Study Report Number: SAG/0211PFC-1131-01

Version Number: 1.0

STUDY REPORT

A Multicentre, Randomised, Placebo-controlled, Double-blind Study of the Efficacy, Safety, and Pharmacokinetics of Lubiprostone in Paediatric Subjects Aged ≥6 Years to <18 Years with Functional Constipation

Date of Report: 28 March 2017

Cross Reference Number: SAG/0211PFC-1131

1. TITLE PAGE

CLINICAL STUDY REPORT

A MULTICENTRE, RANDOMISED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY OF THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF LUBIPROSTONE IN PAEDIATRIC SUBJECTS AGED ≥6 YEARS TO <18 YEARS WITH FUNCTIONAL CONSTIPATION

Study No.: SAG/0211PFC-1131-01

Study Drug Name: Lubiprostone

Phase 3

IND #: 59,623

Sponsor: Sucampo AG
Baarerstrasse 22, CH-6300, Zug, Switzerland
Tel: +41 41 726 3030; Fax: +41 41 726 3031

Medical Monitor/Expert: Joseph Fawole, MBBS, MPH
Medical Monitor
Sucampo Pharmaceuticals, Inc.

Sponsor Contact: Shadreck Mareya, PhD
Director, Clinical Program Management
Sucampo Pharmaceuticals, Inc.

Coordinating Principal Investigator: Carlo DiLorenzo, MD
Date of First Subject Observation: 13 December 2013
Date of Last Subject Observation: 27 July 2016
Date of Report: 28 March 2017
Date of Previous Report: None

This study, and the archival of all essential documents, was conducted in compliance with Good Clinical Practice (GCP) and other applicable regulatory requirements.

SIGNATURE PAGE

STUDY TITLE: A MULTICENTRE, RANDOMISED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY OF THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF LUBIPROSTONE IN PAEDIATRIC SUBJECTS AGED ≥6 YEARS TO <18 YEARS WITH FUNCTIONAL CONSTIPATION

Study: SAG/0211PFC-1131-01 Development Phase: 3

I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the study.

Principal Investigator: *Carlo DiLorenzo, MD*

Affiliation: *Nationwide Children's Hospital*

Signature: _____ *Date:* _____

Name: *Peter Kiener, D. Phil.*

Title: *Chief Scientific Officer and Head of R&D*

Signature: _____ *Date:* _____

Name: *Steve Caffe, MD*

Title: *SVP, Global PV, RA & Quality*

Signature: _____ *Date:* _____

Name: *Taryn Losch-Beridon, BS, PMP*

Title: *VP, Clinical Development*

Signature: _____ *Date:* _____

Name: *Martin Wang, MStat*

Title: *Director, BDMP*

Signature: _____ *Date:* _____

REPORT AUTHOR

Name: *Peter Lichtlen, MD, PhD, BBA*

Title: *Chief Medical Officer*

Company: *Sucampo AG*

Signature: _____ *Date:* _____

2. SYNOPSIS

Sponsor Name:	Sucampo AG
Study Drug Name:	Lubiprostone
Protocol Number:	SAG/0211PFC-1131

Study Title: A MULTICENTRE, RANDOMISED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY OF THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF LUBIPROSTONE IN PAEDIATRIC SUBJECTS AGED ≥6 YEARS TO <18 YEARS WITH FUNCTIONAL CONSTIPATION

Investigators/Study Centres: This was a multicentre study consisting of 96 investigative sites in the United States, Canada, and Europe. There were 76 sites in the United States, 3 sites in Canada, and 17 in Europe.

Study Period: 13 December 2013 to 27 July 2016

Phase of Development: 3

Objectives: To assess the efficacy, safety, and pharmacokinetics (PK) of oral lubiprostone 12 or 24 mcg capsules dosed twice daily (BID) (based on subject body weight at baseline) as compared to matching placebo BID, when administered orally for 12 weeks in paediatric subjects with functional constipation.

To evaluate the measurement characteristics of the paediatric functional constipation clinical outcome assessments (COAs), including observer-reported outcomes (ObsROs) and patient-reported outcomes (PROs) instruments.

Study Design: Randomised, placebo-controlled, double-blinded, parallel group 12-week study.

Number of subjects (planned and analysed): 570 subjects were planned for the study with 2:1 randomization (380 lubiprostone: 190 placebo). A total of 606 subjects were randomised: 202 subjects to placebo, 233 to lubiprostone 12mcg BID and 171 to lubiprostone 24mcg BID (404 subjects to lubiprostone in total). 444 subjects completed the study, of whom 147 were randomised to placebo and 297 were randomised to lubiprostone.

Diagnosis and main criteria for inclusion:
Eligible subjects were ≥6 years and <18 years of age with a diagnosis of pediatric functional constipation according to ROME III criteria, capable and willing to swallow capsules, willing to discontinue any concomitant medication that affects gastrointestinal motility and presented with less than 3 spontaneous bowel movements (SBMs) per week during the Screening period and at least one of the following for at least 25% of SBMs during each week of the screening period (as reported in the daily diary):

- Modified Bristol Stool Scale Type 1 or 2; and/or

Sponsor Name:	Sucampo AG
Study Drug Name:	Lubiprostone
Protocol Number:	SAG/0211PFC-1131

- Some straining to extreme straining associated with SBMs.

Subjects and parents/guardians had to be willing and capable to fill out their daily diaries.

Exclusion criteria included any potential other/secondary cause of chronic constipation, subjects with planned or previous surgery potentially affecting gastrointestinal motility, subjects with abnormal renal function or laboratory tests at baseline and female subjects of childbearing potential with a positive pregnancy test, refused/was unwilling to undergo pregnancy testing, and/or did not agree to use protocol-specified contraceptive for the duration of the study.

Test Product, Dose, and Mode of Administration [including Lot Number(s)]: Lubiprostone 12 mcg capsule (Lot Number 1361554) and lubiprostone 24 mcg capsule (Lot Number 1394770) for oral administration.

Duration of Treatment: 12 consecutive weeks

Reference Therapy, Dose, and Mode of Administration [including Lot Number(s)]: Placebo capsule matched to active treatment (Lot Number 1393134) for oral administration

Criteria for Evaluation of Safety:

The criteria for evaluation of safety in the SAF Population were:

- Evaluation of adverse events
- Clinical laboratory measures
- Evaluation of DXA scans for the DXA subgroup
- Evaluation of changes in vital signs and physical examination findings

Criteria for Evaluation of Efficacy:

The primary criterion for evaluation of efficacy was the overall SBM response rate of subjects who received oral lubiprostone capsules 12 mcg BID or 24 mcg BID compared with matching placebo BID administered orally for 12 weeks to subjects with paediatric functional constipation (PFC) aged ≥6 years to <18 years in the mITT Population.

Secondary criteria for evaluation of efficacy were:

- Time to first SBM
- Overall change from baseline in straining associated with SBMs
- Overall change from baseline in stool consistency of SBMs
- Overall change from baseline in constipation severity
- Overall change from baseline in abdominal pain
- Overall change from baseline in SBM frequency
- Overall change from baseline in painfulness of SBMs

Sponsor Name:	Sucampo AG
Study Drug Name:	Lubiprostone
Protocol Number:	SAG/0211PFC-1131

- Overall treatment effectiveness
- Overall Investigator's assessment of treatment effectiveness
- Overall treatment response
- SBM within 4, 8, 12, 24, and 48 hours of first dose of study medication
- Overall change from baseline in frequency of production of large diameter stool
- Overall frequency of retentive posturing and excessive stool retention
- Overall change from baseline in PedsQL™ total score evaluated by subject and by parent/legal guardian
- Overall change from baseline in PGIC evaluated by subject and by parent/legal guardian
- Overall change from baseline in Clinician Severity Rating scales
- SBM response rate at Months 1, 2, and 3
- Overall rescue medication use
- Overall change from baseline in BM frequency
- Overall change from baseline in incontinence frequency
- Overall percentage of SBMs in toilet
- Overall percentage of BMs in toilet

For the primary efficacy endpoint of overall SBM response, the Cochran-Mantel-Haenzel (CMH) test stratifying by, baseline SBM frequency (<1.5 or ≥1.5) was to be used for the comparison between the placebo group and the overall lubiprostone group. The treatment differences and confidence intervals (CI) between the lubiprostone total group and placebo was to be calculated. P-values less than or equal to 0.05, or CIs that did not cover zero (0), were to be considered statistically significant. The primary analysis was to be based on the modified intention-to-treat (mITT) Population. The CMH test was also to be applied for the secondary binary efficacy endpoints. For the secondary continuous efficacy endpoints, the van Elteren test using change from baseline by pooled sites was to be used.

For safety analysis, treatment-emergent adverse events (TEAEs) and treatment-related adverse events (TRAEs) will be summarized in terms of incidence by treatment group and overall. Changes from baseline or clinical abnormalities in clinical laboratory data, and vital signs will be summarized by treatment group and overall.

Statistical analyses were also performed for the following subgroups:

- The primary efficacy objective; percentage of 12-week overall SBM responders for the following baseline categories:
  - Gender (male, female)
  - Race (White, Black, All others)

Sponsor Name:	Sucampo AG
Study Drug Name:	Lubiprostone
Protocol Number:	SAG/0211PFC-1131

- Age group (6 to 9, 10 to 13, and 14 to 17 years of age)
- SBM at Randomisation (<1.5, ≥1.5)
- Weight (<50 kg, ≥50 kg)
- BMI (<25, ≥25)

- Treatment-emergent adverse events (TEAEs) and treatment-related AEs (TRAEs) for the following categories,
  - Gender (male, female)
  - Race (White, Black, All others)
  - Age group (6 to 9, 10 to 13, and 14 to 17 years of age)
  - SBM at Randomisation (<1.5, ≥1.5)
  - Weight (<50 kg, ≥50 kg)
  - BMI (<25, ≥25)

Efficacy Results:

The primary endpoint (overall SBM response) was not met in the primary population for efficacy analysis (mITT), while there was a 4.6% greater response in the total lubiprostone BID group (19.0%) compared with the placebo BID group (14.4%); Confidence Intervals (-1.56%, 10.94%); p=0.1609. Similar results were observed in the mITT Population with exclusion of subjects enrolled at study Sites 1064 and 1082 [i.e., the "mITT1" Population]), which is considered as the most relevant population for efficacy analysis in this report and on which additional post-hoc analyses were conducted; there was a 4.1% greater response in the total lubiprostone BID group (19.0%) compared with the placebo BID group (14.9%); Confidence Intervals (-2.35%, 10.49%); p=0.2415.

Subgroup analyses, including post-hoc analyses in the "mITT1" population, demonstrated a statistically significant difference in overall SBM responders in favour of lubiprostone for female subjects of the age of 10-17 years, as assessed by 95% Confidence Intervals (0.7%, 19.0%). When a more stringent overall SBM responder definition was applied post-hoc to the mITT1 population, a statistically significant difference in favour of lubiprostone was demonstrated in the mITT1 Population with 95% Confidence Interval (0.26%, 10.30%). Treatment difference between lubiprostone and placebo reached a similar size in male mITT1 subjects aged 10-17 when only subjects enrolled at secondary or tertiary care centres were considered (post-hoc analysis).

In the full mITT population, a statistically significant increase in first SBM within 4, 8, 12, and 24 hours (p≤0.0353) was noted after the first intake of lubiprostone. Lubiprostone-treated subjects had statistically significantly greater mean overall changes from baseline in key secondary endpoints of overall change from baseline in SBM frequency (p=0.0496), straining (p=0.0178), painfulness of SBMs (p=0.0458) and stool consistency (p=0.0501; 95% confidence interval >0). Investigators rated lubiprostone as statistically significantly more effective than placebo at all

Sponsor Name:	Sucampo AG
Study Drug Name:	Lubiprostone
Protocol Number:	SAG/0211PFC-1131

assessment timepoints and overall (p=0.0014). Patient global impression of change (PGIC) was rated by parents/guardians as statistically significantly improved for lubiprostone versus placebo at all assessment timepoints and overall (p=0.0111).

Safety Results:

A total of 239 out of 400 subjects (59.8%) in the total lubiprostone group and 114 out of 195 subjects (58.5%) in the placebo group experienced at least 1 TEAE; the majority of AEs were mild or moderate in severity.

Significantly more subjects in the lubiprostone group (134/400; 33.5%) experienced treatment-related AEs compared to the placebo group (49/195; 25.1%; p=0.0380).

A total of 11 out of 400 subjects (2.8%) in the total lubiprostone group and 7 out of 195 subjects (3.6%) in the placebo group experienced at least 1 SAE. In the lubiprostone group, 1.0% of subjects (4/400) reported a treatment-related SAE, while equally 1.0% of subjects in the placebo group reported a treatment-related SAE (2/195).

There were no deaths in the study.

Twelve (12) out of 400 subjects in the lubiprostone arm (3.0%) discontinued the study due to a treatment-related adverse event as compared to 3 out of 195 subjects in the placebo group (1.5%).

The most frequent treatment-related AEs in the lubiprostone group were nausea (47 out of 400 [11.8%] vs. 10 out of 195 [5.1%] in the placebo group), abdominal pain (31 out of 400 [7.8%] vs 14 out of 195 [7.2%] in the placebo group) and vomiting (30 out of 400 [7.5%] vs. 5 out of 195 [2.6%] in the placebo group)

Changes in laboratory parameters, vital signs and bone mineral density assessments were not considered clinically important.

Pharmacokinetic Results:

Lubiprostone (parent compound) was not appreciably distributed in the systemic circulation. Of all the concentration sample records, only 1 lubiprostone serum sample had a measurable level, which precluded any exposure lubiprostone based analysis. Also, fewer than 10% of the total number of sample metabolite records included concentrations above the limit of quantification.

Systemic lubiprostone exposure (AUC and Cmax) showed an increasing trend in AEs of nausea, diarrhea, and vomiting, however, this systemic trend was less clear than with AE trends related purely to lubiprostone dose levels administered.

Efficacy signals (in particular SBM frequency) were weaker with increased systemic exposure, as was expected by the local action of lubiprostone.

Conclusions: The study demonstrated clinically important efficacy of lubiprostone compared to placebo taking into account totality of evidence. Although the primary endpoint did not

Sponsor Name:	Sucampo AG
Study Drug Name:	Lubiprostone
Protocol Number:	SAG/0211PFC-1131

demonstrate a statistically significant difference in favour of lubiprostone, several secondary endpoints and additional subgroup analyses demonstrated effectiveness of lubiprostone compared to placebo. This effect was more pronounced in PFC patients aged 10-17 years of age treated with lubiprostone. Most importantly, key secondary endpoints for overall change from baseline in SBM frequency, straining, stool consistency, and painfulness of SBMs all demonstrated a statistically significant difference in favour of lubiprostone. These findings are considered to be of substantial clinical relevance for PFC, given that the pathogenesis of the disorder is suggested to be triggered by hard stools leading to perception of painful defecation and stool withholding.

Lubiprostone was generally safe and well tolerated, although a statistically significantly higher proportion of subjects in the lubiprostone arm (134/400; 33.5%) experienced a treatment-related AE in comparison to the placebo arm (49/195; 25.1%; p=0.0380). Most AEs were of mild to moderate intensity, and only a small percentage of subjects discontinued the trial early due to an AE. No new or unexpected AEs occurred in the study and the majority of AEs were gastrointestinal in nature.

Lubiprostone treatment was demonstrated to have a positive benefit-to-risk profile and provided a clinically relevant benefit to PFC subjects, specifically those in the age group of 10-17 years.

Report Date: 28 March 2017

3. TABLE OF CONTENTS

3.1 TABLE OF TABLES

3.2 TABLE OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS

4.1 Abbreviation Listing

ADME	Absorption, distribution, metabolism and excretion
ADR	Adverse drug reaction
AE	Adverse event
ATC	Anatomic-Therapeutic-Chemical (Class)
AUC	Area under the curve
BID	Twice daily
BM	Bowel movement
BMC	Bone mineral content
BMD	Bone mineral density
CIC	Chronic idiopathic constipation
ClC-2	Type-2 chloride channel
CMH	Cochran Mantel Haenzel
C_{max}	Maximum concentration
COA	Clinical outcome assessment
COMP	Completers (Population)
CTP	Closed testing procedure
DE	Dose escalation (Population)
DSMB	Data Safety Monitoring Board
DXA	Dual-energy X-ray absorptiometry (Population)
EC_{50}	Half maximal effective concentration
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
IB	Investigator's Brochure
IBS-C	Irritable Bowel Syndrome with Constipation
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

IEC	Independent ethics committee
IRB	Institutional Review Board
ITT	Intent-to-Treat (Population)
Kg	Kilogram
LAR	Legally Authorised Representative
LOCF	Last observation carried forward
LOQ	Limit of quantitation
LSMeans	Least Squares Means
Mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Affairs
mITT	Modified Intent-to-Treat (Population)
MOA	Monoamine oxidase (inhibitor)
ObsRO	Observer-reported outcome
OIC	Opioid-induced constipation
PEG	Polyethylene glycol
PFC	Paediatric Functional Constipation
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics
PKA	Protein kinase A
PP	Per Protocol (Population)
PRO	Patient-reported outcome
QD	Once daily
QoL	Quality of Life
RTSM	Randomisation and Trial Supply Management (system)
SAE	Serious adverse event
SAF	Safety (Population)
SAP	Statistical Analysis Plan
SBM	Spontaneous bowel movement
SNRI	Serotonin-norepinephrine reuptake inhibitor
SOP	Standard operating procedures
SSRI	Serotonin-specific reuptake inhibitor
$t_{½}$	Time to half concentration

TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum plasma concentration
TRAE	Treatment-related Adverse Event
UK	United Kingdom
US	United States
WHO-DD	World Health Organisation Drug Dictionary

4.2 Definitions

Abbreviation	Definition
Baseline Period	The baseline period begins with the signing of informed consent at Visit 1 (Screening Visit) and ends on the day prior to randomisation to study treatment (Randomisation Visit).
Final Observation	The last non-missing value in the study for each subject.
Spontaneous Bowel Movement	Any bowel movement (BM) that did not occur within 24 hours after use of rescue medication.
Overall Responder	A subject who qualified as a weekly responder for 9 of 12 weeks during the treatment period with durability demonstrated by at ≥3 of the responder weeks occurring in the last 4 weeks of the treatment period.
Treatment Responder	A subject who remained on treatment for ≥4 weeks, did not drop out due to lack of efficacy and reported ≥1 SBMs over baseline and ≥3 weekly SBMs for 75% of observed treatment weeks overall and for ≥3 of the 4 final weeks of treatment.
Weekly SBM Responder	A subject who had a frequency rate of ≥3 SBMs/week and an increase from baseline of ≥1 SBM/week for that week.

5. ETHICS

5.1 Institutional Review Board

The study protocol and amendments, informed consent forms (ICFs), advertisements, and other information given to study subjects and/or their guardians were reviewed and approved prior to use by the Institutional Review Board (IRB) of each study centre. Each principal investigator (PI) was responsible for informing the IRB of the progress of the study and submitting annual reports.

Information about the Independent Ethics Committees (IECs) and the IRBs is provided in Appendix 16.1.3. This study was conducted in the United States (US), Canada (CA), United Kingdom (UK), the Netherlands (NL), Belgium (BE), France (FR), and Poland (PO).

5.2 Ethical Conduct of Study

Prior to study initiation at each study site, the clinical study protocol and the ICF were reviewed and approved by the IRB or IEC. Refer to Appendix 16.1.1 for the protocol versions and protocol amendments, Appendix 16.1.2 for an example electronic Case Report Form (eCRF), and Appendix 16.1.3 for the list of IRBs and IECs, and Appendix 16.1.4 for the list of investigators, including affiliations and curricula vitae, and other site personnel who participated in the study.

Sucampo AG and its designees carried out all aspects of this study in accordance with the U.S. Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR 50), IRBs (21 CFR 56), and the obligations of clinical investigators (21 CFR 312). U.S. Title 21 CFR on Good Clinical Practice (GCP) is consistent with principles set forth by the Declaration of Helsinki and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The study was registered on clinicaltrials.gov under identification number NCT02042183.

All Investigators reviewed and signed a Food and Drug Administration (FDA) Form 1572 and Sponsor-provided Study Operations Manual which described the Investigator's responsibility according to ICH/GCP guidelines.

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

5.3 Subject Information and Consent

This study was conducted in accordance with GCP. All investigators agreed to comply with 21 CFR 50 and with the World Medical Association Declaration of Helsinki concerning written informed consent and the rights of human subjects. All investigators also agreed to comply with the internal standard operating procedures (SOPs) of Sucampo AG.

It was 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 was obtained, in accordance with applicable local requirements, from minor subjects. Age-appropriate express consent was obtained in accordance with applicable local requirements. Each subject or the subject's LAR, where applicable, was requested to sign the IRB/IEC-approved Informed Consent Form after the subject/LAR had received and read the written subject information and received an explanation of what the study involved, 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 was given to the subject or the subject's LAR.

Subjects (and parent/legal guardian, depending upon age) were reimbursed for reasonable travel costs (if a receipt was provided) for travelling to and from the hospital. Subjects (and parent/legal guardian, depending upon age) were free to withdraw from the study at any time for any reason or could have been withdrawn, if necessary, to protect their health or the integrity of the study.

The subject screening criteria (i.e., inclusion/exclusion criteria) are outlined in Section 9.3 and a copy of the ICF is included in Appendix 16.1.3.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Coordinating Principal Investigator(s):

Carlo Di Lorenzo, MD

Nationwide Children's Hospital

Gastroenterology & Hepatology & Nutrition

700 Children's Dr

Columbus, OH 43205

(614) 722-3450

This was a multicentre study; the names of all participating investigators and study centres, as well as each investigator's curriculum vitae, are included in Appendix 16.1.4.

Following is the administrative structure for this study.

Monitoring and Evaluating Committees:	Independent Data Safety Monitoring Board
Central Laboratory:	Covance Central Labs (formerly LabCorp Clinical Trials)
Study Medical Monitors:	Michael Joseph, MD; Sucampo Consultant (Northern America sites; Dec 2013 – Feb 2016) Thomasz Knurowski, MD; Orion Clinical Services (EU sites; Dec 2013-April 2014) Peter Lichtlen, MD, PhD, BBA; Sucampo AG (EU sites; May 2014 – Feb 2016) Joseph Fawole, MBBS, MPH; Sucampo Pharmaceuticals, Inc. (All sites; Feb 2016 – Study Completion)
Clinical Trial Supply Management:	PCI Services
Electronic data capture (EDC):	OmniComm (TrialMaster)
Electronic diary (eDiary):	ERT, Inc.
Randomisation and Trial Supply Management (RTSM):	Parexel (ClinPhone)
Biostatistician:	Martin Wang (Sucampo Pharmaceuticals, Inc.)
Study Report Writer:	Peter Lichtlen, MD, PhD, BBA (Sucampo AG)

7. INTRODUCTION

7.1 Disease Overview

Standardised diagnostic criteria for paediatric functional constipation (PFC) have been defined by the Rome Committee for Functional Gastrointestinal Disorders.[1] These criteria require that children of a developmental age ≥4 years with insufficient criteria for a diagnosis of irritable bowel syndrome (IBS) have ≥2 of the following at least once each week for 2 months prior to diagnosis: ≤2 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 (BMs); presence of a large faecal mass in the rectum; and history of large diameter stools which may obstruct the toilet.[2]

The prevalence of PFC in children ranges from approximately 1% to 30% with similar prevalence rates for both genders.[3] Constipation, a common problem in all paediatric age groups from newborns to adolescents, accounts for 3% to 10% of visits to general paediatricians and up to 25% visits to pediatric gastroenterologists;[3,4,5,6] severity may vary from mild and short-lived to severe and chronic with faecal impaction.[6]

As with adults, paediatric symptoms of constipation include abdominal distention, infrequent BMs, hard stools, and painful evacuation.[4,5].

As a result of experiencing painful bowel movements, children may avoid defecation thereby entering into a vicious cycle of developing faecal retention due to withholding BMs as a result of the pain experienced from passage of large stools; this can also result in episodes of faecal (overflow) incontinence.[5,7]

Additionally, a recently completed study of psychological adjustment and Quality of Life (QoL) in 1697 adolescents with PFC between 13 and 18 years of age, (mean age 15.06[±1.6]) years, showed a large percentage of children with PFC were suffering with psychological maladjustment and a reduced QoL. Among the personality dimensions used for assessment, children with PFC had statistically significant ($p<0.001$) increases in deficits than controls in all measurement: hostility and aggression, negative self-esteem, negative self-adequacy, emotional unresponsiveness, emotional instability, and negative world view. The total QoL of adolescents with constipation was statistically significantly ($p<0.05$) lower than controls.[8]

A study examined long-term prognosis of 401 children (5 to 18 years of age) who had PFC and who then had constipation as adults. Prognostic factors associated with clinical outcomes were identified. There was a 6-week treatment period with follow-up at 6 and 12 months and annually thereafter for 11 years. Good clinical outcomes were defined as ≥3 BMs per week for ≥4 weeks with ≤2 faecal incontinence episodes per month, regardless of laxative use. Poor clinical outcomes at adult age were associated with older age at onset ($p=0.04$), longer delay between onset and first visit to clinic ($p=0.001$), and lower defecation frequency at study entry ($p=0.03$). Outcomes showed that 25% of children who had PFC continued to have symptoms as adults.[9]

Current medical treatment of PFC is directed at eliminating impacted faeces and restoring regular bowel habits, including passage of soft, normal stools without discomfort. Laxatives may be used to achieve a normal bowel habit and passing a soft stool without pain. Although these treatments are well-established and typically considered safe, for many in the paediatric population they do not provide a satisfying improvement, prompting a need for other therapeutic strategies.[10] Additionally, pharmaceuticals currently available for relief of constipation symptoms are limited, may be challenging to administer to children, and have not demonstrated full recovery from constipation within 6 to 12 months in all children and adolescents.[11] None have been studied in clinical trials of sufficient duration to study long-term benefit applying rigorous, controlled efficacy assessments. Accordingly, effective treatment alternatives are needed to provide relief in children with functional constipation.

7.2 Product Background

Lubiprostone, a synthetic analogue of naturally occurring prostone compounds, is a locally-acting chloride channel activator; when administered orally, it enables secretion of a chloride-enriched (physiological) intestinal fluid into the lumen of the small bowel without affecting serum electrolyte concentrations.[12,13,14] Lubiprostone specifically activates type 2 chloride (ClC-2) channels at the epithelial layer in a dose-dependent and protein kinase A (PKA)-independent (therefore direct) manner;[15,16]

By increasing intestinal fluid secretion, lubiprostone decreases transit time in the intestine, facilitating the passage of stool and alleviating symptoms associated with constipation.[12] Treatment benefits have been demonstrated in many well-controlled clinical trials and in the post-marketing environment. The most common adverse events (AEs) associated with lubiprostone treatment (nausea and diarrhoea) are easily recognised and managed without discontinuing treatment.

In 2006, following many well-controlled, randomised clinical studies in adults, lubiprostone (AMITIZA®) was approved in the US (24 mcg capsules twice daily [BID]) for treatment of adults with chronic idiopathic constipation (CIC); in 2008, the product (8 mcg BID dose) was approved for women ≥18 years old with irritable bowel syndrome with constipation (IBS-C); and in 2013, AMITIZA was approved for opioid-induced constipation (OIC) in adults with chronic, non-cancer pain. Lubiprostone has also been approved for CIC, chronic constipation (CC), IBS-C and OIC in other countries globally.

One multi-centre safety, efficacy, and PK study in PFC was previously performed. A 4-week, open-label, Phase 4 study evaluated lubiprostone 24 mcg BID, 12 mcg BID, or 12 mcg QD based on age and body weight in 127 paediatric subjects <18 years of age and weighing ≥12 kg with a history of constipation.[17]

Overall, 57.3% of subjects in this study reported at least one AE during the study; 31.5% reported at least one treatment-emergent AE (TEAE), and 6.5% withdrew from the study because of a TEAE. Among those subjects who reported a TEAE (assessed by the Investigator as at least possibly related to study drug), incidence was greatest in the lubiprostone 24 mcg BID group (46.9% [15 subjects]). The most commonly reported TEAE was nausea (GI Disorders) in 14.5% of subjects; this incidence was considerably lower than observed for previous clinical studies of lubiprostone 24 mcg in adults with CIC. No other body system had an AE reported by ≥10% of subjects.

In the Phase 4 study mentioned above, SAEs (abdominal pain and sickle cell crisis) were reported in 2 subjects; both subjects had been treated with lubiprostone 12 mcg BID and both adverse events were considered unlikely to be related to lubiprostone. Two subjects (1.6% of 124 safety-evaluable subjects), both treated with lubiprostone 12 mcg QD, experienced severe AEs of pyrexia (not treatment-related) and one subject treated with lubiprostone 12 mcg BID (0.8% of 124 safety-evaluable subjects) reported severe upper abdominal pain (possibly treatment-related).

There were no noted clinically significant trends in the assessment of laboratory values, vital signs, or physical examinations and no subjects died during the study.

Lubiprostone was generally well-tolerated in this population and the study demonstrated improvement from baseline in mean weekly spontaneous bowel movements (SBMs) in all dose groups. In addition, statistically significant improvement from baseline was observed for key SBM-associated symptoms of straining, painfulness and stool consistency in the overall ITT Population.

7.3 Rationale for Study

Although products to treat PFC in children are available and typically considered to be safe, these do not provide adequate or long-term improvement for many subjects; none of them has been formally evaluated in controlled clinical trials of sufficient duration and rigorousness of efficacy assessments. Accordingly, other effective therapeutic strategies are needed. Since lubiprostone has demonstrated increased frequency of SBMs and improvement of constipation-associated symptoms in both adults and in an open-labeled study in children,[17] further evaluation in the paediatric population using well-controlled studies was planned to further evaluate efficacy and safety.

The doses selected for the study reported in this CSR, as well as the proposal of a 1-week dose escalation window, were based on efficacy, safety, and PK data from many studies of CIC in adults[18] and a previous study of lubiprostone conducted in subjects with PFC.[19] Detailed analyses of safety, efficacy and PK data from these studies suggested that a starting dose of lubiprostone 12 mcg BID for children ≥6 years old with a body weight <50kg and a starting dose of 24 mcg BID for children with a body weight ≥50 kg would provide an optimal anticipated benefit-to-risk perspective to subjects. Additionally, a possibility for dose escalation from 12 mcg BID to 24 mcg BID at the end of Study Week 1 was defined in the protocol for subjects who tolerated treatment well, but in whom an insufficient treatment response was observed to address remaining uncertainties about efficacy of a 12 mcg BID dose regimen in PFC subjects with a body weight below 50 kg.

Lubiprostone has a well-documented safety record in clinical studies involving >3,500 adult and paediatric subjects.[20] In view of the unmet medical need for a formally studied and approved pharmaceutical treatment option to treat children and adolescents with PFC, this pivotal, randomised, placebo-controlled 12-week study has been performed. Accordingly, the study reported in this Clinical Study Report (CSR) further characterises the efficacy, safety, and PK of lubiprostone in the paediatric population aged ≥6 to <18 years.

8. STUDY OBJECTIVES

To assess the efficacy, safety, and pharmacokinetics (PK) of oral lubiprostone capsules at 12 or 24 mcg twice daily (BID: based on subject body weight at baseline) compared with matching placebo BID, when administered orally for 12 weeks in subjects with paediatric functional constipation (PFC).

9. INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan: Description

This was a Phase 3, multicentre, double-blind, randomised, placebo-controlled study to assess the efficacy, pharmacokinetics (PK), and safety of oral lubiprostone for treatment of PFC in children.

A total of 606 subjects were randomised to study treatment in a 2:1 lubiprostone: placebo ratio to receive either lubiprostone 12 mcg BID, lubiprostone 24 mcg BID (dose based on subject's weight), or placebo BID. At the time of randomisation, subjects were stratified by age (6 to 9 years, 10 to 13 years, and 14 to 17 years) and baseline SBM frequency (<1.5 or ≥1.5). A 12 mcg BID dose was assigned to subjects who weighed <50 kg and a 24 mcg BID dose was assigned to subjects who weighed ≥50 kg.

Duration of treatment was 12 weeks; total duration of subject participation was 16 weeks starting from the beginning of the Screening Period through to the end of the Follow-up Period. Subsequently, subjects had an opportunity to roll over into the 9-month safety extension study SAG/0211PFC-11S1.

It was planned that 570 subjects (190 for the placebo BID group and 380 for the total lubiprostone BID group) would be enrolled into this study to allow for a 20% attrition rate, and still meet the

necessary patient number of evaluable subjects according to the group size calculation. Eligible subjects were 6 to <18 years of age, and had a documented diagnosis of PFC. Eligible subjects were randomly assigned to treatment with either placebo BID, lubiprostone 12 mcg BID, or lubiprostone 24 mcg BID according to body weight at baseline.

Subjects originally assigned to the lubiprostone 12 mcg BID group had their dose increased to 24 mg BID at Visit 3 (Study Week 1) based upon review of diary-reported efficacy, as well as safety/tolerability, during the first week of treatment. The dose was increased in subjects who had no ongoing AEs considered by the Investigator to be related to study treatment at the time of Visit 3 and who reported <3 SBMs during the first week of study treatment (up to Day 7) or at the time Visit 3 occurred, whichever came first.

The decision concerning dose-escalation was made at the Investigator's discretion for subjects who enrolled in the study under Protocol Amendment version 6.0 or earlier; subjects who enrolled in the study according to Protocol Amendment version 7.0 were to be titrated if they met the following dose escalation criteria: no ongoing AEs assessed by the Investigator as related to study treatment at Visit 3; have reported <3 SBMs during the first week of study treatment (up to Day 7) or at the time of Visit 3, whichever occurred first.

Dose escalation was designated using the Randomisation and Trial Supply Management (RTSM) system in order to maintain blinding. These above described parameters were to be recorded in source documents and approval from the Investigator was to be obtained prior to dose escalation. Any deviations from the dose escalation criteria were to be discussed in advance with the study medical monitor. Data for the titrated subjects were analysed with the group to which they were assigned at the end of Week 1 for all efficacy analyses and, for all safety analyses, with the group they were actually assigned at the time of randomisation. Details concerning the analysis and handling of data for titrated subjects were pre-specified in the statistical analysis plan (SAP).

Interim analyses were neither planned nor performed for this study.

9.2 Discussion of Study Design

In various clinical trials in adults with CIC and OIC, lubiprostone increased the frequency of SBMs and improved constipation-associated symptoms compared to those given placebo.[22]

More specifically, studies in adults with CIC[18] and in children with PFC[19] have demonstrated that lubiprostone improved disease parameters in a clinically and statistically significant manner and has a well-defined and generally favourable safety profile. Based upon results from these studies, the doses of lubiprostone (12 mcg BID and 24 mcg BID) were chosen for further study and analysis in this study in the paediatric population ≥6 years and <18 years of age.

A placebo control group was used in this study because PFC is not a life-threatening condition; accordingly, this period without treatment did not have the potential to place a subject at undue risk of harm. In addition, no other pharmacological treatment is formally approved for PFC treatment as a result of a thorough clinical development program; as such there is no established assay sensitivity for any potential active control to which lubiprostone could have been compared with

according to ICH E10. Finally, during the study, if a subject had a significant need for constipation relief, protocol-defined rescue medication was permitted at the discretion of the Investigator.

In order to reduce the potential burden and stress of participation in this placebo-controlled study, the design allowed for dose escalation for subjects who may have benefitted from a higher dose of study medication. Accordingly, subjects originally assigned to the lubiprostone 12 mcg BID group had a dose escalation to 24 mcg BID at Visit 3 (Week 1) when protocol-defined criteria were met (see Section 9.1).

A schematic representation of the study design is provided in Figure 1 and a schedule of study assessments is presented in Table 1.

