CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-908s005

<u>STATISTICAL REVIEW(S)</u>

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-908/S-005

Drug Name: Amitiza (lubiprostone) capsules

Indication(s):   Treatment of irritable bowel syndrome with constipation

Applicant: Sucampo Pharmaceuticals, Inc.

Date(s):   eCTD dated June 30, 2007; PDUFA April 29, 2008

Review Priority: Standard

Biometrics Division: Division of Biometrics III

Statistical Reviewer: Milton C. Fan, Ph.D. (DB III)

Concurring Reviewers: Mike Welch, Ph.D. (DB III)

Medical Division: Gastroenterology Products (HFD-180)

Clinical Team: Helen Sile, M.D., Ruyi He, M.D. (TL) (HFD-180)

Project Manager: Thomas Moreno (HFD-180)

Keywords: clinical study, placebo-controlled, LOCF

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Lubiprostone (Capsules) was approved January 31, 2006 for the treatment of chronic idiopathic constipation (CIC) in the adult population with recommended dosage of 24 mcg twice daily (BID). This efficacy supplement has been submitted for the additional indication of Irritable Bowel Syndrome with Constipation (IBS-C) using a new strength of the drug product (8 mcg BID).

The sponsor has submitted two pivotal studies (SIB-04131 and SIB-04132) to support the claim. Both studies showed that lubiprostone was superior to placebo for the pre-specified primary efficacy endpoint based on monthly responder for at least two of the three months of study. However, the treatment differences were small at 6.0% and 6.4%, respectively. Moreover, in both studies, superiority was not demonstrated for all secondary endpoints.

Several post-hoc efficacy analyses were conducted by this reviewer by varying the criteria that defined patient response. These sensitivity analyses showed that based on a more stringent definition of responder (monthly responder for all 3 months) lubiprostone was superior to the placebo in one study with a treatment difference of only 4.3%. Based on a less stringent responder definition suggested by the clinical team as more consistent with that used in other IBS-C trials, treatment differences did not reach statistical significance in either study.

From a statistical perspective, the sponsor has provided two adequate and well-controlled studies which show the superiority of lubiprostone to placebo for the treatment of IBS-C; however, the treatment differences are modest and may not be clinically substantial.

1.2 Brief Overview of Clinical Studies

1.2.1 Study SPI/0211SIB-0431

This study was a 12-week, phase III, double-blind, multi-center, randomized efficacy and safety study of oral lubiprostone for the treatment of constipation-predominant irritable bowel syndrome followed by a 4-week blinded randomized withdrawal of lubiprostone.

The primary objective of this study was to demonstrate the efficacy and safety of 12-week administration of oral lubiprostone (8 μg BID) when compared to placebo during Treatment Phase I for the treatment of IBS-C.

The primary efficacy endpoint was the overall responder status. Responder statuses at Month 1, Month 2, and Month 3 were considered key secondary endpoints. The primary and key secondary endpoints were calculated from the weekly assessments of symptom relief (7-point balanced scale) gathered as part of the subject's electronic, diary responses.

The secondary objective of this study was to examine a "rebound effect" or loss of efficacy associated with the withdrawal of lubiprostone treatment. To this end, a 4-week randomized withdrawal period (Treatment Phase II) followed Treatment Phase I in which some subjects who were originally randomized to lubiprostone were switched to placebo while the remaining lubiprostone subjects remained on lubiprostone.

Eligible subjects were assigned in a 2:1 ratio to either lubiprostone or placebo during Treatment Phase I. During the Treatment Phase II, placebo subjects would continue to receive placebo. Subjects assigned to lubiprostone were pre-randomized in a 1:1 ratio to receive either lubiprostone or placebo.

Upon the successful completion of this study, subjects had option of enrolling in a long-term open label study. Eligible subjects were able to received 8 μg lubiprostone BID in the extension study.

At the Randomization Visit (Visit 2), subjects meeting all the inclusion and exclusion criteria were randomized into the study.

Office visits occurred at Week 4 (Visit 4), Week 8 (Visit 5), and Week 12 (Visit 6). At Weeks 4, 8, and 12, the electronic diaries were reviewed for completeness and re-dispensed to the subject along with additional study medication. At Week 12, the subject was dispensed new study medication.

An IBS Quality of Life (QOL) questionnaire was given the subject at the Randomization, Week 4, Week 12, and Week 16 Visits. The questionnaire was designed with 34 questions with five possible responses. These QOL results are considered exploratory by the Clinical Team.

Treatment Phase II was used to evaluate a rebound effect of withdrawal of lubiprostone. At Visit 7/Week 16 (Day 112 ±3), a final office visit was made to assess any changes in the subject's condition. It should be noted that patients were not re-randomized at the beginning of Treatment Phase II, and results from this part of the study are considered to be exploratory.

Use of other constipation or IBS treatment medications was not allowed during the baseline, treatment, or withdrawal periods. However, after 3 consecutive days of not having a spontaneous bowel movement (SBM), if the subject felt the need for relief, the investigator could prescribe a 10 mg bisacodyl suppository (Dulcola suppository). If that was not effective, a Fleet enema could then be prescribed.

The subject answered questions about their IBS including an evaluation of abdominal discomfort/pain, bowel movement frequency rates, evaluation of stool consistency, evaluation of bowel straining, evaluation of constipation severity, evaluation of abdominal bloating, and evaluation of symptom relief. This information was assessed as

part of the daily evaluations recorded in the electronic diary, a palm-held device with a visual display.

1.2.2   Study SPI/0211SIB-0432

The study design for this study was similar to that for Study B-0431 with the exception that this study did not have a 4-week randomized withdrawal period followed treatment phase.

1.3 STATISTICAL ISSUES AND FINDING

Study SIB-0431 showed that lubiprostone was statistically significant compared to placebo group in terms of the primary efficacy endpoint, overall responder rate without LOCF during Treatment Phase I. However, a worst-case analysis (missing response set to failure) did not show statistical significance (p=0.063) which indicates the results are sensitive to this imputation assumption. The treatment difference was modest at about 6%. Furthermore, the superiority was not shown for any secondary efficacy endpoints with exception of monthly responder rate at Month 2.

The efficacy results from study SIB-04131 were replicated in study SIB-0432 for the primary efficacy endpoint. However, the treatment difference was also modest at 6.4%. Furthermore, superiority was not shown for all secondary efficacy endpoints.

This reviewer performed an efficacy analysis using a more clinically meaningful but more stringent efficacy parameter, defining responder as a patient who was a monthly responder for all 3 months and who did not use rescue medication during or within 24 hours prior to the given week, and who did not drop out during the study due to lack of efficacy. In this analysis, patients with missing outcomes were set to as no response. Based on this post-hoc analysis, only study SIB-0432 showed that lubiprostone was superior to the placebo with treatment differences of about 4.3%., which may not be considered clinically meaningful.

Per request from the clinical team, I performed a statistical analysis for "new" monthly responder using a less stringent responder definition and one more consistent with other clinical trials for IBS-C. A subject was considered a "new" monthly responder if symptoms were rated as "significantly relieved" or "moderately relieved" for at least 50% of weeks within a month or at least "a little bit relieved" for all 4 weeks within a month. Results from this statistical analyses showed that treatment differences failed to reach statistical significance for this overall responder rate for both studies. Treatment differences were 7.5% for Study SIB-04131 and 2.4% for Study SIB-04132.

Per this reviewer's request, the sponsor performed a statistical analysis of the number of months that a subject was considered a month responder. In both studies, the treatment difference in terms of number of months that a subject was considered a month responder was a modest 0.18 months or about 5 days.

Per this reviewer's request, the sponsor performed a statistical analysis of weekly responder rates by week. A weekly responder was any week with a response of moderately relieved or significant relieved. No data imputation was used.

It was shown that treatment difference in weekly responder rates reached statistical significance level (p<0.05) only at Week 4 and Week 6 for Study SIB-0431 and at Week 2 and Week 5 for Study SIB-0432. No adjustments for multiplicity were applied.

There were inconsistent results in treatment difference in weekly responder rates between the two studies.

Per this reviewer's request, the sponsor performed three responder analyses for spontaneous bowel movements (SBMs). The responder analyses were as follows:

• a responder is defined as subjects that achieve an average 1 SBM per week increase over baseline.
• a responder is defined as subjects that achieve an average 3 SBMs per week increase over baseline.
• a responder is defined as subjects having an average increase of 1 SBM per week and at least 3 SBMs per week.

These analyses indicated that treatment differences were not statistically significant for all three responder analyses for both studies. The treatment differences were modest, ranging from 1.6% to 5.6% for Study SIB-0431 and 1.6% to 5.2% for Study SIB-0432.

Furthermore, superiority was not shown for any secondary efficacy endpoints for both studies with exception for monthly responder rate at Month 2 for study SIB-0431.

Although both studies showed that the lubiprostone was superior to the placebo for the pre-specified primary efficacy endpoint, the treatment differences were modest with 6.0% and 6.4%, respectively. For a more stringent efficacy endpoint (monthly responder for all 3 months), the reviewer's post-hoc analysis revealed that the lubiprostone was superior to the placebo with treatment differences of about 4.3% for study SIB-0432. For the "new" defined monthly responder which was less stringent than pre-specified monthly responder, the treatment differences failed to reach statistical significance for overall responder rate for both studies.

2. INTRODUCTION

2.1 Overview

The original application for Lubiprostone (Capsules) was approved January 31, 2006 for the treatment of chronic idiopathic constipation (CIC) in the adult population with recommended dosage of 24 mcg twice daily (BID).

This efficacy supplement has been submitted for the additional indication of Irritable Bowel Syndrome with Constipation (IBS-C) using a new strength of the drug product (8 mcg BID).

2.2 Data Sources

The sponsor has submitted three, controlled clinical studies (SIB-0221, SIB-0431, and SIB-0432) and one long-term extension study (SIB-05S1) for the new indication. Studies SIB-0431 and SIB-0432 were carried out using an identical study design, with the exception that study SIB-0431 was followed by a 4-week blinded randomized withdrawal period. These two trials are considered the pivotal studies for this submission. Study SIB-0221 was Phase IIb dose-ranging study that utilized a similar study design and will not be discussed in this review.

Protocols for these two pivotal studies are as follows:

Protocol SPI/0211SIB-0431 entitled: "A 12-week, Multicenter, Double-Blind, Randomized Efficacy and Safety Study of Lubiprostone for the Treatment of Constipation-Predominant Irritable Bowel Syndrome.

Protocol SPI/0211SIB-0432 entitled: "A 12-week, Multicenter, Double-Blind, Randomized Efficacy and Safety Study of Lubiprostone in Subjects with Constipation-Predominant Irritable Bowel Syndrome.

These two study protocols had received statistical reviews and were documented in DFS on June 6, 2005 under IND 66,529.

This submission was submitted in electronic format (eCTD) dated June 30, 2007 located at: \\Cdsesub1\evsprod\NDA021908\0029.

Additional documents reviewed include the sponsor's responses to this reviewer's several statistical information requests. These sponsor documents are dated October 9, 2007, December 3, 2007, and February 7, 2008 and are located at: \\Cdsesub1\evsprod\NDA021908.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study SPI/0211SIB-0431

3.1.1.1 Study Design

This study was a 12-week, phase III, double-blind, multi-center, randomized efficacy and safety study of oral lubiprostone for the treatment of constipation-predominant irritable bowel syndrome followed by a 4-week blinded randomized withdrawal of lubiprostone.

The treatments were divided into two phases. The first phase covered the 12-week treatment period. The second phase covered the 4-week treatment period involving the randomized withdrawal.

The primary objective of this study was to demonstrate the efficacy and safety of 12-week administration of oral lubiprostone (8 μg BID) when compared to placebo during Treatment Phase I for the treatment of IBS-C.

The secondary objective of this study was to examine the rebound phenomenon associated with the withdrawal of lubiprostone treatment. To this end, a 4-week randomized withdrawal period (Treatment Phase II) followed Treatment Phase I in which some subjects who were originally randomized to lubiprostone were switched to placebo while the remaining lubiprostone subjects remained on lubiprostone.

Eligible subjects were assigned in a 2:1 ratio to either lubiprostone or placebo during Treatment Phase I. During the Treatment Phase II, placebo subjects would continue to receive placebo. Subjects assigned to lubiprostone were pre-randomized in a 1:1 ratio to receive either lubiprostone or placebo.

Upon the successful completion of this study, subjects had option of enrolling in a long-term open label study. Eligible subjects were able to received 8 μg lubiprostone BID in the extension study.

The first study visit (Screen Visit; Visit 1) occurred approximately 4 weeks before the first dose of study medication and was assessed in three segments (A, B, C) to determine a subject's ability to meet study criteria. In Segment A, the investigator completed the electronic Bowel Symptom Survey with the subject's responses. If the survey results determined that the subject had met the criteria for c-IBS, the subject would continue to Segment B of the screening process. In Segment B, a subject continued to be screened a review of the inclusion/exclusion criteria, conducted a physical evaluations, and collection of medical and concomitant medication history. A subject completing of the evaluation and meeting the criteria in Segment B would continue to Segment C. In Segment C, the subject's colonoscopy (a flexible sigmoidoscopy was permitted for a subject under 50 years of age) history would be assessed to determine if the procedure

was relevant or needed to be scheduled as appropriate. A subject meeting Segments A, B and C of the screening criteria would be given an electronic diary.

At the Randomization Visit (Visit 2), Visit 4/Week 4 (Day 28 ±3), Visit 6/Week 12 (Day 84±3), and Visit 7/Week 16 (Day 112±3), the subjects were asked to complete the Irritable Bowel Symptom-Quality of Life (IBS-QOL) questionnaire prior to the completion of any other study procedures during that visit. The questionnaire was designed with 34 questions with 5 possible responses.

At the Randomization Visit (Visit 2), subjects meeting all the inclusion and exclusion criteria were randomized into the study.

Office visits occurred at Week 4 (Visit 4), Week 8 (Visit 5), and Week 12 (Visit 6). At Weeks 4, 8, and 12, the electronic diaries were reviewed for completeness and re-dispensed to the subject along with additional study medication. At Week 12, the subject was dispensed new study medication.

A Quality of Life questionnaire was given the subject at the Randomization, Week 4, Week 12, and Week 16 Visits. The questionnaire was designed with 34 questions with 5 possible responses.

Treatment Phase II was used to evaluate any lasting rebound effect of withdrawal of lubiprostone. At Visit 7/Week 16 (Day 112 ±3), a final office was made to assess any changes in the subject's condition.

Use of other constipation or IBS treatment medications was not allowed during the baseline, treatment, or withdrawal period. However, after 3 consecutive days of not having a spontaneous bowel movement (SBM), if the subject felt the need for relief, the investigator might prescribe a 10 mg bisacodyl suppository (Dulcola suppository). If this was not effective, a Fleet enema should then be prescribed.

The subject answered questions about their IBS including an evaluation of abdominal discomfort/pain, bowel movement frequency rates, evaluation of stool consistency, evaluation of bowel straining, evaluation of constipation severity, evaluation of abdominal bloating, and evaluation of symptom relief. This information was assessed as part of the daily evaluations recorded in the electronic diary, a palm-held device with a visual display.

3.1.1.1.1 Treatment Phase I

The primary efficacy endpoint was the overall responder status. Responder statuses at Month 1, Month 2, and Month 3 were considered key secondary endpoints. The primary and key secondary endpoints were calculated from the weekly assessments of symptom relief gathered as part of the subject's electronic, diary responses. Symptom relief was assessed from the 7-point balanced scale associated with the following electronic diary question:

How would you rate your relief of IBS symptoms (abdominal discomfort/pain, bowel habits, and other IBS symptoms) over the past week compared to how you felt before you entered the study?

• Significantly relieved
• Moderately relieved
• A little bit relieved
• Unchanged
• A little bit worse
• Moderately worse
• Significantly worse

A subject was considered a monthly responder if symptoms were rated as at least "moderately relieved" for all 4 weeks within a month or "significantly relieved" for at least 2 weeks within a month provided that:

1. The percent of days with rescue medication use did not increase during the month as compared to baseline and
2. The subjects did not discontinue during the month due to lack of efficacy and
3. There were no ratings during the month of "Moderately worse" or "Significantly worse".

