Addendum 4/26/18 3:30 PM:

The Clinical Review entered into DAARTS on 4/26/2018 at 7am still listed the preliminary draft labeling, but at the time that the review was entered into DAARTS finalized labeling had been agreed upon. In this updated clinical review, the finalized labeling language in section 8.4 of the Prescriber Information (PI) has been updated in section 9.2. The original review was also incorrectly dated 3/28/18, which has been corrected on the cover page of this review.

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	21908
Priority or Standard	Priority
Submit Date(s)	7/28/2017
Received Date(s)	7/28/2017
PDUFA Goal Date	1/28/2017
Revised PDUFA Date	4/28/2018 (3 month extension)
Division / Office	ODE III/DGIEP
Reviewer Name(s)	Elizabeth Hart, M.D.
Review Completion Date	4/26/2018
Established Name	Lubiprostone
(Proposed) Trade Name	Amitiza
Therapeutic Class	Chloride channel activator
Applicant	Sucampo Pharmaceuticals Inc.
Formulation(s)	Capsule
Dosing Regimen	24 mcg twice daily
Indication(s)	Pediatric functional constipation
Intended Population(s)	Children 10-17 years old
Studied Population(s)	Children 6-17 years old

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval action with updated pediatric labeling for a negative study.

1.2 Risk Benefit Assessment

The Sponsor did not demonstrate efficacy of lubiprostone in 6 to 17 year old children with pediatric functional constitpation (PFC), the pediatric correlate of chronic idiopathic constipation (CIC) in adults, based on review of one pivotal 12 week, randomized, double-blind, placebo controlled trial, and 3 supportive studies provided in the efficacy supplement.

For the pivotal trial, the primary efficacy analysis was a comparison of the proportion of overall responders in the lubiprostone arm (who received either 12mcg BID or 24mcg BID) to the placebo group. A patient was considered an "overall responder" if they had ≥ 3 spontaneous bowel movements(SBM)/week and an increase of ≥ 1 SBM/week from baseline in 9 out of 12 weeks of the study including at least 3 of the last 4 weeks in the trial. The result of the prespecified primary analysis was not statistically significant. There were 74/399 (18.5%) responders in the lubiprostone cohort compared to 28/195 (14.4%) responders in the placebo cohort, only a 4.1% treatment difference (p=0.2245). The per protocol analysis of 6-17 year olds comparing responders treated with the proposed lubiprostone dose of 24mcg BID to placebo, favored placebo 0.2% by observed cases and 3.8% by last observation carried forward (LOCF) methodology. The change from baseline in SBM after 1 week, which was a key secondary endpoint in the PFC pivotal trial and the primary endpoint for the related adult condition, CIC trial, demonstrated only a minimal, 0.3, difference between the median SBMs in the lubiprostone and placebo treated subjects in the PFC trial compared to a difference of 2 and 2.3 in the median SBM in the pivotal adult CIC trials. Overall, the totality of the submitted data, including analysis of clinically meaningful secondary endpoints did not demonstrate a significant treatment effect amongst 6-17 year olds with PFC.

Subgroup analyses were also conducted in an effort to identify a clinically relevant population in which a benefit might be demonstrated, but none was identified. Based on the pathophysiology of PFC, reports in the literature that CIC may begin in adolescence and that younger children typically have a significant behavioral component to their constipation, the key sub-group analyses were performed in 12-17 year olds.[1,2] Amongst 12-17 year olds, there were 30/180 (16.7%) responders in the lubiprostone

[1] Tabbers et al. "Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN" Journal of Pediatric Gastroenterology. 58(2). 2014
[2] Solzi et al. "Constipated children different from constipated adults?" Digestive Disease. 2009.

arm compared to 11/86 (12.8%) in the placebo arm; a treatment difference of 3.9% is not clinically or statistically significant. Additional exploratory sub-group analyses focused on identifying patients with more severe PFC, but despite multiple exploratory sub-group analyses, a consistent, clinically meaningful treatment benefit was not identified. Based on the submitted data, this reviewer was unable to identify a clinically relevant population with PFC for whom lubiprostone offered a clinically meaningful treatment benefit.

Without demonstration of efficacy, the benefit-risk profile cannot be favorable. If lubiprostone had demonstrated efficacy, this reviewer believes that the safety profile would not have precluded its use. The safety profile in 6-17 year olds was generally similar to adults. Children may be at risk of deleterious effects on their bone health from lubiprostone based on its mechanism of action and animal data. While a bone signal was not detected in the dual energy X-ray absorptiometry (DXA) sub-study, sample size and methodologic limitations prevent definitely excluding a safety signal affecting bone health. (See Table 1, Benefit-Risk Summary and Assessment for additional details).

Table 1. Table Benefit-Risk Summary and Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• PFC is a common problem of childhood, with an estimated prevalence of 3% worldwide.[3] • PFC can be a serious condition impacting children's health related quality of life (HRQOL), causing fecal incontinence and leading to hospitalizations due to fecal impaction.	PFC is a common pediatric condition that can have a profoundly deleterious impact on day-to-day functioning and HRQOL. While it is not life-threatening, it may be serious condition, associated with hospitalizations.
Current Treatment Options	• There are no FDA approved therapies for PFC. • Treatment is primarily the off-label use of laxatives and non-pharmacological interventions.[4] • 40% of children treated by pediatric gastroenterologist in the U.S. with off-label laxatives remain symptomatic.[5]	There is a clear unmet medical need as PFC can be a serious disease for which there is no currently approved medication. The safety and efficacy of medications used off-label in children with PFC have not

[3] Sood, Manu. "Functional Constipation in Infants and Children: Clinical Features and Differential Diagnosis." Up-to-Date. 2017.
[4] Tabbers et al. "Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN" Journal of Pediatric Gastroenterology. 58(2). 2014.
[5] Tabbers et al. "Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN" Journal of Pediatric Gastroenterology. 58(2). 2014.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		been established.
Clinical Benefit	• For the primary endpoint in the pivotal trial, among 6-17 year old 74/399 (18.5%) lubiprostone treated subjects were responders compared to 28/195 (14.4%) of placebo treated subjects (p=0.22). • The responder analysis among 6-17 year olds in the per protocol analysis of the pivotal trial favored placebo subjects over 24mcg BID subjects in both observed cases and LOCF methodology. • No clinically meaningful sub-population demonstrated a clinically meaningful benefit or statistical significant benefit for the primary endpoint. • Key secondary endpoints did not demonstrate a significant treatment effect in 6-17 year olds. • The key secondary endpoints did not universally trend in favor of lubiprostone over the 12 weeks of the pivotal trial or across sub-populations.	Lubiprostone at the doses tested in the pivotal trial did not demonstrate significant benefit in the primary endpoint, a SBM responder analysis for children 6-17 years old, or a clinically meaningful sub-group within that population with PFC. Additionally, the pivotal study did not demonstrate clinical benefit based on the totality of secondary endpoints in children 6-17 or 12-17 years of age.
Risk and Risk Management	• The most common AEs that occurred in at least 2% of lubiprostone treated subjects in the pivotal PFC trial and were more common in children treated with lubiprostone compared to placebo were nausea, vomiting, headache, diarrhea, gastroenteritis, pyrexia, sinusitis, chest pain and blood iron decreased. • Mechanism and juvenile animal studies suggest there may be a risk of	The overall safety profile appears acceptable if the drug had been determined to be efficacious. The main safety risks identified were similar to those reported and currently labeled for adults. No serious

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	osteopenia/osteoporosis and fractures. The dual-energy X-ray absorptiometry (DXA) sub-study did not demonstrate a bone signal, but due to sample size and methodologic limitations, a signal may not be definitively excluded. • There was a single subject with baseline elevated transaminases who had markedly elevated transaminases that improved following discontinuation of the study drug. The case did not meet Hy's law and he was asymptomatic, so it is unclear if there may be a potential liver signal in children that has not been reported in adults.	clinical safety signals that can be clearly attributed to the drug were identified. Risks to bone health and for elevated transaminases warrant continued investigation and monitoring during other pediatric studies.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This is not applicable.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommendations for new postmarket requirements (PMRs) or commitments.

The following Pediatric Research Equity Act (PREA) PMRs were outstanding at the time of this submission:

- PMR 572-4 Conduct a safety and efficacy study in pediatric patients with chronic idiopathic constipation ages ≥ 6 years to < 18 years.
  - Protocol Submission: 8/26/2013
  - Study Completion: 12/31/2016
  - Final Report: 12/31/2017

- PMR 572-5 Conduct a safety and efficacy study in pediatric patients with chronic idiopathic constipation ages ≥6 months to <6 years.
    - Protocol Submission: 3/31/2018
    - Study Start: 6/30/2018
    - Final Report: 9/30/2020

- PMR 675-3 Conduct a safety and efficacy study of lubiprostone in pediatric patients with irritable bowel syndrome with constipation (IBS-C) ages 6 years to < 18 years. The design will consist of a 12-week mulit-center, double-blinded, placebo-controlled safety and efficacy study.
    - Protocol Submission: 5/1/2017
    - Study Start: 6/30/2020
    - Final Report: 9/30/2020

- PMR 675-4 Conduct an open-label extension safety study of lubiprostone, including a safety evaluation of the effects of lubiprostone treatment on bone growth in pediatric patients ages 6 years to <18 years with irritable bowel syndrome with constipation (IBS-C) who participated in the 12-week efficacy study conducted to address PMR 675-3.
    - Protocol Submission: 5/1/2017
    - Study Start: 6/30/2021
    - Final Report: 9/30/2021

See section 2.5 for further details on regulatory history of these PMRs.

The Sponsor is claiming to have fulfilled PMR 572-4 based on the data contained in this efficacy supplement from study PFC-1131 and 11s1.

Reviewer Comments: This reviewer believes that PMR 572-4 should be considered fulfilled. (Refer to Section 2.5 for additional background on the regulatory history and Section 9.2 for labeling recommendations). The Sponsor conducted a 12 week pivotal study and a long-term extension study with protocols that were agreed upon with the Agency. The Sponsor enrolled over 600 subjects, which is a large study compared to the 479 adults enrolled in the pivotal CIC trials. Although there were conduct issues, ultimately we determined that these issues did not impact the interpretability of the study. (See Section 5.3.1 for further details).

2 Introduction and Regulatory Background

Chronic functional constipation describes chronic constipation that is not due to organic causes. Constipation has been defined as having less than 3 bowel movements per week, and most commonly manifests with painful defecation, but can also cause

abdominal distension, abdominal pain, and fecal incontinence. Due to pain associated with bowel movements, young children will often withhold stool and avoid defecation. This can lead to prolonged fecal stasis in the colon with increased reabsorption of fluids and increase in the size and hardness of the stools, making them more painful to pass and further the cycle of withholding. Additionally, over-time the rectal wall stretches to accommodate the larger fecal mass, which both decreases the urge to stool and causes the anal closure to become less competent, such that fecal incontinence may occur.

The most accepted diagnostic criteria for pediatric functional constipation are the Rome criteria. These criteria were established and subsequently modified by international scientists and clinicians in the field of functional gastrointestinal disorders. Table 2 describes the Rome III criteria (used to define PFC in the efficacy studies submitted in this application).[6] At the time of writing this review, the current definitions of PFC are based on the Rome IV criteria, and the only differences from the Rome III criteria for children ≥ 4 years is that the symptoms must only be present for 1 month instead of 2 months.[7]

Table 2. Rome Criteria for the Diagnosis of PFC in children ≥ 4 years of Age[8]

Rome III
At least 2 of the following present at least once per week for at least 2 months*
≤ 2 defecations in toilet per week
≥ 1 episode of fecal incontinence/ week
History of retentive posturing or excessive volitional stool retention
History of painful or hard bowel movements
Presence of a large fecal mass in the rectum
History of large-diameter stools that may obstruct the toilet

* The symptoms cannot be explained by another medical condition & are insufficient to meet the criteria for IBS

PFC is the most common cause of childhood constipation, accounting for 95% of the cases of constipation in children older than one year of age.[9] PFC accounts for 3 to 5% of all general outpatient pediatric visits and 10 to 25% of all visits to pediatric gastroenterologists. The overall prevalence of PFC has been estimated between 1 to 30%, with a median of 9%.[10] The wide prevalence range appears to be multifactorial,

[6] Rasquin et al. "Childhood functional gastrointestinal disorders:child/adolescent." Gastroenterology. 130. 2006.
[7] Hyams et al. "Functional Disorders: Children and Adolescents." Gastroenterology. 2016.
[8] Rasquin et al. "Childhood functional gastrointestinal disorders:child/adolescent." Gastroenterology. 130. 2006.
[9] Sood, Manu. "Functional Constipation in Infants and Children: Clinical Features and Differential Diagnosis." Up-to-Date. 2017.
[10] Van den Berg et al. "Epidemiology of Childhood Constipation: A Systematic Review" American Journal of Gastroenterology. 101. 2006.

including the use of different definitions of constipation and demographic features of the population studied. Children who are obese and lead a sedentary life and have a modern Western diet are more likely to have PFC. Additionally, children are particularly vulnerable to developing PFC when weaning from breast milk or initiating solid foods, during toilet training, and when starting school.[11]

There is a wide spectrum of severity, from mild and transient to severe and chronic, sometimes necessitating hospitalizations due to fecal impaction. A multi-center cohort study of children's hospitals revealed that 0.65% of all pediatric admissions were for PFC, and these children had a mean 90-day readmission rate of 3.8%.[12] Most children who receive treatment (behavioral, dietary, and/or off-label laxatives) have resolution of their constipation. Amongst those children with more severe constipation who are referred to a gastroenterologist, approximately 50% will have resolution of their constipation and have stopped laxative use after 12 months. However, despite available off-label therapy, 40% of children referred to a pediatric gastroenterologist for PFC remain symptomatic after 6 months despite use of currently available off-label laxatives. Relapses are common, and 20% of children referred to a pediatric gastroenterologist continue to suffer from constipation 10 years after they were initially diagnosed. Children who are treated shortly after they become symptomatic have a better prognosis; a delay of 3 months in initiation of off-label medical therapy is correlated with a longer duration of symptoms and laxative use.[13]

PFC impacts affected children, their families, and society in general due to impairment in quality of life, school absenteeism, parental absenteeism from work, and healthcare costs. International studies have shown that children with PFC have significantly impaired health related quality of life (HRQOL). In one study of 5 to 15 year olds with PFC, abdominal pain was the symptom that accounted for the greatest variability in patient-reported HRQOL.[14] In another study HRQOL was worse for children with PFC compared to children with gastroesophageal reflux disease (GERD) or inflammatory bowel disease (IBD), based on parental and self-report.[15] In children 5 to 18 years old with PFC, abdominal pain had the most significant impact. Another study showed that PFC had a significant impact on physical, emotional, social, and school-function in pre-school children.[16] Children with PFC miss school due to symptoms and for medical care, and their caretakers are also consequently absent from work. It is estimated that

[11] Drossman et al. The Functional Gastrointestinal Disorders, third edition. Allen Press. 2006
[12] Librizzi et al. "Hospital-Level Variation in Practice Patterns and Patient Outcomes for Pediatric Patients Hospitalized with Functional Constipation." Hospital Pediatrics. 7(6). 2017.
[13] Tabbers et al. "Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN" Journal of Pediatric Gastroenterology. 58(2). 2014.
[14] Varni et al. "Gastrointestinal symptoms predictors of health-related quality of life in pediatric patients with functional gastrointestinal disorders." Quality Life Research. 26. 2017.
[15] Youssef et al. "Chronic childhood constipation is associated with impaired quality of life: a case-controlled study." Journal Pediatric Gastroenterology and Nutrition. 41(1). 2005.
[16] Wang et al. "Impact of Functional Constipation on Health-Related Quality of Life in Preschool Children and Their Families in Xi-an, China." PlosOne. 2013.

healthcare costs associated with children who have all causes of constipation (not just PFC) are three times greater than healthcare costs for children without constipation. This equates to an additional $3.9 billion annually in the United States.[17]

2.1 Product Information

Lubiprostone is a prostaglandin E1 metabolite analogue and is formulated in a soft gelatin capsule with liquid contents of lubiprostone and a medium-chain fatty acid triglyceride. The drug substance is a crystalline compound with a molecular weight of 390.46 and a molecular formula of $C_{20}H_{32}O_5F_2$. Lubiprostone selectively activates the type 2 chloride channels located on the intestinal epithelial cell. When these channels are activated, they increase chloride transport into the lumen of the intestine, enhancing fluid secretion into the bowel and improving fecal transit.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no approved therapies for constipation in children. PFC is the pediatric correlate to chronic idiopathic constipation (CIC) in adults. For CIC, Amitiza (lubiprostone), Linzess (linaclotide), and Trulance (plecanatide) are approved. For adults with occasional constipation, polyethylene glycol (PEG) is approved for occasional use, but is also used off-label for chronic constipation.[18]

In children, functional constipation is usually treated with a combination of non-pharmacological therapy and laxatives. Non-pharmacologic therapy includes guidance on toileting behavior, physical activity, and dietary changes. In 2013 when experts from North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) conducted a systematic literature review, there was limited data on non-pharmacological therapy. Based on expert opinion, they recommended normal fiber intake, fluid intake and physical activity. Since some children are primarily sedentary and have minimal fiber intake, interventions to increase their activity and increase their dietary fiber may be beneficial in these children. Regarding behavioral therapy, three systematic reviews were identified comparing laxatives with behavioral therapy to laxatives alone, and found no difference with the addition of behavioral therapy; behavioral therapy was therefore not recommended. Based on expert opinion, the reviews concluded that there may be benefit in referring children with constipation and behavioral abnormalities to mental health providers, and providing explanation,

[17] Liem et al. “Health Utilization and Cost Impact of Childhood Constipation in the United States.” Journal of Pediatrics. 154(2) 2009.
[18] Arnold Wald. “Management of chronic constipation in adults” Up to Date. 2017

demystification and guidance for toilet training.[19] There is evidence from a randomized controlled trial that among children who were compliant with behavioral interventions, rates of remission of constipation were equivalent to children treated with laxatives.[20] Behavioral interventions continue to be recommended by the American Academy of Pediatrics (AAP). [21,22]

No currently marketed laxatives are indicated for PFC or any type of constipation in children. The clinical practice guidelines put forth by NASPGHAN and ESPGHAN recommend polyethylene glycol (PEG) with or without electrolytes as first line therapy for fecal impaction, and enemas if PEG is unavailable. For chronic maintenance therapy of PFC, PEG with or without electrolytes is recommended as first-line therapy. If PEG is unavailable, lactulose is recommended as first-line maintenance therapy. Milk of magnesia, mineral oil, and stimulant laxatives are recommended based on expert opinion as additional or second-line therapy for chronic PFC.[23] Although NASPGHAN and ESPGHAN proposes this treatment algorithm, these products are not approved in children and laxatives are only indicated for short-term use in adults.

2.3 Availability of Proposed Active Ingredient in the United States

Lubiprostone was approved on January 31, 2006 for the treatment of CIC in adults. Currently, it is marketed as 8 mcg and 24 mcg capsules. The 24 mcg capsule is indicated for use in the treatment of adults with CIC and opioid-induced constipation (OIC) for non-cancer pain. The 8 mcg capsule is indicated for use for irritable bowel syndrome with constipation (IBS-C) in adult women and in adult patients with CIC or OIC for non-cancer pain with severely impaired hepatic function.

2.4 Important Safety Issues with Consideration to Related Drugs

Lubiprostone is a prostaglandin E1 analogue. Therefore, it is possible that it may have safety issues similar to other synthetic prostaglandins such as misoprostol (Cytotec). This includes issues related to pregnancy loss and pediatric bone health. However, at the time of initial approval and subsequent safety evaluations, no such issues have been identified. As there are no prostaglandin analogues approved for children, their safety with regards to pediatric bone health has not previously been evaluated. See section 7.4.5 for more details.

[19] Tabbers et al. “Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN” Journal of Pediatric Gastroenterology. 58(2). 2014.
[20] Nolan et al. “Randomized Trial of laxatives in treatment of childhood encopresis.” Lancet. 338 (8766). 1991.
[21] Sood, Manu. “Functional Constipation in Infants and Children: Clinical Features and Differential Diagnosis.” Up-to-Date. 2017.
[22] “Constipation in Children” HealthyChildren.org. Updated 10/2016.
[23] Tabbers et al. “Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN” Journal of Pediatric Gastroenterology. 58(2). 2014.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The IND (59623) was originally submitted to the Agency on December 29, 1999. The NDA (21908) was submitted in 2005, and on 1/31/2006, lubiprostone was approved for the treatment of chronic idiopathic constipation (CIC) in adults. An efficacy supplement for the treatment of IBS-C in women over 18 years of age was approved on 4/29/2008. Another efficacy supplement for the treatment of OIC in adults with chronic, non-cancer pain was approved on 4/19/2013. Please refer to Dr. Brian Harvey's clinical review from 1/30/2006 for the regulatory history related to the IND, and the clinical reviews by Drs. Helen Sile and Farrokh Sohrabi for a detailed regulatory history of the supplements for IBS-C and OIC, respectively. Additional labeling supplements are summarized in Table 3.

Table 3. Labeling Changes Following Initial Approval

Date	Type of Labeling Change
5/2007	Prior Approval Labeling Supplement (Conversion to PLR format)
4/2008	New Indication (IBS-C in women over 18 years of age)
2/2011	Prior Approval Labeling Supplement (Dosage and Administration)
9/2012	Prior Approval Labeling Supplement (Removal of pregnancy Warnings and Precautions & changes to pregnancy and nursing mothers section)
4/2013	New Indication (OIC in adults with chronic, non-cancer pain)
8/2013	Prior Approval Labeling Supplement (CMC)
9/2016	Prior Approval Labeling Supplement (Warnings and Precautions added syncope and hypotension)
8/2017	Prior Approval Labeling Supplement (Limitations of Use added for OIC indication)

Source: Data from DAARTS and FDA Labels and Approval Letters on Drugs at FDA.

The remainder of this section will focus on the regulatory history for PFC. There is no Written Request for pediatric studies. PMRs for PFC were required under PREA at the time of the original approval of lubiprostone for CIC. In 2006, PMR 572-1 was issued for "studies for the treatment of chronic idiopathic constipation in pediatric patients ages 0 to 17 years." Prior to reaching agreement with the Agency on details regarding the study design to satisfy this PMR, the Sponsor conducted study SC-0641, a 4 week open label study in 124 children ages 3-17 years with functional constipation. The Agency did not believe that this study was adequate to fulfill the PMR as it was not placebo-controlled and did not include long-term safety assessments.

Although the final report for PMR 572-1 was initially due on 1/31/2008; several deferral extensions were granted (on 4/16/2014 and 2/11/16) due to challenges in developing a liquid formulation for children less than 6 years of age, substantive changes in scientific understanding of pediatric CIC, and difficulty recruiting. On 2/11/16, at the time of the second deferral extension, the initial PMR was released and replaced by two PMRs,

572-4 and 572-5, to facilitate review of the studies that the Sponsor was already performing separately. The delays related to development of a liquid formulation only applied to children less than 6 years of age. A partial waiver was granted for children less than 6 months of age as studies are impossible or highly impractical as the condition cannot be diagnosed in this age group.

- PMR 572-4: Conduct a safety and efficacy study in pediatric patients with chronic idiopathic constipation ages ≥6 years to < 18 years.
  Milestone Dates: Protocol Submission 8/26/2013
  Study Completion 12/31/2016
  Final Report 12/31/2017

- PMR 572-5: Conduct a safety and efficacy study in pediatric patients with chronic idiopathic constipation ages ≥6 months to <6 years.
  Milestone Dates: Protocol Submission 2/28/2017
  Study Start 3/31/2017
  Final Report 8/30/2019
  Revised Dates: Protocol Submission 3/31/2018
  Study Start: 6/30/2018
  Final Report: 9/30/20

During the pre sNDA meeting that took place on 2/8/17, the Agency recommended that the Sponsor defer initiation of PMR 572-5 until results of study PFC-1131 (the randomized double-blind efficacy and safety trial of lubiprostone in children aged 6-17 years of age with PFC) could be reviewed by the Division.

There have been multiple meetings between the Agency and Sponsor during the course of the pediatric development process for PFC. The relevant meetings and communications are summarized in Table 4.

Table 4. Summary of Key Meetings and Communication between FDA and Sponsor regarding Lubiprostone for Pediatric Functional Constipation in Children ≥ 6 years of age

Date	Type of Communication	Summary
1/31/2006	Approval Letter	PREA PMR issued for pediatric study in children 0-17 years with chronic idiopathic constipation
12/18/2006	Advice Letter from FDA to Sponsor	The PREA study should be a double-blind, placebo-controlled trial to evaluate efficacy and safety of age appropriate formulations of lubiprostone for CIC in children 0 to 17 years, and there needs to be at least 12 months in order to provide adequate safety data.

Date	Type of Communication	Summary
11/13/2008	Type C Meeting	Discuss pediatric study commitments for CIC and IBS-C -Study SC-0641 is unacceptable -In vitro and juvenile animals study to evaluate bone are needed prior to initiation of further pediatric studies
3/19/2013	Type C Meeting	Discuss implications of juvenile non-clinical studies on pediatric safety monitoring -Protocol should assess BMD (bone mineral density), BMC (bone mineral content) and bone growth -Protocol should closely monitor heart rate (HR) and blood pressure (BP) -Justification needed for sampling scheme for PK exposure-response relationship
8/20/2013	Type C Meeting	To reach consensus on study design -ROME III criteria are adequate eligibility criteria and will fulfill PREA studies for CIC -Primary endpoint to be a responder analysis with durability of efficacy over 12 weeks (not change from baseline in SBM frequency)
4/16/2014	Letter	PREA deferral extension granted (final report for pediatric CIC due 12/31/2015)
2/11/16	Letter	Release of original PREA study and reissued as a study in children 6-18 years and 6 months-6 years with reports due 12/31/17 and 12/31/2019, respectively. A formal waiver was granted for children < 6 months.
2/8/2017	Type B/pre-SNDA Meeting	To discuss results of pediatric studies and labeling for a pediatric indication -Aggregate pediatric efficacy & safety data from studies PFC-1131, PFC-11S1, SC-0641, SCMP-303 sufficient to submit an sNDA, but interpretation of this data will be a review issue -Sponsor proposed an indication of patients 10-17 years, and FDA cautioned that although subgroup analyses may be submitted, post-hoc analyses will be reviewed with caution -Primary efficacy analyses to include patients enrolled at all sites, with sensitivity analyses excluding patients from sites that were terminated due to violations -Additional PK data was requested by the Agency

Source: Reviewer's table based on data from DAARTS.

2.6 Other Relevant Background Information

Lubiprostone is not approved for children in any country. Outside the US, lubiprostone is approved in 12 countries (Switzerland, Japan, UK, Ireland, Belgium, Luxembourg, Netherlands, Austria, Germany, Italy, Spain and Canada). The indication for lubiprostone for CIC is more restricted in European countries, where it is indicated in adults for the treatment of CIC when diet or non-pharmacological measures are inappropriate.[24]

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Submission was acceptable for review. The Sponsor submitted all necessary files and data-sets prior to the filing deadline. By the filing deadline, all datasets were navigable. However, in reviewing the data files in detail, it became apparent that certain variables were not appropriately defined or treated according to the statistical analysis plan (SAP). The Agency sent multiple Information Requests (IRs) to the Sponsor, which the Sponsor addressed during the review cycle. Based on these variable and analytic discrepancies, the statistical analysis performed by the FDA differed from the Sponsor's results provided in the CSR. (See Dr. Ling Lan's statistical review for additional details about the Sponsor's statistical data and analysis quality).

3.2 Compliance with Good Clinical Practices

The Sponsor certifies that all submitted studies were performed in accordance with U.S. Code of Federal Regulations (CFR) governing the protection of human subjects, obligations of clinical investigators and the IRB. Specifically, the Sponsor certified that all aspects of these studies were performed in accordance with Good Clinical Practice (GCP), which is consistent with principles set forth by the Declaration of Helsinki and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

However, the Sponsor identified two sites (1064 and 1082) with subject protection, investigational plan and regulatory violations that led the Sponsor to prematurely terminate these sites. Specifically, site 1064, had major data anomalies; there were no screen failures (compared to 46% across other sites), no subject had reported prior therapy (compared to 87% across other sites), no subject required rescue medication

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(compared to 49% across other sites), no subject had AEs (compared to 1.7 per subject across other sites). Due to inadequate case histories, the Sponsor was unable to verify that the subjects at this site actually had PFC. For site 1082, the Sponsor identified problems with the consent for 46% (6/13) of the subjects enrolled. Additionally, the records were inadequate or incomplete. Due to the discontinuation of these sites, 3 subjects were withdrawn from study PFC-1131.

Also, the Sponsor identified multiple protocol violations across the remaining sites. According to the Sponsor, amongst all sites including those that were prematurely terminated, the most common protocol violation was out of window visits (56%) and study procedures problems (42%). The Sponsor identified 22 (3.6%) subjects who did not meet eligibility criteria, 15 (2.5%) subjects who were mis-randomized, 27 subjects (17%) who had poor dosing compliance with lubiprostone (<65% or >120%), and 55 (9%) subjects who used prohibited medications. Protocol violations occurred across all arms of study PFC-1131. The major protocol violations, as defined by the Sponsor, are presented in Table 5.

Table 5. Sponsor's Summary of Major Protocol Violations during Study PFC-1131

Major Protocol Violations	Placebo (n=56)	Lubiprostone Total (n=107)
Key eligibility criteria not met or subjects mis-randomized	10 (18%)	16 (15%)
Prohibited medications or inconsistent use of confounding medications	3 (5%)	13 (12%)
Poor lubiprostone dosing compliance	19 (34%)	20(19%)
Confounding current medical history	24 (43%)	58 (54%)

Source: Sponsor's Table 14.1.3.1 from PFC-1131 CSR.

Reviewer Comments: Based on the data provided by the Sponsor about site 1064, this reviewer agrees with the Sponsor's concern that subjects enrolled at this site may not have had PFC, and the data are likely unreliable. This reviewer is also concerned that safety was not adequately captured in these subjects. However, as only 15 subjects were enrolled at this site, this reviewer believes that problems at this site do not affect the overall interpretability of studies PFC-1131 and PFC-11s1 and the mITT population remains the appropriate primary analysis population for PFC-1131.

This reviewer is concerned by the substantial number of reported protocol violations across the trial. Based on calculations performed by this reviewer, in study PFC-1131, 518 subjects (85%) had any type of protocol violations. Many of these protocol violations relate to incomplete safety assessments with lab tests and bone mineral density (BMD) not being performed or being performed late, early termination, incomplete or delayed collection of secondary efficacy endpoints. In this reviewer's opinion, most of these violations are unlikely to affect the interpretability of ITT efficacy analysis, but could contribute to an incomplete picture of the safety profile of lubiprostone in children.

This reviewer is not concerned with the poor dosing compliance, since only one subject took >120% of the study medication. If this was a large percentage of trial participants, then it would preclude analysis of the doses tested, but one subject will not affect results of the clinical trial. There were less than 6% of subjects in the pivotal trial who took significantly fewer doses of the study medication than specified in the protocol, which is unlikely to affect the outcome of the trial. Compared to a clinical trial, in clinical practice, patients are less likely to have ideal compliance with prescribed therapies, so this non-compliance with the prescribed therapy may be more representative of the effectiveness of the drug in the real-world, post-market setting. As there was an equal number of subjects in the lubiprostone and placebo arms who were non-compliant taking the therapy, it is unlikely that if their non-compliance affected other aspects of the trial, the results would be affected.

This reviewer was initially concerned with reports of falsification of diary data, from which the primary endpoint was derived. However, in response to an information request (IR), the Sponsor clarified this was limited to 2 siblings at one site and only occurred during the baseline period. For those subjects, the falsified data were excluded and new baseline data were collected prior to randomization.

This reviewer is most concerned about 163 major protocol violations which may be clinically relevant. For instance, these protocol violations include subjects who do not have PFC, have other co-morbid conditions that interfere with gastro-intestinal transit, were mis-randomized, used medications to treat constipation prohibited during the trial, and took rescue medications more frequently than indicated per the protocol. Of the subjects who did not have PFC, 26 subjects had IBS, which excludes the diagnosis of PFC according to the Rome III criteria. Therefore, the inclusion of subjects who either do not have constipation or have constipation due to other etiologies could potentially dilute the treatment effect of lubiprostone and contribute to a failed trial. On the other hand, the presence of these protocol violations does not necessarily imply that if only children with PFC were included, lubiprostone would be effective. Further analyses were conducted to ascertain the impact of patients who were erroneously enrolled, and this is discussed further in section 5.3.1.