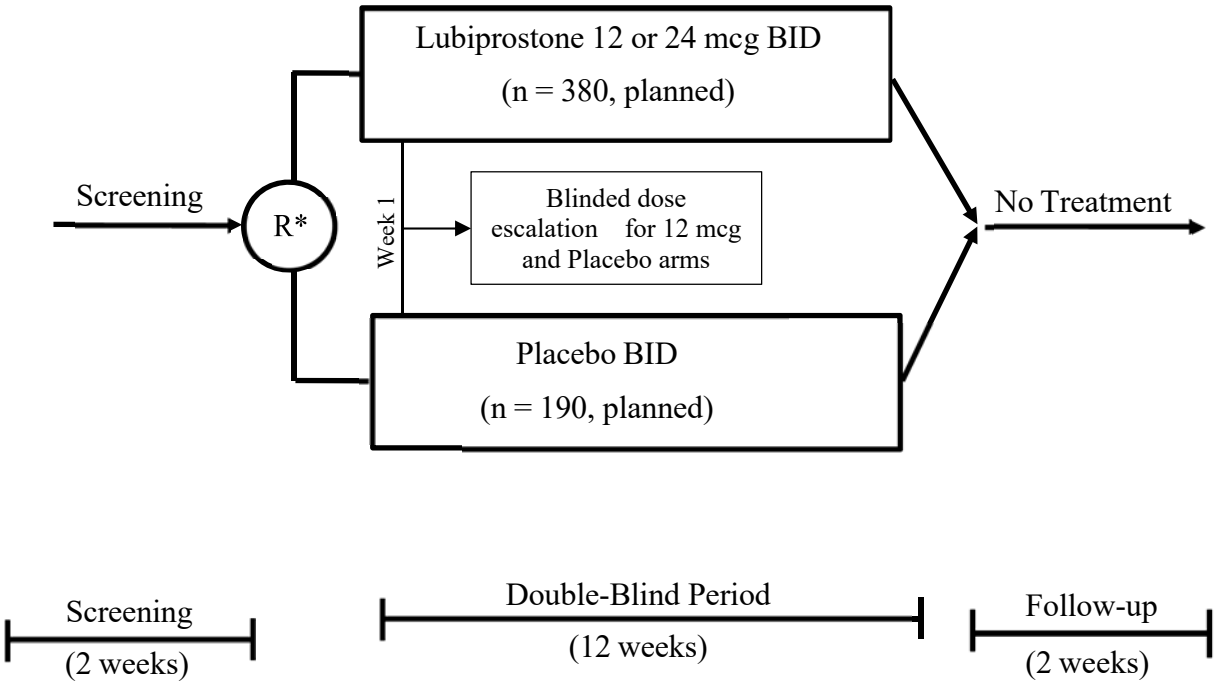

Figure 1. Schematic of the Study Design

Table 1. Schedule of Evaluations

Study Stage	Screen	Rand	Study Treatment and Evaluation (Days 1 to 85)					Follow-up
Study Week	-2	0	1	2	4	8	12	14
Study Day	-14 (-4)	1	8 (±2)	15 (±2)	29 (±3)	57 (±3)	85 (+3)	99 (+3)
Visit Number	1	2	3[a]	4	5	6	7[o]	8[p]
Assessment								
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Demographics	X							
Medical History	X	X						
Vital Signs, Height, Weight[b]	X	X	X		X	X	X	
Physical Exam	X		X[c]		X[c]	X[c]	X	
PK Sampling[d]		X			X			
Blood Chemistry, Haematology, Urinalysis	X		X		X	X[e]	X	
Vitamin D Collection[f]	X							
Pregnancy Test[g]	X	X	X		X	X	X	
Concomitant Meds[h]	X	X	X	X	X	X	X	X
Adverse Events[i]	X	X	X	X	X	X	X	X
BMD & BMC Assess	X[j]						X[k]	
Study Med Distribution[l]		X	X		X	X		
QoL Assessment[m]	X	X			X	X	X	
Study Treatment		X	X	X	X	X	X	
Study Med Collection			X		X	X	X	
Investigator Assessment of Efficacy					X	X	X	
Electronic Diary[n]	X	X	X	X	X	X	X	
PGIC Assessment[q]		X			X	X	X	
Clinician Severity Rating[r]		X			X	X	X	

AE=adverse event; BID=twice daily; BMC=bone mineral content; BMD=bone mineral density; BP=blood pressure; DXA=dual energy x-ray absorptiometry; PFC=paediatric functional constipation; HR=heart rate; PGIC=Patient Global Impression of Change; PK=pharmacokinetic; RTSM=Randomisation and Trial Supply Management; SBM=spontaneous bowel movement; UK=United Kingdom.

a Subjects originally assigned to lubiprostone 12 mcg BID group: dose was increased to 24 mcg BID at Visit 3 (Study Week 1) based upon review of diary-reported efficacy and safety/tolerability, during the first week of treatment. Dose was to be increased in subjects without any ongoing AEs that were assessed by the Investigator as related to study treatment at the time of Visit 3 who have reported <3 SBMs during the first week of study treatment (up to Day 7) or at the time of Visit 3, whichever came first. These parameters were to be recorded in source documents and approval from Investigator was to be obtained prior to dose escalation. Any deviations from the dose escalation criteria were to be discussed in advance with the medical monitor. Dose escalation was designated using the RTSM system in order to maintain blinding;

b Predose vital signs were measured at Visit 2, as well as measurement of HR and BP, 1 hour after first dose of study medication. If changes in BP and/or HR were confirmed to be clinically significantly (as defined in Protocol Section 6.3) at the 1 hour postdose measurement relative to predose, additional measurements were to be taken again at 2 hours and 3 hours postdose. Subjects were asked to remain seated for at least 5 minutes prior to measurement of vital sign parameters. A wall-mounted stadiometer, where available, was to be used for measurement of height. Vital sign assessments were performed prior to PK sampling when these assessments were to be collected at the same visit. The time of all vital sign measurements was to be entered into the source documents. Age-appropriate equipment (e.g., blood pressure cuffs) were to be used for all assessments;

c Abbreviated physical examinations were performed at designated visits;

d PK samples were collected predose and 1 sample was collected between 30 and 90 minutes after dose administration (2 samples total) at Visit 2. A single sample was also collected within approximately 2 to 6 hours after dose administration during Visit 5. Subjects (and parts/legal guardian, depending upon age) were to be instructed to administer the pre-visit dose approximately 2 to 6 hours prior to Visit 5. PK samples were drawn in non-fasting condition. The samples were collected by direct venepuncture. Approximately 8 mL of blood was drawn for each sample; the total of all PK samples was not to exceed 50 mL or 5 mL/kg of body weight;

e Samples were only collected if there was a need for follow-up based on Visit 5 assessments;

f Blood was drawn for serum 25(OH) vitamin D analysis for all subjects who were 6 to 9 years or 14 to 17 years of age at time of signing informed consent;

g Serum pregnancy test were performed for females of childbearing potential at the Screening Visit. Urine pregnancy tests were performed at all other study visits;

h History of medications used within 30 days of the Screening Visit and a full history of all constipation treatment were collected, as well as a history of previously failed constipation treatments;

i AEs were recorded from the time of informed consent/assent. AEs that occurred prior to first dose of study drug were considered non-treatment-emergent.

j BMD and BMC measurement using DXA were performed at Screening in all subjects aged 6 to 9 and 14 to 17 years of age (at the time of signing informed consent) and who met the additional DXA evaluation sub-study eligibility criteria.

k DXA scan, only for those subjects who met criteria for inclusion in the DXA evaluation subgroup. All subjects in the DXA evaluation subgroup who withdrew from the study at or after Visit 6 (Week 8) were encouraged to have a final DXA assessment performed;

l The subject (and parent/legal guardian, depending upon age) was observed as he/she administered the first dose of study medication while in the clinic at Visit 2. Over the next 1 hour, the subject was monitored subject for any adverse reactions. One bottle of study medication was provided at Visit 2, one bottle at Visit 3, one bottle at Visit 5, and one bottle at Visit 6. Subjects were to return the used bottle of study medication at each clinic visit for collection by site personnel for drug accountability. If the study medication bottle was not returned, the bottle of all unused study medication was to be returned to the site at the subsequent office visit. The subject was instructed to take the study medication only from the newly dispensed bottle. The last dose of study medication in this Study SAG/0211PFC-1131 was to be taken the evening before Visit 7;

m Questionnaire was to be completed by subject (and parent/legal guardian, depending upon age) prior to conducting other visit procedures. The screening assessment was considered baseline for the overall study analysis. The assessment on Day 1 was considered baseline for the psychometric evaluation of functional constipation;

n Electronic diaries were to be distributed to parents/legal guardians at the Screening Visit;

o If a subject was eligible and chose to participate in the long-term safety study (Protocol SAG/0211PFC-11S1), this was to be the last visit prior to entry into the safety study and served as the baseline visit for that study; at that time, the first dose of study medication would be administered;

p At the discretion of the Investigator, this visit could have been conducted either in person or by telephone. However, if there were ongoing AEs at the end-of-treatment visit, the subject was to have a clinic visit for follow-up. The following assessments may have been performed: vital signs including weight and height (subjects should have been asked to remain seated for at least 5 minutes prior to measurement of vital sign parameters); abbreviated physical examination; and collection of samples for clinical laboratory analysis. A clinic visit was recommended if any of the following criteria was met: an ongoing AE at the time of or since the previous visit; abnormal clinical laboratory, vital sign, or physical examination results, which should have been further assessed at the Investigator's discretion;

q PGIC was assessed as part of the psychometric evaluation of PFC in English-speaking countries (North America, UK) at Visits 2, 5, 6, and 7. A modified question specifically for the subject (and parent/legal guardian, depending upon age) was also to be assessed at these visits;

r Clinician Severity Rating was assessed as part of the psychometric evaluation of PFC in English-speaking countries (North America, UK) at Visits 2, 5, 6, and 7.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

Subjects who met all the following entry criteria were randomised to the study:

1. Written informed consent was obtained from subject (and parent/legal guardian, depending upon age).
2. Subject was ≥6 years of age and <18 years of age at the time of randomisation.
3. Subject was capable of and willing to swallow capsules.
4. Subject fulfilled the modified Rome III Diagnostic Criteria for Childhood Functional Constipation (Child/Adolescent; Section H3a) as follows:

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

   - Two or fewer defecations in the toilet per week

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

*Criteria fulfilled at least once per week for at least 2 months prior to diagnosis.

5. If subject was taking a concomitant medication (prescribed or over-the-counter) that affects gastrointestinal (GI) motility, he/she was to discontinue use at the time of the Screening Visit (Visit 1); these medications include:
   a. Cholinesterase inhibitors; anti-spasmodic, anti-diarrhoeal, anti-constipation, or prokinetic agents; laxative agents (e.g., PEG 3350), including homeopathic remedies;
   b. Tricyclic antidepressants; and/or
   c. Any medication, at the discretion of the Investigator, known to relieve or cause constipation or constipation-related symptoms, and which the Investigator, based on the medical history of the subject, suspected to be a contributing factor to the subject's chronic constipation, or may otherwise confound the evaluation of treatment response.

   Exceptions: Treatment with anticholinergic agents, SSRIs, SNRIs, or MAO inhibitors was allowed if a stable dose had been used for at least 30 days prior to the Screening Visit and was not likely to change during the study.
6. Subject (and parent/legal guardian, depending upon age) must be willing and able to use or administer recommended (rectal and/or oral) rescue medications, if needed.
7. If subject was taking a fibre supplement (e.g., Metamucil®, PerDiem®, Fybogel), usage must have been at a stable dose and scheduled for at least 30 days prior to the Screening Visit (Visit 1) and not likely to change during the study.
8. Subject (and parent/legal guardian, depending upon age) must have been willing and able to fill out his/her own diary.
9. Subject daily diary was at least 70% compliant for evening/end-of-day assessments during the Screening period.
10. Subject daily diary indicated an average of <3 SBMs per week during the Screening period.
11. Subject had ≥1 of the following for ≥25% of SBMs during each week of the screening period (as reported in the daily diary):
    - Modified Bristol Stool Scale Type 1 or 2; and/or
    - Some straining to extreme straining associated with SBMs.

    Note: Subjects who had no reported SBMs during the Screening Period did not have to meet criteria for BM characteristics, e.g., hard or very hard stools.

9.3.2 Exclusion Criteria

Subjects who met any of the following criteria were excluded from participating in the study:

1. Subject's constipation was known to be attributed to any of the following:
   a. Physical/Mental/Cognitive – any condition, other than constipation, that in the Investigator's opinion would have interfered with meaningful study participation or evaluation.
   b. Anatomic – associated with a mechanical bowel obstruction (tumour, hernia, obstructive polyps, etc.), or pseudo-obstruction.
   c. Neurological – associated with spinal cord disorder, congenital disorder, or Guillain-Barre syndrome.
   d. Endocrine/Metabolic – associated with hypothyroidism, diabetes, hypercalcaemia, or hypokalaemia.
   e. Inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, celiac disease).
   f. Medication – associated with the use of medication known to cause constipation.
2. Subject was a candidate for, or had undergone abdominal surgery including bowel resection, colectomy, gastric bypass surgery (exceptions: appendectomy, cholecystectomy, benign polypectomy and inguinal hernia).
3. Subject had any GI condition, other than constipation, affecting GI motility or defecation.
4. Subject had Hirschsprung's disease.
5. Subject reported episodes of faecal incontinence that were not associated with retention of stool (e.g., non-retentive faecal incontinence, as defined by the Rome III Diagnostic Criteria).
6. Subject had current evidence of untreated faecal impaction at the time of screening.
7. Subject had experienced an unexplained significant weight loss.
8. Subject had a medical/surgical condition that might have interfered with absorption, distribution, metabolism, or excretion of the study medication.
9. Subject had an uncontrolled cardiovascular, liver, or lung disease, neurologic or psychiatric disorder, or other systemic disease the Investigator felt was clinically significant and would have limited the subject's ability to participate in the trial.
10. Subject was currently using an indwelling peritoneal catheter.
11. Subject had impaired renal function identified at the Screening Visit (i.e., serum creatinine concentration >1.5 times the median of normal range).
12. Subject had abnormal laboratory test (haematology, urinalysis, or blood chemistry), that in the Investigator's opinion was clinically significant, unexplained, and would have limited the subject's ability to participate in the trial.
13. Subject had current evidence of, or had been treated for, cancer within the past 5 years.

14. Subject (female of childbearing potential) had a positive pregnancy test, refused/unwilling to have pregnancy testing, and/or did not agree to use protocol-specified contraceptive measures for the duration of the study.
15. Subject (and parent/legal guardian, depending upon age) demonstrated a potential for non-compliance with study protocol (i.e., dosing schedule, visit schedule, diary completion, or study procedures).
16. Subject had received an investigational medication within 30 days prior to the Screening Visit (Visit 1), or planned to participate in another clinical trial during the study period.
17. Subject had received AMITIZA, lubiprostone, SPI-0211, or RU-0211 at any time prior to participation in this study.

9.3.3 Additional Eligibility Criteria for Dual-energy X-ray Absorptiometry Evaluation Subgroup (Subjects 6 to 9 and 14 to 17 Years of Age)

9.3.3.1 Dual-energy X-ray Absorptiometry Evaluation, Subgroup Inclusion Criteria

Subjects who met any of the following criteria were included from the DXA Evaluation Subgroup:

1. Subject was 6- 9 years or 14- 17 years of age at time of signing informed consent.
2. Subject had a BMD Z-score (normalised for age and gender) > -2.0, as assessed by DXA at screening.

9.3.3.2 Dual-energy X-ray Absorptiometry Evaluation Subgroup Exclusion Criteria

Subjects who met all the following entry criteria were excluded in the DXA Evaluation Subgroup:

1. Subject had serum 25(OH) vitamin D level <20 ng/mL at screening.
2. Subject had a history of bone disorders (e.g., rickets, osteogenesis imperfecta, rheumatoid arthritis, severe scoliosis), back surgery/injuries, endocrine disorders, anorexia nervosa, and/or use of anticonvulsants, bisphosphonates, or Depo-Provera.
3. Subject had a history of chronic use of inhaled/oral corticosteroids within 6 months prior to the Screening Visit (Visit 1), or planned to initiate use of inhaled/oral corticosteroids at any point during the study.

9.3.4 Escalation of Study Medication Dose

Subjects originally assigned to the lubiprostone 12 mcg BID group had their dose increased to 24 mcg BID at Visit 3 (Study Week 1) based upon review of diary-reported efficacy, as well as safety/tolerability, during the first week of treatment. The dose was to be increased in subjects who had no ongoing AEs assessed by the Investigator as related to study treatment at the time of Visit 3 and who reported <3 SBMs during the first week of study treatment (up to Day 7) or at the time Visit 3 occurred, whichever came first. Any deviations from the dose escalation criteria were to have been discussed in advance with the study medical monitor. The decision concerning dose-escalation was made at the Investigator's discretion for subjects who enrolled in the study under Protocol Amendment version 6.0 or earlier; subjects who enrolled in the study according to Protocol

Amendment version 7.0 were to be titrated if they met the following dose escalation criteria: no ongoing AEs assessed by the Investigator as related to study treatment at Visit 3; have reported <3 SBMs during the first week of study treatment (up to Day 7) or at the time of Visit 3, whichever occurred first.

The dose escalation procedure was accomplished through the Randomisation and Trial Supply Management (RTSM) system in order to maintain blinding.

The above described parameters were to be recorded in the source documents and approval from the Investigator had to be obtained prior to dose escalation. Any deviations from dose escalation criteria were to be discussed in advance with the medical monitor. Dose escalation was designated using the Randomisation and Trial Supply Management (RTSM) system in order to maintain blinding. The same supply and dosing strategy described in Protocol Section 5.5 continued to be used in the event of dose escalation.

9.3.5 Reduction of Study Medication Dose

A dose reduction may have been initiated by the Investigator if one of the following conditions was reported to site personnel by a subject and had been ongoing for ≥3 days:

- **Nausea –** If a subject was experiencing severe nausea, at the discretion of the Investigator and in consultation with the subject or parent/legal guardian, the study medication may have been reduced to one dose daily (QD).
- **Diarrhoea –** If a subject was experiencing severe diarrhoea, at the discretion of the Investigator and in consultation with the subject or parent/legal guardian, the study medication may have been reduced to QD.
- **Other –** If a subject was experiencing some other type of AE, at the discretion of the Investigator and with approval of the medical monitor, the study medication may have been reduced to QD.

After an AE was reported by a subject, site personnel were to follow the subject for any change in the nature of the event. If the event had not resolved after 3 days, a reduction in dose to QD may have been initiated by eliminating the morning dose of study medication; therefore, the evening dose was the only one taken, once daily. After a dose reduction occurred, the subject may have resumed taking the BID dose regimen at the Investigator's discretion.

Note: At each visit, Investigators were to assess the need for reduction of study medication.

9.3.6 Removal of Subjects from Therapy

A subject was considered to have completed the study after receiving 12 weeks of double-blind treatment and after completion of the Week 12 visit procedures.

Subjects were 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 have withdrawn a subject at any time in the interest of subject safety. The primary reason for withdrawal was to be recorded in the subject's medical record and on the withdrawal form in the eCRF.

Subject participation may have been terminated by the Investigator or Sponsor 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 withdrew from the study early or who were terminated from the study were encouraged to complete the final visit of the treatment period (Visit 7) and the Follow-up Visit (Visit 8) as shown in Table 1.

If a subject withdrew prior to completing the study, the reason for withdrawal was to be documented in the source documents and on the appropriate eCRF page. If the action taken with study medication was listed as permanently withdrawn due to an AE, the reason selected for withdrawal in the eCRF must have been "AE" (i.e., Investigator decision or other category should not have been selected in such cases).

The date of the last dose of medication and all observations collected until the time of withdrawal were to be recorded on the CRF along with the reason for withdrawal.

Any clinically significant abnormal laboratory values or other abnormalities were to be followed by appropriate tests and/or procedures until these values returned to normal or to clinically acceptable levels or could have been attributed to causes other than the study drug.

Attempts were to be made to locate subjects who were lost to follow-up so that as much study information as possible may have been obtained. Every effort was to be made to retrieve dispensed study medication, electronic diaries, and to obtain the general overall status of the subject at the time of withdrawal from the study. The subject's source documents should verify that ≥2 attempts had been made by telephone to locate the subject, and that a final attempt to locate the subject had been made by certified or traceable mail.

9.4 Treatments

9.4.1 Treatments Administered

After eligibility was confirmed and baseline evaluations were completed, subjects were randomised to receive their first dose of study medication of either lubiprostone (12 mcg or 24 mcg BID) or placebo (BID) in a 2:1 ratio:

- Treatment A: Lubiprostone 12 mcg BID or 24 mcg BID (initial dose assignment based on weight); 12 weeks

- Treatment B: Placebo BID; 12 weeks

Randomisation was stratified by age (6 to 9, 10 to 13, and 14 to 17 years of age) and baseline SBM frequency (<1.5 or ≥1.5). Each investigational site randomised subjects to treatment groups using a randomisation code and stratification scheme generated by the RTSM system.

Most study personnel remained blinded until the clinical database was locked. To allow for the execution of clinical trial - related services, the following individuals were 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 PK analyst
- Sponsor Drug Supply Management representative

Emergency unblinding of a subject's assigned treatment by the Investigator is addressed in Protocol Section 4.7.

9.4.2 Identity of Investigational Product

Sucampo AG provided lubiprostone 12 and 24 mcg capsules, as well as matching placebo capsules.

9.4.3 Method of Assigning Subjects to Dosing Groups

Subjects were initially randomised 2:1 to the following treatment arms:

- lubiprostone 12 or 24 mcg BID
- placebo BID.

Subjects were then stratified by age (6 to 9 years, 10 to 13 years, and 14 to <18 years), gender, and baseline SBM frequency (<1.5 or ≥1.5).

Treatment allocation (lubiprostone BID or placebo BID) rather than dose group (12 or 24 mcg) was blinded during this study. Those subjects who weighed <50 kg were given lubiprostone 12 mcg BID; those who weighed ≥50 kg received 24 mcg BID.

A detailed description of the randomisation method is provided in Appendix 16.1.7. Included in this appendix are the randomisation drug codes, subject identifiers, and treatment assigned. Because this was a multicentre study, the information was provided by site. At each investigational site, subjects were randomised to treatment groups using a randomisation code and stratification.

9.4.4 Selection of Doses in the Study

The lubiprostone doses scheduled for evaluation, 12 mcg BID and 24 mcg BID, were selected after consideration of results from nonclinical pharmacology, toxicology, and PK studies of lubiprostone and after review of clinical data from many studies conducted in adults with CIC[18] and a study conducted in children with PFC.[19]

Subjects originally assigned to the lubiprostone 12 mcg BID group who did not have an ongoing AE assessed by the Investigator as related to study treatment had a dose increase to 24 mcg BID at Visit 3 (Study Week 1) if they reported <3 SBMs during the first week of study treatment (up to Day 7) or at the time of Visit 3, whichever occurred first. This was based upon review of diary-reported efficacy and safety/tolerability report. See Section 9.3.4 for further details.

9.4.5 Selection and Timing of Dose for Each Subject

Following randomisation, each subject was allocated to treatment with either lubiprostone BID (12 mcg or 24 mcg) or placebo BID. The dose of lubiprostone was determined by weight: those who weighed <50 kg were given lubiprostone 12 mcg BID; those who weighed ≥50 kg received 24 mcg BID.

Lubiprostone (and matching placebo) was to be taken BID on each treatment day (one dose in the morning and one dose in the evening, ≥5 hours apart) and was provided as soft gelatin capsules to be swallowed whole (not chewed or broken apart) with meals and ≥8 ounces of fluid.

9.4.6 Blinding

To maintain the blind, study medication bottles were labeled with directions for use and all identifying information, except the identity of the drug. Study medications (lubiprostone and placebo) were identical in appearance and packaged in identical containers.

9.4.7 Prior and Concomitant Therapy

9.4.7.1 Prior Medication

A summary of prior medications discontinued prior to the first dose of study medication is provided for constipation and GI-related medications in Table 14.1.6.2.

9.4.7.2 Concomitant Medication

Concomitant medications, ongoing at the start of or started after the first dose of study medication, were reported using the World Health Organization Drug Dictionary (WHO-DD) and are presented by Anatomic-Therapeutic-Chemical (ATC) Class and generic name in Table 14.1.6.1.

The use of a daily fibre supplement was permitted if the schedule of use and dose had been stable for at least 30 days prior to the Screening Visit. The schedule of use and dose of the daily fibre supplement was not to change during the course of the study. Any fibre supplement used was to be documented as a concomitant medication.

9.4.7.3 Excluded Medication

The following medications were to be excluded during the course of the study and were to be discontinued from the Screening Visit through study completion:

- Anti-spasmodics,
- Cholinesterase inhibitors,
- Anti-diarrhoeal medications,
- Anti-constipation medications (Linzess™/Constella™, Relistor®, or Resolor®);
- Prokinetic agents
- Laxative agents (e.g., polyethylene glycol [PEG] 3350), including homeopathic remedies
- Tricyclic antidepressants, and/or
- Any medications, at the discretion of the Investigator, known to relieve or cause constipation or constipation symptoms, and based on the medical history of the subject, the Investigator suspected to be a contributing factor to the subject's chronic constipation, or may have otherwise confound the evaluation of treatment response.

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

These medications were to be documented as concomitant medications. The Sponsor (medical monitor) was to be notified in advance (or as soon as possible thereafter) of any instances when prohibited therapies were taken. Continued participation of the subject was to be at the discretion of the Sponsor.

9.4.7.4 Rescue Medication

If necessary, rescue medication may have been used to help induce a BM. Each subject (and parent/legal guardian, depending upon age) was to be educated about protocol-specified use of rescue medications at the Screening Visit (Visit 1) and throughout the study.

If no BM occurred within a 3-day period, the use of rescue medications was permitted, as shown in Protocol Section 5.7.3.

A summary of rescue medication used is provided for the SAF Population in Table 14.1.6.3.

9.4.8 Treatment Compliance

Site personnel maintained a drug-dispensing log that included subject identification information, dates drug was dispensed, and dates drug was returned. At the final monitoring visits, all study drug was accounted for and all unused study drug was returned to the Sponsor. The drug inventory was stored in a secured area and made available upon request for inspection by a Sponsor representative.

9.5 Efficacy and Safety Measurements

9.5.1 Efficacy and Safety Measures Assessed

A schedule of all efficacy and safety measurements is provided in the Schedule of Evaluations, Table 1.

9.5.2 Appropriateness of Measurements

All safety and efficacy measurements used in this study were considered standard and reliable for the assessment of bowel and abdominal symptoms, including constipation-related symptoms.

9.5.3 Efficacy Measurements

9.5.3.1 Primary Efficacy Variables/Measurements

The primary efficacy variable was:

- Overall SBM response rate
    - The CMH test stratified by baseline SBM frequency (<1.5 or ≥1.5) was used for the comparison between the total lubiprostone group and the placebo group. To determine response rates treatment differences and 95% confidence intervals (CIs) between the lubiprostone total group and placebo were calculated.

9.5.3.2 Secondary Efficacy Variables/Measurements

- Changes from Baseline in Bowel Movement and Spontaneous Bowel Movement Frequency
    - The overall changes from baseline in BM and SBM frequency over the entire 12-week treatment period was determined in addition to determinations of changes from baseline in BM & SBM frequency at each treatment week and at Months 1, 2, and 3, using the van Elteren test stratified by baseline frequency (<1.5 or ≥1.5).
- Monthly SBM Response Rates
    - Analysed using the CMH test stratified by baseline SBM frequency (<1.5 or ≥1.5).
- Time to first SBM
    - The first SBM was documented in the subject's daily diary. Time was computed from the time of first dose to the time of first SBM, in hours. It was calculated as (time of the first SBM – time of the first study medication).
- Number (percent) of subjects with a first SBM within 4, 8, 12, 24, and 48 hours of first study medication dose administration.
    - The percentage of subjects in each treatment group with their first SBM reported within 4, 8, 12, 24, and 48 hours of first dose administration was obtained from the Kaplan-Meier (K-M) life table estimates. The treatment groups were compared using the likelihood-ratio chi-square test.
- Treatment Response

  - The number (percent) of subjects who remained on treatment for at least 4 weeks, did not drop out due to lack of efficacy, and reported ≥ 1 or more SBMs over baseline and ≥ 3 weekly SBMs for 75% of observed treatment weeks overall and for at least 3 of the 4 final weeks of treatment was determined. The statistical method used was the same as for the primary variable.

- Changes from baseline in incontinence frequency
  - The number of incontinence episodes at baseline, weekly, and Months 1, 2, and 3. This was for the subgroup of subjects who reported ≥1 incontinence episode during the baseline period was determined.
- Changes from baseline in production of large diameter stool frequency
  - The number of large diameter stools produced at baseline, weekly, and Months 1, 2, and 3 was determined.
- Painfulness of SBMs
  - Visit values and changes from baseline in painfulness of SBMs were analysed overall, at each treatment week, and each treatment month, applying scores of 0 to 4 (not at all to extremely).
- Proportion of BMs and SBMs in toilet
  - Changes from baseline in the proportion of BMs and SBMs in the toilet were analysed overall, at each treatment week, and at Months 1, 2, and 3.
- Frequency of retentive posturing or excessive volitional stool retention
  - This frequency was analysed overall, at each treatment week, and at Months 1, 2, and 3.
- Changes from baseline in constipation signs and symptoms
  - Mean change from baseline was analysed overall, at each treatment week, and at Months 1, 2, and 3; for the following:
    - Straining associated with SBMs rated 0 to 4 (not at all to extremely, respectively),
    - Stool consistency of SBMs using Modified Bristol Stool Form Scale (5-point scale); the van Elteren test was used for assessment of change from baseline stratified by pooled sites,
    - Abdominal pain, rated 0 to 4 (none to very severe, respectively);
    - Constipation severity, rated 0 to 4 (none to very severe, respectively);
  - Month 1 started with the daily assessment on Day 1 and ended with the daily assessment on Day 29 (Week 4); Month 2 started with the daily assessment on Day 30 and ended with the daily assessment on Day 57 (Week 8); and Month 3 started with the daily assessment on Day 58 and ended with the daily assessment on Day 85 (Week 12). Each week was defined by 168-hour intervals beginning with the day of the first dose of study medication (Day 1). The van Elteren test was used for change from baseline assessments, stratified by pooled sites.

- Treatment effectiveness
    - Collected from the diary and analysed weekly, monthly, and overall using a scale from 1 to 4 (not at all effective to extremely effective, respectively). The van Elteren test was used for change from baseline assessment, stratified by pooled sites.
- Investigator Assessments of Treatment Effectiveness
    - Rated 0 to 4 (not at all effective to extremely effective, respectively) and analysed overall and at Weeks 4, 8, and 12; the van Elteren test stratified by pool sites was used for treatment comparisons.
- Number of faecal impactions weekly and monthly was captured.
- Overall health-related quality of life, measured using the PedsQL™ questionnaire.
    - Four subscales measured physical functioning, emotional functioning, social functioning, and school functioning were used. Change from baseline to visits were assessed. Two summary scores (Psychosocial Health Summary Score and Physical Health Summary Score), and a total score were summarised.
- Patient Global Impression of Change (PGIC)
    - Measurements were done at Randomisation, at Weeks 4, 8, and 12 and overall for English-speaking subjects participating in North America and the UK; Analysis was done using a scale from 1 to 7 (very much improved to very much worse, respectively). The van Elteren test stratified by pooled sites was used for treatment comparisons.
- Clinician Severity Rating Scale
    - Measurements were done at Randomisation, at Weeks 4, 8, and 12 and overall, for English-speaking subjects participating in North America and the UK. Severity rating scales were analysed using a scale from 1 to 5 (absent to very severe, respectively).
- Rescue medication usage
    - Summarised in terms of the number and percent of subjects who used rescue medications and the percent of days that rescue medication was used. Summaries were based on the rescue medication information collected in the daily diary. Calculations were made for the baseline period and for monthly and overall.

9.5.4 Pharmacokinetic Measurements

Exploratory analysis and modeling activities were conducted to achieve the following:

- Explore the systemic exposure of lubiprostone and its metabolite, 15-hydroxy lubiprostone (M3) and determine an appropriate imputation;
- Perform dose response or exposure-response analysis for various efficacy endpoints; and
- Perform correlation analysis between exposure and incidence of TEAEs.

9.5.5 Safety Measurements

All safety variables were assessed for the two lubiprostone doses BID and for placebo BID.

9.5.5.1 Adverse Events

As defined in ICH GCP Guideline E6,[21] an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, disease, or exacerbation of a pre-existing condition temporarily associated with the use of a medicinal (investigational) product, whether or not it was considered related to the medicinal product. For this study, all safety information was collected from the time informed consent was signed and any untoward medical occurrence after screening was defined as an AE. Adverse events reported after initiation of study medication were defined as treatment-emergent AEs (TEAEs).

In this study, faecal impaction was captured as an AE. However, these events of faecal impaction were to be used for the efficacy analysis of faecal impaction frequency during the study (see Section 11.4.1.2.14).

In this study, analyses of TEAEs and TRAEs were performed for the following categories:

- Gender (male, female)
- Race (White, Black, All others)
- Age group (6 to 9, 10 to 13, and 14 to 17 years of age)
- SBM at Randomisation (<1.5, ≥1.5)
- Weight (<50 kg, ≥50 kg)
- BMI (<25, ≥25).

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

9.5.5.2 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening (i.e., subject was at risk of death at the time of the event. It did not refer to an event that hypothetically might have caused death if it were more severe);
- requires inpatient hospitalisation or prolongation of existing hospitalisation;
    - This criterion applied if the event required inpatient hospitalisation and resulted in an overnight stay in hospital or, in the opinion of the Investigator, the event prolonged an existing hospitalisation.
    - Hospitalisations for <24 hours with no admission are not considered “hospitalisation.”

- A hospitalisation (including hospitalisation for an elective procedure or routinely scheduled treatment or pre-planned procedures) for a pre-existing condition which had not worsened did not constitute an SAE.

- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is an important medical event (i.e., an event that may not have fit the other criteria for an SAE listed above but, based upon appropriate medical judgment, may have jeopardised the subject or may have required intervention to prevent one of the outcomes listed above). Examples of such events (per 21 CFR 312.32) are blood dyscrasias or convulsions that did not result in hospitalisation or development of drug dependency or drug abuse.

9.5.5.3 Non-serious Adverse Event

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

9.5.5.4 Severity

The severity of each AE was determined based on the following criteria:

- **Mild:** Transient symptoms, no interference with the subject's daily activities. 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; hospitalisation possible.

9.5.5.5 Relationship to Study Medication

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

- **Unrelated:** Concurrent illness, concurrent medication, or other known cause was clearly responsible for the AE; or, based upon available information regarding subject history, disease process, relationship of AE to dosing, and drug pharmacology, a relationship between the drug and the AE was unlikely;
- **Possible:** The AE followed a reasonable sequence from the time of study 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 made a relationship improbably (but not impossible). Disease or other drugs provided plausible explanations;
- **Probably:** The AE followed a reasonable sequence from the time of study drug administration, followed a known response pattern of the drug treatment class, was confirmed by improvement on stopping study drug; was the most likely of all causes.

Event with reasonable time relationship to drug intake:

- Unlikely to have been attributable to disease or other drugs,
- Response to withdrawal was clinically reasonable, or
- Rechallenge was not required.

- **Definite:** The AE followed a reasonable sequence from the time of study drug administration, followed a known response pattern of the drug treatment class, was confirmed by improvement on stopping study drug; and no other reasonable cause exists.

9.5.5.6 Onset and Duration

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

9.5.5.7 Recording and Reporting of Adverse Events

All AEs were to be recorded in the source document and applicable eCRF(s) from the time informed consent is signed until the end of study. AEs occurring prior to the first dose of study drug were considered non-treatment emergent. Any ongoing AEs were to be followed until they were resolved, stabilised, or until 30 days after the end of treatment exposure. The Investigator was to notify the Sponsor at any time when an SAE was 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) were to be recorded on source document, IRE Reporting Form, and applicable eCRF(s), then reported to the Sponsor or designee using the IRE Reporting Form, as specified in Protocol Section 7.2.1.

All AEs that had not resolved by the end of the study, or that had not resolved upon discontinuation of the subject's participation in the study, were followed until either:

- the event resolved;
- the event stabilised;
- the event returned to baseline, if a baseline value was available;
- the event could have been attributed to medication other than the study medication, or to other reasons than study conduct; or
- the Investigator did not anticipate any further improvement or worsening of the event.

All AEs, regardless of seriousness, severity or presumed relationship to study medication, were to be recorded using medical terminology in the source document and in the eCRF. Whenever possible, diagnoses were to be given when signs and symptoms were due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion were reported as "upper respiratory infection"). Investigators were to 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 were to be recorded in the source document and reported according to Sponsor instructions.

9.5.5.8 Reporting of Immediately Reported Events

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

- All Serious adverse events
- All pregnancies
- Events of Special Interest[1]
  - Hepatotoxicity
  - Anaphylaxis, including anaphylactoid reaction and anaphylactic shock

Immediately Reportable Events, such as SAEs, were to be recorded on the AE source document and eCRF. In addition, any IRE occurring during the clinical study had to be reported within 24 hours to the Sponsor or designee using the IRE Form or the Pregnancy Report Form. The initial report of an IRE was to be documented on the study IRE Form, signed by the Investigator, and submitted by facsimile. The Investigator had to 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 were to be followed immediately by a facsimile of the IRE form signed by the Investigator. Investigators were not to leave oral reports of IREs on any voicemail aside from the Sponsor's Medical Monitor or designee. Details of the AE reporting requirement were also outlined in a safety reporting plan.

The Sponsor assumed responsibility for reporting of expedited and periodic safety reports to the appropriate regulatory authorities. The Sponsor reported to the Investigators any new safety events occurring in other studies. The Investigator may have needed to report SAEs to the appropriate IRB/IEC in accordance with local regulations.

9.5.5.9 Reporting of Pregnancies

Any pregnancy occurring in a female subject after the first intake of study medication, while not an AE, was considered an IRE. It was to be reported within 24 hours of the Investigator learning of the event using an IRE Pregnancy Report Form. Any subject who became pregnant, was to 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 is to be collected to the extent possible.

[1] NOTE: The following events were removed from the list of immediately reportable "events of special interest", in accordance with FDA feedback on the topic, per administrative memorandums issued to investigative sites on 04FEB2016 and 05APR2016: chest pain/chest discomfort, dyspnea/shortness of breath/difficulty breathing, and liver enzyme increased.

9.5.5.10 Outcome

The Investigator was to 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 was expected. Loss to follow-up implied the Investigative site was no longer aware of the participant's whereabouts and was unable to obtain current contact information. All attempts to contact the participant were to be captured in the appropriate trial source document.

9.5.5.11 Symptoms of the Disease under Study

Symptoms of the disease under study were not to be classified as AEs provided they were 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.

9.5.6 Clinical Laboratory Measures

Change in the value of a laboratory test can represent an AE if the change is clinically relevant or if, during treatment with an investigational medication, a value shifts from normal to pathological or if there is worsening of an already pathological value. A determination was made by the Investigator, based on the subject's clinical condition, if a change in a laboratory value was clinically significant and was, therefore, an AE.

For continuous laboratory values, mean changes from pre-treatment to post-treatment visits were summarised using descriptive statistics. The treatment group differences for mean changes from baseline were analysed using a one-way analysis of variance (ANOVA) and presented the between group mean change from baseline with the 95% CI, standard error, and P-value.

Shift tables were provided for laboratory parameters with normal reference ranges and categorised as low, within, and above the reference normal ranges.

Blood samples for haematology and biochemistry and urine samples for urinalysis were collected as indicated in Table 1. The following laboratory parameters were monitored during the study:

- **Haematology:**

  Hemoglobin, hematocrit, red blood cell count, white blood cell absolute counts with differentials (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count, mean corpuscular volume, mean corpuscular hemoglobin concentration, and mean corpuscular hemoglobin.

- **Biochemistry:**

  Total cholesterol, triglycerides, glucose, total protein, albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, lactate dehydrogenase, total bilirubin, direct bilirubin, blood urea nitrogen, uric acid, creatinine, sodium, potassium, chloride, calcium, phosphorus, and magnesium.

- **Urinalysis:**

  Protein, glucose, ketones, occult blood, pH, specific gravity, and microscopic examination.

Laboratory assays were performed by an accredited central laboratory facility. Urine pregnancy tests were performed at the clinical sites. All results were reviewed by the Investigator to determine clinical significance. Any abnormalities persisting at the end of the study were followed until resolution, or until they reached a clinically stable endpoint per the Investigator's discretion.

9.5.7 Pregnancy Status

For female subjects of child-bearing potential, the following tests were performed to determine pregnancy status:

- Serum pregnancy test at Visit 1.
- Urine pregnancy test at Visits 2, 3, 5, 6, and 7.

Any pregnancy that occurred after the first dose of study medication, although not an AE, was to be considered an IRE. Using a Pregnancy Report Form, it was to be reported within 1 day after the Investigator gained knowledge of the event. Any subject who became pregnant was to be removed from the study and followed for the duration of the pregnancy. Follow-up information concerning outcome of the pregnancy and any postnatal sequelae in the infant were required to be reported.

9.5.7.1 Vital Signs and Physical Examination

Vital signs included height, weight, systolic and diastolic blood pressure, heart rate, respiration rate, Body Mass Index (BMI), and temperature. These were assessed at the time points shown in Table 1. Any new findings were reviewed by the Investigator to determine clinical significance; these were to be reported as AEs.

Changes in any aspect of physical examination were identified. Those determined to be abnormal were reviewed by the Investigator to determine clinical significance; these were to be reported as AEs.

9.5.7.2 Additional Assessments

Bone growth was assessed for a DXA subgroup who comprised subjects that were 6 to 9 years or 14 to 17 years of age.

The DXA evaluation subgroup included subjects who met the DXA eligibility criteria and for whom pre- and post-treatment DXA scans were performed for the following assessments:

- Percent changes from baseline in Bone Mineral Density (BMD) and Bone Mineral Content (BMC)
- Change from baseline in BMD Z-scores
- Changes from baseline in height and weight Z-scores

Bone growth assessments were analysed by treatment groups. Treatment comparisons between the total lubiprostone group and the placebo group were performed using ANOVA and a 2-sided t-test at the 0.05 level of significance.

A blood sample was collected at screening from subjects who were 6 to 9 years or 14 to 17 years of age for serum (OH) vitamin D analysis.

Clinical fractures were captured as AEs.

The reliability, construct validity, ability to detect change, and clinically meaningful change of functional constipation measures was assessed. The dossier (Psychometric Validation of the Pediatric Functional Constipation Instruments) and the SAP (Measurement Properties Statistical Analysis Plan) provide details on the assessments.

9.6 Data Quality Assurance

To ensure the accuracy and reliability of data, qualified Investigators and appropriate study sites were chosen, protocol procedures were reviewed with the Investigator and associated personnel prior to the study, and periodic monitoring visits were made by the Sponsor or designee.

Compliance was achieved through a combination of study-specific audits of investigational sites and vendor audits at regular intervals of the Sponsor's systems for data handling, analysis, and reporting. Audit Certificates are provided in Appendix 16.1.8. eCRFs were reviewed for accuracy and completeness by the Sponsor or designee during on-site monitoring visits; any discrepancies were resolved with the Investigator or designees, as appropriate. The data were to be entered into the clinical study database and verified for accuracy and completeness. Source documents and drug accountability records were reviewed.