A subject was considered an overall responder if he or she was a responder for at least two out of any three months during Treatment Phase I.

3.1.1.1.2 Treatment Phase II

All subjects who took at least one dose of the study medication dispensed at Visit 6 comprised the Randomized Withdrawal (RW) population. This population was used for all analyses of data collected during Treatment Phase II with the exception of the analysis of relapse rates. Three treatment groups were summarized by the sponsor. Group 1 represented subjects who received lubiprostone during Treatment Phase I and Treatment Phase II. Group 2 represented subjects who received lubiprostone during Treatment Phase I and placebo during Treatment Phase II. Group 3 represented subjects who received placebo during Treatment Phase I and Treatment Phase II. The treatment assignments for Treatment Phase II were made by randomization prior to the start of Treatment Phase I.

The subset of RW subjects who were overall responders during Treatment Phase I comprised Phase I Responders (PIR) population. This population was used for determining relapse and for selected analyses of Treatment Phase II data. Assuming an expected overall responder rate of 14.6% for placebo subjects and 29.4% for lubiprostone subjects and achieving 90% power for varying responder rate estimates, the sponsor proposed a sample size of 570 subjects with 2:1 randomization ratio (380 lubiprostone subjects and 190 placebo subjects). This number was chosen to protect against all but the

most conservative responder rate estimate scenario, which would have required 797 total subjects to achieve 90% power.

3.1.1.2 Sponsor's Analysis

A total of 590 patients were randomized to treatment groups (396 in lubiprostone and 194 in placebo). Of which 588 were treated with study medication (395 in lubiprostone and 193 in placebo).

A total of 436 subjects (73.9%) completed Treatment Phase I of the study. The main reasons for discontinuation during Treatment Phase I were voluntary withdrawal (11.4%), AE (4.9%), lack of efficacy (3.1%), and lost to follow-p (2.0%).

During Treatment Phase II, the 436 subjects who completed Treatment Phase I were randomized to the following groups: P/P (139 subjects), L/P (146 subjects), and L/L (151 subjects). Overall, 16 subjects (3.7%) discontinued during Treatment Phase II.

The overall proportion of subjects with violations was similar for all 3 months (6.7% for Month 1, 7.2% for Month 2, and 5/7% for Month 3). At Months 1 and 2, similar proportions of lubiprostone and placebo subjects had protocol violations; at Month 3, proportionally more lubiprostone subjects had protocol violations (6.2% vs. 4/7%).

Five hundred eighty-three (583) subjects (193 placebo; 390 lubiprostone) made up the ITT population; 522 subjects (172 placebo; 350 lubiprostone) made up the overall PP population; 436 subjects (139 placebo; 297 lubiprostone) made up the study completers proportion; 436 subjects (139 P/P; 146 L/P; 151 L/L) made up the RW population; and 51 subjects made up the PIR population.

3.1.1.2.1 Planned Analysis

3.1.1.2.1.1 Treatment Phase I

The primary efficacy analysis was based upon the comparison of overall responder rates between the two treatment groups. A Cochran-Haenszel (CMH) test, stratified by center, was used to test the null hypothesis of equal overall responder rates between the two treatment groups vs. the alternative hypothesis of non-equality

Responder status at Month 1, Month 2, and Month 3 were considered key secondary endpoints. The remaining secondary efficacy endpoints included the subject's evaluation of abdominal discomfort/pain, evaluation of abdominal bloating, bowel movement frequency rates, evaluation of stool consistency, evaluation of bowel straining, evaluation of constipation severity, and evaluation of symptom relief.

Analyses of quality of life were performed on the overall score and the following subcategories: dysphoria, interference with activity, body image, healthy worry, food

avoidance, social reaction, sexual and relationship. The changes from baseline were evaluated.

A subject was considered to have completed Treatment Phase I once the subject reached and completed all visits up to and including Visit 6. A subject was considered to have completed Treatment Phase II once the subject reached and completed Visit 7 approximately 4 weeks after Visit 6. A subject was considered as having completed the study once the subject completes all visits up to and including Visit 8.

For efficacy, the set of all randomized subjects who took at least one dose of double-blind study medication and had at least one treatment-period diary entry was referred to as the Intent-to-Treat (ITT) dataset. Subjects in the ITT population were grouped with the Treatment Phase I group to which they were randomized, regardless of which treatment they actually received. This dataset was used for the primary analysis. Subjects who did not comply with the treatment regimen, who took disallowed concomitant medication, or who were found to have other significant deviation from the protocol was considered protocol violators. If more than 5% of all subjects were protocol violators, then key efficacy analyses was also based on the Per Protocol (PP) Population, which excluded subjects who were deemed protocol violators and/or data points that might have been influenced by protocol violations.

No attempt was made to impute individual daily diary ratings that were either missing from the dataset or had missing values. Rather, baseline, weekly, and monthly calculations of daily diary data addressed the issue of missing data individually.

For responder endpoints, for a subject's responder status during a given month, missing symptom relief ratings during the month were treated as rating of "Unchanged" relief. Therefore, any month with fewer than 4 non-missing symptom relief ratings, would have however many imputations of "unchanged" relief were necessary to bring the total number of ratings for the month up to 4. This included ratings that were missing because they applied weeks after study discontinuation. Therefore, all ITT subjects would have a non-missing responder status for Month 1, Month 2, and Month 3 and would, consequently have a non-missing overall responder status.

Supportive analyses of the responder rates were also performed. For these, the same responder definition was used, but they were based on symptom relief ratings that had been imputed via the LOCF algorithm if the original value was missing.

For all other secondary efficacy endpoints, the "last observation carried forward" (LOCF) technique was used to impute missing values primarily caused by early withdrawal from the study. For a given subject, the most recent non-missing treatment-period data point was carried forward to subsequent data points where data were missing. Supportive analyses of the secondary endpoints were also conducted by not performing any missing value imputation.

Since the primary endpoint analysis was based on a single statistical analysis, the type I error rate for the primary endpoint was controlled at α=0.05. If statistical significance was declared as a result of the primary efficacy analysis, then the analyses of the three key secondary endpoints (the Month 1, Month 2. and Month 3 responder rates) were protected from multiple comparisons by a combined use of sequential and closed testing procedures. The order in which tests was performed is as follows:

1. If the overall test is significant, then performed a combined test of both Months 1 and 2
2. If the combined Months 1 and 2 test was significant, then Month 1 and 2 could be tested independently and simultaneously
3. If the tests for Month 1 and Month 2 were both significant, then Month 3 could be tested independently

Each individual test was conducted at α=0.05 level to declared significance. If any individual test resulted in a p-value >0.05, the testing procedure stopped. The closed testing procedure involved with Step 1 and Step 2 was based on the methodology proposed by Lehmacher et al. (1991) ["Procedures for Two-Sample Comparisons with Multiple Endpoints Controlling the Experimentwise Error Rate", Biometrics 47, pp. 511-521]. The sponsor claimed that using this 3-step approach, the overall experiment-wise error rate for the primary and key secondary efficacy analyses was also held at α=0.05.

The method of analysis of each step was described below.

- For Step 1, the number of responder months was summed for each subject, so that each subject received a score of 0, 1, or 3. A CMH test, stratified by center, was used to test the null hypothesis of equal row mean scores between the two treatment groups vs. the alternative hypothesis of non-equality. If this test resulted in a p-value ≤0.05, the procedure advanced into Step 2. Otherwise the procedure stopped.

- In Step 2, Month 1 and Month 2 tested individually and simultaneously. Like the test for the overall responder rates, CMH tests, stratified by center, was used to compare responder rates for each month individually. Statistical significance was declared for any test that resulted in a p-value ≤0.05. If statistical significance was declared for both Month 1 and Month 2, then the testing procedure advanced into Step 3. Otherwise the procedure stopped.

- In Step 3, Month 3 tested individually. Again, a CMH tests, stratified by center, was used to compare Month 3 responder rates between the two treatment groups. If test resulted in a p-value ≤0.05, then statistical significance at Month 3 was declared.

No attempt was made to control for multiple comparisons of the other secondary endpoints.

The change from baseline in mean abdominal discomfort/pain, abdominal bloating and constipation severity during Months 1, 2, and 3 were analyzed. The change from baseline

was calculated as the baseline value subtracted from the average of all diary ratings during the given month. For these treatment period daily diary assessments, each month was defined by 28-day intervals beginning with the day of the first dose of study medication (Day 1). Similarly, each week was defined by 7-day intervals beginning with the day of the first dose of study medication (Day 1).

The treatment effect from analysis of covariance (ANCOVA) was used to test for differences between the treatment groups. In addition to treatment group, the ANCOVA model controlled for center and the baseline value was used as a covariate.

Weekly bowel movement (BM) frequency rates were calculated as follows:

BM Frequency=(7 x Number of BMs)/(Number of days)

Where the number of days is the number of days during the week (7-day interval) or month (28-day interval) that the subject was in the study and taking study medication, per the diary.

For the weekly analyses, the number of days was generally 7 unless a subject discontinued study medication in the midst of a treatment week. For the Week 1 analysis, if the number of days was less than 4, then the data was considered insufficient and the BM rate was missing. If the number of days during Weeks 2-12 was less than 4, then the most recent data from days during the previous week was combined with data from the current week in order to bring the number of days up to 4. If the number of days for a given week was 0, then the LOCF method imputed the frequency rate from the rate used for the most recent week. A similar algorithm was used for the monthly analyses.

In order to control for potential baseline differences between treatment groups, the change in BM frequency rate was used for analysis.

In addition to BM frequency rates, analyses were also performed on spontaneous BM (SBM) frequency rate where an SBM was defined as a BM that did not occur after use of a rescue medication on the same day. Results were analyzed by van Elteren tests stratified by center.

Subjects were asked to rate their average stool consistency and their bowel straining for any spontaneous BMs that may have occurred during the day. The average stool consistency rating was calculated for each week (7-day period) and month (28-day period). Analysis was based on the change from baseline.

An analysis of covariance (ANCOVA) was used to control center and the baseline value (the covariate). If the model assumption did not hold, then van Elteren tests stratified by center would be used instead.

Subjects were asked weekly to evaluate their symptom relief. CMH test stratified by center was used to compare weekly symptom relief ratings between treatment groups.

The same test was used to evaluate the mean of the all symptom relief ratings during the month.

Analyses of the domain (dysphoria, interference with activity, body image, heath worry, food avoidance, social reaction, sexual, and relationship) and overall IBS Quality of Life scores were based on changes from baseline. An analysis of covariance (ANCOVA) was be used to control for treatment, center, and the baseline score. If the model assumption did not hold, then van Elteren tests stratified by center would be used instead.

3.1.1.2.1.2 Treatment Phase II

For determining a subject responder status during Month 4, missing symptom relief ratings during the month were treated as rating of "Unchanged" relief. For all other efficacy endpoints, the LOCF technique was used to impute missing values. Treatment Phase I data was generally not used to impute missing data from Treatment Phase II.

Since the objective of examining the rebound phenomenon was essentially a safety matter, no attempt was made to control for multiple comparisons of the treatment groups during Treatment Phase II.

Month 4 responder rates were calculated for Group 1 and Group 2 in the PIR population and for all three treatment groups in the RW population. Overall responders from Treatment Phase I was considered as having relapsed if they were not responders during Month 4. Comparisons of Month 4 responder rate was made for the following groups:

1. Group 1 vs. Group 2 in the PIR population
2. Group 2 in the PIR population vs. Group 3 in the RW population
3. Group 3 vs. Group 2 vs. Group 3 in the RW population

Comparison #2 specifically addressed the issues of rebound. Specifically, there was evidence of a rebound effect if the responder rate for Treatment Phase I responders who were switched to placebo was significantly less than the responder rates for subjects who toke placebo during both treatment phases. Comparison #1 addressed whether subjects who were switched to placebo were more likely to relapse after one month compared to subjects who were kept on lubiprostone. Comparison #3 addressed the effectiveness of lubiprostone after 4 months of treatment and the potential residual effects of lubiprostone after the drug had been withdrawn compared to placebo treatment after 4 months.

The change from baseline in mean abdominal discomfort/pain ratings, abdominal bloating and constipation severity evaluations during Weeks 13-16 and for all of Month 4 were analyzed. The treatment groups 1, 2, and 3 in the RW population were compared. The treatment group effect from an analysis of covariance (ANCOVA) was used to test for differences between the treatment groups. In addition to treatment group, the ANCOVA model controlled for center and the baseline value was used as covariate.

SBM frequency rate during Weeks 13-16 and for all of Month 4 was calculated. SBM rate changes from baseline was be analyzed by CMH tests stratified by center using modified ridit scores.

Average SBM stool consistency and bowel straining changes from baseline during Weeks 13-16 and for all of Month 4 was calculated. An analysis of covariance (ANCOV) was used to control for center and the baseline value. If the model assumption did not hold, then van Elteren tests stratified by center would be used instead.

Subject evaluations of symptom relief form Weeks 13-16 and for all of Month 4 were analyzed. CMH tests stratified by center were used to compare weekly symptom relief ratings between treatment groups. The same test was used to evaluate the mean of all ratings during Month 4.

Analyses of the domain (dysphoria, interference with activity, body image, heath worry, food avoidance, social reaction, sexual, and relationship) and overall IBS Quality of Life scores was be based on changes from baseline. An analysis of covariance (ANCOVE) was used to control for treatment, center, and the baseline score. If the model assumption did not hold, then van Elteren tests stratified by center would be used instead.

3.1.1.2.2 Treatment Group Comparability

The summary of results of comparability of treatment groups at baseline for all randomized patients is given in Appendix Table 1.

As seen from Appendix Table 1, no statistically significant differences between the two treatment groups were observed for demographic and baseline characteristics.

3.1.1.2.3 Sponsor's Analysis of Primary Efficacy Parameter

The primary efficacy parameter for this study was overall responder rate without LOCF during Treatment Phase I. A subject was considered an overall responder if he or she was a responder for at least two out of any three months during Treatment Phase I. The summary of results of sponsor's analysis of primary efficacy variable is given below.

Summary of Overall Responder Rate
Intent-to-Treat Population without LOCF
Study SPI/0211SIB-0431

	Treatment Group		
	Placebo	Lubiprostone	
Time point	(N=193)	(N=390)	p-Value²
Status	n (%)	n (%)	
Overall			
Responder	15 (7.8)	54 (13.8)	0.029*
Non-responder	178 (92.2)	336 (86.2)	

¹ Overall responders are defined as subjects who are monthly responders for at least 2 out of any 3 months during Treatment Phase I.

² p-Value is from a CMH test stratified by pooled-center.

* p ≤ 0.05 (significant).

As seen from table above, for the ITT population without LOCF, the difference between the two treatment groups was statistically significant. Similar results were observed for the ITT population with LOCF (18.2% vs. 9.8%; p=0.009), PP population without LOCF (14.6% vs.7.6%; p=0.014), and the study completers population without LOCF (17.2% vs. 10.1%; p=0.061).

3.1.1.2.4 Sponsor's Analyses of Secondary Efficacy Parameters

3.1.1.2.4.1 Treatment Phase I

3.1.1.2.4.1.1 Monthly Responder Rate

Monthly responder rates without LOCF were considered key secondary endpoints, and they were analyzed by the stepwise procedure. The summary of results of sponsor's analyses of monthly responder rates for ITT population without LOCF are given below.

