/liver enzyme increased
    - 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 and followed for the duration of the pregnancy. 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 current Medical Dictionary for Regulatory Activities (MedDRA)® terminology.

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. Due to the titration aspect of the preceding double-blinded study (SAG/0211PFC-1131), bottles will not specifically identify whether they contain lubiprostone 12 or 24 mcg so as to maintain the prior blind. Dose assignment will only be known in subjects who were at least 50 kg in weight at the time of randomisation in the preceding study (SAG/0211PFC-1131). All dose assignments will be handled by the IXRS and will continue to maintain blinding with respect to the treatment assignment in the preceding trial. Investigators will be provided with subject treatment dose information associated with their study participants upon finalisation of the Clinical Study Report.

8.1 Determination of Sample Size

The sample size goal is based on the expected attrition that would occur and the remaining number of safety evaluable subjects at each timeframe during the study.

8.2 Datasets Analysed

Two analysis populations, Safety population and the modified Intent-to-Treat (mITT) population and these will be defined as follows:

- **The Safety population** will consist of all enrolled subjects who take at least one dose of study medication.
- **The mITT population** will include all enrolled subjects who take at least one dose of study medication and have at least one treatment period diary entry.

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.

Baseline disease status will be assessed by constipation history, baseline period assessments of the subject's evaluation of BM frequency rates, SBM frequency rates, stool consistency, bowel straining, abdominal pain, constipation severity, incontinence episodes, occurrence of large diameter stools, retentive posturing, and the health-related quality of life using the PedsQL™ questionnaires. These data will be summarized with descriptive statistics as outlined above.

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

Assessments of actual exposure to study medication and rescue medication will be made based on the eCRF and diary data. 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.

In this study, faecal impaction and bone fractures will be captured as AEs. The events of faecal impaction will be used for the analysis of the faecal impaction frequency during the study (see Section 8.6.2.6).

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 Bone Growth Assessments

Bone growth will be assessed on the DXA subgroup population (i.e., those subjects who were aged 6 to 9 or 14 to 17 at the time of enrolment into the SAG/0211PFC-1131 study, and who were qualified to participate and enrolled in the DXA substudy). Bone-related DXA endpoints will include:

- Percent changes from baseline in BMD and BMC;
- Change from baseline in BMD Z-scores and in height-adjusted Z-scores;
- Changes from baseline in height and weight Z-scores.

Details on analyses by age, race, and gender subgroups are provided in the SAP.

8.5.6 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.

8.5.7 Pharmacokinetic Evaluations

A population pharmacokinetic analysis will be performed using the concentration-time data from the sparse PK samples in this study. The analysis may include data from other studies with lubiprostone in adults, paediatric subjects, or healthy volunteers. A separate analysis plan for the population pharmacokinetic analysis will be prepared prior to database lock.

8.5.8 Subgroup and Exploratory Analyses

Upon completion of pivotal phase 3 studies, analyses of any under-represented subgroups such as males and non-whites will be performed on the pooled data from the pivotal studies. Details pertaining to these analyses will be specified in the SAP.

8.6 Analysis of Efficacy

8.6.1 General Inferential Principles

The following principles apply for all inferential analyses of efficacy: All tests are two-tailed at a significance level of $\alpha = 0.05$.

8.6.1.1 Missing Data

Details on handling of missing data are described in the SAP.

8.6.1.2 Multiplicity

No interim analyses will be performed and therefore no multiplicity adjustments will need to be made to account for them.

8.6.1.3 Multicentre Studies

Region and/or centre effects will be explored as detailed in the SAP.

8.6.2 Efficacy Endpoints

8.6.2.1 Overall and Monthly Change from Baseline in BM and SBM Frequency

Changes from baseline in BM and SBM frequency will be analysed overall, and at each month from Months 1 through Month 9. A month is defined as a 4-week period; e.g., Month 1 is Weeks 1-4; Month 2 is Weeks 5-8; Month 3 is Weeks 9-12. The SBM frequency rate per week will be computed as specified in Section 8.6.2.1. The analyses of the months will utilize the same methods as those used in the analysis of weeks.

