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RESEARCH**

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**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

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Established Name	SPI-0211 (Lubiprostone)
Trade Name	Amitiza
Therapeutic Class	Prostaglandin metabolite analogue
Applicant	Sucampo Pharmaceuticals, Inc.

Priority Designation	Standard
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Formulation	Oral capsule
Dosing Regimen	8 mcg B.I.D
Indication	Treatment of irritable bowel syndrome with constipation
Intended Population	Adults age 18 years and older

## Table of Contents

<b>1</b>	<b>EXECUTIVE SUMMARY .....</b>	<b>5</b>
1.1	Recommendation on Regulatory Action.....	5
1.2	Recommendation on Postmarketing Actions .....	5
1.2.1	Risk Management Activity.....	5
1.2.2	Required Phase 4 Commitments .....	5
1.2.3	Other Phase 4 Requests .....	5
1.3	Summary of Clinical Findings.....	5
1.3.1	Brief Overview of Clinical Program .....	5
1.3.2	Efficacy .....	6
1.3.3	Safety .....	9
1.3.4	Dosing Regimen and Administration .....	11
1.3.5	Drug-Drug Interactions .....	12
1.3.6	Special Populations .....	12
<b>2</b>	<b>INTRODUCTION AND BACKGROUND .....</b>	<b>12</b>
2.1	Product Information.....	13
2.2	Currently Available Treatment for Indications.....	14
2.3	Availability of Proposed Active Ingredient in the United States.....	14
2.4	Important Issues With Pharmacologically Related Products.....	14
2.5	Presubmission Regulatory Activity.....	14
2.6	Other Relevant Background Information .....	15
<b>3</b>	<b>SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES .....</b>	<b>15</b>
3.1	CMC (and Product Microbiology, if Applicable).....	15
3.2	Animal Pharmacology/Toxicology.....	15
<b>4</b>	<b>DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY.....</b>	<b>15</b>
4.1	Sources of Clinical Data .....	15
4.2	Tables of Clinical Studies.....	16
4.3	Review Strategy .....	18
4.4	Data Quality and Integrity .....	18
4.5	Compliance with Good Clinical Practices.....	18
4.6	Financial Disclosures.....	19
<b>5</b>	<b>CLINICAL PHARMACOLOGY .....</b>	<b>19</b>
5.1	Pharmacokinetics.....	19
5.2	Pharmacodynamics.....	19
5.3	Exposure-Response Relationships.....	19
<b>6</b>	<b>INTEGRATED REVIEW OF EFFICACY .....</b>	<b>20</b>
6.1	Indication.....	20
6.1.1	Methods.....	20
6.1.2	General Discussion of Endpoints.....	21
6.1.3	Study Design.....	22
6.1.4	Efficacy Findings.....	24
6.1.5	Clinical Microbiology.....	71
6.1.6	Efficacy Conclusions.....	71
<b>7</b>	<b>INTEGRATED REVIEW OF SAFETY .....</b>	<b>72</b>
7.1	Methods and Findings .....	72
7.1.1	Deaths .....	73
7.1.2	Other Serious Adverse Events .....	73
7.1.3	Dropouts and Other Significant Adverse Events.....	76
7.1.3.1	Overall Profile of Dropouts .....	76

7.1.3.2	Adverse Events Associated with Dropouts .....	77
7.1.4	Common Adverse Events .....	83
7.1.4.1	Eliciting Adverse Events Data in the development program .....	85
7.1.4.2	Appropriateness of Adverse Event categorization and preferred terms .....	85
7.1.4.3	Incidence of Common Adverse Events .....	86
7.1.4.4	Identifying Common and Drug-related Adverse Events .....	87
7.1.5	Additional Analyses and Explorations .....	88
7.1.6	Laboratory Findings .....	101
7.1.7	Vital Signs .....	110
7.1.8	Physical Examinations .....	111
7.1.9	Electrocardiograms (ECGs) .....	112
7.1.9.1	Overview of ECG Testing in the Clinical Program .....	112
7.1.10	Immunogenicity .....	113
7.1.11	Human Carcinogenicity .....	113
7.1.12	Special Safety Studies .....	113
7.1.13	Withdrawal Phenomena and/or Abuse Potential .....	115
7.1.14	Human Reproduction and Pregnancy Data .....	117
7.1.15	Assessment of Effect on Growth .....	117
7.1.16	Overdose Experience .....	117
7.1.17	Postmarketing Experience .....	118
7.2	Adequacy of Patient Exposure and Safety Assessments .....	119
7.2.1	Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety .....	119
7.2.2	Demographics .....	124
7.2.3	Description of Secondary Clinical Data Sources Used to Evaluate Safety .....	125
7.2.4	Adequacy of Overall Clinical Experience .....	125
7.2.5	Adequacy of Special Animal and/or In Vitro Testing .....	125
7.2.6	Adequacy of Routine Clinical Testing .....	125
7.2.7	Adequacy of Metabolic, Clearance, and Interaction Workup .....	125
7.2.8	Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study .....	126
7.2.9	Assessment of Quality and Completeness of Data .....	126
7.2.10	Additional Submissions, Including Safety Update .....	126
<b>8</b>	<b>ADDITIONAL CLINICAL ISSUES .....</b>	<b>126</b>
8.1	Dosing Regimen and Administration .....	126
8.2	Drug-Drug Interactions .....	128
8.3	Special Populations .....	128
8.4	Pediatrics .....	128
8.5	Advisory Committee Meeting .....	128
8.6	Literature Review .....	128
8.7	Postmarketing Risk Management Plan .....	129
<b>9</b>	<b>OVERALL ASSESSMENT .....</b>	<b>129</b>
9.1	Conclusions .....	129
9.2	Recommendation on Regulatory Action .....	134
9.3	Recommendation on Postmarketing Actions .....	134
9.4	Risk Management Activity .....	134
9.5	Other Phase 4 Requests .....	134
9.6	Comments to Applicant .....	134

<b>10</b>	<b>APPENDICES .....</b>	<b>135</b>
10.1	Review of Individual Study Reports .....	135
10.2	Line-by-Line Labeling Review .....	204
	<b>REFERENCES .....</b>	<b>207</b>

## **1 EXECUTIVE SUMMARY**

### **1.1 Recommendation on Regulatory Action**

The medical officer recommends an approval action to be taken for oral lubiprostone 16 mcg/day (8 mcg capsules b.i.d) for the treatment of constipation predominant irritable bowel syndrome in women  $\geq$  18 years old. Approval of Lubiprostone 16 mcg/day (8 mcg capsules bid) for the treatment of constipation predominant irritable bowel syndrome is contingent upon the sponsor incorporating the Food and Drug Administration's recommended changes to the Lubiprostone drug label and adhering to the required Phase IV commitment studies.

### **1.2 Recommendation on Post-marketing Actions**

#### **1.2.1 Risk Management Activity**

No new risk management activity required with this supplemental NDA.

#### **1.2.2 Required Phase 4 Commitments**

The medical officer recommends that the sponsor perform a Phase IV commitment study to determine the safety and efficacy of Lubiprostone in the pediatric population. This study should be in accordance with the Pediatric Research Equity Act of 2007. The sponsor has requested a waiver for the age group 0-5 years old and a deferral for ages 6-17 years old. A pediatric plan along with the deferral has been submitted for the age group 6-17. The medical officer has reviewed the pediatric waiver and agrees with the waiver. The pediatric plan has been reviewed by the medical officer and will be reviewed by PerC.

#### **1.2.3 Other Phase 4 Requests**

The sponsor should consider conducting studies to establish efficacy and safety of Lubiprostone at the 16 mcg bid dose in constipation predominant irritable bowel syndrome.

### **1.3 Summary of Clinical Findings**

#### **1.3.1 Brief Overview of Clinical Program**

This application includes three comparative efficacy studies; SIB-0221, SIB-0431 Treatment Phase I, and SIB-0432. The clinical program also includes a treatment phase II to study SIB-0431 known as a randomized withdrawal study. Study SIB-0221 was a multi-center, placebo-controlled, double-blind, parallel-group, phase II study which assessed the safety and efficacy of different dose regimens of oral Lubiprostone compared to placebo for relief of symptoms of constipation predominant irritable bowel syndrome. Studies SIB-0431 Treatment Phase I and SIB-0432 were multi-center, parallel group, double-blind, placebo-controlled, Phase III studies of 12 weeks duration with the same design except for the randomized withdrawal portion of study SIB-0431. The studies, SIB-0431 Treatment Phase I and SIB-0432 were designated as the pivotal studies for this application. These two Phase III pivotal studies assessed the efficacy and safety of oral 16 mcg Lubiprostone compared to placebo for the treatment of constipation predominant irritable bowel syndrome. One of the pivotal studies, SIB-0431 Treatment Phase I was followed by a 4 week randomized withdrawal study, SIB-0431 Treatment Phase II, which

was designed to assess the rebound phenomenon and lasting efficacy of Lubiprostone 16 mcg. The three aforementioned comparative efficacy studies (SIB-0221 16 mcg arm, SIB-0431 Treatment Phase I and SIB-0432) were combined using the Intent to Treat (ITT) population for meta-analyses into a grouping called the pooled cohort. The pooled cohort consisted of all ITT subjects excluding the Lubiprostone 32 mcg and 48 mcg dose groups (1347 - 49 - 45) 1253 subjects (433 placebo, 820 16 mcg Lubiprostone) in 150 centers across the United States.

Since the Agency did suggest that a randomized withdrawal study be performed during the pre-NDA meeting, the sponsor did submit a randomized withdrawal study, SIB-0431 Treatment Phase II. The study SIB-0431 Treatment Phase II was a 4 week multi-center, placebo-controlled, phase III randomized withdrawal study that was designed to assess the rebound phenomenon and the lasting efficacy of Lubiprostone 16 mcg. In the analysis, these subjects are referred to as the randomized withdrawal group (RWG). Study SIB-0431 Treatment Phase II treated 436 subjects that had completed SIB-0431 Treatment Phase I (139 Placebo/Placebo, 146 Lubiprostone/Placebo, 151 Lubiprostone/Lubiprostone) at 65 centers across the United States.

This application also includes one long-term safety and efficacy study, SIB-05S1. The long term safety study, SIB-05S1, was multi-center, open label, phase III study which assessed the safety of 16 mcg of Lubiprostone as the primary endpoint when administered for 36 weeks. The secondary objective of the study was to collect additional efficacy data regarding 16 mcg Lubiprostone. In the analysis, the subjects from this particular study were referred to as the long term group. The long term safety and efficacy study enrolled a total of 522 subjects in 104 centers across the United States.

### 1.3.2 Efficacy

A total of 1366 subjects with constipation predominant irritable bowel syndrome were involved (randomized) with the clinical development program of Lubiprostone. Two adequate and well-controlled Phase III efficacy studies demonstrated that administration of Lubiprostone 8 mcg bid provides relief of symptoms of constipation predominant irritable bowel syndrome in the adult population in comparison with the administration of placebo (6% to 6.4%). Statistical significance was attained for the primary endpoint; the overall responder rate during the 12 week treatment period, for both pivotal studies. The primary efficacy analysis was based on the overall responder rate during the 12 week treatment period. An overall responder was defined as a subject that was a monthly responder for at least 2 out of the 3 months during the 12 week treatment period.

Overall and Monthly responder definitions were based on the weekly assessments of global symptom relief obtained as part of the subject's electronic diary responses. Global symptom relief was assessed with the following weekly 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? The rating was based on 7 point balanced scale: **3** = Significantly relieved, **2** = Moderately relieved, **1** = A little bit relieved, **0** = Unchanged, **-1** = A little bit worse, and **-2** = Moderately Worse. A Monthly responder was defined as a subject whose symptoms were rated as "**Moderately relieved**" for all 4 weeks within a month or "**Significantly relieved**" for at least 2 weeks within a month provided three conditions were met: 1. the percent of days of rescue medication use did not increase during the month as compared to baseline, 2. the subject did not discontinue the study during the month due to lack of efficacy, 3. the subject had no ratings of "**Moderately worse**" or "**Significantly worse**" during the month.

Outlined below are the overall responder rate data from the Intent-to-Treat (ITT) population without Last-Observation-Carried-Forward (LOCF) imputation method.

### **EXECUTIVE SUMMARY Table 1:**

#### **Overall Responder Rate in the ITT Population without LOCF: Lubiprostone 16 mcg vs. Placebo**

Study	Study Arm	Overall	N	(%)	Responder Difference	p-Value
<b>SIB-0431 Treatment Phase I</b>	Placebo N=193	<b>Responder</b>	<b>15</b>	<b>7.8</b>	6%	0.029*
		Non-Responder	178	92.2		
	Lubiprostone 16 mcg N=390	<b>Responder</b>	<b>54</b>	<b>13.8</b>		
		Non-Responder	336	86.2		
<b>SIB-0432</b>	Placebo N=192	<b>Responder</b>	<b>11</b>	<b>5.7</b>	6.4%	0.023*
		Non-Responder	181	94.3		
	Lubiprostone 16 mcg N=379	<b>Responder</b>	<b>46</b>	<b>12.1</b>		
		Non-Responder	333	87.9		
<b>Pooled (SIB-0431 Treatment Phase I + SIB-0432)</b>	Placebo N=385	<b>Responder</b>	<b>26</b>	<b>6.8</b>	6.2%	0.001~
		Non-Responder	359	93.2		
	Lubiprostone 16 mcg N=769	<b>Responder</b>	<b>100</b>	<b>13.0</b>		
		Non-Responder	669	87.0		

Reviewer's table modified from Table 2.7.3.3-5, page 42 of 106, Summary of Clinical Efficacy and from Table 11-3, page 65 of 89, Clinical Study Report and from Table 11-2, page 57 of 75, Clinical Study Report

\*p-value is from a CMH test stratified by pooled-center

~p-value is from CMH test stratified by study

As noted above in the executive summary table 1, in both pivotal studies (SIB-0431 Treatment Phase I and SIB-0432), the overall responder rates in the Lubiprostone group were higher (range: 12.1%-13.8%) than that in the placebo group (range: 5.7%-7.8%). The difference was statistically significant in SIB-0431 Treatment Phase I and SIB-0432. In the pooled group, the overall responder rate was 13.0% for Lubiprostone 16 mcg subjects and 6.8% for placebo subjects and the difference was statistically significant, p=0.001. In both well-controlled studies, the difference in overall responder rates between treatment groups was similar. The difference between the placebo treatment group and the Lubiprostone 16 mcg treatment group was 6% in study SIB-0431 Treatment Phase I and 6.4% in study SIB-0432. In the pooled group, the difference in overall responder rate between subjects that received placebo and active treatment was 6.2%. Treatment with Lubiprostone 16 mcg maybe a valuable treatment option for subjects suffering from constipation predominant IBS. When comparing the results to placebo, Lubiprostone demonstrated a marginal clinically meaningful (6%) difference in overall responder rate during the 12 week treatment period (the primary efficacy endpoint) in both the well-controlled studies. In each individual study (SIB-0431 Treatment Phase I and SIB-0432), the non-responder rate in the Lubiprostone 16 mcg treatment group was relatively high at 86.2% and 87.9% respectively. Another concerning factor was the placebo response (7.8% study SIB-0431 Treatment Phase I and 5.7% study SIB-0432) in each of the studies.



Even though both pivotal studies had the same secondary endpoints, the studies did not attain statistical significance for the same secondary endpoints. Statistical significance for Lubiprostone 8 mcg bid over placebo for the treatment of constipation predominant irritable bowel syndrome was observed in the following secondary efficacy variables: monthly responder rate at month 2, monthly stool consistency at months 1 and 2, monthly degree of straining at months 1 and 2 for study SIB-0431 Treatment Phase I and monthly symptom relief at month 2 and overall irritable bowel syndrome-quality of life at last visit for study SIB-0432. The secondary efficacy endpoints were many and included Daily abdominal discomfort/pain; Daily abdominal bloating; Frequency rates of spontaneous bowel movements (SBMs); Frequency rates of bowel movements (BMs); Daily stool consistency associated with SBMs; Daily degree of straining associated with SBMs; Daily severity of constipation associated with SBMs; Irritable bowel syndrome quality of life (IBS-QOL) assessment; Weekly symptom relief; and Weekly treatment effectiveness.

Lubiprostone was slightly better than placebo in most of the secondary endpoints. In one of the secondary endpoints daily abdominal discomfort/pain, Lubiprostone subjects had an average mean reduction of 0.35 units on the 5 point scoring scale at month 1, 0.46 units at month 2, and 0.48 units at month 3 when compared to baseline. Placebo subjects on the other hand, revealed an average mean reduction of 0.26 units on the 5 point scoring scale at month 1, 0.32 units at month 2 and 0.35 units at month 3 compared to baseline. Both Lubiprostone and placebo did reduce abdominal pain from a rating range of moderate-severe (2-3) to mild-moderate (1-2); however, the decrease was slightly larger in the Lubiprostone treated group which resulted in more ratings closer to the mild range. Treatment with Lubiprostone 16 mcg did slightly increase the frequency of spontaneous bowel movements more than treatment with placebo in the range of 0.12-0.33. In both pivotal studies, (SIB-0431 Treatment Phase I and SIB-0432), the mean change in SBM frequency rates in the Lubiprostone group was higher for all monthly time points (range: 1.51-1.59) than that in the placebo group (range: 1.21-1.41) except in Month 3 of SIB-0432 where it was similar to placebo (1.42 Lubiprostone vs. 1.43 Placebo). The difference between placebo and the Lubiprostone treatment groups was not statistically significant at all time points in the pivotal studies (SIB-0431 Treatment Phase I and SIB-0432). Furthermore, the evidence to support that treatment with Lubiprostone 8 mcg bid dose resulted in the increase of spontaneous bowel movements over a 12 week period is questionable. When the difference between taking placebo and Lubiprostone treatment does not result in an increase of  $\geq 1$  SBM, it leads one to question the clinical meaningfulness of 0.33 SBM increase.

There were a total of 1253 ITT subjects in the pooled group (PG) and 520 safety evaluable subjects in the Long-term Safety group (LTS). The demographic characteristics of these study populations were relatively consistent yet somewhat limited across all three phase III (SIB-0431 Treatment Phase I, SIB-0432, SIB-05S1) and one phase II (SIB-0221) studies. The overall subject population was predominantly female (91.6% - PG; 92.9% - LTS) and mostly Caucasian (77.7% - PG; 79.8% - LTS). The average proportion of subjects  $\geq 65$  years old in the pooled population was only 8.1% (SIB-0221, SIB-0431 Treatment Phase I, SIB-0432). The literature cites that the prevalence of irritable bowel syndrome is more common in females (2:1 ratio Female to Male); therefore, the intended target population has been studied in this clinical trial. It is difficult to make any conclusions regarding efficacy in males as there were only 105 male subjects (8.4%) in the PG and 97 male subjects (8.4%) in the pivotal studies (SIB-0431 Treatment Phase I and SIB-0432). Having noted the limitations in the application's patient population, Lubiprostone was analyzed by the primary efficacy variable in three subpopulations; gender (female, male), race (white, non-white), and age [ $18 \leq \text{Age} < 65$ ], ( $65 \leq \text{Age}$ )]. Females, whites and subjects  $18 \leq \text{Age} \leq 65$  revealed statistically significant results for the primary

efficacy endpoint favoring Lubiprostone 8 mcg bid over placebo. In the age group  $\geq 65$ , Lubiprostone 8 mcg bid did not show any difference from placebo (10.5% Placebo, 10.3% Lubiprostone) in the overall responder rate which was the primary efficacy variable. The overall efficacy of Lubiprostone 8 mcg bid reveals marginal benefit over placebo. However, given the fact that there is no FDA approved treatment on the market for constipation predominant irritable bowel syndrome, it may prove to be beneficial in women (6.2%) under the age of 65. The reduction in symptoms of constipation predominant irritable bowel syndrome was demonstrated in the short term studies (up to 12 weeks) and long term studies (up to 13 months).

### 1.3.3 Safety

The clinical trials within this supplemental new drug application established a favorable safety and tolerability profile for Lubiprostone 8 mcg bid in adult population with constipation predominant irritable bowel syndrome.

There were a total of 1361 subjects treated (1366 randomized - 5 never dosed) in the safety population, of which 1105 subjects received active drug and 256 received only placebo. Of the 1105 subjects that received all doses of Lubiprostone, 779 subjects received only all doses of Lubiprostone and 326 subjects received both placebo and Lubiprostone 16 mcg. One thousand and eleven subjects (1105 - 49-45) received Lubiprostone 16 mcg/day (8 mcg bid) in all the studies combined (SIB-0221, SIB-0431 Treatment Phase I and II, SIB-0432 and SIB-05S1). In the long term safety study, SIB-05S1, 520 subjects (522 - 2 never dosed) were treated with Lubiprostone 8 mcg bid for 9 months but were exposed to Lubiprostone for longer durations due to their previous treatment assignments in the well-controlled studies (SIB-0431 Treatment Phase I and II and SIB-0432): 179 subjects received Lubiprostone for 9 months, 80 subjects received Lubiprostone for 12 months, and 261 subjects received Lubiprostone for 13 months.

One subject died in the entire clinical development program. A male subject age 71 years old who was randomized to the Lubiprostone/Placebo group and was receiving Lubiprostone died of sudden cardiac arrest. He was enrolled in study SIB-0431 Treatment Phase I, and the last dose of Lubiprostone was taken on study day 72. No autopsy report was provided.

The occurrence of serious adverse events in the studied population was relatively low. Four placebo subjects (0.9%) reported 7 serious adverse events (SAEs) with no preferred term SAE being reported by more than one subject. Seven subjects taking Lubiprostone 16 mcg (0.8%) reported 9 treatment emergent SAEs. Two Lubiprostone subjects reported 4 SAEs (cardiac arrest, atrial fibrillation, coronary artery disease and mitral valve incompetence) in the cardiac disorders system organ class (SOC). One SAE of chest pain that was reported as non-cardiac in nature was considered treatment related. In the open label treatment period, 10 subjects reported 11 treatment emergent SAEs. Syncope was the only SAE preferred term reported by more than 1 subject.

Across all active doses of Lubiprostone (N=926) in the safety evaluable population from the well-controlled studies, the most commonly reported adverse event preferred terms were nausea (12.3%), diarrhea (8.2%), headache (4.3%), upper respiratory tract infection (4.1%), abdominal pain (4.0%), and urinary tract infection (4.0%). Comparatively for placebo (N=435), the corresponding reports of adverse events in the above preferred terms were: nausea (6.4%), diarrhea (5.3%), headache (4.4%), upper

respiratory tract infection (2.3%), abdominal pain (5.3%), and urinary tract infection (3.4%). In the open label treatment period, the most commonly reported adverse events were similar to the ones reported in the well-controlled trials: diarrhea (8.8%), nausea (6.5%), urinary tract infection (6.5%), headache (4.0%), abdominal pain (3.5%) and upper respiratory tract infection (2.9%).

An analysis of cumulative adverse event incidence rates, time to first adverse events and a Cox proportional hazard analysis for the occurrence of any adverse event (nausea, diarrhea, vomiting, headache, dizziness, syncope, peripheral edema, fatigue, dyspnea, cardiac disorders) indicated that subjects taking Lubiprostone were more likely than placebo subjects to experience most adverse events with the exception of abdominal pain. The risk of experiencing nausea, diarrhea, and headache was greatest within the first few days of treatment (2-5 days), and it did not increase over time to any appreciable degree. However, the risk of experiencing vomiting and fatigue was greatest three weeks into treatment (Day 22-28). Even though peripheral edema, syncope, dyspnea, and cardiac disorders were more likely to occur in Lubiprostone subjects, it was difficult to predict the timing of occurrence during treatment. Dizziness, on the other hand, was more likely to be experienced by subjects  $\geq 65$  years old (hazard ratio=2.271,  $p=0.0757$ ) and also more likely to occur later in the treatment period (Day 253-280). According to the Cox regression analysis, the only adverse event that was more likely to occur in females was nausea (hazard ratio=1.970;  $p=0.0826$ ).

The frequency of withdrawal for Lubiprostone 16 mcg (8 mcg bid) in the well-controlled safety group was lower than for the placebo subjects. Overall 2.3% of placebo subjects and 1.9% of Lubiprostone 16 mcg subjects withdrew because of gastrointestinal adverse events. The breakdown of gastrointestinal adverse events in the well-controlled safety population that led to withdrawal for at least 1% of subjects was nausea (1.2%) for the Lubiprostone 16 mcg group and abdominal pain (1.4%) for the placebo group. The types and frequencies of the individual AEs that led to withdrawal were generally similar across the well-controlled studies, and these results were similar to those observed in the open label safety study. Gastrointestinal disorders were once again the most common system organ class for AEs leading to withdrawal. Adverse events that led to withdrawal in the open label long term safety study for at least 1% of subjects was diarrhea (1.3%). Only one subject discontinued in the randomized withdrawal study due to abdominal distension (0.7%).

The clinical and laboratory data presented in this application including biochemistry, hematology, urinalysis, vital signs and physical examination data appeared clinically acceptable for a population of subjects with constipation predominant irritable bowel syndrome who are otherwise considered generally healthy. ECG and bilateral hand X-rays were evaluated in the dose response study SIB-0221 at baseline and at final assessment. Lubiprostone at doses of 16 mcg, 32 mcg, and 48 mcg per day for 12 weeks showed no evidence of effect on heart rate, cardiac conduction, cardiac repolarization or morphological changes. Although formal lumbar and hip bone densitometry analysis would have provided a more accurate reflection of Lubiprostone's effect on bone metabolism, Lubiprostone did not appear to cause a negative impact on bone density.

To date, no adequate and well controlled studies of Lubiprostone in pregnant or lactating women have been conducted. In fact pregnant women were excluded from all clinical trials of Lubiprostone, and any woman who became pregnant during a study was immediately discontinued from study participation. Two pregnancies were reported during the development of Lubiprostone. Of the 2 pregnancies, one woman had a healthy baby, and the other woman was diagnosed with an ectopic pregnancy. The ectopic pregnancy was resolved by an elective procedure. Given the lack of controlled human pregnancy data

from the clinical trials, the labeling of Lubiprostone should reflect the absence of data for pregnant women or women who could become pregnant.

The addition of Lubiprostone 8 mcg bid for the treatment of constipation predominant irritable bowel syndrome provides a much safer alternative than the only available product at this time. Zelnorm was initially approved on July 24, 2002 and then withdrawn from the market on March 30, 2007 due to cardiovascular adverse event findings. It can be obtained from the sponsor through a treatment IND for adult females under the age of 55 who are identified to be appropriate candidates for Zelnorm by their physicians. Therefore, Lubiprostone with its marginal efficacy in some subjects under the age of 65 can be a viable and definitely safer alternative. The results of the clinical studies of Lubiprostone 8 mcg bid provide marginal efficacy but considerable safety and tolerability data up to 52 weeks duration in a population of patients with constipation predominant irritable bowel syndrome when compared to no treatment at all. Lubiprostone like most prescription medications is accompanied by some mild and often short-lived side effects, however; these effects are balanced by relief of symptoms of constipation predominant irritable bowel syndrome.

### **1.3.4 Dosing Regimen and Administration**

The sponsor's proposed dose of Lubiprostone is 8 mcg bid. In this reviewer's opinion the adequacy of dose finding in this supplemental New Drug Application was appropriate, but limited due to lack of exploration of certain findings. The dose response study SIB-0221 evaluated dose levels of 16 mcg/day (8 mcg bid), 32 mcg/day (16 mcg bid), and 48 mcg/day (24 mcg bid) over a 12 week period. The results of this study showed that all 3 doses of Lubiprostone were more effective than placebo in relieving symptoms of constipation predominant irritable bowel syndrome; however, the Lubiprostone 16 mcg and 32 mcg dose revealed similar efficacy results. In general, the likelihood of experiencing gastrointestinal adverse events (AEs) such as nausea and diarrhea did appear to increase with increasing Lubiprostone dose. However, there were adverse events such as abdominal distension that occurred with the same frequency in the placebo group as in the 32 mcg and the 48 mcg Lubiprostone group (5 subjects each). The sponsor was concerned about the discontinuation rates and the frequency of gastrointestinal adverse events which was higher in the higher doses of Lubiprostone. The reviewer agrees partially with this rationale as the 48 mcg dose had the highest frequency of diarrhea, nausea, and vomiting relative to placebo, 16 mcg and 32 mcg Lubiprostone dose groups.