Summary of Monthly Responder Rate[1]
ITT Population without LOCF
Study SPI/0211SIB-0431

Timepoint Status	Placebo (N=193)		Lubiprostone (N=390)		p–Value[2]
			Treatment Group		
Month 1					
Responder	12	6.2%	39	10.0%	0.098
Non–responder	181	93.8%	351	90.0%	
Month 2					
Responder	18	9.3%	62	15.9%	0.028*
Non–responder	175	90.7%	328	84.1%	
Month 3					
Responder	20	10.4%	62	15.9%	0.069
Non–responder	173	89.6%	328	84.1%	

Cross Reference: Listing 16.2.6.2; Appendix 16.1.9.2.14.2.2.1
[1] Monthly responders are defined as subjects with symptoms rated as at least 'Moderately relieved' for all 4 weeks within a month or 'Significantly relieved' for at least 2 weeks within a month. Other conditions apply as defined in Protocol Section 9.2.2.
[2] p–Values are from CMH tests stratified by pooled–center.
* p–Value is significant according to the testing procedure defined in Protocol Section 12.1.4.3.1.

As seen from table above, step 1 of the testing procedure yielded a statistically significantly result for ITT population without LOCF. At month 2, lubiprostone group had statistically significant higher responders than placebo group.

The summary of results of sponsor's analysis of monthly responder rate by month for ITT population with LOCF, ITT Population without LOCF, completer without LOCF, and the PP population without LOCF are given in Appendix Table 2.

Similar results were also observed at each month for ITT population with LOCF, completer without LOCF, and the PP population without LOCF.

3.1.1.2.4.1.2 Subject Evaluation of Abdominal Discomfort/Pain

The summary of results of sponsor's analysis of abdominal discomfort/pain by month for ITT population with LOCF, ITT Population without LOCF, and the PP population with LOCF are given in Appendix Table 3.

As seen from Appendix Table 3, the differences in mean change from baseline between treatment groups were not statistically significant at Months 1, 2, and 3 in abdominal discomfort/pain for ITT population with LOCF.

Similar results were also observed at each month for ITT population without LOCF and the PP population with LOCF.

3.1.1.2.4.1.3 Subject Evaluation of Abdominal Bloating

The summary of results of sponsor's analysis of abdominal bloating by month for ITT population with LOCF, ITT Population without LOCF, and the PP population with LOCF are given in Appendix Table 4.

As seen from Appendix Table 4, the differences in mean change from baseline between treatment groups were not statistically significant at Months 1, 2, and 3 in abdominal bloating for ITT population with LOCF.

Similar results were also observed at each month for ITT population without LOCF and the PP population with LOCF.

3.1.1.2.4.1.4 Bowel Movement Frequency rates

Frequency rates of SBMs and BMs for ITT population with LOCF, ITT Population without LOCF, and the PP population with LOCF are summarized by month in Appendix Tables 5 and 6, respectively.

As seen from Appendix Tables 5 and 6, the differences in mean change from baseline between treatment groups were not statistically significant at Months 1, 2, and 3 in bowel movement frequency rates for ITT population with LOCF.

Similar results were also observed at each month for ITT population without LOCF and the PP population with LOCF.

3.1.1.2.4.1.5 Subject Evaluation of Stool Consistency

The summary of results of sponsor's analysis of stool consistency by month for ITT population with LOCF, ITT Population without LOCF, and the PP population with LOCF are given in Appendix Table 7.

As seen from Appendix Table 7, the differences in mean change from baseline between treatment groups were statistically significant at Months 1 and 2 but were not statistical significant at Month 3 in stool consistency for ITT population with LOCF.

Similar results were also observed at each month for ITT population without LOCF and the PP population with LOCF.

3.1.1.2.4.1.6 Subject Evaluation of Degree of Straining

The summary of results of sponsor's analysis of degree of straining by month for ITT population with LOCF, ITT Population without LOCF, and the PP population with LOCF are given in Appendix Table 8.

As seen from Appendix Table 8, the differences in mean change from baseline between treatment groups were marginally statistically significant at Months 1 and 2 but were not statistical significant at Month 3 in degree of straining for ITT population with LOCF.

Similar results were also observed at each month for ITT population without LOCF and the PP population with LOCF.

3.1.1.2.4.1.7 Subject Evaluation of Constipation Severity

The summary of results of sponsor's analysis of constipation severity by month for ITT population with LOCF, ITT Population without LOCF, and the PP population with LOCF are given in Appendix Table 9.

As seen from Appendix Table 9, the differences in mean change from baseline between treatment groups were not statistically significant at Months 1, 2, and 3 in constipation severity for ITT population with LOCF.

Similar results were also observed at each month for ITT population without LOCF and the PP population with LOCF.

3.1.1.2.4.1.8 Subject Evaluation of Symptom Relief

The summary of results of sponsor's analysis of constipation severity by month for ITT population with LOCF, ITT Population without LOCF, and the PP population with LOCF are given in Appendix Table 10.

As seen from Appendix Table 10, the differences in mean rating of symptom relief between treatment groups were not statistically significant at Months 1, 2, and 3 in symptom relief for ITT population with LOCF.

Similar results were also observed at each month for ITT population without LOCF and the PP population with LOCF.

3.1.1.2.4.1.9 IBS Quality of Life

The summary of results of sponsor's analysis of IBS-QOL at Week 4, Week 12 and Last (visit) for ITT population without LOCF is given in Appendix Table 11.

As seen from Appendix Table 11, the differences in mean change from baseline between treatment groups were not statistically significant at Week 4, Week 12, and Last (visit) for overall score or any the domain scores in symptom relief for ITT population without LOCF.

3.1.1.2.4.2 Treatment Phase II

A summary of responder rates at Month 4 is given below for L/P group and L/L group of the Phase I Responder population.

Summary of Responder Rates[1] at Month 4
Phase I Responder Population
Study SPI/0211SIB-0431

Timepoint Status	Lubiprostone/ Placebo (N=30)		Lubiprostone/ Lubiprostone (N=21)		p-Value[2]
Month 4					
Responder	12	40.0%	8	38.1%	0.971
Non-responder	18	60.0%	13	61.9%	

Cross Reference: Listing 16.2.6.2; Appendix 16.1.9.2.14.2.18.1
[1] Monthly responders are defined as subjects with symptoms rated as at least 'Moderately relieved' for all 4 weeks within a month or 'Significantly relieved' for at least 2 weeks within a month. Other conditions apply as defined in Protocol Section 9.2.2.
[2] p-Value is from a CMH test stratified by pooled-center.
* p <= .05

As seen table above, the proportion of subjects who were responders at Month 4 (i.e., at the end of Treatment Phase II) was similar for the L/P group and L/L group.

A summary of responder rates at Month 4 is given below for the P/P group from the Randomized Withdrawal population and the L/P group from the Phase I Responder population.

Summary of Responder Rates[1] at Month 4
Phase I Responder and Randomized Withdrawal Populations
Study SPI/0211SIB-0431

| Timepoint Status | Treatment Group | | p–Value[2] |
	Placebo/Placebo (Randomized Withdrawal) (N=139)	Lubiprostone/Placebo (Phase I Responders) (N=30)	
Month 4			
Responder	11 7.9%	12 40.0%	<0.001*
Non−responder	128 92.1%	18 60.0%	

————————

Cross Reference: Listing 16.2.6.2; Appendix 16.1.9.2.14.2.18.2
[1] Monthly responders are defined as subjects with symptoms rated as at least 'Moderately relieved' for all 4 weeks within a month or 'Significantly relieved' for at least 2 weeks within a month. Other conditions apply as defined in Protocol Section 9.2.2.
[2] p–Value is from a CMH test stratified by pooled−center., comparing the Lubiprostone/Placebo group in the PIR population to the Placebo/Placebo group in the Randomized Withdrawal population.
* p <= .05

As seen from table above, the proportion of Month 4 responders in the L/P group was significantly higher than the proportion in the P/P group.

A summary of responder rates at Month 4 is given below for L/P group and L/L group of Randomized Withdrawal population. As seen from this table, the proportion of responders at Month 4 was higher for L/L group than for P/P group, but the difference was not statistically significant.

Summary of Responder Rates[1] at Month 4
Randomized Withdrawal Population
Study SPI/0211SIB-0431

| | Treatment Group | | |
| | Placebo/
Placebo
(N=139) | Lubiprostone/
Lubiprostone
(N=151) | |
Timepoint Status			p-Value[2]
Month 4			
Responder	11 7.9%	17 11.3%	0.415
Non-responder	128 92.1%	134 88.7%	

Cross Reference: Listing 16.2.6.2; Appendix 16.1.9.2.14.2.18.3
[1] Monthly responders are defined as subjects with symptoms rated as at least
 'Moderately relieved' for all 4 weeks within a month or 'Significantly relieved'
 for at least 2 weeks within a month. Other conditions apply as defined in
 Protocol Section 9.2.2.
[2] p-Value is from a CMH test stratified by pooled-center.
* p <= .05

3.1.1.3 Reviewer's Comments and Evaluation

3.1.1.3.1 Reviewer's Comments on Sponsor's ITT Population

The sponsor's ITT analysis did not include all randomized patients. It excluded more patients in lubiprostone group than in placebo group (6 vs. 1). So, the sponsor's ITT analysis may be biased in favor of lubiprostone group.

For a "true" ITT analysis, the p-value would be 0.0405 by Fisher's exact test.

3.1.1.3.2 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Variable

Although the sponsor's results achieved statistical significance for the pre-specified primary efficacy endpoint, the treatment difference was modest at 6.0%, which might not be considered clinically significant.

3.1.1.3.2.1 Sensitivity Analysis for Overall Responder

Per this reviewer's request, the sponsor performed a sensitivity analysis for overall responder. The summary of results is given below.

```
                        Study 0431
                      Treatment Group
Timepoint           Placebo              Lubiprostone
Status              (N=193)              (N=390)              p-Value²

Overall (LOCF)
     Responder       19   9.8%            71  18.2%           0.009*
     Non-responder  174  90.2%           319  81.8%

Overall (Observed Cases)
     Responder       15   7.8%            54  13.8%           0.029*
     Non-responder  178  92.2%           336  86.2%

Overall (Worst Case Scenario)
     Responder       15   7.8%            50  12.8%           0.063
     Non-responder  178  92.2%           340  87.2%
_____
Cross Reference: Listing 16.2.6.2; Appendix 16.1.9.2.14.2.1.1
¹ Overall responders are defined as subjects who are monthly responders
for at least two out of any three months during Treatment Phase I.
² p-Value is from a CMH test stratified by pooled-center
     •   p <= .05
```

As seen from table above, the p-values ranged from 0.009 (LOCF) to 0.063 (worst case).
There were difference of 4 overall responders for lubiprostone between the observed case
and worst case; none for placebo. Thus the sponsor's result based on observed cases
should not be considered robust.

3.1.1.3.2.2 Reviewer's Analysis of Responder for 3 Months

In the sponsor's analysis of primary efficacy endpoint, a subject was considered an
overall responder if he or she was a responder for at least two out of any three months
during Treatment Phase I.

For a more stringent primary efficacy endpoint, a subject was considered a responder if
he or she was a responder for three months. The results would be as follows:

Number of Subjects who were Responder for 3 Months
Study SPI/0211SIB-0431
(ITT Population)

Placebo	Lubiprostone	Difference	P-value	95% Confidence Interval
4/193 (2.1%)	17/390 (4.4%)	2.3%	0.2370	(-0.6%, 5.1%)

Compiled by this reviewer.
P-value was obtained using Fisher's exact test.

As seen from table above, the treatment difference was small and was not statistically
significant.

3.1.1.3.2.3 Subgroup Analysis

The primary efficacy parameter for this study was overall responder rate without LOCF
during Treatment Phase I.

Subgroup analyses were performed on the number of patients who were overall responders without LOCF during Treatment Phase I by age, gender and race.

Number of Patients who were Overall Responders by Subgroup
ITT Population without LOCF
Study SPI/0211SIB-0431

Subgroup	Lubiprostone	Placebo	Difference	95% C. I.
Gender				
Male	4/35 (11%)	0/13 (0%)	11%	(10.5%, 76.7%)
Female	50/355 (14%)	15/180 (8%)	6%	(4.5%, 307%)
Age				
18 to 64	50/361 (14%)	14/173 (8%)	6%	(10.8%, 36.3%)
≥65	4/29 (14%)	1/20 (5%)	9%	(-47.7%, 27.7%)
Race				
Black	10/53 (19%)	2/29 (7%)	8%	(-2.0%, 26.0%)
White	40/293 (14%)	12/142 (9%)	5%	(-0.8%, 11.2%)
Hispanic	4/43 (9%)	1/18 (6%)	3%	(-9.9%, 17.4%)

Compiled by this reviewer.

 As seen from table above, treatment difference was consistent among all subgroups.

3.1.1.3.2.4 Number of Months

Per this reviewer's request, the sponsor performed a statistical analysis of the number of months that a subject was considered a month responder. The treatment difference was 0.18 months (0.51 for lubiprostone and 0.33 for placebo), or about 5 days. So, the treatment difference in terms of number of months that a subject was considered a month responder was modest.

3.1.1.3.2.5 "New" Monthly Responder

Per request from the clinical team, the sponsor provided a new data set including "new" monthly responder. This reviewer performed a statistical analysis for "new" monthly responder (as defined below) at Month 1, Month 2, and Month 3 for Study SPI/0211SIB-0431.

A subject is considered a new monthly responder if symptoms were rated as "significantly relieved" or "moderately relieved" for at least 50% of weeks within a month or at least "a little bit relieved" for all 4 weeks within a month provided that:

1. The percent of days of rescue medication use did not increase during the month as compared to baseline and
2. The subjects did not discontinue during the month due to lack of efficacy and
3. There were no ratings during the month of "Moderately worse" or "Significantly worse."

3.1.1.3.2.5.1 Overall Responder Rate

Results from statistical analyses of overall responder rate for "new" monthly responder for ITT analysis for Study SPI/0211SIB-0431 are given below. In this analysis, a patient with a missing observation is considered a non-responder.

Summary of Overall Responder Rate for " New" Monthly Responder
Study SPI/0211SIB-0431
(Reviewer's ITT Analysis)

Placebo	Lubiprostone	Difference	P-value
52/193 (26.9%)	134/390 (34.4%)	7.5%	0.0706

Compiled by this reviewer.
P-value was obtained using Chi-square test.

As seen from table above, for "new" defined monthly responder, the treatment difference failed to achieve statistical significance for the overall responder rate.

3.1.1.3.2.5.2 Monthly Responder Rate

Results from statistical analysis of "new" monthly responder for observed case analysis and ITT analysis are given below.

Number of Subjects who were " New" Monthly Responder
Study SPI/0211SIB-0431
(Observed Case)

Month	Placebo	Lubiprostone	Difference	P-value
1	51/177 (28.8%)	133/365 (36.4%)	7.6%	0.0788
2	55/164 (33.5%)	142/344 (41.3%)	7.8%	0.0940
3	55/145 (37.9%)	127/322 (39.4%)	1.5%	0.7569

Compiled by this reviewer.
P-value was obtained using Chi-square test.

Number of Subjects who were " New" Monthly Responder
Study SPI/0211SIB-0431
(Reviewer's ITT)

Month	Placebo	Lubiprostone	Difference	P-value
1	51/193 (26.4%)	133/390 (34.1%)	7.7%	0.0605
2	55/193 (28.5%)	142/390 (36.4%)	7.9%	0.0573
3	55/193 (28.5%)	127/390 (32.6%)	4.1%	0.3187

Compiled by this reviewer.
P-value was obtained using Chi-square test.

As seen from tables above, for "new" defined monthly responder, the treatment difference failed to achieve statistical significance at Month 1, Month 2, and Month 3 for both sponsor's and reviewer's ITT analyses..

3.1.1.3.2.5.3 Responder for 3 Months

For a more stringent primary efficacy endpoint, where a subject was considered a responder if he or she was a "new" monthly responder for three months. The results would be as follows:

Number of Subjects who were "New" Responder for 3 Months
Study SPI/0211SIB-0431
(ITT Population)

Placebo	Lubiprostone	Difference	P-value	95% Confidence Interval
24/193 (12.4%)	62/390 (15.9%)	3.5%	0.3209	(-2.4%, 9.4%)

Compiled by this reviewer.
P-value was obtained using Fisher's exact test.