With regards to subjects using prohibited study medications to treat constipation and relieve constipation symptoms, this violation could affect the interpretation of lubiprostone's effect on SBMs and constipation symptomatology. For instance, if other laxatives were started during the trial or rescue medications were used but not recorded appropriately, then it could falsely appear as though subject's constipation was improving due to lubiprostone. On the other hand, if subjects were given rescue laxatives when they did not actually require them, then lubiprostone may falsely appear to lack efficacy. These problems would be exacerbated if use of prohibited medications was not evenly distributed between the lubiprostone and placebo cohorts. Further analyses were conducted to ascertain the impact of patients who erroneously took other medications to treat their constipation, and this is discussed further in section 5.3.1.

To assess the overall impact of patients who had any potentially clinically significant protocol violations, a sensitivity analyses for the primary efficacy endpoint excluding these subjects was performed. Ultimately, this reviewer determined that these conduct issues did not impact the interpretability of the trial. (Refer to section 5.3.1 for further details and discussion).

Due to concerns with data quality and integrity, a request for Office of Scientific Investigations (OSI) audit was placed for this sNDA. At the request of DGIEP, site 1082 was selected due to the concerns regarding subject protection identified by the Sponsor. Additionally, in consultation with OSI, DGIEP requested 2 additional U.S. sites for inspection, site 1011 and 1087. These sites were chosen as they had enrollment of at least 10 subjects and an OSI audit was feasible (based on personnel availability for the priority review and hurricane recovery). OSI concluded based on their review that the Clinical Study Report (CSR) appears to accurately capture the conduct of study, PFC-1131, the pivotal trial for this supplement. Since the CSR describes multiple protocol violations, the quality of the data for approval is a review issue. See section 5.3.1 for a detailed discussion of quality issues related to interpretability of study results. For details of the audit, please refer to the Clinical Inspection Summary (CIS) by Dr. Susan Leibenhaut.

3.3 Financial Disclosures

The Sponsor certified that they did not enter into any financial arrangement with any of the clinical investigators and that none of the investigators had a proprietary interest in the drug or equity in the company.

Reviewer Comments: No concerns.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new CMC data was submitted. There are no manufacturing concerns with the approved and currently marketed product.

4.2 Clinical Microbiology

This section is not applicable.

4.3 Preclinical Pharmacology/Toxicology

No new toxicology data was presented in this efficacy supplement. A previously conducted in vitro culture rat osteoblast and osteoclast study (#665358) and a juvenile rat study (#670665) raised concerns about the effects of lubiprostone on skeletal growth, bone mineral density and bone mineral content. This juvenile animal study also raised concerns about changes in hemodynamic parameters in rats. These safety signals were investigated in the pediatric clinical trials, studies PFC-1131 and PFC-11s1, that were submitted in this application. (See Section 7.4.5 of this review for more details on the clinical studies to assess bone health). The current labeling describes the results of non-clinical carcinogenesis studies, mutagenesis and fertility studies.[25] (See Dr. Babatunde Emmanuel Akinshola's review for additional details on non-clinical toxicology).

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Lubiprostone is a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion without altering serum sodium and potassium concentrations. Lubiprostone acts by specifically activating chloride channel type 2 (CIC-2) which a normal constituent of the apical membrane of the human intestine, thereby facilitating the passage of stool. Patch clamp cell studies in human cell lines have indicated that the majority of the biological activity of lubiprostone and its metabolites is observed on the apical (luminal) portion of the gastrointestinal epithelium.

[25] Amitiza label (https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021908s011lbl.pdf)

4.4.2 Pharmacodynamics

A formal PD study was not submitted in this supplement.

4.4.3 Pharmacokinetics

Lubiprostone has low systemic bioavailability; it is rapidly metabolized following oral administration. The plasma levels of lubiprostone can not be quantified, but M3, the measurable active metabolite of lubiprostone can be quantified. The PK of M3 was studied in pediatric patients during the development of lubiprostone for PFC. While PK samples were collected from the pivotal trial, PFC-1131, and the extension trial, PFC-11s1, only 3% of these samples had measurable M3 concentrations which are insufficient data to evaluate PK from these studies. The PK parameters of M3 were derived only from the dose ranging study, SC-0641. The half-life of M3 ranges from 0.9 to 1.4 hours. There was an increase in Cmax and AUC in a dose proportional manner following single-dose administration of 12mcg and 24mcg of lubiprostone in children who weighed at least 36 kg. The mean AUC and Cmax was higher for children as body weight decreased. Children less than 24kg had the highest absorption, but this did not exceed the supra-therapeutic PK studies in adults. (Refer to Dr. Sojeong Yi's clinical pharmacology review for an in-depth pharmacology review.)

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Sponsor conducted one pivotal study, PFC-1131, which is a multi-center, randomized, placebo controlled double blind study to evaluate the PK, safety and efficacy of lubiprostone for the treatment of children 6-17 years with PFC. Children were randomized 2:1 to lubiprostone (12mcg BID if <50kg or 24mcg BID if >50kg) or placebo, and children treated with 12mcg BID could be dose escalated to 24mcg BID after 1 week.

The Sponsor submitted supportive data from 3 studies, PFC-11s1, SCMP 211-303, and SC-0641. Study PFC-11s1 is a 36 week, multi-center, open-label, uncontrolled extension of study PFC-1131 conducted primarily to assess safety and tolerability of lubiprostone in children with PFC. All eligible children who received drug in PFC-1131 continued on the same dose of lubiprostone during PFC-11s1, and children who were treated with placebo during PFC-1131 were treated with lubiprostone (12mcg BID if <50kg or 24mcg BID if >50kg) during this study. Study SCMP-303 is a multi-center, uncontrolled, open-label 24 week safety study in children 6-17 years old with PFC (although not based on Rome III criteria since not limited to ≤ 3 SBM/week) who were treated with lubiprostone (12mcg BID if <50kg and 24mcg BID if >50kg). Study SC-

0641 is a multi-center, open-label, uncontrolled 4 week study of 3 levels of lubiprostone (12mcg daily, 12mcg BID, 24mcg BID) in children <17 years old who weighed at least 12kg with PFC.

Table 6 summarizes the studies provided by the Sponsor that are relevant to the efficacy and safety evaluation of lubiprostone for PFC. No other studies were submitted with this application, and all studies were performed by the Sponsor.

Table 6. Summary of Clinical Trials Submitted in sNDA

Trial ID Location (No. of Centers)	Trial Design Duration of Treatment	Product, Dose & Route	Number of Subjects	Duration	Population
PFC-1131* 76 U.S. sites 20 Inter-national sites	Double-blind, Randomized, Multicenter, Placebo controlled Efficacy, Safety & PK	Placebo 12mcg or 24mcg Lubiprostone BID oral	Randomized: 606 Treated: 595 Completed: 444#	12 weeks	PFC Rome III 6-17 yo
PFC-11s1 67 U.S sites 18 Inter-national sites	Open-label, Multi-Center extension study Efficacy, Safety & PK	Lubiprostone 12mcg or 24 mcg BID oral	Treated: 419 Completed: 333	36 weeks	PFC Rome III 6-17 yo who completed PFC-1131
SCMP-303 13 U.S. sites	Open-label, multicenter Safety Study	Lubiprostone 12mcg or 24 mcg BID oral	Treated: 87 Completed: 53	24 weeks	PFC (Rome III except not limited to ≤ 3 SBM/wk) 6-17 yo
SC-0641 22 sites	Open-label, multicenter PK, Safety & Efficacy	Lubiprostone oral 12mcg daily, 12 mcg BID, 24 mcg BID	Treated: 124 Completed: 109	4 weeks	PFC (Rome III) <17 yo ≥ 12kg

* This includes all study sites (including the two sites in which the Sponsor detected irregularities and chose to prematurely discontinue participation in the study).
# The definition of completers for PFC-1131 is based on at least 86 days of therapy as per the SAP.
Source: Table designed by the clinical reviewer based on Sponsor's data contained in Final Study Reports for study PFC-1131, PFC-11s1, SCMP-303 and SC-0641 and information about completers from Summary of Safety table 2.7.4.1.2.

5.2 Review Strategy

The efficacy review is based primarily on data from study PFC-1131, the only randomized, controlled trial submitted in this application. In addition to the prespecified primary analysis, the Sponsor performed multiple post-hoc analyses assessing secondary endpoints in sub-populations, especially in children 10-17 years old and females. The efficacy analysis in this review is focused on the pre-specified analyses in the SAP and clinically relevant sub-groups, specifically, adolescents 12-17 years, who may respond to lubiprostone more similarly to adults with CIC compared to younger children based on their size, development, and being less likely to exhibit with-holding behaviors. Additional sensitivity analyses focus on the subset of patients who actually have PFC and patients with more severe constipation.

The safety review is primarily based on data from the controlled trial, in order to have a concurrent comparison group. Additional safety data analyses are based on the overall safety cohort, which includes all children who received at least one dose of lubiprostone during study PFC-1131, PFC-11s1, SC-0641 or SCMP-303, and from the long-term safety cohort, which includes children who were exposed to at least 6 months of lubiprostone. Bone health was analyzed in the sub-population of subjects from study PFC-1131 and PFC-11s1 who enrolled in the DXA sub-study. (See section 5.3 for details of the specific studies, section 6 for a detailed review of efficacy and section 7 for a detailed review of safety.)

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol Summary, Study PFC-1131: A Multicenter, Randomized, Placebo-controlled, Double-blind study of the Efficacy, Safety and Pharmacokinetics of Lubiprostone in Pediatric Subjects Aged ≥ 6 years to <18 Years with Functional Constipation

5.3.1.1 Trial Design

This is a double-blind, parallel group, randomized controlled trial to assess safety and efficacy of two doses (12mcg BID or 24 mcg BID, based on weight) of lubiprostone over 12 weeks of therapy in children 6-17 years of age with PFC.

The study involved 6 study visits and 2 telephone assessments or 5 study visits and 3 telephone assessments based on investigator preference and presence of AEs at the final visit.

The initial visit was a screening visit that occured on day -14. If subjects were eligible at the screening visit, they were instructed not to take laxatives or other concomitant medications affecting GI motility (as specified in the inclusion/exclusion criterion) and to complete a daily electronic stool diary. The second visit was on study day 1, during

which eligibility was confirmed based on review of diary records during the prior 2 weeks.

Randomization occurs during this second visit, study day 1. Randomization is stratified by age (6-9, 10-13, 14-17 years), sex, and baseline SBM (<1.5 or ≥1.5). The randomization is 2:1 to lubiprostone, and the dose of lubiprostone (12mcg or 24mcg BID) is based on weight. Study medication begins on the day of randomization.

The third visit occurs on day 7. During this visit, it is determined if the dose of study drug should be altered based on AEs or lack of efficacy (as described under Dosing).

Additional clinic visits occur at week 4, 8 and 12, and during these visits clinical assessments are performed. Telephone assessments occur at week 2 and week 14 (or 2 weeks after discontinuation for subjects' whom drop-out) with a focus on assessing changes in concomitant medications and AEs. The final study contact for PFC-1131 is 2 weeks after the 12 weeks of blinded therapy, at week 14; although pregnancies and ongoing AEs are followed after this visit.

See Figure 1 for an overview of the PFC-1131 study design.

Figure 1. Overview of Study Design for PFC-1131

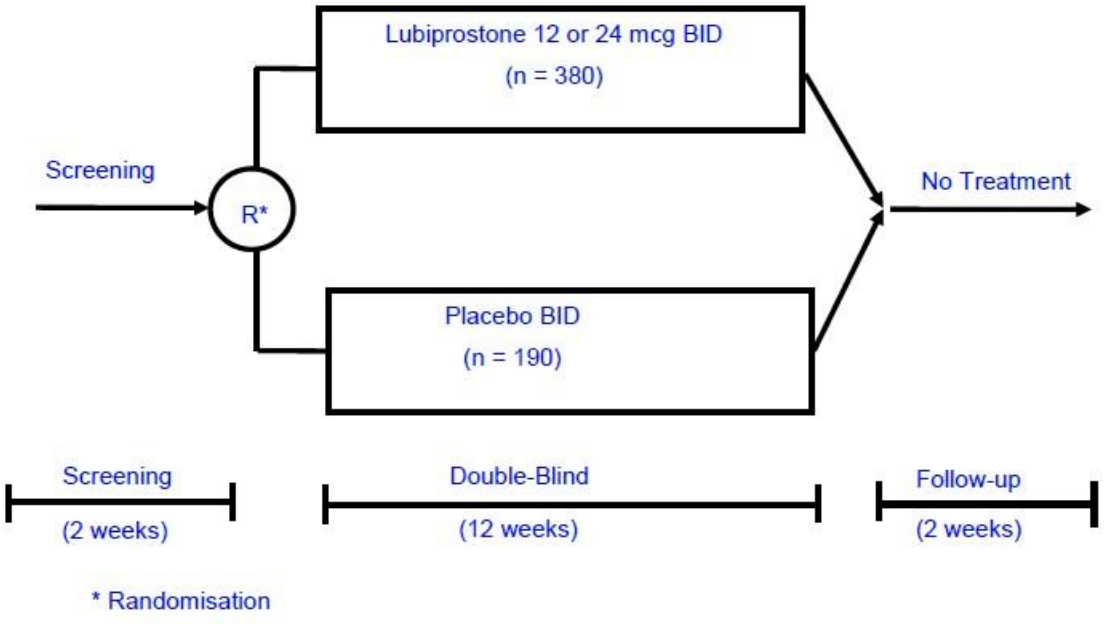

Figure provided by Sponsor PFC-1131 Protocol Version 7 page 29.

Reviewer Comments: This reviewer agrees that a double-blind control trial is an appropriate study design for this pivotal trial. As there are no approved therapies for PFC, a placebo control group is ethical and appropriate.

5.3.1.2 Objectives

- To assess the efficacy, safety and PK of lubiprostone at 12 and 24 mcg BID as compared to placebo, when administered orally, based on weight, for 12 weeks in children 6-17 years of age with PFC.

- To evaluate the measurement characteristics of PFC clinical outcome assessments (COAs).

5.3.1.3 Endpoints

The primary endpoint is overall SBM response, where a responder has ≥ 3 SBMs/week and an increase from baseline of ≥1 SBM/week for 9 out of 12 weeks of treatment (including 3 of the last 4 weeks of the study).

Secondary endpoints for efficacy and safety include the following:

- Change from baseline in SBM over the 12-week treatment period
- Monthly SBM responder during 3 of 4 weeks
- Change from baseline in BM and SBM during each week and month of treatment
- Time to first SBM following study drug administration
- Percentage of subjects with SBMs within 4, 8, 12, 24 and 48 hours after first administration of study drug
- Change from baseline in straining associated with SBMs, stool consistency of SBMs, abdominal pain, constipation severity, treatment effectiveness overall and based on weekly and monthly assessments during treatment
- Overall health-related quality of life based on pedsQL (Pediatric Quality of Life Inventory)
- Increase of ≥ 1 SBM from baseline and ≥ 3 weekly SBM for 75% of observed treatment weeks including 3 of the 4 final treatment weeks in subjects treated for at least 4 weeks (who did not drop out due to lack of efficacy)
- Frequency of incontinence episodes overall, weekly and monthly during treatment amongst patients who had incontinence at baseline
- Change from baseline in frequency of large diameter stools overall, weekly and monthly
- Frequency of fecal impaction overall, weekly and monthly during treatment
- Proportion of BMs and SBMs in the toilet overall, weekly and monthly during treatment
- Frequency of retentive posturing or excessive volitional stool retention overall, weekly and monthly during treatment
- Incidence of AE
- Changes in laboratory parameters, vital signs and physical exam

- Incidence of clinical fractures

There are additional secondary endpoints related to PK and evaluation of instruments for assessing Observer and patient reported outcomes.

Reviewer Comments: The primary endpoint is a responder definition that was proposed by the Division and has been used as the basis for the approval of constipation drugs for CIC and IBS-C. The responder definition captures sustained improvement, which is important for a chronic condition, such as PFC. Constipation has been defined by physicians as fewer than 3 bowel movements per week, which is one of the Rome 3 diagnostic criteria for PFC and captured by this endpoint. Patients often define constipation as a multi-symptom disorder that includes hard stools, straining, pain when passing a bowel movement, and fecal incontinence. These symptoms are captured as secondary endpoints, which this reviewer believes is appropriate especially since capturing symptoms may be less reliable in children compared to adults, especially in this study where parents/guardians rather than the children record data on signs and symptoms of constipation.

5.3.1.4 Trial Population

Key Inclusion Criteria:

- ≥6 years and < 18 years old
- PFC based on Rome III Criteria
    - ≥ 2 symptoms at least once per week for at least 2 months in a child with a developmental age of 4 years and insufficient criteria to diagnose IBS
        - ≤ 2 defecations in the toilet per week
        - > 1 episode of fecal incontinence per week
        - History of retentive posturing or excessive volitional stool retention
        - History of painful or hard bowel movements
        - Presence of a large fecal mass in the rectum
        - History of large diameter stools which may obstruct the toilet
- No concomitant medications that affect GI motility (after screening visit)
    - Cholinesterase inhibitors, anti-spasmodics, anti-diarrheal, anti-constipation, prokinetic agents, laxatives, homeopathic remedies, tricyclics, and other medications that are known to cause or relieve constipation or constipation related symptoms
        - Except anticholinergic agents, selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs) where the dose has been stable for ≥ 30 days and is unlikely to change during the study
- If taking a fiber supplement must be on a stable dose for ≥ 30 days and unlikely to change during the study

- Complete 70% of daily stool diary during screening and have evidence of constipation on the diary
    - Average < 3 stools/week during screening period and
        - MBSS 1 or 2 for at least 25% of SBM each week (if SBM reported) and/or
        - Some to extreme straining associated with SBMs (if SBM reported)
- Comply with study procedures including stool diary and use of rescue medications

Key Exclusion Criteria:

- Constipation due to an etiology other than functional constipation
    - Anatomic, neurologic, endocrine, metabolic, inflammatory bowel disease (IBD), medication or other physical/mental/cognitive
- Other conditions besides PFC affecting GI anatomy or motility
    - Hirschprung's disease
    - Eligible for or has undergone bowel resection, colectomy, gastric bypass
- Fecal incontinence not associated with stool retention
- Untreated fecal impaction at time of screening
- Medical/surgical condition that may interfere with the absorption, distribution, metabolism or excretion of the study medication
- Other significant medical problems
    - Indwelling peritoneal catheter
    - Unexplained weight loss
    - Cancer or was treated for cancer within the past 5 years
    - Uncontrolled cardiovascular, liver, lung, or systemic disease, or neurologic or psychiatric disorder that would limit ability to participate
    - Renal impairment (Cr >1.5 times median of normal range)
    - Pregnant
- Unwilling to undergo pregnancy testing or use protocol specified contraceptive measures
- Previously received lubiprostone
- Use of any investigational medication in the past 30 days
- Demonstrates non-compliance during the screening period

<u>Reviewer Comments</u>: The inclusion criteria are appropriate as PFC was defined by the Rome III criteria at the time that the study was performed. Under the updated Rome IV criteria, children who met criteria for PFC under Rome III continue to meet criteria for PFC. The enrollment criteria allowed for a heterogenous population of children with PFC; they do not predispose to a severe subset of children, which in this reviewer's opinion will enable the results to be generalizable to 6-17 year olds with PFC. However,

including patients with mild, recently diagnosed PFC, may increase the placebo response rate as these patients are more likely to improve spontaneously.[26]

5.3.1.5 Dosing

At screening, subjects were randomized to lubiprostone or placebo. Subjects randomized to lubiprostone, received 12mcg BID if they weighed less than 50kg and 24mcg BID if they weighed at least 50kg. After 1 week of treatment, subjects less than 50kg with less than 3 SBM and no treatment related side effects, dose could be increased from 12mcg BID to 24mcg BID for the remainder of the trial. The protocol also had guidelines for reducing the dose of lubiprostone due to side effects emerging during the trial.

Subjects were instructed to take the study medication twice a day, once in the morning and once in the evening with meals and at least 8 ounces of fluid. All doses were to be taken at least 5 hours apart. Subjects received 64 capsules of study medication, 28 days plus a 4-day overage, to provide sufficient drug for the month between clinic visits. Subjects were instructed to return the used bottle of study medication at each clinic visit, and capsule counts were to be documented in the eCRF. The subject's parent or guardian were also supposed to record the actual number and times doses of study drug are taken each day in the eDiary. Drug omissions were captured in the eDiary and the eCRF by each site.

5.3.1.6 Scheduled Study Procedures and Safety Assessments

The schedule of study procedures, including efficacy and safety assessments is summarized in Table 77.

Electronic Diary

Subjects and their parents/legal guardians completed an electronic stool diary every evening about constipation related events and symptoms during the previous 24 hours. Specifically, the electronic diary collected information about whether the child took both doses of study medication and at what time, whether and what other medication the child took for their constipation, whether and at what time the child had a BM in the past 24 hours, the parent's impression of the severity of the child's constipation in the past 24 hours, whether the BM clogged the toilet, and based on the child's input what the BM looked like, amount the child had to strain to have BM, whether it was painful to have a BM, and severity of abdominal pain. The electronic stool diary could also record BMs and use of laxatives in real-time. (See Appendix 1 for details on the data collected in the eDiary.)

Data from the electronic diary were used to evaluate the primary efficacy endpoint and multiple secondary efficacy endpoints.

[26] Tabbers et al. "Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN" Journal of Pediatric Gastroenterology. 58(2). 2014.

Table 7. Study Procedures during PFC-1131

SCHEDULE OF EVALUATIONS

Study Stage	Screening	Randomisation	Study Treatment and Evaluation (Day 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	4	5	6	7	8
Visit Type	Screening	Randomisation	Clinic Examination[1]	Telephone Assessment	Clinic Examination	Clinic Examination	End-of-Treatment Clinic Examination[16]	Follow-up Assessment[18]
Assessment								
Informed Consent/Assent	X							
Inclusion/Exclusion Criteria Review	X	X						
Demographics	X							
Medical History	X	X						
Vital Signs, Height, and Weight[2]	X	X	X		X	X	X	
Physical Examination	X		X[3]		X[3]	X[3]	X	
Pharmacokinetic Sampling[4]		X			X			
Blood Chemistry, Hematology, Urinalysis	X		X		X	X[5]	X	
Vitamin D Blood Collection[6]	X							
Pregnancy Test[7]	X	X	X		X	X	X	
Concomitant Medications[8]	→	→	→	→	→	→	→	→
Adverse Events[9]	→	→	→	→	→	→	→	→
BMD and BMC Assessments	X[10]						X[11]	
Study Medication Distribution[12]		X	X		X	X		
QoL Assessment[13]	X	X			X	X	X	
Study Treatment		→	→	→	→	→	→	
Study Medication Collection			X		X	X	X	
Investigator Assessment of Treatment Effectiveness					X	X	X	
Electronic Diary[14]	→	→	→	→	→	→	→	
PGIC Assessment[17]		X			X	X	X	
Clinician Severity Rating[18]		X			X	X	X	

[1] Subjects assigned to the 12mcg BID group may be dose escalated to 24mcg BID during this visit
[2] Use age-appropriate equipment; HR & BP to obtained before dose and 1 hour after dose, with measurements repeated q1 hour x 2 if clinically significant change
[3] Abbreviated PE
[4] Non-fasting PK samples by direct venipuncture
[5] Only if abnormal values at prior clinic visit
[6] Only for subjects who are 6-9 or 14-17 years
[7] Serum at screening and urine for all other visits
[8] At screening will include history of all prior constipation treatment (including failed therapy) and all medications used in past 30 days
[9] AEs prior to first dose of study drug will not be considered TEAE
[10] Only for those subjects who may meet the criteria for DXA sub-study
[11] Only for those subjects enrolled in the DXA sub-study
[12] The first dose is observed, and the remainder of doses are self-administered from the newly distributed medication bottle. The old study medication should be returned to the site at each visit.
[13] Should be performed before other study procedures during the study visit.
[14] Distributed to subjects' parents or legal guardians at screening visit and should be completed nightly.
[15] If subject enrolls in PFC-11s1, this visit will be the final visit of study PFC-1131 and the baseline visit for PFC-11s1.
[16] This may be a telephone or clinic visit, but if there are ongoing AEs this must be a clinic visit.
[17] Patient Global Impression of Change will only be performed in English speaking countries.
[18] This will only be performed in English speaking countries.

This table is replicated from Sponsor's Protocol PFC-1131 version 7 page 19 and 20. Footnotes provided by the Sponsor have been abbreviated by the clinical reviewer.

*Reviewer Comments: This reviewer is concerned that the eDiary may not have reliably captured the subjects' stooling pattern and constipation symptoms since irrespective of the child's age and maturity, parents/guardians completed the eDiary. All enrolled children were school age, and so parents/guardians did not accompany them throughout the day to observe their stooling. Each subject had to report to their parent/guardian about constipation signs and symptoms and then the parent/guardian recorded this in the eDiary. C*hildren and especially adolescents may be un*comfortable talking about their bowel habits with their parents/guardians daily for 14 weeks, which could lead to falsification of reporting. Typically, adolescents are encouraged to complete a patient reported outcome measure (e.g. eDiary) rather than have a parent/ guardian complete this on their behalf. Additionally, if children are unable to record BMs at the time they occurred, they may forget about them especially if their symptoms have improved.*

5.3.1.7 Rescue Medication

Subjects were not permitted to take rescue medication within 48 hours of the first dose of study drug. Otherwise, in the event of no BM within a 3 day period, rescue medication was permitted. If there was no response to the initial rescue medication, additional doses could be given.

Withdrawal of Subjects

Subjects may have been terminated prior to completion of the clinical trial for AE, lack of efficacy, subject choice, loss to follow-up, non-compliance, Investigator decision, Sponsor request, or any other reason that Investigator and Sponsor agree to. The reason for a subject's withdrawal or premature termination was recorded in the eCRF and the subject was supposed to return to clinic for an end of study visit at the end of the treatment period (visit 7) a follow-up visit (visit 8) as described above.

5.3.1.9 Statistical Analysis Plan (SAP)

Six study populations were defined in the SAP:

- Modified Intention to Treat (mITT): All randomized subjects who take at least one dose of study medication and have at least one post-treatment efficacy assessment. Subjects whose dose was escalated at the end of week 1 were analyzed with the dose group to which they were ultimately treated. This population was used for the primary efficacy analysis.
- Intent to Treat (ITT): This population includes all subjects who were randomized. This population was used for supportive analyses.
- Per Protocol (PP): This population includes all randomized subjects without any major protocol violations (met inclusion/exclusion criterion, no concurrent diagnosis of IBS, no use of prohibited medications, randomized per protocol, had medication compliance between 65% to

120% of scheduled doses). This population was used for supportive analyses.

- Completers (Comp): This includes all randomized subjects who completed at least 84 days of treatment. This population was used for supportive analyses.
- Dose Escalation (DE): This population includes all randomized subjects <50kg who received 1 week of lubiprostone 12mcg BID and then received lubiprostone 24mcg BID. This population was used for supportive analyses of efficacy and to assess treatment emergent adverse events (TEAE) and treatment related adverse events (TRAE) in the safety analysis.
- Safety: This includes all randomized subjects who took at least one dose of study drug. Subjects were analyzed based on the actual treatment received; although subjects whose dose was adjusted during the study were analyzed based on the dose originally administered.
- DXA Population: This includes all subjects who were enrolled in the DXA sub-study and remained eligible for the DXA sub-study throughout study PFC-1131. This population was used for analysis of bone safety. (See section 5.3.3 for additional details about the DXA sub-study)

The primary efficacy analysis was a comparison of SBM overall responder in the lubiprostone arm (either dose) compared to the placebo arm in the mITT population. A SBM was defined as a BM that does not occur within 24 hours after rescue medication use. (If multiple BMs were recorded at the same time, this was counted as a single BM for the purpose of calculating the number of SBMs.) A weekly responder was defined as a subject who has at least 3 SBMs/week and an increase from baseline of at least 1 SBM/week for that week. SBM frequency rate is calculated as 7 multiplied by the number of SBMs recorded, divided by the number of observed days (with partial days for the first dose of study medication). If there were less than 4 days worth of diary data completed in a week, then the SBM rate for that week was considered missing. An overall responder was defined as a weekly responder for 9 out of the total 12 weeks of study, including 3 of the last 4 weeks of the trial.

The primary efficacy analysis used the Cochran-Mantel-Haenzel (CMH) test stratifying by baseline SBM frequency (<1.5 or ≥1.5) for the comparison between the placebo group and the overall lubiprostone group on overall SBM response. The primary analysis was based on a non-responder imputation.

For key secondary endpoints, the close testing procedure (CTP) principle to account for inflation of the Type I error due to multiplicity. Specifically, sequential testing in a step-down manner was performed, such that once a non-significant p-value ($p \geq 0.05$) occurs all subsequent analyses were considered exploratory, multiplicity was no longer controlled. and no longer controlled for multiplicity by the close testing procedure

principle. The CMH test was applied for the secondary binary efficacy endpoints. For the secondary continuous efficacy endpoints, the van Elteren test using change from baseline stratified by pooled sites was used.

Sensitivity analyses were conducted using the Last Observation Carried Forward (LOCF) imputations for binary and continuous post-baseline efficacy variables where the only post-baseline values were carried forward up to each time point a new evaluation was available.

For additional details about the SAP, please refer to the statistical review by Dr. Ling Lan.

Reviewer Comments: This reviewer generally finds the efficacy analysis plan described in the SAP to be appropriate. This reviewer agrees with the Sponsor's decision to analyze children whose dose of lubiprostone was increased from 12mcg BID to 24mcg BID at the end of week 1 with subjects initially treated with 24mcg BID in order to assess efficacy of 24mcg dose in children less than 50kg. There are additional sub-group analyses that this reviewer believes are clinically informative, but were not specified in the SAP. (See section 6.1.5 and 6.1.7 for details on these analyses including results).

5.3.1.10 Amendments

The initial protocol under which the first subject was treated was version 3 incorporating amendment 2, dated November 26, 2013. Following enrollment of the first subject in December 2013, there were 4 amendments to the protocol. The majority of the changes made in these amendments were for clarification, but major substantive changes are described below:

- Version 7 (9/25/15):
  - The dose escalation criteria were now specified for the 12mcg BID cohort during visit 3, where previously criteria were suggested but the decision was left to the Investigator. This version of the protocol specified that during visit 3, subjects in the 12mcg BID cohort who had less than 3 SBM during the first week of study treatment and have no ongoing AEs that the Investigator considered related to study treatment, should subsequently receive 24mcg BID.
- Version 6 (9/2/15):
  - The enrollment criteria were revised, and the specification that subjects could not have IBS was reintroduced.
- Version 5 (4/14/15):
  - The enrollment criteria were revised, and subjects with IBS were permitted to enroll in the study.
  - Baseline PGIC in English speaking countries was added to the protocol, previously PGIC was only collected during visits 5, 6, and 7.

  - Sample size was revised to 570 (based on a 20% attrition rate)
- Version 4 (4/15/2014):
  - The Investigator's assessment of treatment effectiveness will be collected at visit 5 and visit 6, rather than just at visit 7.
  - The PGIC was added for English speaking countries and will be collected at visits 5, 6 and 7.
  - The Clinician Severity Rating was added and will be collected in English speaking countries during visits 1, 2, 5, 6 and 7.
  - PedsQL was added at visit 2.
  - The proposed analysis plan changed (including definition of mITT)

Reviewer Comments: This reviewer is concerned that patients with IBS-C were included during the 4 months that version 5 was in effect. Based on Rome 3 criteria, PFC and IBS-C are different conditions and drugs that work for one may not work for the other. Therefore, it has been the Agency's position, which has been conveyed to the Sponsor, that PFC needs to be studied separately from IBS-C. Therefore, the inclusion of patients with IBS-C may have confounded the primary analysis results. However, despite there being 24 patients with IBS-C at baseline enrolled in PFC-1131, a sensitivity analyses did not show a significant impact on the primary endpoint that would alter efficacy conclusions. (See section 6.1.4).

Additionally, since PGIC and Clinician Severity Ratings were added to the protocol after approximately 25% of subjects had been enrolled, the power to assess a treatment effect on these secondary endpoints is reduced.

The initial lack of uniform criteria to increase lubiprostone from 12mcg BID to 24mcg BID after 1 week of treatment in subjects less than 50kg, led 53 subjects who could have been treated with 24mcg BID to be treated with 12mcg BID instead. This does not impact the primary efficacy analysis since the prespecified analysis compares any dose of lubiprostone to placebo, but it reduced the power of sensitivity analyses comparing the Sponsor's proposed 24mcg BID dose to placebo. Also, it reduces the potential available safety data of 24mcg BID in children less than 50kg by almost 30%.

5.3.1.11 Trial Results

Conduct issues related to this trial are described below. Section 6 contains detailed efficacy data and section 7 contains safety data from this trial.

5.3.1.12 Conduct Issues

As discussed in section 3.2, there were multiple conduct issues with this trial. The major protocol violations that may have impacted the interpretability of the trial results include 15 subjects who were mis-randomized, at least 30 subjects who did not have PFC, 52 subjects who took prohibited medications to treat their constipation during the trial and 57 subjects who used rescue mediations more frequently than allowed per the protocol.