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

9.6.1 Data Collection and Monitoring

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

The eCRFs were 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, and were to always reflect the latest observations on the subjects participating in the study.

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

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

Dates of the monitoring visits were to be recorded by the monitor in a study site visit log kept at the site. The first post initiation monitoring visit was usually made as soon as possible after enrolment began. At these visits, the monitor compared the data entered into the eCRFs with the hospital or clinic records (source documents). Source documentation was to 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 were to be reviewed with the Investigator prior to the study. Findings from this review of eCRFs and source documents were to be discussed with the Investigator. The Sponsor expected that during monitoring visits, the Investigator and study coordinator would be available, the original source documentation, regardless of media, would be available, and a suitable environment would be provided for review of study-related documents.

9.7 Statistical Methods Planned and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

Statistical analyses were performed for the core study and descriptions are provided in detail in the SAP, which was finalised prior to locking and unblinding of the database.

Analyses were performed for the following subgroups:

- The primary efficacy objective; percentage of 12-week overall responders at baseline for the following categories:
  - Gender (male, female)
  - Race (White, Black, All others)
  - Age group (6 to 9, 10 to 13, and 14 to 17 years of age)
  - SBM at Randomisation (<1.5, ≥1.5)
  - Weight (<50 kg, ≥50 kg)
  - BMI (<25, ≥25)
- TEAEs and treatment-related AEs (TRAEs) for the following categories,
  - Gender (male, female)
  - Race (White, Black, All others)
  - Age group (6 to 9, 10 to 13, and 14 to 17 years of age)
  - SBM at Randomisation (<1.5, ≥1.5)
  - Weight (<50 kg, ≥50 kg)
  - BMI (<25, ≥25)
- Bone assessments among the DXA subgroup for the following categories:
  - Gender (male, female)
  - Race (White, Black, All others)
  - Age group (6 to 9 and 14 to 17 years of age)

9.7.1.1 Data Sets Analysed

The analysis populations used in this study were:

- The Modified Intent-to-treat (mITT) Population included all randomised subjects who took ≥1 dose of study medication and had ≥1 efficacy assessment. This population was used for all efficacy analyses, demographic and baseline characteristic data.
- The mITT1 Population is a pre-specified analysis population which consists of the mITT Population *excluding* subjects from Sites 1064 and 1082 because of serious compliance issues at those sites with potential data integrity issues. While the mITT1 population was a pre-specified analysis population as per the Statistical Analysis Plan, the mITT1 Population also represents the population for which post-hoc efficacy analyses described throughout this study report were conducted.
- The Intent-to-treat (ITT) Population included all randomised subjects and was used for supportive analyses.
- The Per Protocol (PP) Population included all randomised subjects who had no major protocol violations.
- The Completers (COMP) Population included all randomised subjects who completed ≥84 days of treatment and was used for supportive analyses.
- The Safety (SAF) Population included all randomised subjects who took ≥1 dose of double blind study medication. This population was used for all analyses of safety and for a supportive demographic summary.
- The Dose Escalation (DE) Population included all randomised subjects who had dose escalation at the end of Week 1. This population was used for supportive analyses of primary efficacy and for an additional summary of TEAEs and TRAEs in the safety analyses.
- The Dual Energy X-ray Absorptiometry (DXA) Population included all randomised subjects who were 6 to 9 years old or 14 to 17 years old and met the additional DXA evaluation sub-study entry criteria and remained eligible for the entire study with baseline and post-baseline DXA Scans. This population was used for the analysis of bone growth assessments.
- The mITT2 Population was defined post-hoc and refers to a subset of the mITT1 Population that were enrolled at North American investigative sites.
- The mITT3 Population was defined post-hoc and refers to a subset of the mITT1 Population that excludes subjects who demonstrated major non-compliance with protocol-defined rescue medication use. Major non-compliance was defined as use of rescue medications every 3 days regardless of occurrence of bowel movements in a given week for at least two independent study weeks.

9.7.1.2 Subject Disposition

The number of subjects was tabulated by region, country, investigator site, and overall for all randomised subjects. The ITT, mITT, PP, COMP, SAF, DE, and DXA Populations were

summarised by treatment group and overall. Subject disposition, including subjects randomised, subject treated, subjects who completed study, subjects discontinued from study, and reasons for premature discontinuation were summarised for each treatment group and overall.

The reason for discontinuation was summarised with number (percentages) for each discontinuation reason, which were summarised and recorded on the eCRF by the following categories:

- AE
- Lack of efficacy
- Subject choice
- Lost to Follow-up
- Non-Compliance with study drug
- Investigator decision
- Sponsor request; or
- Any other reason upon agreement between the Investigator and the Sponsor.

9.7.1.3 Protocol Violations

Subjects who had ≥1 major protocol violation were excluded from the PP Population. Examples of major protocol violations are poor overall compliance with study medication or taking medications excluded during the study.

9.7.1.4 Demographics and Baseline Characteristics

Subject demographic data was summarised by treatment group and overall with descriptive statistics. Summaries included mean, median, standard deviation (SD), minimum and maximum for continuous variables, and counts and percentages for each level of categorical variables (Tables 14.1.4.1–14.1.4.4 for the mITT Population; Tables 14.1.12.1–14.1.12.4 for the mITT1 Population).

Baseline disease status (Tables 14.1.5.1–14.1.5.2 for the mITT Population; Tables 14.1.13.1–14.1.13.2 for the mITT1 population) was 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 health-related QoL using the PedsQL™ questionnaires. These data were summarised with descriptive statistics. The PedsQL™ questionnaire has 4 subscales: physical functioning, emotional functioning, social functioning, and school functioning; in addition, two summary scores (Psychosocial Health Summary Score and Physical Health Summary Score), and a total score were summarised. Treatment comparisons were presented using T-test for continuous variables and Cochran Mantel Haenzel (CMH).

SBM frequency rate was calculated as 7 x number of SBMs/number of days observed.

Comparisons between total lubiprostone with placebo were performed using the following scores, instruments, and interpretations:

PGIC scores:

Response Choices	Very Much Improved	Much Improved	Minimally Improved	No Change	Minimally Worse	Much Worse	Very Much Worse
	1	2	3	4	5	6	7

PedsQL™ Questionnaires[22]:

Response Choices	Never	Almost Never	Sometimes	Often	Almost Always
Raw Scores	0	1	2	3	4

The modified 5-point Bristol Stool Scale[23] to describe stool consistency:

	Separate hard lumps, like nuts (hard to pass)	Sausage-shaped, but lumpy	Like a sausage or snake, smooth and soft	Fluffy pieces with ragged edges, a mushy stool	Watery, no solid pieces
Type	1	2	3	4	5

Bowel straining and painfulness of SBMs:

	Not at All	A Little	Some	Quite a Bit	Extremely
Scores	0	1	2	3	4

Constipation severity and abdominal pain:

	None	Mild	Moderate	Severe	Very Severe
Scores	0	1	2	3	4

Clinician Severity Rating Scale:

	Absent	Mild	Moderate	Severe	Very Severe
Scores	1	2	3	4	5

9.7.1.5 Extent of Exposure

Assessments of exposure to study medication were made based on eCRF and diary data. Results are summarised in Table 14.1.7 for the mITT Population and in Table 14.1.15 for the mITT1 Population.

In both the mITT and mITT1 Populations, there was negligible difference between the placebo BID and total lubiprostone BID groups in mean total exposure, mean total daily dose, compliance, and subjects who were ≥70% compliant.

The difference in measures of extent of exposure between the mITT and mITT1 Populations was minimal as well.

9.7.1.6 Analysis of Efficacy

9.7.1.6.1 General Inferential Principles

The following principles were applied for all inferential analyses of efficacy: all tests are two-tailed at a significance level of α=0.05.

9.7.1.6.2 Titrated Subjects

Details concerning the analysis and handling of data for titrated subjects were pre-specified in the SAP Sections 3.1.1, 3.1.2, 3.1.3, 3.1.6, and 3.3. For the mITT, ITT, COMP, and DE Population analyses, data for titrated subjects were analysed with the group to which they were assigned at the end of Week 1 for all efficacy and baseline analyses. For safety analyses, data was obtained from the group they were actually assigned to at randomisation. A separate analysis of the primary endpoint was also performed for those subjects who had dose escalation.

9.7.1.6.3 Missing Data

Details concerning handling of missing data are provided in SAP Section 3.3.4.

9.7.1.6.4 Multiplicity

Inferential tests for treatment comparisons of key secondary efficacy endpoints were performed in accordance with the closed testing procedure (CTP) principle to account for inflation of a type 1 error due to hypothesis testing of multiple key secondary endpoints, as described in SAP Section 3.3.7 for the CTP structure method.

9.7.1.6.5 Multicentre studies

Statistical analyses were based on data pooled across clinical sites in aggregate, retaining clinical site in the model. However, if the model did not converge using pooled sites, pooling by region may have be used instead. All sites were grouped into 2 regions: North America (NA) and European Union (EU). Sites in the US and Canada were grouped into the NA region and sites in Europe were grouped into the EU region, as shown in SAP Section 3.3.6.

9.7.1.7 Analysis of Safety

Safety analyses included reporting of AEs, physical examinations, bone growth assessments, laboratory, and vital sign measurements. Safety analyses were performed on the SAF Population, except for bone growth assessments which were performed on the DXA Population. Clinical fractures were captured as AEs and the incidence of clinical fractures was analysed by System Organ Class (SOC) and Preferred Term (PT).

For continuous bone growth assessments, laboratory parameters, vital signs data, and treatment group differences for mean changes from baseline were analysed using a one-way ANOVA with treatment as the main effect.

Fisher's exact test was used to analyse treatment group differences for qualitative categorical variables. Categorical data were summarised using frequencies and percentages. The number of non-missing values was provided.

Statistical inference was based on a 2-sided significance level of 0.05 when rounded to 3 decimal places. The last evaluation prior to the first dose of study medication was used as Baseline for all analyses, as shown in SAP Section 8.1.

9.7.2 Determination of Sample Size

The study design consisted of two doses of lubiprostone (12 or 24 mcg BID based on subject's weight) and placebo BID. Subjects were randomised in a 2:1 (lubiprostone to placebo) ratio, stratified by age at the time of randomisation (6 to 9, 10 to 13, and 14 to 17), gender, and baseline SBM frequency (<1.5 or ≥1.5).

Assuming overall response rates of 10% for placebo BID and 21% for lubiprostone BID, a 5% two-sided type I error rate, and an allocation ratio of 1:2 for placebo BID and lubiprostone BID, sample sizes of 304 subjects for lubiprostone BID and 152 for placebo BID would provide 86% power to detect a difference between the group proportions of 11%. The two-sided Z test was used with pooled variance. Assuming a 20% attrition rate, a total of 570 subjects (380 for lubiprostone BID and 190 for placebo BID) were to be enrolled to this study, as shown in SAP Section 2.4.

9.8 Changes in the Conduct of the Study or Planned Analysis

Changes in the conduct of the study and/or planned analyses instituted after the start of the study are provided in amendments and protocol versions.

The original study protocol SAG/0211PFC-1131, version 1.0 was dated 28 June 2013. The following amendments were made to the protocol:

- Amendment 1 (07 October 2013);
- Amendment 2 (26 November 2013);
- Amendment 3 (15 April 2014);
- Amendment 4 (14 April 2015);
- Amendment 5 (2 September 2015); and
- Amendment 6 (25 September 2015).

The original protocol, protocol amendments, and the protocols (Versions 2 through 7) revised to include the amendments, are provided in Appendix 16.1.1. In addition to minor word changes for clarity, typographical corrections, section renumbering, and updating of study personnel, the following major changes were made and reflected in Amendment 1:

- Update in Biostatistician and Medical Monitor personnel;
- Update in contact information for SAE reporting;
- Update to the eligibility criteria associated with bowel movement characteristics;
- Change in the primary endpoint to overall SBM response based on FDA's recommendation; and
- Addition of events of special interest (chest pain, dyspnea, hepatotoxicity/liver enzyme increased, anaphylaxis).

The following major change was made and reflected in Amendment 2:

- Clarification of contraception specifications.

The following major changes were made and reflected in Amendment 3:

- Added evaluation of measurement characteristics of the PFC clinical outcome measure assessments; and
- Clarified eligibility to DXA subgroup;

The following major changes were made and reflected in Amendment 4:

- Update to Medical Monitor personnel information in Europe; and
- Eligibility update to allow subjects with a concurrent diagnosis of IBS.

The following major change was made and reflected in Amendment 5:

- Eligibility update to exclude subjects with concurrent diagnosis of IBS.

The following major change was made and reflected in Amendment 6:

- Revision of dose escalation instructions to require dose escalation by Investigator for subjects who may benefit from a higher dose of study medication.

The original study SAP, version 1.0, was dated 02 December 2013. One updated version of the SAP (version 2.0; 11 August 2016) was also issued. The original SAP, changes to the SAP, and both versions are provided in Appendix 16.1.9. In addition to minor word changes for clarity, typographical corrections, section renumbering, and updating of study personnel, the following major changes were made:

- Added analyses for populations excluding Sites 1064 and 1082;
- Added additional summary of treatment-related AE analysis;
- Patient Global Impression of Change and Clinician Severity Rating Scales were added per the protocol Amendment 3; and
- Included additional secondary efficacy endpoints in the close testing procedure.

Following finalization of SAP version 2.0 and unblinding of the 1131 database, a number of post-hoc analyses were generated for the purposes of further characterizing the efficacy/treatment response profile of lubiprostone in subjects with PFC. These analyses (Tables 14.2.51.1.1 through 14.2.68.2), though not defined *a priori*, are included within this CSR, and are denoted as post-hoc in Section 14.2.

10. STUDY SUBJECTS

10.1 Disposition of Subjects

A total of 606 subjects were randomly assigned to study treatment in the mITT Population (Table 14.1.2): 202 to placebo BID, 233 to lubiprostone 12 mcg BID, and 171 to lubiprostone 24 mcg BID,

for a total of 404 lubiprostone subjects, approximately twice as many as placebo. There were 101 (16.7%) subjects who discontinued early and 505 (83.3%) subjects who completed the study.

In all treatment groups of the total population, the most common reasons for discontinuation were:

- Withdrawal by the subject: 16 (7.9%) subjects in the placebo BID group; 12 (5.2%) in the lubiprostone 12 mcg BID group; and 9 (5.3%) in the lubiprostone 24 mcg BID group, for a total of 37 (6.1%) subjects, followed by
- AE: 6 (3.0%) subjects in the placebo BID group; 9 (3.9%) in the lubiprostone 12 mcg BID group; and 8 (4.7%) in the lubiprostone 24 mcg BID group, for a total of 23 (3.8%) subjects.

A summary of subject disposition for the mITT Population is provided in Table 2 below. The mITT1 population, which excludes subjects enrolled at Sites 1064 and 1082 (see Table 14.1.10), comprises 22 fewer subjects than the mITT Population (Table 14.1.2); 194 subjects were assigned to placebo BID, 225 to lubiprostone 12 mcg BID, and 165 to lubiprostone 24 mcg BID, for a total of 390 lubiprostone subjects. Reasons for discontinuation from treatment in the mITT1 Population were the same as in the mITT Population and numerically very similar to the mITT population.

A summary of randomised subjects by centre for the mITT Population is provided in Table 14.1.1.1 and for the mITT1 Population in Table 14.1.9.1.

Table 2. Summary of Subject Disposition (All Randomised Subjects; mITT Population)

	Treatment Groups[a]				
Subjects	**Placebo BID N=202 n (%)**	**Lubiprostone 12 mcg BID N=233 n (%)**	**Lubiprostone 24 mcg BID N=171 n (%)**	**All Lubiprostone Groups Total N=404 n (%)**	**All Treatment Groups Total N=606 n (%)**
Subjects randomised	202 (100.0)	233 (100.0)	171 (100.0)	404 (100.0)	606 (100.0)
Subjects treated	195 (96.5)	231 (99.1)	169 (98.8)	400 (99.0)	595 (98.2)
Subjects completed	166 (82.25)	196 (84.1)	143 (83.6)	339 (83.9)	505 (83.3)
Subjects discontinued	36 (17.8)	37 (15.9)	28 (16.4)	65 (16.1)	101 (16.7)
Reason for discontinuation					
Adverse event	6 (3.0)	9 (3.9)	8 (4.7)	17 (4.2)	23 (3.8)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lack of efficacy	3 (1.5)	2 (0.9)	2 (1.2)	4 (1.0)	7 (1.2)
Lost to follow-up	2 (1.0)	5 (2.1)	4 (2.3)	9 (2.2)	11 (1.8)
Non-compliance with study drug	3 (1.5)	2 (0.9)	0 (0.0)	2 (0.5)	5 (0.8)
Investigator decision	2 (1.0)	4 (1.7)	3 (1.8)	7 (1.7)	9 (1.5)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study Terminated by Sponsor[b]	1 (0.5)	2 (0.9)	0 (0.0)	2 (0.5)	3 (0.5)
Withdrawal by subject	16 (7.9)	12 (5.2)	9 (5.3)	21 (5.2)	37 (6.1)
Other	3 (1.5)	1 (0.4)	2 (1.2)	3 (0.7)	6 (1.0)

BID=twice daily.
a. All subjects, including those whose dose was titrated at the end of Week 1, were summarised with the dose group to which they were assigned at randomisation.
b. This category includes subjects discontinued from the study upon closure of Sites 1064 and 1082 by the Sponsor.
Source: Table 14.1.2

10.2 Protocol Deviations

Prior to database lock, a blinded review of all data, including those subjects with documented protocol deviations, was conducted to determine which subjects had deviations that met violator criteria specified in SAP Section 3.1.3 for exclusion from the PP Population.

A subject may have had more than one protocol violation and may also have had the same protocol violation more than once.

In the mITT Population, there were 56 subjects in the placebo BID group, 28 in the lubiprostone 12 mcg BID group, and 79 in the lubiprostone 24 mcg BID group who met the criteria for exclusion from the PP Population, as shown in Table 14.1.3.1. A summary of protocol deviations by category is shown in Table 14.1.3.2 for the mITT Population. The most commonly reported deviations across all treatment groups in the mITT Population included out-of-window visits (55.8% of subjects) and issues with study procedures (42.1% of subjects).

The proportion of subjects who were deemed protocol violators by dose group and therefore were excluded from the PP Population was similar for the mITT1 Population. Protocol violation and deviation information are shown in Tables 14.1.11.1 and 14.1.11.2, respectively, for the mITT1 Population.

Individual by-subject listings of reported protocol deviations are shown in Listing 16.2.2.3.

11. EFFICACY EVALUATION

11.1 Data Sets Analysed

Throughout this Clinical Study Report (CSR), data are presented using two populations: the mITT and mITT1 Populations (i.e., the mITT Population excluding subjects from Sites 1064 and 1082; see Section 9.7.1.1 for further details). While the mITT Population represents the main population for efficacy evaluations discussed and presented as in-text tables, the mITT1 population is considered the most relevant population for analysis; accordingly, post-hoc analyses conducted and presented in this clinical study report are for the mITT1 population. Additionally, results are presented for both observed case and LOCF analyses for all pre-specified analyses.

For the mITT Population, distribution of all randomised subjects to the various analysis populations is provided in Table 14.1.1.2.; populations are further described in Section 9.7.1.1. For the mITT1 Population, this distribution is summarised in Table 14.1.9.2.

Information concerning individual subjects is provided in Listing 16.2.1.3.

In the population including subjects from Sites 1064 and 1082, randomised subjects were distributed to the treatment groups as shown in Table 3.

Table 3. Summary of Study Populations (All Randomised Subjects; mITT Population)

	Treatment Groups			
Population	Placebo BID (N)	Lubiprostone 12 mcg BID (N)	Lubiprostone 24 mcg BID (N)	All Treatment Groups Total (N)
ITT	202	233	171	606
mITT	195	231	168	594
PP	146	178	119	443
COMP	147	181	116	444
SAF	195	231	169	595
DE	0	0	124	124
DXA	60	75	44	179

BID=twice daily; COMP=Completers; DE=Dose Escalation; DXA=Dual-energy X-ray Absorptiometry; ITT=Intent-to-treat; mITT=modified Intent-to-treat; PP=Per Protocol; SAF=Safety.
Source: Table 14.1.1.2

11.2 Demographic and Other Baseline Characteristics

11.2.1 Subject Demographics

Demographics are summarised for the mITT Population in Table 14.1.4.1 and are presented in Table 4. Demographics for the mITT1 Population are summarised in Table 14.1.12.1. Demographics are provided for individual subjects in Listing 16.2.4.1.

In both treatment groups in the mITT and the mITT1 Populations, the majority of subjects were White and not Hispanic or Latino. The percentage of females and males, the percentages of subjects in each of the three age range groups, and the mean BMI in both treatment groups were all similar. The main exception was that the mITT Population had a larger proportion of subjects of Hispanic ethnicity vs. the mITT1 Population (20.2% vs. 17.3%, respectively).

Demographics for the complete SAF, PP, and DXA Populations are provided in Table 14.1.4.2, Table 14.1.4.3, and Table 14.1.4.4.

Demographics for the SAF, PP, and DXA Populations excluding Sites 1064 and 1082 are provided in Table 14.1.12.2, Table 14.1.12.3, and Table 14.1.12.4, respectively.

In the SAF and PP Populations, as in the mITT and mITT1 Populations, there were no meaningful differences in demographics across the treatment groups. Comparisons between the SAF Populations with and without data from Sites 1064 and 1082 were negligible, with the same increase in proportion of Hispanic subjects as observed for the comparison of mITT Populations with and without these sites.

In the DXA Population (both with and without Sites 1082 and 1064), there were statistically significant differences with respect to country of enrollment (p=0.0122 and p=0.0135, respectively).

Table 4. Demographics (mITT Population)

Category		Treatment Groups[a] Placebo BID N=195	Lubiprostone 12 mcg BID N=107	Lubiprostone 24 mcg BID N=292	All Lubiprostone Groups Total N=399 n (%)	p-Value[b]
Sex, n (%)	Female	106 (54.4)	53 (49.5)	163 (55.8)	216 (54.1)	0.9919
	Male	89 (45.6)	54 (50.5)	129 (44.2)	183 (45.9)	
Age (years)	n	195	107	292	399	0.9051
	Mean (SD)	11.2 (3.16)	8.8 (2.40)	12.0 (3.12)	11.1 (3.25)	
Age Group, n (%)	6 – 9 years	66 (33.8)	68 (63.6)	74 (25.3)	142 (35.6)	0.8889
	10 – 13 years	78 (40.0)	35 (32.7)	118 (40.4)	153 (38.3)	
	14 – 17 years	51 (26.2)	4 (3.7)	100 (34.2)	104 (26.1)	
Race, n (%)	American Indian or Alaska Native	3 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0.1415
	Asian	3 (1.5)	0 (0.0)	3 (1.0)	3 (0.8)	
	Black or African American	39 (20.0)	8 (7.5)	59 (20.2)	67 (16.8)	
	Native Hawaiian or Other Pacific Islander	1 (0.5)	0 (0.0)	1 (0.3)	1 (0.3)	
	White	138 (70.8)	86 (80.4)	222 (76.0)	308 (77.2)	
	Other	11 (5.6)	13 (12.1)	7 (2.4)	20 (5.0)	
Ethnicity, n (%)	Hispanic or Latino	44 (22.6)	17 (15.9)	59 (20.2)	76 (19.0)	0.3325
	Not Hispanic or Latino	151 (77.4)	90 (84.1)	233 (79.8)	323 (81.0)	
Height (cm)	n	195	107	292	399	0.7442
	Mean (SD)	148.0 (16.43)	134.7 (13.16)	152.2 (16.08)	147.5 (17.18)	
Weight (kg)	n	195	107	292	399	0.7687
	Mean (SD)	48.4 (20.10)	32.5 (8.93)	53.5 (20.61)	47.8 (20.47)	
Body Weight Group, n (%)	<50 kg	109 (55.9)	107 (100.0)	129 (44.2)	236 (59.1)	0.3884
	≥50 kg	86 (44.1)	0 (0.0)	163 (55.8)	163 (40.9)	
BMI (kg/m^2)	n	195	107	292	399	0.7734
	Mean (SD)	21.2 (5.39)	17.6 (3.13)	22.3 (5.90)	21.1 (5.69)	

ANOVA=analysis of variance; BID=twice daily; CMH=Cochran Mantel Haenzel.

a. All subjects, except those whose dose was titrated at the end of Week 1, are summarised with the dose group to which they were assigned at randomisation.

b. For treatment comparisons between the lubiprostone total group and the placebo group, a one way ANOVA was used for continuous variables and a CMH test stratified by pooled sites was used for categorical variables.

Source: Table 14.1.4.1

11.2.2 Key Baseline Characteristics

Key baseline characteristics are summarised by categorical and continuous variables. Categorical variables for the mITT and mITT1 Populations are provided in Table 14.1.5.1 and Table 14.1.13.1, respectively; continuous variables for the mITT and mITT1 Populations are provided in Table 14.1.5.2 and Table 14.1.13.2, respectively. Baseline characteristics are provided by individual subject in Listing 16.2.4.2.

In the mITT and mITT1 Populations, comparisons between the placebo BID group and the total lubiprostone BID group at baseline were performed using a one-way ANOVA. For diary data, baseline was defined as the average rating during the 2-week period prior to randomisation; for non-diary data, baseline value was determined by the last non-missing measurement on or before the first dose of study medication. See Section 9.7.1.4 for interpretations.

Categorical Variables

In categorical variables, there were minimal differences between the treatment groups. Differences between the mITT and mITT1 Populations were negligible, except for a slightly higher proportion of subjects having a history of failed constipation treatment in the mITT1 Population vs. the mITT Population (74.3% vs. 72.4%, respectively).

Continuous Variables

In the mITT and mITT1 Populations, the differences between the placebo BID group and the total lubiprostone BID group were minimal and non-significant with the only exception that the patient global assessment by parents was rated statistically significantly worse for subjects randomised to the lubiprostone treatment at baseline as compared to subjects randomised to placebo treatment. In other words, according to parent's/guardian's rating, subjects randomised to the lubiprostone arm were considered to be in a worse disease state at baseline than those randomised to the placebo arm (Table 14.1.5.2 for the mITT Population (p=0.0226); Table 14.1.13.2 for the mITT1 Population (p=0.0158)).

The differences in continuous variables between the mITT and mITT1 Populations were minimal.

11.2.3 Prior, Concomitant, Rescue, and Excluded Medications

The most commonly used prior medications (for constipation and GI-related indications), concomitant medications, and rescue medications during this study are discussed below for the SAF Populations with and without Sites 1064 and 1082. All medications were classified according to the World Health Organisation Drug Dictionary (WHO-DD).

11.2.3.1 Prior Constipation and Gastrointestinal-Related Medications

Table 14.1.6.2 and Table 14.1.14.2 summarise the specific prior constipation and GI-related medications and percentage of use in the SAF Populations with and without Sites 1082 and 1082, respectively.

In the SAF Population that includes all investigative sites, use of prior constipation medication by the placebo BID and total lubiprostone BID groups was similar: 78.5% and 82.5% subjects, respectively. The most commonly used prior constipation medication was Miralax, which was used previously by 53.3% and 57.0% of subjects, respectively.

In the SAF Population that excludes Sites 1064 and 1082, use of prior medication by the placebo BID and total lubiprostone BID groups was 80.9% and 85.0%, respectively, which was similar to use in the SAF Population inclusive of all sites; again, the most commonly used prior constipation medication was Miralax, which was used previously by 55.3% and 59.1% of subjects, respectively.

11.2.3.2 Concomitant Medications

Table 14.1.6.1 and Table 14.1.14.1 summarise the specific concomitant medication and percentage of use in the SAF Populations with and without Sites 1082 1064 and 1082, respectively.

In the SAF Population that includes all investigative sites, use of concomitant medication by the placebo BID and total lubiprostone BID groups was similar: 73.3% and 75.3% subjects, respectively. The most commonly used class of concomitant medications was analgesics by 20.0% and 18.3% of subjects, respectively.

In the SAF Population that excludes Sites 1064 and 1082, use of concomitant medication by the placebo BID and total lubiprostone BID groups was 76.1% and 77.7%, respectively, which was similar to use in the SAF Population inclusive of all sites; the most commonly used class of concomitant medications was analgesics, which were used by 20.7% and 18.7% of subjects, respectively.

11.2.3.3 Rescue Medications

Table 14.1.6.3 and Table 14.1.14.3 summarise the specific rescue medication and percentage of use in the SAF Populations with and without Sites 1064 and 1082, respectively.

In the SAF Population that includes all investigative sites, use of rescue medication by the placebo BID and total lubiprostone BID groups was similar: 62.1% and 62.5% subjects, respectively. The most commonly used rescue medication in the placebo BID and total lubiprostone BID groups was bisacodyl, used by 23.1% and 23.8% of subjects, respectively.

In the SAF Population that excludes Sites 1064 and 1082, use of rescue medication by the placebo and total lubiprostone groups was 63.8% and 64.5%, respectively, which was similar to use in the SAF Population inclusive of all sites; again, the most commonly used rescue medication in the placebo BID and total lubiprostone BID groups was bisacodyl, used by 23.9% and 24.6% of subjects, respectively.

For the populations including all investigative sites, monthly and overall rescue medication use for the mITT and PP Populations are provided in Table 14.2.23.1 and Table 14.2.23.2, respectively. For the populations excluding Sites 1064 and 1082 subjects, this is provided in Table 14.2.48.1 and Table 14.2.48.2, respectively While there was no statistically significant difference in the percentage of rescue medications users between treatment arms, there was typically a small trend in subjects randomised to lubiprostone to use rescue medications less frequently than subjects randomised to receive placebo.

11.2.3.4 Excluded Medications

A list of medications excluded during the study is found in Protocol Section 5.7.1.

11.2.4 Medical History

Table 14.1.8 and Table 14.1.16 provide summaries of medical history for the SAF Populations with and without Sites 1064 and 1082, respectively. As expected, for both populations, all (100.0%) subjects reported gastrointestinal (GI) disorders.

In the SAF Population that includes all investigative sites, the greatest frequency of morbidity was constipation, followed by menarche, abdominal pain, and ADHD. The difference between the percentage of subjects in the placebo BID and total lubiprostone BID groups with common morbidities was minimal with the exception of ADHD with 3.9% more subjects in the total lubiprostone BID group.

In the SAF Population that excludes Sites 1064 and 1082, the greatest frequency of morbidity was constipation, followed by menarche, abdominal pain, and ADHD. The difference between the percentage of subjects in the placebo BID and total lubiprostone BID groups with common morbidities was minimal with the exception of ADHD with 4% more subjects in the total lubiprostone BID group.

11.3 Measurement of Treatment Compliance

The median duration of treatment in the mITT Population for the total lubiprostone BID and placebo groups was the same: 85 days. The mean compliance in the placebo BID group was 86.54% and 86.37% in the total lubiprostone BID group, as shown in Table 14.1.7. The median duration of treatment in the mITT1 Population for the total lubiprostone BID and placebo groups was also the same: 85 days. The mean compliance was 86.55% in the placebo BID group and 86.71% in the total lubiprostone BID group, as shown in Table 14.1.15.

11.4 Efficacy Results and Tabulations of Individual Subject Data

11.4.1 Efficacy Endpoints

In both the mITT and mITT1 Populations, treatment groups were compared for all critical measures of efficacy (primary and secondary endpoints), as well as for benefit/risk assessment(s). All endpoints are presented for the mITT and mITT1 Populations, as appropriate. In-text tables are typically presented for the mITT1 Population (and subgroups thereof further described below), while typically reference is made to summary tables in Section 14 for corresponding data in the mITT Population without showing that data as in-text tables.

11.4.1.1 Primary Endpoint

11.4.1.1.1 Overall SBM Response

The primary efficacy endpoint was the overall SBM response rate of subjects who received oral lubiprostone capsules 12 mcg or 24 mcg BID compared with matching placebo BID administered orally for 12 weeks to subjects with PFC aged ≥6 years to <18 years in the mITT Population.

Overall SBM response to treatment in observed and LOCF case analyses for the mITT and mITT1 Populations are shown in Table 14.2.1.1 and Table 14.2.26.1, respectively; for the ITT Population, with and without Sites 1064 and 1082, in Table 14.2.1.2 and Table 14.2.26.2, respectively; for the COMP Population, with and without Sites 1064 and 1082, in Table 14.2.1.3 and Table 14.2.26.3, respectively; for the PP Population, with and without Sites 1064 and 1082, in Table 14.2.1.4 and Table 14.2.26.4, respectively; and for the DE Population, with and without Sites 1064 and 1082, in Table 14.2.1.5 and Table 14.2.26.5, respectively. Overall results for observed and LOCF case analyses in the mITT Population are summarised in Table 5.

Overall, in the observed case analysis of the mITT Population, there was a 4.6% greater response in the total lubiprostone BID group (19.0%) compared with the placebo BID group (14.4%); p=0.1609. Results were similar in the mITT1 LOCF case analysis: a 3.1% greater response in total lubiprostone BID (23.1%) compared with placebo BID (20.0%) was observed; p=0.4056. Results were essentially the same in the mITT1 Population while treatment differences in favour of lubiprostone were slightly smaller.

In the ITT, COMP, and PP Populations, both with and without Sites 1064 and 1082, the percentages of overall responders were similar to the response rates observed for the mITT and mITT1 Populations, i.e., greater response rates in the total lubiprostone BID group vs the placebo BID group. There were no appreciable differences between the populations regardless of whether data from Sites 1064 and 1082 were included. There were no statistically significant differences between the treatment groups in any of the populations analysed.

Table 5. Overall SBM Response (Observed and LOCF Case Analyses; mITT Population)

	Treatment Groups		
	Placebo N=195 n (%)	All Lubiprostone Groups Total N=399 n (%)	p-Value[a]
Observed case analysis			
Responders	28 (14.4)	76 (19.0)	0.1609
LOCF case analysis			
Responders	39 (20.0)	92 (23.1)	0.4056

CMH=Cochran Mantel Haenzel; LOCF=last observation carried forward; mITT=modified Intent-to-treat; SBM=Spontaneous bowel movement.
a. p-Value from a CMH test stratified by SBM frequency at randomisation (<1.5 vs ≥1.5).
Overall responder: a subject who qualified as a weekly responder for 9 of 12 weeks during the treatment period with durability demonstrated by ≥3 of the responder weeks occurring during the last 4 weeks of the treatment period.
Weekly responder: a subject who has a frequency rate of ≥3 SBMs/week and an increase from baseline of ≥1 SBM/week for that week.
Baseline: the average rating during the 2-week period prior to randomisation.
Source: Table 14.2.1.1

11.4.1.1.2 Subgroup and Post-hoc Analyses on Overall SBM Response

In order to investigate effects of lubiprostone vs. placebo on overall SBM response in clinically relevant subgroups, additional subgroup analyses, including post-hoc analyses, were conducted and results are presented below. These analyses were conducted for observed cases for the mITT1 Population and further subgroups derived thereof. The reason why these analyses were done for the mITT1 population rather than for the mITT population were serious concerns with data integrity of subjects enrolled at Sites 1064 and 1082 which lead to early termination of these sites. It should be re-iterated that for the same reason, the mITT1 population represents a prospectively defined analysis population for efficacy analysis as per the Statistical Analysis Plan. Several factors that were driving higher overall SBM response in the lubiprostone arm vs. placebo in the mITT1 Population were identified as follows (see Table 6):

- Treatment with the 24 mcg BID dose of lubiprostone;

- Status of previous laxative failure in medical history;
- Enrollment of subjects at North American study sites (defined as mITT2 Population for analysis); and
- Compliance with protocol-defined rules for intake of rescue medication (defined as mITT3 Population for analysis).

Analyses of the impact of study sites' geographic location on overall SBM responder rates revealed that a substantial number of subjects enrolled at European sites complied poorly with the protocol-specified rule for use of rescue medication[1] which has major impact on SBM counts and SBM-related assessments (secondary endpoints) given the definition of an SBM[2]. In fact, instead of using rescue medication only if no bowel movement had occurred for 3 days, these subjects used rescue medication every 3 days consecutively, i.e., irrespective of whether a bowel movement had occurred within the three previous days. The majority of subjects in Europe thus used rescue medication as an add-on treatment to lubiprostone (or placebo) in stable dosing intervals for a substantial period (≥2 study weeks during the 12-week study). Such non-compliance with the protocol-defined rescue clause only very rarely occurred in subjects enrolled at North American study sites (which comprised 87.7% of the total study population enrolled; Table 14.1.9.1). This observation may be reflective of a somewhat different treatment pattern in North America vs. Europe. For this reason, overall SBM response data were also evaluated for the subgroup of subjects enrolled only at North American study sites (mITT2 Population; post-hoc analysis, Table 6 and Table 7). In addition, in order to address non-compliance with protocol-defined rescue medication use in a fully comprehensive, strictly data-driven rather than geography-driven approach, overall SBM response was also evaluated in the subgroup of subjects who followed the rescue clause without major deviations (≥2 study weeks during the 12-week study) across all study sites in the mITT1 Population, independent of their geographic location (mITT3 Population; post-hoc analysis, Table 6 and Table 7). As there was high overlap of subjects included in the mITT2 and mITT3 Populations, results for these two post-hoc populations were generally very similar; for this reason, in most of the following tables only results for the mITT2 Population are shown.

The relative effect size of the 12 mcg BID dose of lubiprostone in regards to overall SBM response rates vs. the placebo control appeared to be generally lower than the effect size of the 24 mcg BID dose (Table 6). Indeed, in the subgroup of subjects who were initially assigned to the 12 mcg BID dose (subjects with a body weight of <50kg), but who were subsequently escalated to the 24 mcg BID dose at the end of Week 1 (12 mcg BID (DE) group), a pronounced treatment difference in favour of lubiprostone was observed (Table 6).

The history of previous laxative failure was captured as a baseline parameter in the trial. Roughly 75% of subjects reported failure of previous laxative therapy at baseline (see Table 14.1.13.1). In the mITT1 Population, there was no difference between the overall lubiprostone treatment arm and matching placebo for the overall SBM responder analysis in the approximately 25% of subjects enrolled who did not have a history of previous failure to laxative treatment (Table 14.2.51.2.4). This contrasts with subjects with a history of previous laxative failure in whom differences between

[1] The rescue medication clause in the protocol stated that use of rescue medication was only to be used if no bowel movement had occurred within a 3-day period – i.e. not every 3 days independent of occurrence of bowel movements.
[2] An SBM is defined as a bowel movement which does not occur within 24 hours after intake of a rescue medication.

treatment arms were clearly pronounced. Table 6 and Table 7 illustrate the impact of previous laxative failure status on the outcome of the overall SBM responder endpoint in the mITT1 Population, as well as in the derived mITT2 and mITT3 subpopulations.