As seen from table above, the treatment difference was small and was not statistically significant for "new" monthly responder.

3.1.1.3.3 Reviewer's Comments on Sponsor's Analyses of Secondary Efficacy Variables

No multiplicity adjustment was pre-specified and applied to secondary efficacy endpoints with exception of month responder rate at Month 1, Month 2, and Month 3.

3.1.1.3.3.1 Weekly Responder Rate

Per this reviewer's request, the sponsor performed a statistical analysis of weekly responder rates by week. A weekly responder was any week with a response of moderately relieved or significant relieved. No data imputation was used. The summary of results is given Appendix Table 12.

As seen from Appendix Table 12, treatment difference in weekly responder rates reached statistical significance level ($p<0.05$) only at Week 4 and Week 6 without adjusting for multiplicity.

3.1.1.3.3.2 Responder Analysis for Spontaneous Bowel Movement

Per this reviewer's request, the sponsor performed three responder analyses for spontaneous bowel movements (SBMs). The responder analyses were as follows:

• a responder is defined as subjects that achieve an average 1 SBM per week increase over baseline.
• a responder is defined as subjects that achieve an average 3 SBM per week increase

over baseline.
• a responder is defined as subjects having an average increase of 1 SBM per week and at least 3 SBMs per week.

The results of these responder analyses for SBMs are given in Appendix Table 13.

As seen from Appendix Table 13, treatment difference was not statistically significant for all three responder analyses. The treatment differences were modest, ranged from 1.6% to 5.6%.

3.1.1.3.4 Reviewer Comments on Treatment Phase II

Subjects assigned to lubiprostone in Treatment I were pre-randomized at the beginning of Treatment Phase I in a 1:1 ratio to receive either lubiprostone or placebo for Treatment Phase II. Without re-randomization at the end of Treatment Phase I, there was potential for imbalance that might be caused in Treatment Phase I, e.g., by differential dropout and compliance rates.

All efficacy analyses in Treatment Phase II should be considered as explorative analysis. There was insufficient power to detect treatment differences. Furthermore, the protocol stated that the objective of Treatment Phase II was to examine the rebound phenomenon, which was essentially a safety matter.

3.1.2 Study SPI/0211SIB-0432

3.1.2.1 Study Design

The study design for this study was similar to those for Study B-0431 with the exception that this study did not have a 4-week randomized withdrawal period followed treatment phase.

3.1.2.2 Sponsor's Analysis

A total of 581 patients were randomized to treatment groups (387 in lubiprostone and 194 in placebo). Two subjects in the lubiprostone group were randomized but not treated.

A total of 454 subjects (78.1%) completed the study (303 in lubiprostone and 151 in placebo). The most common reasons for discontinuation were voluntary withdrawal (6.0%), AE (5.7%), lack of efficacy (4.5%), and lost to follow-up (2.1%).

The overall proportion of subjects with violations was similar for all 3 months (4.7% for Month 1, 4.6% for Month 2, and 4.0% for Month 3). At each month, proportionally more lubiprostone subjects than placebo subjects had protocol violations: (5.3% vs. 3.6 at Month 1; 5.8% vs. 2.1% at Month 2; 5.0% vs. 2.1 at Month 3).

Five hundred seventy-one (571) subjects (192 placebo; 379 lubiprostone) made up the ITT population; 530 subjects (179 placebo; 351 lubiprostone) made up the overall PP

population; 454 subjects (151 placebo; 303 lubiprostone) made up the study completers proportion.

3.1.2.2.1 Planned Analysis

The planned analysis was similar to that for Treatment Phase I for Study SPI/0211SIB-0431.

3.1.2.2.2 Treatment Group Comparability

The summary of results of comparability of treatment groups at baseline for all randomized patients is given in Appendix Table 14.

As seen from Appendix Table 14, no statistically significant differences between the two treatment groups were observed for demographic and baseline characteristics with exception of rescue medication, at least moderate straining ≥25 of the time, and stool consistency that was at least hard ≥25 of the time.

Rescue medication was used on a significantly higher percentage of days by placebo subjects (mean=15.23%) than lubiprostone subjects (mean=11.72%; p=0.030). Additionally, significantly more lubiprostone subjects than placebo subjects reported at least moderate straining ≥25 of the time (92.9% vs. 85.4%; p=0.004), and stool consistency that was at least hard ≥25 of the time (97.4% vs. 89.6%; p<0.001).

3.1.2.2.3 Sponsor's Analysis of Primary Efficacy Parameter

The primary efficacy parameter for this study was overall responder rate without LOCF. The summary of results of sponsor's analysis of primary efficacy variable is given below.

Summary of Overall Responder Rate
Intent-to-Treat Population without LOCF
Study SPI/0211SIB-0432

	Treatment Group		
	Placebo	Lubiprostone	
Time point	(N=192)	(N=379)	p–Value[2]
Status	n (%)	n (%)	
Overall			
Responder	11 (5.7)	46 (12.1)	0.023*
Non–responder	181 (94.3)	333 (87.9)	

[1] Overall responders are defined as subjects who are monthly responders for at least 2 out of any 3 months during the Treatment Period.

[2] p–Value is from a CMH test stratified by pooled–center.

* p ≤ 0.05 (significant).

As seen from table above, for the ITT population without LOCF, the difference between the two treatment groups was statistically significant. Similar results were observed for the ITT population with LOCF (17.7% vs. 10.4%; p=0.031), PP population without LOCF (12.8% vs.6.1%; p=0.024), and the study completers population without LOCF (14.2% vs. 7.3%; p=0.039).

3.1.2.2.4 Sponsor's Analyses of Secondary Efficacy Parameters

The secondary efficacy parameters included monthly responder rates, subject evaluation of abdominal discomfort/pain, subject evaluation of abdominal bloating, bowel movement frequency rates, subject evaluation of stool consistency, subject evaluation of degree of straining, subject evaluation of constipation severity, subject evaluation of symptom relief, and IBS quality of life.

3.1.2.2.4.1 Monthly Responder Rate

Monthly responder rates without LOCF were considered key secondary endpoints, and they were analyzed by the stepwise procedure. The summary of results of sponsor's analyses of monthly responder rates for ITT population without LOCF are given below.

Summary of Monthly Responder Rate[1]
ITT Population without LOCF
Study SPI/0211SIB-0432

| Timepoint Status | Treatment Group | | p–Value[2] |
	Placebo (N=192)	Lubiprostone (N=379)	
Month 1			
Responder	13 6.8%	37 9.8%	0.303
Non–responder	179 93.2%	342 90.2%	
Month 2			
Responder	19 9.9%	61 16.1%	0.047
Non–responder	173 90.1%	318 83.9%	
Month 3			
Responder	11 5.7%	51 13.5%	0.008
Non–responder	181 94.3%	328 86.5%	

Cross Reference: Listing 16.2.6.2; Appendix 16.1.9.2.14.2.2.1
[1] Monthly responders are defined as subjects with symptoms rated as at least 'Moderately relieved' for all 4 weeks within a month or 'Significantly relieved' for at least 2 weeks within a month. Other conditions apply as defined in Protocol Section 9.2.2.
[2] p–Values are from CMH tests stratified by pooled–center.
[*] p–Value is significant according to the testing procedure defined in Protocol Section 12.4.3.1.

As seen from table above, step 1 of the testing procedure did not yield a statistically significantly result for ITT population without LOCF. Thus, statistically significant p-values at Month 2 and Month 3 were not considered statistically significant for this analysis.

The summary of results of sponsor's analysis of monthly responder rate by month for ITT population with LOCF, ITT Population without LOCF, completer without LOCF, and the PP population without LOCF are given in Appendix Table 15.

Similar results were also observed at each month for ITT population with LOCF, completer without LOCF, and the PP population without LOCF.

3.1.2.2.4.2 Subject Evaluation of Abdominal Discomfort/Pain

The summary of results of sponsor's analysis of abdominal discomfort/pain by month for ITT population with LOCF, the ITT population without LOCF and the PP population with LOCF are given in Appendix Table 16.

As seen from Appendix Table 16, the differences in mean change from baseline between treatment groups were not statistically significant at Months 1, 2, and 3 in abdominal discomfort/pain for ITT population with LOCF.

Similar results were also observed at each month for the ITT population without LOCF and the PP population with LOCF.

3.1.2.2.4.3 Subject Evaluation of Abdominal Bloating

The summary of results of sponsor's analysis of abdominal bloating by month for ITT population with LOCF, the ITT population without LOCF, and the PP population with LOCF are given in Appendix Table 17.

As seen from Appendix Table 17, the differences in mean change from baseline between treatment groups were not statistically significant at Months 1, 2, and 3 in abdominal bloating for ITT population with LOCF.

Similar results were also observed at each month for ITT population without LOCF and the PP population with LOCF.

3.1.2.2.4.4 Bowel Movement Frequency Rates

Frequency rates of SBMs and BMs for ITT population with LOCF, the ITT population without LOCF, and the PP population with LOCF are summarized by month in Appendix Tables 18 and 19, respectively .

As seen from Appendix Tables 18 and 19, the differences in mean change from baseline between treatment groups were not statistically significant at Months 1, 2, and 3 in bowel movement frequency rates for ITT population with LOCF.

Similar results were also observed at each month for ITT population without LOCF and the PP population with LOCF.

3.1.2.2.4.5 Subject Evaluation of Stool Consistency

The summary of results of sponsor's analysis of stool consistency by month for ITT population with LOCF, the ITT population without LOCF, and the PP population with LOCF are given in Appendix Table 20.

As seen from Appendix Table 20, the differences in mean change from baseline between treatment groups were statistically significant at Months 1 and 2 but were not statistical significant at Month 3 in stool consistency for ITT population with LOCF.

Similar results were also observed at each month for ITT population without LOCF and the PP population with LOCF.

3.1.2.2.4.6 Subject Evaluation of Degree of Straining

The summary of results of sponsor's analysis of degree of straining by month for ITT population with LOCF, the ITT population without LOCF, and the PP population with LOCF are given in Appendix Table 21.

As seen from Appendix Table 21, the differences in mean change from baseline between treatment groups were marginally statistically significant at Months 1 and 2 but were not statistically significant at Month 3 in degree of straining for ITT population with LOCF.

Similar results were also observed at each month for ITT population without LOCF and the PP population with LOCF.

3.1.2.2.4.7 Subject Evaluation of Constipation Severity

The summary of results of sponsor's analysis of constipation severity by month for ITT population with LOCF, the ITT population without LOCF, and the PP population with LOCF are given in Appendix Table 22.

As seen from Appendix Table 22, the differences in mean change from baseline between treatment groups were not statistically significant at Months 1, 2, and 3 in constipation severity for ITT population with LOCF.

Similar results were also observed at each month for ITT population without LOCF and the PP population with LOCF.

3.1.2.2.4.8 Subject Evaluation of Symptom Relief

The summary of results of sponsor's analysis of constipation severity by month for ITT population with LOCF, the ITT population without LOCF, and the PP population with LOCF are given in Appendix Table 23.

As seen from Appendix Table 23, the differences in mean rating of symptom relief between treatment groups were not statistically significant at Month 2 in symptom relief for ITT population with LOCF.

Similar results were also observed at each month for ITT population without LOCF and the PP population with LOCF.

3.1.2.2.4.9 IBS Quality of Life

The summary of results of sponsor's analysis of IBS-QOL by month for ITT population without LOCF is given in Appendix Table 24.

As seen from Appendix Table 24, at the end of study time point, the difference in mean change from baseline between treatment groups was statistically significant for overall score for ITT population without LOCF.

3.1.2.3 Reviewer's Comments and Evaluation

3.1.2.3.1 Reviewer's Comments on Sponsor's ITT Population

The sponsor's ITT analysis was not true ITT analysis. It did not include all randomized patients. It excluded more patients in lubiprostone group than in placebo group (8 vs. 2). So, sponsor's ITT analysis might tend to be biased in favor of lubiprostone group.

3.1.2.3.2 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Variable

Even, sponsor's results achieved statistical significance for pre-specified primary efficacy endpoint, but the treatment difference was modest with 6.4%, which might not be considered as clinically significant.

3.1.2.3.2.1 Sensitivity Analysis for Overall Responder

Per this reviewer's request, the sponsor performed a sensitivity analysis for overall responder. The summary of results is given below.

```
                           Study 0432
                        Treatment Group
Timepoint            Placebo                   Lubiprostone
Status               (N=192)                   (N=379)                p-Value²

Overall (LOCF)
     Responder       20 10.4%                   67 17.7%               0.031*
     Non-responder   172 89.6%                  312 82.3%

Overall (Observed Cases)
     Responder       11   5.7%                  46 12.1%               0.023*
     Non-responder   181 94.3%                  333 87.9%

Overall (Worst Case Scenario)
     Responder       8   4.2%                   37   9.8%              0.027*
     Non-responder   184 95.8%                  342 87.9%
_____
Cross Reference: Listing 16.2.6.2; Appendix 16.1.9.2.14.2.1.1
¹ Overall responders are defined as subjects who are monthly responders
for at least two out of any three months during Treatment Phase I.
² p-Value is from a CMH test stratified by pooled-center
* p <= .05
```

As seen from table above, the sponsor's results seem to be robust.

3.1.2.3.2.2 Reviewer's Analysis of Responder for 3 Months

In the sponsor's analysis of primary efficacy endpoint, a subject was considered an overall responder if he or she was a responder for at least two out of any three months during Treatment Phase I.

For more stringent primary efficacy endpoint, a subject was considered a responder if he or she was a responder for three months. The results would be as follows:

Number of Subjects who were Responder for 3 Months
Study SPI/0211SIB-0432
(ITT Population)

Placebo	Lubiprostone	Difference	P-value	95% Confidence Interval
1/192 (0.5%)	18/379 (4.8%)	4.3%	0.0057	(1.9%, 6.6%)

Compiled by this reviewer.
P-value was obtained using Fisher's exact test.

As seen from table above, it achieved statistical significance, but the treatment difference was modest of 4.3%, which might not be considered as clinically significant.

3.1.2.3.2.3 Subgroup Analysis

The primary efficacy parameter for this study was overall responder rate without LOCF.

Subgroup analyses were performed on the number of patients who were overall responder without LOCF by age, gender, and race.

Number of Patients who were Overall Responders by Subgroup
ITT Population without LOCF
Study SPI/0211SIB-0432

Subgroup	Lubiprostone	Placebo	Difference	95% C. I.
Gender				
Male	4/36 (11%)	1/13 (8%)	3%	(-15.4%, 57.7%)
Female	42/343 (12%)	10/179 (6%)	6%	(11.8%, 36.1%)
Age				
18 to 64	44/350 (13%)	8/174 (5%)	8%	(8.4%, 33.0%)
≥65	2/29 (7%)	3/18 (17%)	-10%	(17.1%, 79.3%)
Race				
Black	7/49 (15%)	2/21 (10%)	5%	(-11.2%, 20.7%)
White	36/302 (12%)	9/156 (6%)	6%	(1.0%, 11.3%)
Hispanic	3/25 (12%)	0/12 (0%)	12%	(-0.7%, 24.7%)

Compiled by this reviewer.

As seen from table above, treatment difference was consistent among all subgroups with exception for age.

3.1.2.3.2.4 Number of Months

Per this reviewer's request, the sponsor performed a statistical analysis of the number of months that a subject was considered a month responder. The treatment difference was 0.18 months (0.51 for lubiprostone and 0.34 for placebo). It turned out be about 5 days. So, the treatment difference in terms of number of months that a subject was considered a month responder was modest.

3.1.2.3.2.5 "New" Monthly Responder

Per request from the clinical team, the sponsor provided a new data set including "new" monthly responder. This reviewer performed a statistical analysis for "new" monthly responder (as defined below) at Month 1, Month 2, and Month 3 for Study SPI/0211SIB-0432.

A subject is considered a new monthly responder if symptoms were rated as "significantly relieved" or "moderately relieved" for at least 50% of weeks within a month or at least "a little bit relieved" for all 4 weeks within a month provided that:

1. The percent of days of rescue medication use did not increase during the month as compared to baseline and
2. The subjects did not discontinue during the month due to lack of efficacy and there were no ratings during the month of "Moderately worse" or "Significantly worse".