Mis-randomization occurred because weight or baseline SBM was incorrectly entered into the randomization and trial supply management (RTSM) system by study staff. The RTSM system dynamically assigned treatment based on stratification factors including baseline SBM frequency and weight to ensure site randomization balance, and therefore it is not known which treatment each of these children would have been assigned if their baseline data had been correctly entered into the RTSM system. There were 2 children whose weight was mis-entered into the RTSM and were dosed with lubiprostone 24mcg BID instead of 12mcg BID. There were 2 children who were given the wrong bottle of study medication at time of randomization, but the treatment happened to be identical.

The potential impact of having enrolled subjects who did not have PFC, used prohibited medications during the study to relieve constipation, or used rescue medications more frequently than indicated per protocol was further investigated by assessing the distribution of these subjects across the treatment and placebo arms and by age ranges, which is presented in Table 8.

Table 8. Major Clinically Relevant Conduct Issues during PFC-1131 in Placebo and Lubiprostone treated Children 6-12 and 12-17 years old in the mITT Population

Issues with Trial Conduct	Placebo n=195			Lubiprostone Total n=399		
n, (%)	6-11 yo	12-17 yo	6-17 yo	6-11 yo	12-17 yo	6-17 yo
Does not have PFC*	3 (3)	8 (9)	**11 (6)**	7 (3)	12 (7)	**19 (5)**
Used prohibited meds to relieve constipation#	15 (14)	11 (13)	**26 (13)**	16 (7)	10 (6)	**26 (6)**
Took rescue medications more frequently than indicated per protocol	15 (14)	9 (11)	**24 (12)**	18 (8)	15 (8)	**33 (8)**

Source: Table made by the Clinical Reviewer based on Sponsor's 12/8 response to our IR.
~ Includes subjects who were initially randomized to lubiprostone 24mcg BID and subjects whose lubiprostone dose was escalated to 24mcg BID after 1 week of therapy
*Not meeting key inclusion criteria including being between 6-18 years of age, diagnosis of PFC based on Rome III criteria, and having <3 SBM/week during screening and/or exclusion criterion (where constipation is due to causes other than PFC including Hirshprung's disease, non-retentive fecal incontinence or IBS.
# Use of laxatives, prokinetics, anti-spasmodics, or new fiber supplements that are prohibited per protocol.
yo=years old

Reviewer Comments: This reviewer does not believe that mis-randomization likely affects the interpretability of the trial. There were only 2 subjects who received a different treatment compared to what they were assigned, and both of these children may have ultimately been dose escalated to the dose of lubiprostone that they received. Although, it is not possible to assess the treatment that should have been assigned

based on the dynamic randomization process, mis-randomization occurred in less than 2.5% of the study population.

Although the Sponsor identified 30 enrolled subjects who did not have PFC; this reviewer identified 5 additional subjects who did not have PFC at enrollment.[27] There is a possibility that additional subjects may have not met diagnostic criteria for PFC due to having greater than an average of 3 stools/week at baseline off any constipation therapy. The protocol required 10 of 14 (70%) baseline diary days to be completed, and only 2 enrolled subjects (1 in the lubiprostone arm and 1 in placebo arm) did not meet this inclusion criterion. However, there were 190 (31%) subjects who did not complete all baseline daily stool diary entries, and they were randomized equally to placebo and lubiprostone. If these subjects all had moderate to severe constipation, the incomplete baseline data would not change the possibility of subjects having less than 3 stools/week and a diagnosis of PFC. However, in subjects with mild constipation, who already had 2.5 SBM/week recorded, an additional SBM would have led them not to meet the criteria for PFC and made them ineligible for the study. Of the 65 placebo subjects who were missing baseline diary data, 5 subjects had an average of at least 2.5 SBM/week during baseline.[28] Of the 125 subjects in the lubiprostone cohort who were missing some baseline diary data, 13 subjects had an average of at least 2.5 SBM/week.[29] When subjects who did not have PFC or may not have had PFC based on baseline diary data are excluded, 92% of subjects in this pivotal trial had PFC and they were evenly distributed between the placebo and lubiprostone arm, so ultimately this reviewer believes that the enrollment of a small number of subjects without PFC does not preclude interpreting the data from this trial.

The use of prohibited medicines to treat constipation was 13% in the placebo arm compared to 6.5% in the lubiprostone arm among 6-17 year olds. This may have affected the trial outcome especially if these subjects were driving the placebo response rate. However, when the outcomes of these subjects were analyzed, the overall responder rate was low compared to the population who did not take prohibited medications. Patients who took prohibited medications for their constipation were more likely to withdraw from the trial than those who did not take medications for their constipation, but this did not differ between the placebo and lubiprostone arms. There was only a 4% response rate in the placebo cohort who took prohibited constipation medication compared to an overall placebo response rate of 14% in the entire study. There was a 12% response rate in the lubiprostone arm who took prohibited constipation medication compared to an overall response rate of 19%.

[27] Subjects with >3 SBM during screening and/or diagnosis of IBS based on Sponsor's ADMH and ADSL datasets.
[28] The median SBM/week was 2.5, range 2.5-2.8 and mean was 2.6 ± 0.15 SBM. These calculations were performed by the reviewer based on Sponsor's ADSL dataset.
[29] The median SBM/week was 2.5, range 2.5-2.8 and mean was 2.6 ± 0.12 SBM/week. These calculations were performed by the reviewer based on Sponsor's ADSL dataset.

There was a slight predominance of subjects in the placebo arm compared to the lubiprostone arm who used rescue medications more frequently than allowed per the protocol. Subjects who used rescue medication more frequently than specified had fewer SBM relative to their total BMs, since the SAP excludes BM that occurred within 24 hours of use of rescue medication as being considered a SBM. This would be expected to reduce the overall response rate and prejudice the study in favor of lubiprostone as more placebo subjects took rescue medications more frequently. As the overall trial results do not suggest benefit of lubiprostone, this conduct issue would not be expected to have impacted the findings of the study PFC-1131. However, it is also possible that the use of regular laxative may have had some sustained benefit and actually increased SBM frequency and SBM responder rate. If this was the case, then a higher placebo response rate could have led to a failed trial. Subjects in the lubiprostone cohort who received more rescue medications than indicated had a 10% lower response rate than the overall mITT, and subjects in the placebo cohort had a 6% higher than expected SBM rate than the overall mITT population. As the response rate was not impacted in a uniform direction in both the control and lubiprostone arms of this study, this reviewer does not believe that the use of more frequent than expected rescue medications had a profound impact on SBM rate. Since the overall number of subjects who used laxatives more frequently than indicated was small relative to the overall study population, this reviewer does not believe that the use of more frequent rescue medications ultimately impacted the findings or interpretability of study PFC-1131.

To further examine the impact of the cumulative conduct issues, the primary responder analyses was performed in the per protocol population and in the population without major clinically relevant population. These analyses showed a response rate for the lubiprostone and placebo arms that was similar to the mITT. The similar, non-significant treatment effect further support this reviewer's conclusion that the conduct issues do not ultimately impact the results and interpretability of the trial. (See section 6.1.4 for further details).

5.3.2 Protocol Summary - Study PFC-11S1: A Multicenter, Long-Term, Safety, Efficacy and Pharmacokinetics Study of Lubiprostone in Pediatric Subjects Aged ≥ 6 years to <18 Years with Functional Constipation

This is an open-label, uncontrolled trial in which long-term safety, efficacy and PK of two doses of lubiprostone (12 mcg and 24 mcg BID) are tested in children 6-17 years old with PFC who completed the double-blind, 12-week, randomized trial (study PFC-1131). This trial is 36 weeks in duration, so subjects initially treated in PFC-1131 will have 40 weeks of treatment and 42 weeks of safety data. Efficacy was assessed using an eDiary as performed in PFC-1131.

Details of this trial are provided in Appendix 2. Safety results are described in section 7.

Reviewer Comments: Overall this reviewer finds the study acceptable to assess long-term safety, but is concerned that efficacy data will not be interpretable as there is no control group. PFC has both a high spontaneous resolution rate and a high recurrence rate so it is not possible to extrapolate a long-term placebo response rate from the short-term response rate obtained in study PFC-1131. Additionally, this reviewer continues to have concerns with the use of an eDiary completed by parents/guardians to assess stool frequency and constipation symptoms especially in adolescents. (Refer to reviewer comments in section 5.3.1.6 for further details).

With respect to safety, this reviewer believes that overall the assessments are appropriate for evaluating major safety signals in the pre-marketing setting. To minimize site variability and investigator interpretation errors, a central laboratory and age appropriate reference ranges were used including for heart rate and hypertension. The protocol limitations for assessing safety include that abnormal vital signs were not required to be repeated which can introduce measurement error and uncertainty. Additionally, the protocol does not provide pediatric reference range for hypotension or require assessment for orthostatic hypotension, which may lead to under-reporting of orthostatic hypotension. Furthermore, while the protocol acknowledges that use of a stadiometer is the preferred method for assessing height, it does not require sites to have this equipment. Therefore, this reviewer is concerned that measurement error could dilute a safety signal of an affect on linear growth if all subjects are not measured using appropriate equipment throughout the study.

5.3.3 PFC-1131/11s1 DXA Sub-study

Trial Design/Objective

At the time of enrollment in PFC-1131, eligible subjects were able to enroll in a DXA sub-study to evaluate short-term effects of lubiprostone on bone health. Specifically, the sub-study examined if lubiprostone appears to have a safety signal affecting bone health in children (6-9 years) and adolescents (14-17 years) with PFC.

Endpoints

The safety endpoints in PFC-1131/PFC-11s1 related to the DXA sub-study include:

- Changes from baseline in BMC and BMD (including BMD z-score and BMD height-adjusted z-scores)
- Changes from baseline in height and weight z-scores

Trial Population

The major eligibility criteria included:

- 6-9 years old or 14-17 years old at time of enrollment
- Screening DXA z-score >-2
- Screening serum 25-vitamin D level ≥ 20 ng/ml

- No use of oral or inhaled corticosteroids in the past 6 months or plans to initiate use
- No history of bone disease (e.g. rickets, osteogenesis imperfecta, severe scoliosis, back surgery/injury)
- No history of anorexia nervosa, rheumatoid arthritis or other endocrine disorder
- No use of anticonvulsants, bisphosphonates or depo-provera

Scheduled Study Procedures and Safety Assessments

DXA of lumbar spine and total body less head (TBLH) are performed at screening, week 12 (the end of study PFC-1131) and week 48 (the end of study PFC-11s1). Height is measured during visits when DXA scans are performed. Subjects who withdraw from the study are still encouraged to return for follow-up DXA study. For subjects with a >4% decline from screening in BMD at any skeletal site, should have a follow-up DXA 6-12 months later.

Statistical Analysis

Change from baseline in BMC, BMD, BMD z-score, BMD height-adjusted z-score and height z-score will be calculated for the entire DXA population and sub-group (sex, race, and age group) may be performed.

Reviewer Comments: This study was not designed to compare BMD and BMC in children treated with lubiprostone compared to placebo as children only received placebo for 12 weeks which is likely insufficient duration to detected changes in BMD by DXA. A minimum of 6 months is recommended by the International Society of Clinical Densitometry between scans in children to detect changes in BMD based on the precision of DXA.[30] Total body less head (TBLH) and the lumbar spine selected for measurement of BMD and BMC are the preferred skeletal sites in growing children.[31] Height z-scores will control for short stature and growth delay. Therefore, this reviewer believes that if lubiprostone has a large, acute deleterious effect on bone, this study could detect it.

Children who are at risk for osteopenia from other etiologies have been excluded from this study. However, the Sponsor excluded children between 9-14 years of age, and that unnecessarily reduced the sample size in this sub-study. Although DXA is the preferred method for clinical detection of bone density, it does not detect changes in micro and microarchitecture that can predispose to fragility fractures and osteoporosis. Changes in micro-architecture were detected in the rat studies using peripheral quantitative computed tomography (pQCT).

[30] Shepherd et al. "Optimal monitoring time interval between DXA measures in children." Journal of Bone Mineral Research. 26(11); 2011.
[31] Gordon et al. "2013 Pediatric Position Development Conference: executive summary and reflections." Journal Clinical Densitometry. 17; 2014.

Trial Results
The results of this sub-study are described in Section 7.4.5.

5.3.4 Study SCMP-303: A 6-month, Open-Label Safety Study of Lubiprostone in Pediatric Subjects Aged ≥ 6 years to <18 Years with Functional Constipation

This was an open-label, uncontrolled, 6-month safety study of 2 doses of lubiprostone (12mcg and 24mcg BID) in children 6-17 years of age with PFC. As in PFC-1131 and PFC-11s1, doses were weight based, children less than 50kg were treated with 12mcg BID and children greater or equal to 50kg were treated with 24mcg BID. The children enrolled in this study were permitted to have less severe constipation (with more frequent SBM) compared to study PFC-1131 and PFC-11s1. There was no eDiary and safety assessments were similar to those performed in PFC-1131 and PFC-11s1.

Details of this trial are provided in Appendix 3. Safety results are described in section 7.

Reviewer Comments: This reviewer does not believe that any informative efficacy data can be obtained from this trial as there is no control group and no real-time assessment of SBM and constipation symptoms; the only efficacy assessment is at the end of the open-label treatment period by the investigator.

This reviewer believes that the study can provide informative 6 month safety data, but it is limited by the lack of control group. The limitations of a lack of concurrent control group are the same as exist in PFC-11s1; it is not possible to detect whether AEs are attributable to the drug, the disease or reflect background rates within the pediatric population. Since subjects did not record symptoms in real time and adverse events (other than SAEs) were only captured during infrequent study visits, children and their parents may have under-reported adverse events. Additionally, the population enrolled in this study may be less severe than the population enrolled in PFC-1131/PFC-11s1 which may affect the AEs and SAEs they experience.

5.3.5 Study SC-0641: A Multi-center, Open-labeled Study of Safety, Efficacy and Pharmokinetics of Lubiprostone in Pediatric Patients with Constipation

Trial Design
This is an open-label, uncontrolled, 4 week trial of children who are < 17 years with constipation in which multiple dosing regimens of lubiprostone were tested (based on subjects age and weight) to assess PK, and short-term efficacy and safety. The children enrolled in this study were allowed to be younger and smaller than the other studies that were conducted as part of the PFC development program. The doses

tested were selected for investigation based on allometric scaling from adult dosing for CIC.

Further details of the protocol are provided in Appendix 4.

Reviewer Comments: This reviewer believes that this trial was acceptable for evaluating PK, but offers limited utility for evaluating efficacy. Specifically, the lack of a control group, the short duration of the study, small sample size and limited uniformity for use of rescue medication limit the interpretability of efficacy data from this trial. This reviewer believes that having adolescents complete the electronic diary themselves rather than a parent or guardian is a strength of this trial, but does not overcome the overall design limitations.

Some safety data from this trial can be informative as appropriate safety parameters were collected. However, the population enrolled in the trial includes younger children than the Sponsor is seeking an indication for. The 4 week duration does not provide any long-term safety data, which is needed for a drug that is intended to be used chronically.

Trial Results

Safety results are presented in Section 7.

The Sponsor reports that 127 patients were enrolled in this study and 124 patients were treated with lubiprostone. Table 9 summarizes the population and treatment outcome by age and weight. Unlike the pivotal trial submitted to support this application, study PFC-1131, the primary efficacy analyses of this study was change from baseline in number of SBMs after 1 week.

Table 9. Dose Cohorts Change in SBM frequency after 1 week in SC-0641 mITT Population

	12mcg daily (n=27)	12mcg BID (n=65)	24 mcg BID (n=32)
Demographics			
Sex	15 M (56%)/ 12 F (44%)	41 M (63%)/ 24 F (37%)	9 M (28%)/ 23 F (72%)
Age	Mean 5.5 ± 1.7 Med 5 (3-9) yo	Mean 10.3 ± 2.8 Med 10 (6-17) yo	Mean 13.9 ± 3 Med 14 (6-17) yo
Weight	Mean 19.9 ± 2.8 Med 19.3 (14-25) kg	Mean 43.4 ± 18 Med 36.6 (22.1-101.9) kg	Mean 60 ± 16.9 Med 57.3 (36-99) kg
Change in SBM from baseline	Mean 0.9 ± 2.6 Med 0.4 (-1.8 – 12)	Mean 1.6 ± 2 Med 1 (-1.5 – 7.9)	Mean 2.3 ± 2.4 Med 2.4 (-0.7 – 8.9)
p-value	0.07	<0.0001	<0.0001

Source: Data from Sponsor's table listing CSR0211-09-001 legacy clinical report Tables 14.2.1.1.1 and 14.1.2. (Demographic data provided for the entire ITT population, but since there was no imputation of missing data, the mean and median for change in SBM from baseline excludes 2 subjects in the 12mcg daily cohort, 3 subjects in the 12mcg BID cohort and 2 subjects in the 24mcg BID cohort.

Based on these results and an overall tolerability of all doses tested, the Sponsor considered the 12mcg BID and 24mcg BID doses of lubiprostone as most appropriate for clinical development for PFC in 6-17 year olds, including the pivotal trial, PFC-1131.

Reviewer Comments: This reviewer agrees that these results support the doses investigated in the pivotal study that enrolled patients ages 6-17 years. It is possible that an alternative dose that the Sponsor did not study would be more efficacious than either the 12mcg BID or 24mcg BID doses.

6 Review of Efficacy

Efficacy Summary

In this reviewer's assessment, the 12 week, double-blind randomized pivotal clinical trial of lubiprostone in children 6-17 years with PFC, study PFC-1131, failed to demonstrate effectiveness based on the primary pre-specified endpoint, a SBM responder analysis, in the entire study population or in any clinically relevant sub-population. This reviewer's analysis of the totality of the clinical data, including analysis of clinically meaningful secondary endpoints did not support effectiveness of lubiprostone for PFC in children 6-17 years old or 12-17 years old.

6.1 Indication

The proposed indication is "treatment of pediatric functional constipation (PFC)" in patients aged 10 to 17 years.

Reviewer Comments: This reviewer agrees that an indication for PFC is appropriate based on the Rome III definition of PFC and the primary endpoint from the randomized, double-blind study, PFC-1131. Specifically, a weekly responder is defined as a subject having an increase of at least 1 SBM/week from baseline and at least 3 SBM per week, and an overall responder if the subject is a weekly responder for 9 out of 12 weeks including 3 of the last 4 weeks, indicating that the response is maintained. This reviewer believes that the primary efficacy endpoint, change in SBM frequency during week 1, used in study SC-0641 and as a key secondary efficacy endpoint in the pivotal trial, study PFC-1131, could only support acute relief of constipation.

With respect to the requested age range, 10-17 years, this reviewer is concerned that there is no biological reason to support differential drug efficacy in this sub-group relative to other subgroups. The Sponsor simply stated that statistical efficacy was demonstrated in females 10-17 years of age, but did not provide a biologic rationale for this observation. This reviewer believes there may be a rationale for adolescents, 12-17-year-old, to respond differently than younger children. The literature describes some patients with CIC as having symptoms that begin as adolescents.[32] Therefore, in order to explore whether the efficacy of lubiprostone was similar in adolescents to adults with CIC, sub-group analyses were conducted in 12-17 year-olds. Further discussion of these analyses can be found in section 6.1.5 and 6.1.6.

6.1.1 Methods

In this sNDA, the primary efficacy data that the Sponsor submitted is from PFC-1131, a single multi-center, parallel group, double-blind, placebo-controlled 12-week efficacy trial. Subjects, 6-17 years of age with PFC based on Rome III criteria were treated with either placebo, 12mcg lubiprostone BID or 24 mcg lubiprostone BID. Subjects were randomized 2:1 to receive lubiprostone, and received 12mcg BID if they weighed less than 50kg and 24 mcg BID if they weighed at least 50kg. After 1 week, subjects receiving 12mcg BID could be dose escalated to 24 mcg. Subjects parents/guardians completed an eDiary nightly that captured use of study medication, rescue medication, bowel movement number and characteristics and symptoms of constipation over the past 24 hours. Weekly rescue medication was allowed if there was no BM during the prior 3 days. Efficacy data was gathered from the eDiary. Subjects were defined as weekly responders if they completed at least 4 days of diary entries and had *an increase of at least 1 SBM/week from baseline and at least 3 SBM per week. An overall*

[32] Solzi et al. "Constipated children different from constipated adults?" Digestive Disease. 2009.

responder was defined as a subject who was a weekly responder for 9 out of 12 weeks including 3 of the last 4 weeks, indicating that the response is maintained. (See section 5.3.1 for further details about the trial design).

The Sponsor submitted supportive efficacy data from PFC-11s1, a 36 week open-label, long-term extension trial during which all subjects were treated with 12mcg BID or 24 mcg BID of lubiprostone and SBMs and constipation symptoms were assessed based on the eDiary used in the pivotal trial. (See section 5.3.2 for further details about this trial).

The Sponsor also submitted supportive efficacy data from study SC-0641, a 4 week open-label, uncontrolled study of children 4-17 years with constipation. See section 5.3.4 for further details about this trial.)

Reviewer Comments: This reviewer believes that the data from PFC-1131, the double-blind, randomized trial, contains the most informative efficacy data in this submission. (See Reviewer comments in section 5.3.1 for a more comprehensive critique of this study). PFC-11s1 provides long-term data, but is limited since it was open-label and there is typically a high placebo response in constipation trials.

This reviewer believes that study SC-0641 does not provide interpretable efficacy data. Study SC-0641 was an open-label trial without a concurrent control group, and since there is typically a high placebo response in constipation trials, this reviewer does not believe that the efficacy data from this trial is interpretable. Further this trial was only 4 weeks in duration so it is not possible to evaluate whether the response was sustained. Therefore, the remainder of section 6 will only include an efficacy analysis from study PFC-1131 and PFC-11s1.

6.1.2 Demographics

Table 10 presents baseline demographic data for study PFC-1131, the well-controlled study in this submission, excluding cases for which the information was not available or unknown. Both studies primarily enrolled non-Hispanic Caucasians from the U.S. There was a slight predominance of females. The mean and median age of enrollment was 11 years. In general, there were fewer 14-17 years olds enrolled compared to the other age groups. The mean and median weight was just under 50kg. There was a wide spectrum of BMI, with some children being underweight and others being morbidly obese. There was no statistical difference with respect to demographic characteristics between the placebo and treatment arms. The 12mcg lubiprostone group only included children < 50kg and therefore differed from the other cohorts with respect to weight and age (as in childhood, older age is associated with greater weight). There was a slightly higher proportion of males in the 12mcg lubiprostone cohort compared to the placebo or

24 mcg lubiprostone cohort. The mITT population did not significantly differ from the ITT.

Table 10. Baseline Demographic Characteristics for PFC-1131 mITT Population

Variable	PFC-1131			
	Placebo (n=195)	Lubiprostone Total (n=399)	Lubiprostone 12mcg (n=107)	Lubiprostone 24 mcg^ (n=292)
Sex, n(%)				
Male	89(46)	183 (46)	54 (50)	129 (44)
Female	106 (54)	216 (54)	53 (50)	163 (56)
Race, n(%)				
Alaskan Native/ American Indian	3 (2)	0	0	0
Asian/ Hawaiian/ Pacific Islander	4 (2)	4 (1)	0	4 (1)
Black/ African American	39 (20)	67 (17)	8 (8)	59 (20)
White	138 (71)	308 (77)	86 (80)	222 (76)
Other	11 (6)	20 (5)	13 (12)	7 (2)
Ethnicity, n(%)				
Hispanic	44 (23)	76 (19)	17 (16)	59 (20)
Non-Hispanic	151 (77)	323 (81)	90 (84)	233 (80)
Age (years)				
Mean +/- SD	11 (3)	11 (3)	9 (2)	12 (3)
Median (Range)	11 (6-17)	11 (6-17)	9 (6-17)	12 (6-17)
Age Group				
6-9 years	66 (34)	142 (36)	68 (64)	74 (25)
10-13 years	78 (40)	153 (38)	35 (33)	118 (40)
14-17 years	51 (26)	104 (26)	4 (4)	100 (34)
Weight (kg)				
Mean +/- SD	48 (20)	48 (20)	33 (9)	54 (21)
Median (Range)	45 (18-121)	46 (17-123)	30 (17-50)	53 (18-123)
Weight Group, n(%)				
< 50 kg	109 (56)	236 (59)	107 (100)	129 (44)
≥ 50 kg	86 (44)	163 (41)	0	163 (56)
BMI (kg/m^2)				
Mean +/- SD	21 (5)	21 (6)	18 (3)	22 (6)
Median (Range)	21 (12-40)	20 (12-41)	17 (12-33)	22 (13-41)
Country, n(%)				
USA	167 (86)	344 (86)	96 (90)	248 (85)
Other	23 (14)	49 (14)	11 (10)	40 (15)

Source: Data from Sponsor's Table 14.1.4.1 PFC-1131 CSR.
^This includes subjects who were initially randomized to 24mcg BID and subjects who were titrated to 24mcg BID after 1 week of 12mcg BID.

Baseline constipation status was determined by nightly and weekly responses in a constipation related eDiary that was completed 2 weeks prior to administration of the first dose of study drug. Additional data about subjects' prior medical therapy for constipation was obtained from medical history elicited at screening. Table 11 summarizes history of constipation therapy and baseline constipation status for study PFC-1131, the well-controlled study, for the mITT.

Table 11. Baseline Constipation History for PFC-1131 mITT Population

Variable	PFC-1131			
	Placebo (n=195)	LUB Total (n=399)	LUB 12mcg (n=107)	LUB 24 mcg^ (n=292)
History of Constipation Therapy n(%)				
Yes	189 (97)	389 (98)	103 (96)	286 (98)
No	6 (3)	10 (2)	4 (4)	6 (2)
Failed prior Constipation Therapy n(%)				
Yes	141 (72)	289 (72)	73 (68)	216 (74)
No	54 (28)	110 (28)	34 (32)	76 (26)
Screening Average Weekly BM Frequency				
Mean ± SD	1.7±1	1.7±0.9	1.7±0.8	1.7±0.9
Median (Range)	1.5 (0-6)	1.7 (0-6)	1.7 (0-3)	1.7 (0-6)
Screening Average Weekly SBM Frequency				
Mean +/- SD	1.4±0.9	1.4±0.8	1.4±0.9	1.4±0.8
Median (Range)	1.5 (0-3)	1.5 (0-3.5)	1.5 (0-3.25)	1.5 (0-3.5)
Baseline SBM Frequency Group n(%)				
<1.5 SBM	90 (46)	171 (43)	42 (39)	129 (44)
≥1.5 SBM	105 (54)	228 (57)	65 (61)	163 (56)
SBM Stool Consistency at Screening				
Mean ± SD	2.1 (0.7)	2.1 (0.7)	2.1 (0.6)	2.2 (0.7)
Median (Range)	2 (1-4.3)	2 (1-4)	2 (1-4)	2 (1-4)
SBM Bowel Straining at Screening				
Mean ± SD	2.5 (1.1)	2.5 (0.9)	2.6 (0.9)	2.5 (0.9)
Median (Range)	2.5 (0-4)	2.6 (0-4)	2.6 (0-4)	2.6 (0-4)
Painfulness of SBM at Screening				
Mean ± SD	2.2 (1.2)	2.2 (1.1)	2.2 (1.1)	2.2 (1)
Median (Range)	2.2 (0-4)	2 (0-4)	2 (0-4)	2.2 (0-4)
Abdominal Pain at Screening				
Mean ± SD	1.8 (1)	1.8 (1)	1.6 (0.8)	1.8 (1)
Median (Range)	1.8 (0-4)	1.8 (0-4)	1.6 (0-4)	1.9 (0-4)
Stool Incontinence Episodes at Screening				
Mean ± SD	0.1 (0.4)	0.1 (0.3)	0.1 (0.3)	0.1 (0.2)
Median (Range)	0 (0-2.5)	0 (0-2.5)	0 (0-2.5)	0 (0-2)
Clinician Baseline Severity Rating				
Mean ± SD	3.5 (0.7)	3.5 (0.7)	3.5 (0.7)	3.5 (0.8)
Median (Range)	3 (2-5)	3 (1-5)	3 (2-5)	3 (1-5)

Variable	PFC-1131			
	Placebo (n=195)	LUB Total (n=399)	LUB 12mcg (n=107)	LUB 24 mcg^ (n=292)
Parent Global Impression at Baseline				
Mean ± SD	**4.3 (0.9)**	**4.5 (1)***	4.6 (1)	4.5 (1)
Median (Range)	**4 (1-7)**	**4 (1-7)**	4 (2-7)	4 (1-7)
Child Global Impression at Baseline				
Mean ± SD	4.1 (1.2)	4.2 (1)	4.2 (1.2)	4.2 (1)
Median (Range)	4 (1-7)	4 (1-7)	4 (1-7)	4 (1-7)
Screening Rescue Medication Use				
Mean ± SD	1 (1.8)	1 (1.9)	1 (1.8)	1 (1.9)
Median (Range)	0 (0-8)	0 (0-11)	0 (0-8)	0 (0-11)

Source: Data from Sponsor's Table 14.1.5.1 and 14.1.5.2.
SBM defined as any BM that did not occur within 24 hours after the use of a rescue laxative.
Stool consistency (MBBS): 1=hard lumps (hard to pass), 2=sausage shaped but lumpy, 3=sausage or snake (smooth and soft), 4=fluffy pieces with ragged edges (mushy), 5=watery, no solid pieces.
Bowel straining: 0=Not at all, 1=a little, 2=some, 3=quite a bit, 4=extremely.
Constipation severity and Abdominal Pain: 0=none, 1=mild, 2=moderate, 3=severe, 4=very severe
*p=0.02 for parent impression of total lubiprostone group compared to placebo
^This includes subjects who were initially randomized to 24mcg BID and subjects who were titrated to 24mcg BID after 1 week of 12mcg BID.

Overall, the placebo and lubiprostone arms were well balanced. Almost all subjects had received medical therapy for their constipation, and that therapy was effective for only about a quarter of the patients enrolled. While the median baseline SBM frequency in all cohorts was 1.5 stools/week, there was a wide range of stooling frequency, with some subjects in each cohort having no stools and others having more than 3 SBM per week. Use of rescue medication at baseline was uncommon, and occurred in less than half of the subjects.

In addition to an average of less than 3 stools/week, constipation was defined as having at least 25% of SBM during the screening as being MBSS 1 or 2 and/or having some or extreme straining associated with SBM. Those subjects who did not have SBM during screening, were excluded from analysis of stool consistency, bowel straining and painfulness of SBM. During screening (174/194) 90% of placebo subjects had a SBM and during screening (351/399) 88% of the lubiprostone treated subjects had a SBM. These numbers are comparable and therefore the characteristics of the SBM at screening can be compared and are comparable between the lubiprostone and placebo cohorts.

Reviewer Comments: The lubiprostone and placebo cohort were comparable with respect to demographics and baseline constipation severity. This reviewer believes that SBM frequency is the most important baseline constipation characteristic since this is what is used to determine efficacy response. The placebo and lubiprostone treated subjects had the same mean and median number of SBM.

The only statistically significant difference at baseline was on parental assessment of baseline constipation severity being less severe in the placebo cohort. While this is statistically significant (p=0.02), this reviewer does not believe that it actually represents a clinically significant difference in constipation severity since there was no difference in patient or clinician measures of constipation severity or objective measures of constipation symptoms. Baseline constipation severity was only assessed in a subset of the population (75-78%) as this assessment was added to the protocol after 151 subjects had been enrolled.

This reviewer also concludes that overall the population enrolled in this trial did not have very severe constipation. At baseline, most patients did not require rescue medication and stool incontinence was very rare. Therefore, it is possible that this trial did not demonstrate efficacy of lubiprostone because the population enrolled did not have severe enough constipation, which would reflect a type 2 error. However, as discussed in section 6.1.7, based on sub-population analyses conducted by this reviewer, it does not appear as though children with severe PFC had a high response rate to lubiprostone at the doses tested.

Doses received in Study PFC-1131 following the first week when subjects were dose escalated based on age and weight are summarized in Table 12 and Table 13. There were 231 subjects who were initially randomized to lubiprostone and assigned to the dose 12mcg BID because they weighed less than 50 kg. Of these subjects, 124 (54%) were dose escalated after 1 week to receive 24mcg BID and 107 (46%) subjects remained on 12mcg BID. Most of the subjects who were not dose escalated were not constipated (based on having >3 SBM/week) after 1 week on lubiprostone 12 mcg BID. Only 7 (3%) subjects treated with lubiprostone 12mcg BID were not dose escalated due to side effects. (The subjects who were not dose escalated due to side effects are discussed in further detail in section 7.2.2.)

