U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	021-908
Supplement #:	016 (SDN 0188 & SN 1511) pediatric supplement efficacy
Related IND #:	059,623
Product Name:	AMITIZA (lubiprostone, capsules 24 mcg twice daily)
Indication(s):	Pediatric functional constipation in patients aged 6-17 years
Applicant:	Sucampo Pharma Americas, Inc.
Dates:	Stamp date: 7/28/2017 PDUFA date: 4/28/2018
Review Priority:	Priority
Biometrics Division:	III
Statistical Reviewer:	Ling Lan, PhD
Concurring Reviewers:	George Kordzakhia, PhD. (Team Leader)
Medical Division:	DGIEP
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Keywords: Pediatric study, subgroup analyses, compliance, robustness of evidence, data quality, post-hoc analyses

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1 EXECUTIVE SUMMARY

Lubiprostone (AMITIZA) is a synthetic analogue of prostone compounds as a locally-acting chloride channel activator. It indicates for the treatment of pediatric functional constipation (PFC) in patients aged 6-17 years old. The sponsor is currently seeking indication in PFC among subjects of 10-17 years of age.

This statistical review focuses on a 12-week double-blinded randomized controlled Phase III study SAG/0211PFC-1131 (hereafter referred to as Study 1131). Study 1131 compared the overall spontaneous bowel movement (SBM) response rate in Weeks 1-12 between lubiprostone (LUB) arm and the placebo arm among PFC subjects aged 6 to 17 years with < 3 SBM/week at baseline. A total of 594 eligible subjects were enrolled from 96 study sites in the US, Canada and EU, 399 subjects were randomized to receive 12 weeks of LUB 12 or 24 mcg capsules dosed twice daily (BID) (based on subject body weight at baseline) and 195 subjects received placebo BID. The randomization was stratified by age (6 to 9 years, 10 to 13 years, and 14 to 17 years), gender and baseline SBM frequency group (<1.5 or ≥1.5) on a ratio of 2:1. The primary analysis used Cochran-Mantel-Haenzel (CMH) test stratified by baseline SBM frequency based on non-responder imputation data from the modified intent-to-treat (mITT) population.

The sponsor reported that subjects randomized to LUB had a numerically higher overall SBM response rate than those randomized to placebo (19% vs.14.4%) with treatment difference of 4.6% (95% confidence interval: -1.6% – 10.9%) and a p-value of 0.16. None of the key secondary endpoints achieved statistical significance based on the pre-specified hierarchical testing procedure in the mITT population.

Sponsor's post-hoc subgroup analysis of the primary endpoint in female subjects aged 10-17 years showed numerically higher overall SBM response rates in the LUB arm as compared to the placebo arm (difference of 9.8% and p-value of 0.06) after excluding subjects enrolled at study Sites 1064 and 1082. However, among female subjects of 6-9 years of age, the placebo arm had numerically 10.3% higher response rate than that in the LUB arm.

The reviewer identified the following statistical issues which reflected the inconsistencies between the submitted clinical study report (CSR) and the statistical analyses plan (SAP):

1. Based on the SAP, the definition of the overall SBM responder required, in particular, a patient to be a weekly responder for at least three out of the last four weeks of the double-blind treatment period (Weeks 9-12). The sponsor's derivation of the primary endpoint used at least 3 out of the last 4 weeks prior to the week at which patient dropped out. Based on this more liberal requirement, two patients (subject IDs (b) (6)) were classified as responders by the sponsor, although they did not meet the responder criteria specified in the SAP.
2. The sponsor used two binary variables, IVSBMGR1 and SBMBLGR1, to classify patients based on baseline SBM frequency (<1.5 or ≥1.5). Primary efficacy analysis results, reported in the CSR, used variable IVSBMGR1 with site entry errors which was confirmed by the sponsor in the IR response dated 12/9/2017. Based on variable

IVSBMGR1, 9 subjects were incorrectly assigned to the "≥1.5" baseline SBM group, although their baseline SBM frequency was <1.5; and 8 subjects were categorized as baseline SBM frequency "<1.5" when they reported ≥ 1.5 SBM/week at baseline. Variable SBMBLGR1 reported the correct baseline SBM group for all subjects.

3. Study 1131 was designed to support the original indication in PFC patients aged 6-17 years. After the data was unblinded, the sponsor proposed to focus on PFC patients of 10-17 years of age only based on post-hoc analyses by age groups in female subjects.
4. In 2016, the sponsor requested to exclude Sites 1064 and 1082 from the mITT population due to the issues with compliances in these two sites. The Division recommended efficacy analyses using both the mITT population and the mITT population excluding patients enrolled at study sites 1064 and 1082. This reviewer noticed that, age subgroup analyses in female subjects aged 10-17 years were not submitted in the mITT population (i.e. population including data from Sites 1064 and 1082).
5. The CSR reported two different numbers of completers. In their response to the information request the sponsor stated that there were two study completer definitions, one by the study investigators (resulted in 505 completers, Table 2 of the CSR) and one by the SAP (resulted in 444 completers, Page 5 of the CSR). The submission provided dropout reasons only for patients who were considered dropouts by site inspectors. For subjects who did not complete 12 weeks of treatment but were categorized as completers by the site inspector, the reason of early termination is unknown. Therefore, it is not feasible to summarize the dropout (missing data) pattern for Study 1131.

The agency determined multiple issues with the sponsor's submission and issued several IR's asking/requesting for additional analyses. The review clock was extended accordingly. The reviewer's analyses reported a non-significant primary efficacy endpoint with a treatment difference of 4.1% (95% CI: -2.0% – 10.4%; p-value: 0.22) in the mITT population based on dataset free of entry errors on baseline SBM frequency group and corrected primary responses.