The primary efficacy variable in SIB-0221 was the change from baseline in mean abdominal discomfort ratings during month 1, and the original responder definition utilized in study SIB-0221 was modified after the end of phase II meeting. During this particular end-of-phase II meeting, the Agency did recommend that the sponsor explore other doses besides Lubiprostone 8 mcg bid for the phase III trials using the new responder definition. The dose response study SIB-0221 was powered to test statistical differences between placebo and Lubiprostone 48 mcg dose. The 48 mcg dose group did produce statistically significant differences in the primary and most secondary efficacy analysis. It was also associated with a significant amount of gastrointestinal adverse events. An argument can be made that the sponsor should have chosen the 32 mcg/day dose as it had similar AEs of nausea and diarrhea as the 16 mcg/day dose and yet was still more efficacious than placebo. This reviewer thinks that the Lubiprostone 32 mcg dose should have been explored in the phase III studies utilizing the modified responder definition in order to further delineate the association of certain adverse events seen in SIB-0221. Lubiprostone has not been adequately tested in subjects with renal or hepatic impairment;

therefore, recommendations on dose modifications in such special populations cannot be made. The effects of food were not evaluated in this supplemental application.

### 1.3.5 Drug-Drug Interactions

Drug-drug interactions assessment was not performed as part of the supplemental drug application. The sponsor did perform these studies with the initial application for Lubiprostone 24 mcg bid for chronic idiopathic constipation treatment.

### 1.3.6 Special Populations

- Safety and effectiveness of Lubiprostone in **pediatric** patients has not been established.
- The clinical studies for Lubiprostone included a somewhat limited proportion of subjects aged 65 and older (8.1% in the pooled group). The actual observed values of effectiveness did not provide evidence that Lubiprostone 16 mcg was better than placebo in the 65 and older subgroup. The overall responder rate which was the primary efficacy variable was 10.3% in the Lubiprostone 16 mcg group and 10.5% in the placebo group. In the monthly responder rates, Lubiprostone 16 mcg group (range: 8.6%-19.0%) demonstrated a higher rate than placebo group (range: 7.9%-10.5%) at all monthly time points. In the age group  $\geq 65$ , the difference in the monthly responder rate between placebo and Lubiprostone 16 mcg subjects did not increase as the months progressed (Months 1, 2, and 3: 0.7%, 8.5% and 4.2%, respectively). The difference in the monthly responder rates between placebo and Lubiprostone 16 mcg subjects had more variation and was lower than that seen in the general study population especially in months 1 and 3.
- Lubiprostone has not yet been adequately studied in subjects who have **renal impairment**.
- Lubiprostone has not yet been adequately studied in subjects who have **hepatic impairment**.
- There have been no adequate and well controlled studies of Lubiprostone in **pregnant women**.
- The excretion of Lubiprostone or its metabolite in the milk of **nursing mothers** has not been evaluated.

## 2 INTRODUCTION AND BACKGROUND

Irritable Bowel Syndrome (IBS) is a chronic medical condition that is characterized by recurrent abdominal pain and discomfort and altered bowel habits. It is one of a group of functional gastrointestinal disorders. The diagnosis is based on the Rome criteria and the exclusion of physical, laboratory and structural abnormalities. IBS has a prevalence of approximately 12% in the United States and worldwide. Age of onset of Irritable bowel syndrome varies, but the incidence appears to increase in adolescents and peaks in the third and fourth decade of life. It is usually diagnosed before the age of 50, and onset after 50 years of age is unusual. It has a 2:1 Female predominance.

The cause of irritable bowel syndrome (IBS) is not known at this time. There are a few hypotheses regarding the pathophysiology of IBS. It is believed that IBS patients have altered motility, visceral hypersensitivity and altered visceral sensation of pain. Psychosocial stressors have been proposed to exacerbate symptoms of irritable bowel syndrome. There is also evidence that reveals infection and inflammation may contribute to the symptoms associated with IBS.

According to the Rome III criteria, a patient has to have continuous or intermittent symptoms of abdominal discomfort for at least 6 months before the diagnosis of IBS can be considered. Furthermore, the listed criteria below have to be present for the last 3 months with symptom onset at least 6 months

prior to diagnosis. The most widely accepted definition of IBS is the one established by the Rome III classification method: Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with 2 or more

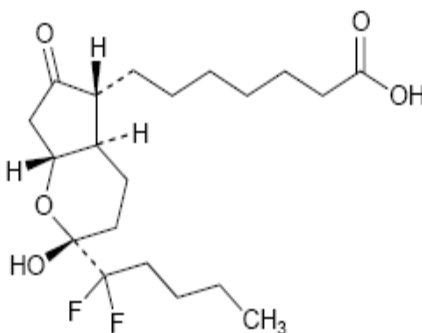
1. Improvement with defecation and
2. Onset associated with a change in frequency of stool and
3. Onset associated with a change in form (appearance) of stool

IBS is further sub-typed into four groups based on stool form. The classification of stool form can be accomplished using the Bristol Stool Form Scale. The four sub-types are known as: 1. IBS with constipation (IBS-C), 2. IBS with diarrhea (IBS-D), 3. Mixed IBS (IBS-M), and 4. Un-sub-typed IBS. Irritable bowel syndrome with constipation (IBS-C) is diagnosed when a patient has hard or lumpy stools  $\geq 25\%$  and loose (mushy) or watery stools  $< 25\%$  of bowel movements. The Bristol Stool Form scale can be used as an aide to characterize the type of stools that the patient experiences in the absence of any use of anti-diarrheals or laxatives.

Since the cause of IBS-C is not known and it is a multi-symptom disease, the goal of therapy is to provide treatment that alleviates all the symptoms. Currently, however, in clinical practice, the treatments treat the individual symptoms of IBS and IBS-C. If a patient has more constipation symptoms, the patient is usually prescribed a fiber or laxative. If bloating and distension occurs, the patient may be prescribed an antispasmodic or dietary modification. If a patient complains of abdominal pain, the patient may receive tricyclic anti-depressants. Drug therapy is now aiming to change the focus from treating the dominant symptom to addressing the multi-symptomatic nature of the disease.

## 2.1 Product Information

### Chemical structure of Lubiprostone



Lubiprostone is a unique prostaglandin E1 metabolite. The drug substance is a crystalline compound with a molecular weight of 390.46 and a molecular formula of C<sub>20</sub>H<sub>32</sub>O<sub>5</sub>F<sub>2</sub>. Lubiprostone drug product for oral administration is formulated in a soft gelatin capsule with liquid contents of Lubiprostone in medium-chain fatty acid triglyceride.

It is classified as a potent and selective activator of chloride channel type 2. Activation of this chloride channel type 2, which is located on the intestinal epithelial cell, increases chloride transport into the lumen of the intestine, enhances fluid secretion into the bowels and improves fecal transit. It has been shown that the activation of the chloride channels by Lubiprostone occurs only on the apical (luminal) membrane; there was no effect on the basolateral membrane. This indicates that Lubiprostone in the plasma will not cause an effect on the intestine by activating channels located on the basolateral (blood)

membrane. Therefore, Lubiprostone causes secretion of a chloride rich intestinal fluid without affecting sodium and potassium concentrations in the serum.

## **2.2 Currently Available Treatment for Indications**

There are no FDA approved over-the-counter or prescription products for the treatment of irritable bowel syndrome with constipation (IBS-C). Zelnorm is a 5HT<sub>4</sub> (serotonin type 4) agonist that acts as a promotility agent in the gastrointestinal tract by mimicking the natural effects of serotonin through normalization of impaired gut motility, inhibition of visceral sensitivity and stimulation of intestinal secretion. It was initially approved on July 24, 2002 for the treatment of IBS-C. It was withdrawn from the market on March 30, 2007 due to cardiovascular adverse events finding; however, it can be obtained under certain conditions for short term use.

## **2.3 Availability of Proposed Active Ingredient in the United States**

Lubiprostone was approved on January 31, 2006 for the treatment of chronic idiopathic constipation at 24 mcg bid dose.

## **2.4 Important Issues with Pharmacologically Related Products**

Lubiprostone is a prostaglandin E1 analogue. It is the first in a new class of drugs that promotes a chloride-rich intestinal fluid secretion through activation of the chloride channels on the apical membrane of the human intestine. The review team that approved Lubiprostone 24 mcg bid dose performed a careful search through the Lubiprostone database and the potential for this drug to have similarities to other synthetic prostaglandins such as misoprostol and Cytotec.

## **2.5 Pre-submission Regulatory Activity**

- On March 7, 2005 an End-of-phase II meeting was held between the Agency and the sponsor (Sucampo) to discuss plans for phase III study protocols which included discussions of the primary efficacy endpoint, duration of long term safety exposure and number of subjects exposed to long term treatment. The Agency suggested that the sponsor perform a randomized withdrawal to evaluate rebound phenomenon and duration of drug efficacy following discontinuation. There was a recommendation from the Agency of the need to include global assessment of symptom relief as part of the monthly responder definition and to adjust the ratings scale to include worsening symptoms. There was also a suggestion made to evaluate additional dose levels in the sponsor's proposed phase III studies to establish efficacy.
- The sponsor submitted a proposed pediatric study request and a request for the issuance of a Written Request from the Agency on August 18, 2006. The request was denied on December 18, 2006 since there were some issues with the study design.
- On March 5, 2007, a pre-NDA meeting was held between the Agency and the sponsor to discuss the revised classification of Rome II to Rome III and its applicability to the Lubiprostone 8 mcg bid in IBS-C population study. The Agency recommended that the sponsor follow the original protocol design and statistical analytical plan using the Rome II criteria. There was also discussions surrounding safety datasets and adverse events reporting format.
- The NDA was submitted to the Agency on June 29, 2007.

## **2.6 Other Relevant Background Information**

- On November 20, 2007, there was a Type C meeting held between the Agency and the sponsor. The meeting was held to discuss issues regarding secondary endpoints and the statistical analysis.

## **3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

### **3.1 CMC (and Product Microbiology, if Applicable)**

The CMC review is on-going at this time and details on the new formulation and dosage will be included in the Agency's chemistry review.

### **3.2 Animal Pharmacology/Toxicology**

Lubiprostone underwent extensive animal testing for general pharmacologic, toxicological, genotoxic and antigenic effects in various species as part of the original marketing application. No further animal studies were required with this supplemental application.

## **4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY**

### **4.1 Sources of Clinical Data**

The sources of clinical data used in this review are the submitted clinical trials with NDA 21-908 supporting Lubiprostone 8 mcg bid capsules for the treatment of irritable bowel syndrome with constipation in adults. Two randomized double-blinded multi-centered placebo controlled, pivotal efficacy trials (Studies SIB-0431 Treatment Phase I and SIB-0432) in patients with irritable bowel syndrome were included and reviewed in this New Drug Application. One long-term, open-label safety study (SIB-05S1) was reviewed, and a multi-center double-blinded randomized placebo-controlled Phase 2 dose response study (SIB-0221) was also reviewed. A 4-week randomized withdrawal (SIB-0431 Treatment Phase II) was also reviewed. Previous Agency reviews of studies conducted using Lubiprostone 24 mcg bid and higher doses in adults with chronic idiopathic constipation and healthy subjects contributed information to this particular review process.



## 4.2 Table of Clinical Studies

Study ID	Number of Study Centers  Locations	Study Start Enrollment Status, Date  Subjects Enrolled/Planned	Design  Control Type	Study Objective	Study & Control Drugs  Dose, Route & Regimen	Number of Subjects Treated/Completed	Duration	Gender F/M  Median Age (range)	Diagnosis  Inclusion Criteria	Primary Endpoints
<b>SIB-0221</b>	20  United States	April 2003  Completed; June 2004  195/200	Double-blind, randomized multicenter  Placebo	Safety and Efficacy	<b>Oral Lubiprostone</b> 8 mcg BID 16 mcg BID 24 mcg BID  <b>Oral Placebo</b> 0 mcg BID	52/42 49/33 45/30  48/41	12 weeks	175/18  46 years (range = 19-74 years)	IBS-C  1. Rome II criteria 2. Bowel Symptom Survey 3. See Footnote 1	Change from baseline in abdominal discomfort/pain during treatment Month 1
<b>SIB-0431</b>	65  United States	May 2005  Completed; July 2006  590/570	Double-blind, randomized multicenter  Placebo	Efficacy and Safety	<b>Oral Lubiprostone</b> 8 mcg BID  <b>Oral Placebo</b> 0 mcg BID	395/297 (DB*)  193/139 (DB*) See Footnote 2 for RW*	16 weeks  12 weeks (DB)*  4 weeks (RW)*	535/48  47 years (range = 19-85 years)	IBS-C  1. Rome II criteria 2. Bowel Symptom Survey 3. See Footnote 1	Overall Responder rate
<b>SIB-0432</b>	65  United States	May 2005  Completed; August 2006  581/570	Double-blind, randomized multicenter  Placebo	Efficacy and Safety	<b>Oral Lubiprostone</b> 8 mcg BID  <b>Oral Placebo</b> 0 mcg BID	385/303  194/151	12 weeks	522/49  47 years (range = 18-79 years)	IBS-C  1. Rome II criteria 2. Bowel Symptom Survey 3. See Footnote 1	Overall Responder rate
<b>SIB-05S1</b>	104  United States	September 2005  Completed; November 2006  522/500	Open Label multicenter  None	Safety	<b>Oral Lubiprostone</b> 8 mcg BID	520/304	36 weeks	483/37  47 years (range = 21-82 years)	IBS-C  Completion of SIB-0431 or SIB-0432 with ≥70% study medication compliance	Adverse Events, laboratory values, vital signs, weight, physical exam

\*DB= double-blind (Treatment Phase I); RW= Randomized Withdrawal (Treatment Phase II)

<sup>1</sup>During the screening/baseline period, subjects were required to have 2 of the following:

- abdominal discomfort/pain that was at least mild in severity; and
- any 2 of the following:

Amitiza/lubiprostone capsules

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- fewer than 3 spontaneous bowel movements (SBMs)/week at least 25% of the time (in SIB-0431 & SIB-0432, subjects with no SBMs during baseline period were not required to meet either of the 2 remaining criteria);
- at least 25% of the SBMs recorded a straining assessment of moderate or greater severity
- at least 25% of the SBMs recorded stool consistency assessment of hard or very hard stool

<sup>2</sup>139/131 placebo/placebo subjects, 146/143 Lubiprostone/Placebo subjects, and 151/146 Lubiprostone/Lubiprostone subjects (Treated/Completed RW period, Treatment Phase II of SIB-0431)

Results of the two pivotal studies and the one long term safety and efficacy study will be presented and discussed in detail in the following sections of this review.

### **4.3 Review Strategy**

The medical reviewer thoroughly reviewed the sponsor's two pivotal studies and one long term safety and efficacy study both individually and as pooled data. The medical reviewer evaluated such studies with equal regard to efficacy and safety. The sponsor's 4-week randomized withdrawal study and the dose response study SIB-0221 were also reviewed in the integrated safety and efficacy analyses and highlighted by the medical officer throughout this review.

### **4.4 Data Quality and Integrity**

The Division of Scientific Investigations (DSI) was consulted by the Agency for this supplemental New Drug Application. DSI inspected 4 separate clinical investigational sites: Site # 151, study SIB-0431; Site # 164, study SIB-0431; Site # 205, study SIB-0432; Site # 236, study SIB-0432. Dr. Edward Sargent participated in studies SIB-0431 and SIB-05S1. During a DSI investigation, it was revealed that his clinical site (Site # 151) did not keep adequate and accurate records. The investigator and sub-investigator signatures entered on subjects' physical exam forms, laboratory and ECG report forms were that of the study coordinator rather than the responsible/examining clinicians. The signature irregularities made it difficult to ensure the accuracy of the physical exams and verification of the laboratory and ECG data. Therefore, data generated at site # 151 for study SIB-0431 are considered unacceptable in support of the efficacy and safety application for Lubiprostone 8 mcg bid for irritable bowel syndrome with constipation. At the request of the Agency, the sponsor did perform an analysis of the overall responder rate for study SIB-0431 and pooled data excluding all the data generated from site # 151. The overall responder rate excluding subjects from site # 151 for Lubiprostone treated subjects in study SIB-0431 was 13.0% vs. 7.1% for placebo treated subjects,  $p=0.035$ . In the ITT population for the pooled data excluding subjects from site #151, Lubiprostone treated subjects had an overall responder rate of 12.6% vs. 6.4% for placebo treated subjects,  $p=0.002$ . The treatment difference excluding data from site #151 in study SIB-0431 was 5.9% and 6.2% in the pooled group which was similar to the results obtained when the site was included; however, the  $p$  value obtained without data from site # 151 was slightly larger than that obtained with inclusion of subjects from site # 151.

### **4.5 Compliance with Good Clinical Practices**

According to the sponsor, all of the studies were conducted in accordance with U.S. Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR 50), IRBs (21 CFR 56), and the obligations of clinical investigators (21 CFR 312). However, one of the investigators, Dr. Edward Sargent was found to have violated [21 CFR 312.60], which is the failure to conduct investigations according to the signed investigator statement. Furthermore, he was also in violation of [21 CFR 312.62 (b)], which is a failure to maintain adequate and accurate case histories of all observed and pertinent data on each individual during a trial. Per the sponsor, all studies were conducted in accordance with U.S. Title 21 CFR on Good Clinical Practices (GCPs) which is consistent with the ethical principles set forth the Declaration of Helsinki, the International Conference on Harmonization, and the Food and Drug Administration, however, the inspection revealed otherwise as stated previously.

## 4.6 Financial Disclosures

The sponsor provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangements with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The sponsor also certified that each clinical investigator had no proprietary interest in this product or significant equity in the sponsor as defined by 21 CFR 54.2(b). As defined by 21 CFR (f), the sponsor certified that no clinical investigator was the receipt of any significant payments of any sorts. However, there were

two investigators (Drs. (b) (6)) that had received substantial financial compensation (disclosed figures > \$50,000 + other undisclosed amounts). Therefore, the Agency asked the sponsor to perform an analysis of the (b) (6) without utilizing the data from those specific investigators' study sites. In study (b) (6) (excluding the 2 investigators' site), the overall responder rate for subjects treated with Lubiprostone (b) (6) was (b) (6) for subjects treated with placebo, (b) (6). The treatment difference was (b) (6). In study (b) (6) (excluding the 2 investigators' site), the overall responder rate for subjects treated with Lubiprostone (b) (6) was (b) (6) for subjects treated with placebo, (b) (6). The treatment difference was (b) (6). The overall responder rates for both (b) (6) studies without using the data from Drs. (b) (6) was similar to the data obtained with the use of the 2 investigators' data.

## 5 CLINICAL PHARMACOLOGY

### 5.1 Pharmacokinetics

There were no further pharmacokinetics profile studies conducted for this supplemental indication. All the pharmacokinetics studies were conducted with the original submission, and they were reviewed and evaluated thoroughly as part of the original NDA.

### 5.2 Pharmacodynamics

There were no further pharmacodynamics effects studies conducted for this supplemental indication. All the pharmacodynamics studies were conducted with the original submission, and they were reviewed and evaluated thoroughly as part of the original NDA.

### 5.3 Exposure-Response Relationships

As Lubiprostone was originally planned to be marketed as an orally administered product, all clinical dose response studies for Lubiprostone were evaluated via this route of administration.

The Phase II study SIB-0221 employed multi-center, parallel-group, double blind, parallel-controlled study design involving 4 groups of approximately 50 subjects diagnosed with constipation-predominant irritable bowel syndrome (IBS-C). The data gained from the previous studies utilizing Lubiprostone 24 mcg bid in adults with chronic idiopathic constipation led to the proposed dosing levels for the Phase II study SIB-0221. Preliminary analysis performed by the sponsor of a sub-group of diagnosed or self-reported irritable bowel syndrome subjects within the phase III chronic idiopathic constipation study provided some of the early data for design of the SIB-0221 study. The study SIB-0221 evaluated dose levels of 16 mcg/day, 32 mcg/day, and 48 mcg/day over a 12 week treatment period. All subjects took

the study medication bid that was either provided as placebo bid or oral Lubiprostone 16 mcg/day (2-Placebo and 1-8 mcg capsules bid), 32 mcg/day (1 Placebo and 2-8 mcg capsules bid) and 48 mcg/day (3-8 mcg capsules bid). The primary objective of the study was to determine the safety and tolerability of different doses of oral Lubiprostone compared with placebo for relief of IBS-C symptoms when administered for 12 weeks. Results of this study showed that all 3 doses of Lubiprostone were more effective than placebo in decreasing abdominal pain at Month 1. The 16 mcg and the 48 mcg dose groups showed similar decreases (0.45 unit vs. 0.46 unit, respectively) in abdominal pain at Month 1, whereas the 32 mcg dose group had a smaller reduction in abdominal pain (0.40 unit). The overall tolerability of the 16 mcg (8 mcg bid) dose was considered better than the 48 mcg/day (24 mcg bid) dose, even though the 48 mcg/day (24 mcg bid) dose revealed greater changes from baseline on multiple secondary endpoints. The sponsor was also concerned of the greater discontinuation rates due to adverse events (AEs) that occurred in subjects taking the 32 mcg (16 mcg bid) and the 48 mcg (24 mcg bid) doses compared to placebo and the 16mcg (8 mcg bid) dose groups. Therefore, the sponsor chose to develop the 16 mcg/day (8 mcg bid) dose for further Phase III development.

## **6 INTEGRATED REVIEW OF EFFICACY**

### **6.1 Indication**

The proposed indication of this supplemental New Drug Application is for oral Lubiprostone 8 mcg twice daily for the treatment of constipation predominant irritable bowel syndrome (IBS-C).

#### **6.1.1 Methods**

The efficacy evaluation for this supplemental New Drug Application was based on a total of three adequate and well-controlled studies: SIB-0221, SIB-0431 Treatment Phase I and Treatment Phase II, and SIB-0432; and one long term, open-label safety and efficacy study: SIB-05S1.

The two pivotal efficacy studies, SIB-0431 Treatment Phase I and SIB-0432 were multi-center, parallel-group double-blind, placebo controlled studies whose primary objective was to evaluate lubiprostone for its proposed indication, treatment of constipation predominant irritable bowel syndrome (IBS-C). These studies were evaluated both individually and pooled. Included in one of the pivotal studies SIB-0431 was a Treatment phase II or randomized withdrawal study, whose primary objectives were to analyze the rebound phenomenon and the lasting effect of Lubiprostone in the treatment of IBS-C.

Study SIB-0221 was a Phase II multi-center, parallel-group, double-blind, placebo controlled study involving three dose levels of lubiprostone, 16 mcg, 32 mcg and 48 mcg given in b.i.d dosing to determine the safety and tolerability of different dose regimens.

The medical officer will perform a detailed, integrated review of the aforementioned studies.

## 6.1.2 General Discussion of Endpoints

### **Primary Efficacy Endpoint**

- **Overall Responder Rate during the 12 week treatment period.**

An overall responder was defined as a subject that was a monthly responder for at least 2 out of the 3 months during the 12 week treatment period. Overall and Monthly responder definitions were based on the weekly assessments of global symptom relief obtained as part of the subject's electronic diary responses. Global symptom relief was assessed from the 7 point balanced scale associated with the following weekly 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?

- 3 Significantly relieved
- 2 Moderately relieved
- 1 A little bit relieved
- 0 Unchanged
- 1 A little bit worse
- 2 Moderately Worse
- 3 Significantly Worse

### **Secondary Efficacy Endpoints**

- **Monthly Responder Rates during the 12 week treatment period.**

A Monthly responder was defined as a subject whose symptoms were rated as “**Moderately relieved**” for all 4 weeks within a month or “**Significantly relieved**” for at least 2 weeks within a month provided the three conditions were met:

1. The percent of days of rescue medication use did not increase during the month as compared to baseline.
2. The subject did not discontinue the study during the month due to lack of efficacy.
3. The subject had no ratings of “**Moderately worse**” or “**Significantly worse**” during the month.

If a subject had a missing symptom relief rating for a particular week, the missing symptom relief was designated as “unchanged” relief. If the number of ratings were less than 4 for a month, all the missing data received a rating of “unchanged” in order to bring the total number of ratings up to 4 for a month. Study drop-outs were handled in the same manner. Therefore, all ITT subjects had a non-missing responder status for all months. Consequently, subjects who discontinued the study also had a non-missing overall responder status.

Other secondary efficacy endpoints included:

- **Daily abdominal discomfort/pain**
- **Daily abdominal bloating**
- **Frequency rates of Spontaneous Bowel Movements (SBMs)**

- **Frequency rates of Bowel Movements (BMs)**
- **Daily stool consistency associated with SBMs**
- **Daily degree of straining associated with SBMs**
- **Daily severity of constipation associated with SBMs**
- **Irritable Bowel Syndrome Quality of Life (IBS-QOL) assessment**
- **Monthly symptom relief**
- **Weekly treatment effectiveness**

### 6.1.3 Study Design

The two Phase III efficacy studies submitted to support this supplemental New Drug Application for the treatment of constipation-predominant irritable bowel syndrome (IBS-C) were randomized, double-blind, placebo-controlled studies which included a 4 week baseline period for the confirmation of IBS-C symptoms and severity of disease, a 12 week active treatment period and a 2 week follow-up period. The study populations were well controlled across both studies as both had the same inclusion/exclusion criteria. The inclusion criteria focused primarily on the definition of IBS and IBS-C as set forth by the Rome II classification. Subjects were required to have features listed below that were recorded in their electronic diary during the 4 week baseline period. The baseline features that were required were as follows:

- Abdominal discomfort/pain with an average monthly assessment that was at least mild or greater in severity; and
- any 2 of the following:
- Fewer than 3 SBMs/week at least 25% of the time (subjects with no SBMs during the baseline period were not required to satisfy either of the following criteria);
  - at least 25% of the SBMs associated with a straining assessment of moderate or greater severity;
  - at least 25% of the SBMs associated with a stool consistency assessment of hard or very hard stool.

The exclusion criteria mainly targeted subjects with significant chemical or physiological anomalies or conditions that represented potential confounding factors for the planned statistical analyses. Subjects were excluded from the study if they had documented mechanical obstruction, organic disorders of the bowel (such as inflammatory bowel disease, ulcerative colitis, Crohn's Disease), constipation secondary to a documented cause (such as surgery, bowel resection), clinically significant cardiovascular, liver, lung, neurological, or psychiatric disorders, or clinically significant laboratory abnormalities.

One of the Phase III studies, SIB-0431 also had a Treatment Phase II, which was a 4 week randomized withdrawal study that occurred following the 12 week Treatment Phase I. The randomization of subjects for the Treatment Phase II study was performed prior to the start of Treatment phase I. Similar inclusion/exclusion criteria were applied for the Treatment Phase II. The follow-up period for study SIB-0431 occurred at the end of 16 weeks instead of at the end of 12 weeks like it did for study SIB-0432. This was due to the 4 week randomized withdrawal portion that followed study SIB-0431 Treatment Phase I. In addition, the study SIB-0431, had an extra IBS-QOL measurement obtained at the end of week 16, which was the last office visit for the randomized withdrawal portion.

For ease of evaluation, three subject populations were created for the evaluation of clinical efficacy.

1. **Pooled Group (PG):** The pooled group consisted of all the Intent to Treat (ITT) population in the well-controlled trials (SIB-0221 16 mcg arm, SIB-0431 Treatment Phase I, SIB-0432). The ITT population was subjects who were randomized, took at least one dose of double blind study drug and had at least one treatment-period diary entry. If a subject was randomized to one treatment and received the other treatment due to an error, data analysis was based on the original treatment group assignment. This population was used for all efficacy analysis. For the overall responder rate, monthly responder rate, and monthly symptom relief, the pooled group was composed of ITT subjects from studies SIB-0431 Treatment Phase I and SIB-0432. The primary and three secondary endpoints for the dose response study SIB-0221 were different from the endpoints of the two pivotal studies, SIB-0431 Treatment Phase I and SIB-0432; but the 3 well-controlled studies did have other secondary endpoints that were the same.

2. **Randomized Withdrawal Group (RWG):** This group consisted of subjects that participated in the 4 week randomized withdrawal portion (also known as Treatment Phase II) of the SIB-0431 study that compared Lubiprostone to placebo. The RW phase (Treatment Phase II) evaluated the rebound, relapse, and lasting effects of Lubiprostone treatment. These results are discussed separately.