Table 12. Study Arm following Dose Escalation in PFC-1131 mITT based on Age and Weight

	6-11 year olds			12-17 year olds		
	<50kg (n=282)	>50kg (n=45)	All (n= 327)	<50kg (n=57)	>50kg (n=210)	All (n=267)
Placebo	91	18	109	17	69	86
12 mcg Lubiprostone BID	93	0	93	14	0	14
24 mcg Lubiprostone BID	98	27	125	26	141	167

Source: Reviewer's table based on Sponsor's PFC-1131 ADSL dataset and limited to mITT flag "yes" and safety flag "yes" with treatment based on planned treatment for period 2 (after week 1 dose escalation).

Table 13. PFC-1131 Study Arm following Dose Escalation based on Sex, Weight and Sponsor's Age Sub-Groups

	6-9 year olds			10-13 year olds			14-17 year olds		
	<50kg (n=200)	>50kg (n=8)	All (n=208)	<50kg (n=126)	>50kg (n=105)	All (n=231)	<50kg (n=13)	>50kg (n=142)	All (n=155)
Placebo	63 (M 34/ F 29)	3 (M 2/ F 1)	66 (M 36/ F 30)	43 (M 20/ F 23)	35 (M 17/ F 18)	78 (M 37/ F 41)	2 (M 1/ F 1)	49 (15 M/ F 34)	51 (M 16/ F 35)
12 mcg BID Lubiprostone	68 (M 42/ 26 F)	0	68 (M 42/ F 26)	35 (M 12/ F 23)	0	35 (M 12/ F 23)	4 (M 0/ F 4)	0	4 (M 0/ F4)
24 mcg BID Lubiprostone	69 (M 33/ F 36)	5 (M 3/ F 2)	74 (M 36/ F 38)	48 (M 27/ F 21)	70 (M 36/ F 34)	118 (M 63/ F 55)	7 (M 2/ F 5)	93 (M 29/ F 64)	100 (M 31/ F 69)

Source: Reviewer's table based on data from Sponsor's PFC-1131 ADSL dataset and limited to mITT flag "yes" and safety flag "yes" with treatment based on planned treatment for period 2 (after week 1 dose escalation).

Reviewer Comments: Interpretation of a dose efficacy relationship may not be possible, especially if there is a difference in response between younger and older children or males and females. Very few adolescents between 12-17 year old were treated with 12mcg BID of lubiprostone. There was a higher proportion of adolescents compared to younger children whose dose of lubiprostone was escalated from 12mcg to 24 mcg, which this reviewer believes is likely due to chance based on the small number of children under 50kg who were eligible for dose escalation. Of the children treated with 12mcg BID lubiprostone, there were more males who were less than 10 years of age and more females who were over 10 years of age.

6.1.3 Subject Disposition

In study PFC-1131, the well-controlled study in this submission, a total of 1201 patients were screened and only 606 were randomized. There were 595 (49.5%) patients identified as screen failures either during the screening visit or at the end of the 14 day screening period. Table 14 summarizes the reason for screen failure. There were 53 subjects who did not meet multiple enrollment criteria, but each of these subjects are only listed once in Table 14.

Table 14. Reason for Screen Failures in Study PFC-1131

Reason for Screen Failure	Number of Subjects^, n (%) n=595
No Informed Consent/Assent	5 (1)
Not meeting Rome III Criteria for PFC	44 (7)
Have another condition affecting GI motility/defecation	3 (<1)
SBM during 14 day screening period is not consistent with PFC	411 (69)
More than avg 3 SBM/week during 14 day screening period*	345 (58)
<25% SBMs are modified BSS 1 or 2 or associated with some to extreme straining during 14 day screening period*	101 (17)
Use of prohibited medication/unwilling to discontinue	21 (4)
Unable/unwilling to swallow capsule, take rescue medication, complete daily diary or refrain from becoming pregnant	9 (2)
<70% daily diary completed during 14 day screening period	29 (5)
Untreated fecal impaction	3 (<1)
Other significant illness (includes uncontrolled disease, cancer in past 5 years, use of peritoneal catheter, unexplained weight loss, abnormal labs)	10 (2)
Demonstrates potential for non-compliance	59 (10)

Table made by the Reviewer based on Sponsor's dataset LIST_SF submitted 1/25/18
*There are 35 subjects who did not meet either SBM criteria
^ 53 subjects had multiple reasons for screen failures, but in this table, only the most important is listed. Not having PFC was considered more important and demonstrating potential for non-compliance was considered the least important.

Reviewer Comments: The demographics of the children who were excluded due to screen failures were very similar to the children who were actually enrolled. Specifically, 239 (40%) of the children were male. The median age of children who screen failed was 10 years, and the mean age was 10 years (± 3), which is equivalent to the enrolled population.

Table 15 summarizes the disposition of all randomized subjects enrolled in study PFC-1131, the well-controlled study submitted in this application. Amongst the 606 subjects who were enrolled in PFC-1131, 419 (69%) continued into the long-term extension study, PFC-11s1.

Table 15. Disposition of Randomized Subjects PFC-1131

Disposition, n(%)	Placebo	LUB Total	LUB 12mcg*	LUB 24 mcg*
Randomized	202	404	233	171
Safety	195 (97)	400 (99)	231 (99)	169 (99)
mITT	195 (97)	399 (99)	107 (46)	168 (98)
Completed	147 (73)	297 (74)	181 (78)	116 (68)
Per-Protocol	146 (72)	297 (74)	178 (76)	119 (70)
Dose Escalation	0	124 (31)	124 (53)	0
Discontinued	55 (27)	65 (16)	52 (22)	55 (32)
Reason for Discontinuation				
Treated <84 days but no discontinuation reason provided^	19 (9)	42(10)	15 (6)	17 (6)
Available Discontinuation Reason	36 (18)	65 (16)	37 (16)	28 (16)
Withdrawal by subject	16 (7)	21 (5)	12 (5)	9 (5)
Adverse event	6 (2)	17 (4)	9 (4)	8 (5)
Lost to follow-up	2 (<1)	9 (2)	5 (2)	4 (2)
Lack of efficacy	3 (1)	4 (1)	2 (1)	2 (1)
Sponsor decision (incl site closure)	1 (<1)	2 (<1)	2 (<1)	0
Investigator decision	2 (<1)	7 (1)	4 (2)	3 (2)
Other	3 (1)	3 (<1)	1 (<1)	2 (1)

Source: Reviewer's table based on Sponsor's response to question 1 from IR 12/8/17, tables 14.1.3.1 and 14.1.2, and table 5 from CSR PFC-1131.
* The lubiprostone dose cohorts are based on the dose randomized to, so subjects who were dose escalated are analyzed with the 12mcg BID cohort rather than the 24mcg BID cohort
^ The Sponsor provided reasons for dropouts based on 505 completers determined by the site Investigators rather than the 444 completers defined as completing ≥ 84 days of therapy based on the pre-specified SAP.

Reviewer Comments: Based on the definition of completers in the SAP of >84 days of treatment, 73% of subjects completed study PFC-1131, with an equal percentage of completers in the placebo and lubiprostone treatment arms.

There were 10% more completers in the 12mcg cohort than the 24mcg cohort. However, it is difficult to determine the impact that the actual dose received had on discontinuation during PFC-1131 as 53% of subjects in the 12mcg lubiprostone cohort were treated with 24mcg BID after receiving 1 week of 12mcg lubiprostone.

The reason for discontinuation was recorded for 62% of subjects who withdrew from the pivotal trial, and was recorded equally for the placebo and lubiprostone arms. The most common reason for discontinuation in both placebo and lubiprostone treated patients was patient/family decision to withdraw. Their decision to withdraw may have been influenced by side effects, lack of efficacy, burden of the trial, and/or other unrelated external factors. These issues cannot be teased apart based on the collected data.

Adverse events were the second most common reported reason for withdrawal from the trial, and were twice as common in the lubiprostone cohort compared to placebo. The dose of lubiprostone does not appear to impact rate of discontinuation from AEs in the pivotal trial. However, the analysis comparing withdrawal due to AEs was based upon the dose subjects were randomized to receive rather than the dose of lubiprostone they were actually receiving at the time of withdrawal. Over 50% of subjects in the 12mcg cohort were receiving 24mcg BID, so it is possible that the analysis method impacted the conclusion regarding dose impacting adverse events leading to discontinuation. (This is further discussed in section 7.3.3)

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint is the overall SBM response rate of subjects who received lubiprostone (12 mcg BID or 24 mcg BID) compared with placebo treated subjects in children 6-17 years of age in the mITT. The SAP prespecifies a non-responder imputation, such that missing data was imputed as a non-responder for that week. The Sponsor claims that while neither the results of observed cases nor LOCF analyses were statistically significant, there is a favorable treatment difference in favor of lubiprostone. The Sponsor's analysis is shown in Table 16.

Table 16. Sponsor's Analysis of SBM Response Rate in mITT PFC-1131

	Lubiprostone (12 or 24 mcg) N = 399 n (%)	Placebo N = 195 n (%)	Difference: L-P (%)	P-value
Observed Case Analysis Responders	76 (19.0)	28 (14.4)	4.6	0.1609
LOCF Case Analysis Responders	92 (23.1)	39 (20)	3.1	0.4056

Source: Reproduced Sponsor's table 5 from PFC-1131 CSR.

The Sponsor's analysis of the primary endpoint was repeated using the corrected variables and methods described in the SAP by FDA statistical reviewers, and the results were not statistically significant, as shown in Table 17. (See Dr. Ling Lan's review for additional details).

Table 17. FDA's Analysis Overall SBM response rates in the mITT population for Study PFC-1131

	Lubiprostone (12 or 24 mcg) N = 399 n (%)	Placebo N = 195 n (%)	Difference: L-P (%)	P-value*
Non-responder imputation	74 (18.5)	28 (14.4)	4.1	0.2245

Source: Dr. Ling Lan, FDA statistician
* P-value based on a CMH test stratified by baseline SBM frequency (<1.5 vs ≥1.5).
This result was based on the pre-specified responder status (corrected for subjects with IDs 1011-162 and 1079-110) and the baseline SBM frequency group. Note the sponsor used the SBM frequency at randomization.

The Sponsor also conducted the responder analysis in the per protocol population and the population who definitively had PFC and did not have major clinically relevant protocol violations, and the results are shown in Table 18.

Table 18. PFC-1131 Sponsor's Analysis of SBM Response Rate in mITT, Per Protocol Population and Population Without Major Clinically Relevant Protocol Violations

	Placebo	Lubiprostone			Treatment Difference	
		Total	12 mcg	24 mcg^	$L_{Total} - P$	$L_{24mcg} - P$
Observed Case Analysis Responders, n(%)						
Per Protocol	26 (17.8) n=146	63 (21.2) n=297	25 (30.9) n=81	38 (17.6) n=216	**(3.4) p=0.4**	**(-0.2)**
Population with PFC and No Major Clinically Relevant Protocol Violations#	19 (13.6) n=140	58 (18.6) n=311	25 (28.4) n=88	33 (14.8) n=223	**(5) p=0.2**	**(1.2)**
mITT	28 (14.4) n=195	76 (19) n=399	29 (27.1) n=107	47 (16.1) n=292	**(4.6) p=0.16**	**(1.7)**
LOCF Case Analysis Responders, n(%)						
Per Protocol	32 (21.9) n=146	66 (22.2) n=297	27 (33.3) n=81	39 (18.1) n=216	**(0.3) p=0.94**	**(-3.8)**
Population with PFC and No Major Clinically Relevant Protocol Violations#	27 (19.3) n=140	70 (22.5) n=311	30 (34.1) n=88	40 (17.9) n=223	**(3.2) p=0.47**	**(1.4)**
mITT	39 (20) n=195	92 (23.1) n=399	36 (33.6) n=107	56 (19.2) n=292	**(3.1) p=0.40**	**(-0.8)**

Source: Modified from Sponsor's table 14.2.1.1 and 14.2.1.4 from PFC-1131 Study Report and 14.2.75.3.1
#The population excludes patients without PFC (>3 stools/week at baseline or constipation due to other etiology including IBS), may not have had PFC (average > 2 SBM at baseline and missing baseline data from stool diary), used rescue medication more frequently than specified in the protocol, and/or used prohibited medications to treat constipation.
^Includes subjects whose dose was titrated to 24mcg BID after 1 week

Reviewer Comments: This study did not demonstrate that lubiprostone had a statistically significant or clinically meaningful treatment benefit for PFC. The overall number of subjects whose constipation responded to lubiprostone was small and the treatment difference between the treated patients and placebo was also small. The Sponsor's proposed treatment dose of 24mcg BID appeared less effective than placebo in the mITT population based on LOCF analyses and in the per protocol population by both observed and LOCF analyses. To explain the apparent lack of efficacy, this reviewer considered whether the results may have been due to an inadequate study design or limitations attributable to study conduct, that the doses studied were ineffective or that lubiprostone is ineffective for PFC.

The possibility that study design and conduct may have resulted in a negative study was considered and explored. The placebo response rate in the trial was higher than that predicted when power calculations were performed. Prior to initiating the trial, the Sponsor predicted a response rate of 21% for the total lubiprostone group and 10% for the placebo response rate. Based on the actual response rate of 18.9% in the lubiprostone group and 14.4% in the placebo group, in order for the study to be adequately powered the sample size should have been larger. Therefore, there remains a possibility that no statistically significant effect was seen despite one existing. Even without there being a statistically significant difference, this reviewer believes that the small responder difference is unlikely to represent a substantial treatment benefit from lubiprostone.

Poor adherence can also dilute a treatment effect, and contribute to type 2 error. The per-protocol analysis therefore introduces bias that may favor the drug. However, both the Sponsor's per protocol analysis and the analysis of subjects with PFC who did not have clinically relevant protocol violations in 6-17 year olds did not demonstrate a significant treatment benefit; the results were similar to the mITT population. This suggests that conduct issues themselves were not responsible for the lack of observed efficacy.

Lack of efficacy of a drug can be due to inappropriate selection of the studied dose. The primary responder analysis is based on a comparison of placebo to both doses of lubiprostone 12mcg and 24mcg. The Sponsor proposed a dose of 24mcg for the treatment of PFC, but the overall lubiprostone responders are being driven by the 12mcg cohort. The observed SBM response rate for the 12mcg BID cohort was 27.1%, whereas the response rate for the 24mcg BID cohort, including those subjects whose dose was escalated from 12mcg to 24mcg after 1 week, was 16.1%, based on the Sponsor's analysis.[33] Based on the available PK data from the dose-ranging study, SC-0641, the Cmax and AUC increase in a dose-proportional manner, so there is not a biological explanation as to why the 12mcg dose would be more effective. While it might have been possible that the dose escalation cohort, subjects initially in the 12mcg

[33] Table 14.2.1.1 from CSR PFC-1131.

lubiprostone cohort who were not responders during week 1 who were subsequently treated with 24mcg lubiprostone and analyzed with that cohort, diluted the treatment effect of the 24mcg cohort because they were a refractory subgroup of patients; however, when this issue was explored, it was not found to be the case. The 24mcg BID cohort, excluding subjects whose dose was escalated had an observed SBM response rate of 17.9%, 9% lower than subjects only treated with 12mcg BID.[34]

As PFC and CIC are different conditions, it is also possible that while lubiprostone is efficacious for CIC, it does not adequately address the multifactorial etiology of constipation in PFC. The behavioral withholding component appears to this reviewer to be less likely to be impacted by lubiprostone's mechanism of action, suggesting that younger children may be less responsive to lubiprostone. However, this was not supported by multiple subgroups analyses, including in adolescents who are less likely to have withholding, that also did not demonstrate a meaningful treatment benefit. (See section 6.1.5 and section 6.1.7 for additional details).

This reviewer concludes that the Sponsor has not demonstrated effectiveness of lubiprostone for PFC in children 6-17 years old in an adequately designed and conducted experiment.

6.1.5 Analysis of Secondary Endpoints(s)

The Sponsor claims that effectiveness of lubiprostone can be demonstrated from the well-controlled study, PFC-1131, based on improvement in multiple secondary and exploratory endpoints in lubiprostone treated children compared to placebo treated children.

The first key secondary endpoint the Sponsor specified was time to first SBM within 48 hours of first treatment. The Sponsor reports that 51% of all lubiprostone treated subjects compared to 45% of placebo treated subjects in the mITT had first SBM within 48 hours; this was not statistically significant (p=0.13).

Reviewer Comments: The SAP describes a hierarchical design with close testing procedure with a sequential step-down for secondary endpoints. Since the primary outcome and first key secondary endpoint are not significant, all subsequent secondary endpoints are not statistically valid. All analyses of secondary endpoints are exploratory and subject to inflation of type 1 error due to hypothesis testing of multiple endpoints. Therefore, the positive trends described by the Sponsor are hypothesis generating rather than evidence of efficacy. (See Dr. Ling Lan's statistical review for further details).

In addition to not being statistically significant, this reviewer does not believe that

[34] Reviewer's analysis based on Sponsor's revised ADEFF dataset submitted 1/5/18.

time to first laxation, or percent of subjects with first laxation at 8, 12, 24 or 48 hours informs the overall assessment of efficacy in PFC, since it is a chronic condition for which treatment benefit should be measured in weeks rather than hours.

In this reviewer's opinion, the most clinically informative secondary endpoint is change from baseline in SBM after 1 week and 4 weeks of therapy. These endpoints represent the primary evidence for effectiveness of lubiprostone in CIC. Therefore, by assessing these endpoints in children with PFC, a comparison of lubiprostone's short-term efficacy can be made to adults with CIC. Since adolescents with PFC are less likely to have withholding behaviors compared to younger children, this reviewer hypothesizes that adolescents with PFC may respond to lubiprostone more similarly to adults with CIC. A sub-group analysis in 12-17 year olds explores whether their response in change in SBM after 1 and 4 weeks of therapy is comparable to adults with CIC.

Table 199 summarizes *SBM after 1 and 4 weeks of therapy in the pivotal trial for adults with CIC and children with PFC.*

Table 19: SBM Frequency after 1 and 4 weeks of Treatment in Pivotal Trials for Adults with CIC and Children with PFC (PFC-1131)

Population	Study	Study Arm	Baseline Mean±SD Median	Week 1 Mean±SD Median	Week 4 Mean±SD Median	Week 1 Change from Baseline Mean±SD Median	Week 4 Change from Baseline Mean±SD Median
Adult CIC	Pivotal Study SCO131	**Placebo** (n=122)	1.6 ± 1.3 1.5	3.5 ± 2.3 3	2.9 ± 2.4 2.3	1.9 ± 2.2 1.5	1.3 ± 2.5 1
		LUB 24mcg BID (n=120)	1.4 ± 0.8 1.5	5.7 ± 4.4 5	5.3 ± 4.7 4	**4.3 ± 4.3 3.5**	**3.9 ± 4.6 3**
		p-value		0.0001	0.0002		
	Pivotal Study 2 SCO232	**Placebo** (n=118)	1.5 ± 0.8 1.5	4 ± 2.7 3.5	3.5 ± 2.9 3	2.5 ± 2.6 1.5	1.9 ± 2.7 1.5
		LUB 24mcg BID (n=119)	1.3 ± 0.9 1.5	5.9 ± 4 5	5.6 ± 4.6 5	**4.6 ± 4.1 3.8**	**4.1 ± 4.8 3**
		p-value		<0.0001	0.0068		
PFC	**PFC-1131 6-17 yo**	**Placebo** (n=195)	1.4 ± 0.9 1.5	2.5 ± 2.1 2.2	2.7 ± 2.5 2	1.1 ± 2.1 0.7	1.2 ± 2.5 0.5
		LUB 12 or 24 mcg BID (n=399)	1.4 ±0.8 1.5	2.6 ± 2.1 2.2	2.9 ± 2.5 2.3	**1.2 ± 2.1 1**	**1.5 ± 2.5 1**
		p-value*		0.1974	0.1149		
	PFC-1131 12-17 yo	**Placebo** (n=86)	1.4 ± 0.8 1.5	2.5 ± 2.1 2.2	2.4± 1.8 2	1 ± 2.1 0.5	0.9 ± 1.7 0.5
		LUB 12 or 24 mcg BID (n=180)	1.4 ±0.8 1.5	2.6 ± 2 2.2	2.7 ± 1.8 2.6	**1.2 ± 1.9 1.2**	**1.3 ± 1.6 1**
		p-value		0.2376	0.1149		

Source: Data from Sponsor's table 14.2.4.1.1 and table 14.2.76.1.1.1 from Sponsor's IR response from 12/8/2017, Amitiza drug label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021908s015lbl.pdf, accessed 1/10/18.
* p-value based on Van Elteren test stratifies by SBM frequency at randomization (<1.5 or ≥ 1.5) and pooled site.

The change in SBM at week 1 and week 4 is minimal for children with PFC treated with lubiprostone compared to adults with CIC. This analysis also supports that adolescents have a similar short-term change in SBM after lubiprostone as younger children despite differences in with-holding behavior. Despite the potential similarities between adolescents with PFC and adults with CIC, adolescents do not appear to respond similarly to adults with CIC. (See Section 6.1.7 for additional sub-group efficacy analyses in 12-17 year olds.)

Another potentially informative secondary endpoint is overall change from baseline in SBM frequency, which is the primary endpoint initially proposed by the Sponsor. There is an overall trend towards benefit in the lubiprostone cohort compared to placebo at week 12 compared to baseline in PFC-1131. In the mITT population, the mean change was 1.38 ± 1.72 in the combined lubiprostone cohort compared to 1.15 ± 1.76 in the placebo cohort. This reviewer does not believe that a mean difference after 12 weeks of therapy of 0.23±0.15 SBM represents a clinically meaningful difference. In addition, this reviewer is suspicious of the trend since the confidence intervals for the placebo and lubiprostone treated subjects substantially overlap weekly, monthly and overall assessments in the mITT population.[35]

Constipation symptoms of abdominal pain, painfulness of SBM and frequency of incontinence episodes seem to this reviewer to be the most clinically important secondary endpoints to assess symptoms of constipation. These endpoints are also part of the Rome expert opinion on core secondary endpoints for clinical trials for PFC.[36] *None of the endpoints demonstrate a clinically meaningful difference between lubiprostone and placebo treated subjects. Table 20 summarizes these endpoints in the mITT population.*

Table 20. *Sponsor's Analysis of Clinically Relevant Secondary Endpoints for Constipation Symptoms in Placebo and Lubiprostone treated subjects in mITT Population PFC-1131*

Endpoint	Placebo	Lubiprostone Total	Difference Lub-P
Abdominal Pain Overall mean change from baseline^#	-0.35±0.76	-0.42±0.84	0.07
Painfulness of SBM Overall mean change from baseline^#	-0.65±1.1	-0.81±1.02	0.16
Overall mean change from baseline in incontinence frequency episodes^	0.07±0.48	0.04±0.37	-0.03

Source: Data from Sponsor's Table 14.2.16.1.1, 14.2.17.1.1, 14.2.8.1.1
^ Based on observed case analysis
# Based on a 4 point scale with 1 being mild and 4 being severe.

All secondary endpoints, including those that are clinically meaningful do not trend towards showing benefit in lubiprostone treated subjects. Overall mean change from

[35] Sponsor's table 14.2.4.1.1 from PFC-1131 Study Report.
[36] Koppen et al. "Recommendations for pharmacological clinical trials in children with functional constipation: the Rome foundation pediatric subcommittee on clinical trials." Neurogastroenterology and Motility. 2018.

baseline in overall frequency of retentive posturing or excessive volitional stool retention, and overall change from baseline in large diameter stool frequency had a trend favoring placebo in the mITT population based on observed case analysis.[37] For multiple secondary endpoints, including the clinically meaningful endpoints of overall change in abdominal pain and painfulness of SBM, the benefit in the lubiprostone total arm was driven by the 12mcg BID treatment arm. The mean treatment benefit was 0.04 and 0.07 points higher in the lubiprostone 12mcg cohort than the 24 mcg cohort for overall change from baseline in abdominal pain and painfulness of SBM, respectively. Therefore, this reviewer is not concerned that the combination of the 12mcg and 24mcg cohort for the efficacy analysis of secondary endpoints is diluting the treatment of effect of the Sponsor's proposed 24mcg BID treatment dose.

However, this reviewer does not understand from a biologic perspective why for certain endpoints, the 12mcg BID dose appears more effective than the 24mcg BID dose of lubiprostone. The PK data of the M3 metabolite of lubiprostone does not explain why the 12mcg BID dose might be more effective than 24mcg BID for any endpoint. While the dose escalation parameters might have biased against the 24mcg cohort, the overall SBM response rate and other secondary outcome measures were similar for subjects initially randomized to lubiprostone 24mcg BID and those subjects whose dose was escalated to 24mcg BID after being treated with 12mcg for 1 week. The differences between the 12mcg and 24mcg lubiprostone cohorts were preserved when the subjects whose dose was escalated were excluded. This reviewer therefore postulates that confounding unmeasured variables may impact interpretation of the data, and believes that small, statistically non-significant results should be viewed cautiously rather than relied on for determination of efficacy. In summary, this reviewer does not believe that the totality of data from the secondary endpoints demonstrates a treatment benefit for lubiprostone for PFC in children 6-17 years of age.

6.1.6 Other Endpoints

Based on the results of section 6.1.4 and 6.1.5, this section is not relevant.

6.1.7 Subpopulations

The Sponsor conducted pre-specified sub-group analyses by age and sex in the mITT population for overall SBM responders. Amongst subjects 10-13 years old, the lubiprostone treated subjects had 9.9% more overall SBM responders than the placebo arm (p=0.04). This treatment effect was not seen in 6-9 year olds or 14-17 year olds. Males and females generally responded similarly to lubiprostone with equivalent overall treatment effects. These results are summarized in Table 21.

[37] Based on Sponsor's Study Report PFC-1131 section 11.4.1.2 and tables 14.2.8.1.1, 14.2.12.1.1, 14.2.9.1.1.

Table 21. Sponsor's Pre-Specified Subgroup Analyses by Age and Sex for Overall SBM Response Rate in the mITT Population of PFC-1131.

	Lubiprostone (12 or 24 mcg) N = 399	Placebo N = 195	Difference: L-P (%)	P-value*
Age in years				
6-9	22.5 (32/142)	22.7 (15/66)	-0.2	0.98
10-13	16.3 (25/153)	6.4 (5/78)	9.9	0.04
14-17	18.3 (19/104)	15.7 (8/51)	2.6	0.70
Sex				
Female	20.8 (45/216)	16.0 (17/106)	4.8	0.31
Male	16.9 (31/183)	12.4 (11/89)	4.6	0.33

* P-value based on a CMH test stratified by SBM frequency at randomization (<1.5 vs ≥1.5)
Note this table reported %(n/N).
Source: Sponsor's table 14.2.25.1.1 from PFC-1131.

The Sponsor claims lubiprostone demonstrated effectiveness in 10-17 year olds based on post-hoc sub-group analyses. Specifically, the Sponsor reports that 10-17 year old females treated with lubiprostone had a mean SBM response rate that was 9.9% greater than subjects treated with placebo in a post-hoc observed case analysis of the mITT1 population, which is the mITT population excluding sites that were discontinued by the Sponsor. Despite the Sponsor reporting that 10-17 year old males treated with lubiprostone only have a SBM response rate that is 2.2% greater than placebo subjects in the mITT1 population, the Sponsor still claims that lubiprostone is effective in males. The Sponsor bases this claim on comparable response rates between males and females in additional post-hoc sub-group analyses. Table 22 summarizes the post-hoc analyses that the Sponsor claims demonstrate a treatment effect in 10-17 year olds.

Table 22. Sponsor's Post-Hoc subgroup analyses in 10-17 year olds by Sex on Overall SBM Response Rate in Various Sub-Populations of the mITT1 population in PFC-1131

Population	Parameters	Male	Female	Total
mITT1 & Treated at Secondary or Tertiary Care Centers	Lubiprostone Responders	9/56	13/67	22/123
	Placebo Responders	2/21	41	7/62
	Treatment Difference	**6.6%**	**7.2%**	**6.6%**
mITT1 & History of Prior Laxative Failure	Lubiprostone Responders	9/74	23/112	32/186
	Placebo Responders	5/39	5/55	10/94
	Treatment Difference	**-0.7%**	**11.4%**	**6.6%**
mITT1 & Treated at Secondary or Tertiary Care Centers & History of Prior Laxative Failure	Lubiprostone Responders	6/41	10/52	16/93
	Placebo Responders	1/19	4/33	5/52
	Treatment Difference	**9.4%**	**7.1%**	**7.6%**
mITT1 & Treated North America & History of Prior Laxatives	Lubiprostone Responders	7/60	22/96	29/156
	Placebo Responders	4/35	2/41	6/76
	Treatment Difference	**0.2%**	**18%**	**10.7%**

Source: Sponsor's Table 10 from PFC-1131 CSR.

Reviewer Comments: This reviewer did not find the Sponsor's sub-group analysis to be convincing evidence of a treatment benefit. In the pre-specified age sub-group analyses, a treatment benefit was only demonstrated in 10-13 year olds. This apparent statistical benefit may be the result of multiple comparisons being performed without statistical adjustment for multiple comparisons. It does not make biological sense to the reviewer or the Sponsor that 10-13 year olds would respond differently from younger and older children. The Sponsor claims that 10-17 year olds are the relevant treatment population since withholding is more likely to occur in children less than 10 years of age. However, this claim was not supported by the literature. In this reviewer's opinion, 10 years of age appears to be an arbitrary cut-off, separating young children from pre-teens. This reviewer believes that adolescents, 12-17 year olds, represent a more clinically relevant, distinct sub-population. There are reports of CIC beginning in adolescence, which suggests that adolescents with PFC may share disease

characteristics with adults with CIC, and thus may be more likely to respond to lubiprostone which has already proven to be effective in CIC.[38]

To evaluate the efficacy of lubiprostone in 12-17 year olds, the primary responder analysis was performed for 12-17 year olds in the mITT population, for females and responder analysis for the primary endpoint and multiple sensitivity analyses were performed and are shown in Table 2323.

Table 23. Subgroup analyses by age and gender for overall SBM response rates %(n/N) in the mITT population for PFC-1131

	Lubiprostone (12 or 24 mcg) n = 399	Placebo n = 195	Difference: L-P (%)	P-value*
Age				
6-11 yo	20.1 (44/219)	15.6 (17/109)	**4.5**	0.4
12-17 yo	16.7 (30/180)	12.8 (11/86)	**3.9**	0.39
Female age groups				
6-11 yo	22.1 (23/104)	21.6 (11/51)	**0.5**	0.94
12-17 yo	17.9 (20/112)	10.9 (6/55)	**7.0**	0.19
Conduct Issues 12-17 yo				
No Conduct Issues[#]	17.1 (14/82)	18.9 (7/37)	**-1.85**	0.8
No Clinically Meaningful Conduct Issues^	15.9 (22/138)	14.5 (9/62)	**1.4**	0.8

Source: Analysis of age and female gender were performed by Dr. Ling Lan, FDA statistician. Analysis excluding conduct issues were adapted from Sponsor's table 14.2.75.3.2, 14.2.75.1.2.
* Analysis based on observed cases and p-value based on a CMH test stratified by baseline SBM frequency (<1.5 vs ≥1.5).
^ Excludes subjects who do not meet diagnosis of PFC, including a diagnosis of IBS, baseline had missing diary data and greater than 2 stools/week, did not use rescue medications more frequently than specified in the protocol and subjects who took concomitant medications for constipation are imputed as treatment failures
[#] Excludes subjects who did not meet eligibility criteria (excluding DXA sub-study), had IBS, used prohibited medications (including taking rescue medications more frequently than indicated), took >120% of doses or had missing baseline diary data.

Lubiprostone does not have a substantial treatment effect in 12-17 year olds with PFC. The effect is greatest in females, but still not significant. There is no postulated etiology for why females might respond differently from males. PFC affects an equal number of males and females, so the difference is not due to an insufficient number of males enrolled, as occurred in the trials for IBS-C. It appears as though the treatment difference is driven by a lower placebo response rate among adolescent females, which appears to be due to chance. Post-hoc analyses such as these may introduce type 1 error, so the lack of statistical significance suggests that the treatment effect in females 12-17 year olds is not robust.

[38] Solzi et al. "Are constipated children different from constipated adults" Digestive Diseases. (17) 1999.

To further investigate the possibility that adolescents may respond similarly to adults with CIC, a sensitivity analysis in adolescents who were diagnosed with PFC at or after 12 years of age was performed, and the results are shown in Table 24. However, even this analysis did not demonstrate a meaningful treatment benefit of lubiprostone.

Table 24. SBM Responders Among Adolescents Diagnosed with PFC ≥ 12 years of age from mITT Population of PFC-1131

	Placebo	Lubiprostone (12 or 24mcg)	Treatment Difference Lub-P	p-value
Observed Cases	16% (4/25)	19/7% (14/71)	**3.72%**	0.71
LOCF	24% (6/25)	25.4% (18/71)	**1.35%**	0.97

Source: Data from Sponsor's table 14.2.75.4 in response to IR from 12/8/2017.