In general, the pivotal efficacy study, Study 1131, did not demonstrate statistically significant treatment effect of the LUB for PFC patients aged 6-17 years per the pre-specified analyses on the primary endpoint, the overall SBM response, and key secondary endpoints in the mITT population. The post-hoc subgroup analyses in female subjects by age were not powered and did not demonstrate consistent numerical treatment difference across the age groups on overall SBM response across age groups. In conclusion, Study 1131 did not show statistically significant nor numerically consistent treatment effect of LUB as compared to the placebo in PFC subjects aged 6-17 years in terms of overall SBM responder rates. We conclude that the LUB (24 mcg BID) is non-effective for the treatment of PFC in pediatric population 6-17 years of age.

2 INTRODUCTION

2.1 Overview

Lubiprostone (AMITIZA) is a synthetic analogue of prostone compounds and functions as a locally-acting chloride channel activator. Lubiprostone (LUB, 24 mcg BID) was approved on January 31, 2006, for the treatment of chronic idiopathic constipation in adults, and on April 19, 2013, for opioid-induced constipation due to the usage of opioids for chronic, non-cancer pain. On April 29, 2008, LUB in a lower strength formulation (8 mcg BID) was approved as a treatment for irritable bowel syndrome with constipation in adult women.

In this pediatric supplement application, the sponsor intended to evaluate the effect of LUB in the treatment of pediatric functional constipation (PFC) in patients 6-17 years of age based on one pivotal Phase III placebo-controlled study SAG/0211PFC-1131, and supportive studies, including a long-term efficacy study SAG/0211PFC-11Sl (an extension to Study 1131), SCMP-0211-303, and SPI/0211SC-0641.

Study 1131 was completed in July 2016. After reviewing the study efficacy data, the sponsor decided to pursue indication in PFC among subjects aged 10-17 years.

The statistical efficacy review of this application focuses on Study 1131 only. A brief summary of Study 1131 is provided in Table 1 below.

Table 1 Overall summary of Study 1131

Phase and Design	Treatment Period	Efficacy Endpoints	Study Population
Phase III multicenter, double blinded, placebo-controlled randomized (2:1) clinical trial	12 weeks LUB (12 or 24 mcg capsule, BID):Placebo = (233:171):202	Primary: the overall spontaneous bowel movement (SBM) response rate 30 key secondary endpoints	PFC subjects aged ≥6 years to <18 years

2.2 Data Sources

Data sets for Study 1131 were submitted electronically. The full electronic path by the CDER EDR is: \\CDSESUB1\evsprod\NDA021908\0188\m5\datasets\sag-0211pfc-1131\analysis\adam\datasets.

The electronic data set (ADEFF) includes efficacy endpoints. However, several information requests were issued to clarify potential data quality issues.
Table 2 below lists the issued statistical related information requests (IRs) with Windows EDR paths for the responses.

Table 2 Related information requests to the sponsor and the responses

Issued	Responded	Issues	Path for responses
11/9/17	12/9/17	Major IR on the inconsistencies with the SAP, imputation method used for primary analyses, rules used to determine the primary endpoint and analyses on overall SBM changes from baseline	\\CDSESUB1\evsprod\NDA021908\0204
10/6/2017	10/13/2017	Which baseline SBM group variable contains site entry error, IVSBMGR1 or SBMBLGR1, for 17 subjects;	\\CDSESUB1\evsprod\NDA021908\0200
9/25/17	9/26/17	Analyses results on overall SBM response in both gender and across age groups (6-9 and 10-17; 6-11 and 12-17) in mITT and PP population.	\\CDSESUB1\evsprod\NDA021908\0196\
9/18/17	9/22/17	Reason caused differences in two variables recording baseline SBM, IVSBMGR1 and SBMBLGR1 for 17 subjects; Request the denominator definition used for the primary endpoint	\\CDSESUB1\evsprod\NDA021908\0191

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The primary efficacy dataset of Study 1131 is dataset ADEFF, which contains majority of information needed for the primary analyses. The reviewer identified the following data quality and analyses issues which resulted in a major amendment of this submission.

1. Based on the SAP, the definition of the overall SBM responder required, in particular, a patient to be a weekly responder for at least three out of the last four weeks of the double-blind treatment period (Weeks 9-12). The sponsor's derivation of the primary endpoint used at least 3 out of the last 4 weeks prior to the week at which patient dropped out. Based on this more liberal requirement, two patients (subject IDs (b) (6) were classified as responders by the sponsor, although they did not meet the responder criteria specified in the SAP.
2. The sponsor used two binary variables, IVSBMGR1 and SBMBLGR1, to classify patients based on baseline SBM frequency (<1.5 or ≥1.5). Primary efficacy analysis results, reported in the CSR, used variable IVSBMGR1 with site entry errors which was confirmed by the sponsor in the IR response dated 12/9/2017. Based on variable IVSBMGR1, 9 subjects were incorrectly assigned to the "≥1.5" baseline SBM group, although their baseline SBM frequency was <1.5; and 8 subjects were categorized as baseline SBM frequency "<1.5" when they reported ≥ 1.5 SBM/week at baseline. Variable SBMBLGR1 reported the correct baseline SBM group for all subjects.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 1131 is a randomized placebo-controlled double-blinded parallel group 12-week Phase III study. The primary objective is to compare the overall SBM response rate during Weeks 1-12 between the LUB arm and the placebo arm among PFC subjects aged 6 to 17 years. The SBM frequency was collected from parent reported daily diaries. A spontaneous BM is defined as any BM that did not occur within 24 hours after use of rescue medication. The overall SBM responder definition refers to Section 3.2.1.1 below.

Eligible subjects included PFC patients ≥6 years and <18 years of age with less than 3 SBMs per week during the screening period and at least one of the following for at least 25% of SBMs during each week of the screening period: modified Bristol Stool Scale Type 1 or 2; and/or some straining to extreme straining associated with SBMs.