3.1.2.3.2.5.1 Overall Responder Rate

Results from statistical analyses of overall responder rate for "new" monthly responder for ITT analysis for Study SPI/0211SIB-0432 are given below. In this analysis, patient with missing observation is considered to "failure."

Summary of Overall Responder Rate for " New" Monthly Responder
Study SPI/0211SIB-0432
(Reviewer's ITT Analysis)

Placebo	Lubiprostone	Difference	P-value
55/192 (28.7%)	118/378 (31.1%)	2.4%	0.5410

Compiled by this reviewer.
P-value was obtained using Chi-square test.

As seen from table above, for "new" defined monthly responder, the treatment difference was not statistically significant for overall responder rate.

3.1.2.3.2.5.2 Monthly Responder Rate

Results from statistical analysis of "new" monthly responder for observed case analysis and ITT analysis are given below.

Number of Subjects who were " New" Monthly Responder
Study SPI/0211SIB-0432
(Observed Case)

Month	Placebo	Lubiprostone	Difference	P-value
1	60/179 (33.5%)	126/361 (34.9%)	1.4%	0.7501
2	62/166 (37.4%)	128/326 (39.3%)	1.9%	0.6801
3	43/156 (27.6%)	109/303 (36.0%)	8.4%	0.0698

Compiled by this reviewer.
P-value was obtained using Chi-square test.

Number of Subjects who were " New" Monthly Responder
Study SPI/0211SIB-0432
(Reviewer's ITT)

Month	Placebo	Lubiprostone	Difference	P-value
1	60/192 (31.3%)	126/379 (33.3%)	2.0%	0.6308
2	62/192 (32.3%)	128/379 (33.8%)	1.5%	0.7227
3	43/192 (22.4%)	109/379 (28.8%)	6.4%	0.1041

Compiled by this reviewer.
P-value was obtained using Chi-square test.

As seen from tables above, for "new" defined monthly responder, the treatment difference was not statistically significant at Month 1, Month 2, and Month 3.

3.1.2.3.2.5.3 Responder for 3 Months

For more stringent primary efficacy endpoint, a subject was considered a responder if he or she was a "new" monthly responder for three months. The results would be as follows:

Number of Subjects who were "New" Responder for 3 Months
Study SPI/0211SIB-0432
(ITT Population)

Placebo	Lubiprostone	Difference	P-value	95% Confidence Interval
18/192 (9.4%)	63/379 (16.6%)	7.2%	0.0219	(1.7%, 12.8%)

Compiled by this reviewer.
P-value was obtained using Fisher's exact test.

As seen from table above, it achieved statistical significance for "new" monthly responder, but the treatment difference was modest of 7.2%, which might not be considered as clinically significant.

3.1.2.3.3 Reviewer's Comments on Sponsor's Analyses of Secondary Efficacy Variables

No multiplicity adjustment was pre-specified and applied to secondary efficacy endpoints with exception of month responder rate.

3.1.2.3.3.1 Weekly Responder Rate

Per this reviewer's request, the sponsor performed a statistical analysis of weekly responder rates by week. A weekly responder was any week with a response of moderately relieved or significant relieved. No data imputation was used. The summary of results is given Appendix Table 25.

As seen from Appendix Table 25, treatment difference in weekly responder rates reached statistical significance level ($p < 0.05$) only at Week 2 and Week 5 without adjusting for multiplicity.

3.1.2.3.3.2 Responder Analysis for Spontaneous Bowel Movement

Per this reviewer's request, the sponsor performed three responder analyses for spontaneous bowel movements (SBMs). The responder analyses were as follows:

• a responder is defined as subjects that achieve an average 1 SBM per week increase over baseline.
• a responder is defined as subjects that achieve an average 3 SBM per week increase over baseline.

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• a responder is defined as subjects having an average increase of 1 SBM per week and at least 3 SBMs per week.

The results of these responder analyses for SBMs are given in Appendix Table 26.

As seen from Appendix Table 26, treatment difference was not statistically significant for all three responder analyses. The treatment differences were modest, ranged from 1.6% to 5.2%.

3.2 Evaluation of Safety

3.2.1 Study SPI/0211SIB-0431

Overall, 312 subjects (53.1%) reported at least 1 AE during the study; of these subjects, 106 (55.2%) were in the placebo group and 206 (52.0%) were in the lubiprostone group. One hundred thirty-four subjects overall (22.8%) reported at least 1 treatment-related AE; of these subjects, 42 (21.9%) were in the placebo group and 92 (23.2%) were in the lubiprostone group. Thirty subjects (5.1%) withdrew from the study because of an AE; of these subject, 10 (5.2%) were in the placebo group and 20 (5.1%) were in the lubiprostone group. One subject in the lubiprostone group died during Treatment Phase I.

At the SOC (system/organ/class) level, there was a significant difference between treatment groups in the proportion of subject reporting at least 1 vascular disorder (2.6% of placebo subjects vs. 0.5% of lubiprostone subjects; p=0.028). As expected, the most common body system for AEs was gastrointestinal disorders (21.4% for placebo vs. 27.8% for lubiprostone). Nausea (9.9%), diarrhea (6.6%), and abdominal pain (5.8%) were the only AEs reported by at least 5% of subjects overall. Nausea (11.9% vs. 5/6%) and diarrhea (7.1% vs. 5.7%) were reported more frequently among lubiprostone subjects than placebo subjects.

3.2.2 Study SPI/0211SIB-0432

Overall, 276 subjects (47.7%) reported at least 1 AE during the study; of these subjects, 91 (46.7%) were in the placebo group and 185 (48.2%) were in the lubiprostone group. One Hundred sixteen subjects overall (20.0%) reported at least 1 treatment-related AE; of these subjects, 39 (20.0%) were in the placebo group and 77 (20.1%) were in the lubiprostone group, Thirty-one (5.4%) withdrew from the study because of an AE; of these subject, 15 (7.7%) were in the placebo group and 16 (4.2%) were in the lubiprostone group.

At the SOC (system/organ/class) level, there were no significant differences between treatment groups in the proportion of subjects reporting at least 1 AE. As expected, the most common body system for AEs was gastrointestinal disorders (21.0% for placebo vs. 24.2% for lubiprostone). Nausea (7.8%) and diarrhea (5.7%) were the only AEs reported by at least 5% of subjects overall. Nausea (8.9% vs. 5/6%) and diarrhea (6.0% vs. 5.1%) were reported more frequently among lubiprostone subjects than placebo subjects.

4.   FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.1.1 Study SPI/0211SIB-0431

The primary efficacy parameter for this study was overall responder rate without LOCF during Treatment Phase I.

Subgroup analyses were performed on the number of patients who were overall responder without LOCF during Treatment Phase I by age, gender and race.

Number of Patients who were Overall Responders by Subgroup
ITT Population without LOCF
Study SPI/0211SIB-0431

Subgroup	Lubiprostone	Placebo	Difference	95% C. I.
Gender				
Male	4/35 (11%)	0/13 (0%)	11%	(10.5%, 76.7%)
Female	50/355 (14%)	15/180 (8%)	6%	(4.5%, 307%)
Age				
18 to 64	50/361 (14%)	14/173 (8%)	6%	(10.8%, 36.3%)
≥65	4/29 (14%)	1/20 (5%)	9%	(-47.7%, 27.7%)
Race				
Black	10/53 (19%)	2/29 (7%)	8%	(-2.0%, 26.0%)
White	40/293 (14%)	12/142 (9%)	5%	(-0.8%, 11.2%)
Hispanic	4/43 (9%)	1/18 (6%)	3%	(-9.9%, 17.4%)

Compiled by this reviewer.

As seen from table above, treatment difference was consistent among all subgroups.

4.1.2 Study SPI/0211SIB-0432

The primary efficacy parameter for this study was overall responder rate without LOCF.

Subgroup analyses were performed on the number of patients who were overall responder without LOCF by age, gender, and race.

Number of Patients who were Overall Responders by Subgroup
ITT Population without LOCF
Study SPI/0211SIB-0432

Subgroup	Lubiprostone	Placebo	Difference	95% C. I.
Gender				
Male	4/36 (11%)	1/13 (8%)	3%	(-15.4%, 57.7%)
Female	42/343 (12%)	10/179 (6%)	6%	(11.8%, 36.1%)
Age				
18 to 64	44/350 (13%)	8/174 (5%)	8%	(8.4%, 33.0%)
≥65	2/29 (7%)	3/18 (17%)	-10%	(17.1%, 79.3%)
Race				
Black	7/49 (15%)	2/21 (10%)	5%	(-11.2%, 20.7%)
White	36/302 (12%)	9/156 (6%)	6%	(1.0%, 11.3%)
Hispanic	3/25 (12%)	0/12 (0%)	12%	(-0.7%, 24.7%)

Compiled by this reviewer.

As seen from table above, treatment difference was consistent among all subgroups with exception for age.

5.   SUMMARY AND CONCLUSION

5.1 Statistical Issues and Collective Evidence

Study SIB-0431 showed that lubiprostone was statistically significant compared to placebo group in terms of the primary efficacy endpoint, overall responder rate without LOCF during Treatment Phase I. However, a worst-case analysis (missing response set to failure) did not show statistical significance (p=0.063) which indicates the results are sensitive to this imputation assumption. The treatment difference was modest at about 6%. Furthermore, the superiority was not shown for any secondary efficacy endpoints with exception of monthly responder rate at Month 2.

The efficacy results from study SIB-04131 were replicated in study SIB-0432 for the primary efficacy endpoint. However, the treatment difference was also modest at 6.4%. Furthermore, superiority was not shown for all secondary efficacy endpoints.

This reviewer performed an efficacy analysis using a more clinically meaningful but more stringent efficacy parameter, defining responder as a patient who was a monthly responder for all 3 months and who did not use rescue medication during or within 24 hours prior to the given week, and who did not drop out during the study due to lack of efficacy. In this analysis, patients with missing outcomes were set to as no response. Based on this post-hoc analysis, only study SIB-0432 showed that lubiprostone was superior to the placebo with treatment differences of about 4.3%., which may not be considered clinically meaningful.

Per request from the clinical team, I performed a statistical analysis for "new" monthly responder using a less stringent responder definition and one more consistent with other clinical trials for IBS-C. A subject was considered a "new" monthly responder if symptoms were rated as "significantly relieved" or "moderately relieved" for at least 50% of weeks within a month or at least "a little bit relieved" for all 4 weeks within a month. Results from this statistical analyses showed that treatment differences failed to reach statistical significance for this overall responder rate for both studies. Treatment differences were 7.5% for Study SIB-04131 and 2.4% for Study SIB-04132.

Per this reviewer's request, the sponsor performed a statistical analysis of the number of months that a subject was considered a month responder. In both studies, the treatment difference in terms of number of months that a subject was considered a month responder was a modest 0.18 months or about 5 days.

Per this reviewer's request, the sponsor performed a statistical analysis of weekly responder rates by week. A weekly responder was any week with a response of moderately relieved or significant relieved. No data imputation was used.

It was shown that treatment difference in weekly responder rates reached statistical significance level (p<0.05) only at Week 4 and Week 6 for Study SIB-0431 and at Week 2 and Week 5 for Study SIB-0432. No adjustments for multiplicity were applied.

There were inconsistent results in treatment difference in weekly responder rates between the two studies.

Per this reviewer's request, the sponsor performed three responder analyses for spontaneous bowel movements (SBMs). The responder analyses were as follows:

• a responder is defined as subjects that achieve an average 1 SBM per week increase over baseline.
• a responder is defined as subjects that achieve an average 3 SBMs per week increase over baseline.
• a responder is defined as subjects having an average increase of 1 SBM per week and at least 3 SBMs per week.

These analyses indicated that treatment differences were not statistically significant for all three responder analyses for both studies. The treatment differences were modest, ranging from 1.6% to 5.6% for Study SIB-0431 and 1.6% to 5.2% for Study SIB-0432.

Furthermore, superiority was not shown for any secondary efficacy endpoints for both studies with exception for monthly responder rate at Month 2 for study SIB-0431.

Although both studies showed that the lubiprostone was superior to the placebo for the pre-specified primary efficacy endpoint, the treatment differences were modest with 6.0% and 6.4%, respectively. For a more stringent efficacy endpoint (monthly responder for all 3 months), the reviewer's post-hoc analysis revealed that the lubiprostone was superior to

the placebo with treatment differences of about 4.3% for study SIB-0432. For the "new" defined monthly responder which was less stringent than pre-specified monthly responder, the treatment differences failed to reach statistical significance for overall responder rate for both studies.

5.2 Conclusions and Recommendation

Lubiprostone (Capsules) was approved January 31, 2006 for the treatment of chronic idiopathic constipation (CIC) in the adult population with recommended dosage of 24 mcg twice daily (BID). This efficacy supplement has been submitted for the additional indication of Irritable Bowel Syndrome with Constipation (IBS-C) using a new strength of the drug product (8 mcg BID).

The sponsor has submitted two pivotal studies (SIB-04131 and SIB-04132) to support the claim. Both studies showed that lubiprostone was superior to placebo for the pre-specified primary efficacy endpoint based on monthly responder for at least two of the three months of study. However, the treatment differences were small at 6.0% and 6.4%, respectively. Moreover, in both studies, superiority was not demonstrated for all secondary endpoints.

Several post-hoc efficacy analyses were conducted by this reviewer by varying the criteria that defined patient response. These sensitivity analyses showed that based on a more stringent definition of responder (monthly responder for all 3 months) lubiprostone was superior to the placebo in one study with a treatment difference of only 4.3%. Based on a less stringent responder definition suggested by the clinical team as more consistent with that used in other IBS-C trials, treatment differences did not reach statistical significance in either study.

From a statistical perspective, the sponsor has provided two adequate and well-controlled studies which show the superiority of lubiprostone to placebo for the treatment of IBS-C; however, the treatment differences are modest and may not be clinically substantial.

6. APPENDIX

Table 1 Summary of Demographic and Baseline Characteristics --- Protocol SPI/0211SIB-0431

Characteristics	(ITT Subjects) Placebo (N=193)	Lubiprostone (N=390)	Between Treatment p-value
Sex			0.355
Male	13 (6.7%)	35 (9.0%)	
Female	180 (93.3%)	355 (91.0%)	
Race			0.103
White	142 (73.6%)	293 (75.1%)	
Black	29 (15.0%)	53 (13.6%)	
Asian	1 (0.5%)	0 (0.0%)	
Hispanic	18 (9.3%)	43 (11.0%)	
American Indian/ Alaska Native	0 (0.0%)	1 (0.3%)	
Other Races	3 (1.6%)	1 (0.8%)	
Age (months)			0.198
Mean (SD)	48.1 (12.6)	46.7 (12.7)	
Age			0.231
18 to 64	173 (89.6%)	361 (92.6%)	
≥65	20 (10.4%)	29 (7.4%)	
Height (in)			0.626
N	193	388	
Mean (SD)	64.8 (3.10)	64.9 (2.90)	
Weight (lb)			0.118
N	192	387	
Mean (SD)	164.3 (40.3)	159.4 (32.3)	
Abdominal Discomfort/ Pain			0.885
Mean (SD)	2.09 (0.693)	2.08 (0.665)	
Abdominal Bloating			0.877
Mean (SD)	2.28 (0.735)	2.27 (0.686)	
Constipation Severity			0.441
Mean (SD)	2.29 (0.643)	2.24 (0.652)	
Weekly SBM Frequency			0.814
Mean (SD)	3.69 (3.324)	3.76 (3.185)	
Percent Rescue Med Usage			0.550
Mean (SD)	14.05 (20.922)	12.96 (20.666)	

Copied from Tables 14-1.4, 14-1.6
P-values are based on t-tests for age, height, and weight.
P-values are based on Chi-square tests for categorical variables and binary variables.