Table 6. Overall SBM Response: Subgroup/Post-hoc Analyses on Primary Endpoint (Observed Case Analysis for mITT1, mITT2 and mITT3 Populations)

	Lubiprostone Treatment Groups			
	12 mcg BID n/N (% responders)	**12mcg BID (DE) n/N (% responders)**	**24 mcg BID n/N (% responders)**	**Total n/N (% responders)**
mITT1 Population with History of Previous Laxative Failure				
Placebo	7/31 (22.6%)	1/45 (2.2%)	9/64 (14.1%)	17/140 (12.1%)
Lubiprostone	19/73 (26.0%)	12/89 (13.5%)	22/124 (17.7%)	53/286 (18.5%)
p-Value vs. Placebo*	0.7222	**0.0475#**	0.5090	0.0946
Mean Treatment Difference	3.4%	11.3%	3.7%	6.4%
mITT2 Population				
Placebo	12/44 (27.3%)	4 /51 (7.8%)	8/70 (11.4%)	24/165 (14.5%)
Lubiprostone	24/94 (25.5%)	14/104 (13.5%)	28/138 (20.3%)	66/336 (19.6%)
p-Value vs. Placebo*	0.8201	0.3341	0.1229	0.1757
Mean Treatment Difference	-1.7%	5.6%	8.9%	5.1%
mITT2 Population with History of Previous Laxative Failure				
Placebo	7/31 (22.6%)	0 /34 (0.0%)	6/53 (11.3%)	13/118 (11.0%)
Lubiprostone	16/67 (23.9%)	11/75 (14.7%)	20/100 (20.0%)	47/242 (19.4%)
p-Value vs. Placebo*	0.8487	**0.0212#**	0.1774	**0.0436#**
Mean Treatment Difference	1.3%	14.7%	8.7%	8.4%
mITT3 Population				
Placebo	10/37 (27.0%)	4 /55 (7.3%)	9/72 (12.5%)	23/164 (14.0%)
Lubiprostone	27/99 (27.3%)	15/105 (14.3%)	28/148 (18.9%)	70/352 19.9%)
p-Value vs. Placebo*	0.9809	0.2322	0.2524	0.1846
Mean Treatment Difference	0.2%	7.0%	6.4%	5.9%
mITT3 Population with History of Previous Laxative Failure				
Placebo	6/26 (23.1%)	0 /39 (0.0%)	8/56 (14.3%)	14/121 (11.6%)
Lubiprostone	18/70 (25.7%)	12/79 (15.2%)	21/112 (18.8%)	51/261 (19.5%)
p-Value vs. Placebo*	0.8559	**0.0123#**	0.4717	0.0736
Mean Treatment Difference	2.6%	15.2%	4.5%	7.9%

n=Number of responders in respective treatment arm; N=Total number of subjects assigned to respective treatment arm; DE= Dose escalation (from 12 mcg BID to 24 mcg BID at the end of Study Week 1)
mITT1: All mITT subjects excluding those enrolled at Sites 1064 and 1082
mITT2: Subset of North American subjects from mITT1 Population (post-hoc)
mITT3: Subset of subjects from mITT1 Population who did not demonstrate major non-compliance with protocol-defined rescue medication use. Major non-compliance was defined as use of rescue medications every 3 days regardless of occurrence of bowel movements in a given week for at least two independent study weeks (post-hoc).

* P-value is from a CMH test stratified by SBM frequency at randomisation (< 1.5 or ≥ 1.5) for Lubiprostone 12 mcg BID vs. Placebo (Weight < 50 kg without DE), Lubiprostone 12 mcg BID (DE) vs. Placebo (Weight < 50 kg with DE), and Lubiprostone 24 mcg BID vs. Placebo (Weight ≥50 kg); **# p<0.05**.
Source: Table 14.2.51.1.2, Table 14.2.51.2.1, Table 14.2.51.1.3, Table 14.2.51.2.2, Table 14.2.51.1.4, Table 14.2.51.2.3, Table 14.2.52.1.1, Table 14.2.52.2.1, Table 14.2.52.1.2, Table 14.2.52.2.2

Table 7. Impact of Previous Laxative Failure Status on Overall SBM Response (Observed Case, Post-hoc Analysis)

	Subpopulation without Previous Laxative Failure			Total Population			Subpopulation with Previous Laxative Failure		
Population	N (L:P) n (L:P) n (L:P)%	Δ	p-Value*	N (L:P) n (L:P) n (L:P)%	Δ	p-Value*	N(L:P) n(L:P) n (L:P)%	Δ	p-Value*
mITT1	99:48 20:11 20.2%:22.0%	-2.7%	n.a.	385:188 73:28 19.0%:14.9%	4.1%	0.2415	286:140 53:17 18.5%:12.1%	6.4%	0.0946
mITT2	94:47 19:11 20.2%:23.4%	-3.2%	n.a.	336:165 66:24 19.6%:14.5%	5.1%	0.1757	242:118 47:13 19.4%:11.0%	8.4%	**0.0436#**
mITT3	87:40 18:9 20.7%:22.5%	-1.8%	n.a.	318:145 65:22 20.4%:15.2%	5.3%	0.1846	231:105 47:13 20.3%:12.4%	8.0%	0.0736

N (L: P): Number of subjects enrolled to population (Lubiprostone: Placebo)
n (L: P): Number of overall SBM responders in population (Lubiprostone: Placebo)
n (L: P) %: Percentage of overall SBM responders in population (Lubiprostone: Placebo)
Δ: Mean treatment difference in overall SBM response (%)
* p-Values are from a CMH test stratified by SBM frequency at randomisation (< 1.5 or ≥ 1.5) for Lubiprostone Overall vs. Placebo Overall; **# p<0.05.**
mITT1: All mITT subjects excluding those enrolled at Sites 1064 and 1082
mITT2: Subset of North American subjects from mITT1 Population (post-hoc)
mITT3: Subset of subjects from mITT1 Population who did not demonstrate major non-compliance with protocol-defined rescue medication use. Major non-compliance was defined as use of rescue medications every 3 days regardless of occurrence of bowel movements in a given week for at least two independent study weeks (post-hoc).
Source: Table 14.2.26.1, Table 14.2.51.2.1, Table 14.2.51.2.2, Table 14.2.51.2.3, Table 14.2.51.2.4, Table 14.2.51.2.5, Table 14.2.52.2.1, Table 14.2.52.2.2, Table 14.2.52.2.3

A statistically significant difference in the percentage of overall SBM responders in favour of lubiprostone was observed in the mITT2 (North American) subpopulation with a history of previous failure of laxatives. The primary endpoint was also met in subjects who underwent dose escalation to 24 mcg BID in all subpopulations of subjects with a history of previous laxative failure (mITT1-mITT3). This discriminating treatment difference between treatment arms in these comparisons is mainly driven by a variable percentage of placebo responders; while in subjects with a history of previous laxative failure, placebo responder rates were comparably low, responder rates were comparably high in placebo-treated subjects without a history of previous laxative failure (Table 7). In contrast, the overall SBM response rates in subjects assigned to lubiprostone are similar in the total population and in the two subpopulations of subjects with or without a history of previous laxative failure. This finding, suggestive of a more pronounced treatment difference in more severe, more difficult to treat PFC subjects, triggered a post-hoc analysis in which the stringency of the

overall SBM responder definition was increased (Table 8). In this post-hoc analysis the following overall responder definition was applied:

- An overall responder is defined as a subject who qualifies as a weekly responder for 9 out of 12 weeks during the treatment period, with durability demonstrated by at least 3 of the responder weeks occurring in the last 4 weeks of the 12-week study period.
- A weekly responder is defined as a subject who has a frequency rate of ≥ 3 SBMs/week and an increase from baseline of ≥ **2** SBMs/week for that week.

In other words, stringency was increased by the requirement of at least 2 additional SBMs to occur in a given treatment week as compared to baseline in order to qualify a subject as a weekly responder.

Table 8. Overall SBM Response Applying Increased Stringency (Observed Case, Post-hoc Analysis)

Population	N (L:P) n (L:P) n (L:P)%	Mean Treatment Difference	p-Value*	95% Confidence Interval
mITT1	385:188 49:14 12.7%:7.4%	5.3%	0.0557	**0.26%-10.3%****
mITT1 with history of previous laxative failure	286:140 39:9 13.6%:6.4%	7.2%	**0.0246#**	**1.52%-12.89%****
mITT2	336:165 44:12 13.1%:7.3%	5.8%	**0.0485#**	**0.46-11.18%****
mITT2 with history of previous laxative failure	242:118 34:7 14.0%:5.9%	8.1%	**0.0196#**	**2.01%-14.23%****

N (L:P): Number of subjects enrolled to population (Lubiprostone: Placebo)
n (L:P): Number of overall SBM responders in population (Lubiprostone: Placebo)
n (L:P) %: Number of overall SBM responders in population (Lubiprostone: Placebo)
* P-value is from a CMH test stratified by SBM frequency at randomisation (< 1.5 or ≥ 1.5) for Lubiprostone Overall vs. Placebo Overall; **# p<0.05; ** 95% Confidence Interval >0**
mITT1: All mITT subjects excluding those enrolled at Sites 1064 and 1082
mITT2: Subset of North American subjects from mITT1 Population (post-hoc)
Source: Table 14.2.54.1, Table 14.2.54.2, Table 14.2.54.3, Table 14.2.54.4

Indeed, increasing stringency of the overall SBM responder definition increased the separation between treatment arms, thus supporting the interpretation of trial data that suggests that lubiprostone specifically improves overall SBM response at a clinically important level at least in a subset of subjects. There was a significant difference in the percentage of "stringent overall SBM responders" in the subgroup of subjects with a history of previous laxative failure in both the mITT1 and mITT2 Populations. Statistical significance was also demonstrated for the total mITT2 Population and statistical significance was also achieved in the total mITT1 Population when

assessing statistical significance by 95% confidence intervals; in all populations assessed the confidence interval was above 0.

Table 9 provides an additional post-hoc analysis on the overall SBM response for the subgroup of subjects enrolled at secondary or tertiary care centres, again in an attempt to evaluate the relative treatment effect of lubiprostone-treated vs. placebo-treated subjects in a likely more severe, and more comprehensively characterized PFC population (see Section 11.4.7 for more background).

Table 9. Overall SBM Response in Subjects Enrolled at Secondary/Tertiary Care Centres (Observed Case, Post-hoc Analysis)

Population	N (L:P) n (L:P) n (L:P)%	Mean Treatment Difference	p-Value*
mITT1 Population			
Subgroup of Subjects Enrolled at Secondary/Tertiary Care Centres	188:93 35:13 18.6%:14.0%	4.6%	0.2624
+ history of previous laxative failure	140:74 27:8 19.3%:10.8%	8.5%	0.1042
+ no evidence of non-compliance with protocol-defined rescue medication use	121:59 26:5 21.5%:8.5%	13.0%	**0.0302#**
mITT2 Population			
Subgroup of Subjects Enrolled at Secondary/Tertiary Care Centres	141:70 28:9 19.9%:12.9%	7.0%	0.1634
+ history of previous laxative failure	97:52 21:4 21.6%:7.7%	14.0%	**0.0285#**
+ no evidence of non-compliance with protocol-defined rescue medication use	89:45 20:3 22.5%:6.7%	15.8%	**0.0200#**

N (L:P): Number of subjects enrolled to population (Lubiprostone: Placebo)
n (L:P): Number of overall SBM responders in population (Lubiprostone: Placebo)
n (L:P) %: Number of overall SBM responders in population (Lubiprostone: Placebo)
* P-value is from a CMH test stratified by SBM frequency at randomisation (< 1.5 or ≥ 1.5) for Lubiprostone Overall vs. Placebo Overall; **# p<0.05**
mITT1: All subjects excluding subjects from Sites 1064 and 1082
mITT2: All North American subjects excluding subjects from Sites 1064 and 1082 (post-hoc)
Source: Table 14.2.52.2.4, Table 14.2.52.2.5, Table 14.2.52.2.6, Table 14.2.52.2.7, Table 14.2.52.2.8, Table 14.2.52.2.9

Indeed, this post-hoc analysis of overall SBM response rate in subjects enrolled at secondary/tertiary sites demonstrated an increased relative effect of lubiprostone vs. placebo on the overall SBM responder endpoint, with demonstrated statistical significance in several of the mITT1 and mITT2 subgroups. Again, this increase in relative response rate was driven by a decrease in the placebo responder rate in this potentially more severe/more homogenous population of PFC subjects that were enrolled at secondary/tertiary care centres vs. the total trial population.

Finally, additional subgroup analyses looked at the impact of gender and age groups on the effect size and treatment differences on overall SBM response between study arms; these analyses are summarized in Table 10. For age groups, the data in Table 10 are split for subjects aged 6 to 9

years vs. 10 to 17 years. This is because in young PFC patients, a strong underlying behavioural/withholding component is present, which may delay the onset of an increase in SBMs per week until after the vicious cycle of hard stool perception that lead to an avoidance of defecation, is broken.[24,25] This underlying psychological factor, that is particularly relevant in younger patients, may make it difficult for a subject to become an overall SBM responder.

Table 10 demonstrates in females aged 10 to 17 years there is a clearly increased treatment difference for lubiprostone-treated subjects vs. placebo-treated subjects, when compared to the total population (6 to 17 years) of females (e.g., 9.84% vs. 4.33% in the mITT1 Population). In fact, although there are obviously fewer subjects in this subgroup of 10 to 17-year-old females than in the full 6 to 17-year-old female population, this treatment difference even becomes statistically significant when considering confidence intervals (e.g., in females 10 to 17-years-old in the mITT1 Population, p=0.0600, however with 95% confidence interval >0). This increased treatment difference in 10 to 17-year-old females becomes more pronounced when looking only at those subjects with a status of previous laxative failure (e.g., for the mITT1 Population, treatment difference increases to 11.4%). Furthermore, in this total (6 to 17-year-old) female subgroup with status of previous laxative failure, the treatment difference between lubiprostone- and placebo-treated subjects becomes statistically significant in favour of lubiprostone when considering confidence intervals (e.g., in mITT1 females with a history of previous laxative failure, p=0.0713, however with 95% confidence interval >0). This effect in the total female study population is mainly driven by the fact that in females 6 to 9 years of age with history of previous laxative failure, a positive trend in favour of lubiprostone can be detected while the drug is ineffective in regards to overall SBM response in the total subgroup of females aged 6 to 9 (e.g., in females 6 to 9 years of age in mITT1 Population with status of previous laxative failure, treatment difference vs. placebo is 5.0% in favour of lubiprostone, while in females 6 to 9 years old in the mITT1 Population, the treatment difference is 10.3% in disfavour of lubiprostone).

In males, the treatment differences between lubiprostone and placebo on overall SBM response are modest in the full mITT1 or mITT2 Populations (i.e., 3.85% and 5.31% in mITT1 and mITT2, respectively), and there is no positive impact of previous laxative failure on treatment difference between study arms observed (i.e., treatment difference in total male populations with history of previous laxative failure drops to 1.98% and 3.17% in mITT1 and mITT2, respectively). However, when only looking at male subjects who were enrolled at secondary or tertiary care centres – which are expected to represent a population of more accurately (e.g., vs. IBS-C) diagnosed, more severe PFC subjects in comparison to subjects enrolled at primary care centres – treatment differences between lubiprostone and placebo observed in males aged 10 to 17 years are very similar as in females of the same age group (6.55% vs. 7.21% in males vs. females). Even more so, the treatment difference in male subjects aged 10 to 17 with history of previous laxative failure enrolled at secondary or tertiary care centres increases to 9.37%, which suggests that there is actually no difference in the responder rates between females and males between 10 and 17 years of age when PFC subjects are seen at specialist sites.

In summary, combined subgroup analyses for gender and age effects on the overall SBM responder endpoint presented in Table 10 suggest that lubiprostone may represent an effective treatment vs. placebo for properly diagnosed, severe PFC subjects in the age group of 10 to 17 years.

Table 10. Overall SBM Response in Genders and Across Age Groups (Observed Case, Pre-specified and Post-hoc Analyses)

Population Parameter	Age Category (age in years)	Gender		Total Population
		Male	Female	
mITT1				
N (L:P)	Total (6-17)	177:84	208:104	385:188
n (L:P)		30:11	43:17	73:28
δ (L:P)%		3.85%	4.33%	4.1%
p-Value*		0.4275	0.3787	0.2415
N (L:P)	6-9	75:36	62:29	137:65
n (L:P)		15:5	15:10	30:15
δ (L:P)%		6.11%	-10.3%	-1.18%
p-Value*		0.4381	0.2972	n.a.
N (L:P)	10-17	102:48	146:75	248:123
n (L:P)		15:6	28:7	43:13
δ (L:P)%		2.21%	9.84%	6.8%
p-Value*		0.7115	**0.0600#**	0.0906
mITT1 with History of Previous Laxative Failure				
N (L:P)	Total (6-17)	126:65	160:75	286:140
n (L:P)		18:8	35:9	53:17
δ (L:P)%		1.98%	9.88%	6.4%
p-Value*		0.6712	**0.0713#**	0.0946
N (L:P)	6-9	52:26	48:20	100:46
n (L:P)		9:3	12:4	21:7
δ (L:P)%		5.77%	5.00%	5.78%
p-Value*		0.5066	0.6538	0.4089
N (L:P)	10-17	74:39	112:55	186:94
n (L:P)		9:5	23:5	32:10
δ (L:P)%		-0.66%	11.44%	6.6%
p-Value*		n.a.	**0.0614#**	0.1475
mITT2				
N (L:P)	Total (6-17)	153:77	183:88	336:165
n (L:P)		28:10	38:14	66:24
δ (L:P)%		5.31%	4.86%	5.1%
p-Value*		0.2999	0.3562	0.1757
N (L:P)	6-9	67:33	55:28	122:61
n (L:P)		15:5	12:10	27:15
δ (L:P)%		7.24%	-13.9%	-2.46%
p-Value*		0.3981	0.1506	n.a.
N (L:P)	10-17	86:44	128:60	214:104
n (L:P)		13:5	26:4	39:9
δ (L:P)%		3.75%	13.65%	9.6%
p-Value*		0.5138	**0.0173****	**0.0273****
mITT2 with History of Previous Laxative Failure				
N (L:P)	Total (6-17)	105:58	137:60	242:118
n (L:P)		16:7	31:6	47:13
δ (L:P)%		3.17%	12.63%	8.4%
p-Value*		0.4782	0.0361**	0.0436**
N (L:P)	6-9	45:23	41:19	86:42
n (L:P)		9:3	9:4	18:7
δ (L:P)%		6.96%	0.9%	4.26%
p-Value*		0.4682	0.9682	0.5665
N (L:P)	10-17	60:35	96:41	156:76
n (L:P)		7:4	22:2	29:6
δ (L:P)%		0.24%	18.04%	10.7%
p-Value*		0.7977	**0.0105****	**0.0324****

Population Parameter	Age Category (age in years)	Gender		Total Population
		Male	Female	
mITT1 Subjects Enrolled at Secondary or Tertiary Care Centres				
N (L:P)	Total (6-17)	90:39	98:54	188:93
n (L:P)		16:4	19:9	35:13
δ (L:P)%		7.52%	2.72%	4.64%
p-Value*		0.2457	0.6016	0.2624
N (L:P)	6-9	34:18	31:13	65:31
n (L:P)		7:2	6:4	13:6
δ (L:P)%		9.5%	-11.4%	0.65%
p-Value*		n.c.	n.a.	0.8906
N (L:P)	10-17	56:21	67:41	123:62
n (L:P)		9:2	13:5	22:7
δ (L:P)%		6.55%	7.21%	6.60%
p-Value*		0.3964	0.3064	0.1921
mITT1 Subjects Enrolled at Secondary or Tertiary Care Centres with History of Previous Laxative Failure				
N (L:P)	Total (6-17)	66:34	74:40	140:74
n (L:P)		11:3	16:5	27:8
δ (L:P)%		7.84%	9.12%	8.47%
p-Value*		0.2842	0.2212	0.1042
N (L:P)	6-9	25:15	22:7	47:22
n (L:P)		5:2	6:1	11:3
δ (L:P)%		6.7%	13.0%	9.77%
p-Value*		n.c.	n.c.	0.3557
N (L:P)	10-17	41:19	52:33	93:52
n (L:P)		6:1	10:4	16:5
δ (L:P)%		9.37%	7.11%	7.59%
p-Value*		0.2886	0.3681	0.1939

N (L: P): Number of subjects enrolled to population (Lubiprostone: Placebo)
n (L: P): Number of overall SBM responders in population (Lubiprostone: Placebo)
n (L: P) %: Number of overall SBM responders in population (Lubiprostone: Placebo)
δ: Mean treatment difference (%) between treatment arms
n.c.: Not calculated; Data derived from respective data in total and 10 to 17-year-old population: not formally programmed.
n.a.: Not applicable; p-values not shown if treatment difference is in favour of placebo.
* P-value is from a CMH test stratified by SBM frequency at randomisation (< 1.5 or ≥ 1.5) for Lubiprostone Overall vs. Placebo Overall; **** p<0.05; # 95% confidence interval > 0.**
mITT1: All subjects excluding subjects from Sites 1064 and 1082
mITT2: All North American subjects excluding subjects from Sites 1064 and 1082 (post-hoc)
Source: Table 14.2.26.1, Table 14.2.53.1, Table 14.2.52.3.9, Table 14.2.52.2.10, Table 14.2.52.3.3, Table 14.2.51.2.2, Table 14.2.53.3, Table 14.2.52.3.11, Table 14.2.52.2.12, Table 14.2.52.3.5, Table 14.2.51.2.1, Table 14.2.53.2, Table 14.2.52.3.10, Table 14.2.52.2.11, Table 14.2.52.3.4, Table 14.2.51.2.3, Table 14.2.53.4, Table 14.2.52.3.12, Table 14.2.52.2.13, Table 14.2.52.3.6, Table 14.2.52.2.4, Table 14.2.52.3.1, Table 14.2.52.4.1, Table 14.2.52.2.14, Table 14.2.52.3.7, Table 14.2.52.2.6, Table 14.2.52.3.2, Table 14.2.52.4.2, Table 14.2.52.2.15, Table 14.2.52.3.8

11.4.1.2 Key Secondary Efficacy Endpoints

Results of all key secondary efficacy endpoints are reported in this section. Interpretations of scores and scales used in reporting these endpoints are provided in Section 9.7.1.4. A summary of results for key secondary endpoints in the mITT1 population is presented in Table 14.2.49.

11.4.1.2.1 Time-to-First SBM and Percentage of Subjects with a First SBM within 4, 8, 12, 24, and 48 Hours of First Dose of Study Medication Administration

For the population subjects from all investigative sites, a summary of overall mean changes in time-to-first SBM and percentage of subjects with a first SBM within 4, 8, 12, 24, and 48 hours of first dose of study medication administration are provided by treatment groups in Table 14.2.6.1, Table 14.2.6.2, and Table 14.2.6.3 for the mITT, COMP, and PP Populations, respectively. Table 11 provides the data on all endpoints for the mITT Population.

Table 11. Median Time-to-First SBM and Percentage of Subjects with a First SBM within 4, 8, 12, 24 and 48 Hours of First Study Medication Administration (mITT Population)

	Treatment Groups		
Time to First SBM (Hours)	Placebo N=195 No. at Risk (% with SBM)	All Lubiprostone Groups Total N=399 No. at Risk (% with SBM)	p-Value[a]
0	195 (0.0%)	399 (0.0%)	
4	181 (7.2%)	347 (13.0%)	**0.0275***
8	169 (13.3%)	312 (21.8%)	**0.0114***
12	162 (16.9%)	300 (24.8%)	**0.0271***
24	150 (23.1%)	271 (32.1%)	**0.0216***
48	107 (45.1%)	193 (51.4%)	0.1365
Median [95% C.I.]	53.0 [45.8, 72.3]	46.3 [31.5, 50.8]	0.1014

SBM=Spontaneous bowel movement.
a. Proportions are compared using a likelihood-ratio chi-square test. Median times are compared using the Cox proportional hazards regression model; ***p<0.05.**
Source: Table 14.2.6.1

Comparison of data for the mITT1 Population demonstrates that lubiprostone allowed a significantly larger number of subjects than placebo-treated subjects to experience a first SBM within 8 and 24 hours after intake of the first dose of study medication. Differences between the treatment arms at other timepoints assessed, as well as the median time to first SBM were not statistically significantly different between treatment arms; however, there was always a strong trend in favour of lubiprostone-treated subjects. Data in the PP Population not including data from Sites 1064 and 1082 were very similar, again demonstrating a statistically significant difference in favour of lubiprostone-treated subjects at 8 and 24 hours (Table 14.2.31.3), while data in the COMP Population, despite consistent strong numerical trends in favour of lubiprostone did not demonstrate statistically significant differences between treatment arms.

Table 14.2.31.1, Table 14.2.31.2, and Table 14.2.31.3 provide the same data for the populations excluding subjects from Sites 1064 and 1082 (mITT1, COMP1, and PP1 Populations, respectively). Table 14.2.59 provides the same (post-hoc) data for the mITT2 Population. In the mITT1 Population, there was a statistically significant difference in the percentage of subjects experiencing a first SBM at 8, 12, and 24 hours after intake of the first study medication (Table 14.2.31.1). In the mITT2 Population, results were highly similar to the mITT1 Population with demonstration of a

statistically significant difference in favour of lubiprostone in the percentage of subjects with a first SBM after 4, 8, 12 and 24 hours, respectively.

11.4.1.2.2 Change from Baseline in Straining Associated with SBMs

One of the key secondary efficacy endpoints was the mean change from baseline in straining associated with SBMs in subjects who received lubiprostone 12 mcg or 24 mcg BID compared with matching placebo BID.

For the mITT Population, mean and median changes from baseline in degree of straining associated with SBMs in observed case and LOCF analyses are provided by week, month, and overall in Table 14.2.13.1.1 and Table 14.2.13.1.2, respectively. For the PP Population these data are shown in Table 14.2.13.2.1 and Table 14.2.13.2.2, respectively, for observed case and LOCF analyses. Overall results for observed case and LOCF analyses in the mITT Population are summarised in Table 12.

For the mITT1 Population, overall results are provided in Table 14.2.38.1.1 and Table 14.2.38.1.2, respectively, for observed case and LOCF analyses. Observed case and LOCF analysis of the PP Population excluding subjects from Sites 1064 and 1082 are shown in Table 14.2.38.2.1 and Table 14.2.38.2.2, respectively. Finally, results for observed case analysis of the (post-hoc) mITT2 Population are provided in Table 14.2.57.

There was a statistically significant difference in favour of lubiprostone for the key secondary endpoint of overall change from baseline in straining associated with SBMs in the mITT Population (Table 12), as well as for the mITT1 Population for both observed and LOCF cases. The same was true for the post-hoc mITT2 Population. At Month 1, in the mITT Population observed case analysis, the mean decrease (i.e., improvement) was -0.81 Units in the total lubiprostone BID group compared with -0.55 Units in the placebo BID group, which represented a statistically significant difference (p=0.0026). At Month 2, the mean decreases were -0.95 Units and -0.91 Units in the total lubiprostone BID and placebo BID groups, respectively, though the difference was not statistically significant. At Month 3, the mean decreases were -1.08 Units and -0.82 Units in the total lubiprostone BID and placebo BID groups, respectively, again representing a statistically significant difference (p=0.0410). Results were minimally different for the LOCF analysis of the mITT Population, with a statistically significant difference (p=0.0019) in mean change between treatment groups observed at Month 1. Monthly results were also similar in the mITT1 Population and the mITT2 Populations. Overall, differences in values between the mITT and mITT1 Populations, and between observed case and LOCF analyses, were negligible with statistical significance between treatment arms similar for the two populations.

Similar mean changes in the total lubiprostone BID group were shown for weekly analyses in the mITT Population, in both observed case and LOCF analyses. The greatest mean changes from baseline in total lubiprostone BID occurred at Week 12 in observed case and LOCF analyses: -1.20 Units and -1.06 Units, respectively. There were statistically significant differences in favour of lubiprostone at some study weeks.

Similar results were found in the mITT1 Population, for observed case and LOCF analyses for greatest mean changes from baseline in the total lubiprostone BID group: -1.20 Units and -1.05 Units, respectively, at Week 12, and for the mITT2 Population observed case analysis (-1.26 Units).

Results were generally numerically similar in the respective PP Populations for overall, monthly, and weekly assessments.

Mean straining scores in the mITT Population lubiprostone treatment arm dropped from a score of 2.55 (some to quite a bit) at baseline to 1.35 (a little to some) at Week 12 (Table 14.2.13.1.1).

Table 12. Overall Mean Change from Baseline in Straining Associated with SBMs (Observed and LOCF Case Analyses, mITT Population)

	Treatment Groups	
Analysis Parameter	**Placebo BID N=174**	**Total Lubiprostone BID N=351**
Observed Cases		
n	168	345
Mean (SD)	-0.72 (1.093)	-0.92 (0.979)
95% CI	-0.89, -0.56	-1.02, -0.82
p-Value[a]		**0.0178***
LOCF		
n	168	345
Mean (SD)	-0.74 (1.094)	-0.92 (0.992)
95% CI	-0.91, -0.58	-1.03, -0.82
p-Value[a]		**0.0341***

BID=twice daily; CI=confidence interval; LOCF=last observation carried forward; mITT=modified Intent-to-treat; SBM=spontaneous bowel movement; SD= standard deviation.
a. p-Value is from a van Elteren test stratified by SBM frequency at randomisation (<1.5 or ≥1.5) and pooled sites; ***p<0.05.**
Baseline was defined as the average rating during the 2-week period prior to randomisation.
Source: Table 14.2.13.1.1, Table 14.2.13.1.2.

11.4.1.2.3 Change from Baseline in Stool Consistency Associated with SBMs

Another key secondary efficacy endpoint was the overall mean change from baseline in stool consistency associated with SBMs in subjects who received oral lubiprostone 12 mcg or 24 mcg BID compared with matching placebo BID.

For the mITT Population, mean and median changes from baseline in stool consistency associated with SBMs for observed case and LOCF analyses are provided by week, month, and overall in Table 14.2.14.1.1 and Table 14.2.14.1.2, respectively, and for the PP Population including subjects from all investigative sites, these analyses are shown in Table 14.2.14.2.1 and Table 14.2.14.2.2, respectively. Overall results for observed and LOCF cases in the mITT1 Population are summarized in Table 13.

For observed case and LOCF analyses of stool consistency, overall results for the mITT1 Population are provided in in Table 14.2.39.1.1 and Table 14.2.39.1.2, respectively, and in Table 14.2.39.2.1 and Table 14.2.39.2.2 for the PP Population excluding subjects enrolled at Sites 1064 or 1082,

respectively. Finally, results for observed cases for the mITT2 Population are provided in Table 14.2.58.

There was a statistically significant difference in favour of lubiprostone for the key secondary endpoint of overall change from baseline in stool consistency associated with SBMs in the mITT1 Population (p=0.0350 for observed case analysis and p=0.0362 for LOCF analysis)) and for the observed cases in the post-hoc mITT2 Population (LOCF analysis was not done for this population). For the mITT Population (Table 13), results were close to reaching statistical significance (p=0.0501 and p=0.0500 for observed cases and LOCF, respectively). However, the 95% confidence interval for the treatment differences between lubiprostone and placebo remained >0 in the mITT observed case analysis, providing additional evidence for statistical significance. At Month 1, in the mITT Population in observed cases, mean improvement was 0.49 Units in the total lubiprostone BID group compared with 0.34 Units in the placebo BID group, a statistically significant difference (p=0.0081). At Month 2, mean improvement was 0.47 Units and 0.38 Units in the total lubiprostone BID and placebo BID groups, respectively (p=0.1174). At Month 3, the mean decrease was 0.56 Units and 0.36 Units in the total lubiprostone BID and placebo BID groups, respectively, the difference approaching statistical significance (p=0.0598). Results were minimally different in the LOCF analysis of the mITT Population, with a statistically significant difference in mean change between treatment groups at Month 1 and approaching significance in Month 2 (p=0.0066 and p=0.0774, respectively). Monthly results were similar in the mITT1 Population with a statistically significant difference between treatment groups favouring lubiprostone at Month 1 for observed cases (p=0.0065). Differences in values between the mITT and mITT1 Populations, and between observed case and LOCF analyses, were negligible with statistical significance between treatment arms similar to the mITT Population. In the post-hoc mITT2 Population, results demonstrated a statistically significant difference in favour of lubiprostone in the observed case analysis at Month 1 and Month 3 (p=0.0061 and p=0.0291, respectively); LOCF analysis was not done for this population.

Similar improvement in the total lubiprostone BID group was shown in weekly analyses in the mITT Population for observed case and LOCF analyses, with the greatest observed mean change from baseline of 0.58 Units at Week 9 (observed case analysis) and 0.53 at Weeks 2 and 3 (LOCF analysis). Similar results were found in the mITT1 Population for observed case and LOCF analyses, with the greatest observed mean change from baseline of 0.58 Units at Weeks 3 and 9 (observed case analysis) and 0.54 Units at Week 3 (LOCF analysis), for observed case and LOCF analysis, as well as for the post-hoc mITT2 Population (observed case analysis; 0.60 Unit change from baseline at Weeks 10 and 12). There were statistically significant differences in favour of lubiprostone at some study weeks in all populations.

Results were generally numerically similar in the respective PP Populations for overall, monthly, and weekly assessments.

Mean stool consistency scores in the mITT lubiprostone treatment arm improved from a score of 2.15 (close to “sausage-shaped but lumpy”) at baseline to 2.70 (close to “normal”) at Week 12. Group medians in the lubiprostone treatment arm improved from a score of 2.0 at baseline to 3.0 at Week 12 (Table 14.14.1.1).

Table 13. Overall Mean Change from Baseline in Stool Consistency Associated with SBMs (Observed Case and LOCF Analyses, mITT Population)

Analysis Parameter	Treatment Groups	
	Placebo BID N=174	Total Lubiprostone BID N=351
Observed Cases		
n	168	345
Mean (SD)	0.35 (0.666)	0.49 (0.683)
95% CI	0.25, 0.46	0.41, 0.56
p-Value[a]		**0.0501#**
LOCF		
n	168	345
Mean (SD)	0.36 (0.698)	0.47 (0.719)
95% CI	0.25, 0.46	0.40, 0.55
p-Value[a]		0.0500

BID=twice daily; CI=confidence interval; LOCF observation carried forward; mITT=modified Intent-to-treat; SBM=spontaneous bowel movement; SD= standard deviation.
a. p-Value is from a van Elteren test stratified by SBM frequency at randomisation (<1.5 or ≥1.5) and pooled sites; ***p<0.05.**
 # 95% confidence interval > 0.
Baseline was defined as the average rating during the 2-week period prior to randomisation.
Source: Table 14.2.14.1.1, Table 14.2.14.1.2.

11.4.1.2.4 Change from Baseline in Constipation Severity

For the mITT Population, results of overall mean and median changes from baseline in constipation severity for observed case and LOCF analyses are provided by week, month, and overall in Table 14.2.15.1.1 and Table 14.2.15.1.2, respectively. For the PP Population, these data are shown in Table 14.2.15.2.1 and Table 14.2.15.2.2, respectively. Overall results for observed case and LOCF analyses in the mITT Population are summarised in Table 14.

For the mITT1 Population, overall results are provided in Table 14.2.40.1.1 and Table 14.2.40.1.2, respectively, and for the PP Population excluding subjects enrolled at Sites 1064 or 1082 in Table 14.2.40.2.1 and Table 14.2.40.2.2, respectively.

There was a numerical trend in favour of lubiprostone vs. placebo in regards to overall changes from baseline in constipation severity, however no statistically significant differences between treatment arms were observed (Table 14). At Month 1, in the observed case analysis of the mITT1 Population, the mean decrease (i.e., improvement) in constipation severity was -0.40 Units in the total lubiprostone BID group compared with -0.28 Units in the placebo BID group. At Month 2, the mean decrease was -0.61 Units and -0.54 Units in the lubiprostone BID and placebo BID groups, respectively. At Month 3, the mean decrease was -0.71 Units and -0.57 Units in the lubiprostone BID and placebo BID groups, respectively. None of these differences were statistically significant while there was a consistent numerical trend in favour of lubiprostone during all treatment months. For the LOCF analysis of the mITT1 Population, there was a statistically significant difference (p=0.0450) in favour of lubiprostone in mean change between treatment groups at Month 1. Monthly results were similar in the mITT1 Population. Differences in values between the mITT and mITT1 Populations, and between observed case and LOCF analyses, were negligible.

Similar improvements in the lubiprostone BID group was shown in weekly analyses for the mITT Population, for both observed case and LOCF analysis. The greatest observed mean changes from baseline were 0.74 Units and 0.67 Units, respectively, at Week 10. Similar results were found in the mITT1 Population. Weekly results were statistically significant in favour of lubiprostone at isolated study weeks in the respective populations.

Mean constipation severity scores in the lubiprostone treatment arm improved from a score of 2.21 (somewhat worse than moderate, moderate representing a score of 2.0) to 1.48 (mild-to-moderate) at Week 12 (Table 14.15.1.1).

Table 14. Overall Mean Change from Baseline in Constipation Severity (Observed Case and LOCF Analyses, mITT Population)

Analysis Parameter	Treatment Groups: Placebo BID N=195	Treatment Groups: Total Lubiprostone BID N=399
Observed Cases		
n	195	399
Mean (SD)	-0.45 (0.737)	-0.54 (0.809)
95% CI	-0.55, -0.35	-0.62, -0.46
p-Value[a]		0.3756
LOCF		
n	195	399
Mean (SD)	-0.45 (0.763)	-0.54 (0.828)
95% CI	-0.56, -0.34	-0.62, -0.46
p-Value[a]		0.3413

BID=twice daily; CI=confidence interval; LOCF=last observation carried forward; mITT=modified Intent-to-treat; SD= standard deviation.
a. p-Value is from a van Elteren test stratified by SBM frequency at randomisation (<1.5 or ≥1.5) and pooled sites. Baseline was defined as the average rating during the 2-week period prior to randomisation.
mITT1: All subjects excluding subjects from Sites 1064 and 1082
Source: Table 14.2.15.1.1, Table 14.2.15.1.2.

11.4.1.2.5 Change from Baseline in Abdominal Pain

For the mITT Population, mean and median changes from baseline in degree of abdominal pain in observed case and LOCF analyses are provided by week, month, and overall in Table 14.2.16.1.1 and Table 14.2.16.1.2, respectively. Overall results for observed case and LOCF analyses in the mITT Population are summarised in Table 15. For observed case and LOCF analyses of the mITT1 Population, overall results are provided in Table 14.2.41.1.1 and Table 14.2.41.1.2, respectively.

For the PP Population, results of observed case and LOCF analyses are shown in Table 14.1.16.2.1 and Table 14.1.16.2.2, respectively. For the PP Population not including subjects enrolled at Sites 1064 or 1082, results are in Table 14.2.41.2.1 and Table 14.2.41.2.2, respectively.

There was a numerical trend in favour of lubiprostone vs. placebo in regards of overall change from baseline in abdominal pain, however no statistically significant difference between treatment arms was observed (Table 15). At Month 1, in the observed case analysis of the mITT1 Population, the

mean decrease (i.e., improvement) in abdominal pain was -0.30 Units in the total lubiprostone BID group compared with -0.23 Units in the placebo BID group. At Month 2, the mean decrease was 0.47 Units and -0.40 Units in the total lubiprostone BID and placebo BID groups, respectively. At Month 3, the mean decrease was -0.58 Units and -0.46 Units in the total lubiprostone BID and placebo BID groups, respectively. None of these differences was statistically significant while there was a consistent numerical trend in favour of lubiprostone in all treatment months. Results were similar monthly in the mITT1 Population. Differences in values between the mITT and mITT1 Populations and between observed case and LOCF analyses were negligible.

Similar improvement in the total lubiprostone BID group was shown in weekly analyses in the mITT Population, for both observed case and LOCF analyses. The greatest mean change from baseline was -0.59 Units at Week 12 in the observed case analysis. In LOCF analysis of the mITT Population, the largest mean change was -0.51 Units, at Week 12. These weekly results were not statistically significant, however, though there was a consistent numerical trend in favour of lubiprostone.