Eligible subjects were randomized in a 2:1 ratio to receive LUB 12 or 24 mcg capsules dosed twice daily (BID) (based on subject body weight at baseline) or placebo BID. The randomization was stratified by age (6-9 years, 10-13 years, and 14-17 years), gender and baseline SBM frequency group (<1.5 or ≥1.5).

3.2.1.1 Primary endpoint

In 2013, the Division recommended to consider the overall spontaneous bowel movement (SBM) response rate as a primary efficacy endpoint, and to move, the overall change from baseline in SBM frequency, which was originally proposed by the sponsor as the primary endpoint, to the set of the key secondary endpoints.

An overall responder is defined as a subject who qualifies as a weekly responder for 9 out of 12 weeks during the treatment period, with durability demonstrated by at least 3 of the responder weeks occurring in the last 4 weeks of the treatment period.

A weekly responder is defined as a subject who has a frequency rate of ≥ 3 SBMs/week and an increase from baseline of ≥ 1 SBM/week for that week. Baseline is defined as the average rating during the 2-week period prior to randomization. A missing weekly responder status was imputed as non-responder for the primary analysis.

The weekly SBM frequency rate was calculated as 7 × number of SBMs/number of days observed. The number of days observed is the number of days with entries in the electronic diary during the week that the subject was actively enrolled in the study and taking study medication. If less than 4 days of data are available for a given week, then the data will be considered insufficient and the weekly SBM frequency rate will be considered missing for that week.

3.2.1.2 Secondary endpoints

A complete list of all secondary efficacy endpoints presented in the hierarchical order based on the sequential closed testing procedure (SCTP) is as follows. Note that overall changes from baseline in SBM Frequency was calculated as the difference between the overall weekly SBM frequency for all evaluable weeks during Weeks 1-12 and the baseline weekly SBM frequency.

1) Time-to-First SBM
2) Overall Change from Baseline in Straining Associated with SBMs
3) Overall Change from Baseline in Stool Consistency of SBMs
4) Time to First SBM within 24 Hours of First Study Medication
5) Time to First SBM within 48 Hours of First Study Medication
6) Overall Change from Baseline in Constipation Severity
7) Overall Change from Baseline in Abdominal Pain
8) Overall Changes from Baseline in SBM Frequency
9) Overall Change from Baseline in Painfulness of SBMs
10) Overall Treatment Effectiveness
11) Overall Investigator's Assessment of Treatment Effectiveness
12) Overall Treatment Response
13) Time to First SBM within 12 Hours of First Study Medication
14) Time to First SBM within 8 Hours of First Study Medication
15) Time to First SBM within 4 Hours of First Study Medication
16) Overall Change from Baseline in Production of Large Diameter Stool Frequency
17) Overall Frequency of Retentive Posturing Excessive Volitional Stool Retention
18) Overall Change from Baseline in PedsQLTM Total Score by Subject
19) Overall Change from Baseline in PedsQLTM Total Score by Parent/Guardian
20) Overall Change from Baseline in PGIC by Subject
21) Overall Change from Baseline in PGIC by Parent/Guardian
22) Overall Change from Baseline in Clinician Severity Rating Scales
23) Month 1 SBM Response Rate
24) Month 2 SBM Response Rate
25) Month 3 SBM Response Rate
26) Overall Rescue Medication Use
27) Overall Changes from Baseline in BM Frequency
28) Overall Change from Baseline in Incontinence Frequency
29) Overall Proportion of SBMs in Toilet
30) Overall Proportion of BMs in Toilet

3.2.2 Statistical Methodologies

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 LUB group on overall SBM response. The primary analysis was based on the modified

intention-to-treat (mITT) population which included all randomized subjects who took at least one dose of study medication and had at least one post-treatment-initiation efficacy assessment.

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

The key secondary endpoints analyses used the SCTP principle to account for inflation of the Type I error due to multiplicity. The SCTP structure is as follows. The statistical testing of the key secondary endpoints proceeded in a sequential step-down manner based on the sequential order listed in Section 3.2.1.2 of this review. If a statistically significant p-value was found ($P<0.05$), the statistical testing would continue until a non-significant p-value was found ($P\geq0.05$). Once a non-significant p-value occurred, all subsequent significance tests would be considered not statistically significant and exploratory.

Missing SBM data was defined as: if less than 4 days of data are available for a given week, then the data was considered insufficient and the weekly SBM rate was treated as missing for that week. For the primary efficacy analysis, non-responder imputation was used for missing weekly SBM frequency, weekly SBM response, and overall SBM response.

An alternative imputation for sensitivity analysis was the last observation carried forward (LOCF) for binary and continuous post-baseline efficacy variables. Only post-baseline values were carried forward up to each time point of evaluation for subjects who had missing assessments on weekly and monthly efficacy endpoints.

Statistical analyses of the primary endpoint were also performed for the following subgroups: gender (male, female), race (white, black, others), age group (6 to 9 years, 10 to 13 years, and 14 to 17 years), SBM at randomization (<1.5, ≥1.5), weight (<50 kg, ≥50 kg) and BMI (<25, ≥25).

3.2.3 Patient Disposition, Demographic, Baseline Characteristics

Study 1131 was a multicenter study consisting of 96 investigative sites in the United States, Canada, and Europe. There were 76 sites in the United States, 3 sites in Canada, and 17 in Europe.

A total of 606 subjects were randomized: 202 subjects to placebo and 404 subjects to LUB in total (233 to LUB BID 12 mcg:24 mcg = 233:171) in a 2:1 ratio. The mITT population included 594 subjects (LUB 12 mcg: n = 231, LUB 24 mcg: n = 168, and placebo: n = 195). A total of 444 subjects completed the study, of whom 147 were randomized to placebo and 297 were randomized to LUB (Table 4). Based on the SAP, subjects were considered completers if they had at least 84 days of the double-blind treatment. Note that the sponsor calculated and summarized the dropouts based on 505 completers determined by the site investigators in Table 3.