Table 1 Summary of Demographic and Baseline Characteristics --- Protocol SPI/0211SIB-0431

Characteristics	((ITT Subjects) Placebo (N=193)	Lubiprostone (N=390)	Between Treatment p-value
Weekly BM Frequency			0.664
Mean (SD)	4.48 (3.168)	4.61 (3.436)	
SBM Consistency			0.582
N	187	375	
Mean (SD)	2.74 (0.661)	2.78 (0.640)	
SBM Straining			0.673
N	187	375	
Mean (SD)	2.41 (0.733)	2.38 (0.721)	
<3 SBMs/Week≥25% of time			0.532
Yes	151 (78.2%)	293 (75.1%)	
No	42 (21.8%)	93 (23.8%)	
Missing	0 (0.0%)	4 (1.0%)	
Straining ≥moderate ≥25% of the Time			0.904
Yes	179 (92.7%)	354 (90.8%)	
No	9 (4.7%)	20 (5.1%)	
Exempt	5 (2.6%)	12 (3/1%)	
Missing	0 (0.0%)	4 (1.0%)	
Consistency ≥hard ≥25% of the Time			0.648
Yes	185 (95.9%)	371 (95.1%)	
No	3 (1.6%)	3 (0.8%)	
Exempt	5 (2.6%)	12 (3.1%)	
Missing	0 (0.0%)	4 (1.0%)	

Copied from Tables 14-1.4, 14-1.6
P-values are based on t-tests for continuous variables.
P-values are based on Chi-square tests for categorical variables and binary variables.

Table 2 Summaries of Monthly Responder Rate --- Protocol SPI/0211SIB-0431

Month Treatment Group	ITT Subjects with LOCF	ITT subjects without LOCF	ITT subjects who completed the study	PP subject without LOCF
Month 1				
Placebo , n	193	193	139	187
Responder	15 (7.8%)	12 (6.2%)	11 (7.9%)	12 (6.6%)
Lubiprostone, n	390	390	296	375
Responder	43 (11.0%)	39 (10.0%)	37 (12.5%)	38(10.5%)
Difference (Lub-Pla)	3.2%	3.8%	4.6%	3.9%
P-value	0.174	0.098	0.160	0.097
Month 2				
Placebo , n	193	193	139	187
Responder	21 (10.9%)	18 (9.3%)	17 (12.2%)	16 (8.9%)
Lubiprostone, n	390	390	296	375
Responder	73 (18.7%)	62 (15.9%)	54 (18.2%)	59(16.3%)
Difference (Lub-Pla)	7.8%	6.6%	6.0%	7.4%
P-value	0.016*	0.028*	0.149	0.015*
Month 3				
Placebo , n	193	193	139	187
Responder	28 (14.5%)	20 (10.4%)	19 (13.7%)	17 (9.2%)
Lubiprostone, n	390	390	296	375
Responder	83 (21.3%)	62 (15.9%)	61 (20.6%)	60(16.4%)
Difference (Lub-Pla)	6.8%	5.5%	6.9%	7.2%
P-value	0.053	0.069	0.081	0.019

Copied from Table 14.2.2.1 – 14.2.2.4.
P-values are from CMH tests stratified by pooled-center.
*P-value is significant according to the testing procedure.

Table 3 Summaries of Abdominal Discomfort/Pain at Month 1, 2, and 3 --- Protocol SPI/0211SIB-0431

Month Treatment Group Statistic	ITT Subjects with LOCF	ITT subjects without LOCF	Per Protocol Subjects with LOCF	
Baseline				
Placebo , n	193	193	187	
Mean (Std Dev)	2.09 (0.693)	2.09 (0.693)	2.09 (0.683)	
Median	2.07	2.07	2.07	
Lubiprostone, n	390	390	375	
Mean (Std Dev)	2.08 (0.665)	2.08 (0.665)	2.08 (0.659)	
Median	2.02	2.02	2.00	
P-value	0.975	0.975	0.993	
Month 1				
Placebo , n	193	193	181	
Mean (Std Dev)	1.81 (0.740)	1.81 (0.740)	1.81 (0.718)	
Median	1.79	1.79	1.79	
Lubiprostone, n	390	390	363	
Mean (Std Dev)	1.78 (0.740)	1.78 (0.740)	1.80 (0.744)	
Median	1.73	1.73	1.76	
P-value	0.852	0.852	0.860	
Month 2				
Placebo , n	193	168	179	
Mean (Std Dev)	1.71 (0.768)	1.69 (0.780)	1.72 (0.768)	
Median	1.69	1.68	1.71	
Lubiprostone, n	390	355	362	
Mean (Std Dev)	1.65 (0.838)	1.62 (0.832)	1.65 (0.822)	
Median	1.51	1.50	1.52	
P-value	0.646	0.758	0.482	
Month 3				
Placebo , n	193	145	184	
Mean (Std Dev)	1.73 (0.801)	1.67 (0.812)	1.74 (0.800)	
Median	1.72	1.63	1.73	
Lubiprostone, n	390	329	366	
Mean (Std Dev)	1.65 (0.835)	1.60 (0.817)	1.66 (0.827)	
Median	1.58	1.56	1.60	
P-value	0.277	0.403	0.095	

Copied from Tables 14.2.3.1, 14.2.3.2, and 14.2.3.3,
p-values are based on van Elteren tests adjusted for pooled center.

Table 4 Summaries of Abdominal Bloating at Month 1, 2, and 3 --- Protocol SPI/0211SIB-0431

Month Treatment Group Statistic	ITT Subjects with LOCF	ITT subjects without LOCF	Per Protocol Subjects with LOCF
Baseline			
Placebo , n	193	193	187
Mean (Std Dev)	2.28 (0.735)	2.28 (0.735)	2.29 (0.725)
Median	2.19	2.19	2.22
Lubiprostone, n	390	390	375
Mean (Std Dev)	2.27 (0.686)	2.27 (0.686)	2.28 (0.680)
Median	2.19	2.19	2.18
P-value	0.987	0.987	0.906
Month 1			
Placebo , n	193	193	181
Mean (Std Dev)	2.04 (0.796)	2.04 (0.796)	2.04 (0.778)
Median	2.00	2.00	2.00
Lubiprostone, n	390	390	363
Mean (Std Dev)	1.97 (0.773)	1.97 (0.773)	1.98 (0.769)
Median	1.90	1.90	1.92
P-value	0.615	0.615	0.393
Month 2			
Placebo , n	193	168	179
Mean (Std Dev)	1.93 (0.837)	1.94 (0.851)	1.93 (0.832)
Median	1.96	1.93	1.96
Lubiprostone, n	390	355	362
Mean (Std Dev)	1.85 (0.876)	1.82 (0.873)	1.86 (0.863)
Median	1.75	1.70	1.76
P-value	0.286	0.338	0.379
Month 3			
Placebo , n	193	145	184
Mean (Std Dev)	1.91 (0.873)	1.84 (0.884)	1.92 (0.870)
Median	1.96	1.80	1.96
Lubiprostone, n	390	329	366
Mean (Std Dev)	1.84 (0.869)	1.79 (0.851)	1.85 (0.863)
Median	1.79	1.77	1.79
P-value	0.337	0.781	0.286

Copied from Tables 14.2.5.1, 14.2.5.2, and 14.2.5.3.
p-values are based on van Elteren tests adjusted for pooled center.

Table 5 Summaries of SBM Frequency Rates at Month 1, 2, and 3 --- Protocol SPI/0211SIB-0431

Month
  Treatment Group
    Statistic
	ITT Subjects
	with LOCF
		ITT subjects
		without LOCF
			Per Protocol
			Subjects with
			LOCF

Baseline			
Placebo , n	193	193	187
Mean (Std Dev)	3.69 (3.324)	3.69 (3.324)	3.66 (3.307)
Median	3.11	3.11	3.11
Lubiprostone, n	390	390	375
Mean (Std Dev)	3.76 (3.185)	3.76 (3.185)	3.72 (3.206)
Median	3.25	3.25	3.25
P-value	0.660	0.660	0.698
Month 1			
Placebo , n	185	122	173
Mean (Std Dev)	4.91 (3.274)	4.91 (3.274)	4.91 (3.253)
Median	4.25	4.25	4.25
Lubiprostone, n	382	382	357
Mean (Std Dev)	5.32 (3.696)	5.32 (3.696)	5.29 (3.755)
Median	5.00	5.00	5.00
P-value	0.117	0.117	0.184
Month 2			
Placebo , n	186	168	172
Mean (Std Dev)	5.10 (3.829)	5.26 (3.932)	5.00 (3.579)
Median	4.33	4.63	4.44
Lubiprostone, n	383	355	355
Mean (Std Dev)	5.37 (3.820)	5.52 (3.874)	5.32 (3.820)
Median	5.00	5.0	5.00
P-value	0.334	0.289	0.348
Month 3			
Placebo , n	186	145	177
Mean (Std Dev)	5.08 (3.911)	5.397 (3.829)	5.04 (3.944)
Median	4.45	3.829	4.38
Lubiprostone, n	383	329	359
Mean (Std Dev)	5.29 (3.875)	5.45 (3.928)	5.28 (3.906)
Median	4.75	5.0	4.75
P-value	0.242	0.547	0.183

Copied from Tables 14.2.7.1, 14.2.7.2, and 14.2.7.3.
p-values are based on van Elteren tests adjusted for pooled center.

Table 6 Summaries of BM Frequency Rates at Month 1, 2, and 3 --- Protocol SPI/0211SIB-0431

Month
  Treatment Group
    Statistic
	ITT Subjects
	with LOCF
		ITT subjects
		without LOCF
			Per Protocol
			Subjects with
			LOCF

Baseline			
Placebo , n	193	193	187
Mean (Std Dev)	4.48 (3.168)	4.48 (3.168)	4.47 (3.148)
Median	3.96	3.96	3.96
Lubiprostone, n	390	390	375
Mean (Std Dev)	4.61 (3.436)	4.61 (3.436)	4.58 (3.468)
Median	3.90	3.90	3.89
P-value	0.798	0.798	0.841
Month 1			
Placebo , n	185	185	173
Mean (Std Dev)	5.37 (3.042)	5.37 (3.042)	5.36 (3.049)
Median	4.75	4.75	4.75
Lubiprostone, n	382	382	357
Mean (Std Dev)	5.85 (3.535)	5.85 (3.535)	5.82 (3.573)
Median	5.25	5.25	5.25
P-value	0.108	0.108	0.196
Month 2			
Placebo , n	186	168	172
Mean (Std Dev)	5.58 (3.694)	5.69 (3.817)	5.44 (3.411)
Median	5.00	5.13	4.88
Lubiprostone, n	383	355	355
Mean (Std Dev)	5.86 (3.590)	5.93 (3.679)	5.83 (3.588)
Median	5.25	5.25	5.25
P-value	0.483	0.399	0.565
Month 3			
Placebo , n	186	145	177
Mean (Std Dev)	5.53 (3.773)	5.69 (3.760)	5.50 (3.797)
Median	5.00	5.12	5.00
Lubiprostone, n	383	329	359
Mean (Std Dev)	5.78 (3.674)	5.84 (3.785)	5.78 (3.707)
Median	5.25	5.25	5.12
P-value	0.491	0.710	0.412

Copied from Tables 14.2.7.1, 14.2.7.2, and 14.2.7.3.
p-values are based on van Elteren tests adjusted for pooled center.

Table 7 Summaries of Stool Consistency at Month 1, 2, and 3 --- Protocol SPI/0211S1B-0431

Month Treatment Group Statistic	ITT Subjects with LOCF	ITT subjects without LOCF	Per Protocol Subjects with LOCF
Baseline			
Placebo , n	187	187	182
Mean (Std Dev)	2.74 (0.661)	2.74 (0.661)	2.75 (0.666)
Median	2.71	2.71	2.71
Lubiprostone, n	375	375	360
Mean (Std Dev)	2.78 (0.640)	2.78 (0.640)	2.78 (0.646)
Median	2.80	2.80	2.80
P-value	0.644	0.644	0.582
Month 1			
Placebo , n	191	191	179
Mean (Std Dev)	2.42 (0.665)	2.42 (0.665)	2.43 (0.667)
Median	2.38	2.38	2.38
Lubiprostone, n	378	378	353
Mean (Std Dev)	2.25 (0.694)	2.25 (0.694)	2.27 (0.698)
Median	2.25	2.25	2.25
P-value	0.006	0.006	0.010
Month 2			
Placebo , n	192	165	178
Mean (Std Dev)	2.37 (0.696)	2.34 (0.664)	2.37 (0.711)
Median	2.28	2.28	2.29
Lubiprostone, n	382	352	354
Mean (Std Dev)	2.25 (0.711)	2.25 (0.692)	2.25 (0.723)
Median	2.25	2.24	2.22
P-value	0.030	0.077	0.0028
Month 3			
Placebo , n	192	144	183
Mean (Std Dev)	2.34 (0.699)	2.30 (0.656)	2.35 (0.697)
Median	2.28	2.26	2.29
Lubiprostone, n	382	323	358
Mean (Std Dev)	2.26 (0.714)	2.26 (0.688)	2.26 (0.721)
Median	2.20	2.19	2.20
P-value	0.130	0.248	0.113

Copied from Tables 14.2.9.1, 14.2.9.2, and 14.2.9.3.
p-values are based on van Elteren tests adjusted for pooled center.

Table 8 Summaries of Degree of Straining at Month 1, 2, and 3 --- Protocol SPI/0211SIB-0431

Month Treatment Group Statistic	ITT Subjects with LOCF	ITT subjects without LOCF	Per Protocol Subjects with LOCF
Baseline			
Placebo , n	187	187	182
Mean (Std Dev)	2.41 (0.733)	2.41 (0.733)	2.42 (0.734)
Median	2.30	2.30	2.31
Lubiprostone, n	375	375	360
Mean (Std Dev)	2.38 (0.721)	2.38 (0.721)	2.39 (0.712)
Median	2.33	2.33	2.36
P-value	0.789	0.789	0.836
Month 1			
Placebo , n	191	191	179
Mean (Std Dev)	2.04 (0.783)	2.04 (0.783)	2.07 (0.769)
Median	2.00	2.00	2.03
Lubiprostone, n	378	378	353
Mean (Std Dev)	1.86 (0.767)	1.86 (0.767)	1.86 (0.772)
Median	1.80	1.80	1.81
P-value	0.050	0.050	0.022
Month 2			
Placebo , n	192	165	178
Mean (Std Dev)	1.98 (0.831)	1.94 (0.813)	1.99 (0.840)
Median	2.00	1.97	2.00
Lubiprostone, n	382	352	354
Mean (Std Dev)	1.81 (0.834)	1.79 (0.832)	1.83 (0.836)
Median	1.76	1.73	1.79
P-value	0.049	0.169	0.0040
Month 3			
Placebo , n	192	144	183
Mean (Std Dev)	1.96 (0.836)	1.91 (0.817)	1.98 (0.821)
Median	2.00	1.93	2.0
Lubiprostone, n	382	323	358
Mean (Std Dev)	1.83 (0.853)	1.79 (0.843)	1.84 (0.853)
Median	2.80	1.78	1.82
P-value	0.348	0.650	0.235

Copied from Tables 14.2.11.1, 14.2.11.2, and 14.2.11.3.
p-values are based on van Elteren tests adjusted for pooled center.