3. **Long term group (LTG):** This group consisted of ITT subjects from study SIB-05S1 which is the long term safety and efficacy study that spanned 9 to 13 months. The trial was a Phase III, open-label, long-term safety study that was designed to capture safety data during treatment with oral Lubiprostone at a dose of 16 mcg/day (8 mcg/b.i.d) administered for 36 weeks. Efficacy data collected in these studies were subjective in nature; however, the same subjective assessments were also performed as part of the well-controlled, double-blind, randomized, placebo-controlled studies. The open label study did not utilize the overall responder rate as an efficacy variable. Furthermore, the SIB-05S1 study used a modified definition of a monthly responder as one of the efficacy variables. These results contributed to the overall evaluation of Lubiprostone efficacy by providing a comparison of results of some of the same efficacy assessments in both open label and double-blind studies and by demonstrating the persistence of efficacy over time, specifically 9, 12 and 13 months.

#### **Medical officer comments**

*Overall, the randomization process used in the pivotal studies generated treatment groups that were well balanced with regards to baseline demographic characteristics and past medical histories.*

*The use of placebo as a comparator in studies SIB-0221, SIB-0431 Treatment Phase I and II, and SIB-0432 was appropriate as subjects were permitted to administer rescue medication if a significant need for relief existed for their constipation and abdominal pain prior to it becoming a possible life threatening condition.*

*Although the long term safety study did not provide a direct comparison, only side-by-side contrasting analysis of the efficacy results with the pooled group, it did demonstrate continued efficacy of Lubiprostone 16 mcg. The efficacy results in the open label study may be confounded by the fact that modification to the monthly responder definition was made. The new monthly responder definition in the open label study does not take into account the use of rescue medication each month compared to baseline.*



***The two 12 week pivotal trials were an acceptable duration given that the one long-term safety and efficacy trial provided up to 9, 12 and 13 months of efficacy measures despite the differences in the monthly responder definition.***

The **statistical analytical plan** was outlined in each individual study report.

In studies SIB-0431 Treatment Phase I and SIB-0432, the overall and the monthly responder rates analyses were performed on Intent-to-Treat (ITT) subjects without using last-observation-carried forward principle (LOCF). The ITT subjects were subjects who were randomized, took at least one dose of double blind study drug and had at least one treatment-period diary entry. If a subject was randomized to one treatment and received the other treatment due to an error, data analysis was based on the original treatment group assignment. 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 week or month where data was missing. The LOCF technique was applied to weekly and monthly averages and not to data from daily ratings. This method of imputation was used for the non-key secondary efficacy endpoints with the exception of irritable bowel syndrome–quality of life (IBS-QOL). The sponsor did perform supportive analyses of the overall and monthly responder rates using LOCF.

Demographic characteristics (age, height, gender, and race) were summarized by treatment group and overall by using descriptive statistics. The comparability of demographic and baseline variables between pooled centers was evaluated by analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables.

For the primary efficacy analysis, a Cochran Mantel-Haenszel (CMH) test stratified by pooled center was used. Small centers were pooled when necessary. This procedure tested the null hypothesis of equal overall responder rates between Placebo and Lubiprostone 16 mcg at the end of 12 week treatment period versus the alternate hypothesis of non-equality between the 2 groups. All tests for treatment effects were two tailed, at a significance level of 5%. For the monthly responder rates, which were key secondary efficacy endpoints, the sponsor utilized a combination of closed and sequential testing procedures to declare significance while protecting the experimental-wise Type I error rate of  $\alpha = 0.05$ . If the primary analysis of overall responder rates was significant, then the 3-step testing procedure was applied. This 3-step procedure is described in detail in the statistical analytical plan and also in the Agency's statistical review.

The long term group (LTG) of study SIB-05S1 had its efficacy analysis performed on the ITT population. The randomized withdrawal group (RWG) of study SIB-0431 Treatment Phase II, used the randomized withdrawal population and the phase I responder population to perform analyses.

#### **6.1.4 Efficacy Findings**

##### **Phase III Pivotal Studies SIB-0431 Treatment Phase I and SIB-0432**

Both studies SIB-0431 Treatment Phase I and SIB-0432 evaluated subjects with IBS-C and compared efficacy and safety of 16 mcg/day (8 mcg b.i.d) Lubiprostone versus placebo. In both studies, following a 4 week baseline period, subjects received 12 weeks of double-blind medication. No dose escalation was permitted during either study; however, a dose reduction to once daily was permitted at the

discretion of the investigator. Each study was powered to detect a 12% difference in responder rate between the placebo and Lubiprostone 16 mcg groups during the 12 week treatment period. The studies were comparable with respect to the number of subjects treated and analyzed; 583 subjects in study SIB-0431 Treatment Phase I and 571 subjects in study SIB-0432. The two pivotal studies were also similar with regard to the overall mean number of days the subject population was on the study drug; 74.6 for SIB-0431 Treatment Phase I and 74.5 for SIB-0432.

**Table 1: Demographics for ITT Subjects of Pivotal Studies**

Variable/Statistic		Study SIB-0431 Treatment Phase I			Study SIB-0432		
Variable	Category	Placebo	Lubiprostone 16 mcg	Total	Placebo	Lubiprostone 16 mcg	Total
Subject Number	N	193	390	583	192	379	571
Age (years)	Mean	48.1	46.7	47.2	47.3	45.5	46.1
	SD	12.55	12.74	12.69	13.34	12.93	13.08
	Median	48.0	47.0	47.0	48.0	46.0	47.0
	Range	20.0-85.0	19.0-83.0	19.0-85.0	18.0-79.0	19.0-79.0	18.0-79.0
Height (inches)	Mean	64.8	64.9	64.9	65.0	64.7	64.8
	SD	3.09	2.90	2.96	3.34	3.15	3.21
	Median	64	64.5	64.5	64.7	64.0	64.5
	Range	56.2-74.0	57.0-75.0	56.2-75.0	59.0-85.0	53.8-76.0	53.8-85.0
Gender	Female	180 (93.3)	355 (91.0)	535 (91.8)	179 (93.2)	343 (90.5)	522 (91.4)
	Male	13 (6.7)	35 (9.0)	48 (8.2)	13 (6.8)	36 (9.5)	49 (8.6)
Race	Caucasian	142 (73.6)	293 (75.1)	435 (74.6)	156 (81.3)	302 (79.7)	458 (80.2)
	African-American	29 (15.0)	53 (13.6)	82 (14.1)	21 (10.9)	49 (12.9)	70 (12.3)
	Hispanic	18 (9.3)	43 (11.0)	61 (10.5)	12 (6.3)	25 (6.6)	37 (6.5)
	Asian	1 (0.5)	0 (0.0)	1 (0.2)	1 (0.5)	3 (0.8)	4 (0.7)
	American Indian/Alaska Native	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Other	3 (1.6)	0 (0.0)	3 (0.5)	2 (1.0)	0 (0.0)	2 (0.4)

Reviewer's table, modified from Table 2.7.3.3-4, page 34 of 106, Summary of Clinical Efficacy

**Table 1 Continued: Demographics for ITT Population in Study SIB-0221 and Pooled Group**

Variable/Statistic		Dose Response Study SIB-0221*			Pooled Group (SIB-0221*, SIB-0431 Treatment Phase I, SIB-0432)		
Variable	Category	Placebo	Lubiprostone 16 mcg	Total	Placebo	Lubiprostone 16 mcg	Total
Subject Number	N	48	51	99	433	820	1253
Age (years)	Mean	44.6	46.5		47.4	46.1	46.6
	SD	11.08	10.14		12.77	12.69	12.72
	Median	46.0	47.0		48.0	46.0	47.0
	Range	24.0-69.0	23.0-72.0		18.0-85.0	19.0-83.0	18.0-85.0
Height (inches)	Mean	65.33	64.42		64.9	64.8	64.8
	SD	3.357	3.148		3.23	3.03	3.10
	Median	66.0	64.0		64.8	64.5	64.5
	Range	54.0-73.0	58.0-76.0		54.0-85.0	53.8-76.0	53.8-85.0
Age Group	18 ≤ Age < 65				393 (90.8)	759 (92.6)	1152 (91.9)
	Age ≥ 65				40 (9.2)	61 (7.4)	101 (8.1)
Gender	Female	44 (91.7)	47 (92.2)	91 (91.9)	403 (93.1)	745 (90.9)	1148 (91.6)
	Male	4 (8.3)	4 (7.8)	8 (8.1)	30 (6.9)	75 (9.1)	105 (8.4)
Race	Caucasian	40 (83.3)	40 (78.4)	80 (80.8)	338 (78.1)	635 (77.4)	973 (77.7)
	African-American	2 (4.2)	5 (9.8)	7 (7.1)	52 (12.0)	107 (13.0)	159 (12.7)
	Hispanic	6 (12.5)	5 (9.8)	11 (11.1)	36 (8.3)	73 (8.9)	109 (8.7)
	Asian	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	3 (0.4)	5 (0.4)
	American Indian/Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
	Other	0 (0.0)	1 (2.0)	1 (1.0)	5 (1.2)	1 (0.1)	6 (0.5)

Reviewer's table, modified from Table 2.7.3.3-4, page 34 of 106, Summary of Clinical Efficacy

\*Study SIB-0221 excludes data from Lubiprostone 32 mcg and 48 mcg arm

As noted above in table 1, the baseline demographic information was similar throughout the pooled group (PG). For the overall pooled population, the mean age was 46.6 years, whereas in the individual studies, the mean ranged from 44.6 years (study SIB-0221) to 48.1 years (Study SIB-0431 Treatment Phase I). Of the 1253 subjects that were treated in the PG, 101 (8.1%) were older or equal to 65 years of age and 1152 (91.9%) were ≥ 18 and < 65 years old. The subject population in the pooled group was predominantly female, 1148/1253 (91.6%). The female gender dominance was generally similar across all three trials with 91.8% females in study SIB-0431 Treatment Phase I, 91.4% females in study SIB-0432 and 91.9% females in study SIB-0221. The majority of the subjects in the pooled group were Caucasian (77.7%). This racial distribution was also seen across all three trials with 74.6% Caucasian in

SIB-0431 Treatment Phase I, 80.2% Caucasian in SIB-0432, and 80.8% Caucasian in study SIB-0221. Other demographic statistics such as mean height ranged from 64.42 inches to 65.33 inches in SIB-0221 and was similar across the three well-controlled studies.

### **Medical officer comments**

*The literature notes that throughout the world, about 10-20% of adults and adolescents have symptoms consistent with IBS. Most studies also find a female predominance. The demographic data indicates a pooled female gender predominance of 91.6% which reasonably reflects the gender distribution of the intended market population for Lubiprostone. The diagnosis of IBS is rare after the age of 50 and tends to peak in the third and fourth decade of life. In the pooled group, the large number of subjects (91.9%) in the age group less than 65 years old probably reflects the intended target population for Lubiprostone.*

### **PRIMARY EFFICACY VARIABLE**

#### ▪ OVERALL RESPONDER RATE DURING THE 12 WEEKS

As defined in the sponsor's statistical analytical plan, the primary efficacy analysis was based upon the overall responder rate during the 12 week treatment period. An overall responder was defined as a monthly responder for at least 2 out of the 3 months during the 12 week treatment period. Overall and monthly responder definitions were based on the weekly assessments of global symptom relief obtained as part of the subject's electronic diary responses. Global symptom relief was assessed based on the 7 point balanced scale associated with the following weekly 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?

- 3 Significantly relieved
- 2 Moderately relieved
- 1 A little bit relieved
- 0 Unchanged
- 1 A little bit worse
- 2 Moderately Worse
- 3 Significantly Worse

Outlined below are the overall responder rate data from the Intent-to-Treat (ITT) population and the pooled group without Last-observation-Carried-Forward imputation method. The pooled group for the primary efficacy variable consisted of the ITT population from the two pivotal studies SIB-0431 Treatment Phase I and SIB-0432 because the primary endpoint in study SIB-0221 was different. The primary endpoint for the dose response study SIB-0221 was the mean change in abdominal discomfort/pain during month 1.

**Table 2: Overall Responder Rates in ITT Population without LOCF and Pooled Group**

Study	Study Arm	Overall	N	%	Responder Difference	p-Value
<b>SIB-0431 Treatment Phase I</b>	Placebo N=193	<b>Responder</b>	<b>15</b>	<b>7.8</b>	6%	0.029*
		Non-Responder	178	92.2		
	Lubiprostone 16 mcg N=390	<b>Responder</b>	<b>54</b>	<b>13.8</b>		
		Non-Responder	336	86.2		
<b>SIB-0432</b>	Placebo N=192	<b>Responder</b>	<b>11</b>	<b>5.7</b>	6.4%	0.023*
		Non-Responder	181	94.3		
	Lubiprostone 16 mcg N=379	<b>Responder</b>	<b>46</b>	<b>12.1</b>		
		Non-Responder	333	87.9		
<b>Pooled (SIB-0431 Treatment Phase I + SIB-0432)</b>	Placebo N=385	<b>Responder</b>	<b>26</b>	<b>6.8</b>	6.2%	0.001~
		Non-Responder	359	93.2		
	Lubiprostone 16 mcg N=769	<b>Responder</b>	<b>100</b>	<b>13.0</b>		
		Non-Responder	669	87.0		

Reviewer's table modified from Table 2.7.3.3-5, page 42 of 106, Summary of Clinical Efficacy and from Table 11-3, page 65 of 89, Clinical Study Report and from Table 11-2, page 57 of 75, Clinical Study Report

\*p-value is from a CMH test stratified by pooled-center

~p-value is from CMH test stratified by study

As noted above in table 2, in both pivotal studies (SIB-0431 Treatment Phase I and SIB-0432), the overall responder rates in the Lubiprostone group were higher (range: 12.1%-13.8%) than that in the placebo group (range: 5.7%-7.8%). The difference was statistically significant in SIB-0431 Treatment Phase I and SIB-0432. In the pooled group, the overall responder rate was 13.0% for Lubiprostone and 6.8% for placebo and the difference was statistically significant, p=0.001. In both well-controlled studies, the difference in overall responder rates between treatment groups was similar. The difference between the placebo treatment group and the Lubiprostone 16 mcg treatment group was 6% in study SIB-0431 Treatment Phase I and 6.4% in study SIB-0432. In the pooled group, the difference in overall responder rate between subjects that received placebo and active treatment was 6.2%.

### **Medical officer comments**

*Although the responder difference between the treatment groups is only 6%, from a clinical perspective, treatment with Lubiprostone 16 mcg maybe a valuable treatment option for subjects suffering from constipation predominant IBS.*

### **Key Secondary Efficacy Variable**

#### **▪ Monthly Responder Rates during the 12 week treatment period**

A Monthly responder was defined as a subject whose symptoms are rated as “Moderately relieved” for all 4 weeks within a month or “Significantly relieved” for at least 2 weeks within a month provided the three conditions were met:

1. The percent of days of rescue medication use did not increase during the month as compared to baseline.
2. The subject did not discontinue the study during the month due to lack of efficacy.
3. The subject had no ratings of “Moderately worse” or “Significantly worse” during the month.

If a subject had a missing symptom relief rating for a particular week, the missing symptom relief was designated as “unchanged” relief. If the number of ratings were less than 4 for a month, all the missing data received a rating of “unchanged” in order to bring the total number of ratings up to 4 for a month. Study drop outs were handled in the same manner. Therefore, all ITT subjects had a non-missing responder status for all months. Consequently, subjects who discontinued the study also had a non-missing overall responder status.

Multiple efficacy variables were controlled in the monthly responder analyses via further testing procedures. Once the primary analysis of overall responder rate was significant, the 3 step testing procedure was utilized to test at the  $\alpha = 0.05$  level for each month individually and simultaneously and in a combined manner. The 3 step analysis procedure is described in detail in the sponsor’s statistical analytical plan and also in the Agency’s statistical review.

**Table 3: Monthly Responder Rates in Intent-to-Treat Population without LOCF and Pooled Group**

Study	Treatment period	Study Arms	Status	N	(%)	Responder Difference	p-Value
<b>SIB-0431 Treatment Phase I</b>	Month 1	Placebo N=193	<b>Responder</b>	<b>12</b>	<b>6.2</b>	3.8%	0.098*
			Non-Responder	181	93.8		
		Lubiprostone 16 mcg N=390	<b>Responder</b>	<b>39</b>	<b>10.0</b>		
			Non-Responder	351	90.0		
	Month 2	Placebo N=193	<b>Responder</b>	<b>18</b>	<b>9.3</b>	6.6%	<b>0.028*~</b>
			Non-Responder	175	90.7		
		Lubiprostone 16 mcg N=390	<b>Responder</b>	<b>62</b>	<b>15.9</b>		
			Non-Responder	328	84.1		
	Month 3	Placebo N=193	<b>Responder</b>	<b>20</b>	<b>10.4</b>	5.5%	0.069*
			Non-Responder	173	89.6		
		Lubiprostone 16 mcg N=390	<b>Responder</b>	<b>62</b>	<b>15.9</b>		
			Non-Responder	328	84.1		
<b>SIB-0432</b>	Month 1	Placebo N=192	<b>Responder</b>	<b>13</b>	<b>6.8</b>	3%	0.303*
			Non-Responder	179	93.2		
		Lubiprostone 16 mcg N=379	<b>Responder</b>	<b>37</b>	<b>9.8</b>		
			Non-Responder	342	90.2		
	Month 2	Placebo N=192	<b>Responder</b>	<b>19</b>	<b>9.9</b>	6.2%	0.047*
			Non-Responder	173	90.1		
		Lubiprostone 16 mcg N=379	<b>Responder</b>	<b>61</b>	<b>16.1</b>		
			Non-Responder	318	83.9		
	Month 3	Placebo N=192	<b>Responder</b>	<b>11</b>	<b>5.7</b>	7.8%	0.008*
			Non-Responder	181	94.3		
		Lubiprostone 16 mcg N=379	<b>Responder</b>	<b>51</b>	<b>13.5</b>		
			Non-Responder	328	86.5		
<b>Pooled (SIB-0431 Treatment Phase I + SIB-0432)</b>	Month 1	Placebo N=385	<b>Responder</b>	<b>25</b>	<b>6.5</b>	3.4%	0.055 <sup>#</sup>
			Non-Responder	360	93.5		
		Lubiprostone 16 mcg N=769	<b>Responder</b>	<b>76</b>	<b>9.9</b>		
			Non-Responder	693	90.1		
	Month 2	Placebo N=385	<b>Responder</b>	<b>37</b>	<b>9.6</b>	6.4%	<b>0.003<sup>#~</sup></b>
			Non-Responder	348	90.4		
		Lubiprostone 16 mcg N=769	<b>Responder</b>	<b>123</b>	<b>16.0</b>		
			Non-Responder	646	84.0		
	Month 3	Placebo N=385	<b>Responder</b>	<b>31</b>	<b>8.1</b>	6.6%	0.001 <sup>#</sup>
			Non-Responder	354	91.9		
		Lubiprostone 16 mcg N=769	<b>Responder</b>	<b>113</b>	<b>14.7</b>		
			Non-Responder	656	85.3		

Reviewer's table modified from Table 2.7.3.3-6, page 43 of 106, Summary of Clinical Efficacy and from Table 14.2.2.1, page 65 of 89, Clinical Study Report and from Table 14.2.2.1, page 57 of 75, Clinical Study Report

\*p-value is from a CMH test stratified by pooled-center

<sup>#</sup>p-value is from a CMH test stratified by study

<sup>~</sup>p-value is significant according to the defined testing procedure

As noted in table 3, in each of the pivotal studies (SIB-0431 Treatment Phase I and SIB-0432), the Lubiprostone 16 mcg group (range: 9.8%-16.1%) demonstrated a higher monthly responder status than placebo (range: 5.7%-10.4%) at all monthly time points. The difference between the placebo and Lubiprostone 16 mcg groups became more pronounced over time in study SIB-0432 (months 1, 2, and 3: 3%, 6.2%, 7.8%, respectively) and in the pooled population (Months 1, 2, and 3: 3.4%, 6.4%, and 6.6% respectively). However, in study SIB-0431 Treatment Phase I, the difference in the monthly responder rates between placebo and Lubiprostone groups did not increase at all time points (Months 1, 2, and 3: 3.8%, 6.6%, and 5.5%, respectively). Statistically significant differences between the treatment groups were observed in Month 2 for the pooled population and for SIB-0431 Treatment Phase I study.

### **Medical Officer Comments**

*Treatment with Lubiprostone revealed a 3% to 7.8% better monthly responder rate above placebo treatment in a few subjects when taken over a course of 3 months. The most consistent and similar responder rate difference between treatment groups was seen at month 2 across 2 well controlled-studies (6.6% in SIB-0431 Treatment Phase I and 6.2% in SIB-0432).*

### **Other Secondary Efficacy Variables:**

The secondary efficacy endpoints in this supplemental New Drug Application were as follows:

- Daily abdominal discomfort/pain
- Daily abdominal bloating
- Frequency rates of Spontaneous Bowel Movements (SBMs)
- Frequency rates of Bowel Movements (BMs)
- Daily stool consistency associated with SBMs
- Daily degree of straining associated with SBMs
- Daily severity of constipation associated with SBMs
- Irritable Bowel Syndrome Quality of Life (IBS-QOL) assessment
- Weekly symptom relief
- Weekly treatment effectiveness

### **Abdominal Discomfort/Pain**

A summary of monthly abdominal discomfort for the Intent-to-Treat (ITT) population with the last observation carried forward (LOCF) is presented below in table 4. The monthly abdominal discomfort rating was averaged for each subject and for all days in a given month. Month 1 started on the first dose date and ended 27 days later (Day 28). Each subsequent month represented 28 days period following the previous month. To decrease the variation that could occur from observed data, the sponsor decided to use change from baseline as the variable for comparison. Change from baseline was calculated as baseline value subtracted from post baseline value. The baseline value represented the average of the entries from the 28 days prior to randomization, visit 2. The post baseline value was the average of all diary ratings during the given month. A Wilcoxon signed-rank tests was used within the treatment groups to determine if there was significant changes from baseline. To test for differences between treatment groups, the van Elteren tests stratified by pooled center was used. If a subject had missing monthly averages, the LOCF method using the most recent non-missing treatment period data points from the same treatment phase was carried forward to subsequent data points where data were missing.



The assessment of abdominal discomfort/pain was based on the daily diary question: How would you rate your abdominal discomfort/pain today? The scale used by subjects to evaluate and rate their abdominal discomfort in their electronic diary was as follows:

Abdominal discomfort/pain:   **0** Absent  
  **1** Mild  
  **2** Moderate  
  **3** Severe  
  **4** Very Severe

**Table 4: Mean Change in Abdominal Discomfort/pain in ITT subjects with LOCF and Pooled Group**

Study	Treatment Period	Study Arms	Mean Abdominal Discomfort Rating	Mean Change from Baseline	p-Value
<b>SIB-0221</b>	Baseline	Placebo N=48	2.02		0.6605 <sup>\$</sup>
		Lubiprostone 16 mcg N=51	2.18		
	Month 1	Placebo N=48	1.83	-0.19	0.0330 <sup>+</sup>
		Lubiprostone 16 mcg N=51	1.73	-0.45	
	Month 2	Placebo N=48	1.79	-0.23	0.0392 <sup>++</sup>
		Lubiprostone 16 mcg N=51	1.66	-0.52	
	Month 3	Placebo N=48	1.68	-0.34	0.1895 <sup>+</sup>
		Lubiprostone 16 mcg N=51	1.62	-0.56	
<b>SIB-0431 Treatment Phase I</b>	Baseline	Placebo N=193	2.09		0.975 <sup>#</sup>
		Lubiprostone 16 mcg N=390	2.08		
	Month 1	Placebo N=193	1.81	-0.27	0.852 <sup>#</sup>
		Lubiprostone 16 mcg N=390	1.78	-0.29	
	Month 2	Placebo N=193	1.71	-0.37	0.646 <sup>#</sup>
		Lubiprostone 16 mcg N=390	1.65	-0.43	
	Month 3	Placebo N=193	1.73	-0.36	0.277 <sup>#</sup>
		Lubiprostone 16 mcg N=390	1.65	-0.42	

<sup>\$</sup> p-value based on the ANCOVA model controlling for pooled center

<sup>+</sup> p-values based on pair-wise comparisons with Placebo using the ANCOVA model LSMeans

<sup>\*</sup> significant differences from placebo using the multiple comparisons step-down procedure

<sup>#</sup> p-values are from van Elteren tests stratified by pooled-center

Abdominal discomfort scale: 0 (Absent), 1 (Mild), 2 (Moderate), 3 (Severe), 4 (Very Severe)

**Table 4 Continued: Mean Change in Abdominal Discomfort/pain in ITT subjects with LOCF and Pooled Group**

Study	Treatment Period	Study Arms	Mean Abdominal Discomfort Rating	Mean Change from Baseline	p-Value
<b>SIB-0432</b>	Baseline	Placebo N=192	2.08		0.973 <sup>#</sup>
		Lubiprostone 16 mcg N=379	2.07		
	Month 1	Placebo N=192	1.79	-0.29	0.663 <sup>#</sup>
		Lubiprostone 16 mcg N=379	1.75	-0.32	
	Month 2	Placebo N=192	1.75	-0.33	0.224 <sup>#</sup>
		Lubiprostone 16 mcg N=379	1.63	-0.44	
	Month 3	Placebo N=192	1.73	-0.35	0.271 <sup>#</sup>
		Lubiprostone 16 mcg N=379	1.60	-0.47	
<b>Pooled (SIB-0221, SIB-0431 Treatment Phase I + SIB-0432)</b>	Baseline	Placebo N=433	2.08		0.900 <sup>~</sup>
		Lubiprostone 16 mcg N=820	2.08		
	Month 1	Placebo N=433	1.80	-0.27	0.172 <sup>~</sup>
		Lubiprostone 16 mcg N=820	1.76	-0.32	
	Month 2	Placebo N=433	1.74	-0.34	0.011 <sup>~</sup>
		Lubiprostone 16 mcg N=820	1.64	-0.44	
	Month 3	Placebo N=433	1.72	-0.35	0.013 <sup>~</sup>
		Lubiprostone 16 mcg N=820	1.63	-0.45	

Reviewer's table modified from Table 2.7.3.3-8, page 45 of 106, Summary of Clinical Efficacy and from Table 14.2.1.1, page 148 of 350, Clinical Study Report and from Table 14.2.3.1, page 66 of 89, Clinical Study Report and from Table 14.2.3.1, page 58 of 75, Clinical Study Report

<sup>#</sup>p-values are from van Elteren tests stratified by pooled-center

<sup>~</sup>Baseline p-values are based on the treatment effect from an ANOVA model controlling for study

<sup>~</sup>Monthly p-values are based on the treatment effect from ANCOVA model controlling for study and using the baseline values as co-variant

Abdominal discomfort scale: 0 (Absent), 1 (Mild), 2 (Moderate), 3 (Severe), 4 (Very Severe)

As noted above in table 4, there were no statistically significant differences in the mean baseline abdominal discomfort ratings among treatment groups in the three individual studies and the pooled group. The mean change from baseline was higher in the Lubiprostone 16 mcg group (range: 0.29-0.56) at all time points compared to the placebo group (range: 0.19-0.37) in studies SIB-0221, SIB-0431 Treatment Phase I, and SIB-0432, and the pooled group, but no statistical significance was achieved in the individual pivotal studies SIB-0431 Treatment Phase I and SIB-0432. At months 2 (p=0.011) and 3

( $p=0.013$ ) in the pooled population, the mean decreases from baseline in the Lubiprostone treatment group was statistically significant. At month 2 in study SIB-0221, the difference in change from baseline in the Lubiprostone treatment group compared with placebo treatment group using the multiple comparisons step down procedure was statistically significant ( $p=0.0392$ ). In the dose ranging study, SIB-0221 the change in abdominal discomfort/pain during month 1 was the primary endpoint, and it was not statistically significant for the Lubiprostone 16 mcg dose group using the multiple comparisons step-down procedure.