Table 3 Sponsor's summary of subject disposition in all randomized subjects

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

a. All subjects, including those whose dose was titrated at the end of Week 1, were summarized with the dose group to which they were assigned at randomization.
b. This category includes subjects discontinued from the study upon closure of Sites 1064 and 1082 by the Sponsor.
Source: Table 2 on Page 58 of Study 1131 CSR.
Reviewer's Remark: The sponsor calculated and summarized the dropouts based on 505 completers determined by the site investigators instead of the 444 completers defined by the pre-specified SAP.

Table 4 Reviewer's summary of subject disposition among all randomized subjects

n (%)	Placebo N=202	LUB 12 mcg N=233	LUB 24 mcg N=171	All LUB Groups N=404	Total N=606
Subjects randomized	202	233	171	404	606
Subjects completed	147 (72.8)	181 (77.7)	116 (67.8)	297 (73.5)	444 (73.3)
Subjects discontinued	55 (27.2)	52 (22.3)	55 (32.2)	107 (26.5)	162 (26.7)

The subject demographic and baseline characteristics were summarized in Table 5 for the mITT population. Majority of subjects were from US (87.7%) and Caucasian (77.2%). The distribution of gender, age groups (10-year cutoff or 12-year cutoff), mean BMI, baseline SBM groups, and history of constipation treatment were numerically similar in both treatment groups.

Table 5 Baseline demographics and characteristics in the mITT population

	Lubiprostone (n=399)	Placebo (n=195)
Demographics*		
Age in years	11.1±3.25	11.2±3.16
Age group (10-17 years)	257 (64.4)	129 (66.2)
Age group (12-17 years)	180 (45.1)	86 (44.1)
Female	216 (54.1)	106 (54.4)
Age group (10-17 years)	151 (69.9)	76 (71.7)
Age group (12-17 years)	112 (51.9)	55 (51.9)
White	308 (77.2)	138 (70.8)
Body weight group (>= 50 kg)	163 (40.9)	86 (44.1)
BMI	21.1±5.69	21.2±5.39
Country (US)	350 (87.7)	172 (88.2)
Baseline characteristics*		
SBM group (< 1.5)	171 (42.9)	90 (46.2)
SBM group at randomization (< 1.5)	175 (43.9)	87 (44.6)
History of Constipation Therapy	389 (97.5)	189 (96.9)
History of Failed Constipation Treatment	289 (72.4)	141 (72.3)
SBM frequency	1.40±0.83	1.42±0.85
BM frequency	1.72±0.87	1.72±1.02
Bowel Straining Associated with SBMs	2.54±0.87	2.49±1.08

* Mean±SD for continuous variables and n (%) for categorical variables
Source: Table 4, 14.1.5.1, 14.1.5.2 of Study 1131 CSR, verified by the reviewer.

3.2.4 Efficacy Results and Conclusions

This section reports results on the primary efficacy endpoint and one of the key secondary endpoints, overall change from baseline in SBM frequency. The latter was the primary endpoint in the initial submission but was moved to the key secondary endpoint based on the Division's recommendation.

Reviewer's Remark: On November 3, 2015 (Site 1064) and June 17, 2016 (Site 1082), the sponsor informed the FDA of early termination of the participation of two study sites (1064 and 1082) due to potential non-compliance of these sites with the investigational plan and applicable regulations. During the Type B pre-NDA meeting on 2/8/2017, the Division noted in the meeting minutes that "*The primary efficacy analysis should include patients enrolled at study sites 1064*

and 1082; however, sensitivity analyses based on the population excluding patients from these study sites should be submitted in the sNDA.

Upon submission of the sNDA, provide details regarding the types of site violations and subject level efficacy and safety data for review. For comparison, we recommend you conduct sensitivity analyses of the efficacy data which: a) include patients enrolled at these study sites, and b) exclude patients at these study sites. If the results of these analyses differ from the primary analysis, the interpretation of that discrepancy will be a review issue."

3.2.4.1 Primary endpoint

The sponsor's CSR reported that there were 19% overall SBM responders in the LUB arm and 14.4% overall SBM responders in the placebo arm with a treatment difference of 4.6% and a p-value of 0.16 as presented in Table 6. [Reviewer's Remark: Primary analysis was based on the non-responder imputation. Table 6 of the CSR refers to the non-responder imputation data as observed case data]. Sponsor's sensitivity analysis based on LOCF imputed dataset was consistent with primary analysis findings and showed statistically non-significant treatment difference of 3.1% between the LUB arm and the placebo arm (p-value 0.41; Table 6).

The statistical reviewer determined that, in the sponsor's analysis, 17 patients were incorrectly classified at baseline by the SBM frequency groups (<1.5 or ≥1.5 bowel movements per week) due to site entry errors. Also, responder status for subjects with IDs (b) (6) was incorrectly calculated. After recalculation of the responder status, the reviewer's analysis resulted in 18.5% overall SBM responder for the LUB arm and 14.4% for the placebo arm with 4.1% treatment difference and p-value of 0.22 (Table 7), based on the stratified CMH test with baseline SBM frequency classification free of entry errors (presented in Table 7).

Table 6 Sponsor's results on the overall SBM response rates [%(n/N)] in the mITT population

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

CMH=Cochran Mantel Haenzel; LOCF=last observation carried forward; mITT=modified Intent-to-treat; SBM=Spontaneous bowel movement.
a. p-Value from a CMH test stratified by SBM frequency at randomisation (<1.5 vs ≥1.5).
Overall responder: a subject who qualified as a weekly responder for 9 of 12 weeks during the treatment period with durability demonstrated by ≥3 of the responder weeks occurring during the last 4 weeks of the treatment period.
Weekly responder: a subject who has a frequency rate of ≥3 SBMs/week and an increase from baseline of ≥1 SBM/week for that week.
Baseline: the average rating during the 2-week period prior to randomisation.
Source: Table 5 on Page 65 of Study 1131 CSR (sag-0211pfc-1131-body.pdf).
Reviewer's Remark: In sponsor's analysis, 17 patients were incorrectly classified at baseline due to site entry errors, and subjects with IDs (b) (6) had incorrect responder status.