8.6.2.2 Overall and Monthly Change from Baseline in Incontinence Frequency

This analysis will be performed for subjects who are fully toilet-trained and for the subset of subjects presenting with incontinence at baseline. Change from baseline in incontinence frequency will be analysed overall, and at each month during Months 1 through 9 as described in Section 8.6.2.2.

8.6.2.3 Overall and Monthly Change from Baseline in Production of Large Diameter Stool Frequency

This analysis will be performed for subjects who are fully toilet-trained. Change from baseline in the production of large diameter stool frequency will be analysed overall, and at Months 1 through 9 as described in Section 8.6.2.2.

8.6.2.4 Overall and Monthly Change from Baseline in Proportion of BMs and SBMs in Toilet

This analysis will be performed for subjects who are fully toilet-trained. Change from baseline in the proportion of BMs and SBMs in the toilet will be analysed overall, and at each month during Months 1 through 9 as described in Section 8.6.2.2.

8.6.2.5 Overall and Monthly Change from Baseline in Frequency of Faecal Impaction

Change from baseline in faecal impaction frequency will be analysed overall, and at each month during Months 1 through 9 as described in Section 8.6.2.2.

8.6.2.6 Overall and Monthly Change from Baseline in Frequency of Retentive Posturing or Excessive Volitional Stool Retention

Change from baseline in retentive posturing or excessive volitional stool retention frequency will be analysed overall, and at each treatment month during Months 1 through 9 as described in Section 8.6.2.2.

8.6.2.7 Overall and Monthly Change from Baseline in Constipation Signs and Symptoms

Mean changes from baseline will be generated based on subject reported data as to the degree of:

- Straining associated with SBMs;
- Stool consistency of SBMs;
- Abdominal pain associated with SBMs; and
- Constipation severity.

The following rating scales will be used:

Stool consistency: Modified Bristol Stool Form Scale (5-point scale);

Bowel straining: 0=Not at all, 1=A little, 2=Some, 3=Quite a bit, 4=Extremely

Constipation severity and abdominal pain: 0=Absent, 1=Mild, 2=Moderate, 3=Severe, 4=Very severe.

The overall change from baseline will be calculated as the baseline value subtracted from the average of all diary ratings, where the baseline value will represent the average rating during the 2-week screening period of the previous study (SAG/0211PFC-1131). The change from baseline for a week (7-day period) or month (4-week period) will also be calculated as the baseline value subtracted from the average of all diary ratings during a week or month.

Stool Consistency

The analysis of stool consistency will focus on consistency assessments associated with SBMs. The average stool consistency rating will be calculated for each month (4-week period), excluding measurements recorded within 24 hours after rescue medication intake.

Analyses will be based on the change from baseline, where the baseline value will represent the average stool consistency rating from all SBMs during the 2- week screening period of the previous study (SAG/0211PFC-1131). The van Elteren test using the change from baseline stratified by pool centre and stratified by study for the pooled group will be used.

Straining

Bowel straining will be analysed in a method similar to stool consistency.

Constipation Severity

The changes from baseline in mean constipation severity ratings at each month during Months 1 through 9 will be analysed. The change from baseline will be calculated as the baseline value subtracted from the average of all diary ratings during the given month. For these daily diary assessments, each month will be defined by 4-week intervals beginning with the day of the first dose of study medication (Day 1). For example, Month 1 will start with the daily assessment on Day 1 and end with the daily assessment on Day 29 (Week 4), Month 2 will start with the daily assessment on Day 30 and end with the daily assessment on Day 57 (Week

8), and Month 3 will start with the daily assessment on Day 58 and end with the daily assessment on Day 85 (Week 12). Each week will be defined by 7-day intervals beginning with the day of the first dose of study medication (Day 1).

The van Elteren test using the change from baseline stratified by pooled centre for the individual studies and stratified by study for the pooled group will be used.

Abdominal Pain

Abdominal pain will be analysed similarly to constipation severity. Summary tables for the monthly change from baseline will also be presented.

8.6.2.8 Monthly SBM Response

A monthly responder is defined as a subject who is a weekly responder for 3 of 4 weeks per month. A weekly responder is defined as a subject who has a frequency rate of ≥ 3 SBMs/week and an increase from baseline of ≥ 1 SBM/week for that week. Analyses of the frequency rates of SBMs per month will be performed using the van Elteren test, stratified by pooled centres.