### **Medical officer comments**

*Lower mean monthly abdominal discomfort scores represent an overall lessening of patient discomfort. The aforementioned table demonstrates that treatment with Lubiprostone 16 mcg results in an average mean reduction of 0.35 units on the 5-point scoring scale at month 1, 0.46 units at month 2, and 0.48 units at month 3 when compared to baseline. In comparison, the placebo group revealed an average mean reduction of 0.26 units on the 5-point scoring scale at month 1, 0.32 units at month 2, and 0.35 units at month 3. Most of the Lubiprostone and placebo subjects in the 3 individual studies had a baseline abdominal discomfort/pain that was between 2 and 3 which is moderate to severe. During treatment with Lubiprostone, the subjects' abdominal discomfort did decrease into the range of mild to moderate. Placebo also had similar decreases in abdominal discomfort in the 3 individual studies (1.68-1.83); however, in the ratings scale it appears that Lubiprostone treatment may have decreased the abdominal discomfort closer to the rating of mild (1.60-1.78).*

### **Abdominal Bloating**

A summary of monthly abdominal bloating for the Intent-to-Treat population and the pooled group with LOCF is presented below in table 5. The monthly abdominal bloating rating was averaged for each subject and for all days in a given month. The mean change in abdominal bloating was analyzed in the same manner as the mean change in abdominal discomfort/pain. The assessment of abdominal bloating was based on the daily diary question: How would you rate your abdominal bloating today? The scale used by subjects to evaluate and rate their abdominal bloating in their electronic diary was as follows:

Abdominal Bloating:

- 0** Absent
- 1** Mild
- 2** Moderate
- 3** Severe
- 4** Very Severe

**Table 5: Mean Change in Abdominal bloating in ITT subjects with LOCF and Pooled Group**

Study	Treatment Period	Study Arms	Mean Abdominal Bloating Rating	Mean Change from Baseline	p-Value
<b>SIB-0221</b>	Baseline	Placebo N=48	2.27		0.6204 <sup>s</sup>
		Lubiprostone 16 mcg N=51	2.33		
	Month 1	Placebo N=48	2.08	-0.18	0.0231 <sup>+</sup>
		Lubiprostone 16 mcg N=51	1.90	-0.42	
	Month 2	Placebo N=48	2.01	-0.26	0.0631 <sup>+</sup>
		Lubiprostone 16 mcg N=51	1.84	-0.49	
	Month 3	Placebo N=48	1.93	-0.34	0.1392 <sup>+</sup>
		Lubiprostone 16 mcg N=51	1.77	-0.56	
<b>SIB-0431 Treatment Phase I</b>	Baseline	Placebo N=193	2.28		0.987 <sup>#</sup>
		Lubiprostone 16 mcg N=390	2.27		
	Month 1	Placebo N=193	2.04	-0.24	0.615 <sup>#</sup>
		Lubiprostone 16 mcg N=390	1.97	-0.30	
	Month 2	Placebo N=193	1.93	-0.35	0.286 <sup>#</sup>
		Lubiprostone 16 mcg N=390	1.85	-0.42	
	Month 3	Placebo N=193	1.91	-0.37	0.337 <sup>#</sup>
		Lubiprostone 16 mcg N=390	1.84	-0.43	

<sup>s</sup> p-value based on the ANCOVA model controlling for pooled center

<sup>+</sup> p-values based on pair-wise comparisons with Placebo using the ANCOVA model LSMeans

<sup>#</sup> p-values are from van Elteren tests stratified by pooled-center

Abdominal bloating scale: 0 (Absent), 1 (Mild), 2 (Moderate), 3 (Severe), 4 (Very Severe)

**Table 5 Continued: Mean Change in Abdominal bloating in ITT subjects with LOCF and Pooled Group**

Study	Treatment Period	Study Arms	Mean Abdominal Bloating Rating	Mean Change from Baseline	p-Value
<b>SIB-0432</b>	Baseline	Placebo N=192	2.24		0.931 <sup>#</sup>
		Lubiprostone 16 mcg N=379	2.24		
	Month 1	Placebo N=192	1.95	-0.28	0.945 <sup>#</sup>
		Lubiprostone 16 mcg N=379	1.93	-0.31	
	Month 2	Placebo N=192	1.91	-0.33	0.352 <sup>#</sup>
		Lubiprostone 16 mcg N=379	1.82	-0.43	
	Month 3	Placebo N=192	1.89	-0.35	0.180 <sup>#</sup>
		Lubiprostone 16 mcg N=379	1.79	-0.45	
<b>Pooled (SIB-0221, SIB-0431 Treatment Phase I + SIB-0432)</b>	Baseline	Placebo N=433	2.26		0.934 <sup>~</sup>
		Lubiprostone 16 mcg N=820	2.26		
	Month 1	Placebo N=433	2.01	-0.25	0.059 <sup>~</sup>
		Lubiprostone 16 mcg N=820	1.95	-0.31	
	Month 2	Placebo N=433	1.93	-0.33	0.016 <sup>~</sup>
		Lubiprostone 16 mcg N=820	1.83	-0.43	
	Month 3	Placebo N=433	1.90	-0.36	0.024 <sup>~</sup>
		Lubiprostone 16 mcg N=820	1.81	-0.45	

Reviewer's table modified from Table 2.7.3.3-9, page 47 of 106, Summary of Clinical Efficacy and from Table 14.2.11.1, page 68 of 92, Clinical Study Report and from Table 14.2.5.1, page 66 of 89, Clinical Study Report and from Table 14.2.5.1, page 58 of 75, Clinical Study Report

<sup>#</sup>p-values are from van Elteren tests stratified by pooled-center

<sup>~</sup>Baseline p-values are based on the treatment effect from an ANOVA model controlling for study

<sup>~</sup>Monthly p-values are based on the treatment effect from ANCOVA model controlling for study and using the baseline values as co-variant

Abdominal bloating scale: 0 (Absent), 1 (Mild), 2 (Moderate), 3 (Severe), 4 (Very Severe)

As noted above in table 5, there were no statistically significant differences in the mean baseline abdominal bloating ratings among the Lubiprostone and placebo treatment groups in the 3 individual studies and among the pooled population. The mean change from baseline was higher in the Lubiprostone 16 mcg group (range: 0.30-0.56) at all time points compared to the placebo group (range: 0.18-0.37) in studies SIB-0221, SIB-0431 Treatment Phase I, and SIB-0432, and the pooled population, but no statistical significance was achieved in any of the individual studies SIB-0221, SIB-0431 Treatment Phase I and SIB-0432. At months 2 (p=0.016) and 3 (p=0.024) in the pooled population, the mean change in abdominal bloating from baseline in the Lubiprostone group was statistically significant relative to placebo treatment group.

### **Medical officer comments**

*Lower mean monthly abdominal bloating scores represent an overall lessening of patient discomfort. The aforementioned table demonstrates that treatment with Lubiprostone 16 mcg results in an average mean reduction of 0.34 units on the 5-point scoring scale at month 1, 0.44 units at month 2, and 0.47 units at month 3 when compared to baseline. Comparatively, the placebo group revealed an average mean reduction of 0.24 units on the 5-point scoring scale at month 1, 0.32 units at month 2,*

*and 0.36 units at month 3. It appears that treatment with Lubiprostone may cause a greater reduction than placebo in patient's abdominal bloating to the point that it can improve it from the range of 2-3 which is moderate-severe to 1-2 which is mild-moderate.*

#### **Frequency rates of Spontaneous Bowel Movements (SBMs) and Bowel Movements (BMs)**

Spontaneous bowel movements (SBMs) were bowel movements that occur independent of rescue medication usage. The subject determined whether a bowel movement on any given day was the result of rescue medication use on that particular day. The subject recorded in a diary each evening the number of bowel movements and classified it as spontaneous based on the above criteria. The frequency rate was determined by the formula below:

Monthly SBM frequency rate =  $28 \times (\text{Number of SBMs}) / (\text{Number of days})$

where the number of days was the number of days during the month (28-day interval) that the subject was in the study and taking the study drug. For SBM rate calculations for the month that began the treatment Phase I (month 1) required at least 4 days of data. If less than 4 days of data were available for Month 2 or Month 3, then the most recent data from days during the previous month were combined with days from the current month in order to bring the number of days up to 4. Outlined below are the SBM rate data from the Intent-to-Treat population and the pooled group using LOCF imputation method.

**Table 6: Spontaneous Bowel Movement Frequency rates in ITT Population with LOCF and Pooled Group**

Study	Treatment Period	Study Arms	SBM Frequency Rate	Change from Baseline	p-Value
<b>SIB-0221</b>	Baseline	Placebo N=48	4.26		0.0753 <sup>\$</sup>
		Lubiprostone 16 mcg N=51	3.73		
	Month 1	Placebo N=48	4.92	0.66	0.0976 <sup>+</sup>
		Lubiprostone 16 mcg N=51	5.52	1.81	
	Month 2	Placebo N=48	5.03	0.77	0.0087 <sup>+</sup>
		Lubiprostone 16 mcg N=51	5.38	1.67	
	Month 3	Placebo N=48	4.85	0.58	0.0807 <sup>++</sup>
		Lubiprostone 16 mcg N=51	5.49	1.77	
<b>SIB-0431 Treatment Phase I</b>	Baseline	Placebo N=193	3.69		0.660 <sup>#</sup>
		Lubiprostone 16 mcg N=390	3.76		
	Month 1	Placebo N=193	4.91	1.21	0.117 <sup>#</sup>
		Lubiprostone 16 mcg N=390	5.32	1.54	
	Month 2	Placebo N=193	5.1	1.41	0.334 <sup>#</sup>
		Lubiprostone 16 mcg N=390	5.37	1.59	
	Month 3	Placebo N=193	5.08	1.39	0.242 <sup>#</sup>
		Lubiprostone 16 mcg N=390	5.29	1.51	

<sup>\$</sup>p-value based on CMH tests for non-zero correlation using modified ridit scores and stratifying by pooled center

<sup>+</sup>p-values for pair-wise comparisons vs. Placebo are based on van Elteren tests stratified by pooled-center

<sup>\*</sup>significant differences from Placebo using the multiple comparisons step-down procedure

<sup>#</sup>p-values are from van Elteren tests stratified by pooled-center

**Table 6 Continued: Spontaneous Bowel Movement Frequency rates in ITT Population with LOCF and Pooled group**

Study	Treatment Period	Study Arms	SBM Frequency Rate	Change from Baseline	p-Value
<b>SIB-0432</b>	Baseline	Placebo N=192	3.98		0.254 <sup>#</sup>
		Lubiprostone 16 mcg N=379	4.05		
	Month 1	Placebo N=192	5.28	1.29	0.391 <sup>#</sup>
		Lubiprostone 16 mcg N=379	5.58	1.55	
	Month 2	Placebo N=192	5.4	1.39	0.275 <sup>#</sup>
		Lubiprostone 16 mcg N=379	5.63	1.61	
	Month 3	Placebo N=192	5.43	1.42	0.722 <sup>#</sup>
		Lubiprostone 16 mcg N=379	5.44	1.43	
<b>Pooled (SIB-0221, SIB-0431 Treatment Phase I + SIB-0432)</b>	Baseline	Placebo N=433	3.88		0.937 <sup>~</sup>
		Lubiprostone 16 mcg N=820	3.89		
	Month 1	Placebo N=433	5.08	1.18	0.019 <sup>~</sup>
		Lubiprostone 16 mcg N=820	5.45	1.56	
	Month 2	Placebo N=433	5.23	1.33	0.139 <sup>~</sup>
		Lubiprostone 16 mcg N=820	5.49	1.61	
	Month 3	Placebo N=433	5.21	1.32	0.369 <sup>~</sup>
		Lubiprostone 16 mcg N=820	5.37	1.49	

Reviewer's table modified from Table 2.7.3.3-10, page 49 of 106, Summary of Clinical Efficacy and from Table 14.2.3.1, page 63 of 92, Clinical Study Report and from Table 14.2.7.1, page 67 of 89, Clinical Study Report and from Table 14.2.7.1, page 59 of 75, Clinical Study Report.

<sup>#</sup>p-values are from van Elteren tests stratified by pooled-center

<sup>~</sup>Baseline p-values are based on the treatment effect from an ANOVA model controlling for study

<sup>~</sup>Monthly p-values are based on the treatment effect from ANCOVA model controlling for study and using the baseline values as the co-variate.

SBM Frequency Rate:  $28 \times [(\text{Number of SBMs})/(\text{Number of Days Observed for that Month})]$

As noted above in table 6, there were no statistically significant differences in the mean baseline SBM frequency rates among both the treatment groups in the 2 pivotal studies SIB-0431 Treatment phase I and SIB-0432 and in the pooled population. In the dose ranging study SIB-0221, the placebo subjects and the Lubiprostone subjects were not well matched at baseline. The placebo subjects (4.26 SBMs) were less constipated than the Lubiprostone subjects (3.73 SBMs) at baseline in study SIB-0221. In both pivotal studies, (SIB-0431 Treatment Phase I and SIB-0432), the mean change in SBM frequency rates in the Lubiprostone group was higher for all monthly time points (range: 1.51-1.59) than that in the placebo group (range: 1.21-1.41) except in Month 3 of SIB-0432 where it was similar to the placebo group (1.42 Lubiprostone vs. 1.43 Placebo). The difference between placebo and the Lubiprostone treatment groups was not statistically significant at all time points in the pivotal studies (SIB-0431 Treatment Phase I and SIB-0432). In the pooled group, the mean baseline SBM frequency was 3.88 for placebo and 3.89 for Lubiprostone 16 mcg group. For Months 1-3 in the pooled population,



Lubiprostone 16 mcg group demonstrated a greater increase in mean SBM frequency rate than the placebo group, but the difference was statistically significant only at Month 1 (p=0.019).

### **Medical officer comments**

*Treatment with Lubiprostone 16 mcg offers some increase in the spontaneous bowel movement rate. When comparing results before and after treatment, lubiprostone does seem to provide an average of  $\geq 1.5$  increase in spontaneous bowel movements for the 12 week treatment period in the two well-controlled studies, SIB-0431 Treatment Phase I and SIB-0432. In the study SIB-0221, the mean change in SBM frequency rates in the Lubiprostone group was higher for all monthly time points (range: 1.67-1.81) than that in the placebo group (range: 0.58-0.77); however, the placebo and Lubiprostone treatment subjects were not well matched. This baseline difference in SBM frequency rate between treatment groups makes it difficult to make any conclusions regarding the results obtained from that particular study. As noted in table 6, the mean baseline SBM frequency for Lubiprostone was in the range of 3.76 to 4.05. After treatment initiation with Lubiprostone, the mean SBM frequency rate was increased and maintained to a value of  $\geq 5.2$ . Of note, the change from baseline analyses did reveal an appreciable placebo effect. Given that the mean changes from baseline in the Lubiprostone 16 mcg group is a maximum of 0.38 SBMs greater than the mean changes in the placebo group in the pooled population, evidence is questionable to support that Lubiprostone at the 16 mcg dose increases SBM rate. The greatest treatment difference between Lubiprostone and placebo was 0.33 SBMs (in study SIB-0432) which makes one doubt its clinical meaningfulness (to be clinically meaningful, it should at least produce  $\geq 1$  SBMs increase compared to placebo treatment).*

### **Bowel Movements (BMs)**

Bowel Movements that occurred due to the use of rescue medications were documented each evening by subjects in their electronic diary. The frequency rate of BMs during a given month was analyzed in the same manner as the frequency rate of spontaneous bowel movements (SBMs).

**Table 7: Bowel Movement Frequency rates in Intent-to-Treat Population with LOCF and Pooled group**

Study	Treatment Period	Study Arms	Mean BM Frequency Rate	Change from Baseline	p-Value
<b>SIB-0221</b>	Baseline	Placebo N=48	4.72		0.2129 <sup>s</sup>
		Lubiprostone 16 mcg N=51	4.28		
	Month 1	Placebo N=48	5.22	0.51	0.1072 <sup>+</sup>
		Lubiprostone 16 mcg N=51	5.84	1.57	
	Month 2	Placebo N=48	5.35	0.63	0.0324 <sup>+</sup>
		Lubiprostone 16 mcg N=51	5.74	1.47	
	Month 3	Placebo N=48	5.24	0.52	0.0242 <sup>+</sup>
		Lubiprostone 16 mcg N=51	5.94	1.67	
<b>SIB-0431 Treatment Phase I</b>	Baseline	Placebo N=193	4.48		0.798 <sup>#</sup>
		Lubiprostone 16 mcg N=390	4.61		
	Month 1	Placebo N=193	5.37	0.88	0.108 <sup>#</sup>
		Lubiprostone 16 mcg N=390	5.85	1.22	
	Month 2	Placebo N=193	5.58	1.10	0.483 <sup>#</sup>
		Lubiprostone 16 mcg N=390	5.86	1.23	
	Month 3	Placebo N=193	5.53	1.04	0.491 <sup>#</sup>
		Lubiprostone 16 mcg N=390	5.78	1.15	

<sup>s</sup>p-value based on CMH tests for non-zero correlation using modified ridit scores and stratifying by pooled center

<sup>+</sup>p-values for pair-wise comparisons vs. Placebo are based on van Elteren tests stratified by pooled-center

<sup>#</sup>p-values are from van Elteren tests stratified by pooled-center

**Table 7 Continued: Bowel Movement Frequency rates in Intent-to-Treat Population with LOCF and Pooled group**

Study	Treatment Period	Study Arms	Mean BM Frequency Rate	Change from Baseline	p-Value
<b>SIB-0432</b>	Baseline	Placebo N=192	5.14		0.368 <sup>#</sup>
		Lubiprostone 16 mcg N=379	4.82		
	Month 1	Placebo N=192	6.03	0.87	0.060 <sup>#</sup>
		Lubiprostone 16 mcg N=379	6.09	1.30	
	Month 2	Placebo N=192	6.10	0.95	0.290 <sup>#</sup>
		Lubiprostone 16 mcg N=379	6.07	1.29	
	Month 3	Placebo N=192	6.13	0.97	0.495 <sup>#</sup>
		Lubiprostone 16 mcg N=379	5.95	1.17	
<b>Pooled (SIB-0221, SIB-0431 Treatment Phase I, SIB-0432)</b>	Baseline	Placebo N=433	4.80		0.546 <sup>~</sup>
		Lubiprostone 16 mcg N=820	4.69		
	Month 1	Placebo N=433	5.65	0.84	0.005 <sup>~</sup>
		Lubiprostone 16 mcg N=820	5.96	1.28	
	Month 2	Placebo N=433	5.79	0.98	0.101 <sup>~</sup>
		Lubiprostone 16 mcg N=820	5.95	1.27	
	Month 3	Placebo N=433	5.77	0.95	0.201 <sup>~</sup>
		Lubiprostone 16 mcg N=820	5.87	1.19	

Reviewer's table modified from Table 1.2.5.1.1, page 48 of 106, Summary of Clinical Efficacy and from Table 14.2.3.1, page 63 of 92, Clinical Study Report and from Table 14.2.7.1, page 67 of 89, Clinical Study Report and from Table 14.2.7.1, page 59 of 75, Clinical Study Report.

<sup>#</sup>p-values are from van Elteren tests stratified by pooled-center

<sup>~</sup>Baseline p-values are based on the treatment effect from an ANOVA model controlling for study

<sup>~</sup>Monthly p-values are based on the treatment effect from ANCOVA model controlling for study and using the baseline values as the co-variant.

BM Frequency Rate:  $28 \times [(\text{Number of BMs})/(\text{Number of Days Observed for that Month})]$

In comparing tables 6 and 7, the mean change in spontaneous bowel movement frequency rates were higher than the mean change in bowel movement frequency rates in both the placebo and Lubiprostone treatment groups in the 2 pivotal studies SIB-0431 Treatment Phase I and SIB-0432, which is unexpected given the fact that bowel movement frequency rates were reflective of concomitant rescue medication use. In each of the three studies as well as the pooled population, Lubiprostone 16 mcg group demonstrated a greater change in mean BM frequency rate than placebo at all monthly time points, but reached statistical significance only at Month 1 (p=0.005) in the pooled population.

### **Stool Consistency**

A summary of monthly stool consistency for the Intent-to-Treat population with LOCF and the pooled group is presented below in table 8. According to the sponsor's statistical analytical plan, the degree of stool consistency was averaged for each subject and for all SBMs in a given month. Analysis was based on the change from baseline, where the baseline value represented the average stool consistency ratings from all the SBMs during the 28-day baseline period (prior to randomization or visit 2). Average degree of stool consistency was analyzed by van Elteren tests stratified by pooled center. In order to assess the change from baseline, the Wilcoxon signed-rank tests was performed within each treatment group. Stool consistency was based on the daily diary question: What was the average stool consistency of your spontaneous bowel movements? The scale used by subjects to evaluate and rate their stool consistency in their electronic diary was as follows:

Stool consistency:   **0** Very Loose (watery)  
                                  **1** Loose  
                                  **2** Normal  
                                  **3** Hard  
                                  **4** Very Hard (little balls)

**Table 8: Summary of Monthly Stool Consistency in the ITT population with LOCF and Pooled Group**

Study	Treatment Period	Study Arms	Mean Stool Consistency Rating	Mean Change from Baseline	p-Value
<b>SIB-0221</b>	Baseline	Placebo N=48	2.54		0.5128 <sup>\$</sup>
		Lubiprostone 16 mcg N=51	2.81		
	Month 1	Placebo N=48	2.44	-0.11	0.0374 <sup>++</sup>
		Lubiprostone 16 mcg N=51	2.22	-0.54	
	Month 2	Placebo N=48	2.34	-0.21	0.1637 <sup>+</sup>
		Lubiprostone 16 mcg N=51	2.19	-0.56	
	Month 3	Placebo N=48	2.37	-0.17	0.1654 <sup>+</sup>
		Lubiprostone 16 mcg N=51	2.20	-0.54	
<b>SIB-0431 Treatment Phase I</b>	Baseline	Placebo N=193	2.74		0.644 <sup>#</sup>
		Lubiprostone 16 mcg N=390	2.78		
	Month 1	Placebo N=193	2.42	-0.33	0.006 <sup>#</sup>
		Lubiprostone 16 mcg N=390	2.25	-0.51	
	Month 2	Placebo N=193	2.37	-0.38	0.030 <sup>#</sup>
		Lubiprostone 16 mcg N=390	2.25	-0.53	
	Month 3	Placebo N=193	2.34	-0.41	0.130 <sup>#</sup>
		Lubiprostone 16 mcg N=390	2.26	-0.52	

<sup>\$</sup>p-value based on the ANCOVA model controlling for pooled center

<sup>+</sup>p-values based on pair-wise comparisons with Placebo using the ANCOVA model LSMeans

<sup>\*</sup>Significant difference from Placebo using the multiple comparisons step-down procedure

<sup>#</sup>p-values are from van Elteren tests stratified by pooled-center

**Table 8 Continued: Summary of Monthly Stool Consistency in the ITT population with LOCF and Pooled Group**

Study	Treatment Period	Study Arms	Stool Consistency Rating	Mean Change from Baseline	p-Value
<b>SIB-0432</b>	Baseline	Placebo N=192	2.76		0.597 <sup>#</sup>
		Lubiprostone 16 mcg N=379	2.75		
	Month 1	Placebo N=192	2.38	-0.37	0.151 <sup>#</sup>
		Lubiprostone 16 mcg N=379	2.27	-0.47	
	Month 2	Placebo N=192	2.35	-0.41	0.177 <sup>#</sup>
		Lubiprostone 16mcg N=379	2.25	-0.50	
	Month 3	Placebo N=192	2.35	-0.39	0.082 <sup>#</sup>
		Lubiprostone 16 mcg N=379	2.25	-0.49	
<b>Pooled (SIB-0221, SIB-0431 Treatment Phase I + SIB-0432)</b>	Baseline	Placebo N=433	2.73		0.397 <sup>~</sup>
		Lubiprostone 16 mcg N=820	2.77		
	Month 1	Placebo N=433	2.41	-0.32	<0.001 <sup>~</sup>
		Lubiprostone 16 mcg N=820	2.26	-0.49	
	Month 2	Placebo N=433	2.36	-0.38	0.004 <sup>~</sup>
		Lubiprostone 16 mcg N=820	2.24	-0.51	
	Month 3	Placebo N=433	2.35	-0.38	0.006 <sup>~</sup>
		Lubiprostone 16 mcg N=820	2.25	-0.51	

Reviewer's table modified from Table 2.7.3.3-11, page 51 of 106, Summary of Clinical Efficacy and from Table 14.2.5.1, page 65 of 92, Clinical Study Report and from Table 14.2.9.1, page 68 of 89, Clinical Study Report and from Table 14.2.9.1, page 60 of 75, Clinical Study Report.

<sup>~</sup>p-values are from van Elteren tests stratified by study

Stool Consistency rating: 0 (Very Loose), 1 (Loose), 2 (Normal), 3 (Hard), 4 (Very Hard)

As noted above at the individual study level and for the pooled group, the mean baseline stool consistency was similar in both treatment groups. In all studies and the pooled population, the mean change in stool consistency in the Lubiprostone group was higher for all monthly time points (range: 0.47-0.56) than that in the placebo group (range: 0.11-0.41). The difference was statistically significant at month 1 (p=0.0374) in study SIB-0221, month 1 (p=0.006) and 2 (p=0.030) in study SIB-0431 Treatment Phase I and in each time point (p ≤ 0.006) in the pooled group.

### **Medical officer comments**

*The lower mean stool consistency numbers represent an overall softening of stool. Although this secondary efficacy variable is strictly a subjective assessment, the aforementioned table 8 demonstrates that treatment with Lubiprostone 16 mcg results in an average mean improvement of 0.50 units on the 5-point scoring scale at month 1, 0.53 units at month 2 and 0.52 units at month 3 when compared to baseline. Comparatively, the placebo group revealed an average mean*

*improvement of 0.28 units on the 5-point scoring scale at month 1, 0.35 units at month 2 and 0.34 units at month 3. Considering that the Lubiprostone subjects had a range of mean baseline stool consistency rating of 2.75-2.81 which corresponds to a range between normal (2) and hard (3), a decrease of 0.5 units on the 5 point scoring scale, would soften their stool adequately to normalize (2.25-2.31) it. Lubiprostone treatment seems to shift the stool consistency from a rating that was closer to hard to one that is near the normal range. Therefore, from a clinical perspective, the mean improvement of 0.5 units exhibited in the Lubiprostone group may represent the relief of a patient's discomfort by softening the stool from a "hard" consistency to a near "normal" consistency or from "very hard" consistency that may lead to obstipation to a near "hard" yet still evacuative consistency.*

### **Degree of Straining**

A summary of monthly degree of straining for the Intent-to-Treat population and pooled group with LOCF is presented below in table 9. According to the sponsor's statistical analytical plan, the degree of straining was analyzed in the same manner as stool consistency. Degree of straining was based on the daily diary question: How would you rate your average straining with your spontaneous bowel movements? The scale used by subjects to evaluate and rate their degree of straining in their electronic diary was as follows:

Degree of Straining:

- 0** Absent
- 1** Mild
- 2** Moderate
- 3** Severe
- 4** Very Severe

**Table 9: Summary of Monthly Degree of Straining in ITT population with LOCF and Pooled Group**

Study	Treatment Period	Study Arms	Mean Degree of Straining Rating	Mean Change from Baseline	p-Value
<b>SIB-0221</b>	Baseline	Placebo N=48	2.22		0.7298 <sup>\$</sup>
		Lubiprostone 16 mcg N=51	2.44		
	Month 1	Placebo N=48	2.00	-0.31	0.0471 <sup>++</sup>
		Lubiprostone 16 mcg N=51	1.85	-0.63	
	Month 2	Placebo N=48	1.92	-0.36	0.0231 <sup>++</sup>
		Lubiprostone 16 mcg N=51	1.74	-0.75	
	Month 3	Placebo N=48	1.87	-0.43	0.1342 <sup>+</sup>
		Lubiprostone 16 mcg N=51	1.76	-0.73	
<b>SIB-0431 Treatment Phase I</b>	Baseline	Placebo N=193	2.41		0.789 <sup>#</sup>
		Lubiprostone 16 mcg N=390	2.38		
	Month 1	Placebo N=193	2.04	-0.36	0.050 <sup>#</sup>
		Lubiprostone 16 mcg N=390	1.86	-0.53	
	Month 2	Placebo N=193	1.98	-0.43	0.049 <sup>#</sup>
		Lubiprostone 16 mcg N=390	1.81	-0.58	
	Month 3	Placebo N=193	1.96	-0.45	0.348 <sup>#</sup>
		Lubiprostone 16 mcg N=390	1.83	-0.56	

<sup>\$</sup>p-value based on the ANCOVA model controlling for pooled center

<sup>+</sup>p-values based on pair-wise comparisons with Placebo using the ANCOVA model LSMeans

<sup>\*</sup>Significant difference from Placebo using the multiple comparisons step-down procedure

<sup>#</sup>p-values are from van Elteren tests stratified by pooled-center

Degree of Straining: 0 (Absent), 1 (Mild), 2 (Moderate), 3 (Severe) and 4 (Very Severe)



**Table 9 Continued: Summary of Monthly Degree of Straining in ITT Population with LOCF and Pooled Group**

Study	Treatment Period	Study Arms	Mean Degree of Straining Rating	Mean Change from Baseline	p-Value
<b>SIB-0432</b>	Baseline	Placebo N=192	2.39		0.668 <sup>#</sup>
		Lubiprostone 16 mcg N=379	2.39		
	Month 1	Placebo N=192	1.96	-0.42	0.163 <sup>#</sup>
		Lubiprostone 16 mcg N=379	1.85	-0.54	
	Month 2	Placebo N=192	1.91	-0.50	0.110 <sup>#</sup>
		Lubiprostone 16 mcg N=379	1.77	-0.62	
	Month 3	Placebo N=192	1.89	-0.50	0.146 <sup>#</sup>
		Lubiprostone 16 mcg N=379	1.76	-0.63	
<b>Pooled (SIB-0221, SIB-0431 Treatment Phase I + SIB-0432)</b>	Baseline	Placebo N=433	2.38		0.962 <sup>~</sup>
		Lubiprostone 16 mcg N=820	2.39		
	Month 1	Placebo N=433	2.00	-0.38	0.001 <sup>~</sup>
		Lubiprostone 16 mcg N=820	1.85	-0.54	
	Month 2	Placebo N=433	1.94	-0.45	0.002 <sup>~</sup>
		Lubiprostone 16 mcg N=820	1.79	-0.61	
	Month 3	Placebo N=433	1.92	-0.47	0.020 <sup>~</sup>
		Lubiprostone 16 mcg N=820	1.79	-0.60	

Reviewer's table modified from Table 2.7.3.3-12, page 53 of 106, Summary of Clinical Efficacy and from Table 14.2.7.1, page 66 of 92, Clinical Study Report and from Table 14.2.11.1, page 69 of 89, Clinical Study Report and from Table 14.2.11.1, page 61 of 75, Clinical Study Report.