Table 7 Reviewer's results on the overall SBM response rates [%(n/N)] in the mITT population

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

* P-value based on a CMH test stratified by baseline SBM frequency (<1.5 vs ≥1.5)
Source: Reviewer's results

3.2.4.2 Key secondary endpoint: change from baseline in SBM frequency

Since primary endpoint was not statistically significant, none of the key secondary endpoints achieved statistical significance based on the pre-specified hierarchical testing procedure in the mITT population and in the mITT population excluding subjects enrolled at Sites 1064 and 1082 (Table A 2 and Table A 3). Also, the first in the testing hierarchy key secondary endpoint, time-to-first SBM, reported statistically non-significantly different median survival time (nominal p-value 0.10) comparing the LUB arm and the placebo arm in the mITT population.

This section focuses on one of the key secondary endpoints, overall change from baseline in SBM frequency, which is the original primary endpoint proposed by the sponsor during the IND phase of this application. In this exploratory analysis, the reviewer compares overall change from baseline in SBM between treatment arms using the statistical method for the primary endpoint: the CMH test stratified by one factor, the baseline SBM frequency group. The sponsor used two stratification factors, SBM group at randomization and pooled sites for the same comparison based on the SAP.

The overall change from baseline in SBM frequency (1.38±1.72 per week) is not significantly higher than that in the placebo arm (1.15±1.76 per week) with a nominal p-value of 0.06. The calculation of the change from baseline in overall SBM frequency used baseline SBM frequency and the overall SBM frequency during Weeks 1-12, Weeks 1-4 and Week 4 in the efficacy dataset. The reviewer conducted van Elteren test stratified by baseline SBM frequency (<1.5 or ≥1.5) to be consistent with analyses setup for the current primary endpoint.

Table 8 Overall change from baseline in SBM frequency in mITT population

	Lubiprostone (12 or 24 mcg)	Placebo	Difference: (mean)	P-value*
Weeks 1-12	N=391	N=194		
	1.38±1.72	1.15±1.76	0.23	0.06 (0.05**)
Weeks 1-4	N=391	N=193		
	1.35±1.84	1.17±1.91	0.18	0.10 (0.08**)
Week 4	N=370	N=183		
	1.54±2.46	1.25±2.47	0.29	0.04 (0.06**)

* P-value are based on van Elteren test stratified by SBM frequency at baseline (<1.5 or ≥1.5)
** van Elteren test stratified by baseline SBM frequency (<1.5 or ≥1.5) and an additional stratification of pooled site reported in Table 14.2.73.1.1 of the sponsor's sag-0211pfc-1131-tables-14-1-3-1-14-2-80.pdf in the IR response dated 12/08/2017
Source: Reviewer's analyses

3.2.4.3 Conclusion

The pivotal efficacy study, Study 1131, did not demonstrate statistically significant treatment effect of the LUB arm compared with placebo arm in PFC patient population aged 6-17 years per the pre-specified analyses on the primary endpoint and key secondary endpoints in the mITT population.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section summarizes both sponsor's and reviewer's subgroup analyses results for the primary endpoint, overall SBM frequency. [Reviewer's Remark: In the sponsor's analysis, two subjects, IDs (b) (6), had incorrectly assigned responder status.]

In addition to the subgroup analyses by gender, race, and age, the sponsor submitted post-hoc analysis results in female subjects aged 10-17 years and proposed to include an indication for the age subgroup of 10-17 years in their prescribing information. These sponsor's post-hoc subgroup analyses were not pre-specified or adjusted for multiplicity and, thus, are considered purely exploratory. The age subgroup analysis, conducted by the reviewer, focused on age subgroups of 6-11 years and 12-19 years which were considered more clinically relevant by the DGIEP.

4.1 Gender, Race and Age

In the SAP, the sponsor planned the subgroup analyses by age (6-9 years, 10-13 years, and 14-17 years), gender and race (white, black, and other). The sponsor's submission did not include efficacy results by region.

The subgroup analysis results are presented in Table 9 for the mITT population. In most of the investigated subgroups, overall SBM response rate was numerically larger in the LUB arm with the exception of the black subgroup and the age subgroup of 6-9 years.

Table 9 Sponsor's subgroup analyses by age, gender and race for overall SBM response rates in the mITT population

	Lubiprostone (12 or 24 mcg)	Placebo	Difference: L-P (%)
Age in years	**N = 399**	**N = 195**	
6-9	22.5 (32/142)	22.7 (15/66)	-0.2
10-13	16.3 (25/153)	6.4 (5/78)	9.9
14-17	18.3 (19/104)	15.7 (8/51)	2.6
Gender			
Female	20.8 (45/216)	16.0 (17/106)	4.8
Male	16.9 (31/183)	12.4 (11/89)	4.6
Race			
White	20.5 (63/308)	15.9(22/138)	4.5
Black	11.9 (8/67)	15.4 (6/39)	-3.5
Other	20.8(5/24)	0(0/18)	20.8

Note this table reported %(n/N).
Source: Table 14.2.25.1.1 of the sponsor's sag-0211pfc-1131-section14.pdf verified by the reviewer
Reviewer's Remark: In the sponsor's analysis, two subjects, IDs (b) (6), had incorrect responder status.

The reviewer conducted subgroup analyses by age (12-year cutoff), gender, race, and region (for the results please refer to Table 10 below). The results were generally consistent with the sponsor's. In most of the subgroups numerical trend was in favor of the LUB with the exception of black subgroup and non-US regional subgroup.