8.6.2.9 Treatment Effectiveness

Measurements of treatment effectiveness will be collected via the diary at weekly intervals as well as overall 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.

8.6.2.10 Health-related Quality of Life

Health-related quality of life will be measured using the PedsQL™ questionnaire.

The PedsQL™ questionnaire has 4 subscales: physical functioning, emotional functioning, social functioning, and school functioning; in addition, there is a total score. Summary evaluations of response for every domain and total score at each timepoint will be provided by treatment arm. For each subscale and for the total score, the change from baseline at each visit will be analysed.

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 Principal Investigator will be required to electronically sign the eCRFs casebook for each subject. Laboratory reports must be reviewed, signed, and dated by an appropriate Investigator and filed with the source documents. Any laboratory findings out of the normal range should indicate the clinical significance (clinically significant [CS] or not-clinically significant [NCS]) of the results on both the source document and the corresponding eCRF.

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

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

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

The dates of the monitoring visits will be recorded by the monitor in a study site visit log to be kept at the site. The first post initiation visit will usually be made as soon as possible after enrolment has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). Source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of AEs, administration of concomitant medication, medication receipt/dispensing/return records, and study medication administration information. Specific items required as source documents will be reviewed with the Investigator prior to the study. Findings from this review of eCRFs and source documents will be discussed with the Investigator. The Sponsor expects that, during monitoring visits, the Investigator and study coordinator, will be available, the original source documentation, regardless of media, will be available, and a suitable environment will be provided for review of study-related documents.

9. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study will be conducted in accordance with current applicable regulations, International Conference on Harmonisation (ICH), European Union (EU) Directive 2001/20/EC[17] 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, ICH GCP Guideline E6[14]and EU Directive 2001/20/EC.[17]

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 Indemnity/liability and Insurance

Sponsor will adhere to the recommendations of the Association of British Pharmaceutical Industry (ABPI) Guidelines. If appropriate, a copy of the Indemnity document will be supplied to the Investigator before study initiation.

Sponsor will ensure that suitable insurance cover is in place prior to the start of the study.

9.1.4 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.

9.1.5 End of Trial Notification

With respect to investigational sites within the EU, the Sponsor will submit an end of trial notification to individual Member States and IECs within 90 days of the end of the trial in accordance with EU Directive 2001/20/EC.[17]

The end of trial notification should be made when:

- the trial ends in the territory of the member state(s) concerned; and

- the complete trial has ended in all participating centres in all countries within and outside the EU.

For the purposes of this notification, the end of the complete trial will be defined as the last subject/last visit in all participating centres in all countries within and outside the EU and the end of trial in a member state will be defined as the last subject last visit in that member state.

However, if recruitment into the trial as a whole is on-going and there is a possibility that further subjects may be recruited into the trial in a member state where there are currently no active subjects, the end of trial notification for that member state will be deferred until it is certain that no further subjects will be recruited into the study in that member state.

9.1.6 Submission of Summary of Clinical Study Report to Competent Authorities of Concerned Member States and IECs

The Sponsor will provide a summary of the Clinical Study Report within one year of the end of the complete trial to the competent authority of the concerned Member State(s) as required by the regulatory requirement(s) and to comply with the Community guideline on Good Clinical practice. The Sponsor will provide the IECs with a copy of the same summary.

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[14], EU Directive 2001/20/EC[17], 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 as soon as possible, but prior to the end of the study, 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 Directive 2001/83/EC and ICH E3.[18]

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.

For investigational sites outside the EU, 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; for investigational sites within the EU, this can be done by the Sponsor, the Investigator or for multicentre studies the Coordinating Principal Investigator, according to national provisions. 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 study site personnel.

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

9.2.3.2 Recording, Access and Retention of Source Data

Source data to be reviewed during this study will include, but is not limited to: subject's medical file, subject diary cards, original laboratory reports, 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[19] 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).[20]

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)[21], 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 local requirements, from minor subjects.

All consent and assent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's LAR, where applicable, is requested to sign the IRB/IEC approved Subject Informed Consent Form after the subject/LAR 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/assent forms must remain in each subject's study file and must be available for verification by Study Monitors at any time.