<sup>~</sup>p-values are from van Elteren tests stratified by study

<sup>#</sup>p-values are from van Elteren tests stratified by pooled-center

Degree of Straining: 0 (Absent), 1 (Mild), 2 (Moderate), 3 (Severe) and 4 (Very Severe)

As noted above, there was no statistically significant differences in the mean baseline degree of straining in both treatment groups in the individual studies and for the pooled group. At all post-baseline evaluation time points for each study and in the pooled group, the mean change in degree of straining (range: 0.53-0.75) in the Lubiprostone 16 mcg group was higher than the values in the placebo group (range: 0.31-0.50). The difference was statistically significant at month 1 and month 2 in SIB-0221 and SIB-0431 Treatment Phase I ( $p \leq 0.050$ ) and in each time point ( $p \leq 0.020$ ) in the pooled group.

### **Medical officer comments**

*The lower mean degree of straining numbers represent an overall improvement in patient discomfort. Although this secondary efficacy variable is strictly a subjective assessment, table 9 demonstrates that treatment with Lubiprostone 16 mcg results in an average mean improvement of 0.56 units on the 5-point scoring scale at month 1, 0.64 units at month 2 and 0.63 units at month 3 when compared to baseline. In comparison, the placebo group revealed an average mean improvement of 0.37 units on*

*the 5-point scoring scale at month 1, 0.44 units at month 2 and 0.46 units at month 3. Considering that the Lubiprostone subjects had a range of mean baseline degree of straining rating of 2.38-2.44, a decrease of 0.56 to 0.64 units on the 5 point scoring scale, would shift their degree of straining from the moderate-severe range into the mild-moderate range (1.74-1.88). Therefore, from a clinical perspective, the mean improvement of 0.56 to 0.64 units exhibited in the Lubiprostone group may represent the relief of a patient's discomfort by reducing their degree of straining from a "moderate" straining to "mild" straining which indirectly may reduce complications such as hemorrhoids or Valsalva-induced syncope.*

### **Severity of Constipation**

A summary of monthly constipation severity for the Intent-to-Treat population and the pooled group with LOCF is presented below in table 10. Per the sponsor's statistical analytical plan, the analysis of constipation severity was performed in a similar manner to the analysis of abdominal discomfort/pain. The assessment of constipation was based on the daily diary question: How would you rate your constipation today? The scale used by subjects to evaluate and rate their constipation severity in their electronic diary was as follows:

**Severity of Constipation:**

- 0** Absent
- 1** Mild
- 2** Moderate
- 3** Severe
- 4** Very Severe

**Table 10: Summary of Monthly Severity of Constipation in the ITT Population with LOCF and Pooled Group**

Study	Treatment Period	Study Arms	Mean Constipation Severity Rating	Mean Change from Baseline	p-Value
<b>SIB-0221</b>	Baseline	Placebo N=48	2.13		0.9871 <sup>\$</sup>
		Lubiprostone 16 mcg N=51	2.24		
	Month 1	Placebo N=48	1.92	-0.21	0.0325 <sup>+*</sup>
		Lubiprostone 16 mcg N=51	1.76	-0.48	
	Month 2	Placebo N=48	1.86	-0.27	0.1323 <sup>+</sup>
		Lubiprostone 16 mcg N=51	1.74	-0.50	
	Month 3	Placebo N=48	1.82	-0.31	0.1111 <sup>+</sup>
		Lubiprostone 16 mcg N=51	1.68	-0.56	
<b>SIB-0431 Treatment Phase I</b>	Baseline	Placebo N=193	2.29		0.514 <sup>#</sup>
		Lubiprostone 16 mcg N=390	2.24		
	Month 1	Placebo N=193	1.99	-0.29	0.159 <sup>#</sup>
		Lubiprostone 16 mcg N=390	1.83	-0.41	
	Month 2	Placebo N=193	1.89	-0.40	0.064 <sup>#</sup>
		Lubiprostone 16 mcg N=390	1.74	-0.50	
	Month 3	Placebo N=193	1.88	-0.41	0.111 <sup>#</sup>
		Lubiprostone 16 mcg N=390	1.73	-0.51	

<sup>\$</sup>p-value based on the ANCOVA model controlling for pooled center

<sup>+</sup>p-values based on pair-wise comparisons with Placebo using the ANCOVA model LSMeans

<sup>\*</sup>Significant difference from Placebo using the multiple comparisons step-down procedure

<sup>#</sup>p-values are from van Elteren tests stratified by pooled-center

Severity of Constipation: 0 (Absent), 1 (Mild), 2 (Moderate), 3 (Severe) and 4 (Very Severe)

**Table 10 Continued: Summary of Monthly Severity of Constipation in ITT Population with LOCF and Pooled Group**

Study	Treatment Period	Study Arms	Mean Constipation Severity Rating	Mean Change from Baseline	p-Value
<b>SIB-0432</b>	Baseline	Placebo N=192	2.21		0.577 <sup>#</sup>
		Lubiprostone 16 mcg N=379	2.20		
	Month 1	Placebo N=192	1.88	-0.33	0.185 <sup>#</sup>
		Lubiprostone 16 mcg N=379	1.79	-0.41	
	Month 2	Placebo N=192	1.79	-0.42	0.373 <sup>#</sup>
		Lubiprostone 16 mcg N=379	1.70	-0.51	
	Month 3	Placebo N=192	1.80	-0.42	0.339 <sup>#</sup>
		Lubiprostone 16 mcg N=379	1.67	-0.53	
<b>Pooled (SIB-0221, SIB-0431 Treatment Phase I + SIB-0432)</b>	Baseline	Placebo N=433	2.24		0.663 <sup>~</sup>
		Lubiprostone 16 mcg N=820	2.22		
	Month 1	Placebo N=433	1.94	-0.30	0.001 <sup>~</sup>
		Lubiprostone 16 mcg N=820	1.80	-0.42	
	Month 2	Placebo N=433	1.84	-0.39	0.008 <sup>~</sup>
		Lubiprostone 16 mcg N=820	1.72	-0.50	
	Month 3	Placebo N=433	1.84	-0.40	0.005 <sup>~</sup>
		Lubiprostone 16 mcg N=820	1.70	-0.52	

Reviewer's table modified from Table 2.7.3.3-13, page 55 of 106, Summary of Clinical Efficacy and from Table 14.2.9.1, page 67 of 92, Clinical Study Report and from Table 14.2.13.1, page 69 of 89, Clinical Study Report and from Table 14.2.13.1, page 61 of 75, Clinical Study Report.

<sup>~</sup>p-values are from van Elteren tests stratified by study

<sup>#</sup>p-values are from van Elteren tests stratified by pooled-center

Severity of Constipation: 0 (Absent), 1 (Mild), 2 (Moderate), 3 (Severe) and 4 (Very Severe)

As noted above in table 10, there were no statistically significant differences in the mean baseline constipation severity in both treatment groups in the individual studies and for the pooled population. At all post-baseline evaluation time points for each study and in the pooled group, the mean changes in constipation severity (range: 0.41-0.56) in the Lubiprostone 16 mcg group were higher than the values in the placebo group (range: 0.21-0.42). The difference was statistically significant at month 1 in study SIB-0221 (p=0.0325) and in each time point ( $p \leq 0.008$ ) in the pooled group. The lower scores in the Lubiprostone 16 mcg group indicated a lessening of constipation severity in subjects taking the study drug.

### **Medical officer comments**

*The lower mean monthly constipation severity scores represent an overall improvement in patient discomfort. Although this secondary efficacy variable is strictly a subjective assessment, the aforementioned table demonstrates that treatment with Lubiprostone 16 mcg results in an average mean improvement of 0.43 units on the 5-point scoring scale at month 1, 0.50 units at month 2 and 0.53 units at month 3 when compared to baseline. Comparatively, the placebo group revealed an average mean improvement of 0.28 units on the 5-point scoring scale at month 1, 0.37 units at month 2 and 0.39 units at month 3. These secondary efficacy findings of constipation severity show that treatment with Lubiprostone 16 mcg is slightly better than treatment with placebo.*

### **Assessment of Symptom Relief**

A summary of monthly symptom relief for the Intent-to-Treat population and pooled group with LOCF is presented in table 11. During the 12 week treatment period, subjects were asked weekly to evaluate their symptom relief. The monthly symptom relief scores were averaged for each subject and for the weeks in a given month. Mean monthly symptom relief scores between treatment groups were analyzed by the CMH tests stratified by pooled center. Symptom relief assessment was based on a weekly 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? The scale used by subjects to evaluate and rate their symptom relief in their electronic diary was as follows:

Symptom Relief:

- 3 Significantly relieved
- 2 Moderately relieved
- 1 A Little bit relieved
- 0 Unchanged
- 1 A Little bit Worse
- 2 Moderately Worse
- 3 Significantly Worse

**Table 11: Summary of Monthly Symptom Relief in ITT Population with LOCF and Pooled Group**

Study	Treatment period	Study Arm	Mean Symptom Relief Rating	p-Value
<b>SIB-0431 Treatment Phase I</b>	Month 1	Placebo N=193	0.57	0.378 <sup>#</sup>
		Lubiprostone 16 mcg N=390	0.66	
	Month 2	Placebo N=193	0.59	0.144 <sup>#</sup>
		Lubiprostone 16 mcg N=390	0.76	
	Month 3	Placebo N=193	0.57	0.168 <sup>#</sup>
		Lubiprostone 16 mcg N=390	0.74	
<b>SIB-0432</b>	Month 1	Placebo N=192	0.60	0.300 <sup>#</sup>
		Lubiprostone 16 mcg N=379	0.69	
	Month 2	Placebo N=192	0.55	0.023 <sup>#</sup>
		Lubiprostone 16 mcg N=379	0.79	
	Month 3	Placebo N=192	0.56	0.073 <sup>#</sup>
		Lubiprostone 16 mcg N=379	0.75	
<b>Pooled (SIB-0431 Treatment Phase I + SIB-0432)</b>	Month 1	Placebo N=385	0.59	0.226 <sup>~</sup>
		Lubiprostone 16 mcg N=769	0.67	
	Month 2	Placebo N=385	0.57	0.009 <sup>~</sup>
		Lubiprostone 16 mcg N=769	0.77	
	Month 3	Placebo N=385	0.56	0.022 <sup>~</sup>
		Lubiprostone 16 mcg N=769	0.75	

Reviewer's table modified from Table 2.7.3.3-14, page 56 of 106, Summary of Clinical Efficacy and from Table 14.2.15.1, page 70 of 89, Clinical Study Report and from Table 14.2.15.1, page 62 of 75, Clinical Study Report.

<sup>~</sup>p-values are from CMH test stratified by study

<sup>#</sup>p-values are from CMH test stratified by pooled-center

Symptom Relief Scale: -3 (Significantly worse), -2 (Moderately worse), -1 (A little bit worse), 0 (Unchanged), 1 (A little bit relieved), 2 (Moderately relieved), 3 (Significantly relieved)

At all evaluation time points, the mean symptom relief scores for subjects in studies SIB-0431 Treatment Phase I and SIB-0432 and the pooled population were higher in the Lubiprostone 16 mcg treatment group than in the placebo treatment group. The difference was statistically significant at month 2 in both SIB-0432 (p=0.023) and in the pooled group (p=0.009). At month 3 in the pooled group, the difference did also reach statistical significance (p=0.022).

**Medical officer comments**

*As noted above in table 11, the higher mean symptom relief scores represent the patients' subjective impression of overall improvement in their symptoms. All the Lubiprostone treatment groups' scores remained 0.7 units and above in months 2 and 3 which represents a little bit of relief during most of the 12 week treatment period. Even though placebo subjects also rated their symptoms in the range of "unchanged" to "a little bit relieved", it appears that the Lubiprostone subjects were further on the rating scale to achieving "a little bit relieved".*

**Irritable Bowel Syndrome Quality of life (IBS-QOL) assessment**

A summary of IBS-QOL for the Intent-to-Treat population without the LOCF is presented in table 12. The IBS-QOL questionnaire is a series of 34 questions developed by Drossman, et al. Subjects completed IBS-QOL questionnaire at randomization, week 4, and week 12 office visits. Analyses of overall IBS-QOL scores were based on changes from baseline. Missing values were not imputed at the various time points but there was a "Last Value" time point, which represented the last value recorded during the treatment period. An ANCOVA was used to control for treatment, pooled center and the baseline score. In order to assess the change from baseline, the paired t-test was performed within each treatment group.

**Table 12: Summary of IBS Overall Quality of Life Scores in ITT subjects without LOCF and Pooled Group**

Study	Treatment period	Study Arm	Mean IBS-QOL score	Mean Change from Baseline	p-Value
<b>SIB-0221</b>	Baseline	Placebo N=48	61.79		0.9011 <sup>\$</sup>
		Lubiprostone 16 mcg N=51	55.66		
	Week 4	Placebo N=48	68.75	7.47	0.0136 <sup>+</sup>
		Lubiprostone 16 mcg N=51	71.10	14.70	
	Week 12	Placebo N=48	72.82	11.80	0.0472 <sup>+</sup>
		Lubiprostone 16 mcg N=51	74.92	18.54	
	End of Study	Placebo N=48	72.27	10.48	0.0553 <sup>+</sup>
		Lubiprostone 16 mcg N=51	72.76	16.82	
<b>SIB-0431 Treatment Phase I</b>	Baseline	Placebo N=193	54.8		0.488 <sup>#</sup>
		Lubiprostone 16 mcg N=390	56.2		
	Week 4	Placebo N=193	65.3	12.6	0.359 <sup>#</sup>
		Lubiprostone 16 mcg N=390	69.3	13.4	
	Week 12	Placebo N=193	70.6	16.8	0.588 <sup>#</sup>
		Lubiprostone 16 mcg N=390	74.1	16.7	
	Last Phase I Value	Placebo N=193	70.7	15.6	0.804 <sup>#</sup>
		Lubiprostone 16 mcg N=390	72.0	15.5	

<sup>\$</sup>p-values are based on the ANCOVA model controlling for pooled-center

<sup>+</sup>p-values are based on pair wise comparisons with Placebo using the ANCOVA model LSMeans



**Table 12 Continued: Summary of IBS-QOL Scores in ITT subjects without LOCF and Pooled group**

Study	Treatment period	Study Arm	Mean IBS-QOL score	Mean Change from Baseline	p-Value
<b>SIB-0432</b>	Baseline	Placebo N=192	57.6		0.837 <sup>#</sup>
		Lubiprostone 16 mcg N=379	58.0		
	Week 4	Placebo N=192	69.2	12.7	0.971 <sup>#</sup>
		Lubiprostone 16 mcg N=379	70.0	13.0	
	Week 12	Placebo N=192	71.4	13.4	0.062 <sup>#</sup>
		Lubiprostone 16 mcg N=379	74.3	17.3	
	End of Study	Placebo N=192	69.3	11.5	0.008 <sup>#</sup>
		Lubiprostone 16 mcg N=379	72.9	15.3	
<b>Pooled (SIB-0221 + SIB-0431 Treatment Phase I + SIB-0432)</b>	Baseline	Placebo N=433	56.8		0.925 <sup>~</sup>
		Lubiprostone 16 mcg N=820	57.0		
	Week 4	Placebo N=433	67.4	11.9	0.116 <sup>~</sup>
		Lubiprostone 16 mcg N=820	69.8	13.3	
	Week 12	Placebo N=433	71.3	14.4	0.021 <sup>~</sup>
		Lubiprostone 16 mcg N=820	74.2	17.1	
	Last Visit	Placebo N=433	70.2	13.2	0.018 <sup>~</sup>
		Lubiprostone 16 mcg N=820	72.5	15.5	

Reviewer's table modified from Table 1.2.10.1.1, page 56 of 106, Summary of Clinical Efficacy and from Table 14.2.16.1, page 73 of 92, Clinical Study Report and from Table 14.2.17, page 71 of 89, Clinical Study Report and from Table 14.2.17, page 63 of 75, Clinical Study Report.

<sup>~</sup>Baseline p-values are from a two sample t-test, and weekly p-values are for the treatment effect from an ANCOVA model controlling for study and the baseline values

<sup>#</sup>Baseline p-values are from a two sample t-test, and weekly p-values are for the treatment effect from an ANCOVA model controlling for pooled-center and the baseline value.

As noted above in table 12, there was no statistically significant differences in the mean baseline IBS-QOL scores in both treatment groups in the 2 pivotal studies (SIB-0431 Treatment Phase I and SIB-0432) and for the pooled population. In the dose ranging study SIB-0221, the Lubiprostone treatment group and placebo group did not appear to be well matched. At most post-baseline evaluation time points for each study and in the pooled group, the mean changes in IBS-QOL scores in the Lubiprostone 16 mcg group were higher than the values in the placebo group. However, in study SIB-0431 Treatment Phase I, the mean change in IBS-QOL scores in placebo at week 12 (16.8 Placebo vs.

16.7 Lubiprostone) and in the Last Phase I value (15.6 Placebo vs. 15.5 Lubiprostone) was higher than Lubiprostone group, but the difference was not statistically significant. In the pooled group and in study SIB-0432, the difference was statistically significant at last visit ( $p \leq 0.018$ ). At week 12, the pooled group did also reach statistical significance ( $p=0.021$ ).

### **Medical officer comments**

*One of the pivotal studies (SIB-0431 Treatment Phase I) failed to achieve overall IBS-QOL scores that demonstrate treatment with Lubiprostone results in consistent and greater improvement of quality of life compared with placebo. Despite the failure of the one particular study, the greater mean change in the overall IBS-QOL scores for the Lubiprostone treated subjects (in study SIB-0432) may represent the patients' subjective impression of improvement.*

### **Overall Efficacy Comparison of Pivotal Studies**

Studies SIB-0431 Treatment Phase I and SIB-0432 were designed by the sponsor with internal consistency to allow for side-by side comparison of the pivotal studies. Below is a tabular summary and overall efficacy comparison of the pivotal studies in which **X** denotes statistical significance of Lubiprostone 16 mcg over placebo. For the primary efficacy variable, table 13 shows that the results between the pivotal studies were similar in terms of statistically significant differences between the Lubiprostone 16 mcg and placebo, in favor of Lubiprostone 16 mcg.

**Table 13: Summary of Statistical Significance of Efficacy Results  
For Pivotal Studies**

FOR PHASE I STUDIES			
Efficacy Variables	Time Point		
Overall Responder Rate	12 week Treatment Period		
SIB-0431 Treatment Phase I	X		
SIB-0432	X		
Monthly Responder Rates	Month 1	Month 2	Month 3
SIB-0431 Treatment Phase I	NS	X	NS
SIB-0432	NS	NS	NS
Monthly Abdominal Discomfort/Pain			
SIB-0431 Treatment Phase I	NS	NS	NS
SIB-0432	NS	NS	NS

**Table 13 Continued: Summary of Statistical Significance of Efficacy Results  
For Pivotal Studies**

<b>Efficacy Variables</b>	<b>Time Point</b>		
<b>Monthly Abdominal Bloating</b>	<b>Month 1</b>	<b>Month 2</b>	<b>Month 3</b>
SIB-0431 Treatment Phase I	NS	NS	NS
SIB-0432	NS	NS	NS
<b>Monthly Spontaneous Bowel Movement Frequency Rate</b>			
SIB-0431 Treatment Phase I	NS	NS	NS
SIB-0432	NS	NS	NS
<b>Monthly Bowel Movement Frequency Rate</b>			
SIB-0431 Treatment Phase I	NS	NS	NS
SIB-0432	NS	NS	NS
<b>Monthly Stool Consistency</b>			
SIB-0431 Treatment Phase I	X	X	NS
SIB-0432	NS	NS	NS
<b>Monthly Degree of Straining</b>			
SIB-0431 Treatment Phase I	X	X	NS
SIB-0432	NS	NS	NS
<b>Monthly Severity of Constipation</b>			
SIB-0431 Treatment Phase I	NS	NS	NS
SIB-0432	NS	NS	NS
<b>Monthly Symptom Relief</b>			
SIB-0431 Treatment Phase I	NS	NS	NS
SIB-0432	NS	X	NS
<b>Overall IBS-QOL</b>	<b>Week 4</b>	<b>Week 12</b>	<b>Last Visit</b>
SIB-0431 Treatment Phase I	NS	NS	NS
SIB-0432	NS	NS	X

Note: X indicates statistically significant difference ( $p < 0.05$ ) between Lubiprostone 16 mcg and placebo, in favor of Lubiprostone 16 mcg

NS indicates the difference between Lubiprostone 16 mcg and placebo was not significant

### **Medical officer comments**

*As noted above in table 13, the results of the pivotal studies are identical as it relates to the overall responder rate which is the primary efficacy endpoint. The studies, SIB-0431 Treatment Phase I and SIB-0432 revealed no statistically significant differences between Lubiprostone 16 mcg and placebo*

*treatment groups in most of the secondary efficacy variables with the exceptions of the monthly responder rates, monthly stool consistency ratings and degree of straining for months 1 and 2 in SIB-0431 Treatment Phase I study and monthly symptom relief at month 2 and overall IBS-QOL scores at last visit in study SIB-0432. Statistical significance was not achieved in month 3 in all the secondary efficacy variables in both pivotal studies. It is, however, acknowledged that the pivotal studies were not designed to show statistical significance for the secondary endpoints. Although statistical significance was not reached in most secondary efficacy variables in both studies, treatment with Lubiprostone did provide improvements in all the secondary parameters that are slightly better than treatment with placebo. The strong similarity of the results in study SIB-0431 Treatment Phase I and SIB-0432 eliminates study design bias and allows the medical officer to analyze drug efficacy in mutually exclusive patient populations.*

### **Exposure to Rescue Medications**

For the pooled population, at all monthly time points and overall, the proportion of subjects that reported rescue medication use was higher in the Placebo group than in the Lubiprostone 16 mcg group: 44.9% vs. 39.1% during Month 1, 40.8% vs. 35.2% at Month 2, 39.3% vs. 34.9% at Month 3 and 62.9% vs. 53.4% overall. The difference between the groups was significant at Month 1 ( $p=0.046$ ) and overall ( $p=0.002$ ). Mean rescue medication exposure in the pooled group was higher for placebo subjects than Lubiprostone 16 mcg subjects during month 1 and overall and higher for Lubiprostone 16 mcg subjects than placebo subjects in months 2 and 3.

### **Medical officer comments**

*As noted above in the pooled results, the medical officer would expect to see more rescue medication use in a placebo cohort than in a study drug that is efficacious.*

## **COMPARISON OF RESULTS IN SUBPOPULATIONS**

### **Primary Efficacy Variable: Analysis by Gender**

Overall for the well-controlled studies (SIB-0221, SIB-0431 Treatment Phase I and SIB-0432), 31 males took placebo, 75 males took Lubiprostone 16 mcg, 404 female subjects took placebo, and 757 females took Lubiprostone 16 mcg.

As noted below in table 14, in the pooled group (study SIB-0431 Treatment Phase I and SIB-0432), the overall responder rate in the female Lubiprostone group was higher (13.2%) than that in the female placebo group (7.0%). The difference was statistically significant ( $p=0.002$ ). In the pooled male group, the overall responder rate was 3.8% for Placebo and 11.3% for Lubiprostone, but the difference was not statistically significant,  $p=0.270$ .

**Table 14: Summary of Overall Responder Rates by Gender of Pooled Group  
(studies SIB-0431 Treatment Phase I + SIB-0432)**

Category	Study Arm	Overall	N	%	Responder Difference	p-Value
<b>Female</b>	Placebo N=359	<b>Responder</b>	<b>25</b>	<b>7.0</b>	6.2%	0.002
		Non-responder	334	93.0		
	Lubiprostone 16 mcg N=698	<b>Responder</b>	<b>92</b>	<b>13.2</b>		
		Non-Responder	606	86.8		
<b>Male</b>	Placebo N=26	<b>Responder</b>	<b>1</b>	<b>3.8</b>	7.5%	0.270
		Non-responder	25	96.2		
	Lubiprostone 16 mcg N=71	<b>Responder</b>	<b>8</b>	<b>11.3</b>		
		Non-responder	63	88.7		

Reviewer's table modified from Table 1.2.1.1.2, page 61 of 106 Summary of Clinical Efficacy  
p-Value is from CMH test stratified by study.

### Medical officer comments

*Table 14 above demonstrates that the overall responder rate analyzed by gender reveals analogous findings to those in the primary efficacy analysis in Table 2. The gender analysis of Lubiprostone illustrates a 6.2% increase in overall responder rate above placebo group in female subjects and a 7.5% increase in overall responder rate above placebo group in male subjects. Despite the male subjects demonstrating a greater response rate than the female subjects, the difference is not statistically significant. The lack of significance could be due to the small sample size.*

### Key Secondary Efficacy Variable: Analysis by Gender

#### Monthly Responder Rates during the 12 week treatment period

**Table 15: Summary of Monthly Responder Rates by Gender of Pooled Group  
(studies SIB-0431 Treatment Phase I + SIB-0432)**

Category	Treatment period	Study Arm	Status	N	%	Responder Difference	p-Value
<b>Female</b>	Month 1	Placebo N=359	<b>Responder</b>	<b>24</b>	<b>6.7</b>	3.2%	0.082
			Non-responder	335	93.3		
		Lubiprostone 16 mcg N=698	<b>Responder</b>	<b>69</b>	<b>9.9</b>		
			Non-responder	629	90.1		
	Month 2	Placebo N=359	<b>Responder</b>	<b>36</b>	<b>10.0</b>	6.3%	0.005
			Non-responder	323	90.0		
		Lubiprostone 16 mcg N=698	<b>Responder</b>	<b>114</b>	<b>16.3</b>		
			Non-responder	584	83.7		
	Month 3	Placebo N=359	<b>Responder</b>	<b>30</b>	<b>8.4</b>	6.4%	0.003
			Non-responder	329	91.6		
		Lubiprostone 16 mcg N=698	<b>Responder</b>	<b>103</b>	<b>14.8</b>		
			Non-responder	595	85.2		

**Table 15 Continued: Summary of Monthly Responder Rates by Gender of Pooled Group  
(studies SIB-0431 Treatment Phase I + SIB-0432)**

Category	Treatment period	Study Arm	Status	N	%	Responder Difference	p-Value
Male	Month 1	Placebo N=26	<b>Responder</b>	<b>1</b>	<b>3.8</b>	6.1%	0.346
			Non-responder	25	96.2		
		Lubiprostone 16 mcg N=71	<b>Responder</b>	<b>7</b>	<b>9.9</b>		
			Non-responder	64	90.1		
	Month 2	Placebo N=26	<b>Responder</b>	<b>1</b>	<b>3.8</b>	8.9%	0.208
			Non-responder	25	96.2		
		Lubiprostone 16 mcg N=71	<b>Responder</b>	<b>9</b>	<b>12.7</b>		
			Non-responder	62	87.3		
	Month 3	Placebo N=26	<b>Responder</b>	<b>1</b>	<b>3.8</b>	10.3%	0.164
			Non-responder	25	96.2		
		Lubiprostone 16 mcg N=71	<b>Responder</b>	<b>10</b>	<b>14.1</b>		
			Non-responder	61	85.9		

Reviewer's table modified from Table 1.2.2.1.2, page 61 of 106 Summary of Clinical Efficacy  
p-Value is from CMH test stratified by study

As noted in the table 15, the female Lubiprostone 16 mcg group (range: 9.9%-16.3%) demonstrated a higher monthly responder status than female placebo subjects (range: 6.7%-10.0%) at all monthly time points. Similarly, the male Lubiprostone 16 mcg group (range: 9.9%-14.1%) demonstrated a higher monthly responder status than male placebo group (3.8%) at all monthly time points. The difference between the placebo and Lubiprostone 16 mcg group became more pronounced over time in female subjects (months 1, 2, and 3: 3.2%, 6.3%, 6.4% respectively) and in the male population (Months 1, 2, and 3: 6.1%, 8.9%, and 10.3% respectively). Statistically significant differences between the treatment groups were observed in Month 2 for female subjects but no statistically significant results were observed for male subjects.