Mean abdominal pain scores in the mITT lubiprostone treatment arm improved from a score of 1.80 (close to moderate, with moderate represented by a score of 2.0) at baseline to 1.20 (close to mild; mild represented by a score of 1.0) at Week 12 (Table 14.16.1.1)

Table 15. Overall Mean Change from Baseline in Abdominal Pain (Observed Case and LOCF Analyses, mITT Population)

	Treatment Groups	
Analysis Parameter	**Placebo BID N=194**	**Total Lubiprostone BID N=399**
Observed Cases		
n	194	397
Mean (SD)	-0.35 (0.765)	-0.42 (0.842)
95% CI	-0.46, -0.25	-0.50, -0.34
p-Value[a]		0.2079
LOCF		
n	194	397
Mean (SD)	-0.35 (0.784)	-0.42 (0.861)
95% CI	-0.46, -0.24	-0.50, -0.33
p-Value[a]		0.1754

BID=twice daily; CI=confidence interval; LOCF=last observation carried forward; SBM=spontaneous bowel movement; SD= standard deviation.
a. p-Value is from a van Elteren test stratified by SBM frequency at randomisation (<1.5 or ≥1.5) and pooled sites.
Baseline was defined as the average rating during the 2-week period prior to randomisation.
Modified Intent-to-treat Population: all subjects except those whose dose was dose escalated at the end of Week 1 were summarised
with the dose group to which they were assigned at randomisation.
Source: Table 14.2.16.1.1, Table 14.2.16.1.2.

11.4.1.2.6 Change from Baseline in SBM Frequency

For the mITT Population, mean and median changes from baseline in SBM frequency for observed case and LOCF analyses are provided by week, month, and overall in Table 14.2.4.1.1 and Table 14.2.4.1.2, respectively. For the PP Population, these are shown in Table 14.2.4.2.1 and

Table 14.2.4.2.2, respectively. Overall results for observed and LOCF cases in the mITT Population are summarized in Table 16.

For the mITT1 Populations, mean and median changes from baseline in SBM frequency are similarly provided in Table 14.2.29.1.1 and Table 14.2.29.1.2, respectively, and for the PP Population not including subjects enrolled as Sites 1064 or 1082 in Table 14.2.29.2.1 and Table 14.2.29.2.2, respectively. Finally, results for observed cases for the post-hoc mITT2 Population are provided in Table 14.2.56.

There was a statistically significant difference in favour of lubiprostone for the key secondary endpoint of overall change from baseline in SBM frequency in the observed case analysis for the mITT Population (p=0.0496; Table 16), while for the LOCF analysis, the numerical difference in favour of lubiprostone approached statistical significance (p=0.0596). For the mITT1 Population for observed case analysis, statistical significance in favour of lubiprostone was demonstrated (p=0.0470; [Table 14.2.29.1.1]), but was also slightly missed (p=0.0598 [Table 14.2.29.1.2]) for the LOCF analysis. There was also a statistically significant difference in favour of lubiprostone in the observed case analysis of the post-hoc mITT2 Population (p=0.0325, Table 14.2.56). At Month 1, in the observed case analysis of the mITT Population, mean improvement was 1.35 SBMs in the total lubiprostone BID group compared with 1.17 SBMs in the placebo BID group. At Month 2, mean improvement was 1.49 SBMs in the total lubiprostone BID group compared with 1.25 SBMs in the placebo BID group and at Month 3, the mean increase was 1.40 SBMs and 1.07 SBMs in the total lubiprostone BID and placebo BID groups, respectively. Neither of these monthly results were statistically significant. Differences in values between the mITT and mITT1 Populations, and between observed case and LOCF analyses, were negligible with the only exception that there was a statistically significant difference in favour of lubiprostone at Month 1 in the mITT1 observed case analysis (p=0.474: Table 14.2.29.1.1). In the observed case analysis for the post-hoc mITT2 population, similar to the mITT1 Population, a statistically significant difference in favour of lubiprostone was observed at Month 1 (p=0.0263), while treatment differences did not reach statistical significance at Months 2 and 3 despite a strong numerical trend in favour of lubiprostone.

Similar improvements in the total lubiprostone BID group was shown in weekly analyses in the mITT Population, for observed case and LOCF analyses, with the greatest mean change from baseline being 1.54 SBMs and 1.49 SBMs at Week 8 and Week 4 in the observed case and LOCF analyses, respectively (Tables 14.2.4.1 and 14.2.4.2, respectively). Similar results were found in the mITT1 Population, for observed case and LOCF analyses, with greatest mean change of 1.55 at and 1.50 at Week 4, respectively (Tables 14.2.29.1.1 and 14.2.29.1.2, respectively). For the mITT2 Population, a change of 1.58 SBMs was observed at Week 4. Additionally, in the mITT1 population at Week 4, the mean change from baseline in the total lubiprostone BID group was statistically significant (p=0.0393; Table 14.2.29.1.1); the same was the case in the post-hoc mITT2 Population at Weeks 3 and 4 (p=0.0189 and p=0.0466, respectively; Table 14.2.56). In the respective PP Populations, there was a consistent trend in favour of lubiprostone. These weekly results did not reach statistical significance though.

Mean SBM frequency in lubiprostone-treated subjects in the mITT Population increased from 1.40 SBMs per week at baseline to 2.90 SBMs per week at Week 12 (Table 14.2.4.1.1).

Table 16. Overall Change from Baseline in SBM Frequency (Observed Case and LOCF Analyses, mITT Population)

Analysis Parameter	Treatment Groups: Placebo BID N=195	Treatment Groups: Total Lubiprostone BID N=399
Observed Case		
n	194	391
Mean (SD)	1.15 (1.762)	1.38 (1.723)
95% CI	0.90, 1.40	1.20, 1.55
p-Value[a]		**0.0496***
LOCF		
n	194	391
Mean (SD)	1.17 (1.906)	1.36 (1.770)
95% CI	0.90, 1.44	1.19, 1.54
p-Value[a]		0.0596

BID=twice daily; CI=confidence interval; LOCF=last observation carried forward; SBM=spontaneous bowel movement; SD= standard deviation.
a. p-Value is from a van Elteren test stratified by SBM frequency at randomisation (<1.5 or ≥1.5) and pooled sites; ***p<0.05.**
All subjects except those whose dose was dose escalated at the end of Week 1 are summarised with the dose group to which they
were assigned at randomisation.
Source: Table 14.2.4.1.1, Table 14.2.4.1.2.

11.4.1.2.7 Change from Baseline in Bowel Movement Frequency

For the mITT Population, mean and median change from baseline in BM frequency for observed case and LOCF analyses are provided by week, month, and overall in Table 14.2.5.1.1 and Table 14.2.5.1.2, respectively. Overall results for observed case and LOCF analyses in the mITT Population are summarised in Table 17. For the mITT1 Population, mean change from baseline in BM frequency in observed case and LOCF analyses are provided by week, month, and overall in Table 14.2.30.1.1 and Table 14.2.30.1.2, respectively. Finally, this data for the observed case analysis of the post-hoc mITT2 Population is provided in Table 14.2.60.

For the PP Population, results for observed case and LOCF analyses are in Table 14.2.5.2.1 and Table 14.2.5.2.2, respectively. For the PP Population not including subjects from Sites 1064 or 1082, results of observed case and LOCF analyses are in Table 14.2.30.2.1 and Table 14.2.30.2.2, respectively.

There was a strong numerical trend in favour of lubiprostone vs. placebo in regards to overall change from baseline in BM frequency, however, no statistically significant difference between treatment arms was observed (Table 17). At Month 1, in the observed case analysis of the mITT1 Population, mean improvement was 1.35 BMs in the total lubiprostone BID group compared with 1.15 BMs in the placebo BID group. At Month 2, mean change was 1.42 BMs and 1.19 BMs in the total lubiprostone BID and placebo BID groups, respectively. At Month 3, the mean increase was 1.30 BMs and 1.06 BMs in the total lubiprostone BID and placebo BID groups, respectively. While there was a consistent numerical trend in favour of lubiprostone, none of these mean changes were statistically significant.

Results were minimally different in the LOCF analysis of the mITT Population. Monthly results were similar in the mITT1 and mITT2 Populations with no statistically significant differences between treatment groups except for Month 1 in the post-hoc mITT2 Population analysis (p=0.0089 in favour of lubiprostone (Table 14.2.60).

Similar improvements were shown in the total lubiprostone BID group in weekly analyses for the mITT Population, in both observed case and LOCF analyses; the greatest mean change from baseline was 1.51 BMs and 1.46 BMs at Week 3, respectively. Similar results were observed in the mITT1 Population and the post-hoc mITT2 population. There was a statistically significant difference in favour of lubiprostone at isolated study weeks in all three populations (mITT, mITT1, and mITT2), while in the majority of study weeks, across all populations and analyses, there was a consistent trend in favour of lubiprostone. Results in the PP Populations were numerically similar.

Mean BM frequency in the mITT Population was improved from 1.72 BMs at baseline to 3.11 BMs at Week 12 (Table 14.2.5.1.1)

Table 17. Overall Change from Baseline in BM Frequency (Observed Case and LOCF Analyses, mITT Population)

Analysis Parameter	Treatment Groups	
	Placebo BID N=195	Total Lubiprostone BID N=399
Observed Case		
n	194	391
Mean (SD)	1.12 (1.700)	1.32 (1.691)
95% CI	0.88, 1.36	1.15, 1.49
p-Value[a]		0.1052
LOCF		
n	194	391
Mean (SD)	1.17 (1.857)	1.30 (1.734)
95% CI	0.90, 1.43	1.13, 1.47
p-Value[a]		0.1610

BID=twice daily; CI=confidence interval; LOCF=last observation carried forward; BM=bowel movement; SD=standard deviation.
a. p-Value is from a van Elteren test stratified by BM frequency at randomisation (<1.5 or ≥1.5) and pooled sites.
All subjects except those whose dose was dose escalated at the end of Week 1 are summarised with the dose group to which they
were assigned at randomisation.
Source: Table 14.2.5.1.1, Table 14.2.5.1.2.

11.4.1.2.8 Change from Baseline in Painfulness of SBMs

For the mITT Population, mean and median changes from baseline in painfulness of SBMs for observed case and LOCF analyses are provided by week, month, and overall in Table 14.2.17.1.1 and Table 14.2.17.1.2, respectively. Overall results for observed case and LOCF analyses in the mITT Population are summarised in Table 18. For the mITT1 Population, results for the two analyses are provided in Table 14.2.42.1.1 and Table 14.2.42.1.2, respectively.

For the PP Population, results for observed case and LOCF analyses are in Table 14.2.17.2.1 and Table 14.2.17.2.2, respectively. In the PP Population excluding subjects enrolled at Sites 1064 or 1082, these analyses are shown in Table 14.2.42.2.1 and Table 14.2.42.2.2, respectively.

There was a statistically significant difference in favour of lubiprostone in the overall change from baseline in painfulness of SBMs in both observed case analyses for the mITT Population (p=0.0458; Table 18), and mITT1 Population (p=0.0349; Table 14.2.42.1.1), while for the respective LOCF analyses, the numerical difference in favour of lubiprostone approached statistical significance. At Month 1, in the observed case analysis of the mITT Population, mean change was -0.69 Units in the total lubiprostone BID group compared with -0.51 Units in the placebo BID group; this was statistically significant (p=0.0450). At Month 2, the difference between the treatment arms was not statistically different, while at Month 3 mean change was -1.00 Units in the total lubiprostone BID group compared with -0.76 Units in the placebo BID group, which again represented a statistically significant difference in favour of lubiprostone (p=0.0495). Similarly, results for the LOCF analysis in the mITT Population demonstrated a statistically significant difference in favour of lubiprostone at Month 1. In the mITT1 Population, a statistically significant difference in favour of lubiprostone at Months 1 and 3 was demonstrated both in the observed case and LOCF analysis. Differences in values between the mITT and mITT1 Populations and between observed case and LOCF analyses were numerically negligible.

Similar mean changes in the total lubiprostone BID group were shown in weekly analyses in the mITT Population, for observed case and LOCF analyses, with the greatest mean change from baseline in the total lubiprostone BID group being -1.11 and -0.97 at Week 10 for the two analyses, respectively. Treatment differences between treatment arms were statistically significant in favour of lubiprostone at isolated study weeks, while there was a consistent favourable trend for lubiprostone in the majority of study weeks.

Data for the PP Populations, both with and without Sites 1064 and 1082, were very similar, with statistically significant differences in favour of lubiprostone observed overall, for Month 1 and Month 3, as well as for isolated study weeks (Table 14.2.17.2.1, Table 14.2.17.2.2; Table 14.2.42.2.1, Table 14.2.42.2.2)

Painfulness of SBMs in the mITT Population for lubiprostone-treated subjects was improved from 2.23 (“some” to “quite a bit”) at baseline to 1.14 (slightly more than “a little”) at Week 12 (Table 14.2.17.1.1). Results in the other populations were very similar.

Table 18. Overall Change from Baseline in Painfulness of SBMs (Observed Case and LOCF Analyses, mITT Population)

Analysis Parameter	Treatment Groups	
	Placebo BID N=173	Total Lubiprostone BID N=351
Observed Cases		
n	167	345
Mean (SD)	-0.65 (1.132)	-0.81 (1.024)
95% CI	-0.82, -0.48	-0.92, -0.70
p-Value[a]		**0.0458***
LOCF Cases		
n	167	345
Mean (SD)	-0.67 (1.136)	-0.81 (1.040)
95% CI	-0.84, -0.50	-0.92, -0.70
p-Value[a]		0.0802

BID=twice daily; CI=confidence interval; LOCF=last observation carried forward; SBM=spontaneous bowel movement; SD= standard deviation.
a. p-Value is from a van Elteren test stratified by SBM frequency at randomisation (<1.5 or ≥1.5) and pooled sites; ***p<0.05.**
All subjects except those whose dose was dose escalated at the end of Week 1 are summarised with the dose group to which they
were assigned at randomisation.
Source: Table 14.2.17.1.1, Table 14.2.17.1.2.

11.4.1.2.9 Treatment Effectiveness

For the mITT Population, results of treatment effectiveness assessment for observed case and LOCF analyses are provided by week, month, and overall in Table 14.2.18.1.1 and Table 14.2.18.1.2, respectively. Overall results for observed and LOCF cases in the mITT Population are summarised in Table 19. For the mITT1 Population, results are similarly provided in Table 14.2.43.1.1 and Table 14.2.43.1.2, respectively.

For the PP Population, results for observed case and LOCF analyses are shown in Table 14.2.18.2.1 and Table 14.2.18.2.2, respectively. For the PP Population not including subjects from Sites 1064 or 1082, these are shown in Table 14.2.43.2.1 and Table 14.2.43.2.2, respectively.

There was a strong numerical trend in favour of lubiprostone vs. placebo in regards to assessment of overall treatment effectiveness, approaching but slightly missing statistical significance in both the mITT and mITT1 Populations for both the observed case and LOCF analyses ($p \leq 0.0729$ for all analyses; Table 19 shows data for the mITT Population). At the monthly level, for both the mITT and mITT1 Populations, irrespective of conducting the observed case analysis or applying LOCF, there was a statistically significant difference in perceived treatment effectiveness at Month 3 ($p \leq 0.0172$ for all analyses). There was no statistically significant difference in any of the mITT or mITT1 analyses at Month 1 and Month 2, while there was a consistent favourable trend in favour of lubiprostone.

Lubiprostone was consistently rated as more effective as compared to placebo across all mITT Populations and analyses when assessed for weekly treatment effectiveness. Differences reached a statistically significant difference in favour of lubiprostone in 3 out of the 12 study weeks across all analyses of the mITT and mITT1 Populations.

Table 19. Overall Treatment Effectiveness (Observed Case and LOCF Analyses, mITT Population)

Analysis Parameter	Treatment Groups	
	Placebo BID	Total Lubiprostone BID
Observed Case		
n	192	390
Mean (SD)	1.45 (0.994)	1.56 (0.996)
95% CI	1.31, 1.59	1.46, 1.66
p-Value[a]		0.0729
LOCF		
n	192	390
Mean (SD)	1.45 (1.008)	1.57 (1.008)
95% CI	1.31, 1.59	1.47, 1.67
p-Value[a]		0.0647

BID=twice daily; CI=confidence interval; SD= standard deviation
a. p-Value is from a van Elteren test stratified by SBM frequency at randomisation (<1.5 or ≥1.5) and pooled sites.
Score: 0=Not at all effective; 1=A little bit effective; 2=Moderately effective; 3=Quite a bit effective; 4=Extremely effective.
All subjects except those whose dose was dose escalated at the end of Week 1 are summarised with the dose group to which they
were assigned at randomisation.
Source: Table 14.2.18.1.1, 14.2.18.1.2.

11.4.1.2.10 Summary of Investigator's Assessment of Treatment Effectiveness

For the mITT Population, results for investigator assessment of treatment effectiveness at Weeks 4, 8 and 12, as well as overall, are provided in Table 14.2.20.1.1 and Table 14.2.20.1.2, respectively, for observed case and LOCF analyses. Overall results for observed case and LOCF analyses in the mITT Population are summarised in Table 20. For the mITT1 Population, results for the two analyses are provided in in Table 14.2.45.1.1 and Table 14.2.45.1.2, respectively.

In the PP Population, results for observed case and LOCF analyses are provided in Table 14.2.20.2.1 and Table 14.2.20.2.2, respectively. In the PP Population excluding subjects enrolled at Sites 1064 and 1082, these results are provided in Table 14.2.45.2.1 and Table 14.2.45.2.2, respectively.

Investigators assessed lubiprostone as statistically significantly more effective overall, and at all individual assessments at Weeks 4, 8, and 12, in both the mITT and mITT1 Populations irrespective of whether observed case or LOCF analysis was applied. Results were similar in the respective PP analyses, with all analyses demonstrating a statistically significant difference in favour of lubiprostone for overall effectiveness comparison; results were also statistically significantly in favour of lubiprostone for the majority of weekly treatment effectiveness comparisons.

Table 20. Overall Summary of Investigator's Assessment of Treatment Effectiveness (Observed Case and LOCF Analyses, mITT Population)

Analysis Parameter	Treatment Groups	
	Placebo BID	Total Lubiprostone BID
Observed Cases		
n	187	367
Mean (SD)	1.54 (1.108)	1.87 (1.143)
95% CI	1.38, 1.70	1.75, 1.99
p-Value[a]		**0.0014***
LOCF Cases		
n	187	367
Mean (SD)	1.54 (1.107)	1.87 (1.142)
95% CI	1.38, 1.70	1.75, 1.99
p-Value[a]		**0.0014***

BID=twice daily; CI=confidence interval; SD= standard deviation
a. p-Value is from a van Elteren test stratified by SBM frequency at randomisation (<1.5 or ≥1.5) and pooled sites; ***p<0.05.**
Score: 0=Not at all effective; 1=A little bit effective; 2=Moderately effective; 3=Quite a bit effective; 4=Extremely effective.
All subjects except those whose dose was dose escalated at the end of Week 1 are summarised with the dose group to which they
were assigned at randomisation.
Source: Table 14.2.20.1.1, 14.2.20.1.2.

11.4.1.2.11 Overall Treatment Response

The percentage of subjects qualifying as overall treatment responders was numerically higher in the mITT, mITT1, and both PP Populations. For the mITT and PP Population, results are provided in Table 14.2.7. 1 and Table 14.2.7.2, respectively. They are summarized in Table 21.

For the mITT1 Population, results are provided in Table 14.2.32.1 and in Table 14.2.32.2 for the PP Population excluding subjects from Sites #1064 or #1082.

Table 21. Summary of Overall Treatment Response (mITT Population and PP Population)

Population Responder	Treatment Groups Placebo BID N=195 n (%)	Treatment Groups Total Lubiprostone BID N=399 n (%)
mITT		
n	195	399
Yes	33 (16.9%)	79 (19.8%)
No	162 (83.1%)	320 (80.2%)
Treatment Difference[a]		2.88%
95% C.I.[b]		(-3.68%, 9.43%)
p-Value[c]		0.4065
PP)		
n	146	297
Yes	28 (19.2%)	64 (21.5%)
No	118 (80.8%)	233 (78.5%)
Treatment Difference[a]		2.37%
95% C.I.[b]		(-5.54%, 10.29%)
p-Value[c]		0.5280

BID=twice daily; CI=confidence interval; SD= standard deviation
a. The treatment difference is calculated as Lubiprostone minus Placebo.
b. 95% C.I. of the treatment difference is calculated based on the normal approximation of the binomial distribution.
c. p-Value is from a CMH test stratified by SBM frequency at randomisation (<1.5 or ≥1.5). ***p<0.05**
All subjects except those whose dose was dose escalated at the end of Week 1 are summarised with the dose group to which they were assigned at randomisation.
Source: Table 14.2.7.1, Table 14.2.7.2.

11.4.1.2.12 Mean Change from Baseline in Incontinence Frequency Episodes

For the mITT Population, results for mean and median change from baseline in incontinence frequency episodes for observed case and LOCF analyses are provided in Table 14.2.8.1.1 and Table 14.2.8.1.2, respectively. For the mITT1 Population, results for these analyses are provided in in Table 14.2.33.1.1 and Table 14.2.33.1.2, respectively.

For the PP Population, results of observed case and LOCF analyses are in Table 14.2.8.2.1 and Table 14.2.8.2.2, respectively. For the PP Population excluding subjects from Sites 1064 or 1082, these are in Table 14.2.33.2.1 and Table 14.2.33.2.2, respectively.

Analysis of this data was compromised by the fact that the majority of subjects did not report any episode of incontinence during baseline (as expressed by the baseline median value of 0 in all populations). As a result, there was no statistically significant difference between the overall group of lubiprostone-treated subjects vs. placebo-treated subjects in regards of overall change from baseline in the number of incontinence frequencies in any of the populations. However, there was a consistent numerical trend in favour of lubiprostone. In regards to monthly and weekly changes from baseline in the frequency incontinence episodes, there was a statistically significant difference in favour of lubiprostone in both the mITT and mITT1 Populations for both the observed case and

LOCF analyses at Month 3 ($p \leq 0.0106$), as well at isolated study weeks; for all other timepoints, results demonstrated a numerical trend in favour of lubiprostone-treated subjects.

Results for both PP Populations, i.e., with and without Sites 1064 and 1082, were very similar to those in the respective mITT Populations.

Since the number of subjects reported to have incontinence episodes during baseline was low, a post-hoc, observed case analysis of data from the mITT1 Population was conducted. In this post-hoc analysis, evaluation of treatment effects on overall incontinence frequency was done only for the subset of subjects who presented with at least one episode of incontinence during the baseline period. Interestingly, in placebo-treated subjects, the overall incontinence frequency tended to increase during the treatment period of the study, while in the lubiprostone-treated subjects it tended to decrease; the most pronounced effects were in subjects treated with the 24 mcg BID dose of lubiprostone compared to its respective placebo control group. Although the number of subjects evaluable for this efficacy parameter was small and no statistically significant difference was observed, the results suggest a clinically important effect of lubiprostone. The data for this post-hoc analysis is provided in Table 22.

Table 22. Change from Baseline in Overall Incontinence Frequency in Subjects Presenting with Incontinence Episodes During the Baseline Period (Post-hoc Analysis, mITT1 Population)

Treatment Group	n	Mean Change	Median Change	Mean Difference	p-Value[a]
Placebo	16	+0.27	-0.25	-0.46	0.5550
Lubiprostone	45	-0.19	-0.40		
Placebo (Weight ≥50 kg)	5	+0.74	+1.40	-1.24	0.0863
Lubiprostone 24 mcg BID	15	-0.50	-0.50		

a. P-value is from a van Elteren test stratified by SBM frequency at randomisation (< 1.5 or ≥ 1.5) and pooled sites.
n: Number of subjects in the population
Source: Table 14.2.67

11.4.1.2.13 Overall Change from Baseline in Production of Large Diameter Stool Frequency

For the mITT Population, results for mean and median change from baseline in the production of large diameter stools for observed case and LOCF analyses are provided in Table 14.2.9.1.1 and Table 14.2.9.1.2, respectively. For the mITT1 Population, results for these analyses are similarly provided in in Table 14.2.34.1.1 and Table 14.2.34.1.2, respectively.

For the PP Population, results of observed and LOCF cases are in Table 14.2.9.2.1 and Table 14.2.9.2.2, respectively. For the PP Population excluding subjects from Sites 1064 and 1082, these are in Table 14.2.34.2.1 and Table 14.2.34.2.2, respectively.

Analysis of this data was compromised by the fact that the majority of subjects did not report any large diameter stools during baseline (as expressed by a median baseline value of 0 for this parameter in all populations). As a result, there was no statistically significant difference between the treatment arms in any of the mITT, mITT1 or PP Populations, neither in the observed case of

LOCF analyses. However, there was a general numerical trend in regards of a larger change from baseline in the frequency of large diameter stools in the total lubiprostone treatment arm vs. the placebo control arm.

11.4.1.2.14 Change from Baseline in Subjects Who had Faecal Impactions

Change from baseline in subjects who had faecal impaction was assessed in the safety (SAF) Population as this was captured as an adverse event of faecaloma. Data are provided for treatment-emergent and treatment-related events of faecaloma in Table 14.3.1.2.1 and Table 14.3.1.9.1, respectively. The incidence of faecaloma was generally very low, while fewer events occurred in the lubiprostone-treated study arm in comparison to the placebo-treated study arm. Table 23Table 23 summarizes these results.

Table 23. Frequency of treatment-emergent and treatment-related events of fecal impaction (SAF Population)

Event Type	Placebo N=195; (n (%))	12mcg BID N=231, (n(%))	24mcg BID N=169, (n(%))	Lubi Total N=400, (n(%))
TEAEs	7 (3.6%)	8 (3.5%)	3 (1.8%)	11 (2.8%)
TRAEs	4 (2.1%)	3 (1.3%)	1 (0.6%)	4 (1.0%)

Reference: Tables 14.3.1.2.1, 14.3.1.9.1
N: Number of subjects assigned to treatment
N (%): relative number of events in N
TEAE: Treatment emergent adverse event: TRAE: Treatment related adverse event; SAF: Safety Population

11.4.1.2.15 Overall Percentage of SBMs in the Toilet

For the mITT Population, results for mean and median change from baseline in the percentage of SBMs in the toilet for observed case and LOCF analyses are provided in Table 14.2.10.1.1 and Table 14.2.10.1.2, respectively. For the mITT1 Population, results for these analyses are similarly provided in Table 14.2.35.1.1 and Table 14.2.35.1.2, respectively.

For the PP Population, results of observed case and LOCF analyses are in Table 14.2.10.2.1 and Table 14.2.10.2.2, respectively. For the PP Population excluding subjects from Sites 1064 and 1082, these are in Table 14.2.35.2.1 and Table 14.2.35.2.2, respectively.

Analysis of this data was compromised by the fact that the majority of subjects did report to have 100% of SBMs to be in the toilet during the baseline period (as expressed by a median baseline value of 100% for this parameter in all populations). As a result, there was no statistically significant difference between the treatment arms in any of the mITT, mITT1, or PP Populations, neither in the observed case of LOCF analyses for the overall change from baseline in the percentage of SBMs in the toilet. However, there was a general numerical trend in regards of a larger change from baseline in the percentage of SBM in the toilet in the total lubiprostone treatment arm vs. the placebo control arm. In the mITT Population, there was a statistically significant difference in favour of lubiprostone at Month 3 in the observed case analysis and at Week 12 in the LOCF analysis, respectively. In the mITT1 population, in treatment Month 3 and Study Week 12, there was a statistically significant difference in favour of lubiprostone both in the observed case as well as in

the LOCF analysis. Results in the respective PP Population analyses were consistent with the data observed in the mITT Populations.

11.4.1.2.16 Overall Percentage of BMs in the Toilet

For the mITT Population, results for mean and median change from baseline in the percentage of BMs in the toilet for observed case and LOCF analyses are provided in Table 14.2.11.1.1 and Table 14.2.11.1.2, respectively. For the mITT1 Population, results for these analyses are similarly provided in in Table 14.2.36.1.1 and Table 14.2.36.1.2, respectively.

For the PP Population, results of observed case and LOCF analyses are in Table 14.2.11.2.1 and Table 14.2.11.2.2, respectively. For the PP Population excluding subjects from Sites 1064 and 1082, these are in Table 14.2.36.2.1 and Table 14.2.36.2.2, respectively.

Analysis of this data was compromised by the fact that the majority of subjects did report to have 100% of BMs to be in the toilet during the baseline period (as expressed by a median baseline value of 100% for this parameter in all populations). As a result, there was no statistically significant difference between the treatment arms in any of the mITT, mITT1, or PP Populations, neither in the observed case of LOCF analyses for the overall change from baseline in the percentage of BMs in the toilet. However, there was a general numerical trend in regards of a larger change from baseline in the percentage of BMs in the toilet in the total lubiprostone treatment arm vs. the placebo control arm. In the mITT Population there were statistically significant differences in favour of lubiprostone at Month 3 in the observed case analysis and at Week 12 in the LOCF analysis, respectively. In the mITT1 population, in treatment Month 3 and Study Week 12 (and for the LOCF analysis also in Study Week 10), the difference was also statistically significant in favour of lubiprostone, both in the observed case as well as in the LOCF analysis. Results in the respective PP Population analyses were consistent with the data observed in the mITT Populations.

11.4.1.2.17 Overall Summary of Frequency of Retentive Posturing and Excessive Volitional Stool Retention

For the mITT Population, results for weekly, monthly and overall frequency of retentive posturing and excessive volitional stool retention for observed case and LOCF analyses are provided in Table 14.2.12.1.1 and Table 14.2.12.1.2, respectively. For the mITT1 Population, results for these analyses are similarly provided in in Table 14.2.37.1.1 and Table 14.2.37.1.2, respectively. No baseline values were captured for this parameter.

For the PP Population, results of observed case and LOCF analyses are in Table 14.2.12.2.1 and Table 14.2.12.2.2, respectively. For the PP Population excluding subjects from Sites 1064 and 1082, these are in Table 14.2.37.2.1 and Table 14.2.37.2.2, respectively.

Analysis of this data was compromised by the fact that for the majority of subjects no events of retentive posturing and excessive volitional stool retention was reported (as expressed by a median frequency of 0 typically reported for this parameter in all populations at all assessment timepoints). As a result, there was no statistically significant difference between the treatment arms in any of the mITT, mITT1, or PP Populations, neither in the observed case of LOCF analyses.

11.4.1.2.18 Monthly Response Rates

For the mITT Population, monthly responder rates for the observed case and LOCF analyses are provided in Table 14.2.3.1.1 and Table 14.2.3.1.2, respectively. Respective analyses are also provided in Table 14.2.3.2.1 and Table 14.2.3.2.2 for the ITT Population, in Table 14.2.3.3.1 and Table 14.2.3.3.2 for the Completer Population, in Table 14.2.3.4.1 and Table 14.2.3.4.2 for the PP Population, and in Table 14.2.3.5.1 and Table 14.2.3.5.2 for the Dose Escalation (DE) Population. The corresponding data for the population excluding subjects from Sites 1064 and 1082 is provided for the mITT1 population in Table 14.2.28.1.1 and Table 14.2.18.1.2, in Table 14.2.28.2.1 and Table 14.2.28.2.2 for the ITT1 Population, in Table 14.2.28.3.1 and Table 14.2.28.3.2 for the Completer population, in Table 14.2.28.4.1 and Table 14.2.28.4.2 for the PP Population, and in Table 14.2.28.5.1 and Table 14.2.28.5.2 for the DE Population. An additional post-hoc observed case analysis was also done for the mITT2 Population, provided in Table 14.2.55.

There was no statistically significant difference between the treatment arms in any of the mITT or mITT1 Population analyses or in the post hoc analyses for mITT2. However, in all analyses across the different populations there was a consistent trend in favour of lubiprostone (i.e. a higher percentage of monthly responders in the lubiprostone arm). In fact, this trend consistently got stronger month over month across populations and analyses, and resulted in statistically significant differences in favour of lubiprostone in the total population LOCF analyses for the mITT, ITT and Completer Populations at Month 3.

Results for the observed case analysis for monthly SBM responses across study months for the mITT, mITT1 and the post-hoc mITT2 Populations are presented in Table 24.

Table 24. Monthly SBM responder rates

	mITT	mITT1	mITT2
Month 1 Treatment difference	3.9%	3.8%	5.2%
Month 1 p-value	p=0.3212	p=0.3665	p=0.2586
Month 2 Treatment Differences	6.7%	5.9%	6.7%
Month 2 p-value	p=0.0859	p=0.1453	p=0.1285
Month 3 Treatment Difference	6.3%	5.7%	6.8%
Month 3 p-value	p=0.0995	p=0.1487	p=0.1159

Reference: Table 14.2.3.1.1, Table 14.2.28.1.1, Table 14.2.55.
mITT1: All subjects excluding subjects from Sites 1064 and 1082
mITT2: All North American subjects excluding subjects from Sites 1064 and 1082 (post hoc)
Note: A subject who is a weekly responder for at least 3 of the 4 weeks out of a month (during the treatment period) is considered a monthly responder for that 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. Baseline is defined as the average rating during the 2-week period prior to randomisation.

11.4.1.2.19 Overall Change from Baseline in PedsQL Total Score, by Subject

The overall PedsQL™ responses to treatment reported by subjects in the mITT Population are provided for observed cases in Table 14.2.19.1.1.1 and for the LOCF analysis in Table 14.2.19.1.1.2. The overall PedsQL™ responses to treatment reported by subjects in the PP

Population are provided for observed cases in Table 14.2.19.1.2.1 and for the LOCF analysis in Table 14.2.19.1.2.2.

The overall PedsQL™ responses to treatment reported by subjects in the mITT1 Population are provided for observed cases in Table 14.2.44.1.1.1 and for the LOCF analysis in Table 14.2.44.1.1.2. The overall PedsQL™ responses to treatment reported by subjects in the PP Population excluding subjects from Sites 1064 and 1082 are provided for observed cases in Table 14.2.44.1.2.1 and for the LOCF cases in Table 14.2.44.1.2.2.

Besides the total PedsQL™ score, data were reported for specific functioning areas (physical, emotional, social, school functioning) as well as provided as a psychosocial health and Physical Health summary scores. Higher scores generally indicate better quality of life (QoL).

Subjects in both treatment arms rated themselves to have improved from baseline over the treatment period– typically in a statistically significant extent - in all functioning areas, sub scores and total score vs. their respective baseline values. However, no statistically significant difference between the lubiprostone and placebo treatment arms was detected for any functioning arm, sub-score or total score in any of the populations and analyses.

11.4.1.2.20 Overall Change from Baseline in PedsQL Total Score, by Parent/Guardian

The overall PedsQL™ responses to treatment reported by parent/guardian in the mITT Population are provided for observed cases in Table 14.2.19.2.1.1 and for the LOCF analysis in Table 14.2.19.2.1.2. The overall PedsQL™ responses to treatment reported by parent/guardian in the PP Population are provided for observed cases in Table 14.2.19.2.2.1 and for the LOCF analysis in Table 14.2.19.2.2.2.

The overall PedsQL™ responses to treatment reported by parent/guardian in the mITT1 Population are provided for observed cases in Table 14.2.44.2.1.1 and for the LOCF analysis in Table 14.2.44.2.1.2. The overall PedsQL™ responses to treatment reported by parent/guardian in the PP Population excluding subjects from Sites 1064 and 1082 are provided for observed cases in Table 14.2.44.2.2.1 and for the LOCF cases in Table 14.2.44.2.2.2.

Besides the total PedsQL™ score, data was reported for specific functioning areas (physical, emotional, social, school functioning) as well as provided as a psychosocial health and Physical Health summary scores. Higher scores generally indicate better quality of life (QoL).

Parents/Guardians rated subjects in both treatment arms to have improved from baseline over the treatment period– typically in a statistically significant extent - in all functioning areas, sub scores and total score vs. their respective baseline values. However, no statistically significant difference between the lubiprostone and placebo treatment arm was detected for any functioning arm, sub score or total score in any of the populations and analyses.

11.4.1.3 Exploratory Analyses

11.4.1.3.1 Overall Change from Baseline in PGIC, by Parent/Guardian

For the mITT Population, results for mean and median change from baseline for patient global impression of change (PGIC) by parent for observed case and LOCF analyses are provided in Table 14.2.21.1.1.1 and Table 14.2.21.1.1.2, respectively. For the mITT1 Population, results for these analyses are similarly provided in Table 14.2.46.1.1.1 and Table 14.2.46.1.1.2, respectively.

For the PP Population, results of observed case and LOCF analyses are in Table 14.2.21.1.2.1 and Table 14.2.21.1.2.2, respectively. For the PP Population excluding subjects from Sites 1064 and 1082, these are in Table 14.2.46.1.2.1 and Table 14.2.46.1.2.2, respectively.

There was a statistically significant difference in favour of lubiprostone at all timepoints and overall in regards of PGIC as rated by parent/guardian for both the mITT and mITT1 Populations in both observed case and LOCF analyses. Results in the respective PP Populations were consistent with these findings.

11.4.1.3.2 Overall Change from Baseline in PGIC, by Subject

For the mITT Population, results for mean and median change from baseline for patient global impression of change (PGIC) by subjects for observed case and LOCF analyses are provided in Table 14.2.21.2.1.1 and Table 14.2.21.2.1.2, respectively. For the mITT1 Population, results for these analyses are similarly provided in Table 14.2.46.2.1.1 and Table 14.2.46.2.1.2, respectively.

For the PP Population, results of observed case and LOCF analyses are in Table 14.2.21.2.2.1 and Table 14.2.21.2.2.2, respectively. For the PP Population excluding subjects from Sites 1064 and 1082, these are in Table 14.2.46.2.2.1 and Table 14.2.46.2.2.2, respectively.

There was a consistent numerical trend in favour of lubiprostone at all timepoints and overall in regards of PGIC rated by subject for both the mITT and mITT1 Populations in both observed case and LOCF analyses. However, this difference never reached statistical significance. Results in the respective PP Populations were consistent with these findings.

11.4.1.3.3 Overall Changes from Baseline in Clinician Severity Rating Scales

For the mITT Population, results for mean and median change from baseline in clinician severity rating for observed case and LOCF analyses are provided in Table 14.2.22.1.1 and Table 14.2.22.1.2, respectively. For the mITT2 Population, results for these analyses are similarly provided in in Table 14.2.47.1.1 and Table 14.2.47.1.2, respectively.

For the PP Population, results of observed case and LOCF analyses are in Table 14.2.22.2.1 and Table 14.2.22.2.2, respectively. For the PP Population excluding subjects from Sites 1064 and 1082, these are in Table 14.2.47.2.1 and Table 14.2.47.2.2, respectively.

There was a consistent numerical difference in favour of lubiprostone at all timepoints and overall in regards of clinician severity rating for both the mITT and mITT1 Population in both observed

case and LOCF analyses. However, this difference never reached statistical significance. Results in the respective PP Populations were consistent with these findings.

11.4.2 Statistical/Analytical Issues

11.4.2.1 Adjustments for Covariates

Some analyses were adjusted for covariates of SBM frequency at randomisation (< 1.5, and ≥1.5), pooled clinical site, and/or baseline values.

11.4.2.2 Handling of Dropouts or Missing Data

Imputation of missing SBM data is dependent upon the amount of data observed. If <4 days of data were available for a given week, the data were considered insufficient and the rate was missing for that week.

Missing values could have occurred due to a missing visit or a dropout from the study. The last observation carried forward (LOCF) is used when only post-baseline values were carried forward up to each time point of evaluation for subjects who had missing assessments; this would have been used to input certain post-baseline variables. Missing data was to be imputed for efficacy variables only. The LOCF method was to be applied for weekly and monthly efficacy endpoints and was to be applied for the weekly responders used for the calculation of overall response as a sensitivity analysis.

Details concerning handling of missing data are provided in SAP Section 3.3.4.

11.4.2.3 Interim Analyses and Data Monitoring

To ensure that the study was properly powered, the study protocol allowed for a possible interim analysis when treatment data through Week 12 from 50% of subjects was available and monitored. This analysis was not conducted.

Data monitoring: An independent Data Safety Monitoring Board (DSMB) was to monitor safety data on a regular basis throughout the study. Specific details, including frequency stopping criteria, are provided in the DSMB Charter.