For investigational sites outside the EU, the Principal Investigator will provide the sponsor with a copy of the IRB/IEC approved consent/assent forms, and a copy of the IRB/IEC's written approval, prior to the start of the study. For investigational sites within the EU, submission and obtaining IEC approval of the informed consent documentation can be the responsibility of the Sponsor, the Investigator or for multi-centre studies the Coordinating Principal Investigator, according to national provisions. Additionally, if the IRB/IEC required modification of the sample Subject Information and Consent/Assent 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 (and assent where applicable) forms do not meet the standards of applicable regulations and ICH GCP.

9.3.2 Institutional Review Board or Independent Ethics Committee approval

For investigational sites outside the EU, it is the responsibility of the Investigator to submit this protocol, the informed consent/assent 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. For investigational sites within the EU, the applicant for an IEC opinion can be the Sponsor, the Investigator or for multi-centre studies the Coordinating Principal Investigator, according to national provisions. In addition, advertisements must be approved by the IRB/IEC prior to use at the site. Prior to implementing changes in the study, the Sponsor and the IRB/IEC must also approve any revised informed consent/assent 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.

For investigational sites outside the EU, 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; for investigational sites within the EU, this can be done by the Coordinating Principal Investigator, according to national provisions. The Investigator must also keep the local IRB/IEC informed of any serious and significant adverse events.

9.3.3 Measures for Reduction of Stress and Pain in Paediatric Subjects

In consideration of the responsibility to ensure that children are enrolled in clinical research that is both scientifically necessary and ethically sound,[22] the Sponsor has implemented the following measures to reduce the burden and stress of participation in this placebo-controlled trial:

- Use of experienced Investigators and research personnel to appropriately assent/consent study participants. Site staff will be trained at an Investigator Meeting and at Site Initiation Visits;
- Use of sparse PK sampling (population PK) to reduce the number of PK blood samples collected from each subject;
- Minimization of clinic visit frequency for blood chemistry, haematology, and urinalysis collection during the study;
- Minimization of cohorts of patients (to 6-9 and 14-17 year olds) to be subjected to DXA scans;
- Allowing the use of protocol-specified rescue medication for the duration of the study;
- Allowing for dose reduction in cases where subjects are experiencing specific adverse events; and
- Use of a DSMB for monitoring of safety for the duration of the study.

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. The Sponsor will control all data collected during the study, and will abide by the EU Directive on Data Privacy (Directive 95/46/EC) concerning the processing and use of subjects' personal data. For the purpose of data privacy legislation, Sucampo Pharma Europe, Ltd. will be the data controller.

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 EU. 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

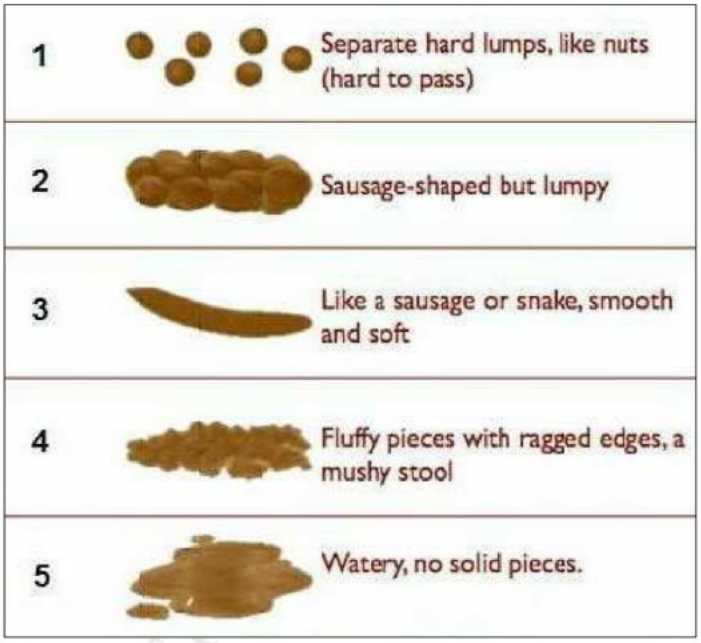
APPENDIX 1 DIARY QUESTIONS (CHILDREN ≥6 TO < 18 YEARS OF AGE)

The electronic diary will be completed each evening by the parent/legal guardian, with certain questions being completed by the subject. Those questions to be completed by the parent/legal guardian are noted as "observer item" and those to be completed by the subject as "patient item" below. In cases where the parent/legal guardian will complete the diary entries, he/she should consult the subject as needed to obtain accurate information (e.g., for recording times of bowel movements). Whenever possible, the same parent/legal guardian should consistently complete the diary.