### **Medical officer comments**

*Table 15 above demonstrates that the monthly responder rate analyzed by gender reveals analogous findings to those in the key secondary efficacy analyses in table 3. The male subjects did have better monthly responder rates; however, the lack of statistical significance maybe due to the small sample size. Also, in the male subjects the placebo responder rate remained constant whereas it increased in the female subjects and was highest at month 2 at 10.0%. Despite the high placebo responder rate in female subjects, Lubiprostone 16 mcg does provide some relief in constipation predominant IBS symptoms over placebo in both genders.*

### **Primary Efficacy Variable: Analysis by Race**

Overall, for the well-controlled studies (SIB-0221, SIB-0431 Treatment Phase I and SIB-0432), there were 339 white subjects that took placebo, 642 white subjects that took Lubiprostone 16 mcg, 96 non-white subjects that took placebo and 190 non-white subjects took Lubiprostone 16 mcg.

As noted below in table 16, in the pooled group (SIB-0431 Treatment Phase I and SIB-0432), the overall responder rate in the white Lubiprostone group was higher (12.8%) than that in the white placebo group

(7.0%). The difference was statistically significant ( $p=0.010$ ). In the pooled non-white group, the overall responder rate was 13.8% for Lubiprostone and 5.7% for placebo, but the difference was not statistically significant,  $p=0.051$ .

**Table 16: Summary of Overall Responder Rates by Race of Pooled Group  
(studies SIB-0431 Treatment Phase I + SIB-0432)**

Category	Study Arm	Overall Status	N	%	Responder Difference	p-Value
<b>White</b>	Placebo N=298	<b>Responder</b>	<b>21</b>	<b>7.0</b>	5.8%	0.010
		Non-responder	277	93.0		
	Lubiprostone 16 mcg N=595	<b>Responder</b>	<b>76</b>	<b>12.8</b>		
		Non-responder	519	87.2		
<b>Non-White</b>	Placebo N=87	<b>Responder</b>	<b>5</b>	<b>5.7</b>	8.1%	0.051
		Non-responder	82	94.3		
	Lubiprostone 16 mcg N=174	<b>Responder</b>	<b>24</b>	<b>13.8</b>		
		Non-responder	150	86.2		

Reviewer's table modified from Table 1.2.1.1.3, page 66 of 106 Summary of Clinical Efficacy  
p-Value is from CMH test stratified by study

### Medical officer comments

*Table 16 above demonstrates that the overall responder status analyzed by race reveals analogous findings to those in the primary efficacy analysis in table 2. The race analysis of Lubiprostone treatment illustrates a 5.8% increase in responder rate above placebo group in white subjects and an 8.1% increase in responder rate above placebo group in non-white subjects. Despite the non-white subjects revealing a greater response than the white subjects, the difference is not statistically significant.*

### Key Secondary Efficacy Variable: Analysis by Race

#### Monthly Responder Rates during the 12 week treatment period

**Table 17: Summary of Monthly Responder Rates by Race of Pooled Group  
(studies SIB-0431 Treatment Phase I + SIB-0432)**

Category	Treatment Period	Study Arm	Status	N	%	Responder Difference	p-Value
<b>White</b>	Month 1	Placebo N=298	<b>Responder</b>	<b>18</b>	<b>6.0</b>	4.1%	0.043
			Non-responder	280	94.0		
		Lubiprostone 16 mcg N=595	<b>Responder</b>	<b>60</b>	<b>10.1</b>		
			Non-responder	535	89.9		
	Month 2	Placebo N=298	<b>Responder</b>	<b>30</b>	<b>10.1</b>	5.9%	0.017
			Non-responder	268	89.9		
		Lubiprostone 16 mcg N=595	<b>Responder</b>	<b>95</b>	<b>16.0</b>		
			Non-responder	500	84.0		
	Month 3	Placebo N=298	<b>Responder</b>	<b>24</b>	<b>8.1</b>	6.5%	0.005
			Non-responder	274	91.9		
		Lubiprostone 16 mcg N=595	<b>Responder</b>	<b>87</b>	<b>14.6</b>		
			Non-responder	508	85.4		

**Table 17 Continued: Summary of Monthly Responder Rates by Race of Pooled Group  
(studies SIB-0431 Treatment Phase I + SIB-0432)**

Category	Treatment Period	Study Arm	Status	N	%	Responder Difference	p-Value
Non-White	Month 1	Placebo N=87	Responder	7	8.0	1.2%	0.750
			Non-responder	80	92.0		
		Lubiprostone 16 mcg N=174	Responder	16	9.2		
			Non-responder	158	90.8		
	Month 2	Placebo N=87	Responder	7	8.0	8.1%	0.076
			Non-responder	80	92.0		
		Lubiprostone 16 mcg N=174	Responder	28	16.1		
			Non-responder	146	83.9		
	Month 3	Placebo N=87	Responder	7	8.0	6.9%	0.112
			Non-responder	80	92.0		
		Lubiprostone 16 mcg N=174	Responder	26	14.9		
			Non-responder	148	85.1		

Reviewer's table modified from Table 1.2.2.1.3, page 67 of 106 Summary of Clinical Efficacy  
p-Value is from CMH test stratified by study

As noted in table 17, the white Lubiprostone 16 mcg group (range: 10.1%-16.0%) demonstrated a higher monthly responder status than white placebo subjects (range: 6.0%-10.1%) at all monthly time points. Similarly, the non-white Lubiprostone 16 mcg group (range: 9.2%-16.1%) demonstrated a higher monthly responder status than non-white placebo group (8.0%) at all monthly time points. The difference between the placebo and Lubiprostone 16 mcg group became more pronounced over time in white subjects (month 1, 2, and 3: 4.1%, 5.9%, 6.5% respectively); but the difference in the monthly responder rate between non-white placebo and the Lubiprostone group did not increase at all time points (Months 1, 2, and 3: 1.2%, 8.1%, and 6.9% respectively). Statistically significant differences between the treatment groups were observed in all monthly time points for white subjects ( $p \leq 0.043$ ) but no statistically significant results were observed for non-white subjects.

### **Medical officer comments**

*Table 17 above demonstrates that the monthly responder rates analyzed by race reveals analogous findings to those in the key secondary efficacy analyses in table 3. The exception is the fact that the difference in responder rate between placebo and Lubiprostone treatment groups at month 1 for non-white subjects is lower than the ITT population monthly responder rates in the pivotal studies, SIB-0431 Treatment Phase I and SIB-0432 (1.2% vs. 3%). In the non-white subjects, despite the placebo monthly responder rates remaining constant (8.0%), there are greater variation across the months (1.2% to 8.1%) in the differences between the monthly responder rates among placebo and Lubiprostone treatment groups. At month 3, the percentage difference between white and non-white Lubiprostone 16 mcg subjects and white and non-white placebo subjects are similar (6.9% non-white vs. 6.5% white).*



**Primary Efficacy Variable: Analysis by Age**

For the well-controlled studies (SIB-0221, SIB-0431 Treatment Phase I and SIB-0432), the number of all randomized subjects that were treated (n) were analyzed in two different age groups. The age groups were classified as follows:

**Table 18: Age Group Designation of Treated Subjects**

Age Group	Ages	Placebo (n)	Lubiprostone 16 mcg (n)	Total
<b>Group 1</b>	$18 \leq \text{age} < 65$	395	771	1166
<b>Group 2</b>	$65 \leq \text{age}$	40	61	101

As noted below in table 19, the overall responder rate in Age Group 1 ( $18 \leq \text{age} < 65$ ) of Lubiprostone subjects was higher (13.2%) than that in the placebo subjects (6.3%). The difference was statistically significant ( $p=0.001$ ). In the Age group 2 ( $65 \leq \text{age}$ ), the overall responder rate was slightly higher in the placebo group (10.5%) than in the Lubiprostone group (10.3%), but the difference was not statistically significant,  $p=0.976$ .

**Table 19: Summary of Overall Responder Rates of Pooled Group (studies SIB-0431 Treatment Phase I + SIB-0432)**

Category	Study Arm	Overall Status	N	%	Responder Difference	p-Value
<b><math>18 \leq \text{Age} &lt; 65</math></b>	Placebo N=347	<b>Responder</b>	<b>22</b>	<b>6.3</b>	6.9%	0.001
		Non-responder	325	93.7		
	Lubiprostone 16 mcg N=711	<b>Responder</b>	<b>94</b>	<b>13.2</b>		
		Non-responder	617	86.8		
<b><math>65 \leq \text{Age}</math></b>	Placebo N=38	<b>Responder</b>	<b>4</b>	<b>10.5</b>	0.2%	0.976
		Non-responder	34	89.5		
	Lubiprostone 16 mcg N=58	<b>Responder</b>	<b>6</b>	<b>10.3</b>		
		Non-responder	52	89.7		

Reviewer's table modified from Table 1.2.1.1.4, page 72 of 106 Summary of Clinical Efficacy  
p-Value is from CMH test stratified by study

**Medical officer comments**

*Table 19 above demonstrates that the overall responder status (studies SIB-0431 Treatment Phase I and SIB-0432) analyzed by age reveals analogous findings to those in the primary efficacy analysis in table 2 except for age group 2. The age analysis of Lubiprostone illustrates a 6.9% increase in overall responder rate above placebo group in age group 1 subjects. Age group 2 ( $\text{age} \geq 65$ ) reveals that the overall responder status of subjects treated with Lubiprostone is no better than placebo but the results lack statistical significance. It should be noted that the lack of statistical significance could be due to the small sample size. It is difficult to derive any meaningful conclusions regarding lack of efficacy in this particular age group.*

**Key Secondary Efficacy Variable: Analysis by Age**

**Monthly Responder Rates during the 12 week treatment period**

As noted in table 20, the Age group 1 ( $18 \leq \text{age} < 65$ ) Lubiprostone 16 mcg group (range: 10.0%-15.8%) demonstrated a higher monthly responder rate than placebo subjects (range: 6.3%-9.5%) at all monthly time points. Similarly, the Age group 2 ( $\text{age} \geq 65$ ) Lubiprostone 16 mcg group (range: 8.6%-19.0%) demonstrated a higher monthly responder rate than placebo group (range: 7.9%-10.5%) at all monthly time points. The difference between the placebo and Lubiprostone 16 mcg treatment groups became more pronounced over time in Age group 1 subjects (month 1, 2, and 3: 3.7%, 6.3%, 6.8% respectively); but the difference in the monthly responder rate between age group 2 ( $\text{age} \geq 65$ ) placebo and the Lubiprostone subjects did not increase as the months progressed (Months 1, 2, and 3: 0.7%, 8.5%, and 4.2% respectively). Statistically significant differences between the treatment groups were observed in all monthly time points for age group 1 ( $18 \leq \text{age} < 65$ ) subjects ( $p \leq 0.049$ ), but no statistically significant results were observed for age group 2 ( $\text{age} \geq 65$ ) subjects.

**Table 20: Summary of Monthly Responder Rates by Age of Pooled Group  
(studies SIB-0431 Treatment Phase I + SIB-0432)**

Category	Treatment period	Study Arm	Status	N	%	Responder Difference	p-Value
<b><math>18 \leq \text{Age} &lt; 65</math></b>	Month 1	Placebo N=347	<b>Responder</b>	<b>22</b>	<b>6.3</b>	3.7%	0.049
			Non-responder	325	93.7		
		Lubiprostone 16 mcg N=711	<b>Responder</b>	<b>71</b>	<b>10.0</b>		
			Non-responder	640	90.0		
	Month 2	Placebo N=347	<b>Responder</b>	<b>33</b>	<b>9.5</b>	6.3%	0.006
			Non-responder	314	90.5		
		Lubiprostone 16 mcg N=711	<b>Responder</b>	<b>112</b>	<b>15.8</b>		
			Non-responder	599	84.2		
	Month 3	Placebo N=347	<b>Responder</b>	<b>28</b>	<b>8.1</b>	6.8%	0.002
			Non-responder	319	91.9		
		Lubiprostone 16 mcg N=711	<b>Responder</b>	<b>106</b>	<b>14.9</b>		
			Non-responder	605	85.1		
<b><math>65 \leq \text{Age}</math></b>	Month 1	Placebo N=38	<b>Responder</b>	<b>3</b>	<b>7.9</b>	0.7%	0.902
			Non-responder	35	92.1		
		Lubiprostone 16 mcg N=58	<b>Responder</b>	<b>5</b>	<b>8.6</b>		
			Non-responder	53	91.4		
	Month 2	Placebo N=38	<b>Responder</b>	<b>4</b>	<b>10.5</b>	8.5%	0.274
			Non-responder	34	89.5		
		Lubiprostone 16 mcg N=58	<b>Responder</b>	<b>11</b>	<b>19.0</b>		
			Non-responder	47	81.0		
	Month 3	Placebo N=38	<b>Responder</b>	<b>3</b>	<b>7.9</b>	4.2%	0.518
			Non-responder	35	92.1		
		Lubiprostone 16 mcg N=58	<b>Responder</b>	<b>7</b>	<b>12.1</b>		
			Non-responder	51	87.9		

Reviewer's table modified from Table 1.2.2.1.4, page 72 of 106 Summary of Clinical Efficacy  
p-Value is from CMH test stratified by study

### **Medical officer comments**

*Table 20 above demonstrates that the monthly responder rates analyzed by age reveal analogous findings to those in the key secondary efficacy analyses in table 3. The exception is the fact that the difference in monthly responder rate between placebo and Lubiprostone treatment groups at month 1 for age group 2 (age  $\geq 65$ ) subjects is lower than that of the ITT population in the pivotal studies, SIB-0431 Treatment Phase I and SIB-0432 (0.7% vs. 3%). In the age group 2 (age  $\geq 65$ ) subjects, the difference in the monthly responder rate between placebo and the Lubiprostone treatment groups demonstrates a greater variation across the months (0.7% to 8.5%). For both age groups, Lubiprostone 16 mcg did provide some relief from symptoms of IBS-C; however, the percentage of responder rate seems to be more consistent in the age group 1. Due to the small sample size in age group 2 (age  $\geq 65$ ), the medical officer is cautious to derive any meaningful conclusions regarding lack of efficacy in this age group.*

### **Subject Disposition**

As noted below in table 21, of the 1271 subjects randomized in the well-controlled studies (SIB-0221, SIB-0431 Treatment Phase I and SIB-0432), a total of 1267 were treated. Of those subjects, 435 took placebo and 832 took Lubiprostone 16 mcg/day. Overall, 973 subjects (76.6%) completed their respective studies, i.e., they completed the end of study visit. In the placebo group, 331 subjects (75.9%) completed, and in the Lubiprostone 16 mcg/day, 642 subjects (76.9%) completed.

**Table 21: Subject Disposition of Pivotal Studies (All Randomized Subjects)**

	Study SIB-0431 Treatment Phase I			Study SIB-0432		
Variable	Placebo N=194 (%)	Lubiprostone 16 mcg N=396 (%)	Total N=590 (%)	Placebo N=194 (%)	Lubiprostone 16 mcg N=387 (%)	Total N=581 (%)
<b>Subjects Randomized</b>	194 (100)	396 (100)	590 (100)	194 (100)	387 (100.0)	581 (100)
<b>Treated</b>	193 (99.5)	395 (99.7)	588 (99.7)	194 (100)	385 (99.5)	579 (99.7)
<b>Not Treated</b>	1 (0.52)	1 (0.25)	2 (0.34)	0 (0.0)	2 (0.52)	2 (0.34)
<b>Completed Subjects</b>	139 (71.6)	297 (75.0)	436 (73.9)	151 (77.8)	303 (78.3)	454 (78.1)

Reviewer's table modified from Table 10-1, page 56 of 89, Clinical Study Report and from Table 10-1, page 51 of 75, Clinical Study Report

**Table 21 Continued: Subject Disposition: Study SIB-0221 + Well Controlled Studies Combined  
(All Randomized Subjects)**

	Dose Response Study SIB-0221*			Well-Controlled Studies <sup>1</sup> (SIB-0221* + SIB-0431 Treatment Phase I + SIB-0432)		
Variable	Placebo N=48 (%)	Lubiprostone 16 mcg N=52 (%)	Total N=100 (%)	Placebo N=436 (%)	Lubiprostone 16 mcg N=835 (%)	Total N=1271 (%)
<b>Subjects Randomized</b>	48 (100)	52 (100)	100 (100)	436 (100)	835 (100.0)	1271 (100)
<b>Treated</b>	48 (100)	52 (100)	100 (100)	435 (99.8)	832 (99.6)	1267 (99.7)
<b>Not Treated</b>	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.23)	3 (0.36)	4 (0.31)
<b>Completed Subjects</b>	41 (85.4)	42 (80.8)	83 (83.0)	331 (75.9)	642 (76.9)	973 (76.6)

Reviewer's table modified from Table 10-1, page 46 of 92, Clinical Study Report and from Table 2.7.3.3-1, page 30 of 106, Summary of Clinical Efficacy

\*Study SIB-0221: excludes 32 mcg and 48 mcg dose subjects

<sup>1</sup>Well Controlled Studies: Study SIB-0221 only includes 16 mcg arm (1366 total randomized – 49 (32 mcg subjects) – 46 (48 mcg subjects) = 1271)

**Table 22: Subject Disposition: SIB-0431 Treatment Phase II (All Randomized Subjects)**

	Study SIB-0431 Treatment Phase II (Randomized Withdrawal)			
Variable	Placebo/Placebo (P/P) N=139 (%)	Lubiprostone/Placebo (L/P) N=146 (%)	Lubiprostone/Lubiprostone (L/L) N=151 (%)	Total N=436 (%)
<b>Subjects Assessed*</b>	139 (100)	146 (100)	151 (100)	436 (100)
<b>Treated</b>	139 (100)	146 (100)	151 (100)	436 (100)
<b>Not Treated</b>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Completed Subjects</b>	131 (94.2)	143 (97.9)	146 (96.7)	420 (96.3)

Reviewer's table modified from Table 10-2, page 57 of 89, Clinical Study Report

\*Subjects Assessed: # of subjects who completed Phase I and who entered Phase II

A summary of subject disposition for the randomized withdrawal group (RWG) is presented above in table 22. During treatment phase II of SIB-0431, the 436 subjects who completed Treatment phase I of SIB-0431 were enrolled as follows: P/P (139 subjects), L/P (146 subjects), and L/L (151 subjects). Overall 436 subjects were treated, and 420 subjects (96.3%) completed the 4 week Treatment Phase II of SIB-0431.

**Table 23: Subject Disposition: Study SIB-05S1 (All Enrolled Subjects)**

	Long Term Safety Study SIB-05S1			
Variable	Placebo/Placebo/ Lubiprostone (P/P/L)N=180 (%)	Lubiprostone/Placebo/ Lubiprostone (L/P/L)N=80 (%)	Lubiprostone/Lubiprostone/ Lubiprostone (L/L/L)N=262 (%)	Total N=522(%)
<b>Subjects Enrolled</b>	180 (100)	80 (100)	262 (100)	522 (100)
<b>Treated</b>	179 (99.4)	80 (100)	261 (99.6)	520 (99.6)
<b>Not Treated</b>	1 (0.56)	0 (0.0)	1 (0.38)	2 (0.38)
<b>Completed Subjects</b>	113 (62.8)	38 (47.5)	153 (58.4)	304 (58.2)

Reviewer's table modified from Table 2.7.3.3-3, page 32 of 106, Summary of Clinical Efficacy

A summary of subject disposition for the long term safety study, SIB-05S1 is presented above in table 23. Overall, 520 subjects were treated, and 304 subjects (58.2%) completed the open label treatment period.

### **Efficacy Findings from Study SIB-0431 Treatment Phase II (Randomized Withdrawal)**

After completion of SIB-0431 Treatment Phase I, the 436 subjects were enrolled in Treatment Phase II or randomized withdrawal portion of study SIB-0431. The Randomized withdrawal study was 4 weeks in duration followed by a 2 week follow-up phone call. The subjects were randomized in a 1:1:1 ratio to their treatment groups for the randomized withdrawal prior to starting Treatment Phase I. The randomized withdrawal study was performed at the suggestion of the Agency that occurred in the March 2005 end of phase II meeting.

The 436 subjects that completed Treatment phase I were divided as follows: 139 placebo subjects that were taking placebo in Treatment phase I continued to take placebo in Treatment Phase II. 297 subjects who were taking Lubiprostone in Treatment Phase I were either randomized to continue Lubiprostone (L/L 151 subjects) or were switched to placebo (L/P 146 subjects) in Treatment Phase II.

**Table 24: Demographics for Subjects during Treatment Phase II  
(Randomized Withdrawal Group)**

Variable/Statistic		Study SIB-0431 Treatment Phase II			
Variable	Category	Placebo/Placebo	Lubiprostone/Placebo	Lubiprostone/Lubiprostone	Total
Subject Number	N	139 (%)	146 (%)	151 (%)	436 (%)
Age (years)	Mean	47.9	45.1	47.9	47.0
	SD	12.77	10.90	13.76	12.59
	Median	48.0	45.0	48.0	47.0
	Range	21.0-82.0	20.0-73.0	20.0-83.0	20.0-83.0
Height (inches)	Mean	65.0	64.8	65.0	64.9
	SD	3.11	2.79	2.96	2.95
	Median	64.5	64.3	65.0	64.8
	Range	56.2-74.0	57.0-74.0	57.0-75.0	56.2-75.0
Gender	Female	128 (92.1)	137 (93.8)	136 (90.1)	401 (92.0)
	Male	11 (7.9)	9 (6.2)	15 (9.9)	35 (8.0)
Race	Caucasian	105 (75.5)	107 (73.3)	121 (80.1)	333 (76.4)
	African-American	19 (13.7)	21 (14.4)	13 (8.6)	53 (12.2)
	Hispanic	11 (7.9)	18 (12.3)	17 (11.3)	46 (10.6)
	Asian	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)
	Other	3 (2.2)	0 (0.0)	0 (0.0)	3 (0.7)

Reviewer's table, modified from Table 11.2, page 60 of 89, Clinical Study Report

As noted above in table 24, the baseline demographic information of the randomized withdrawal group (RWG) was similar to the pooled group (PG). Overall, the mean age was 47, and the mean age ranged from 45.1 years in the L/P group to 47.9 years in both the P/P and L/L groups. The subject population

overall was predominately female, 401/436 (92.0%). The female gender dominance was generally similar across all three treatment groups with 92.1% females in P/P group, 93.8% females in L/P group and 90.1% females in L/L group. The majority of the subjects in the randomized withdrawal study were Caucasian (76.4%). This racial distribution was also seen across all three trials, SIB-0431 Treatment Phase I, SIB-0432, and SIB-0221. Other demographic statistics such as mean height ranged from 64.8 inches in the L/P group to 65.0 inches in both the P/P and L/L groups.

The primary endpoint for the randomized withdrawal portion of SIB-0431 study was the responder rate at month 4. The same definition of monthly responder that was used in both SIB-0431 Treatment Phase I and SIB-0432 studies was also utilized in study SIB-0431 Treatment Phase II. However, in the studies SIB-0431 Treatment Phase I and SIB-0432, the monthly responder rate was a key secondary efficacy endpoint.

**Table 25: Summary of Responder Rates at Month 4 during Treatment Phase II  
Phase I Responder Population**

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

Reviewer's table, modified from Table 14.2.18.1, page 71 of 89, Clinical Study Report

Table 25 addresses whether subjects who were switched to placebo were more likely to relapse after one month compared to subjects who continued Lubiprostone 16 mcg treatment. The higher responder rate (difference of 1.9%) at month 4 when Lubiprostone subjects were switched to placebo indicated that the Lubiprostone subjects were less likely to relapse when treatment was discontinued.

#### **Medical officer comments**

*This analysis could lead one to question whether Lubiprostone had any meaningful clinical effect in the three month treatment period. Patients usually have a relapse of their symptoms (whether it is an elevation of blood pressure or signs and symptoms of depression) when the drug that is treating a particular symptom is discontinued. It should also be noted that the 51 subjects that are included in table 25 are a subset of randomized withdrawal subjects who were overall responders in SIB-0431 treatment phase I. There were 54 subjects that were overall responders in the Lubiprostone 16 mcg treatment group in study SIB-0431 Treatment Phase I. A withdrawal trial is an enrichment design that excludes non-responders; therefore, the design tends to overestimate the effect size. However, in the comparison above, it failed to show any effect even though, it did not achieve statistical significance.*

**Table 26: Summary of Responder Rates at Month 4 during Treatment Phase II  
Phase I Responders and Randomized Withdrawal Populations**

Timepoint Status	Placebo/Placebo (Randomized Withdrawal) N=139	Lubiprostone/Placebo (Phase I Responders) N=30	p-Value
<b>Month 4</b>	N (%)	N (%)	<0.001
<b>Responder</b>	<b>11 (7.9)</b>	<b>12 (40.0)</b>	
Non-Responder	128 (92.1)	18 (60.0)	

Reviewer's table, modified from Table 14.2.18.2, page 71 of 89, Clinical Study Report

The Phase I responder population was defined as a portion of randomized withdrawal subjects who were overall responders during treatment phase I. The randomized withdrawal subjects were defined as all subjects who took at least 1 dose of the study drug dispensed at visit 6 (week 12). The higher responder rate seen in table 26 when Lubiprostone subjects (L/P) were taken off treatment compared to subjects that never received any Lubiprostone treatment (P/P) reveals that the Lubiprostone subjects did not have a worsening of their symptoms when the treatment drug was discontinued abruptly.

#### **Medical officer comments**

*Table 26 is a comparison that indicates subjects who discontinue Lubiprostone treatment without a tapering schedule do not experience a worsening of their IBS-C symptoms. Therefore, using the data in table 26 ( $p < 0.001$ ), one can conclude that there is no rebound phenomenon associated with withdrawal of Lubiprostone treatment.*

**Table 27: Summary of Responder Rates at Month 4 during Treatment Phase II  
Randomized Withdrawal Population**

Timepoint Status	Placebo/Placebo N=139	Lubiprostone/Lubiprostone N=151	Responder Difference	p-Value
<b>Month 4</b>	N (%)	N (%)	<b>3.4%</b>	0.415
<b>Responder</b>	<b>11 (7.9)</b>	<b>17 (11.3)</b>		
Non-Responder	128 (92.1)	134 (88.7)		

Reviewer's table, modified from Table 14.2.18.3, page 71 of 89, Clinical Study Report

Table 27 provides a comparison between the subjects who received placebo (P/P) and the subjects who received Lubiprostone (L/L) throughout the 4 month treatment period. The month 4 responder rate for Lubiprostone subjects was higher than the month 4 responder rate for placebo subjects (11.3% vs. 7.9%), but it was not statistically significant,  $p=0.415$ .

#### **Medical officer comments**

*The higher responder rate in the subjects that received Lubiprostone for all 16 weeks of treatment as compared to subjects that never received any active treatment doses reveals that Lubiprostone*

***treatment has a 3.4% better efficacy rate over placebo at month 4. This is similar to the efficacy rate obtained at month 1 in both pivotal studies SIB-0431 Treatment phase I (3%) and SIB-0432 (3.8%).***

### **6.1.5 Clinical Microbiology**

No microbiology information was included in this supplemental application and nor is it indicated.