Table 10 Reviewer's subgroup analyses by age, gender, race and region for overall SBM response rate in the mITT population

	Lubiprostone (12 or 24 mcg) N = 399	Placebo N = 195	Difference: L-P (%)
Age in years			
6-11	20.1(44/219)	15.6(17/109)	4.5
12-17	16.7(30/180)	12.8(11/86)	3.9
Gender			
Female	19.9(43/216)	16(17/106)	3.9
Male	16.9(31/183)	12.4(11/89)	4.5
Race			
White	19.8(61/308)	15.9(22/138)	3.9
Black	11.9(8/67)	15.4 (6/39)	-3.5
Other	20.8(5/24)	0(0/18)	20.8
Region			
US	19.1(67/350)	14(24/172)	5.1
Non-US	14.3(7/49)	17.4(4/23)	-3.1

Note this table reported %(n/N).
Source: Reviewer's results based on the corrected overall SBM response

4.2 Post-hoc Age Subgroup in Female Subjects

After reviewing Study 1311 efficacy data, the sponsor proposed indication in the age subgroup of 10-17 years. The supporting evidence relied on post-hoc subgroup analysis results in female subjects aged 10-17 years.

The sponsor conducted analyses in various study population: mITT population excluding sites 1064 and 1082; mITT population excluding non-US region and sites 1064 and 1082 and *etc* (Table A 4). The observed treatment difference in this subgroup was larger than in the overall population (for the overall see Table 7). However, exploratory nature of the analyses does not allow to make any statistical inference for this subgroup. In addition, although female subjects aged 10-17 years receiving LUB showed numerically higher overall SBM response rate, LUB was numerically inferior to Placebo in female subjects 6-9 years of age (Table 11). The statistical reviewer analyzed age subgroups of 6-11 years and 12-19 years in the female subpopulation. These age subgroups were considered more clinically relevant by the DGIEP. Based on the reviewer's results below, inconsistent treatment differences between treatment arms on overall SBM response are observed across different age groups.

Table 11 Post-hoc subgroup analyses in female subjects by age for overall SBM response rate

	Lubiprostone (12 or 24 mcg) N = 399	Placebo N = 195	Difference: L-P (%)	P-value
Sponsor's results*				
mITT population excluding Sites 1064 and 1082				
6-9 years	24.2(15/62)	34.5(10/29)	-10.3	0.30
10-17 years	19.2(28/146)	9.3(7/75)	9.8	0.06
mITT population excluding non-US region and Sites 1064 and 1082*				
6-9 years	21.8(12/55)	35.7(10/28)	-13.9	0.15
10-17 years	20.3(26/128)	6.7(4/60)	13.7	0.02
Reviewer's results**				
6-11 years	22.1(23/104)	21.6(11/51)	0.5	0.94
12-17 years	17.9(20/112)	10.9(6/55)	7.0	0.19

* P-value based on a CMH test stratified by SBM frequency at randomization (<1.5 vs ≥1.5). In sponsor's analysis, 17 patients were incorrectly classified at baseline due to site entry errors, and subjects with IDs (b) (6) had incorrect responder status.
** P-value based on a CMH test stratified by baseline SBM frequency (<1.5 vs ≥1.5).

4.3 Conclusion

The subgroup analyses by age (6-11 years, 12-17 years), gender, race and region (US, non-US) showed a numerical trend in favor of the LUB in comparison with placebo for most of the subgroups with the exception of the black subgroup and non-US subgroup.

The post-hoc subgroup analyses in female subjects by age were not pre-specified or adjusted for multiplicity and, thus, are considered purely exploratory. In the female subpopulation, in the age subgroup 12-17 years the observed treatment difference was larger than in 6-11 years.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The reviewer identified the following statistical issues which demonstrated inconsistencies between the CSR and the SAP.

1. Based on the SAP, the definition of the overall SBM responder required, in particular, a patient to be a weekly responder for at least three out of the last four weeks of the double-blind treatment period (Weeks 9-12). The sponsor's derivation of the primary endpoint used at least 3 out of the last 4 weeks prior to the week at which patient dropped out. Based on this more liberal requirement, two patients (subject IDs (b) (6)) were classified as responders by the sponsor, although they did not meet the responder criteria specified in the SAP.
2. The sponsor used two binary variables, IVSBMGR1 and SBMBLGR1, to classify patients based on baseline SBM frequency (<1.5 or ≥1.5). Primary efficacy analysis results, reported in the CSR, used variable IVSBMGR1 with site entry errors which was confirmed by the sponsor in the IR response dated 12/9/2017. Based on variable

IVSBMGR1, 9 subjects were incorrectly assigned to the "≥1.5" baseline SBM group, although their baseline SBM frequency was <1.5; and 8 subjects were categorized as baseline SBM frequency "<1.5" when they reported ≥ 1.5 SBM/week at baseline. Variable SBMBLGR1 reported the correct baseline SBM group for all subjects.

3. Study 1131 was designed to support the original indication in PFC patients aged 6-17 years. After the data was unblinded, the sponsor proposed to focus on PFC patients of 10-17 years of age only based on post-hoc analyses by age groups in female subjects.
4. In 2016, the sponsor requested to exclude Sites 1064 and 1082 from the mITT population due to the issues with compliances in these two sites. The Division recommended efficacy analyses using both the mITT population and the mITT population excluding patients enrolled at study sites 1064 and 1082. This reviewer noticed that, age subgroup analyses in female subjects aged 10-17 years were not submitted in the mITT population (i.e. population including data from Sites 1064 and 1082).
5. The CSR reported two different numbers of completers. In their response to the information request the sponsor stated that there were two study completer definitions, one by the study investigators (resulted in 505 completers, Table 2 of the CSR) and one by the SAP (resulted in 444 completers, Page 5 of the CSR). The submission provided dropout reasons only for patients who were considered dropouts by site inspectors. For subjects who did not complete 12 weeks of treatment but were categorized as completers by the site inspector, the reason of early termination is unknown. Therefore, it is not feasible to summarize the dropout (missing data) pattern for Study 1131.