An additional potential clinically meaningful population includes patients with severe PFC. However, this reviewer does not believe that treatment at a secondary or tertiary care centers is an appropriate proxy for severe disease as referral patterns in the United States may be influenced by geographic proximity and medical insurance coverage. This reviewer also does not believe that prior laxative failure is an appropriate proxy for severe disease, as it is likely influenced by which laxative was previously tried and whether it was tried for an adequate duration. This reviewer believes that prior hospitalizations for PFC and prolonged duration of constipation are better proxies for disease severity. However, these data were not captured. Of the data that were captured during PFC-1131, this reviewer believes less than1.5 SBM per week at baseline and presence of encopresis at baseline may serve as an informative sub-groups with severe PFC for exploratory analysis. Neither of these populations demonstrate a significant or substantial treatment effect, as shown in Table 25. However, there is a trend towards benefit in children 6 to 11 years with severe PFC, which is not consistent with the sub-group of 10 to 17 year olds whom the Sponsor proposes lubiprostone is effective for. This discrepancy highlights the need to pre-specify sub-group analyses to ensure that chance findings do not account for treatment differences.

Table 25. SBM Responders in Children with Severe PFC in mITT of PFC-1131

Population	Parameters	Total	12-17 yo	6-11yo	Male	Female
Baseline SBM <1.5/week	Lubiprostone Responders	27/171 (15.8%)	11/81 (13.6%)	16/90 (17.8%)	12/77 (15.6%)	15/94 (16%)
	Placebo Responders	9/90 (10%)	4/35 (11.4%)	5/55 (9.1%)	6/43 (14%)	3/47 (6.4%)
	Treatment Difference	**5.8%**	**2.2%**	**8.7%**	**1.6%**	**9.6%**
Baseline Encopresis	Lubiprostone Responders	8/46 (17.4%)	1/13 (7.7%)	7/33 (21.2%)	4/30 (13.3%)	4/16 (25%)
	Placebo Responders	2/17 (11.8%)	1/7 (14%)	1/10 (10%)	1/12 (8.3%)	1/5 (20%)
	Treatment Difference	**5.6%**	**-6.3%**	**11.2%**	**5%**	**5%**

Source: Reviewer's Table based on ADEFF and ADSL data-sets from PFC-1131.

This reviewer believes that based on the data submitted by the Sponsor, there does not appear to be a sub-population with PFC for whom lubiprostone is effective. However, *it is possible that a sub-population of children with PFC may exist for whom lubiprostone may be effective for. Demonstrating a beneficial effect of lubiprostone in a sub-population would require that the sub-population be pre-specified, and likely a different trial design, including enrollment of a larger number of subjects in the pre-specified sub-population(s) of interest, and minimizing the placebo response rate.*

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

This section does not apply as efficacy was not established.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This is not relevant as the initial study did not demonstrate efficacy.

6.1.10 Additional Efficacy Issues/Analyses

None performed based on the results of 6.1.4, 6.1.5 and 6.1.7.

7 Review of Safety

Safety Summary

Safety data from four pediatric trials, including one well controlled trial (PFC-1131) and three uncontrolled studies (PFC-11s1, SCMP-303, and SC-0641) were reviewed, and this medical reviewer believes that the safety of lubiprostone in children 6-17 years is generally comparable to the safety of lubiprostone in adults, for which the drug is currently labeled. The most common AEs in children were abdominal pain, nausea, vomiting, headache and diarrhea.

Children exposed to lubiprostone may be at increased risk of poor bone health based on a juvenile rat study showing trends of reduced growth and lower bone density. Although the pediatric DXA sub-study that was performed in subjects enrolled in PFC-1131 and PFC-11s1 showed no evidence of lubiprostone impacting BMD, there were only a small number of subjects who had total body minus head DXA's performed at baseline and after at least 6 months of therapy, so the DXA sub-study may not detect smaller bone health safety signals. Therefore, at this time it is unclear if children are at risk of lubiprostone deleteriously impacting their bone health.

Children may also be at risk of hepatotoxicity, which has not been reported in adults. The concern for this potential safety signal arises from a single case identified in the safety database, in which a pediatric subject with baseline transaminase elevations developed severe elevation and the liver biopsy showed a cholestatic picture with intralobular bile duct damage; the subject returned to baseline following discontinuation of lubiprostone. No other etiology for the elevation in liver enzymes was identified. No other children had significant elevation or shifts toward abnormal transaminase values. In the adult clinical trials, most liver enzyme measurements were within a clinically acceptable range, and shifts towards abnormal values were attributed to alternative etiologies.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Evaluation of safety was primarily based on study PFC-1131, since this was the only controlled trial conducted for this indication. In evaluating safety, a control group is beneficial in determining whether adverse events are due to the study drug or due to the underlying disease or background population rate.

Since the well-controlled population represents less than half of all pediatric subjects exposed to the study drug, a pooled safety database from all pediatric constipation trials

(PFC-1131, PFC-11s1, SCMP-211, SC-0641) was used when appropriate to further inform the safety evaluation. Safety evaluable subjects consisted of all enrolled pediatric subjects who received at least one dose of study treatment during any of the 4 PFC studies. Table 2626 summarizes the entire safety evaluable population. Subjects are analyzed based on the treatment they actually received rather than the treatment they should have been randomized to (in the event that subjects took a medication or dose different than the one assigned). For most analyses, patients were analyzed with respect to whether they received lubiprostone, independent of the dose received.

Within the pooled safety database, additional analyses were conducted to determine if dose (12mcg BID or 24mcg BID) or duration of therapy with lubiprostone affected the incidence or severity of adverse events. Additionally, safety sub-analyses were conducted in adolescents, 12-17 year olds, and in children who weighed less than 50 kg compared to children who weighed more than 50 kg.

Table 26 Safety Evaluable Population

Controlled Double-Blind Trial	Trials Included	Duration	Number of Safety Evaluable Subjects		
			Placebo	Lubiprostone	Total
	PFC-1131	12 weeks	195	400	595
Long-Term (>24 weeks) Open Label Trials	**Trials Included**	**Duration**	**Number of Safety Evaluable Subjects**		
			Placebo	**Lubiprostone**	**Total**
	PFC-11s1 SCMP-303	36 weeks 24 weeks	0	419 87	506
Total Safety Evaluable Population	**Trials Included**	**Duration**	**Number of Safety Evaluable Subjects**		
			Placebo	**Lubiprostone**	**Total**
	PFC-1131 PFC-11s1 SCMP-303 SC-0641	12 weeks 36 weeks 24 weeks 4 weeks	400 0 0 0	195 419 87 124	1225

Source: Reviewer's table based on data from Sponsor's table 2.7.4.1.1

7.1.2 Categorization of Adverse Events

The Sponsor coded AEs using the Medical Dictionary of Regulatory Activities (MedDRA) version 19.1 and classified by MedDRA system organ class (SOC) and preferred term (PT). All AEs observed by the investigator, spontaneously reported by subjects or their parents, or volunteered during open-ended questioning of subjects from the time of the first dose of study drug through the end of the follow-up period were

recorded on the electronic case report forms (eCRFs), regardless of whether or not the events were considered to be related to the study drug. The Sponsor defined treatment-emergent adverse events (TEAEs) as events not present at baseline that occurred after treatment with the study drug or an event present at baseline that worsened after treatment with study drug. TEAE with onset after the first dose of study drug but no later than follow-up were documented.

Reviewer Comments: This reviewer evaluated the appropriateness of the Sponsor's coding by comparing the preferred terms to the verbatim terms recorded by investigators. In general, they were reasonably accurate. However, there was significant splitting of several AEs due to separation of closely related PTs. Therefore, this reviewer recoded AEs from the Sponsor's ADAE datasets for PFC-1131 and the ISS, which includes all subjects in the safety population from all studies. The full recoding is described in Appendix 6. The recoding for abdominal pain is described below as this recoding led to marked differences between the Reviewer's and Sponsor's AE frequency tables.

- *Combined "abdominal pain," "abdominal pain lower," "abdominal pain upper," "upper abdominal pain," "left lower quadrant pain," "left upper quadrant pain," "pain right upper quadrant," "abdominal discomfort," "stomach ache," "stomachache," "stomach cramps," "stomach discomfort," "stomach pain," "abdominal cramp(s)," "abdominal tenderness," "pain gastric," "epigastric pain," "epigastric discomfort," "abdominal pain aggravated" gastrointestinal pain as the same AE (PT "abdominal pain").*

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Sponsor analyzed data from the well-controlled study separately as this had a placebo group that could be used for comparison. The Sponsor also assessed long-term safety by pooling data from studies (PFC-11s1 and SCMP-303). Lastly, to provide a comprehensive safety analysis, the sponsor combined all subjects who received at least one dose of drug during any PFC trial (PFC-1131, PFC-11s1, SCMP-303, SC-0641) in the Integrated Summary of Safety (ISS).

Reviewer Comments: This reviewer agrees with the Sponsor's approach for analyzing the safety data from the PFC trials that have been conducted. As discussed in section 7.1.1, the well-controlled trial, PFC-1131, has a control group which is beneficial for determining whether adverse events are due to the study drug versus due to the underlying disease or background population rate. As drugs can have cumulative toxicity, assessing long-term exposure for a drug that is intended to be taken chronically is important. Lastly, including all pediatric patients exposed to lubiprostone maximizes

the available safety data for analysis. This reviewer believes that data from SC-0641 may be less informative since it includes younger children, lower doses and was a much shorter duration than the other studies (4 weeks compared to 12 weeks, 24 weeks and 36 weeks). As subjects from SC-0641 comprise only 17% of the patients in the overall safety cohort, this reviewer is less concerned that these patients will substantially impact important safety signals.

7.2 Adequacy of Safety Assessments

Safety parameters for the clinical trials included physical examination, vital signs, height, weight, hematology, chemistry, urinalysis and adverse events. These safety parameters are adequate to assess the safety signals reported in adults for whom lubiprostone is an approved therapy. Additionally, a subset of pediatric patients with PFC participated in the DXA sub-study which was conducted to assess bone health, based on a safety signal in juvenile rats. Due to the overall size of the pediatric safety population, uncommon but clinically significant adverse events may not be detected during this clinical development program.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The PFC clinical development program included 940 children who received study drug, of whom 745 received at least one dose of lubiprostone and 195 received at least 1 dose of placebo, with 134 children receiving both placebo (during study PFC-1131) and lubiprostone (during PFC-11s1). At least 529 children were exposed to at least one dose of 24mcg BID, which includes 412 children who were only treated with 24mcg BID and between 117 and 122 children who were initially treated with 12mcg BID but whose dose was subsequently increased to 24mcg BID. There were 430 children who received at least one dose of 12mcg BID, including 124 children who received both 12mcg BID and 24mcg BID as their dose was increased during study PFC-1131. The mean exposure to lubiprostone was 26 weeks (± 18 weeks). 414 children were exposed to lubiprostone for at least 24 weeks and 186 children for at least 48 weeks. The minimum duration of exposure was 1 day and the maximum duration was 478

days. Table 27 summarizes duration of exposure to lubiprostone by dose in children with PFC.

Table 27. Duration of Study Drug Exposure in PFC

Duration of Study Medication	Lubiprostone					Placebo
	All Doses	24mcg BID	12 mcg BID	12 and 24 mcg BID*	12 mcg daily	
Mean (SD)	182 (127)	199 (129)	173 (120)	224 (126)	28 (4)	85 (18)
Median (Range)	194 (1-478)	194 (1-478)	173 (1-434)	268 (1-358)	28 (8-33)	85 (1-114)
≥ 1 day	745 (100)	412 (100)	306 (100)	124 (100)	27 (100)	195 (100)
≥ 1 week	723 (97)	397 (96)	299 (98)	122 (98)	27 (100)	193 (99)
≥ 4 weeks	680 (91)	373 (90)	283 (93)	117 (94)	24 (89)	189 (97)
≥ 8 weeks	551 (74)	332 (81)	219 (72)	108 (87)	0	175 (90)
≥ 12 weeks	519 (70)	309 (75)	210 (69)	102 (82)	0	147 (75)
≥ 24 weeks	414 (56)	237 (58)	177 (58)	80 (65)	0	0
≥ 36 weeks	314 (42)	196 (48)	118 (39)	65 (52)	0	0
≥ 48 weeks	186 (25)	133 (32)	53 (17)	57 (46)	0	0

Source: Adapted and modified from Sponsor's Table 2.3.1.2 in ISS
*Includes subjects who were treated with both 12mcg BID and 24mcg BID, the vast majority of these subjects were dose escalated to 24mcg BID after 1 week on 12mcg BID.

The safety population included predominantly non-Hispanic Caucasians from the United States. There was a slight predominance of females, and fewer 14-17 year olds compared to 6-13 year olds. The demographic data of subjects in the overall safety population was similar to subjects in the well-controlled trial, PFC-1131, and subjects in the long-term safety cohort. The only notable difference is that the long-term safety cohort included a higher number of younger patients than the pivotal trial. See Table 28 for details on demographic characteristics of the safety population.

Table 28. Baseline Demographic Characteristics for Overall Safety Population

Variable	Placebo (n=195)	Lubiprostone All Doses/ Any Duration (n=745)	Lubiprostone 12 or 24mcg BID Long-term Exposure (n=506)
Sex, n(%)			
Male	89(46)	346 (46)	228 (45)
Female	106 (54)	399 (54)	278 (55)
Race, n(%)			
Alaskan Native/ American Indian	3 (2)	1 (<1)	1 (<1)
Asian/ Hawaiian/ Pacific Islander	4 (2)	8 (1)	7 (1)
Black/ African American	39 (20)	120 (16)	79 (16)
White	138 (71)	582 (78)	398 (79)
Other	11 (6)	11 (3)	21 (4)

Variable	Placebo (n=195)	Lubiprostone All Doses/ Any Duration (n=745)	Lubiprostone 12 or 24mcg BID Long-term Exposure (n=506)
Ethnicity, n(%)			
Hispanic	44 (23)	115 (15)	86 (17)
Non-Hispanic	151 (77)	630 (85)	420 (83)
Age (years)			
Mean +/- SD	11 (3)	10.8 ± 3.3	10.9 ± 3.1
Median (Range)	11 (6-17)	11 (6-17)	11 (6-17)
Age Group			
<6 years	0	15	0
6-9 years	66 (34)	276 (37)	192 (38)
10-13 years	78 (40)	276 (37)	196 (39)
14-17 years	51 (26)	178 (24)	118 (23)
Weight (kg)			
Mean +/- SD	48 ± 20	46.5 ± 20.4	46.8 ±19.7
Median (Range)	45 (18-121)	43.5 (14.8-122.7)	43.5 (16.8-122.7)
Weight Group, n(%)			
< 50 kg	109 (56)	459 (62)	304 (60)
≥ 50 kg	86 (44)	286 (38)	202 (40)
BMI (kg/m^2)			
Mean +/- SD	21 ± 5	20.9 ± 5.7	20.9 ± 5.5
Median (Range)	21 (12-40)	19.5 (12.2-53.2)	19.8 (12.2-40.9)
Country, n(%)			
USA	167 (86)	668 (90)	440 (87)
Other	23 (14)	77 (10)	66 (13)

Source: Data from Sponsor's tables 2.7.4.1-6 and 2.7.4.1-9, 2.2.1.1 and 2.2.1.2 from ISS.

The severity of baseline constipation was similar between subjects enrolled in the pivotal trial and the subjects who comprised the long-term safety cohort.

Reviewer Comments: *The safety population appears adequate to detect large safety signals in the pre-market setting including those that occur following prolonged use, of 6 to 9 months' duration. The safety population appears representative of children 6-17 years with PFC in the United States.*

7.2.2 Explorations for Dose Response

Lubiprostone 12mcg BID and 24mcg BID were the two dosing regimens that were primarily tested in children 6-17 years of age. These doses were selected based on results of SC-0641, where the patients treated with 12mcg BID and 24 mcg BID had an

improvement in SBM after 1 week, and subjects treated with 12mcg daily did not have a significant improvement in SBM after 1 week. (See section 5.3.5 for additional details).

Subjects were assigned doses by weight in PFC-1131, PFC-11s1 and SCMP-303; subjects less than 50kg were treated with 12mcg BID and subjects greater than 50kg were treated with 24mcg BID. There were parameters within the protocol that allowed subjects who experienced severe nausea, diarrhea or at the discretion of the Investigator other AEs to have their dose decreased, but no subject had their dose decreased. Only subjects in PFC-1131 who were initially treated with 12mcg BID, had the potential to have their dose increased to 24mcg BID. The protocol specified that after 1 week of 12mcg therapy, a subject's dose should be increased if they were having less than 3 SBM and not having treatment related side effects. Only 3% (8) of eligible subjects did not have their dose increased due to side effects. All subjects with side effects precluding dose escalation were female. Table 2929 summarizes the outcome of subjects potentially eligible for dose escalation in trial PFC-1131.

Table 29 Dosing Outcome for Subjects who Initiated Therapy on Lubiprostone 12mcg in mITT PFC-1131

	6-11 years			12-17 years			Total
	Male n=102	Female n=90	Total n=192	Male n=14	Female n=25	Total n=39	n=231
Dose Escalated to 24mcg BID	52 (51%)	47 (52%)	99 (52%)	10 (71%)	15 (60%)	25 (64%)	124 (54%)
Not Escalated as >3 SBM/week	38 (37%)	27 (30%)	65 (34%)	2 (14%)	2 (8%)	4 (10%)	69 (30%)
Not Escalated due to Side Effects	**0**	**5 (6%)**	**5 (3%)**	**0**	**3 (12%)**	**3 (8%)**	**8 (3%)**
Not Escalated at Investigator's Discretion	12 (12%)	11 (12%)	23 (12%)	2 (14%)	5 (20%)	7 (18%)	30 (13%)

Source: Data from Sponsor's table 14.2.77.

With the exception of the 124 subjects in PFC-1131 whose dose was increased to 24 mcg BID, comparison of dose may be confounded by weight.

Table 3030 summarizes dosing exposure from PFC-1131, PFC-11s1 and SCMP-303 based on age and weight.

Table 30 Lubiprostone Dose Exposure based on Weight and Age in Safety Population PFC-1131, PFC-11s1 and SCMP-303

	12 mcg BID	24mcg BID	
Weight*	**<50 kg**	**<50kg**	**≥ 50kg**
Number of Subjects	317	131	224
Mean Age (± SD)	8.7 ± 2.4	9.6 ± 2.4	13.7 ± 2.2
Median Age (range)	8 (6-17)	9 (6-17)	14 (8-17)

Source: Table designed by reviewer based on ISS ADSL data-set with safety flag=yes; SC-0641 was excluded and subjects only treated with placebo were excluded.
*Weight based on IVWEGR1 for PFC-1131 and WEGTGR1 for SMP-303.

Reviewer Comments: This reviewer does not believe there are adequate data to assess the safety of 12 mcg daily lubiprostone since only 27 children were treated for a maximum of 4 weeks. This reviewer believes that an adequate number of subjects were treated with either 12mcg BID or 24mcg BID lubiprostone to assess pre-market safety of both of these doses. However, for the 24mcg BID dose, there is less safety data available for subjects weighing less than 50 kg; children under 50kg comprise 37% of the total number of children treated with lubiprostone 24mcg BID.

7.2.3 Special Animal and/or In Vitro Testing

None was performed.

7.2.4 Routine Clinical Testing

During each of the trials submitted as part of this sNDA, the Sponsor performed routine clinical testing. Specifically, vital signs, physical examination, height, weight, hematology, chemistry and urinalysis were monitored. See section 7.4.2 for description of laboratory findings, section 7.4.3 for vital sign data, and section 7.6.3 for growth assessments.

Reviewer Comments: These safety parameters are standard and adequate to assess common abnormalities caused by drugs that can be detected from clinical testing. The Sponsor utilized pediatric reference ranges so abnormalities can be appropriately detected. The testing performed during the pediatric development program can detect the laboratory abnormalities (e.g., elevation of AST and ALT) reported in the lubiprostone label based on adult studies, laboratory abnormalities (e.g., electrolyte abnormalities) reported with other constipation medications, and BP and linear growth abnormalities reported in the juvenile animal toxicity studies.

Thus, this reviewer believes that the testing performed is appropriate and the potential limitation in detecting safety signals is based on the lack of a placebo control for the long-term studies, the number of children studied and the duration of exposure.

7.2.5 Metabolic, Clearance, and Interaction Workup

None was performed.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Prostaglandin E2 is an activator of bone remodeling and the increased turn-over can result in osteopenia and osteoporosis. See section 7.4.5 for results of the pediatric DXA sub-study.

Prostaglandins have been shown to stimulate uterine contractility, but this was not specifically studied during the pediatric development program. The two known pregnancies that occurred in adolescents exposed to lubiprostone during the PFC development program did not result in miscarriage. (See section 7.6.2 for additional details). For additional details on the risk of fetal loss and risks during pregnancy refer to the updated label and the review by Division of Maternal Health.

7.3 Major Safety Results

7.3.1 Deaths

No subjects died during any of the studies investigating lubiprostone in PFC.

7.3.2 Nonfatal Serious Adverse Events

There were 18 treatment emergent SAEs during the well-controlled trial, 7 (3.6%) occurred in children being treated with placebo and 11 (2.8%) occurred in children being treated with lubiprostone. The only treatment related SAEs in PFC-1131 occurred in lubiprostone treated children, and they were single cases of hypersensitivity reaction, rash and chest pain. None of these reactions occurred in placebo treated patients. The only other SAEs that occurred more commonly in lubiprostone treated children than placebo treated children were major depression with or without suicidal ideation, infections, rash, and meniscus operation. The only SAEs that occurred in more than one placebo treated child was constipation or fecaloma, which occurred twice as

frequently in placebo subjects compared to lubiprostone treated subjects during PFC-1131.

Within the overall safety population, there were 29 treatment emergent SAEs. For these SAEs, 59% occurred in children taking 24 mcg BID and 41% occurred in children taking 12 mcg BID. SAEs were more common in females (70% of the SAEs), which is slightly disproportionate to the overall number of females in the safety population. SAEs were slightly more common in younger patients, and SAEs rarely occurred within the first week of starting lubiprostone. The study investigator attributed 10 SAEs as definitely or possibly related to the study drug. The most common SAE that resulted in hospitalization was severe constipation (n=4) or fecaloma (n=8). Table 31 summarizes all SAEs that occurred during the PFC development program.

Table 31. Summary of All Treatment Emergent Serious Adverse Events in the Lubiprostone Treated Safety Population

Study/ Subject ID	Age^/ Sex/ Race	Study Drug/ Dose^	Time on Study Drug	Description of Event by Investigator	Relationship per Investigator	Action Taken
(b) (6)	9yo M C	LUB 12mcg	36 weeks	**Hepatotoxicity**	Related	Withdrawn
	10yo F AA	LUB 24 mcg	2 weeks 24 mcg, 3 weeks LUB	**Anaphylactoid Reaction** Facial swelling & tongue discoloration, hospitalized & treated with IV meds	Probably Related	Withdrawn
	10 yo F AA	LUB 12 mcg	SD 4	**Chest Pain**	Possibly Related	No Change
	16 yo M C	LUB 24 mcg	SD 17	**Decreased Consciousness** Hospitalized	Possibly Related	Withdrawn
	13 yo F C	LUB 24 mcg	8 weeks	**Dehydration & IBS-C** Hospitalized for abdominal pain, rectal bleeding & dehydration	Possibly Related	Withdrawn

Study/ Subject ID	Age^/ Sex/ Race	Study Drug/ Dose^	Time on Study Drug	Description of Event by Investigator	Relationship per Investigator	Action Taken
(b) (6)	7yo F AA	LUB 24 mcg	6 weeks 24 mcg, 7 weeks LUB	**Faecoloma & Rash** Hospitalized for clean-out Rash resolved 3 days after lubiprostone stopped	Unrelated (faecoloma) Possibly related (rash)	Withdrawn
	6yo F C	LUB 24 mcg	10 weeks	**Faecoloma & Gastritis** Hospitalized x 2 for clean-out and IVF	Possibly Related	No Change
	9 yo F C	LUB 12 mcg	SD 28	**Faecoloma** Hospitalized, fecal disimpaction under anesthesia	Probably Related	Withdrawn
	14 yo F C	LUB 24 mcg	8 weeks	**Severe Constipation** Hospitalized for clean-out	Probably Related	Temporarily Withheld
	7yo F C	LUB 12 mcg	10 weeks	**Severe Constipation** Hospitalized for clean-out and IVF	Probably Related	No Change
	9 yo M C	LUB 12 mcg	4 weeks; SAE 7 days after stopped LUB	**Abdominal Pain & Fecal Impaction** Hospitalized for manual disimpaction	Unlikely to be related	None, study complete
	6 yo F C	LUB 12 mcg	SD 6	**Faecoloma** Hospitalized for clean-out	Unrelated	Temporarily Held
	13 yo M C	LUB 12 mcg	SD 33	**Faecoloma** Hospitalized for clean-out	Unrelated	Withdrawn
	13 yo M C	LUB 24 mcg	23 weeks	**Faecoloma** Hospitalized for clean-out	Unrelated	Temporarily Withheld
	14 yo F AA	LUB 24 mcg	SD 136	**Constipation** Hospitalized for clean-out	Unrelated	Withdrawn
	10 yo F AA	LUB 24 mcg	22 weeks 24 mcg, 23 weeks LUB	**Fecal Impaction** Hospitalized for manual disimpaction under anesthesia	Unrelated	Temporarily Withheld
	16yo F C	LUB 24mcg	23 weeks	**Constipation & Abdominal Pain** Hospitalized for clean-out	Unrelated	Temporarily Withheld
	8yo M C	LUB 24 mcg	12 weeks 24 mcg, 13 weeks LUB	**Gastrointestinal Obstruction** Hospitalized	Unrelated	Temporarily Withheld

Study/ Subject ID	Age^/ Sex/ Race	Study Drug/ Dose^	Time on Study Drug	Description of Event by Investigator	Relationship per Investigator	Action Taken
(b) (6)	9 yo M C	LUB 12 mcg	SD 67	**Abdominal Pain/Colitis** Hospitalized for severe abdominal pain attributed to "stomach virus" & on CT had colitis	Unrelated	Temporarily Withheld
	18 yo F AA	LUB 24 mcg	SD 156	**Ulcerative Colitis** Hospitalized	Unrelated	Withdrawn
	16 yo F C	LUB 12 mcg	SD 31	**Suicidal Ideation**	Not related	Withdrawn
	15 yo F Mixed-race	LUB 24 mcg	SD 46	**Suicidal Ideation** Hospitalized after ingesting pills with suicidal & homicidal ideation	Unrelated	Withdrawn
	14 yo F C	LUB 24 mcg	SD 58	**Conversion Disorder/Numb leg** Hospitalized for evaluation	Unrelated	No Change
	9 yo F AA	LUB 12 mcg	SD 29	**Coxsackie virus** Hospitalized for hand-foot-mouth disease & hydration	Unrelated	Withdrawn
	8 yo F AA	LUB 24 mcg	19 weeks 24mcg, 20 weeks LUB	**Cellulitis & Abscess** Hospitalized	Unrelated	No change
	8 yo M C	LUB 24 mcg	18 weeks 24 mcg, 19 weeks LUB	**Tonsillar Hemorrhage** Hospitalization prolonged due to complication & need for intubation	Unrelated	Temporarily Withheld
	9 yo F AA	LUB 12 mcg	4 weeks; SAE 12 days after stopped LUB	**Sickle Cell Crisis** Hospitalized	Unlikely to be related	None, study complete

Source: Table created by Reviewer based on narratives SAG/0211PFC-1131-01 CSR, Section 14.3.3; SAG/0211PFC-11s1-01 CSR, Section 14.3.3; SCMP-0211-303-01 CSR, Section 14.3.3; CSR0211-09-001-02, Section 14.4.
^Age and dose are based on the time of SAE.
LUB=Lubiprostone; SD=study day; IV=Intravenous; IVF=Intravenous fluids.

Reviewer Comments: *All SAEs narratives were reviewed and adjudicated by this reviewer:*

This reviewer agrees with the Investigator and believes that lubiprostone likely contributed to the hepatotoxicity in subject (b) (6) *The subject had baseline*

elevation of transaminases of unknown etiology (ALT=75 IU/L 2.5x ULN, AST=48 IU/L, just above the ULN, GGT=84 IU/L, 1.25x ULN, normal total bilirubin, normal alkaline phosphatase). There were small fluctuations in transaminases until week 36 of treatment, when his ALT rose to 483 IU/L (17x ULN), AST rose to 520 IU/L (13x ULN), GGT rose to 577 IU/L (8.9x ULN). Bilirubin increased by 7 umol/L compared to baseline, but remained normal at 9 umol/L. There is no documentation of an increased INR, and therefore this case does not meet Hy's law criteria. He had a mild headache and pyrexia that coincided with rise in LFTs, but he did not have abdominal pain, jaundice, fatigue, fever or other clinical symptoms to suggest severe hepatotoxicity. An intensive evaluation was undertaken to determine the etiology of his elevation in liver enzymes, and no alternative etiology was identified. He had a normal abdominal ultrasound and magnetic resonance cholangiopancreatography (MRCP). A liver biopsy showed cholestatic changes including damage to the intralobular bile ducts, but no steatosis or iron staining. A review of recorded concomitant medications revealed no likely alternative possible hepatotoxic medications. His concomitant medications included infrequent use of 200mg of acetaminophen (which he has been taking for years), oral Ritalin and occasional melatonin which is unlikely to cause his marked elevation of transaminases. Following discontinuation of lubiprostone, within 1 week his transaminases had begun to decrease. While the decline in transaminases and alkaline phosphatase was not linear, his liver function tests returned to baseline within 2 months after discontinuing lubiprostone. (For more details on this case, please see Appendix 6 for chart of LFTs throughout the study and complete liver biopsy results.) Based on the severity of this case and the lack of alternative etiology for his liver enzymes, this reviewer recommends adding this case to the drug label. However, since the patient was asymptomatic, this reviewer believes that it is reasonable to describe the case as rise in liver enzymes rather than hepatotoxicity.

This reviewer agrees with the Investigator that that the "anaphylactoid reaction" was due to the study drug. This reaction does not meet the criteria for anaphylaxis according to the NIAID/FAAN criteria, and thus this reviewer believes that it should be classified as a hypersensitivity reaction. This drug reaction is similar to the hypersensitivity reactions currently described in the drug label under postmarketing experience. This reviewer does not believe that changes to the drug label are indicated.

This reviewer disagrees with the Investigator and agrees with the Sponsor that the case of chest pain was unlikely related to the study drug as the symptoms resolved quickly without intervention and did not re-emerge despite the subject continuing to take the drug. This reviewer believes no changes to the drug label are indicated based on this case.

This reviewer agrees with the Investigator that the depressed level of consciousness reported in one subject might have been due to the study drug as other etiologies were ruled-out. The patient had a normal head computed tomography (HCT), and was not described to be dehydrated or have low BP. Since this was an isolated case and there

is no postulated mechanism based on the drug's mechanism of action, this reviewer does not believe that labeling changes are indicated based on this case.

This reviewer disagrees with the Investigator and does not believe that IBS-C or dehydration reported as SAEs were due to the study drug. The subject had symptoms of IBS-C prior to initiating the trial. While lubiprostone may theoretically cause dehydration, this subject's dehydration was likely caused by decreased oral intake. This reviewer does not believe that labeling changes are indicated based on this case.

The Sponsor did not provide enough information about the rash SAE for this reviewer to adjudicate it and will therefore rely on the Investigator's determination that it was probably related to lubiprostone. This reviewer does not believe that the severity of the rash warrants changes to the drug label.

This reviewer believes that the SAEs of severe constipation/fecalomas that occurred in subjects (b) (6) *reflect underlying constipation that was not adequately treated with lubiprostone. For subject* (b) (6) *this reviewer believes that the discontinuation of lubiprostone at the end of the trial likely led to the need for disimpaction. However, since the trial was short, only 4 weeks in duration, it is possible that lubiprostone was ineffective throughout the trial and the cumulative time without effective therapy for constipation (as all other constipation mediations were not allowed during the trial) led to the subject's hospitalization. This reviewer does not believe that these cases warrant any labeling changes, especially since hospitalization for constipation was more common in the placebo arm compared to the lubiprostone arm of the controlled trial.*

This reviewer is uncertain if lubiprostone could have contributed to the case of gastrointestinal obstruction or colitis based on the data provided on these cases. The Investigators did not believe that these cases were related to the study drug. The current label describes a case of ischemic colitis in an adult who used lubiprostone in the post-marketing setting. This reviewer does not believe changes to the drug label are warranted based on these cases.