11.4.2.4 Multicentre Studies

Statistical analyses were based on data pooled across clinical sites in aggregate, retaining clinical site in the model. However, if the model did not converge using pooled sites, pooling by region may have be used instead. All sites were grouped into 2 regions: (North America (NA) and European Union (EU). Sites in the US and Canada were grouped into the NA region and sites in Europe were grouped into the EU region, as shown in SAP Section 3.3.6.

11.4.2.5 Multiple Comparisons/Multiplicity

Inferential tests for treatment comparisons of key secondary efficacy endpoints were performed in accordance with the closed testing procedure (CTP) principle to account for inflation of a type 1

error due to hypothesis testing of multiple key secondary endpoints, as shown in SAP Section 3.3.7, for the CTP structure method.

11.4.2.6 Use of an "Efficacy Subset" of Subjects

Analyses were performed for the primary efficacy endpoint in subgroups as a percentage of 12-week overall responders at baseline for the following categories:

- mITT Population;
- mITT1 Population;
- ITT Population;
- COMP Population;
- PP Population; and
- DE Population.

In addition, some additional analyses were also conducted for two post-hoc mITT Populations (mITT2 and mITT3; for details see Section 9.7.1.1).

11.4.2.7 Examination of Subgroups

Analyses were performed for the primary efficacy endpoint in subgroups as a percentage of 12-week overall responders at baseline for the following categories:

- Gender (male, female)
- Race (White, Black, All others)
- Age group (6 to 9, 10 to 13, and 14 to 17 years of age)
- SBM at Randomisation (<1.5, ≥1.5)
- Weight (<50 kg, ≥50 kg)
- BMI (<25, ≥25)

Data for these subgroup analyses for the mITT Population for the observed case and LOCF analyses for the primary endpoint are provided in Table 14.2.25.1.1 and Table 14.2.25.1.2, respectively. For the mITT1 Population, results for these analyses are similarly provided in in Table 14.2.50.1.1 and Table 14.2.50.1.2, respectively. For the PP Population, results of observed case and LOCF analyses are in Table 14.2.25.2.1 and Table 14.2.25.2.2, respectively. For the PP Population excluding subjects from Sites 1064 and 1082, these are in Table 14.2.50.2.1 and Table 14.2.50.2.2, respectively.

Results in all these subgroup analyses were consistently demonstrating a numerical trend in favour of lubiprostone. For the mITT and mITT1 Populations, a statistically significant difference in favour of lubiprostone was demonstrated in patients of "other race" as well as in subjects in the age group of 10-13 years in the observed case analysis. Results for female and male subjects on the primary endpoint were similar, while treatment with lubiprostone appeared to be more effective in subjects of other and white race than in subjects of black race. Similarly, lubiprostone appeared to be more effective as per assessment of the primary endpoint in subjects aged 10 to 13 and 14 to 17 than in

subjects 6 to 9 years of age. Lubiprostone also appeared to be more effective in more severely constipated subjects presenting with less than 1.5 SBMs at baseline as compared with those presenting with ≥1.5 SBMs. A combined subgroup analysis for gender and age is also provided in Section 11.4.1.1.2, Table 10. This latter data suggests that lubiprostone may represent an effective treatment vs. placebo for properly diagnosed, severe PFC subjects in the age group of 10-17 years.

In addition, a post-hoc analysis for comparison of treatment effects on the key secondary endpoints of overall change from baseline in SBM frequency, straining and stool consistency was done for the mITT1 Population and the post-hoc mITT2 Population. This data demonstrated consistent treatment effects of lubiprostone across both genders. In the post-hoc mITT2 Population, a statistically significant difference in favour of lubiprostone in male subjects was observed for overall change from baseline in SBM frequency and straining. Results are summarized in Table 25.

Table 25. Comparison of key secondary endpoints (overall change from baseline in SBM frequency, straining and stool consistency) between genders

Endpoint	Females	Total Population	Males
mITT1			
Overall Change from Baseline SBM Frequency: Treatment Difference	0.19 SBMs	0.20 SBMs	0.23 SBMs
Overall Change from Baseline SBM Frequency: p-value	p=0.3664 (N: 204:104)	p=0.0470* (N: 379:188)	p=0.0160* (N:175:84)
Overall Change from Baseline Straining: Treatment Difference	-0.12 Units	-0.21 Units	-0.30 Units
Overall Change from Baseline Straining: p-value	p=0.4013 (N:175:88)	p=0.0184* (N: 334:162)	p=0.0724 (N:159:74)
Overall Change from Baseline Stool Consistency: Treatment Difference	0.16 Units	0.15 Units	0.14 Units
Overall Change from Baseline Stool Consistency: p-value	p=0.2366 (N:175:88)	p=0.0350* (N:334:162)	p=0.5073 (N=159:74)
mITT2			
Overall Change from Baseline SBM Frequency: Treatment Difference	0.19 SBMs	0.20 SBMs	0.22 SBMs

Endpoint	Females	Total Population	Males
Overall Change from Baseline SBM Frequency: p-value	p=0.3417 (N: 180:88)	p=0.0325* (N: 331:165)	p=0.0103* (N:151:77)
Overall Change from Baseline Straining: Treatment Difference	-0.17 Units	-0.25 Units	-0.34 Units
Overall Change from Baseline Straining: p-value	p=0.2389 (N:161:79)	p=0.0093* (N: 300:148)	p=0.0491* (N:139:69)
Overall Change from Baseline Stool Consistency: Treatment Difference	0.16 Units	0.15 Units	0.14 Units
Overall Change from Baseline Stool Consistency: p-value	p=0.1452 (N:161:79)	p=0.0267* (N:300:148)	p=0.3894 (N=139:69)

References: Tables 14.2.61, 14.2.62, 14.2.63, 14.2.29.1.1, 14.2.38.1.1, 14.2.39.1.1, 14.2.56, 14.2.64, 14.2.57, 14.2.65, 14.2.58, 14.2.66
mITT1: All subjects excluding subjects from Sites 1064 and 1082
mITT2: All North American subjects excluding subjects from Sites 1064 and 1082 (post hoc)
p: p-value; derived from respective statistical test specified in the Statistical Analysis Plan; *p<0.05
N: Number of subjects, total lubiprostone arm: placebo arm

11.4.3 Tabulation of Individual Response Data

Individual response data are provided in Appendix 16.2.

11.4.4 Drug Dose, Drug Concentration, and Relationships to Response

Drug dose, drug concentration, and relationships to response are provided in the PK Report, an attachment presented in Appendix 16.4.

11.4.5 Drug–Drug and Drug–Disease Interactions

Drug-drug and drug-disease interaction evaluation were neither planned nor performed in this study.

11.4.6 By-Subject Displays

Weekly and monthly efficacy response data are presented by subject in Listing 16.2.6.1, Listing 16.2.6.2, and Listing 16.2.6.3.

11.4.7 Efficacy Conclusions

For the primary endpoint of overall SBM response, lubiprostone did not demonstrate a statistically significant difference over placebo in the total trial population. However, there is clear statistical evidence that lubiprostone is effective for this endpoint in females at the age of 10 to 17 years (Table 10). Furthermore, if these subjects had previously failed on laxatives, the effects are even more pronounced. The latter is mainly driven by a drop of placebo response in the subjects with a history of previous laxative failure. When considering only subjects enrolled at secondary or tertiary care centres, the effect size of lubiprostone vs. placebo on this endpoint in male subjects of this age category of 10 to 17 was very similar to the effect size observed for females (Table 10 and discussion thereof in Section 11.4.1.1.2). Indeed, assessment of overall SBM response is dependent on the type of enrollment site (primary care vs. secondary or tertiary care centre) as a post-hoc analysis suggested by clinical experts consulted demonstrated (Table 9). The experts advised that PFC patients presenting at primary care centres are often not true, or are only mildly-affected, PFC patients. In fact, the clinical experts felt strongly that for clear-cut definition of a PFC patient, broader ROME III criteria for PFC need to be fulfilled and, in their view, these were challenging for non-specialists to assess and evaluate. The constipation-related eligibility criteria provided in the protocol were considered to be driven too much by "adult CIC thinking" which the experts felt was inaccurate for the PFC population, most prominently with regards to the younger subjects enrolled. The experts also felt that in reality, primary care physicians, even when applying ROME III criteria, would often struggle to discriminate between PFC patients and patients with related disorders such as IBS-C. Thus, the hypothesis was raised that primary care subjects enrolled into the trial in fact may have represented a different population than those enrolled at specialist centres, and the former likely presented with typically milder, less chronic forms of constipation of various origin. The results presented in Table 10 appear to support this hypothesis and suggest lubiprostone had a clinically relevant effect on overall SBM response in properly defined and (ROME III-) diagnosed PFC subjects irrespective of gender.

Lubiprostone demonstrated a statistically significant difference over placebo in various secondary endpoints that are considered key secondary endpoints from a clinical perspective. These comprise secondary endpoints which address SBM-related signs and symptoms. In particular, they include overall change in SBM frequency (a directly SBM-related assessment, a sign), but also overall change from baseline in straining, stool consistency and painfulness associated with SBMs (efficacy parameters indirectly related to SBMs, symptoms). Findings related to fecal incontinence, as well as for the percentage of SBMs and BMs in toilet in the trial, are also supportive of a clinically important effect of lubiprostone in the PFC population assessed, although based on a comparably small number of evaluable subjects. Given that constipation-associated symptoms have similar importance to patients as does BM frequency, and effects in male subjects on these endpoints were very comparable to those in female subjects, the view that male subjects in the age category of 10 to 17 years may benefit to a similar extent from the treatment as do females of that age category is supported.

These conclusions are also supported by the data for investigators' assessment of treatment effectiveness and patient global impression of change (PGIC) by parent/guardian. In both these separate analyses, lubiprostone was rated as statistically significantly more effective; leading to statistically significantly better global disease impression at all timepoints assessed during the trial period.

Several additional efficacy endpoints were assessed for which no statistically significant difference in favour of lubiprostone could be demonstrated. However, for the vast majority of these disease parameters or ratings, consistent numerical trends in favour of lubiprostone were apparent. Interestingly, there were also a number of efficacy parameters for which relative treatment effects of lubiprostone vs. placebo increased over time and occasionally even reached statistical significance in study months or study weeks towards the end of the study. As such, in a holistic view of efficacy data, there is solid evidence that lubiprostone provided clinically relevant benefit to patients suffering from PFC.

A critical element of PFC is a strong behavioural component which is at the origin of the condition, particularity in younger children. This behavioural component expresses itself with a stool withholding pattern that is totally absent in adults and likely has a major influence on the time course by when an increase of SBM numbers can be expected to occur after treatment initiation in PFC patients. Indeed, at the origin of PFC is the child's experience of hard stools that are painful to pass and lead to a behaviour of stool retention to avoid pain.[24,25] Results for the primary endpoint, in particular considering the comparably poor results for this endpoint in subjects 6 to 9 years of age, should be interpreted with this in mind. Especially in younger patients it might take several weeks until patients realize and trust that their stool has become softer and bowel movements will no longer be as painful, only at which time the withholding pattern is likely broken and SBMs increase regularly. For this reason, the differentiation of treatment effects observed between children aged younger than 10 years and those older as presented in Table 10 for the primary endpoint is considered a clinically important finding. The primary endpoint applied in this study is likely not holistic and relevant enough for PFC patients, particularly for younger PFC patients, since only SBM-based and thus not adequately respecting the PFC population characteristics. The underlying psychological barrier in younger patients that expresses itself in stool withholding behaviour may simply be too dominant in these young PFC patients. A more holistic view at PFC should likely consider at least stool consistency, painfulness of bowel movements and lack of overflow incontinence in additions to SBM counts.

In consideration of this concept of a vicious cycle in PFC that starts with hard stools leading to painful experiences during defecation and driving withholding of stool and hence reduction of bowel movement frequency, Sucampo thought about how in the SAG/0211PFC-1131 trial data a potential reversal of the vicious cycle might possibly be evaluated. As hard stools and the experience of painful defecations are at the origin of the condition and the withholding pattern is likely only broken with the experience that stools are no longer hard and painful, an effective treatment would likely first have to improve stool consistency before a sustained increase in bowel movement frequency might be observed. As such, a post-hoc analysis was applied to the mITT1 and mITT2 populations in which – analogous to the SAG/0211PFC-1131 primary endpoint - an "overall stool consistency response" was defined as follows:

- An overall responder is defined as a subject who qualifies as a weekly responder for 9 out of 12 weeks during the treatment period, with durability demonstrated by at least 3 of the responder weeks occurring in the last 4 weeks of the 12-week study period.
- A weekly responder is defined as a subject who has improvement of at least one unit point on the respective ordinal scale (Modified Bristol Stool Scale*) vs. baseline for that week.

Baseline was defined as the average rating during the 2-week baseline period.

*Modified Bristol Stool Form Scale (5-point scale)
1: Separate hard lumps; 2: Sausage-shaped but lumpy; 3: Like a sausage, smooth and soft; 4: Fluffy pieces: 5: Watery, no solid pieces

Table 26 describes the result of this post hoc analysis. Lubiprostone demonstrated a significant difference vs. placebo in this overall stool consistency responder analysis, supporting the concept of a rapid and sustained improvement of stool consistency in the trial population.

Table 26. Overall Stool Consistency response (post hoc)

Population Observed Cases	N (L:P) n (L:P) n (L:P)%	Mean Treatment Difference	p-value
mITT1	385:188 40:7 10.4%:3.7%	6.7%	**0.0066***
mITT2	336:165 38:6 11.3%:3.6%	7.7%	**0.0045***

Reference: Tables 14.2.68.1 and 14.2.68.2
N (L: P): Number of subjects enrolled to population (Lubiprostone: Placebo)
n (L: P): Number of overall SBM responders in population (Lubiprostone: Placebo)
p: p-value. P-value is from a CMH test stratified by SBM frequency at randomisation (< 1.5 or >= 1.5) for Lubiprostone Overall vs. Placebo Overall. *p<0.05
mITT1: All subjects excluding subjects from Sites 1064 and 1082
mITT2: All North American subjects excluding subjects from Sites 1064 and 1082 (post hoc)

Finally, further on this concept of sequence of events, one would expect to see an increasing effect size of the lubiprostone treatment in regards of SBM response rates over time. Although never resulting in a statistically significant treatment difference between treatment arms in the full trial population, an increasing treatment difference in monthly SBM responder rates is observed over time (see Table 24).

In summary, the proposed sequence of events seems to be reflected in the trial data, supporting the view that withholding effects in this PFC population may well have influenced primary endpoint (overall SBM responder) results and further support a revision of the primary endpoint for the future PFC study with lubiprostone in pediatric subjects aged 6 months to 6 years. In fact, it also suggests that PFC subjects of the age 6 to 9 should possibly be assessed by applying such a more age-appropriate endpoint as well. Finally, this data also supports the view that while PFC represents the correlate of CIC in the pediatric population, it should be considered an independent indication as represented by the ROME diagnostic criteria – and ultimately is providing substantial additional evidence that there is clinically meaningful benefit for patients with PFC from treatment with lubiprostone.

11.4.8 PHARMACOKINETIC EVALUATION

This PK report describes the results of a population pharmacokinetic analysis and an exposure-efficacy/safety analysis of lubiprostone and its major metabolite based on data this study and from 2 other clinical studies that are part of the PFC program: Study SPI/0211SC-0641 and Study SAG/0211PFC-11S1. Lubiprostone (parent compound) was not appreciably distributed in the systemic circulation. Of all the concentration sample records, only 1 lubiprostone serum sample

had a measurable level, which precluded any exposure lubiprostone based analysis. Also, fewer than 10% of the total number of sample metabolite records included concentrations above the limit of quantification.

Systemic lubiprostone exposure showed an increasing trend in AEs of nausea, diarrhea, and vomiting, however, this systemic trend was less clear than with AE trends related purely to lubiprostone dose levels (Appendix 16.4).

Efficacy signals were weaker with increased systemic exposure, as was expected by the local action of lubiprostone.

12. SAFETY EVALUATION

12.1 Extent of Exposure

A summary of exposure to study medication for the mITT and mITT1 Populations is provided in Table 14.1.7 and Table 14.1.15, respectively. Subjects in this study received their first study medication, either placebo BID, lubiprostone 12 mcg BID, or lubiprostone 24 mcg BID on Study Day 1 (Visit 2).

Subjects who weighed <50 kg were given lubiprostone 12 mcg BID; whereas those who weighed ≥50 kg received 24 mcg BID. The placebo-treated subjects received placebo BID for the entire 12 weeks of the study.

In both the mITT and mITT1 Populations, the median duration of treatment BID was 85.0 days for the placebo BID group, 85.0 days for the lubiprostone 12 mcg BID group, 84.0 days for the lubiprostone 24 mcg BID group, and 85.0 days for the total lubiprostone BID group.

In the mITT Population the mean daily dose was 1.72 capsules in the placebo BID group, 1.75 capsules in the lubiprostone 12 mcg BID group, 1.69 capsules in the lubiprostone 24 mcg BID group, and 1.70 capsules in the total lubiprostone BID group. Mean compliance was 86.54% in the placebo BID group, 87.40% in the lubiprostone 12 mcg BID group, 86.0% in the lubiprostone 24 mcg BID group, and 86.37% in the total lubiprostone BID group. Exposure and compliance in the total mITT1 Population was highly similar.

12.2 Adverse Events

All subjects in the Safety Population were analysed for AEs.

12.2.1 Brief Summary of Adverse Events

An overall summary of TEAEs in the Safety Population is provided in Table 14.3.1.1.1 and in Table 27. The respective data for the Safety Population excluding subjects enrolled at Sites #1064 and #1082 is provided in Table 14.3.1.22.1.

In the full Safety population of 595 subjects, 353 (59.3%) reported ≥1 AE, 26 (4.4%) had ≥1 severe AE, 18 (3.0%) had ≥1 SAE, 6 (1.0%) who reported ≥1 treatment-related SAE, and 23 (3.9%) subjects who discontinued due to an AE. A total of 183 (30.8%) reported ≥1 TRAE and 15 (2.5%) who discontinued due to a TRAE. There were no deaths during this study.

Table 27. Overview of Treatment-emergent Adverse Events (Safety Population)

	Treatment Groups				
Category	Placebo BID N=195 n (%)	Lubiprostone 12 mcg BID N=231 n (%)	Lubiprostone 24 mcg BID N=169 n (%)	Total Lubiprostone N=400 n (%)	Total N=595 n (%)
Subjects with ≥1 AE	114 (58.5)	142 (61.5)	97 (57.4)	239 (59.8)	353 (59.3)
Subjects with ≥1 Severe AE	12 (6.2)	10 (4.3)	4 (2.4)	14 (3.5)	26 (4.4)
Subjects with ≥1 TRAE	49 (25.1)	76 (32.9)	58 (34.3)	134 (33.5)	183 (30.8)
Subjects with ≥1 SAE	7.(3.6)	9 (3.9)	2 (1.2)	11 (2.8)	18 (3.0)
Subjects with ≥1 Treatment-related SAE	2 (1.0)	4 (1.7)	0 (0.0)	4 (1.0)	6 (1.0)
Subjects who discontinued due to an AE	6 (3.1)	9 (3.9)	8 (4.7)	17 (4.3)	23 (3.9)
Subjects who discontinued due to a TRAE	3 (1.5)	6 (2.6)	6 (3.6)	12 (3.0)	15 (2.5)
Subjects who died due to an AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects who died due to a TRAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AE=adverse event; BID=twice daily; SAE=serious adverse event; TRAE=treatment-related adverse event; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event.
TEAEs any event with an onset date on or after the first dose of study medication and with an onset date no more than 7 days after the last dose of study medication.
All subjects are summarised with the dose group corresponding to the treatment they actually received at the time of randomisation.
Source: Table 14.3.1.1.1.

An overview of AEs and TEAEs is also provided for the DE Population with and without including subjects from Sites 1064 and 1082 in Table 14.3.1.1.2 and Table 14.3.1.22.2.

12.2.2 Display of Adverse Events

Tabular summaries of AEs may be found in Section 14.3, Safety Results.

For the full SAF Population a summary of TEAEs by SOC is presented in Table 14.3.1.2.1 and for TRAEs in Table 14.3.1.9.1. A summary of TEAEs and TRAEs that were severe in intensity is presented in Table 14.3.1.3 and Table 14.3.1.9.3. A summary of treatment-emergent and treatment-related SAEs in the SAF Population is presented Table 14.3.1.4, and Table 14.3.1.9.4. Finally, a summary of TEAEs and TRAEs in the SAF Population that led to discontinuation from the study is presented in Table 14.3.1.5 and Table 14.3.1.9.5, respectively.

Narratives for subjects who had SAEs or AEs that led to discontinuation may be found in Section 14.3.3.

Supportive statistical output for these tables are located in Appendix 16.1.9.2.14.3.1, Appendix 16.1.9.2.14.3.2, Appendix 16.1.9.2.14.3.3, Appendix 16.1.9.2.14.3.4, Appendix 16.1.9.2.14.3.5, and Appendix 16.1.9.2.14.3.6, respectively.

For the SAF Population excluding Sites 1064 and 1082 (hereinafter, "Reduced SAF Population"), a summary of TEAEs by SOC is presented in Table 14.3.1.23.1 and for TRAEs in Table 14.3.1.30.1. A summary of TEAEs and TRAEs that were severe in intensity in the Reduced SAF Population is presented in Table 14.3.1.24 and Table 14.3.1.30.3, respectively. A summary of treatment-emergent and treatment-related SAEs in the Reduced SAF Population is presented in Table 14.3.1.25 and Table 14.3.1.30.4, respectively. A summary of TEAEs and TRAEs in the Reduced SAF Population that led to discontinuation from the study is presented in Table 14.3.1.26 and Table 14.3.1.30.5, respectively.

12.2.3 Analysis of Adverse Events

12.2.3.1 Adverse Events by Body System and Preferred Term

Summaries of TEAEs with an incidence ≥ 2% are provided for the SAF Population by body system and preferred term in Table 28 and summarized in Table 14.3.1.2.1 . Table 14.3.1.23.1 summarises all TEAEs for the Reduced SAF Population.

Overall, the percentages of TEAEs reported by the placebo BID group and the total lubiprostone BID group were similar: 114 (58.5%) subjects and 239 (59.8%), respectively.

In both treatment groups, the most frequently reported TEAEs were in GI disorders: placebo BID group 55 (28.2%) and total lubiprostone BID group 144 (36.0%) followed by infections and infestations: placebo BID group 53 (27.2%) and total lubiprostone BID group 89 (22.3%).

The greater incidence of nausea in the total lubiprostone BID group (57 [14.3%] subjects) compared with the placebo BID group (14 [7.2%] subjects) was statistically significant (p=0.0148), as was the greater incidence of streptococcal pharyngitis in the placebo BID group (11 [5.6%] subjects) compared with the total lubiprostone BID group (8 [2.0%] subjects; p=0.0243).

Table 28. Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term with an Incidence ≥ 2% (Safety Population)

	Treatment Groups				
System Organ Class Preferred Term[a]	Placebo BID N=195 n (%)	Lubiprostone 12 mcg BID N=231 n (%)	Lubiprostone 24 mcg BID N=169 n (%)	Total Lubiprostone N=400 n (%)	p-Value
Subjects with ≥1 TEAE[b]	114 (58.5)	142 (61.5)	97 (57.4)	239 (59.8)	
Gastrointestinal disorders	55 (28.2)	87 (37.7)	57 (33.7)	144 (36.0)	
Nausea	14 (7.2)	32 (13.9)	25 (14.8)	57 (14.3)	0.0148
Vomiting	12 (6.2)	39 (16.9)	6 (3.6)	45 (11.3)	
Abdominal pain	23 (11.8)	21 (9.1)	21 (12.4)	42 (10.5)	
Diarrhoea	6 (3.1)	14 (6.1)	14 (8.3)	28 (7.0)	
Abdominal pain upper	6 (3.1)	16 (6.9)	4 (2.4)	20 (5.0)	

System Organ Class Preferred Term[a]	Treatment Groups Placebo BID N=195 n (%)	Lubiprostone 12 mcg BID N=231 n (%)	Lubiprostone 24 mcg BID N=169 n (%)	Total Lubiprostone N=400 n (%)	p-Value
Faecaloma	7 (3.6)	8 (3.5)	3 (1.8)	11 (2.8)	
Infections and infestations	53 (27.2)	56 (24.2)	33 (19.5)	89 (22.3)	
Nasopharyngitis	8 (4.1)	8 (3.5)	5 (3.0)	13 (3.3)	
Sinusitis	2 (1.0)	7 (3.0)	4 (2.4)	11 (2.8)	
Upper respiratory tract infection	9 (4.6)	5 (2.2)	6 (3.6)	11 (2.8)	
Pharyngitis streptococcal	11 (5.6)	7 (3.0)	1 (0.6)	8 (2.0)	0.0243
Urinary tract infection	3 (1.5)	5 (2.2)	3 (1.8)	8 (2.0)	
Nervous system disorders	17 (8.7)	22 (9.5)	25 (14.8)	47 (11.8)	
Headache	10 (5.1)	15 (6.5)	19 (11.2)	34 (8.5)	
Dizziness	5 (2.6)	7 (3.0)	6 (3.6)	13 (3.3)	
Investigations	14 (7.2)	19 (8.2)	18 (10.7)	37 (9.3)	
General disorders & administration site conditions	8 (4.1)	13 (5.6)	16 (9.5)	29 (7.3)	
Pyrexia	4 (2.1)	10 (4.3)	6 (3.6)	16 (4.0)	
Respiratory, thoracic & mediastinal disorders	9 (4.6)	17 (7.4)	10 (5.9)	27 (6.8)	
Oropharyngeal pain	2 (1.0)	5 (2.2)	3 (1.8)	8 (2.0)	
Injury, poisoning & procedural complications	13 (6.7)	14 (6.1)	5 (3.0)	19 (4.8)	
Psychiatric disorders	7 (3.6)	6 (2.6)	7 (4.1)	13 (3.3)	
Musculoskeletal & connective tissue disorders	8 (4.1)	6 (2.6)	6 (3.6)	12 (3.0)	
Skin & subcutaneous tissue disorders	6 (3.1)	7 (3.0)	5 (3.0)	12 (3.0)	
Reproductive system & breast disorders	3 (1.5)	4 (1.7)	2 (1.2)	6 (1.5)	
Immune system disorders	1 (0.5)	5 (2.2)	(0.0)	5 (1.3)	
Renal & urinary disorders	4 (2.1)	3 (1.3)	1 (0.6)	4 (1.0)	

System Organ Class Preferred Term[a]	Treatment Groups Placebo BID N=195 n (%)	Lubiprostone 12 mcg BID N=231 n (%)	Lubiprostone 24 mcg BID N=169 n (%)	Total Lubiprostone N=400 n (%)	p-Value

BID=twice daily; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
a. Preferred Term is from the MedDRA, v 17.0.
b. Subjects whose dose was escalated at the end of Week 1 are summarised with the dose group to which they were assigned at the time of randomisation.
TEAE=any event with an onset date on or after the first dose of study medication and with an onset date no more than 7 days after the last dose of study medication.
p-Value is from a Fisher's exact test performed to compare incidence rates at Preferred Term, System Organ Class, and "at least one event" level between the placebo group and the total lubiprostone group. Only statistically significant p-Values (<0.05) are presented.
Source: Table 14.3.1.2.1.

These summaries are also provided for the DE Population in Table 14.3.1.2.2 and for the DE population excluding subjects from Sites 1064 and 1082 in Table 14.3.1.23.2.

Tables 14.3.1.8 and Table 14.3.1.9.8 provide an overview on the most frequent (observed in at least 5% of subjects) TEAEs and TRAEs observed in the SAF Population, respectively. Tables 14.3.1.29 and Table 14.3.1.30.8 provide the same information for the Reduced SAF Population, respectively.

Subgroup analyses for TEAEs for comparison by genders for the SAF Population is provided in Table 14.3.1.10.1 and Table 14.3.1.10.2 and for the Reduced SAF Population in Table 14.3.1.31.1. and Table 14.3.1.31.2. Incidence rates of AEs in lubiprostone treated subjects were similar across genders with the exception of nausea which occurred almost twice as frequently in female than in male subjects 17.5% vs. 10.4%).

Subgroup analyses for TEAEs for comparison by races for the SAF Population is provided in Table 14.3.1.11.1 to Table 14.3.1.11.3 and for the Reduced SAF Population in Table 14.3.1.32.1 to Table 14.3.1.32.3. Incidence rates of AEs in lubiprostone treated subjects were similar across races with the exception of nausea and vomiting which occurred more frequently in white subjects than in black subjects treated with lubiprostone (16.6% vs. 6.0% for nausea; 12.7% vs. 7.5% for vomiting; Tables 14.3.1.11.1 and Table 14.3.1.11.2).

Subgroup analyses for TEAEs for comparison by age categories for the SAF Population is provided in Table 14.3.1.12.1 to Table 14.3.1.12.3 and for the Reduced SAF Population in Table 14.3.1.33.1. to Table 14.3.1.33.3. Incidence rates of AEs in lubiprostone treated subjects were similar across age categories with the exception of vomiting which showed an age-dependent decrease and occurred in 17.6% of subjects age 6 to 9 years vs. only in 4.8% of subjects age 14 to 17. Headache was observed more frequently in subjects 10 to 13 years (14.3%) than in subjects 6-9 years (4.9%) or 14 to 17 years (4.8%) (Tables 14.3.1.12.1 to Table 14.3.1.12.3).

Subgroup analyses for TEAEs for comparison for subjects enrolled with less or more than 1.5 SBMs at baseline for the SAF Population is provided in Table 14.3.1.13.1 and Table 14.3.1.13.2 and for the Reduced safety population in Table 14.3.1.34.1. and Table 14.3.1.34.2. Incidence rates of AEs in lubiprostone treated subjects were similar across this parameter with the exception of diarrhoea which occurred more frequently in subjects enrolled with more than 1.5 SBMs at baseline.

Subgroup analyses for TEAEs for comparison for subjects enrolled with less or more than 50kg body weight at baseline for the SAF Population is provided in Table 14.3.1.14.1 and Table 14.3.1.14.2 and for the Reduced SAF Population in Table 14.3.1.35.1. and Table 14.3.1.35.2. Incidence rates of AEs in lubiprostone treated subjects were similar across this parameter with the exception of vomiting which occurred more frequently in subjects enrolled with less than 50 kg body weight vs. those with more than 50 kg body weight at baseline (16.9% vs. 3.6%) and headache which occurred less frequently in those with 50kg body weight at baseline (6.5% vs. 11.2%).

Subgroup analyses for TEAEs for comparison for subjects enrolled with a BMI of less or more than 25 at baseline for the SAF Population is provided in Table 14.3.1.15.1 and Table 14.3.1.15.2 and for the Reduced SAF Population in Table 14.3.1.36.1. and Table 14.3.1.36.2. Incidence rates of AEs in lubiprostone treated subjects were similar across this parameter with the exception of vomiting which occurred more frequently in subjects enrolled with a BMI lower than 25 vs. those with a BMI above 25 at baseline (12.8% vs. 5.7%) and diarrhoea which occurred less frequently in those with a BMI below 25 at baseline (5.8% vs. 11.5%).

12.2.3.2 Adverse Events by Intensity

Analyses and summaries of incidences of all AEs are provided by intensity, body system, and PT, including AEs considered to be possibly or probably related to study drug, and AEs considered to be unrelated to study drug. These are provided in Table 14.3.1.6 and Table 14.3.1.9.6 for TEAEs and TRAEs by maximal intensity and in Table 14.3.1.7 and Table 14.3.1.9.7 by maximal relationship for the SAF Population.

These summaries are also provided for the Reduced SAF Population in Table 14.3.1.27, Table 14.3.1.30.6, Table 14.3.1.28 and Table 14.3.1.30.7, respectively.

The vast majority of TEAEs and TRAEs in both the Total and Reduced SAF Populations were of mild or moderate intensity. In the Total SAF Population, 12 (6.2%) of subjects in the placebo BID group and 14 (3.5%) of subjects in the total lubiprostone BID group reported at least one severe TEAE (Table 14.3.1.3); the only severe TEAE which occurred statistically significantly more frequently in one of the treatment arms was constipation which occurred in 3 (1.5%) placebo-treated subjects and in 0 (0%) lubiprostone-treated subjects. The data for the Reduced SAF population is provided in Table 14.3.1.24. Data on severe TRAEs is provided in Table 14.3.1.9.3: such events occurred in 6 (3.1%) placebo-treated subjects vs. 9 (2.3%) lubiprostone-treated subjects (Table 29). The data for the Reduced SAF population is provided in Table 14.3.1.30.3.

Table 29. Summary of Severe TRAEs in the SAF Population

System Organ Class Preferred term (MedDRA dictionary 17.0)	Placebo BID N=195 n (%)	Lubiprostone 24 mcg BID N=231 n (%)	Lubiprostone 48 mcg BID N=169 n (%)	Lubiprostone Total N=400 n (%)
Subjects With at Least One Treatment-Related Severe Adverse Event[a, b]	6 (3.1)	6 (2.6)	3 (1.8)	9 (2.3)
GASTROINTESTINAL DISORDERS	6 (3.1)	5 (2.2)	2 (1.2)	7 (1.8)
ABDOMINAL PAIN	2 (1.0)	3 (1.3)	2 (1.2)	5 (1.3)
CONSTIPATION	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
FAECALOMA	3 (1.5)	2 (0.9)	0 (0.0)	2 (0.5)
IMMUNE SYSTEM DISORDERS	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
ANAPHYLACTOID REACTION	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
NERVOUS SYSTEM DISORDERS	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
HEADACHE	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)

N: Number of subjects assigned to treatment
n(%): relative number of events in N
[a]Treatment-related severe adverse events are treatment-emergent events with "DEFINITE", "POSSIBLE", or "PROBABLY" relationship to study medication.
[b]Subjects whose dose was escalated at the end of Week 1 are summarized with the dose group to which they actually received at randomisation.
Source: Table 14.3.1.9.3.

12.2.3.3 Adverse Events by Relation to Study Drug

A summary of TRAEs is provided for the Total SAF Population body system and preferred term in Table 14.3.1.9.1 and for the Reduced SAF Population in Table 14.3.1.30.1.

Overall, TRAEs were reported by fewer subjects in the placebo BID group (49 [25.1%] subjects) than in the total lubiprostone BID group (134 [33.5%] subjects); the difference was statistically significant (p=0.0380).

In both treatment groups, the most frequently reported TRAEs were in GI disorders: placebo BID group 34 (17.4%) subjects compared with total lubiprostone BID group 104 (26.0%) subjects; the difference was statistically significant (p=0.0227). This was followed by nervous system disorders with 10 (5.1%) subjects in the placebo BID group and 30 (7.5%) in the total lubiprostone BID group.

The greatest incidences of TRAEs reported in the placebo BID group subjects were abdominal pain (14 [7.2%] subjects) followed by nausea (10 [5.1%]), vomiting (5 [2.6%]), and headache (5 [2.6%]). In the total lubiprostone BID group, the greatest incidences were nausea (47 [11.8%] subjects) followed by abdominal pain (31 [7.8%] subjects), and vomiting (30 [7.5%] subjects). The incidence of nausea and vomiting in the total lubiprostone BID group compared with the placebo BID group (10 [5.1%] and 5 [2.6%] subjects, respectively) were statistically significant (p=0.0111 and p=0.0155, respectively). Table 30 provides the overview on TRAEs occurring in at least 1% of subjects.

Table 30. Summary of Treatment-related Adverse Events by System Organ Class and Preferred Term with an Incidence ⩾1% (Safety Population)

		Lubiprostone			
System Organ Class Preferred term (MedDRA dictionary 17.0)	**Placebo N=195 n (%)**	**12 mcg BID N=231 n (%)**	**24 mcg BID N=169 n (%)**	**Total N=400 n (%)**	**P-value [1]**
GASTROINTESTINAL DISORDERS					
ABDOMINAL PAIN	14 (7.2)	15 (6.5)	16 (9.5)	31 (7.8)	
DIARRHOEA	4 (2.1)	8 (3.5)	13 (7.7)	21 (5.3)	
NAUSEA	10 (5.1)	28 (12.1)	19 (11.2)	47 (11.8)	0.0111*
VOMITING	5 (2.6)	24 (10.4)	6 (3.6)	30 (7.5)	0.0155*
NERVOUS SYSTEM DISORDERS					
HEADACHE	5 (2.6)	9 (3.9)	12 (7.1)	21 (5.3)	

N: Number of subjects assigned to treatment
n(%): relative number of events in N
[1] P-value is from a Fisher's exact test. The test is performed to compare incidence rates at Preferred Term, System Organ Class, and "At Least One Event" level between the placebo group and the overall lubiprostone group. Only statistical significant P-values smaller than 0.05 are presented.
Note: TRAEs with preferred terms occurring more than 5% subjects.
Source: Table 14.3.1.9.1.

Subgroup analyses for TRAEs for comparison by genders for the full SAF Population is provided in Table 14.3.1.16.1 and Table 14.3.1.16.2 and for the Reduced SAF Population in Table 14.3.1.36.1. and Table 14.3.1.36.2. Subgroup analyses for TRAEs for comparison by races for the full SAF Population is provided in Table 14.3.1.17.1 to Table 14.3.1.17.3 and for the Reduced SAF Population in Table 14.3.1.37.1. to Table 14.3.1.37.3. Subgroup analyses for TRAEs for comparison by age categories for the full SAF Population is provided in Table 14.3.1.18.1 to Table 14.3.1.18.3 and for the Reduced SAF Population in Table 14.3.1.38.1. to Table 14.3.1.38.3. Subgroup analyses for TRAEs for comparison for subjects enrolled with less or more than 1.5 SBMs at baseline for the full SAF Population is provided in Table 14.3.1.19.1 and Table 14.3.1.19.2 and for the Reduced SAF Population in Table 14.3.1.39.1. and Table 14.3.1.39.2. Subgroup analyses for TRAEs for comparison for subjects enrolled with less or more than 50 kg body weight at baseline for the full SAF Population is provided in Table 14.3.1.20.1 and Table 14.3.1.20.2 and for the Reduced SAF Population in Table 14.3.1.40.1. and Table 14.3.1.40.2. Subgroup analyses for TRAEs for comparison for subjects enrolled at a BMI of less or more than 25 at baseline for the full SAF Population is provided in Table 14.3.1.21.1 and Table 14.3.1.21.2 and for the Reduced SAF Population in Table 14.3.1.41.1. and Table 14.3.1.41.2.

Incidence rates of TRAEs in lubiprostone-treated subjects were generally similar across all subgroups parameters with the exceptions very similar to those described in Section 12.2.3.1 for TEAEs.

Overall summaries are also provided for the full DE Population in Table 14.3.1.9.2 and for the Reduced DE Population in Table 14.3.1.30.2.

12.2.3.4 DXA Population Analyses Including Clinical Fracture Analysis

Subjects in the total DXA Population were assessed for bone mineral density (Table 14.3.4.5.1 and Table 14.3.4.5.2), bone mineral content (Table 14.3.4.5.3), and bone mineral density Z-score (Table 14.3.4.5.4 - Table 14.3.4.5.7). No significant difference in change from baseline for any of these parameters was detected between the study arms at Week 12. There were also no statistically significant differences between the treatment arms in height, height Z-score, weight and weight Z-score (Table 14.3.4.5.8) or the number of subjects with bone mineral density reduction greater than 4% (Table 14.3.4.5.9).

One clinical fracture occurred in a male subject randomised to the 12mcg BID lubiprostone dose and one in a female subject randomised to placebo BID (Table 14.3.4.5.10).