The diary will be set up so that it may be completed each evening with responses based upon that day's or week's activities, and will also allow for episodic entry of rescue medication use and bowel movements as they occur on a particular day. Episodic entries will be reviewed during the evening diary session.

Item/Instruction Text	Response Options	Subject or Observer
INSTRUCTIONS: DAILY ASSESSMENTS The following questions will be assessed as part of the subject's daily diary. Subject/legal guardian will record their answers to these assessments for the entire duration of the study. Diaries are to be completed from the beginning treatment through the end of the treatment period.		
STUDY MEDICATION Did your child take the Morning Dose today?	Yes No	Observer only item
What time did your child take the Morning Dose?	Morning Dose – xx:xx AM	Observer only item
STUDY MEDICATION Did your child take the Evening Dose today?	Yes No, not yet No, not taking tonight	Observer only item
What time did your child take the Evening Dose?	Evening Dose – xx:xx PM	Observer only item
In the past 24 hours: Did your child take a medication that was different from the study medication to help have a bowel movement?	Yes No	Observer only item;
[If YES] Please indicate the OTHER MEDICINE your child used?	Bisacodyl Senna Picosulfate Other	Observer only item

[X will be equal to the other medicine selected in prior item response.] Did your child take this today or yesterday?	Today Yesterday	Observer only item
X Please record the time of this dose.	[spinner xx:xx]	Observer only item
Confirm you would like to report a Bowel Movement your child had today or yesterday: Today's Date: DD Mon YYYY Yesterday's Date: DD Mon YYYY	Yes No	Observer only item
Did this bowel movement occur today or yesterday?	Today Yesterday	Observer only item
Please record the time of this bowel movement.	[spinner xx:xx]	Observer only item
Did your child have this bowel movement in the toilet?	Yes No I don't know	Observer only item
Did the bowel movement clog the toilet?	Yes No I don't know	Observer only item
Is your child with you right now and available to answer questions about this bowel movement?	Yes No	Observer only item

Read the description and look at the pictures to see which one best matches your bowel movement.	Chumpitazi et al (2010). J Pediatr. October; 157(4): 594–597.[23] 	Patient item **OR** Observer item
How hard did you have to push to have this bowel movement?	0 - Not at all 1 - A little 2 - Some 3 - Quite a bit 4 - Extremely	Patient only item
How much did it hurt when you had this bowel movement?	0 - Not at all 1 - A little 2 - Some 3 - Quite a bit 4 - Extremely	Patient only item
In the past 24 hours: What was the worst pain in your belly today?	0 - none 1 - mild 2 - moderate 3 - severe 4 - very severe	Patient only item
In the past 24 hours How would you rate your child's constipation severity?	0 - none 1 - mild 2 - moderate 3 - severe 4 - very severe	Observer only item
WEEKLY ASSESSMENT The following questions will be assessed each week immediately following the daily diary questions as part of the subject's diary:		

STUDY MEDICATION Over the past week, how well did your child's study medicine help?	0 – not at all effective 1 – a little bit effective 2 – moderately effective 3 – quite a bit effective 4 – extremely effective	Observer only item
Over the past week, how many episodes of retentive posturing did your child have?	[continuous numeric; not applicable]	Observer only item

APPENDIX 2 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)							Diastolic BP (mmHg)						
		← Percentile of Height →							← 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 3 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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16.1.1.2 Protocol Amendment Summaries

SUCAMPO AG

Protocol SAG/0211PFC-11S1 Amendment 3 (Summary of changes)
Date: XX November 2015

Protocol Version 4.0 will incorporate Amendment 3.