This reviewer believes that lubiprostone was unlikely to have contributed to the cases of suicidal ideation in subjects (b) (6) *. Both subjects had a history of depression, so may have been predisposed to suicidal ideation. Subject* (b) (6) *was reported to have had improvements in her symptoms after discontinuing lubiprostone, this coincided with the initiation of sertraline. Lubiprostone and its M3 metabolite have low systemic absorption, and are not believed to cross the blood brain barrier and cause psychiatric symptoms. A review of the FAERS database confirmed that there were no similar cases reported in adults. This reviewer does not believe that labeling changes are warranted based on these cases.*

This reviewer believes that lubiprostone did not contribute to the SAE of conversion disorder. The event did not recur despite the subject staying on lubiprostone. Usually functionally neurologic disorders are triggered by stress or psychologic trauma which can also contribute to constipation symptoms in adolescents. This reviewer does not recommend labeling changes based on this case.

This reviewer believes that the SAE infections in subjects (b) (6) *were unlikely related to the study drug as there is no evidence that this drug affects the immune system and predisposes to infection. This reviewer does not recommend labeling changes based on this case.*

This reviewer also agrees with the Investigator that the case of tonsillar hemorrhage is unlikely related to lubiprostone. Coagulation panels were not obtained during this trial, but bleeding was an uncommon AE in either children or adults, and therefore it is more likely that this SAE was a surgical complication unrelated to lubiprostone. This reviewer does not recommend labeling changes based on this case.

This reviewer believes that subject (b) (6) *had UC prior to enrolling in the trial and her baseline GI symptoms and arthritis were from the UC; she does not have PFC and should not have been enrolled in this trial, and the SAE was not attributable to the study drug. This reviewer does not recommend labeling changes based on this case.*

7.3.3 Dropouts and/or Discontinuations

The disposition of subjects from the controlled trial and long-term, open-label trials are shown in Table 32. Most subjects completed the trial in which they enrolled. Within the controlled trial, a total of 162 subjects (27%) withdrew, and there was no difference in the rate of discontinuation between placebo and lubiprostone treated subjects. The long-term safety cohort had a higher premature discontinuation rate compared to the controlled trial overall and for each dose studied; a total of 173 subjects (34%) withdrew, 32% in the 12mcg cohort and 35.5% in the 24mcg cohort.

The reasons for discontinuation differed between the 12 week controlled trial and the long-term safety cohort. This was most notable for lack of efficacy, which was the reason for study withdrawal in 6.9% of the long-term safety cohort compared to only 1.5% in the placebo group and 1% in the total lubiprostone group in the controlled study.

Table 32. Summary and Etiology for Subjects Discontinuing from PFC-1131, PFC-11s1 and SCMP-303 Safety Population

Variable	Double-Blind Controlled Trial (PFC-1131) (n=595)		Long-term Safety Trials (PFC-11s1 & SCMP-303) (n=506)		
	Placebo (n=195)	LUB Total (n=399)	LUB Total (n=506)	LUB 12mcg (n=213)	LUB 24mcg (n=293)
Disposition, n(%)					
Completed	147 (73)	297 (74)	333 (66)	144 (68)	189 (64)
Total Discontinued	55 (27)	107 (26)	173 (34)	69 (32)	104 (36)
Reason for Discontinuation					
Lost to follow-up	2 (1)	9 (2)	48 (10)	26 (12)	22 (7)
Withdrawal by Subject	13 (7)	19 (5)	41 (8)	15 (7)	26 (9)
Lack of Efficacy	3 (2)	4 (1)	35 (7)	12 (6)	23 (8)
Adverse Event	6 (3)	17 (4)	30 (6)	11 (5)	19 (6)
Investigator Decision	2 (1)	7 (2)	7 (1)	1 (<1)	6 (2)
Study Terminated by Sponsor	1 (<1)	2 (<1)	5 (1)	2 (1)	3 (1)
Pregnancy	0	0	2 (<1)	0	2 (1)
Protocol Violation	0	0	1(<1)	1 (<1)	0
Other Unspecified^	19 (10)	42 (10)	0	0	0

Source: Reviewer's table based on Sponsor's tables 2.7.4.1.2 and 2.7.3.3-1 with modifications for PFC-1131 to account for the difference in completers according to the SAP and according to the Site Investigators.
^For study PFC-1131, the Sponsor only provided a reason for discontinuation for the 90 subjects for whom the study site Investigators classified as non-completers, but there are an additional 61 subjects who do not meet the SAP definition of completers, >84 days of therapy, but the reason for their withdrawal was not recorded.

Within the overall safety cohort, there were a total of 61 subjects who withdrew due to AEs, all of which were treatment emergent (TEAE). A total of 6 patients (3.1%) in the placebo cohort, 18 patients (5.9%) treated with 12mcg lubiprostone BID, and 37 patients (9%) treated with 24mcg lubiprostone BID discontinued prematurely due to AEs. The most common AEs leading to discontinuation were abdominal pain, constipation, nausea, vomiting, dyspnea and hypersensitivity reactions. Table 33 summarizes the population and most common etiologies of subjects who withdrew due to AEs.

Table 33. Adverse Events Leading to Discontinuation in Overall Safety Cohort

n (%)	Placebo (n=195)	LUB 12mcg BID (n=306)	LUB 24mcg BID (n=412)	LUB Total (n=745)
Patients with ≥ 1 AE leading to discontinuation	6 (3.1)	18 (5.9)	37* (9)	56* (7.4)
AEs leading to discontinuation were related to study drug by Investigator (% based on total AEs leading to discontinuation)	3 (50)	15 (83)	29 (78.3)	44 (80)
Weight <50 kg (% based on total AEs leading to discontinuation)	2 (33)	18 (100)	15 (40.5)	33 (58.9)
Adverse Events by PT/SOC n(%)				
GI	5 (2.5)	8 (2.6)	25 (0.6)	33 (4.4)
Constipation/Fecal Impaction	4 (2)	1 (<0.5)	6 (1.4)	7 (0.9)
Abdominal Pain	1 (0.5)	2 (0.6)	7 (1.7)	9 (1.2)
Vomiting	0	3 (1)	1 (<0.5)	4 (0.5)
Nausea	0	0	7 (1.7)	7 (0.9)
Respiratory	0	2 (0.6)	1 (<0.5)	3 (0.4)
Dyspnea	0	2 (0.6)	0	2 (0.3)
Immune System	0	0	3 (0.7)	3 (<0.5)
Hypersensitivity	0	0	3 (0.7)	3 (<0.5)

Source: Reviewer's table based on ISS ADAE dataset, limited to Drug Withdrawn without duplicates based on Reviewer's recoding of AEs and Sponsor's table 2.1.2.2 from ISS.
*The dataset did not contain information on 1 subject treated with 24mcg BID whom the Sponsor stated withdrew due to an AE.

In the controlled trial, PFC-1131, the TRAEs leading to discontinuation that occurred in lubiprostone treated subjects more than placebo subjects were nausea, vomiting, chest pain, hypersensitivity reaction, and pharyngeal edema. Of these AEs, only nausea was responsible for discontinuation by more than one subject. Nausea was responsible for discontinuation by 1% of lubiprostone treated subjects; 3 subjects (1.8%) randomized to the 24mcg BID cohort, 1 subject (0.4%) randomized to the 12mcg BID cohort, and none in the placebo cohort.[39]

Reviewer Comments: As expected based solely on the long-term trials being 2-3 times the duration of the controlled trial, more subjects (8%) withdrew from the long-term trials than the controlled trial. Withdrawal due to lack of efficacy was more common during the long-term trials, but is consistent with the lack of efficacy demonstrated in the controlled trial, and described in section 6.

The AEs leading to discontinuation are all known AEs associated with lubiprostone in adults and are listed in the current label. The most common of these AEs was

[39] Sponsor's table 14.3.1.9.5 from PFC-1131 Study Report.

abdominal pain (when analysis performed using reviewer's recoded PT as described in section 7.1.2). Abdominal pain was the only AE leading to discontinuation in greater than 1% of lubiprostone treated subjects and within the controlled trial was more common in lubiprostone treated subjects than controls. In the overall safety population, there was a delta of 3.1% more AEs leading to discontinuation in subjects treated with 24mcg BID than subjects treated with 12mcg BID of lubiprostone. This suggests that the higher dose is associated with more bothersome AEs. However, this must be interpreted cautiously since the conclusions were based primarily on safety data from uncontrolled studies. This reviewer, does believe that AEs leading to discontinuation were slightly more common at the higher dose, based on data from the controlled trial showing slightly more subjects discontinuing at 24 mcg BID (4.5%) compared to 12mcg BID (3.7%).

7.3.4 Significant Adverse Events

The majority of TEAEs in all treatment groups were mild or moderate in severity. Severe AEs were defined as causing considerable interference with the subject's daily activities. Within the entire safety population, there were 66 serious AEs.[40] The Sponsor identified 26 severe TRAE in the safety population. Severe TRAE occurred in 6 patients (3.1%) treated with placebo, 5 patients (1.6%) receiving lubiprostone 12 mcg BID, and 15 patients (3.6%) receiving lubiprostone 24 mcg BID.

The most commonly reported severe TRAEs were severe abdominal, severe constipation or fecal impaction and severe vomiting, which accounted for 73% of all severe TRAEs. In the overall safety cohort, no AE was responsible for at least 1% of severe TRAEs in the total population exposed to lubiprostone. The severe TRAE PTs that occurred in more than one subject were severe abdominal pain, severe constipation, severe fecal impaction, and severe vomiting. The most common was severe abdominal pain, which occurred in 0.8% of all subjects exposed to lubiprostone, 1.4% (6/412) of all subjects treated with 24mcg BID lubiprostone, 0.3% (1/306) of all subjects treated with 12mcg BID lubiprostone and 1% (2/195) of subjects treated with placebo.[41] The severe TRAEs that occurred in more than 1 subject are listed in Table 34.

[40] Based on Reviewer's calculations of ADAE ISS dataset limited to "severe" for "AEREL".
[41] Based on Reviewer's calculations of ADAE ISS dataset using recoded PTs limited to "severe" for "AEREL" (AE Related), and not "unrelated" for "AEREL", removing duplicates. These results only differed from the Sponsor's analysis with regards to splitting of abdominal pain by the Sponsor into abdominal pain and abdominal pain upper.

Table 34. Severe Treatment Related Adverse Events (TRAEs) Occurring in More than 1 Subject in the Safety Population

n (%)	Placebo (n=195)	LUB 12mcg BID (n=306)	LUB 24mcg BID (n=412)	LUB Total (n=745)
Patients with ≥ 1 severe TRAE	6 (3.1)	5 (1.6)	15 (3.6)	20 (2.7)
Severe TRAE by PT				
Abdominal Pain	2 (1)	1(0.3)	6 (1.4)	7 (0.9)
Constipation/Fecal Impaction	5 (2.6)	2 (0.6)	3 (0.7)	5 (0.7)
Vomiting	0	0	2 (0.5)	2 (0.3)

Source: Sponsor's table 2.4.9.3.2 modified based on reviewer's calculations of ADAE ISS dataset using recoded PTs limited to "severe" for AErel, and not "unrelated" for AEREL, removing duplicates.

Reviewer Comments: Severe abdominal pain and severe vomiting appear more common in lubiprostone treated subjects, especially those patients treated with 24mcg BID. However, this is based on a small number of events primarily derived from uncontrolled studies. There were no episodes of severe vomiting in the controlled trial. During the controlled trial, there were 3 TRAE of severe abdominal pain, all occurred in patients while receiving 24mcg BID lubiprostone, which suggests that severe abdominal pain may be associated with treatment with lubiprostone. Even if this association exists, it is a rare occurrence having occurred in <0.6% of lubiprostone treated subjects in the pivotal trial. Severe abdominal pain is consistent with the established AE profile in adults.

This reviewer believes that severe constipation with or without fecal impaction is likely related to lack of efficacy of the study drug rather than a complication from the study drug.

7.3.5 Submission Specific Primary Safety Concerns

The Warnings and Precautions section of the approved product labeling for adults lists nausea, diarrhea, syncope, hypotension and dyspnea as notable adverse events associated with lubiprostone. Therefore, these AEs represent safety concerns of interest within the pediatric population. Nausea, diarrhea and dyspnea occurred less frequently in children than adults treated with lubiprostone. (See frequency tables in section 7.4.1 for additional details). Syncope was uncommon in children and the cases were less severe than in adults. (See section 7.7 for a detailed discussion of the cases of syncope.)

The Sponsor also pre-specified chest pain/chest discomfort, hepatotoxicity/liver enzymes increased, and anaphylaxis/anaphylactoid reaction and anaphylactic shock as

AEs of special interest. There was one case of chest pain, hepatotoxicity, and anaphylactoid reaction that occurred as SAEs and were discussed in section 7.3.2.

Additionally, based on juvenile rat studies, osteopenia and poor linear growth are additional safety signals of interest. No safety signal related to bone health was identified during the DXA sub-study, but methodologic limitations limit this reviewer's ability to conclude that this equates to the absence of a safety signal. (See section 7.4.5 for analysis of the effects of lubiprostone on BMD and BMC.) A growth safety signal was not identified, but measurement techniques limit this reviewer's confidence in interpreting the height data. (See section 7.6.3 for a detailed discussion on the effects of lubiprostone on linear growth.)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

During the controlled trial, there were 353 subjects (59%) who had at least 1 TEAE, and 183 subjects (30.8%) had TRAE according to the site Investigators. The most common TEAE and TRAE were Gastrointestinal. Among TEAE, the Sponsor identified nausea, vomiting, diarrhea, upper abdominal pain and headache as the most common AEs, occurring in at least 5% of lubiprostone treated patients, and occurring more commonly than in placebo treated patients.[42] The Sponsor also reported that urinary tract infections, dizziness, pyrexia and oropharyngeal pain occurring as TEAEs in at least 2% of lubiprostone treated patients and occurred more commonly than in placebo treated patients.[43]

Reviewer Comments: After recoding the PTs, this reviewer independently analyzed the safety database to assess AEs, TEAEs and TRAEs with an incidence of ≥2% among subjects in the controlled trial treated with any dose of lubiprostone (12 or 24mcg BID) that occurred in a larger percentage of lubiprostone treated subjects than placebo subjects. The most common AEs are listed in Table 35.

[42] Table 14.3.1.8 from PFC-1131 CSR.
[43] Table 28 from PFC-1131 CSR.

Table 35. Adverse Events Reported in ≥ 2% of Lubiprostone Treated Patients and at an Incidence Greater than Placebo for PFC-1131 Safety Population –FDA Reviewer Analysis

Adverse Events Preferred Term	Placebo n = 195 n (%)	Lubiprostone All Doses n = 400 n (%)
Nausea	14 (6.9)	59 (14.6)
Vomiting	12 (5.9)	48 (11.9)
Headache	15 (7.4)	40 (9.9)
Diarrhea	6 (3)	30 (7.4)
Gastroenteritis	4 (2)	20 (5)
Pyrexia	7 (3.5)	19 (4.7)
Sinusitis	3 (1.5)	13 (3.2)
Chest pain	1 (<1)	10 (2.5)
Blood iron decreased	1 (<1)	8 (2)
Rash	3 (1.5)	8 (2)

Source: Table made by Reviewer from Sponsor's ADAE and ADSL Data-Sets from PFC-1131 after re-coding performed by Reviewer (as described in 7.1).

Abdominal pain was the most common AE, but it occurred in an equal percentage of subjects treated with lubiprostone and placebo, 17%, which suggests that abdominal pain may reflect symptoms of PFC rather than the drug. Assessing TEAE and TRAE will enable improved assessment of lubiprostone's impact on abdominal pain. Table 36 summarizes the most common TEAEs and Table 37 summarizes the most common TRAE for PFC-1131. Nausea, vomiting, diarrhea, headache and chest pain are all reported as common adverse reactions in the adults CIC trials in the lubiprostone drug label.

Table 36. Treatment Emergent Adverse Events (TEAEs) Reported in ≥ 2% of Lubiprostone Treated Patients and at an Incidence Greater than Placebo for PFC-1131 Safety Population – FDA Reviewer Analysis

Treatment Emergent Adverse Events by Preferred Term	Placebo n = 195 %	Lubiprostone All Doses n = 400 %
Abdominal Pain	31 (15.9)	66 (16.5)
Nausea	14 (7.2)	57 (14.2)
Vomiting	12 (6.2)	45 (11.2)
Headache	11 (5.6)	34 (8.5)
Diarrhea	6 (3.1)	28 (7)
Gastroenteritis	3 (1.5)	16 (4)
Pyrexia	4 (2)	16 (4)
Dizziness	5 (2.6)	13 (3.2)
Sinusitis	3 (1.5)	11 (2.8)
Chest Pain	0	9 (2.2)
Urinary Tract Infection	3 (1.5)	8 (2)
Oropharyngeal Pain	2 (1)	8 (2)

Source: Table made by Reviewer from Sponsor's ADAE and ADSL Data-Sets from PFC-1131 after re-coding performed by Reviewer (as described in 7.1). The ADAE data-set was limited to TEAE flag "yes".

Table 37. Treatment Related Adverse Events (TRAEs) Reported in ≥ 2% of Lubiprostone Treated Patients and at an Incidence Greater than Placebo for PFC-1131 Safety Population – FDA Reviewer Analysis

Treatment Related^ Adverse Event Preferred Term	Placebo n = 195 n (%)	Lubiprostone All Doses n = 400 n (%)
Nausea	10 (5.1)	47 (11.8)
Abdominal Pain	19 (9.7)	46 (11.5)
Vomiting	5 (2.6)	30 (7.5)
Diarrhea	4 (2)	21 (5.2)
Headache	5 (2.6)	21 (5.2)
Dizziness	4 (2)	12 (3)

Source: Table made by Reviewer from Sponsor's ADAE and ADSL data-sets from PFC-1131 after re-coding performed by Reviewer (as described in 7.1). The ADAE data-set was limited to exclusion of AEREL equals "unrelated".
^ Treatment related was determined by Investigators and includes AEs that were possibly, probably and definitely related to study drug

The most common TRAE in PFC are similar to the already labeled common TRAE in adults with CIC. Abdominal pain was more common in children with PFC than adults with CIC, which is consistent with abdominal pain being described as a common disease characteristic of PFC rather than CIC. The difference in the incidence of treatment-related abdominal pain between lubiprostone and placebo was similar between children with PFC and adults with CIC. Vomiting as a TRAE occurred in 5%

more children with PFC treated with lubiprostone than placebo in PFC, but only 2% more frequently in lubiprostone treated adults with CIC than placebo. Nausea, diarrhea and headaches as TRAE were less common based on absolute numbers and relative to placebo in lubiprostone treated children with PFC than adults with CIC. Overall, this reviewer finds the most common TRAEs to be similar between children with PFC and adults with CIC, as shown in Table 38.

Table 38. Comparison of Most Common Lubiprostone Treatment Related Adverse Events (TRAEs) by Percentage in PFC (Study PFC-1131) and CIC in Adults

Treatment Related^ Adverse Event Preferred Term %	Adult CIC*			PFC (PFC-1131)*		
	Placebo n=316	LUB 24mcg BID n=1113	RD	Placebo n = 195	LUB All Doses n = 400	RD
Gastrointestinal						
Nausea	3	29	**26**	5	12	**7**
Diarrhea	1	12	**11**	2	5	**3**
Abdominal Pain	3	8	**5**	10	12	**2**
Abdominal Distension	2	6	**4**	NA	NA	**NA**
Flatulence	2	6	**4**	NA	NA	**NA**
Vomiting	0	3	**3**	5	8	**3**
Loose Stools	0	3	**3**	NA¥	NA¥	**NA¥**
Abdominal Discomfort°	1	3	**2**	NA¥	NA¥	**NA¥**
Dyspepsia	<1	2	**>1**	NA	NA	**NA**
Nervous System						
Headache	5	11	**6**	3	5	**2**
Dizziness	1	3	**2**	2	3	**1**
General Disorders						
Edema	<1	3	**>2**	NA	NA	**NA**
Fatigue	1	2	**1**	NA	NA	**NA**
Chest Discomfort/Pain	0	2	**2**	NA	NA	**NA**
Respiratory						
Dyspnea	0	2	**2**	NA	NA	**NA**

Source: Table made by Reviewer. Adult CIC data is based on lubiprostone drug label (https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021908s015lbl.pdf accessed 3/1/2018) and PFC data from

Sponsor's ADAE and ADSL PFC-1131 data-sets after re-coding performed by Reviewer (as described in 7.1); the ADAE data-set was limited to exclusion of AEREL equals "unrelated".
^ Treatment related was determined by Investigators and includes AEs that were possibly, probably and definitely related to study drug
*Occurred in at least 2% of subjects receiving any dose of lubiprostone 24mcg BID and occurred more frequently in the study drug than with the placebo.
° Includes "abdominal tenderness", "abdominal rigidity", "gastrointestinal discomfort", "stomach discomfort", and "abdominal discomfort".
¥"Loose stools" were combined with "diarrhea" when PFC AEs were re-coded.
⁑With the exception of "abdominal rigidity," the AE terms comprising "abdominal discomfort" were coded to "abdominal pain" in when PFC AEs were re-coded.
LUB=Lubiprostone; RD=Relative Difference

Since lubiprostone dosing in the PFC development program was primarily based on weight, with most children under 50kg receiving 12mcg BID and children who were at least 50kg receiving 24mcg BID, this reviewer believes that it is important to assess the impact of weight on AEs. *This reviewer assessed the incidence of TEAEs by weight cohort, less than 50 kg and greater than or equal to 50kg in PFC-1131 as this study was controlled and was the only study where children under 50kg received the 24mcg BID dose. There were 246 more TEAE in lubiprostone than placebo treated patients weighing less than 50 kg compared to only 179 more TEAE in lubiprostone than placebo treated pediatric patients weighing at least 50kg. In general, the most common TEAEs were similar between children less than 50 kg and children more than 50 kg, but vomiting was more common in children less than 50kg whereas nausea and headache were more common in children at least 50kg, based on Odds Ratios (OR). See Table 39 for incidence of the most common TEAEs within the entire population based on weight.*

Table 39. Treatment Emergent Adverse Events (TEAEs) by Weight in Safety Population PFC-1131

TEAEs (Listed in order of incidence in all Lubiprostone patients) n (%)	<50 kg			≥ 50 kg		
	Placebo (n=109)	Lubiprostone All Doses (n=236)	OR	Placebo (n=86)	Lubiprostone All Doses (n=166)	OR
Abdominal Pain	16 (14.7)	37 (15.7)	**1.1**	15 (17.4)	29 (17.5)	**1**
Nausea	9 (8.3)	33 (14)	**1.8**	5 (5.8)	24 (14.5)	**2.5**
Vomiting	8 (7.3)	40 (17)	**2.6**	4 (4.7)	5 (3)	**-1.7**
Headache	6 (5.5)	15 (6.4)	**1.2**	5 (5.8)	19 (11.5)	**2**
Diarrhea	3 (2.8)	14 (5.9)	**2.2**	3 (3.5)	14 (8.4)	**2.4**
Gastroenteritis	2 (1.8)	10 (4.2)	**2.4**	1 (1.2)	6 (3.6)	**3.1**
Pyrexia	2 (1.8)	10 (4.2)	**2.4**	2 (2.3)	6 (3.6)	**1.3**
Dizziness	1 (0.9)	7 (3)	**3.3**	4 (4.7)	6 (3.6)	**0.8**
Sinusitis	1 (0.9)	7 (3)	**3.3**	2 (2.3)	4 (2.4)	**1**
Chest Pain	0	4 (1.7)	**4.2***	0	5 (3)	**5.7***
UTI	2 (1.8)	5 (2.1)	**1.2**	1(1.1)	3 (3)	**0.6**

Source: Table by Reviewer based on PFC-1131 datasets ADSL (using "IVWEIGR1" for the weight classification) and ADAE (recoding performed by the Reviewer as described in section 7.1) and calculations using MAED.
*Continuity Correction applied.
OR=Odds Ratio

The relative difference (based on absolute percentages) in treatment emergent vomiting between lubiprostone and placebo was much larger for children less than 50kg than children at least 50kg, 9.7% versus -1.7%. On the other hand, the relative difference between lubiprostone and placebo was much larger for children less than 50kg for treatment emergent headache (5.7% versus 0.9%).

To further investigate these differences, and allow for a consistent comparison to adults with CIC, the reviewer examined TRAE in PFC, and the results are shown in Table 40. As anticipated, the incidence of TRAEs compared to TEAEs are less common in all treatment groups, including placebo, so a comparison between TEAEs in PFC and TRAE in CIC would distort any comparison between incidence of AE in children and adults.

Table 40. Treatment Related Adverse Events by Weight in Safety Population PFC-1131

TRAEs^ (Listed in order of incidence in all Lubiprostone patients) n (%)	<50 kg			≥ 50 kg			Adults CIC~
	Placebo (n=109)	Lubiprostone All Doses (n=236)	RD	Placebo (n=86)	Lubiprostone All Doses (n=166)	RD	RD
Nausea	7 (6.4)	28 (11.8)	5.4	3 (3.5)	19 (11.4)	7.9	26
Abdominal Pain	10 (9.1)	25 (10.6)	1.5	9 (10.5)	21 (12.6)	2.1	5
Vomiting	4 (3.7)	24 (10.2)	6.5	1 (1.1)	6 (4.2)	3.6	3
Diarrhea	1 (0.9)	8 (3.4)	2.5	3 (3.5)	13 (7.8)	4.3	11
Headache	2 (1.8)	9 (3.8)	2	3 (3.5)	12 (7.2)	3.7	6
Dizziness	1 (0.9)	6 (2.5)	1.6	3 (3.5)	6 (4.2)	0.7	2

Source: Table by Reviewer based on PFC-1131 ADAE dataset (recoded by reviewer as described in section 7.1) limited to SAFFL = "Y", TEAEFL = "Y" and "AEREL" = "definite", "possible" or "probably". Treatment based on treatment actually received. Weight based on "IVWEIGR1".
^ Treatment related was determined by Investigator and includes AEs that were possibly, probably and definitely related to study drug.
~ From Amitiza drug label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021908s015lbl.pdf, accessed 3/1/18.
RD=Relative Difference, Lubiprostone percentage – Placebo percentage.

Lubiprostone related nausea and abdominal pain occurred slightly more frequently in children over 50kg compared to children less than 50kg. However, even if the children over 50kg, these TRAEs occurred less frequently in children than adults. The only TRAE that occurred more commonly in children was vomiting, which occurs slightly more frequently in children over 50kg compared to adults with CIC, but over twice as commonly in children under 50kg. However, vomiting in children less than 50kg was also more common in children taking placebo suggesting that smaller and younger children may be more prone to vomiting independent of any drug effect.

There appears to be a dose effect for treatment related vomiting in children less than 50kg, with 16 (57%) cases occurring in children on 24mcg lubiprostone BID compared to 8 (29%) cases occurring in children taking 12mcg lubiprostone BID and 4 (14%) cases in children taking placebo. There was a similar overall dose related trend but with a smaller magnitude for other treatment related GI symptoms in children less than 50kg. See Table 41 for this reviewer's analysis of dose dependent effects of GI TRAEs in children less than 50kg.

Table 41. *Treatment Related GI Adverse Events in Children Less than 50kg in PFC-1131*

TRAEs^ n (%)	Placebo (n=109)	Lubiprostone 12mcg BID (n=107)	Lubiprostone 24 mcg BID* (n=124)
GI SOC^	20 (18.3)	23 (21.5)	38 (30.6)
Nausea	7 (6.4)	10 (9.3)	18 (14.5)
Abdominal Pain	10 (9.1)	11 (10)	15 (12)
Vomiting	4 (3.7)	8 (7.5)	16 (12.9)

Source: Reviewer's table based on ADAE PFC-1131 data-set recoded by the reviewer as described in section 7.1.2.
*Includes subjects whose dose was titrated from 12mcg BID to 24mcg BID of lubiprostone.
^ Based on Sponsor's coding for SOC.

This finding is consistent with the dose dependent increase in GI TEAEs in children less than 50kg described in the clinical pharmacology review based on their analysis of the Sponsor's TEAE. (See Dr Yi's clinical pharmacology review for additional details). A dose related trend for other AEs in children less than 50kg or any AE in children over 50 kg was not detected by this reviewer based on analysis of TRAE in PFC-1131 or by the clinical pharmacology team based on their review of TEAEs in the ISS. (See Dr. Yi's clinical pharmacology review for additional details.)

This reviewer does not believe that the AE frequency or dose dependency in children less than 50kg needs to be added to the drug label as these AEs were generally less common than in adults, mild and self-resolved. The only AE that occurred more frequently in children less than 50kg compared to adults was vomiting, but the incidence of vomiting in children less than 50kg was only 3% more common in lubiprostone than in placebo treated children. This reviewer does not believe that this represents a substantial enough increase in frequency to be added to labeling.

7.4.2 Laboratory Findings

Serum chemistries, hematology and urinalysis were performed in all subjects enrolled in each of the PFC trials. These labs were assessed at baseline and at the end of study, but the interval during the trials varied amongst studies (as described in section 5.3).

Within the overall safety cohort, the Sponsor reports that mean and median changes from baseline for all laboratory parameters were small. There were very few subjects who developed abnormal values during the trial, and even fewer whose abnormal values were considered clinically significant by the Investigators. See Table 42 for summary of abnormal and clinically relevant laboratory abnormalities. None of the

laboratory based AEs were serious, severe, or led to discontinuation from the clinical trials.

Table 42. Summary of Clinically Significant Treatment Emergent Laboratory Abnormalities in the Safety Population

AEs based on Abnormal Investigations	PFC-1131 (Controlled Study)		Overall Safety Population
	Placebo (n=195)	Lubiprostone (n=400)	Lubiprostone (all doses) (n=745)
Hematology			
Anemia*	3 (1.5%)	0	2 (<1%)
Hemoglobin decreased/ Hematocrit decreased	0	2 (<1%)	**8 (1%)**
Neutrophil count decreased	1 (<1%)	1 (<1%)	3 (<1%)
Platelet count increased	0	0	2(<1%)
Other hematology^	1(<1%)	-	**24 (3%)**
Urine			
Hematuria/Blood in urine	0	1 (<1%)	**5 (1%)**
Proteinuria	0	**3 (1%)**	**6 (1%)**
Glycosuria/Glucose present in urine	0	1 (<1%)	2 (<1%)
Pyuria	0	2 (<1%)	8 (1%)
Urine nitrite present/ leukocyte esterase positive	0	**6 (1%)**	**12 (2%)**
Urine specific gravity increased	0	0	4 (<1%)
Other Urine abnormality#	2 (1%)	1 (<1%)	**29 (4%)**
Chemistry			
Potassium increased	0	1 (<1%)	2 (<1%)
Hypokalemia	0	0	1 (<1%)
Phosphorous increased	1	0	3 (<1%)
Phosphorous decreased	0	0	1 (<1%)
Sodium increased	0	1 (<1%)	1 (<1%)
Blood bicarbonate/CO2 decreased	1(<1%)	1 (<1%)	**5 (1%)**
Blood glucose increased	0	0	3 (<1%)
Creatinine increased	0	1 (<1%)	1 (<1%)
Hypercholesterolemia/ Cholesterol Increased	2 (1%)	4 (1%)	**20 (3%)**
Hypertriglyceridemia/ Triglycerides increased	2 (1%)	3 (1%)	**17 (2%)**
ALT increased	0	1 (<1%)	**5 (1%)**
AST increased	0	0	2 (<1%)
Other abnormal LFTs!	3 (2%)	-	10 (1%)
Other abnormal chemistry labs$	2 (1%)	-	35 (5%)

Source: Reviewer's table made from ADAE datasets from PFC-1131 and ISS after recoding performed by this reviewer as described in section 7.1. The Reviewer's results are generally consistent with the data presented in Sponsor's table 2.7.4.3-2, 2.7.4.3-14, 2.7.4.3-12, 2.7.4.3-9, 2.7.4.3-11, 2.7.4.3-8, 14.3.1.6.
*Includes PT "Iron Deficiency Anemia"
^Includes the PTs "lymphocyte count decreased", "neutrophil count increased", "WBC count increased", "WBC decreased," "eosinophil percentage decreased," "MCV decreased," "eosinophil count increased," "MCH decreased," "MCV abnormal," "monocyte count decrease," "neutrophil percentage decreased"
#Includes the PTs "cells in urine," "crystal urine present," "PH urine increased," "UA abnormal," "urine bilirubin increased," "urine ketone body present," "urinary sediment present," "chromaturia," and "urine abnormality"
!Includes the PTs "hepatic enzymes increased," "liver function test increased," "blood alkaline phosphatase increased," "blood lactate dehydrogenase increased"
$Includes the PTs "iron deficiency," "impaired fasting glucose," "vitamin D deficiency," "vitamin D decreased," "blood iron decreased," "blood iron increased," "blood uric acid increased," "blood urea increased," "blood uric acid decreased"

During the controlled study the Sponsor reports no relevant shifts from normal to abnormal urinalysis parameters and only small shifts to abnormal values for hematologic and chemistry parameters. None of these shifts occurred more frequently in the lubiprostone arms compared to placebo. Within the long-term safety cohort, the shifts to abnormal values were rare, mild and often not sustained.