Table 9 Summaries of Constipation Severity at Month 1, 2, and 3 --- Protocol SPI/0211SIB-0431

Month
  Treatment Group
    Statistic
	ITT Subjects
	with LOCF
		ITT subjects
		without LOCF
			Per Protocol
			Subjects with
			LOCF

Baseline			
Placebo , n	193	193	187
Mean (Std Dev)	2.29 (0.643)	2.29 (0.643)	2.28 (0.638)
Median	2.23	2.23	2.23
Lubiprostone, n	390	390	375
Mean (Std Dev)	2.24 (0.652)	2.24 (0.652)	2.25 (0.645)
Median	2.19	2.19	2.20
P-value	0.514	0.514	0.567
Month 1			
Placebo , n	193	193	181
Mean (Std Dev)	1.99 (0.784)	1.99 (0.784)	2.00 (0.770)
Median	2.00	2.00	2.00
Lubiprostone, n	390	390	363
Mean (Std Dev)	1.83 (0.784)	1.83 (0.784)	1.84 (0.785)
Median	1.79	1.79	1.81
P-value	0.159	0.159	0.081
Month 2			
Placebo , n	193	168	179
Mean (Std Dev)	1.89 (0.822)	1.87 (0.826)	1.88 (0.831)
Median	1.85	1.82	1.83
Lubiprostone, n	390	355	362
Mean (Std Dev)	1.74 (0.863)	1.72 (0.848)	1.75 (0.854)
Median	1.72	1.68	1.72
P-value	0.064	0.100	0.0071
Month 3			
Placebo , n	193	145	184
Mean (Std Dev)	1.88 (0.846)	1.79 (0.836)	1.89 (0.841)
Median	1.92	1.71	1.94
Lubiprostone, n	390	329	366
Mean (Std Dev)	1.73 (0.881)	1.68 (0.853)	1.74 (0.879)
Median	1.71	1.64	1.72
P-value	0.111	0.530	0.058

Copied from Tables 14.2.13.1, 14.2.13.2, and 14.2.13.3.
p-values are based on van Elteren tests adjusted for pooled center.

Table 10 Summaries of Symptom Relief at Month 1, 2, and 3 --- Protocol SPI/0211SIB-0431

Month
  Treatment Group
    Statistic
	ITT Subjects
	with LOCF
		ITT subjects
		without LOCF
			Per Protocol
			Subjects with
			LOCF

Month 1			
Placebo , n	177	177	167
Mean (Std Dev)	0.57 (1.088)	0.57 (1.088)	0.55 (1.091)
Median	0.50	0.50	0.50
Lubiprostone, n	365	365	344
Mean (Std Dev)	0.66 (1.212)	0.66 (1.212)	0.65 (1.210)
Median	0.75	0.75	0.75
P-value	0.378	0.378	0.280
Month 2			
Placebo , n	184	164	171
Mean (Std Dev)	0.59 (1.203)	0.64 (1.198)	0.57 (1.204)
Median	0.50	0.71	0.50
Lubiprostone, n	379	344	352
Mean (Std Dev)	0.76 (1.278)	0.84 (1.241)	0.76 (1.260)
Median	0.75	1.00	0.75
P-value	0.144	0.130	0.085
Month 3			
Placebo , n	185	145	176
Mean (Std Dev)	0.57 (1.277)	0.71 (1.234)	0.58 (1.266)
Median	0.50	0.75	0.50
Lubiprostone, n	381	322	358
Mean (Std Dev)	0.74 (1.259)	0.83 (1.196)	0.72 (1.265)
Median	0.75	0.75	0.75
P-value	0.168	0.333	0.188

Copied from Tables 14.2.15.1, 14.2.15.2, and 14.2.15.3.
p-values are based on van Elteren tests adjusted for pooled center.

**Table 11 Summaries of IBS Quality of Life Scores at Week 4, Week 12, and Last ---
Protocol SPI/0211SIB-0431**

Summary of IBS Quality of Life at Week 4, Week 12, and Last
(Intent-to-Treat Population without LOCF)
Study SP1/0211SIB-0431
Overall Score

Week	n	Placebo Mean (St. Dev)	Median	n	Lubiprostone Mean (St. Dev)	Median	P-value
Baseline	183	54.8 (22.31)	56.6	376	56.2 (21.59)	58.1	0.488
Week 4	131	65.3 (21.91)	68.4	297	69.3 (20.81)	74.3	0.359
Week 12	97	70.6 (20.37)	76.5	229	74.1 (20.41)	79.4	0.588
Last	181	70.7 (21.51)	77.9	361	72.0 (21.06)	78.7	0.804

Copied from Table 14-2.17.1.
Baseline p-values are from two-sample t-test, and weekly p-values are for the treatment effect from an
ANOVA model for pooled-center and the baseline value.

Table 12 Weekly Responder Rates --- Protocol SPI/0211SIB-0431

Weekly Responder Rates
Study 0431

Status	Placebo (N=193)		Lubiprostone (N=390)		p-Value[1]
Treatment Group					
Week 1					
Responder	33	19.8%	70	20.3%	0.931
Non-responder	134	80.2%	275	79.7%	
Week 2					
Responder	41	23.6%	93	25.9%	0.575
Non-responder	133	76.4%	266	74.1%	
Week 3					
Responder	42	23.9%	108	29.8%	0.114
Non-responder	134	76.1%	255	70.2%	
Week 4					
Responder	45	25.4%	127	34.8%	0.026*
Non-responder	132	74.6%	238	65.2%	
Week 5					
Responder	44	24.7%	118	31.6%	0.125
Non-responder	134	75.3%	255	68.4%	
Week 6					
Responder	41	22.8%	128	33.8%	0.011*
Non-responder	139	77.2%	251	66.2%	
Week 7					
Responder	47	25.7%	125	33.0%	0.095
Non-responder	136	74.3%	254	67.0%	
Week 8					
Responder	51	27.7%	129	34.0%	0.143
Non-responder	133	72.3%	250	66.0%	
Week 9					
Responder	54	29.2%	116	30.5%	0.793
Non-responder	131	70.8%	264	69.5%	
Week 10					
Responder	44	23.8%	119	31.2%	0.085
Non-responder	141	76.2%	262	68.8%	
Week 11					
Responder	48	26.0%	120	31.5%	0.210
Non-responder	137	74.0%	261	68.5%	
Week 12					
Responder	47	25.4%	122	32.0%	0.119
Non-responder	138	74.6%	259	68.0%	

[1] p-Value is from a CMH test stratified by pooled site

Table 13 Responder Analysis for Spontaneous Bowel Movements --- Protocol SPI/0211SIB-0431

Summary of Responder¹ Rates
Intent–to–Treat Subjects

Status	Placebo (N=193)		Lubiprostone 16 mcg (N=390)		p–Value²
Responder	99	53.2%	210	54.8%	0.832
Non–responder	87	46.8%	173	45.2%	

Responders are defined as subjects who have a change of at least 1 in SBM frequency over the treatment period.

Summary of Responder¹ Rates
Intent–to–Treat Subjects

Status	Placebo (N=193)		Lubiprostone 16 mcg (N=390)		p–Value²
Responder	37	19.9%	85	22.2%	0.597
Non–responder	149	80.1%	298	77.8%	

Responders are defined as subjects who have a change of at least 3 in SBM frequency over the treatment period.

Summary of Responder¹ Rates
Intent–to–Treat Subjects

Status	Placebo (N=193)		Lubiprostone 16 mcg (N=390)		p–Value²
Responder	49	26.3%	122	31.9%	0.216
Non–responder	137	73.7%	261	68.1%	

Responders are defined as subjects who have a change of at least 1 in SBM frequency over the treatment period and have at least 3 SBMs every week during the treatment period.

Table 14 Summary of Demographic and Baseline Characteristics --- Protocol SPI/0211SB-0432

Characteristics	Placebo (N=192)	Lubiprostone (N=379)	Between Treatment p-value
	(ITT Subjects)		
Sex			0.272
Male	13 (6.8%)	36 (9.5%)	
Female	179 (93.2%)	343 (90.5%)	
Race			0.336
White	156 (81.3%)	302 (79.7%)	
Black	21 (10.9%)	49 (12.9%)	
Asian	1 (0.5%)	3 (0.8%)	
Hispanic	12 (6.3%)	25 (6.6%)	
Other Races	2 (1.0%)	0 (0.0%)	
Age (months)			0.132
Mean (SD)	47.3 (13.3)	45.5 (12.9)	
Age			0.479
18 to 64	174 (90.6%)	350 (92.4%)	
≥65	18 (9.4%)	29 (7.6%)	
Height (in)			0.388
N	192	378	
Mean (SD)	65.0 (3.34)	64.7 (3.15)	
Weight (lb)			0.282
Mean (SD)	156.6 (35.58)	160.1 (37.46)	
Abdominal Discomfort/ Pain			0.849
Mean (SD)	2.08 (0.642)	2.07 (0.652)	
Abdominal Bloating			0.932
Mean (SD)	2.24 (0.651)	2.24 (0.682)	
Constipation Severity			0.820
Mean (SD)	2.21 (0.646)	2.20 (0.669)	
Weekly SBM Frequency			0.823
Mean (SD)	3.98 (3.806)	4.05 (3.451)	
Percent Rescue Med Usage			0.030
Mean (SD)	15.23 (15.228)	11.72 (17.514)	

Copied from Tables 14-1.4, 14-1.6
P-values are based on t-tests for age, height, and weight.
P-values are based on Chi-square tests for categorical variables and binary variables.

Table 14 Summary of Demographic and Baseline Characteristics --- Protocol SPI/0211SB-0432 (Continued)

Characteristics	((ITT Subjects) Placebo (N=192)	Lubiprostone (N=379)	Between Treatment p-value
Weekly BM Frequency			0.325
Mean (SD)	5.14 (4.281)	4.82 (3.346)	
SBM Consistency			0.816
N	177	370	
Mean (SD)	2.76 (0.721)	2.75 (0.677)	
SBM Straining			0.978
N	177	370	
Mean (SD)	2.39 (0.753)	2.39 (0.676)	
<3 SBMs/Week≥25% of the time			0.918
Yes	144 (75.0%)	282 (74.4%)	
No	48 (25.0%)	96 (25.3%)	
Missing	0 (0.0%)	1 (0.3%)	
Straining ≥moderate ≥25% of the Time			0.004
Yes	164 (85.4%)	352 (92.9%)	
No	13 (6.8%)	17 (4.5%)	
Exempt	15 (7.8%)	9 (2.4%)	
Missing	0 (0.0%)	1 (0.3%)	
Consistency ≥hard ≥25% of the Time			<0.001
Yes	172 (89.6%)	369 (97.4%)	
No	5 (2.6%)	0 (0.8%)	
Exempt	15 (7.8%)	9 (2.4%)	
Missing	0 (0.0%)	1 (0.3%)	

Copied from Tables 14-1.4, 14-1.6
P-values are based on t-tests for continuous variables.
P-values are based on Chi-square tests for categorical variables and binary variables.

Table 15 Summaries of Monthly Responder Rate --- Protocol SPI/0211SB-0432

Month Treatment Group	ITT Subjects with LOCF	ITT subjects without LOCF	ITT subjects who completed the study	PP subject without LOCF
Month 1				
Placebo , n	192	192	151	191
Responder	14 (7.3%)	13 (6.8%)	12 (7.9%)	13 (7.0%)
Lubiprostone, n	379	379	302	364
Responder	40 (10.6%)	37 (9.8%)	34 (11.3%)	35(9.7%)
Difference (Lub-Pla)	3.3%	3.0%	3.4%	2.7%
P-value	0.278	0.303	0.355	0.366
Month 2				
Placebo , n	192	192	151	191
Responder	23 (12.0%)	19 (9.9%)	18 (11.9%)	19(10.1%)
Lubiprostone, n	379	379	302	364
Responder	68 (17.9%)	61 (16.1%)	56 (18.5%)	59(16.5%)
Difference (Lub-Pla)	5.9%	6.2%	6.6%	6.4%
P-value	0.074	0.047	0.066	0.044
Month 3				
Placebo , n	192	192	151	191
Responder	28 (14.6%)	11 (5.7%)	11 (7.3%)	11 (5.9%)
Lubiprostone, n	379	379	302	364
Responder	86 (22.7%)	51 (13.5%)	50 (16.6%)	47(13.1%)
Difference (Lub-Pla)	8.1%	7.8%	9.3%	7.2%
P-value	0.026	0.008	0.009	0.016

Copied from Table 14.2.2.1 – 14.2.2.4.
P-values are from CMH tests stratified by pooled-center.
*P-value is significant according to the testing procedure.

Table 16 Summaries of Abdominal Discomfort/Pain at Month 1, 2, and 3 --- Protocol SPI/0211SIB-0432

Month Treatment Group Statistic	ITT Subjects with LOCF	ITT subjects without LOCF	Per Protocol Subjects with LOCF
Baseline			
Placebo , n	192	192	191
Mean (Std Dev)	2.08 (0.642)	2.08 (0.642)	2.08 (0.644)
Median	2.04	2.04	2.04
Lubiprostone, n	379	379	364
Mean (Std Dev)	2.07 (0.652)	2.07 (0.652)	2.06 (0.643)
Median	2.04	2.04	2.02
P-value	0.973	0.973	0.886
Month 1			
Placebo , n	191	191	184
Mean (Std Dev)	1.79 (0.747)	1.79 (0.747)	1.79 (0.758)
Median	1.80	1.80	1.78
Lubiprostone, n	378	378	358
Mean (Std Dev)	1.75 (0.745)	1.75 (0.745)	1.74 (0.737)
Median	1.66	1.66	1.65
P-value	0.663	0.663	0.819
Month 2			
Placebo , n	192	171	188
Mean (Std Dev)	1.75 (0.790)	1.73 (0.820)	1.75 (0.792)
Median	1.74	1.68	1.75
Lubiprostone, n	379	338	357
Mean (Std Dev)	1.63 (0.851)	1.57 (0.822)	1.64 (0.852)
Median	1.56	1.50	1.56
P-value	0.224	0.163	0.226
Month 3			
Placebo , n	192	159	188
Mean (Std Dev)	1.73 (0.815)	1.69 (0.842)	1.72 (0.820)
Median	1.74	1.68	1.73
Lubiprostone, n	379	316	360
Mean (Std Dev)	1.60 (0.850)	1.54 (0.820)	1.61 (0.854)
Median	1.61	1.59	1.61
P-value	0.271	0.216	0.418

Copied from Tables 14.2.3.1, 14.2.3.2, and 14.2.3.3,
p-values are based on van Elteren tests adjusted for pooled center.

Table 17 Summaries of Abdominal Bloating at Month 1, 2, and 3 --- Protocol SPI/0211SIB-0432

Month
  Treatment Group
    Statistic
	ITT Subjects
	with LOCF
		ITT subjects
		without LOCF
			Per Protocol
			Subjects with
			LOCF

Baseline			
Placebo , n	192	192	191
Mean (Std Dev)	2.24 (0.651)	2.24 (0.651)	2.24 (0.652)
Median	2.21	2.21	2.21
Lubiprostone, n	379	379	364
Mean (Std Dev)	2.24 (0.682)	2.24 (0.682)	2.23 (0.674)
Median	2.19	2.19	2.19
P-value	0.931	0.931	0.747
Month 1			
Placebo , n	191	191	184
Mean (Std Dev)	1.95 (0.781)	1.95 (0.781)	1.95 (0.787)
Median	1.96	1.96	1.93
Lubiprostone, n	378	378	358
Mean (Std Dev)	1.93 (0.787)	1.93 (0.787)	1.93 (0.780)
Median	1.92	1.92	1.90
P-value	0.945	0.945	0.966
Month 2			
Placebo , n	192	171	188
Mean (Std Dev)	1.91 (0.845)	1.88 (0.869)	1.91 (0.848)
Median	1.88	1.81	1.89
Lubiprostone, n	379	338	357
Mean (Std Dev)	1.82 (0.880)	1.76 (0.849)	1.82 (0.886)
Median	1.82	1.75	1.82
P-value	0.352	0.309	0.406
Month 3			
Placebo , n	192	159	188
Mean (Std Dev)	1.89 (0.863)	1.84 (0.886)	1.88 (0.868)
Median	1.91	1.84	1.91
Lubiprostone, n	379	316	360
Mean (Std Dev)	1.79 (0.870)	1.73 (0.827)	1.80 (0.879)
Median	1.82	1.75	1.84
P-value	0.180	0.272	0.299

Copied from Tables 14.2.5.1, 14.2.5.2, and 14.2.5.3.
p-values are based on van Elteren tests adjusted for pooled center.