5.2 Collective Evidence

The sponsor reported that the primary endpoint (overall SBM response) was not met in the primary population for efficacy analysis (mITT), while there was a 4.6% greater response rate in the total LUB group (19.0%) compared with the placebo group (14.4%) with a p-value of 0.16 (Table 6). The sensitivity analysis on the primary endpoint based on LOCF imputed dataset showed similar efficacy results as the primary analyses with a treatment difference of 3.1% between the LUB arm and the placebo arm (p-value 0.41; Table 6).

This review has identified several statistical issues described in Section 5.1. Based on dataset free of site entry error in baseline SBM groups for 17 subjects and the revised responder status for subjects with IDs (b) (6), the reviewer's calculation resulted in a 4.1% treatment difference (95% CI: -0.02 – 0.10) in the overall SBM response between the LUB arm (18.5%) and the placebo arm (14.4%) with a p-value of 0.22.

Since primary efficacy endpoint did not achieve statistical significance, none of the key secondary endpoints could be formally tested based on the pre-specified hierarchical testing procedure. Aslo, time-to-first SBM, the first key secondary endpoint in the testing hierarchy, was not nominally significant at 0.05 level (p-value 0.10 in the mITT population).

Most of the pre-specified subgroup analyses by age (6-9 years, 10-13 years and 14-17 years), gender, race (white, black and other) and region (US and non-US) for the primary endpoint showed overall SBM response rate was numerically larger in the LUB arm with the exception of the black subgroup and the age subgroup of 6-9 years. The sponsor conducted post-hoc subgroup analyses by age in various female study populations but there was no numerically consistent treatment effect on the primary efficacy endpoint comparing the LUB arm to the placebo arm across age groups with inferior treatment effect in the LUB arm among subjects 6-9 years of age (Table A 4). For example, the sponsor's submission emphasized on the post-hoc subgroup analyses results in female subjects aged 10-17 years (treatment difference 9.8% in favor of LUB; p-value 0.06) in the mITT population excluding sites 1064 and 1082. However, in the 6-9 years subgroup, the treatment difference was -10.3% in favor of Placebo in the same population. The reviewer's analyses confirmed there was no consistently higher overall SBM response rate in female age subgroups (12-year cutoff) for the LUB arm compared with the placebo arm in the mITT population.

5.3 Conclusions and Recommendations

The single Phase 3 efficacy study, Study 1131, did not demonstrate statistically significant treatment effect of the LUB for PFC patients aged 6-17 years per the pre-specified analyses on the primary endpoint, the overall SBM response, and key secondary endpoints in the mITT population.

The post-hoc subgroup analyses in female subjects by age did not show consistent numerical treatment difference across the age groups on overall SBM response. We conclude that the LUB (24 mcg BID) is non-effective for the treatment of PFC in pediatric population 6-17 years of age.

APPENDIX

Table A 1 Summary of studies submitted for sNDA 21-908

Trial ID Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings (Sponsor)
Study 1131 MC, R, DB, PG, 12-week PC trial	lubiprostone (12 or 24 mcg capsules twice daily (BID) based on baseline weight. N randomized (2:1): (LUB 12 mcg or LUB 24 mcg):Placebo = (233:171):202 N mITT: LUB:Placebo = 399:195 N completed: LUB:Placebo = 297:147	Primary: the overall (spontaneous bowel movement) SBM response rate of the LUB arm compared with the placebo arm in subjects with PFC aged ≥6 years to <18 years in the mITT Population. Analysis: Cochran-Mantel-Haenzel (CMH) test stratified by baseline SBM frequency (<1.5 or ≥1.5). Subgroup analyses by gender in mITT1 population excluding Site 1064 and 1082 from the mITT population.	The primary endpoint, overall SBM response rate, was not statistically significant in the mITT population, with a difference of 4.9% (95% CI: (-1.56%, 10.94%); p=0.1609) between the l LUB arm (19.0%) and the placebo arm (14.4%). Subgroup analysis in female subjects of the age of 10-17 years (in the mITT1 population) found numerically larger effect in overall SBM responders with p-value of 0.06 in favor of the LUB arm. However, it was not the case for male mITT1 subgroup (p-value: 0.7115).
Study 11S1 MC, open-label 36-week safety extension study	LUB (oral 12 or 24 mcg BID)/N enrolled = 419	Overall change in SBM frequency from baseline of Study 1131 in subjects who had completed Study 1131.	A favorable difference of 1.47 (95% CI, (1.27-1.66)) in LUB treated subjects over Study 1131 baseline values in overall change in SBM frequency.
Study 303 MC, open-label, 6-month	LUB (oral 12 or 24 mcg ID)/N=87	No formal efficacy assessments conducted	
Study 0641 MC, 4-week Phase 4 open-label study	LUB (12 mcg QD, 24 mcg or 48 mcg BID) /N=127	Change in the SBM frequency during Week 1 from baseline/Wilcoxon signed-rank test	The mean SBM frequency for patients overall at Week 1 was significantly higher than at baseline (3.11 vs. 1.48, respectively; p<0.0001).