Reviewer Comments: *This reviewer agrees with the Sponsor's assessment that there were no safety signals based on the measured laboratory parameters. Based on the SAE of hepatotoxicity, this reviewer analyzed the LFT laboratory data from the controlled trial and the long-term safety cohort. Besides the patient with an SAE of hepatotoxicity, no transaminase value was above 1.5 times the ULN and there was no elevation in direct bilirubin. There is no laboratory data besides the SAE case described in section 7.3.2 to suggest hepatic injury.*

This reviewer believes that the elevations noted in cholesterol and triglycerides are associated with obesity and not the study drug.

7.4.3 Vital Signs

Vital signs, including blood pressure, pulse rate, respiratory rate, temperature, weight and BMI were measured at baseline and end of treatment, including frequently throughout the trials. The intervals at which vital signs were measured in the different trials varied. (Refer to section 5.3 for detailed schedule of assessment of vital signs in each trial).

The Sponsor reports there was a single treatment emergent adverse event of hypotension and a single case of orthostatic hypotension. Both of these cases were determined by the Investigator to be treatment related to lubiprostone. Neither were reported as serious, severe or cause for withdrawal from the study. Besides these cases, there were no adverse events reports of decreased blood pressure within the overall safety cohort. There was a single case of elevated BP reported as a TRAE that led the subject to withdraw from the trial on study day 211.

There was no substantial or consistent trend in change in BP from baseline to 1 hour post first dose of lubiprostone. In the total lubiprostone treatment cohort, the mean increase in systolic blood pressure (SBP) was 0.8 (± 7.3) mmHg and a median change of 1 (range -34 to 25) mmHg.[44] The mean, median and SBP ranges were similar between the two lubiprostone dosing cohorts,12mcg BID and 24 mcg BID, and placebo. Also, over the duration of the trials, there were no substantial shifts in BP. The Sponsor reports there were fewer than 5% of children in the long-term safety cohort treated with any dose of lubiprostone who had a shift from normal SBP to abnormal SBP. The children who had abnormal values, were usually elevated and not persistent. There were 3 (<1%) children who initially had normal SBP and developed a low SBP during the trial; these children were all being treated with lubiprostone 24mcg BID and the low SBP was recorded at the 36 week visit.[45] With respect to diastolic blood pressure (DBP), there were fewer shifts from normal to abnormal, and most were shifts to high values rather than low values.

Heart rate was generally stable within the overall safety cohort. There were 6 cases of treatment related abnormalities in heart rate within the overall safety cohort. This includes 3 cases of palpitations, 2 cases of tachycardia and 1 case of irregular heart rate. While none of these cases were serious or severe, the case of irregular heart rate and palpitation led the subjects to withdraw from the studies. Other than these adverse events, there were very few cases of abnormal heart rates. According to the Sponsor's analysis of the long-term safety cohort, fewer than 5% of lubiprostone treated subjects shifted from normal heart rates to abnormal heart rates. Subjects with abnormal heart rates were more likely to have tachycardia than bradycardia, and the abnormalities were usually transient.[46]

Respiratory rate and temperature were generally normal throughout the trials. There were no reports of asymptomatic tachypnea. There were 2 cases of dyspnea among subjects treated with lubiprostone in the overall safety cohort. Pyrexia is discussed as an adverse event in section 7.4.1.

The Sponsor does not report any weight related safety signals within the overall safety cohort. There was a single subject treated with lubiprostone who had a treatment related adverse event of decreased weight reported. In the controlled trial, children treated with lubiprostone gained a similar amount of weight to children treated with placebo. Height is discussed in section 7.6.3.

Reviewer Comments: Although the safety profile in adults suggest that lubiprostone may contribute to hypotension and low blood pressure, this reviewer does not believe

[44] Sponsor's table 14.3.4.4.1 from ISS.
[45] Sponsor's table 2.6.1.2.1 from ISS.
[46] Sponsor's table 2.6.1.2.1 from ISS.

that the BP data collected during the clinical development program for PFC demonstrates this risk in children. The child who was reported to have hypotension had a lower BP at baseline then when he was reportedly hypotensive. While the risk of hypotension was not demonstrated during the pediatric clinical development program, it does not mean that the risk does not exist. This reviewer finds it reassuring that if there is a risk of hypotension in children it does not appear to be very common.

This reviewer believes that the reports of elevated BP are not drug related. The transient elevations may be due to measurement error and the sustained elevations may be due to confounding variables such as obesity. While there is no control group in the long-term safety cohort, there was no difference in the rate of BP elevation in the controlled trial between lubiprostone and placebo treated subjects. Constipation is more common in obese children, and obesity predisposes to elevated blood pressure.

This reviewer does not believe that the episode of irregular heart rate can be attributed to lubiprostone since the child had a history of a conduction abnormality which could cause the irregular heart rate. Additionally, the irregular heart rate resolved spontaneously while the child continued to take lubiprostone. While there was a single case of tachycardia, there was no trend towards increased heart rate. The absence of a trend towards tachycardia supports that lubiprostone does not cause dehydration and volume depletion in children.

7.4.4 Electrocardiograms (ECGs)

ECGs were not performed in the PFC population. During phase 1 and phase 2 trials in adults, ECGs were performed to assess the effect of lubiprostone on ECG parameters; no association with ECG changes or safety signal was found.

7.4.5 Special Safety Studies/Clinical Trials

A DXA sub-study was performed to assess bone health. There were 179 children enrolled in this study; 60 were treated with placebo and 119 were treated with lubiprostone during the 12 week blinded portion of PFC-1131. The baseline BMD z-score was close to 0. The demographics of this population is described in Table 43.

Table 43. Study PFC-1131: DXA Population Demographics/ Baseline Characteristics

	Placebo N=60 n (%)	**Lubiprostone** N=119 n (%)
Sex		
Female	29 (48)	59 (50)
Male	31 (52)	60 (50)
Age		
Mean (years)	9.9	10.4
6-9 years	42 (70)	75 (63)
14-17 years	18 (30)	44 (37)
Race/Ethnicity		
White	47 (78)	98 (82)
Black/African American	9 (15)	14 (12)
Other*	4 (7)	7 (6)
Hispanic/Latino	14 (23)	20 (17)
Country		
United States	50 (83)	104 (87)
Mean height Z-score	-0.06	0.03
Mean BMD Z-scores		
Lumbar spine	-0.12	0.16
Total body less head	-0.02	0.06

*includes American Indian or Alaska Native (n=1), Asian (n=1), Native Hawaiian or other Pacific Islander (n=1), and "other" (n=8)
Source: CSR Table 14.1.4.4, Table 14.3.4.5.7 and Table 14.3.4.5.8

BMD and BMC were assessed at 12 weeks and 48 weeks are reported in Tables 44 and 454, respectively. There was attrition during the study and missing data; a final lumbar spine DXA with height data was only available in 51% of subjects, and a TBLH DXA with height was only available for 19% subjects.

Table 44. BMD and BMC, Percent Change from Baseline at Week 12 by Treatment Group in DXA Sub-Study

	Placebo N=60	Lubiprostone N=119	LUB – Placebo LS mean difference (95% CI)	p-value*
Lumbar spine BMD, n	42	91		
Mean % change	2.21	1.68	-0.53 (-1.75, 0.70)	0.40
Median % change	1.65	1.11		
Lumbar spine BMC, n	42	91		
Mean % change	3.40	2.83	-0.56 (-2.06, 0.93)	0.46
Median % change	3.43	1.91		
TBLH BMD, n	32	64		
Mean % change	1.24	0.95	-0.29 (-1.20, 0.63)	0.54
Median % change	1.09	0.97		
TBLH BMC, n	32	64		
Mean % change	3.34	2.35	-0.98 (-2.27, 0.30)	0.13
Median % change	2.45	1.93		

Sources: CSR Table 14.3.4.5.2; Table 14.3.4.5.3
BMD represents corrected BMD
*p-value for difference is from an ANOVA model with treatment as the main effect

Table 45. BMD Z-scores, change from baseline at week 48/End of Treatment*

	Lumbar spine Z-score		TBLH Z-score	
	n	Mean change	n	Mean change
Overall	92	-0.03	34	-0.04
Age 6-9 y/o	75	-0.00	27	-0.03
Age 14-17 y/o	17	-0.16	7	-0.11
Male	54	+0.02	15	+0.10
Female	38	-0.11	19	-0.15
White	76	-0.03	26	-0.03
Black	11	+0.03	7	-0.10
Other race	5	-0.18	1	-0.09

*mean changes from baseline in BMD corrected height-adjusted Z-scores until end of treatment in patients assigned to lubiprostone throughout studies PFC-1131 and PFC-11S1 (LOCF)
Sources: ISS Table 2.7.1.7, Table 2.7.1.12.7, Table 2.7.1.13.7, Table 2.7.1.14.7

Reviewer Comments: *This sub-study was also evaluated by Drs. Voss and Kehoe from Division of Bone Reproduction and Urologic Products (DBRUP), refer to the consult for additional details. This reviewer agrees with their interpretation of the results of the study. Specifically, this DXA sub-study did not detect a bone safety signal. After 48 weeks, the mean change for lumbar spine z-score and TBLH z-score were near 0, which is normal. There was no clinical evidence of fragility fractures during PFC-1131/PFC-11s1. The fracture incidence, less than 2% during the year, is within the*

expected range for a pediatric population. For subjects with fractures who had a DXA, all were normal (BMD z-score -0.6 – 1.9).[47]

DBRUP concluded that they do not believe that there is a substantial evidence of a safety signal for lubiprostone with respect to bone and no further investigation appears to be warranted. However, this reviewer does not believe that a safety signal can be ruled out due to methodologic limitations of the performed study. Specifically, the 12 week assessment in which BMD changes were compared between lubiprostone treated subjects and placebo, was of insufficient duration to detect any drug effect on bone. Based on the typical rate of pediatric BMD changes over time in relation to the precision of DXA, the International Society for Clinical Densitometry (ISCD) recommends a minimum of 6 months between DXA scans. The data available at 48 weeks is limited. A height z-score is needed for reliable interpretation of BMD z-score, and there was only and BMD z-score data on 92 children at 48 weeks. TBLH z-score which is the preferred method in children of assessing BMC and BMD, was only available in 34 children.

This reviewer believes that due to the small final sample size due to dropouts and missing data, a safety signal can not be ruled-out and bone health in children exposed to lubiprostone should continue to be studied, as specified in the current PREA PMRs. Since there is a risk to bone health based on the animal studies and this clinical study does not provide adequate power to detect a safety signal, this reviewer recommends that the animal data be added to the label.

Bone health as a safety signal will continue to be evaluated in children 6 months to 6 years with PFC under PMR 572-5, and children 6 years to 17 years under PMR 675-4.

7.4.6 Immunogenicity

Immunogenicity studies were not performed.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Within the overall safety cohort and within the controlled-trial population, the incidence of TEAEs was more common in subjects receiving higher doses of lubiprostone, 24mcg BID compared to 12mcg BID. The most common system/organ classes for TEAEs were the same for both dose cohorts; gastrointestinal disorders, infections and nervous

[47] Van Staa TP et al. “Children and the risk of fractures caused by oral corticosteroids.” Journal Bone Mineral Research. 2003.

system disorders. Abdominal pain, nausea, headache and dizziness were the only TEAEs to occur in 2% more subjects treated with lubiprostone 24mcg BID compared to 12mcg BID in the controlled trial and the overall safety population. In the controlled trial, subjects treated with 24mcg BID only had a slight increase incidence of treatment emergent abdominal pain (1.1%) and dizziness (1.5%) compared to placebo. Vomiting was the only TEAE that occurred more commonly in subjects treated with lubiprostone 12mcg BID compared to 24mcg BID, and this was observed in both the controlled trial and the overall safety population. No other TEAEs substantially differed between the 12mcg BID and 24mcg BID dosing cohort. See Table 46 for a comparison of the most common TEAEs by dose.

Table 46. Incidence of Most Common Treatment Emergent Adverse Events in Controlled Trial & Overall Safety Cohort

Preferred Term n(%)	Controlled Trial PFC-1131				Overall Safety Cohort		
	Placebo (n=195)	LUB 12mcg BID (n=109)	LUB 24mcg BID* (n=295)	RD LUB 24 – LUB 12	LUB 12 mcg BID (n=306)	LUB 24 mcg BID* (n=413)	RD LUB 24 – LUB 12
Total TEAEs	94	112	334		389	646	
Abdominal Pain	31 (15.9)	16 (14.7)	50 (17)	**2.3%**	47 (15.4)	97 (23.5)	**8.1%**
Nausea	14 (7.2)	12 (11)	45 (15.2)	**4.2%**	45 (14.7)	84 (20.3)	**5.6%**
Dizziness	5 (2.6)	1 (0.9)	12 (4.1)	**3.2%**	3 (1)	21 (5.1)	**4.1%**
Headache	11 (5.6)	7 (6.4)	27 (9.2)	**2.7%**	29 (9.5)	55 (13.3)	**3.8%**
Gastroenteritis	3 (1.5)	9 (3)	7 (6.4)	**-3.3%**	5 (1.6)	14 (3.4)	**1.8%**
Abdominal Distension	4 (2)	0	3 (1)	**1%**	11 (3.6)	6 (1.5)	**-2.1%**
Vomiting	12 (6)	15 (13.8)	30 (10.2)	**-3.6%**	48 (15.7)	63 (15.3)	**-0.4%**

Source: Reviewer's table made from Sponsor's ADSL and ADAE datasets from ISS and PFC-1131 using MAED. ADAE datasets contain recoding as described in section 7.1.2 and ADSL dataset limited to TEAE (based on TRTEMFL="Y").
*Includes subjects titrated from lubiprostone 12mcg BID to 24mcg BID in the 24mcg cohort.
RD=Relative Difference; LUB=lubiprostone.

Reviewer Comments: In general, it appears as though AEs are more common in children taking higher doses of lubiprostone. This is consistent with the findings in the clinical pharmacology review, but the specific numbers differ slightly based on recoding performed by this reviewer as described in section 7.1.2. This finding of increased adverse events with increased dose is expected based on adult data. The poor

tolerability of the 24mcg BID dose during the adult IBS-C development program lead to the marketing of the 8mcg BID dose for that indication.

Based on the PK and other safety data, it does not make sense to this reviewer that vomiting would occur more commonly at the 12mcg dose. This reviewer believes that the analysis showing an increased incidence of treatment emergent vomiting in children treated with the 12mcg BID compared to 24mcg BID is flawed based on trial design and confounding variables. Specifically, subjects were not randomly assigned to a dose of lubiprostone, but assigned a dose based on their weight. Weight is known to be closely correlated with age. Younger children were more likely to vomit; in the placebo group children less than 12 years of age were 3 times as likely to have treatment related emesis compared to 12 to 17 years old. Within the controlled trial, the 12mcg lubiprostone cohort was composed primarily of younger children, 64% were between the ages of 6 to 9 years old and only 4% were between 14 to 17 years old. Whereas in the controlled trial the 24mcg BID cohort (even after including children who were dose escalated), was comprised of mostly older children, 34% were between 14 to 17 years old and only 25% were less than 9 years old.[48]

Once age is controlled for, there is a higher incidence of treatment related emesis in the 24mcg BID cohort for each age group, as shown in Table 47. Additionally, of the subjects in the controlled trial with treatment related emesis, 80% of the cases in the lubiprostone group occurred in children treated with 24mcg BID.

Table 47. Treatment Related Emesis by Age and Lubiprostone Dose in PFC-1131

	6-9 years old	***10-13 years old***	***14-17 years old***
Placebo	*3/66 (4.5)*	*1/78 (1.3)*	*1/51 (2)*
Lubiprostone Total	*14/142 (9.9)*	*11/153 (7.2)*	*5/104 (4.8)*
12 mcg BID LUB	*4/68 (5.9)*	*2/35 (5.7)*	*0/4 (0)*
24 mcg BID LUB	*10/74 (13.5)*	*9/118 (7.6)*	*5/100 (5)*

Source: Table made by Reviewer based on Sponsor's ADAE and ADSL data-sets from PFC-1131 after re-coding performed by Reviewer (as described in 7.1.2). The ADAE data-set was limited to exclusion of AEREL equals "unrelated". Treatment related was determined by Investigator and includes AEs that were possibly, probably and definitely related to study drug.
LUB=lubiprostone.

This reviewer does not believe that the AE profile for lubiprostone at 24mcg BID precludes its use in children 6 to 17 years of age as even those AEs that occurred more commonly at the 24mcg BID dose than the lower doses were generally mild and did not lead to discontinuations.

[48] Sponsor's Table 4 from the PFC-1131 Study Report.

7.5.2 Time Dependency for Adverse Events

The Sponsor evaluated time until emergence of the most common AEs in the long-term safety cohort. The cumulative incidence of vomiting, nausea, abdominal pain, headache and diarrhea increased with increased duration of exposure to lubiprostone, as shown in Table 48.

Table 48. Cumulative Incidence of Common Treatment Emergent Adverse Events in the Long-Term Safety Cohort Treated with Any Dose of Lubiprostone

TEAE Preferred Term	7 days	4 weeks	12 weeks	36 weeks	48 weeks
Vomiting	2.8%	6.2%	9.6%	15.5%	17.1%
Nausea	7.7%	9.9%	12.2%	15.9%	16.8%
Abdominal Pain	1.6%	3.6%	5.8%	12.1%	14.5%
Headache	2.6%	4.6%	7.2%	12.5%	13.6%
Diarrhea	1.4%	3%	5.4%	10.6%	12%
Chest Pain	1.4%	1.8%	2.2%	2.4%	2.9%

Source: Sponsor's tables 2.4.10.2.1, 2.4.10.3.1, 2.4.10.4.1, 2.4.10.5.1, 2.4.10.6.1, 2.4.10.7.1 from the ISS. This data was not recoded by the Reviewer.

Based on hazards rates and likelihood ratios calculated by the Sponsor, nausea, diarrhea and chest pain were most likely to initially occur during the first week of treatment. The highest probability of first occurrence of abdominal pain, vomiting and headaches were during the first 4 weeks of treatment.

Reviewer Comments: *As common AEs usually occurred shortly after children started lubiprostone; therefore, this reviewer believes that the 12 week controlled trial was able to detect most common AEs. The long-term incidence of adverse events attributable to lubiprostone cannot be determined as there was no control group in either long-term study. This reviewer believes that some of the long-term treatment emergent side effects are due to the underlying disease, PFC, rather than the drug. Even if all of the AEs were due to lubiprostone, this reviewer does not believe that the long-term adverse event profile alters the overall safety profile of the drug as most AEs were mild and self-resolved while subjects continued on lubiprostone therapy.*

7.5.3 Drug-Demographic Interactions

7.5.3.1 Sex

The percentage of lubiprostone treated subjects who experienced at least one TEAE was comparable between males and females in the controlled trial and the overall safety cohort. Within the controlled trial, TEAE occurred in 56.9% of male lubiprostone

treated subjects and 55.4% of female treated lubiprostone treated subjects.[49] TRAEs occurred in 29.7% of males receiving lubiprostone and 31.9% of females receiving lubiprostone. The reported AEs by preferred term were generally similar between males and females. However, based on an analysis of TEAE, nausea was more common in females, both for subjects treated with lubiprostone and placebo. The relative difference in the rate of nausea between lubiprostone and placebo was higher in females than males, 9.1 vs 4.9% respectively. The incidence of vomiting as a TEAE was similar in males and females treated with lubiprostone, but less common in females than males in the placebo group creating a larger relative difference for females compared to males. While the incidence of treatment emergent abdominal pain was similar between males and females, the relative difference between subjects treated with lubiprostone and placebo was much higher in males treated with lubiprostone, 4.9% in males compared to -2.4% in females. Table 49 describes the most common TEAEs within the entire population for males and females.

Within the long-term safety population, the incidence of AEs was generally similar to the controlled trial. There was no substantial sex difference in the incidence of abdominal pain or vomiting. There was a small sex difference in the frequency of treatment emergent reports of nausea, 17.6% in females and 14.5% in males treated with any dose of lubiprostone.[50]

[49] Sponsor's tables 2.4.1.4.3 from the ISS.
50 Sponsor's table 2.4.2.4.1 from the ISS.

Table 49. Treatment Emergent Adverse Events by Sex in PFC-1131 Safety Population

TEAEs (Listed in order of incidence in all Lubiprostone patients) n (%)	Females			Males		
	Placebo (n=106)	Lubiprostone All Doses (n=241)	OR	Placebo (n=93)	Lubiprostone All Doses (n=185)	OR
Abdominal Pain	21 (19.3)	37 (16.9)	**0.8**	10 (10.8)	29 (15.7)	**1.5**
Nausea	9 (8.3)	38 (17.4)	**2.3**	5 (5.4)	19 (10.3)	**2**
Vomiting	5 (4.6)	24 (11)	**2.6**	7 (7.5)	21 (11.4)	**1.6**
Headache	5 (4.6)	16 (7.3)	**1.6**	6 (6.4)	18 (9.7)	**1.6**
Diarrhea	2 (1.8)	14 (6.4)	**3.7**	4 (4.3)	14 (7.6)	**1.8**
Gastroenteritis	1 (0.9)	9 (4.1)	**4.6**	2 (2.2)	7 (3.8)	**1.8**
Pyrexia	1 (0.9)	10 (4.6)	**5.2**	3 (3.2)	6 (3.2)	**1**
Dizziness	3 (2.8)	8 (3.6)	**1.3**	2 (2.2)	5 (2.7)	**1.3**
Sinusitis	3 (1.4)	3 (2.8)	**0.5**	8 (4.3)	0	**9***
Chest Pain	0	7 (3.2)	**7.7***	2 (1.1)	0	**2.5**
UTI	3 (2.8)	8 (3.6)	**1.3**	0	0	

Source: Table made by Reviewer based on ADSL and ADAE datasets (recoded as described in 7.1) from PFC-1131 and calculations performed using MAED.
*Continuity Correction used.
OR=Odds Ratio

Reviewer Comments: The AE rate and profile was generally similar between males and females. The most striking differences between males and females in this reviewer's opinion are likely related to differences in anatomy for UTIs and are unrelated to the study drug. This reviewer believes that there is no true sex difference for chest pain, sinusitis, pyrexia or gastroenteritis, and the apparent sex differences for these AEs is likely related to chance due to the small number of overall cases. The sex difference for the placebo rate of abdominal pain may reflect a difference in reporting of abdominal pain associated with PFC by females. The girls in this trial may have been more accurate reporters than the boys as the PTs for abdominal pain more commonly include specific locations for the girls rather than the boys. The differences in Odds Ratio for vomiting may reflect differences related to weight, as females tended to weigh less than males, so they may have received a higher dose for weight which may be associated with increased side effects particularly for vomiting. (See reviewer comments in section 7.5.1).

7.5.3.2 Age

The Sponsor analyzed the incidence of AEs between 6-9 year olds, 10-13 year olds and 14-17 year olds. During the controlled trial, there was a similar rate to TEAEs between these age cohorts, 57.3% in 6-9 year olds, 53.7% in 10-13 year olds, and 58.3% in 14-17 year olds. The reported AEs were generally similar in the different age cohorts, with the exception of vomiting, which was more common in 6-9 year olds. Vomiting occurred in 6-9 year olds as a TEAE in 6.9% of placebo patients, 13.9% of 12mcg BID lubiprostone treated patients and 17.7% of 24mcg BID lubiprostone patients compared to 5.1% placebo treated patients and 7.3% of all lubiprostone treated patients 10-17 year olds.[51]

Within the long-term safety cohort, the incidence of TEAEs was similar between the age cohorts and overall more common than in the 12-week controlled trial. There were 72.9% TEAEs in 6-9 year olds compared to 71.9% in 10-13 year olds and 71.2% in 14-17 year olds. The most commonly reported TEAE in the long-term safety cohort were generally similar between the age cohorts and with those reported in the controlled clinical trial. Vomiting continued to be more frequently reported in 6-9 year olds. Abdominal pain was more common in 10-13 year olds and dizziness was more common in 10-17 year olds. Without a control group, it is difficult to determine if abdominal pain or dizziness reflect an age-based treatment effect in the long-term cohort.

Reviewers Comments: This reviewer believes that age-grouping children between 6-11 years and 12-17 years makes more sense based on child development and age-related behavioral components of PFC. Therefore, this reviewer analyzed the most common TEAE in 6-11 and 12-17 year olds and the results are shown in Table 50.

[51] Sponsor's table 2.4.2.6.3 from ISS.

Table 50. Treatment Emergent Adverse Events by Age Group in PFC-1131 Safety Population

TEAEs (Listed in order of incidence in all Lubiprostone patients) n (%)	6-11 years			12-17 years		
	Placebo (n=106)	Lubiprostone All Doses (n=241)	OR	Placebo (n=93)	Lubiprostone All Doses (n=185)	OR
Abdominal Pain	17 (14.7)	34 (15.4)	**1.1**	32 (17.5)	14 (16.3)	**1.1**
Nausea	8 (6.9)	32 (14.5)	**2.3**	6 (7)	25 (13.7)	**2.1**
Vomiting	9 (7.8)	36 (16.3)	**2.3**	3 (3.5)	9 (4.9)	**1.4**
Headache	7 (6)	16 (7.2)	**1.2**	4 (4.6)	18 (9.8)	**2.2**
Diarrhea	4 (3.5)	14 (6.3)	**1.9**	2 (2.3)	14 (7.6)	**3.5**
Gastroenteritis	2 (1.7)	10 (4.5)	**2.7**	1 (1.2)	6 (3.3)	**2.9**
Pyrexia	2 (1.7)	9 (4.1)	**2.4**	2 (2.3)	7 (3.8)	**1.7**
Dizziness	2 (1.7)	5 (2.3)	**1.3**	3 (3.5)	8 (4.4)	**1.3**
Sinusitis	1 (0.9)	7 (3.2)	**3.8**	2 (2.3)	4 (2.2)	**0.9**
Chest Pain	0	3 (1.4)	**3.7***	0	6 (3.3)	**6.3***
UTI	2 (1.7)	5 (2.3)	**1.3**	1 (1.2)	3 (1.6)	**1.3**

Source: Table made by Reviewer based on ADSL and ADAE datasets (recoded as described in 7.1) from PFC-1131 and calculations performed using MAED.
*Continuity Correction used.
OR=Odds Ratio.

The rate of most TEAE among pediatric patients taking lubiprostone did not differ between children under 12 years old and 12 to 17 year olds. The Odds Ratio for TEAEs did differ between adolescents and younger children for sinusitis, chest pain, diarrhea, headaches, and vomiting. This reviewer believes that there were not enough cases of sinusitis or chest pain to accurately make any conclusions regarding an age associated treatment difference. There is no biological rationale that younger children receiving lubiprostone would be predisposed to sinusitis. Therefore, this reviewer does not believe that this represents an important side effect of the drug.

Diarrhea occurred slightly (1.3%) more commonly in adolescents treated with lubiprostone compared to younger children treated with lubiprostone. All treatment emergent diarrhea was considered treatment related by the Investigators in PFC-1131. Since diarrhea was more common in younger children treated with placebo, there appears to be a greater risk of developing treatment related diarrhea in adolescents treated with lubiprostone. Even though treatment related diarrhea is more likely to occur in adolescents compared to younger children, this reviewer does not believe that this needs to be added to the label as the cases were not severe and they were less

common than in adults with CIC. None of the cases of diarrhea were serious or severe and all episodes self-resolved without discontinuation of the study drug. Adults with CIC had a higher rate of treatment related diarrhea than adolescents, 11% compared to 5.3%.

Headaches were more common only in lubiprostone treated adolescents; they occurred in 5.2% more adolescents taking lubiprostone than placebo. There was only a 1.2% difference in the incidence of treatment emergent headaches between lubiprostone and placebo treated children between 6 to 12 years of age. To further investigate the importance of this difference, this reviewer analyzed the frequency of treatment related headaches in adolescents and younger children, which is shown in Table 51. The relative difference between lubiprostone and placebo for treatment related headaches was very similar between adolescents and younger children and less common than occurred in the adult trials for CIC.

Table 51. Treatment Related Headaches by Age Group in PFC-1131 Safety Population

	6-11 Years Old	12-17 Years Old	Adults with CIC[52]
Placebo	1/109 0.9%	3/86 3.5%	5%
Lubiprostone Total	9/219 4.1%	13/180 7.2%	11%
Relative Difference	**3.2%**	**3.7%**	**6%**

Source: Table made by Reviewer based on PFC-1131 data-sets ADSL and ADAE (with AEs recoded as described in section 7.1)

Vomiting was more common in younger children than adolescents irrespective of whether they were taking lubiprostone or placebo. However, the relative difference in treatment emergent vomiting between lubiprostone and placebo was approximately 6 times more in younger children, 8.5% compared to 1.4%. To further investigate the importance of this difference, this reviewer analyzed the frequency of treatment related vomiting in adolescents and younger children, which is shown in Table 52.

[52] Amitiza drug label.

Table 52. Treatment Related Vomiting by Age Group in PFC-1131 Safety Population

	6-11 Years Old	12-17 Years Old	Adults with CIC
Placebo	4/109 3.7%	1/86 1.2%	0%
Lubiprostone Total	23/219 10.5%	7/180 3.9%	3%
Relative Difference	**6.8%**	**2.7%**	**3%**

Source: Table made by Reviewer based on PFC-1131 data-sets ADSL and ADAE (with AEs recoded as described in section 7.1) and Amitiza drug label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021908s015lbl.pdf (accessed 3/1/18).

Vomiting appears to be a more common treatment related adverse event in lubiprostone treated younger children, which may be dose related as discussed in section 7.5.1.

7.5.3.3 Race

Analysis of the overall safety cohort by the Sponsor shows that the percentage of subjects who experienced treatment emergent side effects did not differ by race. TEAEs were experienced by 71.1% of Caucasians, 62.5% blacks, and 67.4% of other races. The commonly reported AEs were generally similar amongst whites and non-whites.

Reviewer Comments: There does not appear to be a difference in AE rate based on race, but the subjects enrolled in the PFC clinical trials were primarily non-Hispanic Caucasians, so there is limited sensitivity to detect a difference in adverse events based on race.

7.5.4 Drug-Disease Interactions

Evaluation of these interactions was not planned or performed.

7.5.5 Drug-Drug Interactions

Evaluation of these interactions was not planned or performed.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity trials were not performed.

7.6.2 Human Reproduction and Pregnancy Data

Females who planned to become pregnant or were pregnant or females who refused to use protocol specified contraceptives were excluded from the trials. In the event that a subject became pregnant, lubiprostone was immediately discontinued. Despite these exclusion criteria, during studies PFC-1131/11s1, two adolescents became pregnant.

- A 16 year old subject treated with 24mcg of lubiprostone BID from prior to conception to 5 weeks gestational age (GA) gave birth at term.
- A 16 year subject treated with 24 mcg of lubiprostone from prior to conception to 4 weeks GA gave birth without complications to a healthy baby.

Reviewer Comments: These two pregnancies are insufficient to draw conclusions regarding the safety of lubiprostone during pregnancy. The cumulative reproduction and pregnancy data was reviewed by Division of Maternal Health. Please see their review and final labeling for information related to lubiprostone and pregnancy and lactation.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Sponsor reports that during the controlled trial there was no difference in height between the placebo treated subjects and the lubiprostone treated subjects. Also, the Sponsor assessed linear growth within the DXA sub-study population over 48 weeks. Amongst the 94 children who were 6-9 year olds, the mean change in height z-score was 0.1. Amongst the 48 adolescents who were 14 to 17 year olds, the mean change in height z-score was 0.53.

Reviewer's Comments: While the Sponsor did not demonstrate a treatment effect on linear growth, this reviewer does not believe that the Sponsor sufficiently analyzed the growth data obtained during the clinical development program.

First, this reviewer does not believe that data from the controlled trial is informative for detecting a growth related safety signal as 12 weeks duration is insufficient to assess growth in pre-pubertal children. The average annualized pre-pubertal growth rate is 5cm/year or approximately 1.2 cm in 12 weeks. This reviewer believes that it is likely

[53] Sponsor's table 2.7.1.8

that measurement variability rather than linear growth accounts for much of the recorded changes in height over the 12 week trial since recommended measurement techniques were not required per the protocol. Specifically, height was not assessed at the same time of day, measured in triplicate or even always using a stadiometer. This reviewer identified multiple patients who shrank, which is clinically unlikely in this patient population, especially since no vertebral fractures were reported.

This reviewer does not believe that the growth data from 14 to 17 year olds is informative as pubertal status for these adolescents was not provided. Most females and some of the males were likely post-pubertal and no longer growing. Even for those adolescents who were still growing, information about the timing and pace of puberty is needed to interpret the height z-scores.