Table 18 Summaries of SBM Frequency Rates at Month 1, 2, and 3 --- Protocol SPI/0211SIB-0432

Month Treatment Group Statistic	ITT Subjects with LOCF	ITT subjects without LOCF	Per Protocol Subjects with LOCF
Baseline			
Placebo , n	192	192	191
Mean (Std Dev)	3.98 (3.806)	3.98 (3.806)	3.99 (3.815)
Median	3.11	3.11	3.11
Lubiprostone, n	379	379	364
Mean (Std Dev)	4.05 (3.451)	4.05 (3.451)	3.99 (3.355)
Median	3.37	3.37	3.37
P-value	0.254	0.254	0.289
Month 1			
Placebo , n	189	189	183
Mean (Std Dev)	5.28 (3.944)	5.28 (3.944)	5.38 (3.947)
Median	4.50	4.50	4.75
Lubiprostone, n	372	372	354
Mean (Std Dev)	5.58 (4.418)	5.58 (4.418)	5.54 (4.269)
Median	4.75	4.75	4.75
P-value	0.391	0.391	0.541
Month 2			
Placebo , n	190	171	186
Mean (Std Dev)	5.40 (4.194)	5.57 (4.198)	5.45 (4.215)
Median	4.50	4.75	4.50
Lubiprostone, n	374	338	352
Mean (Std Dev)	5.63 (4.455)	5.61 (4.402)	5.62 (4.335)
Median	4.75	4.75	4.75
P-value	0.275	0.791	0.223
Month 3			
Placebo , n	190	159	186
Mean (Std Dev)	5.43 (4.442)	5.63 (4.348)	5.49 (4.464)
Median	4.49	4.75	4.53
Lubiprostone, n	374	316	355
Mean (Std Dev)	5.44 (4.290)	5.46 (4.232)	5.45 (4.243)
Median	4.81	4.87	4.93
P-value	0.722	0.829	0.789

Copied from Tables 14.2.7.1, 14.2.7.2, and 14.2.7.3.
p-values are based on van Elteren tests adjusted for pooled center.

Table 19 Summaries of BM Frequency Rates at Month 1, 2, and 3 --- Protocol SPI/0211SIB-0432

Month Treatment Group Statistic	ITT Subjects with LOCF	ITT subjects without LOCF	Per Protocol Subjects with LOCF	
Baseline				
Placebo , n	192	192	191	
Mean (Std Dev)	5.14 (4.281)	5.14 (4.281)	5.15 (4.289)	
Median	4.31	4.31	4.31	
Lubiprostone, n	379	379	364	
Mean (Std Dev)	4.82 (3.346)	4.82 (3.346)	4.76 (3.254)	
Median	4.15	4.15	4.15	
P-value	0.368	0.368	0.331	
Month 1				
Placebo , n	189	189	183	
Mean (Std Dev)	6.03 (3.822)	6.03 (3.822)	6.07 (3.863)	
Median	5.38	5.38	5.50	
Lubiprostone, n	372	372	354	
Mean (Std Dev)	6.09 (4.309)	6.09 (4.309)	6.00 (4.143)	
Median	5.25	5.25	5.25	
P-value	0.060	0.060	0.130	
Month 2				
Placebo , n	190	171	186	
Mean (Std Dev)	6.10 (4.092)	6.12 (4.071)	6.16 (4.112)	
Median	5.25	5.25	5.25	
Lubiprostone, n	374	338	352	
Mean (Std Dev)	6.07 (4.319)	6.04 (4.294)	5.99 (4.151)	
Median	5.00	5.00	5.00	
P-value	0.290	0.577	0.332	
Month 3				
Placebo , n	190	159	186	
Mean (Std Dev)	6.13 (4.336)	6.17 (4.227)	6.20 (4.354)	
Median	5.22	5.19	5.29	
Lubiprostone, n	374	316	355	
Mean (Std Dev)	5.95 (4.189)	5.95 (4.175)	5.86 (4.050)	
Median	5.17	5.25	5.19	
P-value	0.495	0.709	0.751	

Copied from Tables 14.2.7.1, 14.2.7.2, and 14.2.7.3.
p-values are based on van Elteren tests adjusted for pooled center.

Table 20 Summaries of Stool Consistency at Month 1, 2, and 3 --- Protocol SPI/0211SIB-0432

Month
  Treatment Group
    Statistic
	ITT Subjects
	with LOCF
		ITT subjects
		without LOCF
			Per Protocol
			Subjects with
			LOCF

Baseline			
Placebo , n	177	177	176
Mean (Std Dev)	2.76 (0.721)	2.76 (0.721)	2.76 (0.720)
Median	2.74	2.74	2.73
Lubiprostone, n	370	370	356
Mean (Std Dev)	2.75 (0.677)	2.75 (0.677)	2.75 (0.678)
Median	2.75	2.75	2.75
P-value	0.597	0.597	0.647
Month 1			
Placebo , n	181	181	176
Mean (Std Dev)	2.38 (0.621)	2.38 (0.621)	2.38 (0.620)
Median	2.35	2.35	2.35
Lubiprostone, n	372	372	353
Mean (Std Dev)	2.27 (0.717)	2.27 (0.717)	2.28 (0.712)
Median	2.23	2.23	2.23
P-value	0.151	0.151	0.141
Month 2			
Placebo , n	187	165	183
Mean (Std Dev)	2.35 (0.703)	2.34 (0.699)	2.33 (0.693)
Median	2.32	2.29	2.31
Lubiprostone, n	376	330	354
Mean (Std Dev)	2.25 (0.730)	2.24 (0.701)	2.26 (0.719)
Median	2.16	2.16	2.18
P-value	0.177	0.128	0.211
Month 3			
Placebo , n	188	157	183
Mean (Std Dev)	2.35 (0.705)	2.33 (0.667)	2.35 (0.697)
Median	2.29	2.26	2.29
Lubiprostone, n	376	307	358
Mean (Std Dev)	2.25 (0.685)	2.24 (0.643)	2.26 (0.721)
Median	2.15	2.17	2.20
P-value	0.082	0.115	0.113

Copied from Tables 14.2.9.1, 14.2.9.2, and 14.2.9.3.
p-values are based on van Elteren tests adjusted for pooled center.

Table 21 Summaries of Degree of Straining at Month 1, 2, and 3 --- Protocol SPI/0211SIB-0432

Month
  Treatment Group
    Statistic
	ITT Subjects
	with LOCF
		ITT subjects
		without LOCF
			Per Protocol
			Subjects with
			LOCF

Baseline			
Placebo , n	177	177	176
Mean (Std Dev)	2.39 (0.753)	2.39 (0.753)	2.39 (0.755)
Median	2.35	2.35	2.34
Lubiprostone, n	370	370	356
Mean (Std Dev)	2.39 (0.676)	2.39 (0.676)	2.39 (0.675)
Median	2.29	2.29	2.26
P-value	0.668	0.668	0.662
Month 1			
Placebo , n	181	181	176
Mean (Std Dev)	1.96 (0.766)	1.96 (0.766)	1.97 (0.771)
Median	1.94	1.94	1.94
Lubiprostone, n	372	372	353
Mean (Std Dev)	1.85 (0.823)	1.85 (0.823)	1.85 (0.816)
Median	1.78	1.78	1.79
P-value	0.163	0.163	0.194
Month 2			
Placebo , n	187	165	183
Mean (Std Dev)	1.91 (0.846)	1.87 (0.846)	1.90 (0.836)
Median	1.88	1.86	1.88
Lubiprostone, n	376	330	354
Mean (Std Dev)	1.77 (0.886)	1.73 (0.855)	1.79 (0.887)
Median	1.73	1.68	1.75
P-value	0.110	0.377	0.168
Month 3			
Placebo , n	188	157	184
Mean (Std Dev)	1.89 (0.875)	1.85 (0.841)	1.89 (0.884)
Median	1.91	1.91	1.92
Lubiprostone, n	376	307	357
Mean (Std Dev)	1.76 (0.875)	1.74 (0.836)	1.77 (0.885)
Median	1.67	1.67	1.67
P-value	0.146	0.512	0.105

Copied from Tables 14.2.11.1, 14.2.11.2, and 14.2.11.3.
p-values are based on van Elteren tests adjusted for pooled center.

Table 22 Summaries of Constipation Severity at Month 1, 2, and 3 --- Protocol SPI/0211SIB-0432

Month
  Treatment Group
    Statistic
	ITT Subjects
	with LOCF
		ITT subjects
		without LOCF
			Per Protocol
			Subjects with
			LOCF

Baseline			
Placebo , n	192	192	191
Mean (Std Dev)	2.21 (0.646)	2.21 (0.646)	2.21 (0.647)
Median	2.18	2.18	2.18
Lubiprostone, n	379	379	364
Mean (Std Dev)	2.20 (0.669)	2.20 (0.669)	2.20 (0.661)
Median	2.19	2.19	2.19
P-value	0.577	0.577	0.498
Month 1			
Placebo , n	191	191	184
Mean (Std Dev)	1.88 (0.779)	1.88 (0.779)	1.89 (0.783)
Median	1.88	1.88	1.87
Lubiprostone, n	378	378	358
Mean (Std Dev)	1.79 (0.814)	1.79 (0.814)	1.78 (0.803)
Median	1.78	1.78	1.78
P-value	0.185	0.185	0.165
Month 2			
Placebo , n	192	171	188
Mean (Std Dev)	1.79 (0.846)	1.78 (0.856)	1.79 (0.843)
Median	1.78	1.75	1.78
Lubiprostone, n	379	338	357
Mean (Std Dev)	1.70 (0.888)	1.66 (0.862)	1.69 (0.890)
Median	1.68	1.64	1.68
P-value	0.373	0.374	0.319
Month 3			
Placebo , n	192	159	188
Mean (Std Dev)	1.80 (0.859)	1.76 (0.855)	1.79 (0.859)
Median	1.79	1.77	1.78
Lubiprostone, n	379	316	360
Mean (Std Dev)	1.67 (0.888)	1.63 (0.846)	1.68 (0.893)
Median	1.69	1.63	1.70
P-value	0.339	0.430	0.381

Copied from Tables 14.2.13.1, 14.2.13.2, and 14.2.13.3.
p-values are based on van Elteren tests adjusted for pooled center.

Table 23 Summaries of Symptom Relief at Month 1, 2, and 3 --- Protocol SPI/0211SIB-0432

Month
  Treatment Group
    Statistic
	ITT Subjects
	with LOCF
		ITT subjects
		without LOCF
			Per Protocol
			Subjects with
			LOCF

Month 1			
Placebo , n	179	179	173
Mean (Std Dev)	0.60 (1.043)	0.60 (1.043)	0.61 (1.020)
Median	0.67	0.67	0.67
Lubiprostone, n	361	361	343
Mean (Std Dev)	0.69 (1.058)	0.69 (1.058)	0.69 (1.057)
Median	0.75	0.75	0.75
P-value	0.300	0.300	0.406
Month 2			
Placebo , n	184	166	180
Mean (Std Dev)	0.55 (1.256)	0.62 (1.240)	0.56 (1.266)
Median	0.67	0.75	0.71
Lubiprostone, n	365	326	343
Mean (Std Dev)	0.79 (1.140)	0.87 (1.101)	0.79 (1.146)
Median	0.75	0.75	0.75
P-value	0.023	0.011	0.031
Month 3			
Placebo , n	185	156	181
Mean (Std Dev)	0.56 (1.222)	0.64 (1.180)	0.55 (1.230)
Median	0.50	0.67	0.50
Lubiprostone, n	366	303	347
Mean (Std Dev)	0.75 (1.249)	0.86 (1.210)	0.74 (1.259)
Median	0.67	0.75	0.67
P-value	0.073	0.060	0.104

Copied from Tables 14.2.15.1, 14.2.15.2, and 14.2.15.3.
p-values are based on van Elteren tests adjusted for pooled center.

**Table 24 Summaries of IBS Quality of Life Scores at Week 4, Week 12, and Last ---
Protocol SPI/0211SIB-0432**

**Summary of IBS Quality of Life at Week 4, Week 12 and Last
(Intent-to-Treat Population without LOCF)
Study SP1/0211SIB-0432
Overall Score**

Week	n	Placebo Mean (St. Dev)	Median	n	Lubiprostone Mean (St. Dev)	Median	P-value
Baseline	184	57.6 (21.24)	58.8	364	58.0 (21.05)	60.3	0.837
Week 4	149	69.2 (19.07)	72.8	298	70.0 (19.98)	72.8	0.971
Week 12	114	71.4 (20.88)	76.5	220	74.3 (19.62)	77.2	0.062
Last	184	69.3 (21.13)	73.5	366	72.9 (20.13)	77.2	0.0080

Copied from Table 14-2.17.1.
Baseline p-values are from two-sample t-test, and weekly p-values are for the treatment effect from an
ANOVA model for pooled-center and the baseline value.

Table 25 Weekly Responder Rates --- Protocol SPI/0211SIB-0432

Weekly Responder Rates
Study 0432

		Placebo (N=193)		Lubiprostone (N=390)		p-Value[1]
Status						
Week 1						
	Responder	26	14.8%	71	20.3%	0.140
	Non-responder	150	85.2%	279	79.7%	
Week 2						
	Responder	30	16.8%	95	26.5%	0.017*
	Non-responder	149	83.2%	264	73.5%	
Week 3						
	Responder	45	25.1%	101	28.0%	0.547
	Non-responder	134	74.9%	260	72.0%	
Week 4						
	Responder	44	24.6%	107	29.6%	0.251
	Non-responder	135	75.4%	254	70.4%	
Week 5						
	Responder	40	21.9%	113	31.0%	0.018*
	Non-responder	143	78.1%	251	69.0%	
Week 6						
	Responder	46	25.0%	106	29.1%	0.385
	Non-responder	138	75.0%	258	70.9%	
Week 7						
	Responder	50	27.2%	109	29.9%	0.656
	Non-responder	134	72.8%	256	70.1%	
Week 8						
	Responder	48	26.1%	114	31.2%	0.252
	Non-responder	136	73.9%	251	68.8%	
Week 9						
	Responder	44	23.9%	116	31.7%	0.091
	Non-responder	140	76.1%	250	68.3%	
Week 10						
	Responder	46	25.0%	116	31.7%	0.118
	Non-responder	138	75.0%	250	68.3%	
Week 11						
	Responder	52	28.1%	113	30.9%	0.539
	Non-responder	133	72.9%	253	69.1%	
Week 12						
	Responder	46	24.9%	115	31.4%	0.140
	Non-responder	139	75.1%	259	68.6%	

[1] p-Value is from a CMH test stratified by pooled site

Table 26 Responder Analysis for Spontaneous Bowel Movements --- Protocol SPI/0211SIB-0432

Summary of Responder[1] Rates
Intent–to–Treat Subjects

Status	Placebo (N=192)		Lubiprostone 16 mcg (N=379)		p–Value[2]
Responder	96	50.5%	195	52.1%	0.744
Non–responder	94	49.5%	179	47.9%	

Responders are defined as subjects who have a change of at least 1 in SBM frequency over the treatment period.

Summary of Responder[1] Rates
Intent–to–Treat Subjects

Status	Placebo (N=192)		Lubiprostone 16 mcg (N=379)		p–Value[2]
Responder	39	20.5%	69	18.4%	0.528
Non–responder	151	79.5%	305	81.6%	

Responders are defined as subjects who have a change of at least 3 in SBM frequency over the treatment period.

Table 11.9
Summary of Responder[1] Rates
Intent–to–Treat Subjects

Status	Placebo (N=192)		Lubiprostone 16 mcg (N=379)		p–Value[2]
Responder	47	24.7%	112	29.9%	0.226
Non–responder	143	75.3%	262	70.1%	

Responders are defined as subjects who have a change of at least 1 in SBM frequency over the treatment period and have at least 3 SBMs every week during the treatment period.

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 /s/
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Milton Fan
4/25/2008 11:16:12 AM
BIOMETRICS



Mike Welch
4/25/2008 11:42:27 AM
BIOMETRICS
Concur with review.
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