Table A 2 Summary of key secondary efficacy endpoints in the mITT population

Table 14.2.24
Summary of Key Secondary Efficacy Endpoints
mITT Population [1]

Key Secondary Efficacy Endpoint	P-Value
Time-to-First SBM	0.1014 [4]
Overall Change from Baseline in Bowel Straining Associated with SBMs	0.0178* [3]
Overall Change from Baseline in Stool Consistency Associated with SBMs	0.0501 [3]
Time to First SBM Within 24 Hours of First Study Medication	0.0216* [2]
Time to First SBM Within 48 Hours of First Study Medication	0.1365 [2]
Overall Change from Baseline in Constipation Severity	0.3756 [3]
Overall Change from Baseline in Abdominal Pain	0.2079 [3]
Overall Change from Baseline in SBM Frequency	0.0496* [3]
Overall Change from Baseline in Painfulness of SBMs	0.0458* [3]
Overall Treatment Effectiveness	0.0729 [3]
Overall Investigator Assessment of Treatment Effectiveness	0.0014* [3]
Overall Treatment Response	0.3966 [2]
Time to First SBM Within 12 Hours of First Study Medication	0.0271* [2]
Time to First SBM Within 8 Hours of First Study Medication	0.0114* [2]
Time to First SBM Within 4 Hours of First Study Medication	0.0275* [2]
Overall Change from Baseline in Production of Large Diameter Stool Frequency	0.8914 [3]
Overall Frequency of Retentive Posturing Excessive Volitional Stool Retention	0.5790 [3]
Overall Change from Baseline in PedsQL™ Total Score by Subject	0.6041 [3]
Overall Change from Baseline in PedsQL™ Total Score by Parents/Guardian	0.4583 [3]
Overall Change from Baseline in PGIC by Subject	0.1925 [3]
Overall Change from Baseline in PGIC by Parents/Guardian	0.0111* [3]
Overall Change from Baseline in Clinician Severity Rating	0.2894 [3]
Month 1 SBM Response Rate	0.3109 [2]
Month 2 SBM Response Rate	0.0810 [2]
Month 3 SBM Response Rate	0.0938 [2]
Overall Rescue Medication Use	0.5178 [5]
Overall Change from Baseline in BM Frequency	0.1052 [3]
Overall Change from Baseline in Incontinence Frequency	0.4086 [3]
Overall Change from Baseline in Proportion of SBMs in Toilet	0.9052 [3]
Overall Change from Baseline in Proportion of BMs in Toilet	0.7497 [3]

[1] All subjects, except for those whose dose was titrated at the end of Week 1, are summarized with the dose group to which they were assigned at randomization.
[2] Proportions are compared using a likelihood-ratio chi-square test.
[3] P-value is from a van Elteren test stratified by randomized SBM frequency (< 1.5 or >= 1.5) and pooled site.
[4] Median times are compared using the Cox proportional hazards regression model.
[5] P-value is based on a CMH test stratified by randomization SBM frequency (< 1.5 or >= 1.5).
Program:...\program\t_second_eff.sas Date: 18JAN2017

Source: Table 14.2.24 of the sponsor's sag-0211pfc-1131-section14.pdf

Table A 3 Summary of key secondary efficacy endpoints in the mITT population excluding Sites 1064 and 1082

Table 14.2.49
Summary of Key Secondary Efficacy Endpoints
mITT Population [1] Excluding Sites 1064 and 1082

Key Secondary Efficacy Endpoint	P-Value
Time-to-First SBM	0.0924 [4]
Overall Change from Baseline in Bowel Straining Associated with SBMs	0.0184* [3]
Overall Change from Baseline in Stool Consistency Associated with SBMs	0.0350* [3]
Time to First SBM Within 24 Hours of First Study Medication	0.0237* [2]
Time to First SBM Within 48 Hours of First Study Medication	0.1461 [2]
Overall Change from Baseline in Constipation Severity	0.4145 [3]
Overall Change from Baseline in Abdominal Pain	0.2403 [3]
Overall Change from Baseline in SBM Frequency	0.0470* [3]
Overall Change from Baseline in Painfulness of SBMs	0.0349* [3]
Overall Treatment Effectiveness	0.0604 [3]
Overall Investigator Assessment of Treatment Effectiveness	0.0010* [3]
Overall Treatment Response	0.5289 [2]
Time to First SBM Within 12 Hours of First Study Medication	0.0436* [2]
Time to First SBM Within 8 Hours of First Study Medication	0.0197* [2]
Time to First SBM Within 4 Hours of First Study Medication	0.0505 [2]
Overall Change from Baseline in Production of Large Diameter Stool Frequency	0.8254 [3]
Overall Frequency of Retentive Posturing Excessive Volitional Stool Retention	0.3195 [3]
Overall Change from Baseline in PedsQL™ Total Score by Subject	0.6382 [3]
Overall Change from Baseline in PedsQL™ Total Score by Parents/Guardian	0.5555 [3]
Overall Change from Baseline in PGIC by Subject	0.1752 [3]
Overall Change from Baseline in PGIC by Parents/Guardian	0.0071* [3]
Overall Change from Baseline in Clinician Severity Rating	0.1761 [3]
Month 1 SBM Response Rate	0.3372 [2]
Month 2 SBM Response Rate	0.1338 [2]
Month 3 SBM Response Rate	0.1370 [2]
Overall Rescue Medication Use	0.5264 [5]
Overall Change from Baseline in BM Frequency	0.1067 [3]
Overall Change from Baseline in Incontinence Frequency	0.3161 [3]
Overall Change from Baseline in Proportion of SBMs in Toilet	0.8898 [3]
Overall Change from Baseline in Proportion of BMs in Toilet	0.9190 [3]

[1] All subjects, except for those whose dose was titrated at the end of Week 1, are summarized with the dose group to which they were assigned at randomization.
[2] Proportions are compared using a likelihood-ratio chi-square test.
[3] P-value is from a van Elteren test stratified by randomized SBM frequency (< 1.5 or >= 1.5) and pooled site.
[4] Median times are compared using the Cox proportional hazards regression model.
[5] P-value is based on a CMH test stratified by randomization SBM frequency (< 1.5 or >= 1.5).
Program:...\program\t_second_eff.sas Date: 18JAN2017

Source: Table 14.2.29 of the sponsor's sag-0211pfc-1131-section14.pdf

Table A 4 Sponsor's subgroup analyses by age and gender on overall SBM response in various study populations except the mITT population

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

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

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

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

Source: Table 10 on Page 72 of the Study 1131 CSR.

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GEORGE KORDZAKHIA
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