The average change in height z-score reported in 6-9 year olds is reassuring. However, z-score data was only presented for approximately half of the 6-9 year olds in the long-term safety cohort. Therefore, this reviewer calculated the annualized growth rate for all 6-9 year olds while on lubiprostone in the long-term safety cohort. The median annualized growth rate was 5.7 cm/year, ranging from 0 cm to 29cm (after excluding the outliers with negative growth and more than 50cm/year). The mean was 6.2 cm/year with a standard deviation of 4cm/year. Amongst 6-9 year olds, there were 21 subjects with an annualized growth rate of less than 2.5cm/year, which is approximately 4 standard deviations below the mean for this age.[54] This low growth rate does not appear to be explained by comorbid diagnoses; within the entire safety population there were only 5 subjects at risk of poor linear growth (one subject had precocious puberty, one had growth hormone deficiency and 3 had syndromes that may affect growth).[55] In this reviewer's opinion, this represents a large percentage of children with a low growth rate, which may represent a safety signal or it may reflect measurement error.

Growth will be studied in the children 6-18 years with IBS-C under PMR 675-4. Additionally, growth will be assessed as part of the safety evaluation of children 6 months to 6 years with PFC under PMR 572-5.

This reviewer believes that the safety profile of lubiprostone in 6-17 years old does not preclude further pediatric studying of lubiprostone in children. There continues to be a need for approved therapy for PFC especially in very young children and in children with IBS-C. Therefore, this reviewer does not believe that the PMRs should be released. This opinion was supported by the Pediatric Research Committee (PeRC).

[54] Tanner JM et al. "Clinical longitudinal standards for height and height velocity for North American children." The Journal of Pediatrics. 107(3). 1985.
[55] Sponsor's ADMH ISS dataset describes one case of Fetal Alcohol Syndrome, one case of DiGeorge Syndrome, one case of Ehlers-Danlos Syndrome, one case of precious puberty and one case of growth hormone deficiency.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were four cases of overdose in subjects with PFC during the clinical development program. One of these subjects had diarrhea and a joint injury associated with the overdose which resolved in less than 24 hours. The other children were asymptomatic. The current drug label describes the accidental overdose of a 3 year old who took between 168 and 192 mcg lubiprostone and fully recovered. In adults, overdoses of lubiprostone (up to 144 mcg, 3 times the prescribed daily dose) have been associated with nausea, diarrhea, vomiting, dizziness, flushing and dyspnea.

The pharmacologic profile and experience in adults does not suggest that lubiprostone has the potential for drug abuse, including addiction or dependence. The randomized trials of lubiprostone in adults with CIC and IBS-C did not show withdrawal or rebound. Withdrawal and rebound were not studied as part of the clinical development program for PFC.

Reviewer Comments: This reviewer believes that children are likely to experience similar side effects to adults following an overdose of lubiprostone. There is limited data in the application about overdoses in children. The one subject who was symptomatic following the overdose, had diarrhea and a joint injury. Mechanistically, diarrhea would be expected after an overdose and was reported in the adults who had an overdose of lubiprostone. This reviewer believes that the diarrhea was likely due to the overdose, but does not believe that the joint injury represents an important unique safety signal in children. Although details of the overdose are limited, based on the fast resolution, this reviewer believes that it is unlikely that the patient suffered a tendon rupture or other clinically worrisome joint problem. The joint problem may represent a common childhood injury and be unrelated to the overdose. No labeling changes regarding overdose are recommended.

7.7 Additional Submissions / Safety Issues

Syncope was a pre-specified safety issue.

There were a total of 11 children who had treatment emergent syncope in the overall safety cohort. None of the cases were severe or led to discontinuation. The only subject who had a recurrence of syncope, had an alternative etiology; it was not drug related. Only four of the cases were considered treatment related by the Investigators. Of these four treatment related cases, two children were receiving 24mcg BID lubiprostone, one child was receiving 12mcg BID lubiprostone and one child was receiving placebo. No subject was recorded to have hypotension or low blood pressure. None of the children with syncope had diarrhea, vomiting or other risk factors for volume depletion prior to the loss of consciousness. The treatment related cases of syncope occurred 1 week to 29 weeks after initial dosing of lubiprostone.

Reviewer Comments: The cases of syncope that occurred in children were less severe and did not appear to be precipitated by vomiting or diarrhea compared to the cases in adults that led to the addition of syncope to the warnings and precaution section of the Amitiza label.

8 Postmarket Experience

Lubiprostone was initially approved for adults in January 2006. The postmarketing experience is described in the drug label, which was most recently updated August 1, 2017. This labeling update included addition of syncope and hypotension to the "Warnings and Precautions" section of the label based on post-marketing SAE that resulted in hospitalizations. Voluntary postmarketing reports in adults have also included ischemic colitis, hypersensitivity/allergic-type reactions, malaise, tachycardia, muscle cramps/muscle spasms and asthenia, which are described in the drug label.

The most recent Periodic Safety Update Report (PSUR) covers the period from February 1 2016 to January 31, 2017.[56] The cumulative post-marketing data from the United States described in this report is over (b) (4) person years and world-wide is almost (b) (4) person years. The described adverse events are consistent with the current label. There are no reports of exposure to children outside of the clinical trials reviewed in this application supplement.

Reviewer Comments: The experience of children using the drug off-label in the post-marketing setting is unknown. The current label appears to adequately describe the known safety of the drug, including in the post-market setting, and this reviewer believes no additional labeling changes are indicated based on review of post-marketing data.

9 Appendices

9.1 Literature Review/References

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Shepherd et al. “Optimal monitoring time interval between DXA measures in children.” Journal of Bone Mineral Research. 26(11); 2011.

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Sood, Manu. “Functional constipation in infants and children: clinical features and differential diagnosis.” Up-to-Date. 2017.

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Van den Berg et al. “Epidemiology of Childhood Constipation: A Systematic Review” American Journal of Gastroenterology. 101. 2006.

Van Staa TP et al. “Children and the risk of fractures caused by oral corticosteroids.” Journal Bone Mineral Research. 2003.

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9.2 Labeling Recommendations

The finalized language for section 8.4 Pediatric Use:

> Safety and effectiveness have not been established in pediatric patients less than 6 years of age.
>
> Effectiveness has not been established in pediatric patients 6 years and older. Efficacy was not demonstrated for the treatment of Pediatric Functional Constipation (PFC) in a 12 week, randomized, double-blind, placebo controlled trial conducted in 606 patients 6 to 17 years with PFC comparing Amitiza to placebo. The primary efficacy endpoint was an overall response based on spontaneous bowel movement frequency over the duration of the trial; the treatment difference from placebo was not statistically significant. In this age

group, adverse reactions to Amitiza were similar to those reported in adults. In a 36-week, long-term safety extension trial after approximately 9 months of treatment with Amitiza, a single case of reversible elevation of ALT (17-times upper limit of normal [ULN]), AST (13-times ULN), and GGT (9-times [ULN]) was observed in a child with baseline elevated values (less than or equal to 2.5-times ULN).

Juvenile Animal Toxicity Data
In a 13-week oral toxicity study in juvenile rats, a significant decrease in total bone mineral density was observed in female pups at 0.5 mg/kg/day; in male pups, a significantly lower cortical thickness at the tibial diaphysis was observed at 0.5 mg/kg. The 0.5 mg/kg/day dose is approximately 101 times the maximum recommended adult dose of 48 mcg/day, based on body surface area (mg/m^2).

Section 8.1 and 8.2 were updated to include information presented in the Sponsor's Pregnancy and Lactation Report and be consistent with PLLR format. (For additional details, refer to the maternal health review). Section 12.3 was updated for improved clarity. (For additional details refer to the clinical pharmacology review).

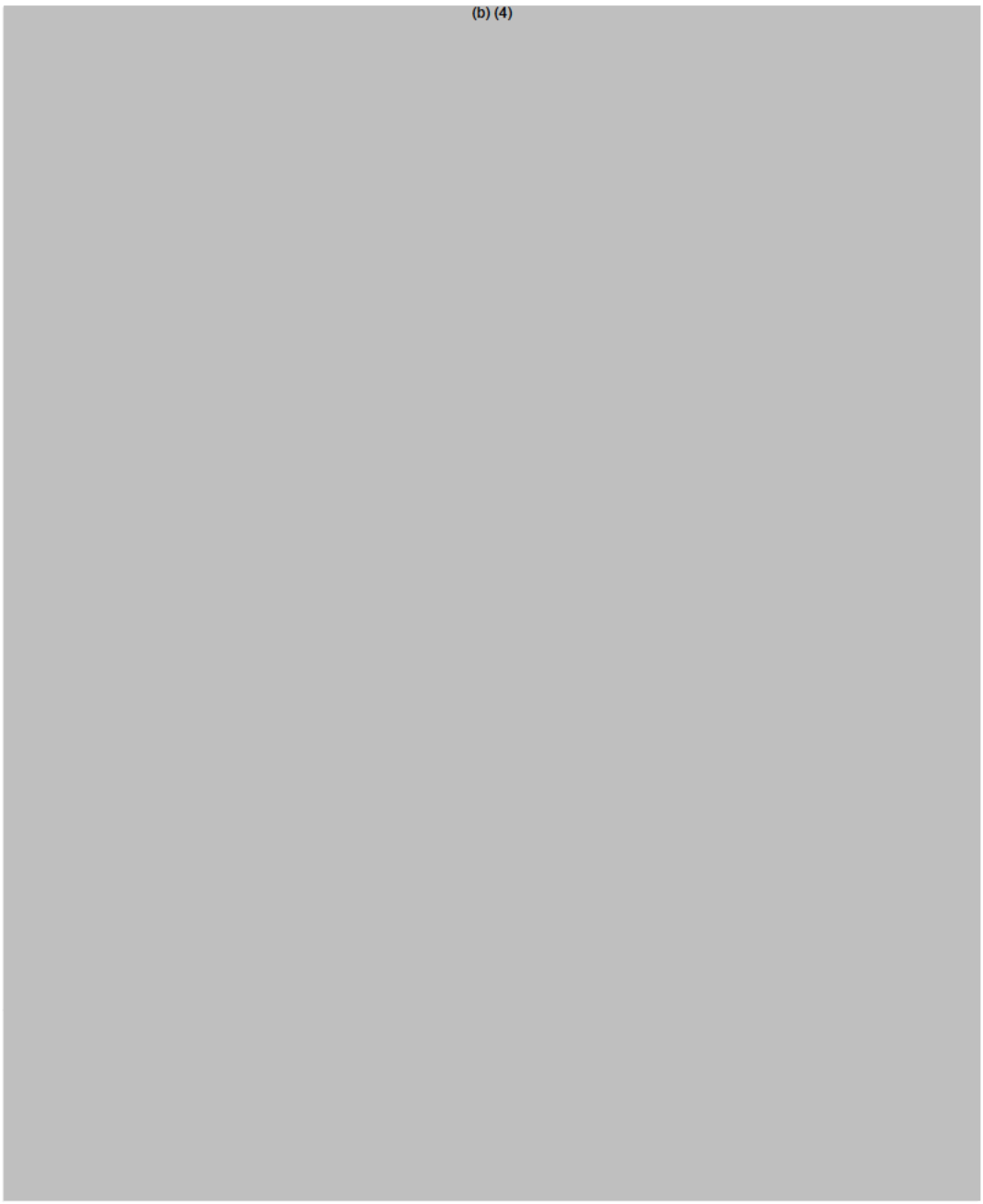
9.3 Advisory Committee Meeting

No advisory committee meeting will be held.

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

(b) (4)


(b) (4)


(b) (4)

Data about Electronic Diary from Appendix 1 of Sponsor's 1131 Protocol Version 7

Appendix 2.

Protocol Summary - Study PFC-11S1: A Multicenter, Long-Term, Safety, Efficacy and Pharmacokinetics Study of Lubiprostone in Pediatric Subjects Aged ≥ 6 years to <18 Years with Functional Constipation

Trial Design

This is an open-label, uncontrolled trial in which long-term safety, efficacy and PK of two doses of Lubiprostone (12 mcg and 24 mcg BID) are tested in children 6-17 years old with PFC who completed the double-blind, 12-week, randomized trial (study PFC-1131). This trial is 36 weeks in duration, so subjects initially treated in PFC-1131 will have 40 weeks of treatment and 42 weeks of safety data.

Objectives

The primary objective was to assess the long-term safety of two doses of lubiprostone (12 and 24mcg BID) in 6-17 year olds with PFC. The other objectives were to assess the long-term efficacy and PK of lubiprostone (12 and 24mcg BID) in 6-17 year olds with PFC.

Endpoints

The safety endpoints were similar to study PFC-1131 and included:

- AEs
- Change from baseline in physical exam, clinical laboratory parameters and vital signs
- Growth
- Bone health from DXA sub-study

The efficacy endpoint in this trial included:

- Overall and monthly changes from baseline with respect to BM and SBM frequency
- Overall and monthly averages and changes from baseline in SBM stool consistency, and straining and abdominal pain associated with SBMs, and constipation severity
- Monthly SBM response (where a monthly responder must be a weekly responder for 3/4 weeks and the weekly responder definition is unchanged from PFC-1131)
- Overall and monthly average assessment of treatment effectiveness and overall health related QOL
- Overall and monthly change from baseline in incontinence episode frequency (for subjects with encoperesis at baseline), fecal impaction,

BMs and SBMs in the toilet, and frequency of retentive posturing or excessive volitional stool retention.

Sparse PK data collected during this study was combined with PK data from other studies as part of a population PK analysis. (See the review by Dr. Sojeong Yi for additional details).

Trial Population

The key inclusion criteria include:

- Completed the entire 12-week treatment period during study PFC-1131
- Continue to be willing and able to comply with abstaining from prohibited medications (same as described for PFC-1131, see section 5.3.1) and complete electronic diary

The key exclusion criteria include:

- Non-compliance with study protocol (including electronic diary) during PFC-1131
- Fecal impaction
- An AE during PFC-1131 that according to Investigator would limit ability to participate in this trial
- A new condition or laboratory test (such as those described in the exclusion criteria for PFC-1131, see section 5.3.1)

Dosing

All subjects received treatment with lubiprostone during this trial. Subjects who were received lubiprostone during PFC-1131, continued on the same dose they received at the end of PFC-1131. All subjects who were on placebo during PFC-1131, were treated with lubiprostone based on weight; subjects weighing less than 50kg received 12 mcg BID and subjects weighing at least 50kg received 24 mcg BID. Subjects treated with 12mcg BID in this study were not be dose escalated. Any subject who had three or more days of severe nausea or severe diarrhea were eligible to have their dose reduced to daily dosing.

To preserve blinding of study PFC-1131, subjects and investigators remained blinded to the dose during PFC-11s1 for subjects who weighed less than 50kg at enrollment.

Subjects took the study medication in the same manner as they did during study PFC-1131. (See section 5.3.1.5 for details).

Scheduled Study Procedures and Safety Assessments

There were 9 visits in this study, of which three were telephone visits. The first visit coincided with the 7th visit of PFC-1131. The study procedures and assessments were the same in this trial as occurred during in PFC-1131. (See Table 5353 for a summary of study visits and procedures). During this study, subjects are allowed rescue

Table 53. Summary of Study Visits and Study Procedures PFC-11s1

SCHEDULE OF EVALUATIONS

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

Note: The Visit numbers in parentheses are in reference to the preceding placebo-controlled study (SAG/0211PFC-1131).
[1] The End-of-Treatment Visit (V7) in study SAG/0211PFC-1131 will serve as the Enrolment Visit and the corresponding assessments are designated above as "V7". Other corresponding visits from preceding study are also designated by the visit number;
[2] Measure predose vital signs at Visit 9, as well as measurement of heart rate and blood pressure 1 hour after the first dose of study medication. If blood pressure and/or heart rate are, according to the Investigator, clinically significantly elevated relative to predose at the 1 hour postdose measurement, additional measurements should be taken again at 2 hours and 3 hours postdose. Subjects should be asked to remain seated for at least 5 minutes prior to measurement of vital sign parameters. A wall-mounted stadiometer, where available, should be used for measurement of height. Vital sign assessments will be performed prior to PK sampling when these assessments are collected at the same visit. Record the time of all vital sign measurements in the source documents. Age-appropriate equipment, e.g., blood pressure cuffs, should be used for all assessments;
[3] Complete comprehensive physical examinations at Enrolment and End-of-Treatment visits. An abbreviated physical examination is to be performed at all other visits;
[4] PK samples will be collected predose and 1 sample between 30 and 90 minutes after dose administration (2 samples total). PK samples will be taken under non-fasting conditions. The samples will be collected via direct venipuncture. Approximately 8 mL of blood will be taken for each sample such that the total of all PK samples does not exceed 50 mL or 5 mL/kg of body weight;
[5] Urine pregnancy tests will be performed at all study visits on subjects of childbearing potential.
[6] All subjects who withdraw from the study after Visit 12 (Month 3) should complete the final visit of the treatment period (Visit 16) and therefore have a final DXA assessment performed. This will only be required for subjects that were originally part of the DXA subgroup. Any subject demonstrating a decline in 4% in BMD at any skeletal site from Screening to End of Treatment should additionally undergo a follow-up DXA assessment 6 to 12 months later;
[7] Observe the subject or parent/legal guardian as he/she administers the first dose of study medication while in the clinic at Visit 9. Over the next 1 hour, monitor subject for any adverse reactions. One bottle of study medication will be provided at Visit 9 and then 3 bottles each at Visits 10, 12 and 14. Subjects should return the used bottle of study medication at each clinic visit for collection by site for drug accountability. If the study medication is not returned, the bottle of all unused study medication should be returned to the site at the subsequent office visit. The subject will be instructed to take the study medication only from the newly dispensed bottle;
[8] Change eDiary mode to new treatment mode (associated with current study - SAG/0211PFC-11S1) at Visit 9.

Source: Sponsor Schedule of Evaluations PFC-11s1 version 4 of protocol page 15-16

medications, and should follow the same guidelines as during PFC-1131. Subjects' parents and guardians should complete the electronic diary nightly as they did during PFC-1131. Subjects may be withdrawn from the trial for the same reasons as during PFC-1131. (See section 5.3.1.6 for additional details).

Statistical Analysis

Efficacy analysis was a mITT analysis including all enrolled subjects who took at least one dose of study medication and had one diary entry during PFC-11s1 treatment period. Continuous variables were summarized by descriptive statistics and categorical data was summarized by counts and percentages. Adverse events were summarized by treatment group (based on the group initially assigned) and overall.

Appendix 3

Study SCMP-303: A 6-month, Open-Label Safety Study of Lubiprostone in Pediatric Subjects Aged ≥ 6 years to <18 Years with Functional Constipation

Trial Design
This was an open-label, uncontrolled, 6-month safety study of 2 doses of lubiprostone (12mcg and 24mcg BID) in children 6-17 years of age with PFC.

Objectives
The primary objective was to evaluate the safety and tolerability of 2 doses of lubiprostone (12 and 24mcg BID) assigned by weight over 24 weeks in children 6-17 years with PFC.

Endpoints
The safety endpoints were AEs, changes from baseline in laboratory parameters, physical exam and vital signs.

Trial Population
The eligibility criteria were the same as for study PFC-1131 except that there were no restrictions on fiber supplements and no diary requirements. If subjects completed an eDiary as part of screening for PFC-1131, they could have 3 or more SBM/week and/or less than 25% of SBMs associated with mBSS type 1 or 2 or some straining associated with SBM.

Scheduled Study Procedures and Safety Assessments
This study involved 24 weeks of lubiprostone therapy and a follow-up visit one week after study drug discontinuation. The study involved a total of 4 study visits and a single telephone assessment. Subjects had a single screening visit to determine eligibility and to obtain demographics, baseline medical history, physical exam, vital signs and laboratory assessments. Study treatment was begun at this visit. After 1 week, there was a telephone assessment of adverse events. At 12 weeks, 24 weeks and 25 weeks repeat assessments of vital signs and laboratory assessments were made. At 24 weeks, a repeat physical exam was performed. Adverse events and changes in concomitant medications were collected throughout the study.

Subjects were instructed to use rescue medication as in study PFC-1131 and PFC-11s1.

No electronic diaries were collected during this study. Although it is a safety study only, efficacy was assessed by Investigator's assessment of treatment effectiveness at the 24 week visit.

Appendix 4

5.3.5 Study SC-0641: A Multi-center, Open-labeled Study of Safety, Efficacy and Pharmokinetics of Lubiprostone in Pediatric Patients with Constipation

Trial Design
This was an open-label, uncontrolled, 4 week trial of children who were less than 17 years with constipation in which multiple dosing regimens of Lubiprostone were tested (based on subjects age and weight) to assess PK, and short-term efficacy and safety.

Objectives
The primary objective was to assess safety and efficacy of Lubiprostone in children with constipation compared to adult data submitted in the NDA for CIC.

Endpoints
The primary efficacy endpoint was the SBM frequency during week 1. Additional efficacy endpoints included SBM during each week of the trial, time to first SBM, percentage of patients with SBM after 24 and 48 hours of first dose of Lubiprostone, weekly responder rate, frequency of incontinence episodes, average degree of straining with SMB, painful SBMs, stool consistency of SBM, abdominal bloating, abdominal discomfort, constipation severity and Investigator's assessment of treatment effectiveness. Safety endpoints included AEs, TEAEs, SAEs, change from baseline in VS and laboratory values.

Trial Population
The major eligibility criteria included:

- PFC based on Rome 3 criteria
- During the 2 week screening period an average of <3 SBM/week and Type 1 or 2 SBM on BSS or SBM associated with straining or no SBM during screening
- At least 12kg and capable of swallowing pills
- <18 years of age
- Able to complete daily stool diary (with or without parental help)
- Willing and able to comply with all study procedures (including discontinuation of other laxatives, administer rescue medication, ≥ 70% completion of stool diary at screening)
- Fecal impaction or history of impaction requiring digital manipulation for removal
- No clinically significant laboratory abnormalities at baseline, conditions that interfere with absorption of study medication or study participation, impaired renal function, unexplained weight loss, history of significant GI surgery or cancer in the past 5 years

Dosing
All subjects were treated with Lubiprostone; dosing was based on age and weight:

Age	Weight	Dose
12-17 years old	≥ 36 kg	24 mcg BID
	≥ 12 kg	12 mcg BID
6-11 years old	> 36 kg	24 mcg BID
	24 kg - <36 kg	12 mcg BID
	≥ 12 kg - <24 kg	12 mcg daily
< 6 years old	≥ 12 kg	12 mcg daily

The Sponsor selected these doses based on allometric scaling from adult dosing for CIC. The doses tested ranged from 0.5mcg/kg to 1.1mcg/kg.

Scheduled Study Procedures and Safety Assessments
The 6 week study included 5 visits and a telephone assessment. The first visit was for screening. During the second visit eligibility was confirmed and the study drug was prescribed. Also, PK sampling was performed in a subset of children following the initial dose of lubiprostone. The subsequent 3 study visits occurred after 1 week and 4 weeks of study drug, and 2 weeks after drug discontinuation. At each of these visits a physical exam, laboratory tests and vital signs were performed, and stool diary and adverse events were reviewed. Adverse events were also reviewed during a telephone assessment after 2 weeks on the study drug.

Throughout the study, subjects were instructed to complete an electronic stool diary nightly (as occurred in studies PFC-1131 and PFC-11s1). However, in this study adolescents,12-17 year-olds, completed the diary themselves and younger children completed the diary independently or with the assistance of a parent rather than parents/guardians completing the diary for all subjects as in study PFC-1131 and PFC-11s1.

Rescue medication was not uniformly prescribed during this study. Rescue medications were prohibited during the first 24 hours after the first dose of study drug and then allowed at the discretion of the investigator if no BM in the past 3 days. PEG was the only prohibited rescue medication.

Statistical Analysis: The primary efficacy endpoint was frequency of SBM at week 1. Wilcoxon signed-rank test was performed to determine if there was a significant change in weekly SBM frequency between baseline and week 1. No imputation was performed. Results were analyzed by age group, weight group and dose level combination.

Appendix 5
Reviewer's Recoding of Sponsor's Preferred Terms

This is the complete list of PT terms this reviewer modified from the Sponsor's AE dataset.

- *Combined "abdominal pain," "abdominal pain lower," "abdominal pain upper," "upper abdominal pain," "left lower quadrant pain," "left upper quadrant pain," "pain right upper quadrant," "abdominal discomfort," "stomach ache," "stomachache," "stomach cramps," "stomach discomfort," "stomach pain," "abdominal cramp(s)," "abdominal tenderness," "pain gastric," "epigastric pain," "epigastric discomfort," "abdominal pain aggravated" gastrointestinal pain as the same AE (PT "abdominal pain").*
- *Combined "abdominal distension," "abdominal bloating," "bloating," "distended abdomen" as the same AE (PT "abdominal distension").*
- *Combined "acid reflux," "dyspepsia," "heartburn," "GERD," "reflux esophagitis," "gastroesophageal reflux," and "esophageal reflux aggravated" as the same AE (PT "acid indigestion").*
- *Combined "diarrhea," "watery diarrhea," "loose stools," and "stools watery" under the same AE (PT "diarrhea").*
- *Combined "emesis," "vomited," "vomiting," and "vomiting aggravated" under the same AE (PT "emesis").*
- *Combined "flatulence," "gas," "gas in stomach" under the same AE (PT "flatulence").*
- *Combined "fecal impaction," "fecaloma," and "impaction fecal" under the same AE (PT "fecal impaction").*
- *Combined "dyspnea," "dyspnoea," "dyspnoea exacerbated," "dypnea exacerbated," "exertional dyspnea," "short of breath," "shortness of breath" under the same AE (PT "dyspnea").*
- *Combined "fainting," "faint," "syncope," "syncope vasovagal," "syncope exertional," and "passed out" under the same AE (PT "syncope).*
- *Combined "light headedness," "dizziness" and "dizziness aggravated" under the same AE (PT "dizziness").*
- Combined "elevated liver enzymes," "ALT increased," "AST increased," "liver function tests raised" under the same AE (PT "elevated liver enzymes").
- Combined "fever," "high temperature," "pyrexia," and "intermittent fever" under the same AE (PT "pyrexia").
- Combined "headache," "frontal headache," "intermittent headache," "headache aggravated," "migraine," and "migraine headache," under the same AE (PT "headache").
- Combined "chest pain," "chest discomfort," "chest tightness," "tightness in chest," under the same AE (PT "chest pain").

- Combined “contact dermatitis,” “eruption,” “dermatitis,” “erythematous eruption,” “erythematous skin rash,” “rash erythematous,” “generalized rash,” “idiopathic urticaria,” “localized rash,” “scarlatina,” “neck rash,” “poison ivy rash,” “poison oak rash,” “pruritic rash,” “rash aggravated,” “rash on face,” “rash over arms,” “skin eruption,” and “skin rash” under the same AE (PT “rash”).
- Combined “hematochezia” and “stool bloody” under the same AE (PT “blood in stool”)
- Combined “flushed face,” “flushing of face,” and “red face” under the same AE (PT “flushing”).
- Combined “difficulty sleeping,” “insomnia exacerbated,” “trouble falling asleep,” and “insomnia” under the same AE (PT “insomnia”).
- Combined “anorexia,” “appetite lost,” “decreased appetite,” and “appetite suppression” under the same AE (PT “anorexia”).
- Combined “back ache,” “back pain,” “backache,” “low back pain,” “low back ache,” and “chronic back pain” under the same AE (PT “back pain”).
- Combined “anxiety,” “anxiety aggravated” and “feeling anxious” under the same AE (PT “anxiety”).
- Combined “blurred vision,” “blurring of vision,” and “hazy vision” as the same AE (PT “blurry vision”).
- Combined “burn blister,” “scald,” “superficial burn,” “burn of fingers” under the same AE (PT “burn”).
- Combined “asthma,” “asthma exacerbated,” “exacerbation of asthma” and “exercise induced asthma” under the same AE (PT “asthma”).
- The 16 different fractures were listed under 14 separate PT terms (fracture of specific bone or region of the body), and this reviewer combined them under the same AE (PT “fracture”).
- The location of abscesses, contusions, lacerations, sprains, joint dislocations and specific joints causing pain were omitted and all abscesses were grouped together under the PT “abscess,” contusions under the PT “contusion,” lacerations under the PT “laceration,” sprains under the PT “sprain”, joint dislocations under the PT “joint dislocation,” and all joint pain was listed under the PT “joint pain”.
- Similar infections even if caused by different organisms were recoded. (When the AE term provided by the investigator elucidated the location of the infection that was used to aid in combining of AEs.)
    - Combined “acute gastroenteritis,” “gastroenteritis,” “enterovirus gastroenteritis,” “stomach flu,” “stomach virus,” and “viral gastroenteritis under the same AE (PT “gastroenteritis”).
    - Combined “pharyngitis,” “acute pharyngitis” “streptococcal pharyngitis,” “streptococcal sore throat,” “viral pharyngitis,” “beta hemolytic streptococcal infection,” “acute nasopharyngitis,” “streptococcal

infection," "sore throat," "throat pain," "pharyngeal erythema," and "pharynx redness of" under the same AE (PT "acute pharyngitis").
    - Combined "acute maxillary sinusitis," "sinus infection," and "sinusitis" under the same AE (PT "acute sinusitis").
    - Combined "acute respiratory tract infection," "chest cold," "cold," "cold symptoms," "common cold," "head cold," "respiratory tract infection," "respiratory tract infection viral," "upper respiratory infection," "viral upper *respiratory tract infection," "nasal congestion," "congestion nasal," "respiratory tract congestion," and "upper respiratory tract congestion" under the same AE (PT "acute upper respiratory tract infection").*
    - *Combined "otitis media," "left otitis media," "bilateral otitis media," and "bilateral otitis externa" under the same AE (PT "ear infection").*
    - *Combined "viral syndrome," "infection viral," "adenovirus infection" under the same AE (PT "viral infection NOS").*
    - *Combined "flu," "influenza," and "influenza A virus infection" under the same AE (PT "influenza").*
- *For laboratory based AEs, abbreviations and full name (e.g. MCH and mean corpuscular hemoglobin), and blood and serum PTs were combined. Since the protocol required that clinically significant investigational abnormalities be reported as AEs, PT "decreased" laboratory value was combined with PT "low" laboratory value, and when reported values were high then PT "increased" laboratory value was combined with "high" laboratory value.*

This reviewer also reviewed the AE terms provided by the investigator, and recoded the PT "incontinence" to "encopresis" when stool incontinence was described in the AE term. A single AE of vomiting was recoded to the PT "gastroenteritis" since the Investigator AE term was "stomach bug vomiting." A single AE of "muscle soreness" was recoded "MVA injury" as the AE term was "muscle soreness after motor vehicle accident".

Appendix 6

Additional details of Subject (b) (6) Hepatotoxicity:

Subject (b) (6) LFTs while on Lubiprostone during PFC-1131 and PFC-11s1

Parameter (unit) [RR]	SCREENING	WEEK 1	WEEK 4	UNSCHEDULED	WEEK 8	WEEK 12	WEEK 13	WEEK 24	WEEK 36	
					(b) (6)					
Amitiza	No	12 mcg BID	12 mcg BID	12 mcg BID	12 mcg BID	12 mcg BID	12 mcg BID	12 mcg BID	12 mcg BID	No
ALT (IU/L)[0-29]	75	87	274	63	59	51	111	66	483	331
AST (IU/L)[0-41]	48	56	86	48	46	47	45	67	521	210
GGT (IU/L)[0-65]	84		151	79					577	486
Direct Bilirubin (mg/dl)[0.0-0.4]									0.3	
Total Bilirubin (mg/dl)[0.1-1.2]									0.5	
LDL (IU/L)[100-250]									346	215
Alkaline Phosphatase (IU/L)[134-349]									799	670
INR									8 (verbal report)	

LFTs following Discontinuation of Lubiprostone

Parameter	(b) (6)		
Amitiza	No	No	No
ALT (IU/L) [0-29]	121	298	69
AST (IU/L) [0-41]	50	265	46
GGT (IU/L) [0-65]		292	103
LDL (IU/L) [100-250]		241	
Alkaline Phosphatase (IU/L) [134-349]	366	405	279
Total Bilirubin (mg/dl) [0.1-1.2]	0.3		0.2

Liver Biopsy Report

Biopsy Liver: (b) (6) The findings were largely cholestatic with damage to the intralobular bile ducts. Most of the duct injury was lymphocytic but in one septal tract there is a neutrophilic infiltrate suggesting a component of ascending cholangitis. Sections from the liver show a well preserved lobular architecture. Most portal tracts are slightly edematous with slight mixed inflammatory infiltrate comprised of lymphocytes with rare plasma cells and scattered eosinophils and neutrophils. Some tracts show a focal prominent ductular reaction often associated with neutrophils. One septal tract shows a slightly dilated interlobular bile duct with a neutrophilic cholangitis with concentric fibrosis. No interface activity is noted. There is no ductopenia or granulomas. The lobules are largely unremarkable except for rare foci of lobular inflammation. There is no steatosis. The trichome stain shows periportal fibrosis. The iron stain is negative. The reticulin and PASD stains support the interpretation. All special stains have working controls.

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/s/

ELIZABETH S HART
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