### **6.1.6 Efficacy Conclusions**

The clinical program with Lubiprostone 16 mcg (8 mcg bid) consisting of two adequate and well-controlled Phase III efficacy studies, one randomized withdrawal study and one phase III, long term safety and efficacy study, demonstrates that administration of Lubiprostone 8 mcg bid provides global symptom relief of constipation predominant irritable bowel syndrome. Statistical significance was attained for the primary efficacy endpoint; the overall responder rate for the 12 week treatment period, for both pivotal studies. Statistical significance for Lubiprostone 8 mcg bid over placebo for the treatment of constipation predominant irritable bowel syndrome was also observed in the following secondary variables: monthly responder rates, monthly stool consistency and monthly degree of straining in study SIB-0431 Treatment Phase I and monthly symptom relief and overall IBS-QOL scores in study SIB-0432.

The overall responder rate during the 12 week treatment period was the protocol defined primary efficacy endpoint for the two pivotal studies in this application. An overall responder was defined as a monthly responder for at least 2 of the 3 months. A monthly responder was defined as a subject whose symptoms were rated as “Moderately relieved” for all 4 weeks in a month or “Significantly relieved” for at least 2 weeks within a month provided the three conditions were met: 1. the percentage of rescue medication usage did not increase during the month compared to baseline, 2. the subject did not discontinue the study during the month due to lack of efficacy, 3. the subject had no ratings of “Moderately worse” or “Significantly worse” during the month. The overall responder rate endpoint seems appropriate as there is no currently validated or surrogate endpoint for this particular disease. The literature and the previous protocol designs that are available from other drugs that were historically approved by the Agency for the treatment of IBS-C also utilized a similar responder definition with a subjective global assessment E. Jan Irvine: Design of Treatment Trials for Functional Gastrointestinal Disorders. Gastroenterology 130: 1538-1551 (2006). The duration of treatment for 12 weeks is considered adequate based on previous clinical trial designs. IBS-C is a fluctuating disease with flares and remissions lasting less than 1 week. Therefore, according to the literature, a minimum duration of 4 weeks that reflects the symptom periodicity and anticipated treatment mechanism is usually recommended.

Both pivotal studies SIB-0431 Treatment Phase I and SIB-0432 demonstrated a modest and sustained efficacy of 6% over placebo during the 12 week treatment period. Although the data is not compelling, Lubiprostone is differentiated from placebo in the primary endpoint and also in the month 4 responder rate (3.4%) in the randomized withdrawal study. Results in study SIB-0431 Treatment Phase I were supported by similar results in study SIB-0432. The secondary efficacy were many and included monthly abdominal discomfort/pain, monthly abdominal bloating, monthly spontaneous bowel movement and bowel movement frequency rates, monthly stool consistency, monthly degree of straining, monthly severity of constipation, monthly symptom relief, and overall IBS-QOL scores.



Importantly, in all the well-controlled trials (SIB-0221, SIB-0431 Treatment Phase I and SIB-0432), all the secondary variable endpoints listed above were slightly better than placebo even though statistical significance was not achieved for most secondary endpoints. Improvements were maintained throughout the treatment period without evidence of rebound effect during the withdrawal phase. It was difficult to conclude whether it improved the frequency rate of spontaneous bowel movements since at month 4 in study SIB-0431 Treatment Phase II, the change from baseline in spontaneous bowel movement frequency rate was worse than placebo (Placebo 2.00 vs. 1.53 Lubiprostone 16 mcg). Also, the two pivotal studies failed to achieve a difference of 1 SBM between placebo and Lubiprostone treated subjects which makes it difficult to translate the results into a clinically meaningful increase in spontaneous bowel movements when the drug is used.

Utilizing the evidence available not only from the sponsor but also the Agency's historical information on drugs previously approved for similar indication and current literature regarding IBS-C treatment, Lubiprostone 8 mcg bid demonstrates an overall improvement in symptoms of constipation predominant IBS in subjects treated over a 12 week period. Furthermore, there is no FDA approved treatment for this particular disease at this time. The efficacy of Lubiprostone based on the primary endpoint might have resulted in larger significant difference from placebo if this particular patient population did not have a tendency to exhibit a variable but large placebo effect, 0% to 84%. E. Jan Irvine: Design of Treatment Trials for Functional Gastrointestinal Disorders. Gastroenterology 130: 1538-1551 (2006). In the open label treatment which had a duration of 9 months, treatment with Lubiprostone 16 mcg continued to demonstrate relief of global symptoms of IBS-C; however, it is difficult to quantify the efficacy as it varied from a low of 12.3% to a high of 57.9%.

## **7 INTEGRATED REVIEW OF SAFETY**

### **7.1 Methods and Findings**

The variables used to assess safety in this supplemental New Drug Application for Lubiprostone 16 mcg b.i.d for relief of symptoms of constipation predominant irritable bowel syndrome were many. Similar methods for safety monitoring were used across all three Phase III trials including: adverse events (AE), vital signs recording, comprehensive physical examinations, clinical laboratory tests including hematology, serum chemistry, and urinalysis.

The overall summary of adverse events for the well-controlled safety group is illustrated below in table 28. Across the 3 well-controlled studies (SIB-0221, SIB-0431 Treatment Phase I, and SIB-0432), 51.7% of placebo subjects and 51.2% of subjects taking Lubiprostone 16 mcg reported at least 1 adverse event (AE). With an increasing dose level, 51.2 % of subjects taking Lubiprostone 16 mcg, 61.2% of subjects taking Lubiprostone 32 mcg and 71.1% of subjects taking Lubiprostone 48 mcg reported at least 1 AE. 20.9% of placebo subjects and 22.4% of Lubiprostone 16 mcg subjects reported at least 1 treatment-related AE. With an increasing dose level, 22.4% of subjects taking Lubiprostone 16 mcg, 42.9% of subjects taking Lubiprostone 32 mcg and 42.2% of subjects taking Lubiprostone 48 mcg reported treatment-related AEs.

Four placebo subjects (0.9%), 7 Lubiprostone 16 mcg subjects (0.8%), 1 Lubiprostone 32 mcg subject (2.0%), and 2 Lubiprostone 48 mcg subjects (4.4%) reported SAE, but only 1 subject in the Lubiprostone 16 mcg group reported treatment-related SAE (0.1%). One subject in the Lubiprostone 16

mcg group died (0.1%). Overall, 6.0% of placebo subjects and 4.7% of Lubiprostone 16 mcg subjects discontinued because of an AE. Upon dose escalation, 4.7% of subjects taking Lubiprostone 16 mcg, 16.3% of subjects taking Lubiprostone 32 mcg, and 13.3% of subjects taking Lubiprostone 48 mcg discontinued because of an AE.

**Table 28: Overall Summary of Adverse Events in the Well-Controlled Safety Group**

Category	Placebo	Lubiprostone 16 mcg	Lubiprostone 32 mcg	Lubiprostone 48 mcg	All Active Doses	Statistic
<b>Subjects N (%)</b>	N=435 (100%)	N=832 (100%)	N=49 (100%)	N=45 (100%)	N=926 (100%)	p-Value
<b>At least one AE</b>	225 (51.7)	426 (51.2)	30 (61.2)	32 (71.1)	488 (52.7)	0.049
<b>At least one treatment related AE</b>	91 (20.9)	186 (22.4)	21 (42.9)	19 (42.2)	226 (24.4)	<0.001
<b>At least one SAE</b>	4 (0.9)	7 (0.8)	1 (2.0)	2 (4.4)	10 (1.08)	0.102
<b>At least one treatment related SAE</b>	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.11)	0.743
<b>Discontinued due to an AE</b>	26 (6.0)	39 (4.7)	8 (16.3)	6 (13.3)	53 (5.72)	0.051
<b>Died due to an AE</b>	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.11)	0.743

Reviewer's table modified from Table 2.7.4.2.1, page 27 of 126, Summary of Clinical Safety  
Includes events with causality ratings of "Possible" or "Probable"  
p-values are obtained from Cochran-Armitage trend tests

### 7.1.1 Deaths

One subject in the Lubiprostone 16 mcg group died (0.1%).

**Subject SIB-0431 Treatment Phase I-104-011:** The subject was a 71 year old male in the Lubiprostone/Placebo treatment group. On study day 74, the subject experienced severe cardiac arrest, and he expired. The last dose of study medication was taken on study day 72.

### 7.1.2 Other Serious Adverse Events

Overall, for the well-controlled safety cohort, four subjects in the placebo group 4/435 (0.9%), seven subjects 7/832 (0.8%) in the Lubiprostone 16 mcg group, one subject 1/49 (2.0%) in the Lubiprostone 32 mcg group, and two subjects 2/45 (4.4%) Lubiprostone 48 mcg group reported SAE. Total of four placebo subjects and seven Lubiprostone 16 mcg subjects reported SAEs in the two main efficacy studies, SIB-0431 Treatment Phase I and SIB-0432. Of the above subjects that reported SAE, five Lubiprostone and two placebo subjects were in the SIB-0431 Treatment Phase I study and two Lubiprostone and two placebo subjects were in SIB-0432 study. The only treatment-related SAE in the 16 mcg Lubiprostone group (subject SIB-0432-215-003) who experienced non-cardiac chest pain occurred in study, SIB-0432. In the dose response study, SIB-0221, one subject in the 32 mcg Lubiprostone group (22-R007 perforated appendicitis) and two subjects (10-R005 cholecystitis and 18-R001 ectopic pregnancy) in the Lubiprostone 48 mcg group reported SAEs.

**Four placebo** subjects experienced a total of seven SAEs as follows:

**Subject SIB-0431-127-010** experienced back pain after a fall that occurred five weeks previously. The event was rated as severe and considered not treatment-related.

**Subject SIB-0431-161-005** experienced rhabdomyolysis attributed to Voltaren usage that was severe in intensity and considered not treatment-related.

**Subject SIB-0432-205-015** diagnosed with small bowel obstruction secondary to adhesions with gangrenous small bowel. The event was identified as severe in intensity and was considered not treatment-related.

**Subject SIB-0432-235-017** experienced an abnormal mammogram which revealed “aggressive cells” that were determined to be “precancerous” after lumpectomy. The event was identified as severe in intensity and was considered not treatment-related.

For the Lubiprostone 16 mcg group, 7 subjects reported a total of 9 SAEs that were considered treatment emergent. Two Lubiprostone subjects reported 4 SAEs (cardiac arrest, atrial fibrillation, coronary artery disease and mitral valve incompetence) in the cardiac disorders system organ class (SOC).

**Subject SIB-0431-104-011** experienced cardiac arrest as mentioned in death summary above.

**Subject SIB-0431-148-024** diagnosed with thyroid gland cancer that was severe in intensity and considered not treatment-related.

**Subject SIB-0431-153-010** diagnosed with breast cancer and hospitalized for left breast mastectomy which was moderate in intensity and considered not treatment-related.

**Subject SIB-0431-129-004** experienced dysuria that was mild in intensity and considered not treatment-related.

**Subject SIB-0431-160-008** experienced atrial fibrillation, coronary artery disease, and mitral valve incompetence. The subject had congestive heart failure and pulmonary edema reported to be the result of mitral valve failure. All these events were severe in intensity and considered not treatment-related.

**Subject SIB-0432-215-003** experienced chest pain with radiation to the right side that was reported as non-cardiac in nature. The event was identified as moderate in intensity and was considered possibly treatment-related.

**Subject SIB-0432-217-017** experienced “stomach cramps” that was diagnosed as cholecystitis. The event was rated as moderate in intensity and considered not treatment-related.

For the Phase III open label study, SIB-05S1, the enrollment was contingent upon the subject’s completion of either study SIB-0431 or SIB-0432. The subjects were enrolled and classified as follows :

Placebo/Placebo/Lubiprostone (P/P/L): 179 took only placebo in SIB-0431 or SIB-0432 before entering the Open label extension (OLE) phase.

Lubiprostone/Placebo/Lubiprostone (**L/P/L**): 80 took Lubiprostone during SIB-0431 Treatment phase I and placebo during the RW (SIB-0431 Treatment Phase II) before entering the OLE phase

Lubiprostone/Lubiprostone/Lubiprostone (**L/L/L**): 261 took Lubiprostone during SIB-0431 Treatment phase I and II or Lubiprostone during SIB-0432 before entering OLE phase

For the long term safety group (LTS) overall, one Placebo/Placebo/Lubiprostone (P/P/L) subject (0.6%), three Lubiprostone/Placebo/Lubiprostone (L/P/L) subjects (3.8%), and six Lubiprostone/Lubiprostone/Lubiprostone (L/L/L) subjects (2.3%) reported at least 1 SAE. Two subjects, 1 in P/P/L treatment group and 1 in L/L/L treatment group reported syncope.

10 Subjects reported 11 SAEs that were considered treatment-emergent as follows:

**Subject SIB-05S1-258-005 (P/P/L)** experienced syncope on study day 44 which was severe in intensity but resolved the same day. On study day 46, the subject again experienced syncope which was moderate in intensity and resolved on the following day. None of the syncopal episodes were considered to be treatment-related.

**Subject SIB-05S1-108-001 (L/P/L)** experienced upper gastrointestinal hemorrhage that was severe in intensity and considered not treatment-related.

**Subject SIB-05S1-147-006 (L/P/L)** experienced dysfunctional uterine bleeding, pelvic mass, and pelvic pain which were all rated as severe in intensity and neither of them were considered treatment-related.

**Subject SIB-05S1-165-009 (L/P/L)** experienced dysmenorrhea that was severe in intensity and considered not treatment-related.

**Subject SIB-05S1-111-012 (L/L/L)** experienced adnexa uteri mass that was severe in intensity and considered not treatment-related.

**Subject SIB-05S1-148-002 (L/L/L)** experienced tendonitis in the left shoulder which was moderate in intensity and considered not treatment-related.

**Subject SIB-05S1-151-001 (L/L/L)** experienced osteoarthritis of the right hip which was moderate in intensity and considered not treatment-related.

**Subject SIB-05S1-203-007 (L/L/L)** experienced intentional drug overdose which was severe in intensity and considered not treatment-related.

**Subject SIB-05S1-220-009 (L/L/L)** experienced left distal ureteral calculi which was severe in intensity and considered not treatment-related.

**Subject SIB-05S1-260-002 (L/L/L)** experienced syncope which was severe in intensity and considered not treatment-related.

### **Medical officer comments**

***The investigators for these trials considered most of the aforementioned SAEs not treatment-related. Given the known pharmacodynamic effect at the 24 mcg bid dose and the fact that there are reported events of syncope, dysmenorrhea, dysfunctional uterine bleeding and ureteral calculi, the medical officer cannot agree with certainty that these SAEs are unrelated to Lubiprostone therapy.***

Most of the SAE preferred terms in the well-controlled studies were each reported by 1 subject and no single SAE preferred term was reported by more than 2 subjects. The SAE preferred terms reported by more than 1 subject were cholecystitis and breast cancer. Additionally, no system organ class (SOC) had a reported SAE frequency > 1%, and all SOC exhibited a frequency range of 0.0%-0.1% except for neoplasms benign, malignant and unspecified (incl cysts and polyps) and cardiac disorders that had a frequency of 0.2% of all subjects taking Lubiprostone 16 mcg. For the open label trial, syncope was the only SAE reported by more than 1 subject

Only one SAE was considered ***possibly treatment-related*** by the investigator. It is detailed below:

**Subject SIB-0432-215-003:** This particular subject was receiving Lubiprostone 8 mcg bid. She was a 69 year old female with past medical history significant for Idiopathic Thrombocytopenic Purpura (ITP), Diastolic Dysfunction, Cerebral Hemorrhage due to ITP, Myocardial Infarction (MI), Hypothyroidism, Hyperlipidemia, Asthma, Pulmonary Embolism (PE), Splenectomy due to ITP, Parathyroidectomy, Hysterectomy and Appendectomy. Concomitant medications included: acetylsalicylic acid, amitriptyline, Atrovastatin, B-Komplex, Glyceryl Trinitrate, Heparin, Levothyroxine sodium, Lisinopril, Metoprolol succinate, morphine, psyllium hydrophilic, mucilloid, salbutamol, and seretide. The subject was hospitalized on study day 2 for chest pain radiating to her right side. She had negative cardiac enzymes and her echocardiographic report revealed EF of 65% without discrete wall motion abnormalities. The subject did have a CT scan that was negative for PE and a SPECT scan that revealed abnormal dobtumaine stress SPECT Radiopharmaceutical Myocardial Scan. The Dobtumaine Stress test revealed a fixed moderate inferior and inferolateral wall MI but no evidence of active ischemia. The subject was treated with heparin and morphine during the hospitalization, and her chest pain was relieved. She was discharged on Study day 3. The study drug was initiated on study day 1, last dose taken was study day 2, and subject discontinued the study on study day 6. Both the treating physician at the hospital and the investigator considered the chest pain to be non-cardiac in nature. The investigator considered the SAE of non-cardiac chest pain to be possibly related to the study drug.

### **Medical officer comments**

***The complaint of chest pain is a common presentation in an emergency room, and the subject has risk factors besides the study drug that can cause the chest pain. It is difficult for the medical reviewer to assign one incidence of chest pain to the study drug with certainty.***

## **7.1.3 Dropouts and Other Significant Adverse Events**

### **7.1.3.1 Overall Profile of Dropouts**

As noted below in table 29, the most common reasons for discontinuation from the well-controlled studies (SIB-0221, SIB-0431 Treatment Phase I, SIB-0432) in both the placebo and the Lubiprostone 16

mcg groups were subjects voluntary withdrawal (8.7% and 8.1%, respectively), adverse events (5.7% and 4.9% respectively), and lack of efficacy (5.0% and 3.7%, respectively).

**Table 29: Subject Discontinuation during Well-Controlled Studies\***  
(All Randomized Subjects)

Reason for Discontinuation	Placebo N=436 (100%) N (%)	Lubiprostone 16 mcg N=835 (100%) N (%)
Adverse Event	25 (5.7)	41 (4.9)
Protocol Violation	1 (0.2)	4 (0.5)
Subjects Voluntary Withdrawal	38 (8.7)	68 (8.1)
Lack Of Efficacy	22 (5.0)	31 (3.7)
Lost to Follow-UP	10 (2.3)	14 (1.7)
Did Not Meet Entry Criteria	1 (0.2)	0 (0.0)
Non-Compliance	6 (1.4)	21 (2.5)
Other	2 (0.5)	14 (1.7)

Reviewer's table modified from Table 2.7.4.1-2, page 15 of 126, Summary of Clinical Safety

\*Well-Controlled Studies = SIB-0221 16mcg arm, SIB-0431 Treatment Phase I, SIB-0432

As noted below in table 30, the most common reasons for discontinuation in P/P/L subjects were voluntary withdrawal (12.2%), lack of efficacy (10.5%), adverse event (6.6%) and lost to follow-up (5.0%). In the L/P/L group, the most common reasons for discontinuation were subject voluntary withdrawal (19.0%), lack of efficacy (17.7%), non-compliance (6.3%) and lost to follow-up (6.3%). In the L/L/L group, the most common reasons for discontinuation were lack of efficacy (14.1%), subject voluntary withdrawal (13.0%), lost to follow-up (4.6%) and non-compliance (4.2%).

**Table 30: Subject Discontinuation in Open Label Study, SIB-05S1 (All Enrolled Subjects)**

Reason for Discontinuation	Placebo/ Placebo/ Lubiprostone (P/P/L) N=181 (100%) N (%)	Lubiprostone/Placebo/ Lubiprostone (L/P/L) N=79 (100%) N (%)	Lubiprostone/Lubiprostone/ Lubiprostone (L/L/L) N=262 (100%) N (%)
Adverse Event	12 (6.6)	1 (1.3)	8 (3.1)
Protocol Violation	0 (0.0)	1 (1.3)	2 (0.8)
Subjects Voluntary Withdrawal	22 (12.2)	15 (19.0)	34 (13.0)
Lack Of Efficacy	19 (10.5)	14 (17.7)	37 (14.1)
Lost to Follow-Up	9 (5.0)	5 (6.3)	12 (4.6)
Did Not Meet Entry Criteria	0 (0.0)	0 (0.0)	0 (0.0)
Non-Compliance	4 (2.2)	5 (6.3)	11 (4.2)
Other	2 (1.1)	0 (0.0)	5 (1.9)

Reviewer's table modified from Table 2.7.4.1-4, page 18 of 126, Summary of Clinical Safety

### 7.1.3.2 Adverse Events associated with Dropouts

Table 31 below is a summary of adverse events leading to study withdrawal for the well-controlled safety cohort. A discussion of this data will follow.

**Table 31: Summary of Adverse Events Leading to Withdrawal (Well-Controlled Safety Group)**

System Organ Class (SOC)	Placebo N=435 (100%)	Lubiprostone 16mcg N=832 (100%)	Lubiprostone 32mcg N=49 (100%)	Lubiprostone 48mcg N=45 (100%)	All Active Doses N=926 (100%)	p-Value
<b>Number</b>	N (%)	N (%)	N (%)	N (%)	N (%)	Number
<b>At least one adverse event leading to withdrawal</b>	26 (6.0)	39 (4.7)	8 (16.3)	6 (13.3)	53 (5.7)	0.051
<b>Gastrointestinal Disorders</b>	10 (2.3)	16 (1.9)	5 (10.2)	5 (11.1)	26 (2.8)	0.001
Nausea	3 (0.7)	10 (1.2)	1 (2.0)	2 (4.4)	13 (1.4)	
Abdominal Pain	6 (1.4)	2 (0.2)	1 (2.0)	1 (2.2)	4 (0.4)	
Diarrhea	2 (0.5)	3 (0.4)	1 (2.0)	2 (4.4)	6 (0.6)	
Abdominal Distension	2 (0.5)	1 (0.1)	2 (4.1)	1 (2.2)	4 (0.4)	
Dyspepsia	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)	
Vomiting	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Rectal hemorrhage	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)	
Flatulence	0 (0.0)	1 (0.1)	1 (2.0)	0 (0.0)	2 (0.2)	
Eructation	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.1)	
Constipation	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Bowel sounds abnormal	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.1)	
Appendicitis perforated	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.1)	
Small intestine gangrene	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Small intestinal obstruction	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Abdominal adhesions	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Fecal Incontinence	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
System Organ Class (SOC)	Placebo N=435 (100%)	Lubiprostone 16mcg N=832 (100%)	Lubiprostone 32mcg N=49 (100%)	Lubiprostone 48mcg N=45 (100%)	All Active Doses N=926 (100%)	p-Value
<b>General disorders and administration site conditions</b>	1 (0.2)	7 (0.8)	0 (0.0)	2 (4.4)	9 (1.0)	0.013
Edema Peripheral	1 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)	
Rigors	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Non-cardiac chest pain	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Influenza Like illness	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Feeling abnormal	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.1)	
Fatigue	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Chest pain	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Chest discomfort	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.1)	
Asthenia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
System Organ Class (SOC)	Placebo N=435 (100%)	Lubiprostone 16mcg N=832 (100%)	Lubiprostone 32mcg N=49 (100%)	Lubiprostone 48mcg N=45 (100%)	All Active Doses N=926 (100%)	p-Value
<b>Nervous System disorders</b>	3 (0.7)	4 (0.5)	1 (2.0)	2 (4.4)	7 (0.8)	0.046
Headache	3 (0.7)	2 (0.2)	1 (2.0)	1 (2.2)	4 (0.4)	
Dizziness	0 (0.0)	1 (0.1)	0 (0.0)	1 (2.2)	2 (0.2)	
Lethargy	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	

<b>Musculoskeletal and connective tissue disorders</b>	2 (0.5)	5 (0.6)	0 (0.0)	1 (2.2)	6 (0.6)	0.353
Back Pain	1 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)	
Arthralgia	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Osteoarthritis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Myalgia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.1)	
Muscle Spasms	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Joint swelling	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Fibromyalgia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
<b>Investigations</b>	4 (0.9)	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)	0.097
Weight Increased	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)	
Blood Lactate dehydrogenase increased	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Aspartate Aminotransferase increased	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Alanine Aminotransferase increased	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Hepatic Enzyme increased	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Blood glucose increased	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
<b>Skin and Subcutaneous tissue disorders</b>	4 (0.9)	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)	0.097
Rash	2 (0.5)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Urticaria generalized	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Pruritus generalized	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Pruritus	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
<b>Respiratory, thoracic and mediastinal disorders</b>	0 (0.0)	4 (0.5)	1 (2.0)	1 (2.2)	6 (0.6)	0.008
Dyspnea	0 (0.0)	3 (0.4)	1 (2.0)	1 (2.2)	5 (0.5)	
Throat Tightness	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Painful Respiration	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
<b>Cardiac disorders</b>	0 (0.0)	3 (0.4)	1 (2.0)	0 (0.0)	4 (0.4)	0.158
Tachycardia	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.1)	
Palpitations	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Mitral Valve Incompetence	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Coronary Artery Disease	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Cardiac Arrest	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Atrial Fibrillation	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>	1 (0.2)	3 (0.4)	0 (0.0)	0 (0.0)	3 (0.3)	0.922
Breast Cancer	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Thyroid Gland Cancer	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Malignant Melanoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
<b>Metabolism and Nutrition disorders</b>	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0.547
Fluid Retention	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	



<b>Infections and Infestations</b>	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.095
Gastrointestinal Viral	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Clostridial Infection	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Cellulitis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
<b>Eye Disorders</b>	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0.547
Mydriasis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Eye Swelling	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
<b>Reproductive system and breast Disorders</b>	0 (0.0)	1 (0.1)	1 (2.0)	0 (0.0)	2 (0.2)	0.126
Ovarian mass	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
Menorrhagia	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.1)	
<b>Ear and Labyrinth Disorders</b>	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0.743
Tympanic Membrane Perforation	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	
<b>Vascular Disorders</b>	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.1)	0.001
Flushing	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.1)	

Reviewer's table modified from Table 1.2.5, page 58 of 126, Summary of Clinical Safety for Lubiprostone

As noted above, in the well-controlled safety population, 6.0% of placebo and 4.7% of Lubiprostone 16 mcg subjects withdrew because of an adverse event. This difference was not statistically significant ( $p=0.051$ ) and similar results were observed in Lubiprostone subjects in study SIB-0431 Treatment Phase I (placebo 5.2%; Lubiprostone 5.1%) and study SIB-0432 (placebo 7.7%; Lubiprostone 4.2%). In study SIB-0221 (placebo 2.1%; Lubiprostone all doses 8.8%), the percentage of subjects withdrawing due to adverse events in all Lubiprostone groups increased as the doses were increased (32 mcg and 48 mcg). The percentage of placebo subjects withdrawing from the three well-controlled studies due to an adverse event did not remain constant; in fact, it varied in the range of 2.1% to 7.7%. Overall, 2.3% of placebo subjects and 1.9% of Lubiprostone 16 mcg subjects withdrew because of an adverse event in the System Organ Class (SOC), Gastrointestinal Disorders. Gastrointestinal adverse events that led to withdrawal for at least 1% of subjects were nausea (1.2%) for the Lubiprostone 16 mcg group and abdominal pain (1.4%) for the placebo group. A significant difference was found in the Respiratory, thoracic and mediastinal disorders SOC; 0.5% of Lubiprostone 16 mcg group withdrew because of these adverse events, while no placebo subjects withdrew ( $p=0.008$ ). Dyspnea (0.4%), throat tightness (0.1%), and painful respiration (0.1%) were the adverse events that led to discontinuation in the Lubiprostone 16 mcg group. Statistically significant differences were also found in the SOC of general disorders and administration site conditions, nervous system disorders, and vascular disorders, but the overall frequencies within these SOC were  $\leq 1\%$  of subjects.