Results were highly similar for comparison between treatment arms across genders, races and age groups, while many of these subgroup comparisons were based on very few subjects only. Results are provided in Table 14.3.4.5.11.1 - Table 14.3.4.5.11.7, Table 14.3.4.5.12.1 - Table 14.3.4.5.12.7 and Table 14.3.4.5.13.1 - Table 14.3.4.5.13.7, respectively.

Subjects in the reduced DXA Population were assessed for bone mineral density (Table 14.3.4.10.1 and Table 14.3.4.10.2), bone mineral content (Table 14.3.4.10.3), and bone mineral density Z-score (Table 14.3.4.10.4 - Table 14.3.4.10.7). No significant difference in change from baseline for any of these parameters was detected between the study arms at Week 12. There were also no statistically significant differences between the treatment arms in height, height Z-score, weight and weight Z-score (Table 14.3.4.10.8) or the number of subjects with bone mineral density reduction greater than 4% (Table 14.3.4.10.9).

One clinical fracture occurred in a male subject randomised to the 12mcg BID lubiprostone dose and one in a female subject randomised to placebo BID (Table 14.3.4.10.10).

Results were highly similar for comparison between treatment arms across genders, races and age groups, while many of these subgroup comparisons were based on very few subjects only. Results are provided in Table 14.3.4.10.11.1 - Table 14.3.4.10.11.7, Table 14.3.4.10.12.1 - Table 14.3.4.10.12.7 and Table 14.3.4.10.13.1 - Table 14.3.4.10.13.7, respectively.

12.2.4 Listing of Adverse Events by Subject

Listing 16.2.7.1 presents details of all AEs by subject.

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1 Listing of Deaths, Other Serious Adverse Events, and Adverse Events Leading to the Discontinuation of Study Medication

There were no deaths reported during the study (see Section 14.3.2). All randomised subjects who reported AEs, including those who withdrew from treatment due to AEs, are shown in Listing 16.2.7.1. A list of all randomised subjects who had SAEs are shown in Listing 16.2.7.2.

12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Adverse Events Leading to the Discontinuation of Study Medication

Narratives for subjects who experienced SAEs, discontinued treatment due to an AE, were hospitalized due to an AE, and had other SAEs are presented in Section 14.3.3.

Data for subjects in the Full SAF Population for treatment-emergent and treatment-related SAEs are provided in Table 14.3.1.4 and Table 14.3.1.9.4, respectively. The same data for the Reduced SAF Population is provided in Table 14.3.1.25 and Table 14.3.1.30.4, respectively. The only treatment-related SAEs which occurred in lubiprostone-treated subjects but not in placebo-treated subjects were single cases of each chest pain, anaphylactoid reaction and rash in subjects randomised to the 12 mcg BID dose of lubiprostone (Table 14.3.1.9.4 and Table 14.3.1.30.4). Data for treatment-related SAEs are also listed in Table 14.3.2.3.

Data for subjects in the Full SAF Population for treatment-emergent and treatment-related adverse events leading to discontinuation are provided in Table 14.3.1.5 and Table 14.3.1.9.5, respectively. The same data for the Reduced SAF Population is provided in Table 14.3.1.26 and Table 14.3.1.30.5, respectively. The only treatment-related adverse events leading to discontinuation which occurred in lubiprostone-treated subjects but not in placebo-treated subjects were 4 cases of nausea (3 in the 24 mcg BID dose group, 1 in the 12 mcg BID dose group), and single cases of each vomiting (12 mcg BID group), chest pain (24 mcg BID group), anaphylactoid reaction (12 mcg BID group), pharyngeal edema (24 mcg BID group) and rash (12 mcg BID group) (Table 14.3.1.9.5 and Table 14.3.1.30.5). Data for treatment-related AEs leading to discontinuation are also listed in Table 14.3.2.4.

12.3.3 Analysis of Deaths, Other Serious Adverse Events, and Adverse Events Leading to the Discontinuation of Study Medication

No deaths occurred in the study. There were few treatment-related SAEs or AEs leading to discontinuation that occurred in lubiprostone-treated subjects only or at a higher incidence than in placebo-treated subjects. These events observed (i.e. nausea, chest pain, anaphylactoid reaction [hypersensitivity/allergic-type reaction; i.e., rash, swelling, throat tightness]) are well-known adverse events of lubiprostone, observed in adult subjects as well and are described in the product label for AMITIZA. Incidence rates of these events in the PFC population assessed in this study were lower than described for adult subjects.

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

Individual laboratory test measurements are provided by subject and abnormal laboratory value in Section 16.2.8 (Individual Laboratory Measurements by Subject). In these listings, laboratory test values above and below the normal reference range, as defined by the central laboratory, are flagged as high (H) or low (L) next to the numerical value.

For the total SAF Population, the summary of haematology laboratory values is provided in Table 14.3.4.1.1 and for the Reduced SAF Population in Table 14.3.4.6.1. The summary for biochemistry laboratory values is provided in Table 14.3.4.2.1 and Table 14.3.4.7.1, respectively. The summary for urinalysis laboratory values is provided in Table 14.3.4.3.1 and Table 14.3.4.8.1, respectively.

Shift tables for haematology, biochemistry and urinalysis laboratory values for the total SAF Population are provided in Table 14.3.4. 1.2, Table 14.3.4.2.2, and Table 14.3.6.4.3.2, respectively. Shift tables for haematology, biochemistry and urinalysis laboratory values for the Reduced SAF Population are provided in Table 14.3.4.6.2, Table 14.3.4.7.2, and Table 14.3.4.8.2, respectively

12.4.2 Evaluation of Each Laboratory Parameter

12.4.2.1 Laboratory Values over Time

There were no statistically significant differences in mean change from baseline levels between treatment arms in the total or Reduced SAF Population for haematology laboratory values (Table 14.3.4.1.1; Table 14.3.4.6.1) other than for the percent of lymphocytes (decrease of 1.4% in the total lubiprostone BID group vs. an increase of 0.5% in the placebo BID group), percent neutrophils (increase of 1.8% in the total lubiprostone BID group vs. decrease of 0.2% in the placebo BID group), neutrophils absolute (increase of $0.1x10^9$/L cells in the total lubiprostone BID group vs. decrease of $0.2x10^9$/L cells in the placebo BID group), mean corpuscular haemoglobin (increase of 0.1pg in total lubiprostone group vs. decrease of 0.1pg in placebo group) and monocytes absolute at Week 4. However, no such differences were observed at any of the other assessment points (Week 1, Week 8, Week 12) and none was considered clinically relevant and not represented by apparent shifts from normal to high or low values in the respective shift table (Table 14.3.4.1.2; Table 14.3.4.6.2).

There were no statistically significant differences in mean change from baseline levels between treatment arms in the total or Reduced SAF Population for biochemistry laboratory values (Table 14.3.4.2.1; Table 14.3.4.7.1) other than for ALT at Week 1 (increase of 0.7 IU in the total lubiprostone BID group vs. decrease of 0.9 IU in the placebo BID group), chloride at Week 4 (decrease of 0.2 mmol/L in the total lubiprostone BID group vs. increase of 0.3 mmol/L in the total placebo group), LDH at Week 4 (decrease of 3.1 IU/L in the total lubiprostone BID group vs. increase of 2.1 IU/L in the total placebo group), GGT at Week 8 (decrease of 0.5 IU/L in the total lubiprostone BID group vs. increase of 0.7 IU/L in the total placebo group), iron at Week 1 and 4 (decrease of 1.2 and 0.9 µmol /L in the total lubiprostone BID group, respectively vs. increase of 0.1 and 0.6 µmol /L in the total placebo group, respectively), and uric acid at Weeks 4 and 8 (decrease in lubiprostone BID treatment arm vs. increase in placebo treatment arm). However, no

such differences were observed at other assessment points and none was considered clinically relevant and not represented by apparent shifts from normal to high or low values in the respective shift table (Table 14.3.4.2.2; Table 14.3.4.7.2).

There were no statistically significant differences in mean change from baseline levels between treatment arms in the total or Reduced SAF Population for urinalysis laboratory values (Table 14.3.4.3.1; Table 14.3.4.8.1) and no apparent relevant shifts from normal to high or low values in the respective shift table (Table 14.3.4.3.2; Table 14.3.4.8.2).

12.4.2.2 Individual Subject Changes

There were no apparent relevant differences in any haematology, biochemical or urine parameters between the two treatment arms in regards of TRAEs as provided in Table 14.3.1.9.1 and Table 14.3.1.30.1 for the total or Reduced SAF Population.

12.4.2.3 Individual Clinically Significant Abnormalities

There were no perceived clinically relevant changes in laboratory parameters in the study.

12.5 Vital Signs, Physical Examinations, and Other Observations Related to Safety

For the total SAF Population, the summaries of vital signs are provided in Table 14.3.4.4.1, and in Table 14.3.4.9.1 for the Reduced SAF Population. Respective shift tables for blood pressure and heart rate are provided in Table 14.3.4.4.2 /Table 14.3.4.4.3 and Table 14.3.4.9.2/ Table 14.3.4.9.3, respectively.

There were no statistically significant differences in mean change from baseline levels between treatment arms in the Reduced SAF Population for any parameters with the exception of heart rate at Week 8 (decrease of 0.6 BPM in the total lubiprostone BID group vs. increase of 1.6 BPM in the placebo group), weight at Week 4, 8 and 12 (difference in relative weight gain between total lubiprostone BID and placebo BID of 0.2-0.5 kg) and BMI at Week 8 and 12 (no change to increase of 0.1 Units of mean BMI in total lubiprostone BID group vs. increase of BMI of 0.2-0.3 Units in the placebo BID group).

None of these changes was considered clinically relevant. In particular, analysis of shift tables for blood pressure and heart rate does not indicate any apparent difference in these parameters between the placebo and lubiprostone arms; in particular, there is no apparent induction of post-treatment hypotension on lubiprostone-treated subjects.

12.6 Safety Conclusions

In general, both doses of lubiprostone were well tolerated and the overall safety profile of lubiprostone observed in the trial is highly consistent with the one described in the current approved label for AMITIZA. As in adults, the AEs in PFC subjects primarily affected the gastrointestinal tract. Most frequently observed AEs were nausea, vomiting, diarrhoea and abdominal pain, while only for nausea and vomiting there was a statistically significant difference in regards of incidence rate observed for the lubiprostone treatment arm vs. the placebo control. The only non-GI associated

AE occurring frequently was headache. Specifically, while the type of AEs observed in the PFC trials was highly similar to what had been previously observed in clinical trials with lubiprostone in adults, the incidence rates of these AEs were in fact generally lower than observed in clinical trials in adults. The only exception to this finding was a slightly increased incidence of vomiting in comparison to incidence rates found in adults; however, the incidence rate of vomiting in placebo subjects was also higher than is observed in placebo-treated adult subjects. The intensity of the vast majority of AEs observed are mild-to-moderate, which is consistent with findings in the adult population. There were some differences in the incidence of these main AEs across genders, races and age groups, however none of these differences resulted in incidence rates substantially different from what is observed with lubiprostone treatment in adult patients.

There were no apparent safety relevant effects on laboratory parameters under lubiprostone treatment.

In addition to standard safety assessments, specific post-dose assessment of blood pressure and heart rate as well as long-term evaluation of bone mineral density parameters by means of DXA scanning has been applied in the study. No apparent clinically relevant differences between treatment arms were observed for any of these parameters.

13. DISCUSSION AND OVERALL CONCLUSIONS

Lubiprostone did not demonstrate statistical superiority vs. placebo for the primary endpoint of overall SBM response in this pivotal trial. However, taking into consideration the discussion of subgroup data on the primary endpoint presented and the results on key secondary endpoints given the lack of formally assessed and approved medical interventions for PFC patients, it is considered that lubiprostone provided clinically relevant medical benefit to patients with PFC, in particular to those of the age of 10 to 17 years and when looking at the data in a holistic clinical perspective.

The primary endpoint applied in this study may not be suitable for PFC patients in the age range of 6-9 years since, in all likelihood, the influence of withholding behaviour and the psychological factors underlying the disorder is too strong to enable the active drug to demonstrate relevant treatment differences vs. placebo on this endpoint.

In the female patients of the age of 10 to 17 years, pronounced efficacy signals on the primary endpoint were observed. In addition, when looking at subgroup data for males aged 10-17 years enrolled at specialist centres only, the effect size of lubiprostone vs. placebo on the primary endpoint of overall SBM response is very comparable to that in these females, suggesting that lubiprostone is likely effective in properly characterized male PFC patients. Lubiprostone demonstrated a statistically significant difference vs. placebo in the most important secondary endpoints in the total trial population (overall change from baseline in SBM frequency, straining, stool consistency and painfulness of SBMs. Given the importance of hard stools and the perception of painfulness of SBMs for the pathogenesis of PFC, these are considered findings of high clinical importance.

The safety profile of lubiprostone observed in this PFC trials is very consistent with what is known from adult patient trials and considered acceptable in an overall benefit-to-risk assessment – while incidence rates of AEs typically associated with the use of lubiprostone (i.e., nausea, diarrhoea,

headache) occur at a lower incidence rate as compared to adults. No unexpected AEs occurred in the study and in particular there is no evidence for effects of lubiprostone on bone growth or vital signs.

In summary, it is concluded that lubiprostone BID treatment is providing a clinically meaningful benefit to PFC patients, at least for those aged 10 to 17 years. A positive benefit-to-risk profile is observed for this age group.

14. TABLES AND FIGURES REFERRED TO BUT NOT DISPLAYED IN THE TEXT

14.1 Disposition, Demographics and Baseline Characteristics

14.1.1.1	Summary of Randomised Subjects by Center (All Randomised Subjects)
14.1.1.2	Summary of Study Population (All Randomised Subjects)
14.1.2	Summary of Subject Disposition (All Randomised Subjects)
14.1.3.1	Summary of Subjects Excluded from the Per-Protocol Population (Subjects Excluded from Per Protocol)
14.1.3.2	Summary of Protocol Deviations (All Randomised Subjects)
14.1.4.1	Summary of Demographics (mITT Population)
14.1.4.2	Summary of Demographics (SAF Population)
14.1.4.3	Summary of Demographics (PP Population)
14.1.4.4	Summary of Demographics (DXA Population)
14.1.5.1	Summary of Baseline Characteristics - Categorical Variables (mITT Population)
14.1.5.2	Summary of Baseline Characteristics - Continuous Variables (mITT Population)
14.1.6.1	Summary of Concomitant Medication (SAF Population)
14.1.6.2	Summary of Prior Constipation and Gastrointestinal Related Medication (SAF Population)
14.1.6.3	Summary of Rescue Medication (SAF Population)
14.1.7	Summary of Exposure to Study Medication (mITT Population)
14.1.8	Summary of Medical History (SAF Population)
14.1.9.1	Summary of Randomised Subjects by Center (All Randomised Subjects, Excluding Sites 1064 & 1082)
14.1.9.2	Summary of Study Population (All Randomised Subjects, Excluding Sites 1064 & 1082)
14.1.10	Summary of Subject Disposition (All Randomised Subjects, Excluding Sites 1064 & 1082)
14.1.11.1	Summary of Subjects Excluded from the Per-Protocol Population (Subjects Excluded from Per Protocol, Excluding Sites 1064 & 1082)
14.1.11.2	Summary of Protocol Deviations (All Randomised Subjects, Excluding Sites 1064 & 1082)
14.1.12.1	Summary of Demographics (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.1.12.2	Summary of Demographics (SAF Population, Excluding Sites 1064 & 1082)
14.1.12.3	Summary of Demographics (PP Population, Excluding Sites 1064 & 1082)
14.1.12.4	Summary of Demographics (DXA Population, Excluding Sites 1064 & 1082)
14.1.13.1	Summary of Baseline Characteristics - Categorical Variables (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.1.13.2	Summary of Baseline Characteristics - Continuous Variables (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.1.14.1	Summary of Concomitant Medication (SAF Population, Excluding Sites 1064 & 1082)
14.1.14.2	Summary of Prior Constipation and Gastrointestinal Related Medication (SAF Population, Excluding Sites 1064 & 1082)
14.1.14.3	Summary of Rescue Medication (SAF Population, Excluding Sites 1064 & 1082)
14.1.15	Summary of Exposure to Study Medication (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.1.16	Summary of Medical History (SAF Population, Excluding Sites 1064 & 1082)

14.2 Efficacy Results

14.2.6.2	Summary of SBMs within 4, 8, 12, 24 and 48 Hours of First Study Medication Administration (COMP Population)
14.2.6.3	Summary of SBMs within 4, 8, 12, 24 and 48 Hours of First Study Medication Administration (PP Population)
14.2.7.1	Treatment Response (mITT Population)
14.2.7.2	Treatment Response (PP Population)
14.2.8.1.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Incontinence Frequency, Observed Cases (mITT Population)
14.2.8.1.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Incontinence Frequency, LOCF (mITT Population)
14.2.8.2.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Incontinence Frequency, Observed Cases (PP Population)
14.2.8.2.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Incontinence Frequency, LOCF (PP Population)
14.2.9.1.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Production of Large Diameter Stool Frequency, Observed Cases (mITT Population)
14.2.9.1.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Production of Large Diameter Stool Frequency, LOCF (mITT Population)
14.2.9.2.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Production of Large Diameter Stool Frequency, Observed Cases (PP Population)
14.2.9.2.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Production of Large Diameter Stool Frequency, LOCF (PP Population)
14.2.10.1.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Proportion of SBMs in Toilet, Observed Cases (mITT Population)
14.2.10.1.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Proportion of SBMs in Toilet, LOCF (mITT Population)
14.2.10.2.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Proportion of SBMs in Toilet, Observed Cases (PP Population)
14.2.10.2.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Proportion of SBMs in Toilet, LOCF (PP Population)
14.2.11.1.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Proportion of BMs in Toilet, Observed Cases (mITT Population)
14.2.11.1.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Proportion of BMs in Toilet, LOCF (mITT Population)
14.2.11.2.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Proportion of BMs in Toilet, Observed Cases (PP Population)
14.2.11.2.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Proportion of BMs in Toilet, LOCF (PP Population)
14.2.12.1.1	Summary of Weekly, Monthly, and Overall Frequency of Retentive Posturing or Excessive Volitional Stool Retention Frequency, Observed Cases (mITT Population)
14.2.12.1.2	Summary of Weekly, Monthly, and Overall Frequency of Retentive Posturing or Excessive Volitional Stool Retention Frequency, LOCF (mITT Population)
14.2.12.2.1	Summary of Weekly, Monthly, and Overall Frequency of Retentive Posturing or Excessive Volitional Stool Retention Frequency, Observed Cases (PP Population)
14.2.12.2.2	Summary of Weekly, Monthly, and Overall Frequency of Retentive Posturing or Excessive Volitional Stool Retention Frequency, LOCF (PP Population)
14.2.13.1.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Straining Associated with SBMs, Observed Cases (mITT Population)

14.2.13.1.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Straining Associated with SBMs, LOCF (mITT Population)
14.2.13.2.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Straining Associated with SBMs, Observed Cases (PP Population)
14.2.13.2.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Straining Associated with SBMs, LOCF (PP Population)
14.2.14.1.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Stool Consistency Associated with SBMs, Observed Cases (mITT Population)
14.2.14.1.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Stool Consistency Associated with SBMs, LOCF (mITT Population)
14.2.14.2.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Stool Consistency Associated with SBMs, Observed Cases (PP Population)
14.2.14.2.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Stool Consistency Associated with SBMs, LOCF (PP Population)
14.2.15.1.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Constipation Severity, Observed Cases (mITT Population)
14.2.15.1.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Constipation Severity, LOCF (mITT Population)
14.2.15.2.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Constipation Severity, Observed Cases (PP Population)
14.2.15.2.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Constipation Severity, LOCF (PP Population)
14.2.16.1.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Abdominal Pain, Observed Cases (mITT Population)
14.2.16.1.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Abdominal Pain, LOCF (mITT Population)
14.2.16.2.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Abdominal Pain, Observed Cases (PP Population)
14.2.16.2.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Abdominal Pain, LOCF (PP Population)
14.2.17.1.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Painfulness of SBMs, Observed Cases (mITT Population)
14.2.17.1.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Painfulness of SBMs, LOCF (mITT Population)
14.2.17.2.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Painfulness of SBMs, Observed Cases (PP Population)
14.2.17.2.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Painfulness of SBMs, LOCF (PP Population)
14.2.18.1.1	Summary of Weekly, Monthly, and Overall Treatment Effectiveness, Observed Cases (mITT Population)
14.2.18.1.2	Summary of Weekly, Monthly, and Overall Treatment Effectiveness, LOCF (mITT Population)
14.2.18.2.1	Summary of Weekly, Monthly, and Overall Treatment Effectiveness, Observed Cases (PP Population)
14.2.18.2.2	Summary of Weekly, Monthly, and Overall Treatment Effectiveness, LOCF (PP Population)
14.2.19.1.1.1	Summary of PedsQL™ Response – Subject Questionnaire, Observed Cases (mITT Population)
14.2.19.1.1.2	Summary of PedsQL™ Response – Subject Questionnaire, LOCF (mITT Population)

14.2.30.2.2	Summary of Weekly, Monthly, and Overall Change from Baseline in BM Frequency, LOCF (PP Population, Excluding Sites 1064 & 1082)
14.2.31.1	Summary of SBMs within 4, 8, 12, 24 and 48 Hours of First Study Medication Administration (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.31.2	Summary of SBMs within 4, 8, 12, 24 and 48 Hours of First Study Medication Administration (COMP Population, Excluding Sites 1064 & 1082)
14.2.31.3	Summary of SBMs within 4, 8, 12, 24 and 48 Hours of First Study Medication Administration (PP Population, Excluding Sites 1064 & 1082)
14.2.32.1	Treatment Response (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.32.2	Treatment Response (PP Population, Excluding Sites 1064 & 1082)
14.2.33.1.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Incontinence Frequency, Observed Cases (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.33.1.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Incontinence Frequency, LOCF (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.33.2.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Incontinence Frequency, Observed Cases (PP Population, Excluding Sites 1064 & 1082)
14.2.33.2.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Incontinence Frequency, LOCF (PP Population, Excluding Sites 1064 & 1082)
14.2.34.1.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Production of Large Diameter Stool Frequency, Observed Cases (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.34.1.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Production of Large Diameter Stool Frequency, LOCF (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.34.2.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Production of Large Diameter Stool Frequency, Observed Cases (PP Population, Excluding Sites 1064 & 1082)
14.2.34.2.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Production of Large Diameter Stool Frequency, LOCF (PP Population, Excluding Sites 1064 & 1082)
14.2.35.1.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Proportion of SBMs in Toilet, Observed Cases (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.35.1.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Proportion of SBMs in Toilet, LOCF (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.35.2.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Proportion of SBMs in Toilet, Observed Cases (PP Population, Excluding Sites 1064 & 1082)
14.2.35.2.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Proportion of SBMs in Toilet, LOCF (PP Population, Excluding Sites 1064 & 1082)
14.2.36.1.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Proportion of BMs in Toilet, Observed Cases (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.36.1.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Proportion of BMs in Toilet, LOCF (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.36.2.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Proportion of BMs in Toilet, Observed Cases (PP Population, Excluding Sites 1064 & 1082)
14.2.36.2.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Proportion of BMs in Toilet, LOCF (PP Population, Excluding Sites 1064 & 1082)
14.2.37.1.1	Summary of Weekly, Monthly, and Overall Frequency of Retentive Posturing or Excessive Volitional Stool Retention Frequency, Observed Cases (mITT Population, Excluding Sites 1064 & 1082 [mITT1])

14.2.37.1.2	Summary of Weekly, Monthly, and Overall Frequency of Retentive Posturing or Excessive Volitional Stool Retention Frequency, LOCF (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.37.2.1	Summary of Weekly, Monthly, and Overall Frequency of Retentive Posturing or Excessive Volitional Stool Retention Frequency, Observed Cases (PP Population, Excluding Sites 1064 & 1082)
14.2.37.2.2	Summary of Weekly, Monthly, and Overall Frequency of Retentive Posturing or Excessive Volitional Stool Retention Frequency, LOCF (PP Population, Excluding Sites 1064 & 1082)
14.2.38.1.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Straining Associated with SBMs, Observed Cases (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.38.1.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Straining Associated with SBMs, LOCF (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.38.2.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Straining Associated with SBMs, Observed Cases (PP Population, Excluding Sites 1064 & 1082)
14.2.38.2.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Straining Associated with SBMs, LOCF (PP Population, Excluding Sites 1064 & 1082)
14.2.39.1.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Stool Consistency Associated with SBMs, Observed Cases (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.39.1.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Stool Consistency Associated with SBMs, LOCF (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.39.2.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Stool Consistency Associated with SBMs, Observed Cases (PP Population, Excluding Sites 1064 & 1082)
14.2.39.2.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Stool Consistency Associated with SBMs, LOCF (PP Population, Excluding Sites 1064 & 1082)
14.2.40.1.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Constipation Severity, Observed Cases (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.40.1.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Constipation Severity, LOCF (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.40.2.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Constipation Severity, Observed Cases (PP Population, Excluding Sites 1064 & 1082)
14.2.40.2.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Constipation Severity, LOCF (PP Population, Excluding Sites 1064 & 1082)
14.2.41.1.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Abdominal Pain, Observed Cases (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.41.1.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Abdominal Pain, LOCF (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.41.2.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Abdominal Pain, Observed Cases (PP Population, Excluding Sites 1064 & 1082)
14.2.41.2.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Abdominal Pain, LOCF (PP Population, Excluding Sites 1064 & 1082)
14.2.42.1.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Painfulness of SBMs, Observed Cases (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.42.1.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Painfulness of SBMs, LOCF (mITT Population, Excluding Sites 1064 & 1082 [mITT1])

14.2.42.2.1	Summary of Weekly, Monthly, and Overall Change from Baseline in Painfulness of SBMs, Observed Cases (PP Population, Excluding Sites 1064 & 1082)
14.2.42.2.2	Summary of Weekly, Monthly, and Overall Change from Baseline in Painfulness of SBMs, LOCF (PP Population, Excluding Sites 1064 & 1082)
14.2.43.1.1	Summary of Weekly, Monthly, and Overall Treatment Effectiveness, Observed Cases (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.43.1.2	Summary of Weekly, Monthly, and Overall Treatment Effectiveness, LOCF (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.43.2.1	Summary of Weekly, Monthly, and Overall Treatment Effectiveness, Observed Cases (PP Population, Excluding Sites 1064 & 1082)
14.2.43.2.2	Summary of Weekly, Monthly, and Overall Treatment Effectiveness, LOCF (PP Population, Excluding Sites 1064 & 1082)
14.2.44.1.1.1	Summary of PedsQL™ Response – Subject Questionnaire, Observed Cases (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.44.1.1.2	Summary of PedsQL™ Response – Subject Questionnaire, LOCF (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.44.1.2.1	Summary of PedsQL™ Response – Subject Questionnaire, Observed Cases (PP Population, Excluding Sites 1064 & 1082)
14.2.44.1.2.2	Summary of PedsQL™ Response – Subject Questionnaire, LOCF (PP Population, Excluding Sites 1064 & 1082)
14.2.44.2.1.1	Summary of PedsQL™ Response – Parent/Guardian Questionnaire, Observed Cases (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.44.2.1.2	Summary of PedsQL™ Response – Parent/Guardian Questionnaire, LOCF (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.44.2.2.1	Summary of PedsQL™ Response – Parent/Guardian Questionnaire, Observed Cases (PP Population, Excluding Sites 1064 & 1082)
14.2.44.2.2.2	Summary of PedsQL™ Response – Parent/Guardian Questionnaire, LOCF (PP Population, Excluding Sites 1064 & 1082)
14.2.45.1.1	Summary of Investigator Assessment of Treatment Effectiveness, Observed Cases (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.45.1.2	Summary of Investigator Assessment of Treatment Effectiveness, LOCF (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.45.2.1	Summary of Investigator Assessment of Treatment Effectiveness, Observed Cases (PP Population, Excluding Sites 1064 & 1082)
14.2.45.2.2	Summary of Investigator Assessment of Treatment Effectiveness, LOCF (PP Population, Excluding Sites 1064 & 1082)
14.2.46.1.1.1	Summary of Patient Global Impression of Change by Parent, Observed Cases (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.46.1.1.2	Summary of Patient Global Impression of Change by Parent, LOCF (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.46.1.2.1	Summary of Patient Global Impression of Change by Parent, Observed Cases (PP Population, Excluding Sites 1064 & 1082)
14.2.46.1.2.2	Summary of Patient Global Impression of Change by Parent, LOCF (PP Population, Excluding Sites 1064 & 1082)
14.2.46.2.1.1	Summary of Patient Global Impression of Change by Subject, Observed Cases (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.46.2.1.2	Summary of Patient Global Impression of Change by Subject, LOCF (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.46.2.2.1	Summary of Patient Global Impression of Change by Subject, Observed Cases (PP Population, Excluding Sites 1064 & 1082)

14.2.46.2.2.2	Summary of Patient Global Impression of Change by Subject, LOCF (PP Population, Excluding Sites 1064 & 1082)
14.2.47.1.1	Summary of Clinician Severity Rating, Observed Cases (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.47.1.2	Summary of Clinician Severity Rating, LOCF (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.47.2.1	Summary of Clinician Severity Rating, Observed Cases (PP Population, Excluding Sites 1064 & 1082)
14.2.47.2.2	Summary of Clinician Severity Rating, LOCF (PP Population, Excluding Sites 1064 & 1082)
14.2.48.1	Summary of Monthly and Overall Rescue Medication Use, Observed Cases (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.48.2	Summary of Monthly and Overall Rescue Medication Use, Observed Cases (PP Population, Excluding Sites 1064 & 1082)
14.2.49	Summary of Key Secondary Efficacy Endpoints (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.50.1.1	Subgroup Analysis of Overall SBM Response, Observed Cases (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.50.1.2	Subgroup Analysis of Overall SBM Response, LOCF (mITT Population, Excluding Sites 1064 & 1082 [mITT1])
14.2.50.2.1	Subgroup Analysis of Overall SBM Response, Observed Cases (PP Population, Excluding Sites 1064 & 1082)
14.2.50.2.2	Subgroup Analysis of Overall SBM Response, LOCF (PP Population, Excluding Sites 1064 & 1082)
Post-Hoc Analyses:	
14.2.51.1.1	Overall SBM Response for Each Individual Placebo and Lubiprostone Group (mITT1 Population)
14.2.51.1.2	Overall SBM Response for Each Individual Placebo and Lubiprostone Group (mITT2 Population)
14.2.51.1.3	Overall SBM Response for Each Individual Placebo and Lubiprostone Group (mITT1 Population, with History of Failed Constipation Treatment)
14.2.51.1.4	Overall SBM Response for Each Individual Placebo and Lubiprostone Group (mITT2 Population, with History of Failed Constipation Treatment)
14.2.51.2.1	Overall SBM Response for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT2 Population)
14.2.51.2.2	Overall SBM Response for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT1 Population, with History of Failed Constipation Treatment)
14.2.51.2.3	Overall SBM Response for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT2 Population, with History of Failed Constipation Treatment)
14.2.51.2.4	Overall SBM Response for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT1 Population, without History of Failed Constipation Treatment)
14.2.51.2.5	Overall SBM Response for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT2 Population, without History of Failed Constipation Treatment)
14.2.52.1.1	Analysis of Overall SBM Response (Observed Case) for Each Individual Placebo and Lubiprostone Group (mITT3 Population)
14.2.52.1.2	Analysis of Overall SBM Response (Observed Case) for Each Individual Placebo and Lubiprostone Group (mITT3 Population, with History of Failed Constipation Treatment)

14.2.52.2.1	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT3 Population)
14.2.52.2.2	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT3 Population, with History of Failed Constipation Treatment)
14.2.52.2.3	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT3 Population, without History of Failed Constipation Treatment)
14.2.52.2.4	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT1 Population, by Primary Care Center vs. Secondary/Tertiary Care Center)
14.2.52.2.5	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT2 Population, by Primary Care Center vs. Secondary/Tertiary Care Center)
14.2.52.2.6	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT1 Population, with History of Failed Constipation Treatment, by Primary Care Center vs. Secondary/Tertiary Care Center)
14.2.52.2.7	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT2 Population, with History of Failed Constipation Treatment, by Primary Care Center vs. Secondary/Tertiary Care Center)
14.2.52.2.8	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT3 Population, with History of Failed Constipation Treatment, by Primary Care Center vs. Secondary/Tertiary Care Center)
14.2.52.2.9	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT2 Population, with History of Failed Constipation Treatment, excluding Subjects with Misuse of Rescue Therapy, by Primary Care Center vs. Secondary/Tertiary Care Center)
14.2.52.2.10	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT1 Population Aged 10-17 Years)
14.2.52.2.11	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT2 Population Aged 10-17 Years)
14.2.52.2.12	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT1 Population Aged 10-17 Years, with History of Failed Constipation Treatment)
14.2.52.2.13	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT2 Population Aged 10-17 Years, with History of Failed Constipation Treatment)
14.2.52.2.14	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT1 Population Aged 10-17 Years, by Primary Care Center vs. Secondary/Tertiary Care Center)
14.2.52.2.15	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT1 Population Aged 10-17 Years, with History of Failed Constipation Treatment, by Primary Care Center vs. Secondary/Tertiary Care Center)
14.2.52.3.1	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE by Gender (mITT1 Population, by Primary Care Center vs. Secondary/Tertiary Care Center)

14.2.52.3.2	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE by Gender (mITT1 Population, with History of Failed Constipation Treatment, by Primary Care Center vs. Secondary/Tertiary Care Center)
14.2.52.3.3	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE by Gender (mITT1 Population Aged 10-17 Years)
14.2.52.3.4	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE by Gender (mITT2 Population Aged 10-17 Years)
14.2.52.3.5	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE by Gender (mITT1 Population Aged 10-17 Years, with History of Failed Constipation Treatment)
14.2.52.3.6	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE by Gender (mITT2 Population Aged 10-17 Years, with History of Failed Constipation Treatment)
14.2.52.3.7	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE by Gender (mITT1 Population, by Primary Care Center vs. Secondary/Tertiary Care Center)
14.2.52.3.8	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE by Gender (mITT1 Population, with History of Failed Constipation Treatment, by Primary Care Center vs. Secondary/Tertiary Care Center)
14.2.52.3.9	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE by Gender (mITT1 Population Aged 6-9 Years)
14.2.52.3.10	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE by Gender (mITT2 Population Aged 6-9 Years)
14.2.52.3.11	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE by Gender (mITT1 Population Aged 6-9 Years, with History of Failed Constipation Treatment)
14.2.52.3.12	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE by Gender (mITT2 Population Aged 6-9 Years, with History of Failed Constipation Treatment)
14.2.52.4.1	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE by Age Group (mITT1 Population, by Primary Care Center vs. Secondary/Tertiary Care Center)
14.2.52.4.2	Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE by Age Group (mITT1 Population, with History of Failed Constipation Treatment, by Primary Care Center vs. Secondary/Tertiary Care Center)
14.2.53.1	Subgroup Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT1 Population)
14.2.53.2	Subgroup Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT2 Population)
14.2.53.3	Subgroup Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT1 Population, with History of Failed Constipation Treatment)

14.2.53.4	Subgroup Analysis of Overall SBM Response (Observed Case) for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT2 Population, with History of Failed Constipation Treatment)
14.2.54.1	Overall SBM Response - Alternative SBM Responder Definition 2 for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT1 Population)
14.2.54.2	Overall SBM Response - Alternative SBM Responder Definition 2 for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT2 Population)
14.2.54.3	Overall SBM Response - Alternative SBM Responder Definition 2 for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT1 Population, with History of Failed Constipation Treatment)
14.2.54.4	Overall SBM Response - Alternative SBM Responder Definition 2 for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT2 Population, with History of Failed Constipation Treatment)
14.2.55	Monthly SBM Response (Observed Cases) for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT2 Population)
14.2.56	Summary of Weekly, Monthly, and Overall Change from Baseline in SBM Frequency, Observed Cases (mITT2 Population)
14.2.57	Summary of Weekly, Monthly, and Overall Change from Baseline in Straining Associated with SBMs, Observed Cases (mITT2 Population)
14.2.58	Summary of Weekly, Monthly, and Overall Change from Baseline in Stool Consistency Associated with SBMs, Observed Cases (mITT2 Population)
14.2.59	Summary of SBMs within 4, 8, 12, 24 and 48 Hours of First Study Medication Administration for Each Individual Placebo and Lubiprostone Group (mITT2 Population)
14.2.60	Summary of Weekly, Monthly, and Overall Change from Baseline in BM Frequency (Observed Cases) Using Ad-hoc Treatment Groups (mITT2 Population)
14.2.61	Summary of Overall Change from Baseline in SBM Frequency (Observed Cases) by Gender (mITT1 Population)
14.2.62	Summary of Overall Change from Baseline in Straining Associated With SBMs (Observed Cases) by Gender (mITT1 Population)
14.2.63	Summary of Overall Change from Baseline in Stool Consistency Associated With SBMs (Observed Cases) by Gender (mITT1 Population)
14.2.64	Summary of Overall Change from Baseline in SBM Frequency (Observed Cases) by Gender (mITT2 Population)
14.2.65	Summary of Overall Change from Baseline in Straining Associated With SBMs (Observed Cases) by Gender (mITT2 Population)
14.2.66	Summary of Overall Change from Baseline in Stool Consistency Associated With SBMs (Observed Cases) by Gender (mITT2 Population)
14.2.67	Summary of Weekly, Monthly, and Overall Mean Change from Baseline in Incontinence Frequency, Observed Cases (mITT1 Population, who Presented with Incontinence at Baseline)
14.2.68.1	Overall Response Analysis 3 in Stool Consistency associated with SBMs for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT1 Population)
14.2.68.2	Overall Response Analysis 3 in Stool Consistency associated with SBMs for Placebo Overall and Lubiprostone Overall Groups with/without DE (mITT2 Population)

14.3 Safety Results

14.3.1 Displays of Adverse Events

14.3.1.12.2	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Age 10 to 13 Years at Randomisation (SAF Population)
14.3.1.12.3	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Age 14 to 17 Years at Randomisation (SAF Population)
14.3.1.13.1	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - SBM at Randomisation < 1.5 (SAF Population)
14.3.1.13.2	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - SBM at Randomisation ≥ 1.5 (SAF Population)
14.3.1.14.1	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Weight at Randomisation < 50 (SAF Population)
14.3.1.14.2	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Weight at Randomisation ≥ 50 (SAF Population)
14.3.1.15.1	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Baseline BMI < 25 kg/m^2 (SAF Population)
14.3.1.15.2	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Baseline BMI ≥ 25 kg/m^2 (SAF Population)
14.3.1.16.1	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - Male (SAF Population)
14.3.1.16.2	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - Female (SAF Population)
14.3.1.17.1	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - White (SAF Population)
14.3.1.17.2	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - Black (SAF Population)
14.3.1.17.3	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - All Other Races (SAF Population)
14.3.1.18.1	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - Age 6 to 9 Years at Randomisation (SAF Population)
14.3.1.18.2	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - Age 10 to 13 Years at Randomisation (SAF Population)
14.3.1.18.3	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - Age 14 to 17 Years at Randomisation (SAF Population)
14.3.1.19.1	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - SBM at Randomisation < 1.5 (SAF Population)
14.3.1.19.2	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - SBM at Randomisation ≥ 1.5 (SAF Population)
14.3.1.20.1	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - Weight at Randomisation < 50 (SAF Population)
14.3.1.20.2	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - Weight at Randomisation ≥ 50 (SAF Population)
14.3.1.21.1	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - Baseline BMI < 25 kg/m^2 (SAF Population)
14.3.1.21.2	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - Baseline BMI ≥ 25 kg/m^2 (SAF Population)
14.3.1.22.1	Overview of Treatment-Emergent Adverse Events (SAF Population, Excluding Sites 1064 and 1082)
14.3.1.22.2	Overview of Treatment-Emergent Adverse Events (DE Population, Excluding Sites 1064 and 1082)
14.3.1.23.1	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (SAF Population, Excluding Sites 1064 & 1082)