The purpose of this amendment is to revise Protocol SAG/0211PFC-11S1 to reflect the following changes:

Amendment 3 Revisions to Protocol SAG/0211PFC-11S1			
Page, Section Number, and Title		**Planned Revisions**	**Rationale**
1	**Global**	General edits were made throughout document for clarification and consistency of information.	Changes made for clarification and consistency of information. Edits were also made to reflect the new sample size estimate of 415 subjects throughout the document.
2	**Page 2, Protocol Signature Page**	**Removed:** [redacted], BS, PMP [redacted] Sucampo Pharma Americas, LLC **Updated:** [redacted], BS, PMP [redacted] Sucampo Pharma Americas, LLC	This change is to capture the name change.
3	**Page 2, Protocol Signature Page**	**Removed:** [redacted], MD EU [redacted] **Updated:** [redacted], MD, PhD, BBA [redacted] Sucampo AG	Per Administrative Change Memo (dated 17 September 2014), this change is to capture the new EU [redacted].
4	**Page 3, Contact Information**	**Updated:** **EU** [redacted] Name [redacted], MD, PhD, BBA Title [redacted] Office Telephone Number [redacted] After Hours Contract Number [redacted] E-mail Address [redacted]	Per Administrative Change Memo (dated 17 September 2014), this change is to capture the new EU [redacted].
5	**Page 11, Protocol Synopsis, Assumed No. of Sites; and Page 22, Section 3, Study Design**	**Previously:** Approximately 100 (North America and Europe) **Revised:** Approximately 130 (North America and Europe)	Number of sites was increased to accommodate the increase in the overall number of subjects required for the study.
6	**Page 11, Protocol Synopsis, Est. No Enrolled Subjects, and Page 22, Section 3, Study Design**	**Previously:** 300 subjects who completed Study SAG/0211PFC-1131 **Revised:** 415 subjects who completed Study SAG/0211PFC-1131	Size sample estimate was revised because the roll over rate from Study SAG/0211PFC-1131 is higher than originally assumed.

Amendment 3 Revisions to Protocol SAG/0211PFC-11S1			
Page, Section Number, and Title		**Planned Revisions**	**Rationale**
7	**Page 12, Protocol Synopsis, Inclusion Criterion #3c; Page 24, Inclusion Criterion #3c;** and **Page 31, Section 5.7.1, (last bullet)**	**Previously:** Any medication, at the discretion of the Investigator, known to cause constipation or constipation-related symptoms. **Revised:** 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.	Edits made to provide clarity regarding medications that could relieve or cause constipation and that may confound the evaluation of treatment response.
8	**Page 16, Protocol Synopsis, Schedule of Evaluations, footnote #6; Page 33, Section 6.1.1, Completion of Study Procedures; and Page 40, Section 6.3, Safety Evaluations**	**Added:** Any subject demonstrating a decline in 4% in BMD at any skeletal site from Screening to End of Treatment should additionally undergo a follow-up DXA assessment 6 to 12 months later.	Added recommendation to match guidance that is provided in the Operations Manual.
9	**Page 30, Section 5.7.1, Excluded Medication**	**Previously:** The following medications are to be excluded during the course of the study and must be discontinued from the Enrolment Visit through study completion: **Revised:** The following medications are to be excluded during the course of the study and must be discontinued from the Enrolment Visit through the end of the first week following the End-of-Treatment Visit:	Sponsor decided that it is fair to let subjects return to their normal constipation meds after a week off study drug. "Treatment-emergent AEs" are usually defined as those that occur within 7 days following discontinuation of study treatment. As such, subjects should at least maintain the prohibited medication exclusion through the end of the first week following End-of-Treatment.

Amendment 3 Revisions to Protocol SAG/0211PFC-11S1			
Page, Section Number, and Title		**Planned Revisions**	**Rationale**
10	**Page 45, Section 7.2.6, Overdose**	**Previously:** 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 IRE (see Section 7.2.1). **Revised:** There are no specific treatments or monitoring guidelines prescribed for subjects with lubiprostone overdose. It will be left to the discretion of the Investigator's clinical judgment on how to provide appropriate symptomatic treatment. Any incidences of overdose with the investigational product will follow the same reporting procedures as an AE (see Section 7.2), and only where applicable, as an IRE (see Section 7.2.1).	Edit was made to clarify that an overdose will be captured as an AE and therefore will follow the same reporting procedures as an AE.

SUCAMPO AG

Protocol SAG/0211PFC-11S1 Summary of changes for Amendment 2
Date: 10 December 2013

Protocol Version 3.0 will incorporate Amendment 2.

The purpose of this amendment is to revise Protocol SAG/0211PFC-11S1 to reflect the following changes:

Amendment 1 Revisions to Protocol SAG/0211PFC-11S1		
	Page, Section Number, and Title	**Planned Revisions**
1	**Pages 13-14, Protocol Synopsis, Objectives, Study Medication and Dose Regimen; and Pages 21, Section 2.1, Objectives**	**Previously:** To assess the long-term safety, efficacy, and pharmacokinetics of oral lubiprostone 12 or 24 mcg capsules dosed twice daily (BID) when administered orally for 36 weeks in paediatric subjects with functional constipation. **Revised:** To assess the long-term safety, efficacy, and pharmacokinetics of oral lubiprostone 12 or 24 mcg capsules dosed twice daily (BID) when administered orally for 36 weeks in paediatric subjects with functional constipation. Evaluation of lubiprostone safety is the primary objective of this study.
2	**Pages 13-14, Protocol Synopsis, Safety Evaluation/Efficacy Evaluation; Page 21-22, Section 2.2, Endpoints; and Pages 49-53, Sections 8.5 and 8.6**	**Previously:** Efficacy endpoints were presented before safety endpoints. **Revised:** Safety endpoints are now presented before efficacy endpoints.

SUCAMPO AG

Protocol SAG/0211PFC-11S1 Summary of changes for Amendment 1
Date: 26 November 2013

Protocol Version 2.0 will incorporate Amendment 1.

The purpose of this amendment is to revise Protocol SAG/0211PFC-11S1 to reflect the following changes:

Amendment 1 Revisions to Protocol SAG/0211PFC-11S1		
	Page, Section Number, and Title	**Planned Revisions**
1	**Page 13, Protocol Synopsis, Exclusion Criteria Number 5** and **Page 26, Section 4.2, Exclusion Criteria Number 5**	**Previously:** Subject (female of childbearing potential) has a positive pregnancy test, or refuses/unwilling to undergo pregnancy testing. **Revised:** 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.**
2	**Page 26, Section 4.4, Contraception Specifications**	**Added New Section:** 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 Contraceptives– must have been used for at least 3 months prior to the Screening Visit (Visit 1); • Intrauterine Device (IUD); or • Double barrier method.
3	**Section 6.1, Study Procedures by Visit** *(specifically Page 35, Section 6.1.2; Page 36, Section 6.1.3.1; Page 37, Section 6.1.3.3; Page 38, Section 6.1.3.4; and Page 39, Section 6.1.4.1)*	**Added total blood volume to be collected at each relevant study visit for clinical laboratory and pharmacokinetic (PK) analyses, as follows:** **Visit 9: 5.5 mL for clinical laboratory samples and 16 mL for PK samples** **Randomization visit (Visit 2): 16 mL** **Visits 10, 12, 14, 16, and 17: 5.5 mL**
4	**Page 59, Section 9.3.3, Measures for Reduction of Stress and Pain in Pediatric Patients**	**Added New Section:** In consideration of the responsibility to ensure that children are enrolled in clinical research that is both scientifically necessary and ethically sound,[22] the Sponsor has implemented the following measures to reduce the burden and stress of participation in this placebo-controlled trial: • Use of experienced Investigators and research personnel to appropriately assent/consent study participants. Site staff will be trained at an Investigator Meeting and at Site Initiation Visits; • Use of sparse PK sampling (population PK) to reduce the number of PK blood samples collected from each subject; • Minimization of regular blood chemistry, haematology, and urinalysis collection during the study (optional collection given at Week 8 visit); • Allowing the use of protocol-specified rescue medication for the duration of the study; • Allowing for dose reduction in cases where subjects are experiencing specific adverse events; and • Use of a DSMB for monitoring of safety for the duration of the study. [22] Roth-Cline MD, Gerson J, Bright P, et al. Ethical considerations in conducting pediatric research. In Pediatric Clinical Pharmacology, 2008.