14.3.1.23.2	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (DE Population, Excluding Sites 1064 & 1082)
14.3.1.24	Summary of Treatment-Emergent Severe Adverse Events by System Organ Class and Preferred Term (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.25	Summary of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.26	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by System Organ Class and Preferred Term (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.27	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.28	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Relationship (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.29	Most Common Treatment-Emergent Adverse Events (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.30.1	Summary of Treatment-Related Adverse Events by System Organ Class and Preferred Term (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.30.2	Summary of Treatment-Related Adverse Events by System Organ Class and Preferred Term (DE Population, Excluding Sites 1064 & 1082)
14.3.1.30.3	Summary of Treatment-Related Severe Adverse Events by System Organ Class and Preferred Term (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.30.4	Summary of Treatment-Related Serious Adverse Events by System Organ Class and Preferred Term (SAF Population, Excluding Sites 1064 and 1082)
14.3.1.30.5	Summary of Treatment-Related Adverse Events Leading to Discontinuation of Study Drug by System Organ Class and Preferred Term (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.30.6	Summary of Treatment-Related Adverse Events by System Organ Class, Preferred Term, and Maximum Severity (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.30.7	Summary of Treatment-Related Adverse Events by System Organ Class, Preferred Term, and Maximum Relationship (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.30.8	Most Common Treatment-Related Adverse Events (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.31.1	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Male (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.31.2	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Female (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.32.1	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - White (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.32.2	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Black (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.32.3	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - All Other Races (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.33.1	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Age 6 to 9 Years at Randomisation (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.33.2	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Age 10 to 13 Years at Randomisation (SAF Population, Excluding Sites 1064 & 1082)

14.3.1.33.3	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Age 14 to 17 Years at Randomisation (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.34.1	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - SBM at Randomisation < 1.5 (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.34.2	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - SBM at Randomisation ≥ 1.5 (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.35.1	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Weight at Randomisation < 50 (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.35.2	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Weight at Randomisation ≥ 50 (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.36.1	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Baseline BMI < 25 kg/m^2 (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.36.2	Subgroup Analysis of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Baseline BMI ≥ 25 kg/m^2 (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.37.1	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - Male (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.37.2	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - Female (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.38.1	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - White (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.38.2	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - Black (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.38.3	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - All Other Races (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.39.1	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - Age 6 to 9 Years at Randomisation (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.39.2	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - Age 10 to 13 Years at Randomisation (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.39.3	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - Age 14 to 17 Years at Randomisation (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.40.1	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - SBM at Randomisation < 1.5 (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.40.2	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - SBM at Randomisation ≥ 1.5 (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.41.1	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - Weight at Randomisation < 50 (SAF Population, Excluding Sites 1064 & 1082)

14.3.1.41.2	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - Weight at Randomisation ≥ 50 (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.42.1	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - Baseline BMI < 25 kg/m^2 (SAF Population, Excluding Sites 1064 & 1082)
14.3.1.42.2	Subgroup Analysis of Treatment-Related Adverse Events by System Organ Class and Preferred Term - Baseline BMI ≥ 25 kg/m^2 (SAF Population, Excluding Sites 1064 & 1082)
14.3.2.1	Listing of Subjects with Treatment-Emergent Serious Adverse Event (SAF Population)
14.3.2.2	Listing of Subjects with Treatment-Emergent Adverse Event Leading to Discontinuation of Study Drug (SAF Population)
14.3.2.3	Listing of Subjects with Treatment-Related Serious Adverse Event (SAF Population)
14.3.2.4	Listing of Subjects with Treatment-Related Adverse Event Leading to Discontinuation of Study Drug (SAF Population)
14.3.4.1.1	Summary of Laboratory Values – Hematology (SAF Population)
14.3.4.1.2	Shift Table of Laboratory Values – Hematology (SAF Population)
14.3.4.2.1	Summary of Laboratory Values – Biochemistry (SAF Population)
14.3.4.2.2	Shift Table of Laboratory Values – Biochemistry (SAF Population)
14.3.4.3.1	Summary of Laboratory Values – Urinalysis (SAF Population)
14.3.4.3.2	Shift Table of Laboratory Values – Urinalysis (SAF Population)
14.3.4.4.1	Summary of Vital Signs, Height, Weight, and BMI (SAF Population)
14.3.4.4.2.1	Shift Table of Vital Signs - Blood Pressure (SAF Population)
14.3.4.4.2.2	Shift Table of Vital Signs - Heart Rate (SAF Population)
14.3.4.5.1	Percent Change from Baseline in Bone Mineral Density (DXA Population)
14.3.4.5.2	Percent Change from Baseline in Corrected Bone Mineral Density (DXA Population)
14.3.4.5.3	Percent Change from Baseline in Bone Mineral Content (DXA Population)
14.3.4.5.4	Change from Baseline in Bone Mineral Density Z-scores (DXA Population)
14.3.4.5.5	Change from Baseline in Corrected Bone Mineral Density Z-scores (DXA Population)
14.3.4.5.6	Change from Baseline in BMD Height-adjusted Z-scores (DXA Population)
14.3.4.5.7	Change from Baseline in BMD Corrected Height-adjusted Z-scores (DXA Population)
14.3.4.5.8	Change from Baseline in Height, Height Z-Score, Weight, and Weight Z-Score (DXA Population)
14.3.4.5.9	Number and Percentage of Subjects with Bone Mineral Density Reduction Greater Than 4% (DXA Population)
14.3.4.5.10	Summary of Treatment-Emergent Clinical Fractures by System Organ Class and Preferred Term (DXA Population)
14.3.4.5.11.1	Percent Change from Baseline in Bone Mineral Density by Gender (DXA Population)
14.3.4.5.11.2	Percent Change from Baseline in Corrected Bone Mineral Density by Gender (DXA Population)
14.3.4.5.11.3	Percent Change from Baseline in Bone Mineral Content by Gender (DXA Population)
14.3.4.5.11.4	Change from Baseline in Bone Mineral Density Z-scores by Gender (DXA Population)

14.3.4.5.11.5	Change from Baseline in Corrected Bone Mineral Density Z-scores by Gender (DXA Population)
14.3.4.5.11.6	Change from Baseline in BMD Height-adjusted Z-scores by Gender (DXA Population)
14.3.4.5.11.7	Change from Baseline in BMD Corrected Height-adjusted Z-scores by Gender (DXA Population)
14.3.4.5.11.8	Change from Baseline in Height, Height Z-Score, Weight, and Weight Z-Score by Gender (DXA Population)
14.3.4.5.11.9	Number and Percentage of Subjects With Bone Mineral Density Reduction Greater Than 4% by Gender (DXA Population)
14.3.4.5.11.10	Summary of Treatment-Emergent Clinical Fractures by System Organ Class and Preferred Term by Gender (DXA Population)
14.3.4.5.12.1	Percent Change from Baseline in Bone Mineral Density by Race (DXA Population)
14.3.4.5.12.2	Percent Change from Baseline in Corrected Bone Mineral Density by Race (DXA Population)
14.3.4.5.12.3	Percent Change from Baseline in Bone Mineral Content by Race (DXA Population)
14.3.4.5.12.4	Change from Baseline in Bone Mineral Density Z-scores by Race (DXA Population)
14.3.4.5.12.5	Change from Baseline in Corrected Bone Mineral Density Z-scores by Race (DXA Population)
14.3.4.5.12.6	Change from Baseline in BMD Height-adjusted Z-scores by Race (DXA Population)
14.3.4.5.12.7	Change from Baseline in BMD Corrected Height-adjusted Z-scores by Race (DXA Population)
14.3.4.5.12.8	Change from Baseline in Height, Height Z-Score, Weight, and Weight Z-Score by Race (DXA Population)
14.3.4.5.12.9	Number and Percentage of Subjects with Bone Mineral Density Reduction Greater Than 4% by Race (DXA Population)
14.3.4.5.12.10	Summary of Treatment-Emergent Clinical Fractures by System Organ Class and Preferred Term by Race (DXA Population)
14.3.4.5.13.1	Percent Change from Baseline in Bone Mineral Density by Age Group at Randomisation (DXA Population)
14.3.4.5.13.2	Percent Change from Baseline in Corrected Bone Mineral Density by Age Group at Randomisation (DXA Population)
14.3.4.5.13.3	Percent Change from Baseline in Bone Mineral Content by Age Group at Randomisation (DXA Population)
14.3.4.5.13.4	Change from Baseline in Bone Mineral Density Z-scores by Age Group at Randomisation (DXA Population)
14.3.4.5.13.5	Change from Baseline in Corrected Bone Mineral Density Z-scores by Age Group at Randomisation (DXA Population)
14.3.4.5.13.6	Change from Baseline in BMD Height-adjusted Z-scores by Age Group at Randomisation (DXA Population)
14.3.4.5.13.7	Change from Baseline in BMD Corrected Height-adjusted Z-scores by Age Group at Randomisation (DXA Population)
14.3.4.5.13.8	Change from Baseline in Height, Height Z-Score, Weight, and Weight Z-Score by Age Group at Randomisation (DXA Population)
14.3.4.5.13.9	Number and Percentage of Subjects with Bone Mineral Density Reduction Greater Than 4% by Age Group at Randomisation (DXA Population)
14.3.4.5.13.10	Summary of Treatment-Emergent Clinical Fractures by System Organ Class and Preferred Term by Age Group at Randomisation (DXA Population)

14.3.4.6.1	Summary of Laboratory Values – Hematology (SAF Population, Excluding Sites 1064 & 1082)
14.3.4.6.2	Shift Table of Laboratory Values – Hematology (SAF Population, Excluding Sites 1064 & 1082)
14.3.4.7.1	Summary of Laboratory Values – Biochemistry (SAF Population, Excluding Sites 1064 & 1082)
14.3.4.7.2	Shift Table of Laboratory Values – Biochemistry (SAF Population, Excluding Sites 1064 & 1082)
14.3.4.8.1	Summary of Laboratory Values – Urinalysis (SAF Population, Excluding Sites 1064 & 1082)
14.3.4.8.2	Shift Table of Laboratory Values – Urinalysis (SAF Population, Excluding Sites 1064 & 1082)
14.3.4.9.1	Summary of Vital Signs, Height, Weight, and BMI (SAF Population, Excluding Sites 1064 & 1082)
14.3.4.9.2.1	Shift Table of Vital Signs - Blood Pressure (SAF Population, Excluding Sites 1064 & 1082)
14.3.4.9.2.2	Shift Table of Vital Signs - Heart Rate (SAF Population, Excluding Sites 1064 & 1082)
14.3.4.10.1	Percent Change from Baseline in Bone Mineral Density (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.2	Percent Change from Baseline in Corrected Bone Mineral Density (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.3	Percent Change from Baseline in Bone Mineral Content (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.4	Change from Baseline in Bone Mineral Density Z-scores (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.5	Change from Baseline in Corrected Bone Mineral Density Z-scores (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.6	Change from Baseline in BMD Height-adjusted Z-scores (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.7	Change from Baseline in BMD Corrected Height-adjusted Z-scores (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.8	Change from Baseline in Height, Height Z-Score, Weight, and Weight Z-Score (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.9	Number and Percentage of Subjects with Bone Mineral Density Reduction Greater Than 4% (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.10	Summary of Treatment-Emergent Clinical Fractures by System Organ Class and Preferred Term (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.11.1	Percent Change from Baseline in Bone Mineral Density by Gender (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.11.2	Percent Change from Baseline in Corrected Bone Mineral Density by Gender (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.11.3	Percent Change from Baseline in Bone Mineral Content by Gender (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.11.4	Change from Baseline in Bone Mineral Density Z-scores by Gender (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.11.5	Change from Baseline in Corrected Bone Mineral Density Z-scores by Gender (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.11.6	Change from Baseline in BMD Height-adjusted Z-scores by Gender (DXA Population, Excluding Sites 1064 & 1082)

14.3.4.10.11.7	Change from Baseline in BMD Corrected Height-adjusted Z-scores by Gender (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.11.8	Change from Baseline in Height, Height Z-Score, Weight, and Weight Z-Score by Gender (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.11.9	Number and Percentage of Subjects with Bone Mineral Density Reduction Greater Than 4% by Gender (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.11.10	Summary of Treatment-Emergent Clinical Fractures by System Organ Class and Preferred Term by Gender (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.12.1	Percent Change from Baseline in Bone Mineral Density by Race (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.12.2	Percent Change from Baseline in Corrected Bone Mineral Density by Race (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.12.3	Percent Change from Baseline in Bone Mineral Content by Race (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.12.4	Change from Baseline in Bone Mineral Density Z-scores by Race (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.12.5	Change from Baseline in Corrected Bone Mineral Density Z-scores by Race (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.12.6	Change from Baseline in BMD Height-adjusted Z-scores by Race (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.12.7	Change from Baseline in BMD Corrected Height-adjusted Z-scores by Race (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.12.8	Change from Baseline in Height, Height Z-Score, Weight, and Weight Z-Score by Race (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.12.9	Number and Percentage of Subjects with Bone Mineral Density Reduction Greater Than 4% by Race (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.12.10	Summary of Treatment-Emergent Clinical Fractures by System Organ Class and Preferred Term by Race (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.13.1	Percent Change from Baseline in Bone Mineral Density by Age Group at Randomisation (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.13.2	Percent Change from Baseline in Corrected Bone Mineral Density by Age Group at Randomisation (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.13.3	Percent Change from Baseline in Bone Mineral Content by Age Group at Randomisation (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.13.4	Change from Baseline in Bone Mineral Density Z-scores by Age Group at Randomisation (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.13.5	Change from Baseline in Corrected Bone Mineral Density Z-scores by Age Group at Randomisation (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.13.6	Change from Baseline in BMD Height-adjusted Z-scores by Age Group at Randomisation (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.13.7	Change from Baseline in BMD Corrected Height-adjusted Z-scores by Age Group at Randomisation (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.13.8	Change from Baseline in Height, Height Z-Score, Weight, and Weight Z-Score by Age Group at Randomisation (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.13.9	Number and Percentage of Subjects with Bone Mineral Density Reduction Greater Than 4% by Age Group at Randomisation (DXA Population, Excluding Sites 1064 & 1082)
14.3.4.10.13.10	Summary of Treatment-Emergent Clinical Fractures by System Organ Class and Preferred Term by Age Group at Randomisation (DXA Population, Excluding Sites 1064 & 1082)

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

DEATHS

There were no deaths during this study.

TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS (SAEs)

Subject Number	Treatment Group	Preferred Term(s)
1003-102	12 mcg BID	Hand-foot-and-mouth disease
1021-176	12 mcg BID (DE)	Cellulitis
1036-120	12 mcg BID	Suicidal ideation
1037-112	12 mcg BID	Faecaloma
1040-102	12 mcg BID (DE)	Faecaloma
1047-102	24 mcg BID	Major depression
1052-103	12 mcg BID (DE)	Faecaloma and Rash
1083-107	12 mcg BID	Faecaloma
1093-107	12 mcg BID (DE)	Anaphylactoid reaction
4405-101	12 mcg BID	Chest pain

SAE=serious adverse event; BID=twice daily; DE=dose escalated to 24 mcg BID at end of treatment week 1.
Source: Listing 16.2.7.2

ADVERSE EVENTS RESULTING IN DISCONTINUATION OF STUDY MEDICATION

Subject Number	Treatment Group	Preferred Term(s)
1005-121	24 mcg BID	Aggression
1011-125	24 mcg BID	Chest pain
1021-121	24 mcg BID	Abdominal pain
1021-131	24 mcg BID	Nausea
1086-119	24 mcg BID	Nausea
1093-103	12 mcg BID	Vomiting
1099-103	12 mcg BID (DE)	Dizziness, Flushing, and Nausea
1101-103	12 mcg BID (DE)	Abdominal pain
3101-102	24 mcg BID	Eructation, Dizziness, Chest Discomfort and Nausea
3101-117	24 mcg BID	Pharyngeal oedema

BID=twice daily; DE=dose escalated to 24 mcg BID at end of treatment week 1.
Source: Listing 16.2.7.1

PREGNANCIES

There were no pregnancies reported for subjects receiving either lubiprostone 12 or 24 mcg BID in this study.

OTHER ADVERSE EVENTS OF SPECIAL INTEREST

There were no other events of special interest reported.

14.3.3 Narratives for Deaths, Serious Adverse Events, and Withdrawals Because of Adverse Events

14.3.3.1 Deaths

There were no deaths during this study.

14.3.3.2 Treatment-Emergent Serious Adverse Events

Subject 1003-102 Hand-foot-and-mouth Disease

Subject 1003-102 was a 9-year-old African American female weighing 44.3 kg at screening and subsequently randomised to lubiprostone 12 mcg on 29MAY2014. The subject experienced the SAE of hand-foot-and-mouth disease on 26JUN2014, approximately study day 29. She was admitted to the hospital for a 2-day history of rash involving her distal extremities and fever which started on the morning of admission. On admission, the rash had worsened and had spread to the face and trunk. Treatment with study medication was subsequently discontinued as well as subject's participation in the study on day 28. Based on subject's symptoms and laboratory results, a diagnosis of atypical coxsackie virus infection was made. After 2 days of hospitalisation, the subject was discharged home and the event was reported resolved on 11JUL2014. Her medical history was significant for chronic constipation for which she was taking Miralax and Dulcolax. Concomitant medication included diphenhydramine, acetaminophen, and hycet. The Clinical Site Investigator assessed the events of rash and fever as unrelated to the lubiprostone treatment.

Subject 1021-176 Cellulitis

Subject 1021-176 was an 8-year-old African-American female weighing 42.18 kg who was randomised to lubiprostone 12 mcg on 28MAR2016. She was subsequently dose escalated to 24 mcg BID regimen at the end of treatment week one. The subject experienced the SAE of cellulitis on study day 82 (17JUN2016), she was admitted for a possible right leg cellulitis after presenting with fever and right leg pain. A right tibia X-ray done at the time was negative and a wound culture was reported as anaerobic, abscess but failed to isolate anaerobes at 3 days. She had an incision and drainage on day 3 of admission (22JUN2016- study day 87) for cellulitis and abscess. Her concomitant medications were clindamycin and sulfamethoxazole. Relevant past medical history included constipation, seasonal allergies, asthma, gastritis, abdominal pain, nausea and vomiting for which subject was taking macrogol 3350 (Miralax), sodium phosphate (Fleet enema), montelukast (Singulair), salbutamol (Albuterol) and omeprazole. Subject was discharged on study day 87 (22JUN2016), with event outcome considered as recovered/resolved. Therapy with study medication was not discontinued during the event. The clinical site investigator assessed the event of right leg cellulitis as unrelated to the study medication.

Subject 1036-120 Suicidal Ideation

Subject 1036-120 was a 16-year-old white female weighing 48.1 kg who was randomised to lubiprostone 12 mcg BID on 16DEC2014. Her medical history included constipation, seasonal allergies and suicidal thoughts. Prior and concomitant medication included loratidine, diphenylhadramine, and colecalciferol. On Study Day 31 (15JAN2015), the subject reported having suicidal thoughts. She was treated with sertraline 25 mg QD. Study medication was discontinued on Study Day 37 (21JAN2015) and she reported that symptoms had improved. Suicidal thoughts were considered resolved by Study Day 45 (29JAN2015). The Investigator assessed suicidal ideation as not related to study medication.

Subject 1037-112 Faecaloma

Subject 1037-112 was a 6-year-old white female weighing 16.8 kg who was randomised to lubiprostone 12 mcg BID on 20AUG2015. On study day 6 (25Aug2015), she was admitted for worsening fecal impaction and was treated with the following concomitant medications: GoLYTELY solution (via nasogastric tube) and intravenous Reglan. Subject had approximately 13 and 11 bowel movements on days 2 and 3 of admission, respectively. While admitted, study medication was temporarily held from the evening dose of study day 6 (25AUG2015) through study day 8 (27AUG2015). Study medication was resumed on study day 9 (28AUG2015) which was also the day she was discharged. Her medical history included chronic functional constipation, failure to thrive, asthma, prematurity, and GoLYTELY bowel clean outs. Concomitant medications included bisacodyl, amoxicillin, Children's pain and fever relief (paracetamol), Pediasure supplement, polyethylene glycol, and sennoside. The clinical site investigator assessed the event as unrelated to the study medication and outcome was considered as recovered.

Subject 1040-102 Faecaloma

Subject 1040-102 was a 9-year-old white female weighing 29.6 kg who was randomised to lubiprostone 12 mcg BID on 15OCT2014. She was subsequently dose escalated to 24 mcg BID regimen at the end of treatment week one. Approximately 28 days after the first dose (11NOV2014), she was diagnosed with fecal impaction and subsequently admitted to the hospital on the same day. While admitted, she received GoLYTELY which was not well tolerated and as such not effective. Subject subsequently underwent fecal disimpaction under general anesthesia without complications. She was discharged on the 3rd day of admission (study day 30). The subject was withdrawn from the on 11NOV2014, study day 28. Medical history included chronic constipation, encopresis, fecal disimpaction, and allergy to amoxicillin. Concomitant medication included senna alexandrina. Study medication was unblinded on 18NOV2014 (study day 35), and the event was considered resolved. The Clinical Site Investigator assessed the event of fecal impaction as probably related to study medication; however, the sponsor judged the relationship of the event to study medication as unlikely given subject's history of chronic constipation, fecal disimpaction and encopresis prior to study participation.

Subject 1047-102 Major Depression

Subject 1047-102 was a 15-year-old black/white female weighing 57.6 kg who was randomised to lubiprostone 24 mcg BID on 15DEC2014. Her medical history included constipation and migraine. Concomitant medications included Senokot (sennoside a+b), bisacodyl, bentyl, Fleet (bisacodyl, sodium phosphate diabesic, sodium phosphate monobasic) and Miralax (macrogol). Approximately

46 days after the first dose (29JAN2015), the subject ingested four unknown white pills given to her by a friend presumed to be pregabalin (Lyrica). The subject was recommended for inpatient hospital admission for suicidal ideation with high risk of suicide and for further evaluation of depression and treatment. The subject denied taking pills in a suicide attempt but agreed to suicidal ideation and thought of harming others. Based on further history and examination, the event of suicidal ideation was changed to Major Depressive Disorder (MDD)/worsening depression. Treatment with fluoxetine hydrochloride and melatonin were commenced. The study medication was withdrawn on 28JAN2015 (study day 45) and the subject was subsequently withdrawn from study on 30JAN2015 (study day 47). She was discharged on 07FEB2015 with the outcome for MDD/worsening of depression considered as resolved, but requiring ongoing therapy. The clinical site investigator assessed the event as unrelated to the study medication and outcome considered as recovered.

Subject 1052-103 Faecaloma, Rash

Subject 1052-103 was a 7-year-old African-American female weighing 21.3 kg who was randomised to lubiprostone 12 mcg BID on 12FEB2015. She was subsequently dose escalated to 24 mcg BID regimen at the end of treatment week one. Her medical history included chronic constipation, fecal impaction, attention deficit disorder and asthma. Concomitant medications included vyvanse, senna, bisacodyl, and normal saline enema. She was hospitalized for rash of moderate intensity and severe fecal impaction on 03APR2015 (study day 51). A KUB (kidney, ureter, bladder) done at the ER confirmed the diagnosis of fecal impaction. Subject was treated with normal saline enema, GoLYTELY, Fleet enema, Macrogol 3350 (PEG 3350), macrogol (Miralax) as well as diphenhydramine hydrochloride. The study medication was withdrawn on study day 51 and she was subsequently withdrawn from the study on study day 54 which was also the day of discharge. Both events (rash and fecal impaction) were considered resolved. In addition, the Clinical Site Investigator assessed and updated the event of fecal impaction as unrelated (previously reported as probably related), and rash as possibly related (previously reported as probably related) to the study medication.

Subject 1083-107 Faecaloma

Subject 1083-107 was a 13-year-old white male weighing 47.6 kg who was randomised to lubiprostone 12 mcg BID 04MAR2016. While the subject was in the clinic for his week 4 visit on 05APR2016 (study day 33), a large mass on the left lower abdomen was noted on physical examination. This was confirmed by CT scan as a fecal impaction. The subject was subsequently admitted to the hospital the following day 06APR2016 (study day 34) and was treated with oral Miralax and Fleet enema. The blinded study medication was temporarily withheld at the time and per investigator's discretion, the subject was withdrawn from the study on 10MAY2016. The subject was discharged from the hospital on 08APR2016 with little or no improvement per a follow-up x-ray. The investigator was of the opinion that the subject would benefit from referral to a specialist due to the severity of the constipation. On further follow-up after discharge from the hospital the event was considered recovered/resolved with sequelae. The Clinical Site Investigator assessed the event as unrelated to the study medication.

Subject 1093-107 Anaphylactoid Reaction

Subject 1093-107 was a 10-year-old African-American female weighing 47.2 kg who was randomised to lubiprostone 12 mcg BID on 07APR2016. She was subsequently dose escalated to 24 mcg BID regimen at the end of treatment week one. Her medical history included asthma, allergic rhinitis, attention deficit hyperactivity disorder (ADHD), menarche, and pediatric functional constipation. Her concomitant medications included ProAir Ventolin (salbutamol sulfate) and cetirizine. The subject presented to the ER with facial swelling and discoloration of tongue on 02MAY2016 (study day 26). A diagnosis of severe anaphylactoid reaction was noted and subject was treated with intravenous medications. Specifically, she was treated with Benadryl, Pepcid (famotidine), saline eye drop and Solu-medrol (methylprednisolone). The event was considered recovered/resolved on 02MAY2016 (study day 26). Study medication was discontinued on 01MAY2016 (study day 25). The investigator assessed the events of facial swelling and discoloration of tongue (anaphylactoid reaction) as probably related to the study medication.

Subject 4405-101 Chest Pain

Subject 4405-101 was a 10-year-old white female weighing 35.7 kg who was randomised to lubiprostone 12 mcg BID on 24NOV2015. Her medical history included constipation. No concomitant medications were reported. On 27NOV2015, approximately study day 4, the subject presented with chest pain described as a tight feeling in the front of her chest of approximately 1 ½ to 2 hours duration. The event was not treated and the subject continued with her routine activities with subsequent spontaneous resolution of the chest pain. The event did not recur with subsequent doses of the study medication and no work up was performed. No action was taken with the study medication. Chest pain was confirmed as serious and the clinical site investigator assessed the event as possibly related to the study drug. However, the sponsor assessed the event of chest pain as unlikely related to lubiprostone based on the spontaneous resolution of the chest pain with no associated symptoms and no recurrence with subsequent doses of lubiprostone.

14.3.3.3 Adverse Events Resulting in Discontinuation of Study Medication

Subject 1005-121 Aggression

Subject 1005-121 was a 15-year-old white male weighing 59.1 kg who was randomised to lubiprostone 24 mcg BID of the blinded study medication on 03NOV2014. His medical history included DiGeorge's syndrome, chronic constipation, erosive esophagitis, hypothyroidism, developmental delay, aggressive behavioural issue, anxiety, hearing loss and BMD z-score less than -2.0. His concomitant medications included Fleet enema, Miralax, Abilify, levothyroxine, fluoxetine, and acetaminophen. The subject developed the non-serious adverse event of aggression on 24NOV2014 described as mild in severity. The subject was subsequently withdrawn from the study on account of this event. His last dose date was 26NOV2014 (approximately 24 days after first dose date). The subject did not receive any treatment for the AE and the outcome was noted as not recovered/not resolved. The investigator assessed the adverse event of aggression as unrelated to study medication.

Subject 1011-125 Chest Pain

The subject was a 16-year-old black female weighing 77.1 kg who was randomised to receive lubiprostone 24 mcg BID on 31OCT2014. Her medical history included constipation, exertional

dyspnoea; during the study, she had allergic rhinitis. Prior medication included macrogol, senna, fluticasone, loratidine, and influenza vaccine. Concomitant medication included loratidine. During her third visit to the study site, although she was asymptomatic at that time, she reported that within 5 minutes after taking her first dose of study medication on Study Day 1 (31OCT2014) and after subsequent doses, she experienced moderately severe chest pain and worsening/exacerbation of exertional dyspnoea lasting for approximately one hour; she had not sought medical care and this was her initial report of symptoms. On Study Day 8 (07NOV2014), an ECG was normal; she was unable to cooperate for a spirometry. Study medication was discontinued at that time. She was monitored for these symptoms; they resolved on Study Day 12 (11NOV2014) and the subject was withdrawn from the study due to the chest pain AE. On Study Day 13 (12NOV2014), her study medication was unblinded. The Investigator assessed the non-serious AEs, chest pain and worsening/exacerbation of exertional dyspnoea, as probably related to study medication.

Subject 1021-121 Abdominal Pain

Subject 1021-121 was a 17-year-old white male weighing 90.7 kg who was randomised to lubiprostone 24 mcg BID on 04MAR2015. His medical history included polycythemia, constipation, gastritis, visceral hyperalgesia, anxiety and hypertension. His concomitant medications included Ex-Lax, glycerine suppository, magnesium citrate, milk of magnesia, Zantac, Lisinopril and buspar. Approximately 4 days after first dose date (07MAR2015), the subject reported the non-serious AE of a mild abdominal pain. The investigator assessed this event as probably related to study medication and the medication was discontinued on 15MAR2015 (study day 12). The event ended on 11MAR 2015 (study day 8) and was considered resolved. There was no treatment reported for the adverse event.

Subject 1021-131 Nausea

Subject 1021-131 was a 9-year-old white male weighing 49.9 kg who was randomised to receive lubiprostone 24 mcg BID on 07MAY2015. His medical history included abdominal pain, constipation, nausea, and seasonal allergies. His concomitant medications included Singulair, gabapentin and omeprazole. Subject developed worsening nausea on study day 2 (08MAY2015). This non-serious event was assessed to be mild and resolved on study day 5 (11MAY2015). However, the AE necessitated the discontinuation of study medication on study day 3 with subsequent withdrawal from the study. However, no treatment was given for the event and the investigator assessed the adverse event of nausea as possibly related to the study medication.

Subject 1086-119 Nausea

Subject 1086-119 was a 12-year-old African-American male weighing 66.5 kg who was randomised to receive lubiprostone 24 mcg BID on 19APR2016. The first dose of study medication was taken on the day following randomisation (20APR2016). His medical history included sickle cell trait, constipation, functional constipation, acid reflux and ADHD. His concomitant medications included vyvanse, Metamucil, Nexium and Miralax. The subject reported the adverse event of nausea on 30APR2016 after being on the study for approximately 11 days. The nausea was noted to be mild in severity, and was not treated. The event was reported as resolved on 14MAY2015 (study day 25). The clinical site investigator assessed the adverse event as probably related to the study medication.

Subject 1093-103 Vomiting

Subject 1093-103 was a 7-year-old white male weighing 24.5 kg who was randomised to receive lubiprostone 12 mcg BID on 29FEB2016. His medical history included functional constipation. No concomitant medications were reported for the subject. The subject reported a moderately severe vomiting on study day 5 (04MAR2016). The adverse event was noted to have ended on study day 14 (13MAR2016) which was also the day that the study medication was withdrawn. No treatment was reported for the adverse event. The clinical site investigator assessed the adverse event of vomiting as definitely related to the study medication and outcome considered as recovered.

Subject 1099-103 Dizziness, Flushing, and Nausea

Subject 1099-103 was a 9-year-old white female weighing 29.1 kg and was randomised to receive lubiprostone 12 mcg BID on 28FEB2016. She was subsequently dose escalated to 24 mcg BID regimen at the end of treatment week one. Subject reported the adverse events of dizziness, flushing and nausea on study day 6. The symptoms were noted to be of moderate severity; however, no treatment was reportedly given to the subject. All adverse events ended on study day 12 and the study medication was withdrawn on the same day. Her medical history included functional constipation, laundry soap allergy, and red dye in food intolerance. Her ongoing concomitant medications included fiber gummies and Tums. The clinical site investigator assessed the adverse events of dizziness, nausea and flushing as definitely related to the study medication and outcome considered as recovered for all the symptoms (AEs).

Subject 1101-103 Abdominal Pain

Subject 1101-103 was a 6-year-old white female weighing 21.6 kg who was randomised to receive lubiprostone 12 mcg BID on 04DEC2015. She was subsequently dose escalated to 24 mcg BID regimen at the end of treatment week one. Her medical history included possible celiac disease, constipation, penicillin allergy, sleep apnea, and tonsillectomy. Her only concomitant medication was lansoyl. Subject reported the adverse event of severe abdominal pain with unknown start date. However, the adverse event was considered treatment emergent. The severe abdominal pain ultimately led to withdrawal of study medication and the last dose day was noted as 31DEC2015 (study day 28). The event was noted as ongoing with outcome considered as unknown. The clinical site investigator assessed the adverse event as probably related to the study medication.

Subject 3101-102 Nausea

Subject 3101-102 was a 16-year-old white female weighing 51.5 kg and was randomised to receive lubiprostone 24 mcg BID on 03DEC2014. Her medical history included abdominal pain due to constipation, constipation, nausea, cystitis, migraine and menarche. Her concomitant medication included forlax, ondansetron, naproxen, omeprazole, and iberogast. The subject reported the adverse event of eructation, dizziness, chest discomfort and nausea on 03DEC2014 (study day 1). All the adverse events were reported to have resolved by 06DEC2014 (study day 4). The adverse events of eructation and dizziness were both mild and the investigator assessed them to be probably related to study medication. The chest discomfort was also mild in severity but assessed by the investigator to be possibly related to study medication. The adverse event of nausea was assessed as moderate in intensity and probably related to study medication; and eventually led to the

discontinuation of subject from the study. The subject was subsequently withdrawn from the study and the last dose date was noted as 05DEC2014 (study day 3).

Subject 3101-117 Pharyngeal Oedema

Subject 3101-117 was a 14-year-old white female weighing 68.3 kg and was randomised to receive lubiprostone 24 mcg BID on 26AUG2015. Her medical history included right lower abdominal pain, constipation, nausea related to constipation, tenosynovitis of both thumbs, and menarche. Her ongoing concomitant medications included paracetamol and forlax. She reported the adverse event of pharyngeal edema on study day 2 (27AUG2015). On study day 3 (28AUG2015), subject reportedly had a dose reduction (from BID to QD) of study medication due to AEs of cold sweat, flushing, dyspnea, abdominal pain and nausea. The initial adverse event of pharyngeal edema was noted to have ended on study day 6 (31AUG2015), but necessitated the withdrawal of the subject from the study with the last dose date recorded as 31AUG2015 (i.e., study day 6). Subject recovered from the event. The investigator assessed the adverse event of pharyngeal edema as mild in intensity and possibly related to the study medication.

14.3.3.4 Pregnancies

There were no pregnancies reported for subjects receiving either lubiprostone 12 or 24 mcg BID in this study.

14.3.3.5 Other Events of Special Interest

There were no other events of special interest reported.

15. REFERENCES

[1] Rasquin A, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, Walker LS. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology 2006Apr;130(5):1527–37.

[2] Rome III Criteria for FC in Children http://www.romecriteria.org/assets/pdf/19_RomeIII_apA_885-898.pdf. Accessed 16 Aug 2016.

[3] van den Berg MM, Benninga MA, Di Lorenzo C. Epidemiology of childhood constipation: a systematic review. Am J Gastroenterol 2006;101:2401–9.

[4] Mota DM, Barros AJ, Santos I, et al. Characteristics of intestinal habits in children under 4 years: detecting constipation. J Pediatr Gastroenterol Nutr 2012;55:451–6.

[5] Biggs WS, Dery WH. Evaluation and treatment of constipation in infants and children. Am Fam Physician 2006;73:469–77.

[6] Unraveling Childhood Constipation. UvA-DARE, The Institutional Repository of the University of Amsterdam (UvA); 2014; http://hdl.handle.net/11245/2.137973. Accessed 23 Aug 2016.

[7] Baker SS, Liptak GS, Colletti RB, Croffie JM, Di Lorenzo C, Ector W, Nurko S. Constipation in infants and children: evaluation and treatment. A medical position statement of the North American Society for Pediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr 1999 Nov;29(5):612–26.

[8] Ranasinghe N, Devanarayana NM, Benninga Ma, et al. Psuchological maladjustment and quality of life in adolescents with constipation. Arch Dis Child. 2016 Jul. pii:archdischild-2016-310694.doi. epub ahead of print. http:www.ncbi.nlm.nih.gov/pubmed/27402734. accessed 17 August 2016.

[9] Kammacher Guerreiro M, Bettinville A, Herzog D. Fecal overflow often affects children with chronic constipation that appears after the age of 2 years. Clin Peds. 2014 Aug;53:885-9.

[10] Bongers ME, Benninga MA, Maurice-Stam H, Grootenhuis MA. Health-related quality of life in young adults with symptoms of constipation continuing from childhood into adulthood. Health Qual Life Outcomes. 2009;7:20.

[11] Pijpers MA, Bongers ME, Benninga MA, et al. Functional constipation in children: a systematic review on prognosis and predictive factors. J Pediatr Gastroenterol Nutr 2010;50:256–68.

[12] Ueno, R. (1997) Mechanism of stimulating action of RU-0211 on intestinal fluid secretion: effects on secretion of electrolytes into the bowel of rats. RTU/SR99-038. R-Tech Ueno (USA), Inc.

[13] Ueno, R. (2002) Enteropooling effects of RU-0211 in C57BL/6 mice: oral administration. SPI/SR02-017. Sucampo Pharmaceuticals, Inc.

[14] Ueno, R. (1991) Water excreting effect of RU-0211 into the bowel in rats. RTU/SR99-037. R-Tech Ueno (USA) Inc.

[15] Cuppoletti, J., Malinowska, D.H., Tewari, K.P., Ueno, R. (2004 Nov) SPI-0211 activates T84 cell chloride transport and recombinant human ClC-2 chloride currents. Am J Physiol Cell Physiol 287(5):C1173–83.

[16] Cuppoletti, J. (2002) Effect of RU-0211 on recombinant and native intestinal cell ClC-2 Cl- channels. RTU/SR02-009. Sucampo Pharmaceuticals, Inc.

[17] Hyman PE, Di Lorenzo C, Prestridge LL, et al. Lubiprostone for the treatment of functional constipation in children. JPBN 2013 Mar:58(3).

[18] AMITIZA® (lubiprostone) Investigator's Brochure, Edition 17 (March 2016), pp 26-27. Sucampo, AG.

[19] Joseph, M., and Joswick, T. (2009) A multi-center, open-labeled study of the safety, efficacy and pharmacokinetics of lubiprostone in pediatric patients with constipation. CSR0211-09-001-01. Sucampo Pharma Americas, Inc.

[20] AMITIZA® (lubiprostone) Investigator's Brochure, Edition 17 (March 2016), p10. Sucampo, AG.

[21] ICH GCP Guideline – ICH Topic E6 R1) Guideline for Good Clinical Practice.

[22] RedsQL™ Scoring Algorithm. www.pedsql.org/score.html accessed 14 September 2016.

[23] Chumpitazi BP, Lane MM, Czyzewski DI, Weidler EM, Swank PR, Shulman RJ. Creation and initial evaluation of a Stool Form Scale for children. The Journal of pediatrics. 2010 Oct 31;157(4):594-7.

[24] Solzi GF and Di Lorenzo C. Are constipated children different from constipated adults? Dig Dis 1999;17:308-315.

[25] Nurko S and Zimmermann LA. Evaluation and treatment of constipation in children and adolescents. Am Fam Physician 2014;90:82-90.