**Table 32: Summary of Adverse Events leading to Withdrawal  
(Long Term Safety Population)**

System Organ Class (SOC)	Lubiprostone 16 mcg N=520 (100%)
<b>At least One adverse event leading to withdrawal N (%)</b>	<b>25 (4.8)</b>
<b>Gastrointestinal Disorders</b>	<b>14 (2.7)</b>
Diarrhea	7 (1.3)
Nausea	3 (0.6)
Abdominal Distension	3 (0.6)
Vomiting	1 (0.2)
Swollen Tongue	1 (0.2)
Gastroesophageal reflux disease	1 (0.2)
Constipation	1 (0.2)
Abdominal Pain upper	1 (0.2)
Abdominal Pain	1 (0.2)
<b>Skin and Subcutaneous tissue disorders</b>	<b>4 (0.8)</b>
Swelling face	1 (0.2)
Rash	1 (0.2)
Photosensitivity Reaction	1 (0.2)
Hyperhidrosis	1 (0.2)
Erythema	1 (0.2)
<b>Nervous System disorders</b>	<b>3 (0.6)</b>
Dizziness	2 (0.4)
Paraesthesia oral	1 (0.2)
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>2 (0.4)</b>
Pharyngolaryngeal pain	1 (0.2)
Dyspnea	1 (0.2)
<b>Investigations</b>	<b>2 (0.4)</b>
Liver function test abnormal	1 (0.2)
Aspartate Aminotransferase abnormal	1 (0.2)
Alanine Aminotransferase abnormal	1 (0.2)
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>	<b>1 (0.2)</b>
Colon Cancer	1 (0.2)
<b>Infections and Infestations</b>	<b>1 (0.2)</b>
Vaginal Mycosis	1 (0.2)
<b>Blood and Lymphatic system disorders</b>	<b>1 (0.2)</b>
Anemia	1 (0.2)

Reviewer's table modified from Table 3.2.5, page 59 of 126, Summary of Clinical Safety

As noted in table 32, the types and frequencies of the individual adverse events leading to study withdrawal in the long term safety cohort (36-52 weeks) were generally similar to those observed in the well-controlled safety group. Gastrointestinal disorders was once again the most common SOC leading to withdrawal. Adverse events in the long term safety group that led to withdrawal for at least 1 % of subjects were diarrhea (1.3%). The adverse events nausea (0.6%), abdominal distension (0.6%) and dizziness (0.4%) each led to discontinuation for more than 1 subject.

**Table 33: Summary of Adverse Event Incidence Rates by System/Organ/Class**

System Organ Class (SOC) N (%)	Placebo N=435 (100%)	Lubiprostone All Active Doses N=926 (100%)
At least One adverse event	225 (51.7)	488 (52.7)
Gastrointestinal Disorders	95 (21.8)	271 (29.3)
Infections and Infestations	86 (19.8)	178 (19.2)
Nervous System disorders	35 (8.0)	78 (8.4)
Musculoskeletal and connective tissue disorders	25 (5.7)	52 (5.6)
Respiratory, thoracic and mediastinal disorders	10 (2.3)	44 (4.8)
General disorders and administration site conditions	11 (2.5)	36 (3.9)
Metabolism and Nutrition disorders	7 (1.6)	21 (2.3)
Injury, Poisoning and procedural complications	17 (3.9)	20 (2.2)
Investigations	21 (4.8)	19 (2.1)
Skin and Subcutaneous tissue disorders	15 (3.4)	18 (1.9)
Psychiatric disorders	12 (2.8)	16 (1.7)
Reproductive system and breast Disorders	3 (0.7)	16 (1.7)
Cardiac disorders	2 (0.5)	9 (1.0)
Vascular Disorders	6 (1.4)	7 (0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (1.1)	7 (0.8)
Renal and urinary Disorders	1 (0.2)	7 (0.8)
Eye Disorders	8 (1.8)	5 (0.5)
Blood and Lymphatic system disorders	3 (0.7)	5 (0.5)
Immune system Disorders	0 (0.0)	5 (0.5)

Reviewer's table modified from Table 1.2.1.2, page 27 of 126, Summary of Clinical Safety

### **Medical officer comments**

*As noted in table 32, the majority (2.7%) of adverse events that led to subject withdrawal in the long term safety cohort were found within the SOC of Gastrointestinal disorders, which included diarrhea, nausea, and abdominal distension. As noted in table 33, the most common SOC reported for adverse events as a whole were Gastrointestinal disorders, with 29.3% of Lubiprostone subjects reporting. For the SOC Gastrointestinal disorders, the frequency of adverse events in the All Active Doses Group of Lubiprostone (29.3%) was higher than the frequency for Placebo group (21.8%). The sponsor noted that based on Lubiprostone's mechanism of action, certain gastrointestinal side effects in subjects taking Lubiprostone were key pharmacodynamic adverse events and were not unexpected. The medical officer is cautious to dismiss these adverse events as simply "expected" pharmacodynamic events as their frequency in All Active Doses group was higher than the frequency in the placebo group. This reflects clinically meaningful adverse trends which may affect patient compliance. It also appears that the adverse events in the gastrointestinal system disorder such as diarrhea, nausea, abdominal pain and abdominal distension seem to increase as the dose increased. The medical officer is reassured; however, that despite the aforementioned adverse events, only 2.7% withdrew from the long term study due to gastrointestinal adverse events, and the general health of the subjects in the long term safety cohort did not appear to be compromised during the long-term treatment with Lubiprostone 16 mcg.*

#### **7.1.4 Common Adverse Events**

An overall summary of commonly reported adverse events, i.e., those reported by  $\geq 1\%$  of subjects taking Lubiprostone 16 mcg is presented in table 33. Across all active doses of Lubiprostone 52.7% of study drug and 51.7% of placebo subjects reported at least one adverse event, a difference that was not statistically significant. By dose level, 51.2% of subjects taking Lubiprostone 16 mcg, 61.2% of subjects taking Lubiprostone 32 mcg, and 71.1% of subjects taking Lubiprostone 48 mcg reported at least 1 adverse event. The higher proportion of subjects reporting at least 1 adverse event in the higher doses of Lubiprostone probably contributed to the statistical significance,  $p=0.049$ . The most commonly reported adverse events in both the placebo and Lubiprostone groups were in the System Organ Class (SOC), Gastrointestinal Disorders.

The subjects taking Lubiprostone 16 mcg reported 26.9% Gastrointestinal disorder related adverse events whereas the placebo group reported 21.8%. Within the Gastrointestinal disorder SOC, nausea (10.9%) and diarrhea (7.0%) were reported by at least 5% of subjects taking Lubiprostone 16 mcg. There were no other adverse events reported by at least 5% of subjects taking Lubiprostone 16 mcg.

**Table 34: Commonly Reported Adverse Events in the Well-Controlled Safety Group<sup>1</sup>**

System Organ Class (SOC)	Placebo	Lubiprostone 16 mcg	Lubiprostone 32 mcg	Lubiprostone 48 mcg	All Active Doses	Statistic
N (%)	N=435 (100%)	N=832 (100%)	N=49 (100%)	N=45 (100%)	N=926 (100%)	p-Value
<b>At least one adverse event</b>	225 (51.7)	<b>426 (51.2)</b>	30 (61.2)	32 (71.1)	488 (52.7)	0.049
<b>Gastrointestinal Disorders</b>	95 (21.8)	<b>224 (26.9)</b>	25 (51.0)	22 (48.9)	271 (29.3)	<0.001
Nausea	28 (6.4)	<b>91 (10.9)</b>	9 (18.4)	14 (31.1)	114 (12.3)	
Diarrhea	23 (5.3)	<b>58 (7.0)</b>	6 (12.2)	12 (26.7)	76 (8.2)	
Abdominal Pain	23 (5.3)	<b>32 (3.8)</b>	3 (6.1)	2 (4.4)	37 (4.0)	
Abdominal Distension	14 (3.2)	<b>21 (2.5)</b>	5 (10.2)	5 (11.1)	31 (3.3)	
Flatulence	16 (3.7)	<b>24 (2.9)</b>	2 (4.1)	1 (2.2)	27 (2.9)	
Dyspepsia	8 (1.8)	<b>13 (1.6)</b>	4 (8.2)	2 (4.4)	19 (2.1)	
Vomiting	5 (1.1)	<b>11 (1.3)</b>	1 (2.0)	4 (8.9)	16 (1.7)	
Abdominal pain Upper	4 (0.9)	<b>15 (1.8)</b>	0 (0.0)	0 (0.0)	15 (1.6)	
Dry Mouth	2 (0.5)	<b>10 (1.2)</b>	0 (0.0)	1 (2.2)	11 (1.2)	
<b>Infections and Infestations</b>	86 (19.8)	157 (18.9)	9 (18.4)	12 (26.7)	178 (19.2)	0.648
Urinary Tract infection	15 (3.4)	32 (3.8)	0 (0.0)	5 (11.1)	37 (4.0)	
Upper respiratory tract infection	10 (2.3)	31 (3.7)	3 (6.1)	4 (8.9)	38 (4.1)	
Sinusitis	15 (3.4)	29 (3.5)	1 (2.0)	2 (4.4)	32 (3.5)	
Nasopharyngitis	10 (2.3)	16 (1.9)	1 (2.0)	2 (4.4)	19 (2.1)	
Bronchitis	5 (1.1)	15 (1.8)	0 (0.0)	1 (2.2)	16 (1.7)	
Influenza	2 (0.5)	8 (1.0)	0 (0.0)	0 (0.0)	8 (0.9)	
<b>Nervous System disorders</b>	35 (8.0)	63 (7.6)	8 (16.3)	7 (15.6)	78 (8.4)	0.087
Headache	19 (4.4)	35 (4.2)	3 (6.1)	2 (4.4)	40 (4.3)	
Dizziness	10 (2.3)	18 (2.2)	3 (6.1)	2 (4.4)	23 (2.5)	
<b>Musculoskeletal and connective tissue disorders</b>	25 (5.7)	47 (5.6)	1 (2.0)	4 (8.9)	52 (5.6)	0.895
Back Pain	5 (1.1)	12 (1.4)	0 (0.0)	0 (0.0)	12 (1.3)	
Arthralgia	6 (1.4)	10 (1.2)	0 (0.0)	1 (2.2)	11 (1.2)	
<b>Respiratory, thoracic and mediastinal disorders</b>	10 (2.3)	39 (4.7)	2 (4.1)	3 (6.7)	44 (4.8)	0.041
Sinus Congestion	1 (0.2)	8 (1.0)	0 (0.0)	0 (0.0)	8 (0.9)	
<b>General disorders and administration site conditions</b>	11 (2.5)	30 (3.6)	2 (4.1)	4 (8.9)	36 (3.9)	0.039
Fatigue	2 (0.5)	12 (1.4)	0 (0.0)	1 (2.2)	13 (1.4)	

Reviewer's table modified from Table 2.7.4.2-3, page 30 of 126, Summary of Clinical Safety for Lubiprostone

<sup>1</sup>Adverse Events reported by  $\geq 1\%$  in the Lubiprostone 16 mcg group.

p-values are obtained from Cochran-Armitage trend tests

### **Medical officer comments**

*Both placebo and Lubiprostone 16 mcg had similar proportion of subjects reporting at least one adverse event (51.7% vs. 51.2%, respectively). Therefore, it could be inferred that the statistical significance ( $p=0.049$ ) is largely contributed from the adverse events in the higher doses of Lubiprostone 32 mcg (61.2%) and 48 mcg (71.1%). Gastrointestinal adverse events were noticeably more prevalent among subjects taking the study drug than among the placebo subjects. The sponsor argues that these adverse events are not unexpected based upon the pharmacodynamic mechanism of Lubiprostone; an argument that may have merit as a dose dependent increase in adverse events was noted with Lubiprostone. Furthermore, the percentage of adverse events reported in the SOC,*

***Gastrointestinal disorders in the higher doses 32 mcg (51.0%) and 48 mcg (48.9%) is twice the frequency reported by the placebo group (21.8%). This probably contributes largely to the statistically significant difference noted between placebo and Lubiprostone,  $p<0.001$ . The difference between placebo and Lubiprostone at the SOC level (respiratory, thoracic and mediastinal disorders,  $p=0.041$  and general disorders and administration site conditions,  $p=0.039$ ) were statistically significant.***

Table 35 below highlights the adverse events that were reported by at least 1% of Lubiprostone 16 mcg subjects and at a frequency that was at least double the frequency reported in the placebo group. Abdominal pain-upper, influenza, and sinus congestion were only reported in placebo and the Lubiprostone 16 mcg groups whereas dry mouth and fatigue were reported in the higher doses of Lubiprostone. Fatigue and dry mouth each were reported by 2.2% of Lubiprostone 48 mcg subjects, but the 32 mcg Lubiprostone subjects did not report any of the adverse events listed below.

**Table 35: Adverse Events Reported More Commonly in Lubiprostone 16 mcg Subjects than Placebo Subjects<sup>1</sup>**

System Organ Class (SOC)	Placebo	Lubiprostone 16 mcg
N (%)	435 (100)	832 (100)
<b>Gastrointestinal Disorders</b>		
Abdominal Pain Upper	4 (0.9)	15 (1.8)
Dry Mouth	2 (0.5)	10 (1.2)
<b>Infections and Infestations</b>		
Influenza	2 (0.5)	8 (1.0)
<b>Respiratory, thoracic and mediastinal disorders</b>		
Sinus congestion	1 (0.2)	8 (1.0)
<b>General disorders and administration site conditions</b>		
Fatigue	2 (0.5)	12 (1.4)

Reviewer's table modified from Table 2.7.4.2-5, page 33 of 126, Summary of Clinical Safety for Lubiprostone

To be included in this table, an individual AE must have been reported by at least 1% of subjects taking Lubiprostone 16 mcg and its frequency in the Lubiprostone 16 mcg group must have been at least twice the frequency reported in the placebo group<sup>1</sup>

#### 7.1.4.1 Eliciting Adverse Events data in the development program

The primary method of collecting adverse events information was by means of standard questioning, vitals signs and laboratory examination at each clinic visit. Spontaneous reports of adverse events were also captured in the subjects' diaries in their global and abdominal assessments. Such spontaneous reports of adverse events were reported in the case report forms (CRFs). If necessary, the investigator could adjust the subjects' treatment dosage if it was thought, there was a treatment-related adverse event. Any changes in dose were noted in the CRFs.

#### 7.1.4.2 Appropriateness of adverse event categorization and preferred terms

Each adverse event in this supplemental New Drug Application was categorized using System Organ Class (SOC) classification and coded using a MedDRA dictionary of preferred terms.

#### Medical officer comments

***The medical officer felt this system of adverse event categorization and coding was fully comprehensive, however, calculating the incidence of specific adverse events was difficult. For***

*example abdominal pain was reported under abdominal pain-upper, abdominal pain-lower, abdominal tenderness, abdominal discomfort, and stomach discomfort.*

#### 7.1.4.3 Incidence of Common Adverse Events

Across the three well-controlled studies (SIB-0221, SIB-0431 Treatment Phase I, and SIB-0432), the frequency of subjects reporting at least one AE in the placebo subjects (51.7%) and the Lubiprostone 16 mcg subjects (51.2%) was similar. With increasing dose, 61.2% of subjects taking Lubiprostone 32 mcg, and 71.1% of subjects taking Lubiprostone 48 mcg reported at least 1 adverse event,  $p=0.049$ . 20.9% of placebo subjects and 22.4% of Lubiprostone 16 mcg subjects reported at least 1 treatment-related AE, whereas, 42.9% of subjects taking Lubiprostone 32 mcg, and 42.2% of subjects taking Lubiprostone 48 mcg ( $p<0.001$ ), and 24.4% of subjects taking any doses of Lubiprostone reported treatment-related AEs. Four Placebo subjects (0.9%) and seven Lubiprostone 16 mcg subjects (0.8%) reported at least one SAE, and one in the Lubiprostone 16 mcg group (0.1%) was considered treatment-related. One subject in the Lubiprostone 32 mcg group (2.0%), and two subjects in Lubiprostone 48 mcg group (4.4%) reported at least 1 SAE but none of which was considered treatment-related. One subject in the Lubiprostone 16 mcg group (0.1%) died due to an adverse event. Overall 6.0% placebo subjects and 4.7% of Lubiprostone 16 mcg subjects discontinued because of an AE; 16.3% of subjects taking Lubiprostone 32 mcg, and 13.3% of subjects taking Lubiprostone 48 mcg ( $p=0.051$ ), and 5.72% of subjects taking Lubiprostone at any dose discontinued because of an AE. Similar results were observed at the study level, except the difference in proportion of subjects who discontinued because of an AE between placebo (2.1%) and Lubiprostone 16 mcg (5.8%) was significant in SIB-0221 ( $p=0.0175$ ).

**Table 36: Overall Summary of Adverse Events**

Category/Dose Group	Well-Controlled Safety Group	Long Term Safety Group
	N (%)	N (%)
<b>Subjects reporting at least one Adverse Event</b>		
Placebo	225/435 (51.7)	NA
Lubiprostone 16 mcg	426/832 (51.2)	323/520 (62.1)
All Active Doses	488/926 (52.7)	NA
<b>Subjects reporting at least one Treatment-Related Adverse Event</b>		
Placebo	91/435 (20.9)	NA
Lubiprostone 16 mcg	186/832 (22.4)	107/520 (20.6)
All Active Doses	226/926 (24.4)	NA
<b>Subjects reporting at least one Serious Adverse Event</b>		
Placebo	4/435 (0.9)	NA
Lubiprostone 16 mcg	7/832 (0.8)	10/520 (1.9)
All Active Doses	10/926 (1.1)	NA
<b>Subjects reporting at least one Treatment-Related Serious Adverse Event</b>		
Placebo	0/435 (0.0)	NA
Lubiprostone 16 mcg	1/832 (0.1)	0/520 (0.0)
All Active Doses	1/926 (0.11)	NA
<b>Subjects who Discontinued due to an Adverse Event</b>		
Placebo	26/435 (6.0)	NA
Lubiprostone 16 mcg	39/832 (4.7)	25/520 (4.8)
All Active Doses	53/926 (5.7)	NA
<b>Subjects who Died due to an Adverse Event</b>		
Placebo	0/435 (0.0)	NA
Lubiprostone 16 mcg	1/832 (0.1)	0/520 (0.0)
All Active Doses	1/926 (0.11)	NA

Reviewer's table modified from Table 2.7.4.2-1, page 27 of 126, Summary of Clinical Safety and from Table 2.7.4.2-2, page 26 of 126, Summary of Clinical Safety

## Medical officer comments

*As described in table 36, in most cohorts that included placebo and Lubiprostone 16 mcg subjects, the frequencies of reporting AEs were similar. Treatment-related AEs were slightly higher in frequency in the Lubiprostone 16 mcg than placebo (22.4% vs. 20.9%) whereas the frequency of discontinuation due to AEs was slightly higher in placebo subjects than Lubiprostone 16 mcg subjects (6.0% vs. 4.7%, respectively). It is concerning that the frequency of SAEs reported in the Lubiprostone 16 mcg group was 1.9% in the long term safety group and a subject died in one of the well-controlled studies. However, it should be noted that the frequency of SAEs in the Lubiprostone 16 mcg group when compared to placebo was similar (0.8% vs. 0.9%, respectively). Of unknown significance to the medical officer is the high number of placebo subjects reporting at least one adverse event in the well-controlled safety group (51.7%).*

### 7.1.4.4 Identifying common and drug-related adverse events

Table 37 below summarizes the adverse events by casual relationship to the study drug for the well-controlled safety and the long term safety groups. For the well controlled safety cohort, 20.9% of placebo subjects and 24.4% of Lubiprostone subjects reported at least one treatment-related AE. Treatment-related AEs consisted of those AEs with a relationship to the study drug that was “possible”, “probable”, or “definite” in the opinion of the investigator.

**Table 37: Treatment-Related Adverse Events during Well-Controlled Studies and Open label Study**

System/Organ/Class	Placebo N=435	All Active Doses* N= 926	Long Term Safety Group N=520
<b>At least one Treatment-Related Adverse Event</b>	91 (20.9)	226 (24.4)	107 (20.6)
Preferred Term	N (%)	N (%)	N (%)
<b>Gastrointestinal Disorders</b>	59 (13.6)	<b>196 (21.2)</b>	<b>84 (16.2)</b>
Nausea	17 (3.9)	87 (9.4)	18 (3.5)
Diarrhea	18 (4.1)	67 (7.2)	25 (4.8)
Abdominal Pain	18 (4.1)	27 (2.9)	11 (2.1)
Abdominal Distension	10 (2.3)	25 (2.7)	12 (2.3)
Flatulence	11 (2.5)	23 (2.5)	8 (1.5)
Dyspepsia	4 (0.9)	13 (1.4)	--
Abdominal Pain upper	2 (0.5)	9 (1.0)	8 (1.5)
Loose Stools	0 (0.0)	--	5 (1.0)
<b>Nervous System disorders</b>	21 (4.8)	42 (4.5)	14 (2.7)
Headache	12 (2.8)	22 (2.4)	6 (1.2)
Dizziness	6 (1.4)	13 (1.4)	5 (1.0)

Reviewer's table modified from Table 1.2.3, page 36 of 126, Summary of Clinical Safety and from Table 3.2.3, page 37 of 126, Summary of Clinical Safety

-- Indicates that a particular adverse event was not considered treatment-related for  $\geq 1\%$  of Lubiprostone subjects

\*All Active Doses: Study SIB-0221 (16 mcg + 32 mcg + 48mcg) + SIB-0431 Treatment Phase I + SIB-0432 = (52 + 49 + 45) + 395 + 385 = 926



### **Medical officer comments**

*For the well-controlled safety cohort, 20.9% of placebo subjects and 24.4% of Lubiprostone subjects reported at least 1 treatment-related AE. For the long term safety cohort 20.6% of subjects reported at least 1 treatment-related AE. The frequency of treatment-related adverse events in the gastrointestinal SOC is significantly higher in the Lubiprostone group relative to Placebo, (21.2% vs. 13.6%,  $p < 0.001$ , respectively). Nausea, diarrhea, dyspepsia, abdominal distension, and abdominal pain-upper all have higher frequency in the Lubiprostone treated group than placebo and are considered treatment-related. With the increasing dose of Lubiprostone, 32 mcg and 48 mcg respectively, it also appears that the frequency of the treatment-related adverse events such as nausea (18.4% vs. 22.2%), diarrhea (12.2% vs. 26.7%) and abdominal distension (8.2% vs. 11.1%) seem to increase.*

*Of the aforementioned treatment-related AEs, the possible treatment limiting adverse events were that of nausea, diarrhea, and abdominal distension. Nausea is almost 2.5 times more common in the Lubiprostone than placebo groups and increases in frequency to a range of five to six times with doses of 32 mcg and 48 mcg. Diarrhea also has a higher frequency in the Lubiprostone group relative to placebo and appears to be three times to six times more common as the dose escalates to 32 mcg and 48 mcg. Considering that Lubiprostone 48 mcg (24 mcg bid) is used for the treatment of chronic idiopathic constipation, diarrhea is a known effect of that particular dose. Abdominal distension also appears to increase with increasing Lubiprostone dose, but the Lubiprostone 16 mcg dose (1.9%) has a lower frequency of subjects reporting abdominal distension than placebo subjects (2.3%). The 32 mcg Lubiprostone subjects experienced abdominal distension at a frequency rate of 8.2% which is three times the frequency of placebo subjects (2.3%). Similarly, the Lubiprostone 48 mcg subjects experience abdominal distension at a frequency rate of 11.1% which is almost five times the frequency rate of placebo subjects (2.3%). When the preferred terms abdominal pain and abdominal pain-upper (treatment-related) adverse events were combined, placebo subjects have a frequency rate of 4.6% whereas all active doses Lubiprostone subjects have a frequency rate of 3.9%.*

*The L/L/L group (261 subjects) that is part of the long term safety group who had the longest exposure to Lubiprostone 16 mcg (either 48 or 52 weeks) treatment did experience treatment-related adverse events such as abdominal distension (3.1%), abdominal pain (1.1%) and abdominal pain-upper (2.3%) at a frequency rate  $\geq 1\%$ .*

### **7.1.5 Additional Analyses and Explorations**

#### **Nausea**

As shown below in table 38, most reported nausea adverse events were considered treatment-related by the investigator; range 2.6% - 19.2%. Interestingly, relatively few subjects discontinued secondary to nausea (maximum 2.7% in SIB-0221) and relatively fewer subjects reported this adverse event as severe (maximum 0.8% in SIB-0431 Treatment Phase I and long term safety group).

**Table 38: Summary of Important Frequencies for the Adverse Event Nausea (All Active Doses)<sup>1</sup>**

Study or Cohort	Frequency of Nausea (%)	Frequency of Severe Nausea (%)	Frequency of Treatment Related Nausea (%)	Frequency of Withdrawal due to Nausea (%)
<b>SIB-0221</b>	22.6	0.7	19.2	2.7
<b>SIB-0431 Treatment Phase I</b>	11.9	0.8	8.8	0.8
<b>SIB-0431 RW</b>	3.3	0.0	2.6	0.0
<b>SIB-0432</b>	8.9	0.3	6.3	1.6
<b>Well Controlled Safety Group<sup>2</sup></b>	12.3	0.5	9.4	1.4
<b>Long Term Safety Group<sup>3</sup></b>	6.5	0.8	3.5	0.6

<sup>1</sup>Study SIB-0221 included dose groups of Lubiprostone 32 mcg and 48 mcg; all other studies included only 16 mcg dose group

<sup>2</sup>includes data from SIB-0221 all doses of Lubiprostone, SIB-0431 Treatment Phase I, SIB-0432

<sup>3</sup>includes data from study SIB-05S1

The sponsor performed a hazard rate analysis for the occurrence of nausea on All Active Doses of the well-controlled safety group and found that the likelihood of experiencing a first episode of nausea was greatest during the first week of treatment with Lubiprostone. The hazard rate for All Active Doses in the well-controlled safety group was highest in the first 3 days of treatment (HR range: 0.012-0.042). Placebo subjects had a 6.8% (CHR 0.040) likelihood of experiencing nausea while Lubiprostone subjects at any dose had a 12.6% (CHR 0.090) likelihood of experiencing nausea. The likelihood of experiencing nausea also increased with an escalation in dose (11.2% (CHR 0.078) 16 mcg vs. 18.4% (CHR 0.182) 32 mcg vs. 32.0% (CHR 0.215) 48 mcg).

In the randomized withdrawal treatment phase, nausea was observed in the P/P subject group only with a likelihood of 0.7% (CHR 0.001). During the open label treatment period, the cumulative incidence rate of nausea in all active doses group was 7.3% (CHR 0.031). The occurrence of nausea was highest in the P/P/L group (10.9%) compared to the L/P/L group (2.6%) and the L/L/L group (5.9%) with cumulative hazard rate at 0.033 vs. 0.026 vs. 0.031, respectively.

Furthermore, for the L/L/L subjects during the open label treatment, the largest observed individual hazard rate was 0.016 at day 0, a rate that represented 52% of the total risk. Since the events occurred at day 0 prior to being dosed as part of the open label study, the continuing nausea was probably from the prior treatment period. It should also be noted that 90% of the total risk for experiencing nausea was observed by Day 2 in the L/L/L group.

The sponsor also performed a Cox regression analysis that adjusted for gender and age. The Cox regression analysis showed that the rate at which subjects taking any dose of Lubiprostone (after adjusting for gender and age) were to experience nausea was significantly increased relative to placebo (hazard ratio= 1.935; p=0.0015). Similarly after adjusting for treatment group and age group, the rate at which female subjects experienced nausea was increased relative to male subjects (hazard ratio=1.970; p=0.0826).

**Table 39: Cox Proportional Hazard Regression of Incidence Rates for the Time Until the First Occurrence of Nausea**

Total	Number of Events	Number Censored	Percent Censored
1356	144	1212	89.38

Variable	Standard Error	Wald Chi-Square	Hazard Ratio
All Active Doses/Placebo	0.2082	10.0456	1.935
65 ≥ Age / Age < 65	0.3041	0.2226	1.154
Female/Male	0.3906	3.0128	1.970

Reviewer's table modified from Table 1.2.9.2, page 41 of 126, Summary of Clinical Safety

### Medical officer comments

*The cumulative hazard rate analysis for the All Active Doses and the Long term safety cohort suggests that subjects taking lubiprostone were not necessarily at an increased risk of developing nausea over the course of long term treatment rather the greatest risk for occurrence was within the first few days of treatment. Interpreting the hazard ratio in this analysis is difficult given that data was censored if there were no adverse events within the set interval time periods, and no probability distribution curves were provided concurrently. It is reassuring to the medical officer; however, that the frequency of withdrawal due to nausea in the pivotal studies population (0.8% - 1.6%) and the open label study (0.6%) using Lubiprostone 16 mcg exhibited low frequencies. This suggests that when data is inclusive of both shorter and longer duration studies, the rate of withdrawal secondary to nausea was comparable and not more than 2% of subjects in any cohort treated with Lubiprostone 16 mcg dose.*

### Diarrhea

For a drug whose mechanism is to increase chloride-rich intra-luminal intestinal fluid secretions, one potential adverse pharmacodynamic effect may be that of diarrhea. Expectedly most reported diarrhea events were considered treatment-related by the investigator; range 2.0% - 16.4%; however, relatively few subjects discontinued secondary to diarrhea (maximum 2.1% in SIB-0221). The subjects in SIB-0221 had the highest frequency of severe diarrhea (2.7%) compared to all the other well-controlled trials (maximum 0.8%).

**Table 40: Summary of Important Frequencies for the Adverse Event Diarrhea (All Active Doses)<sup>1</sup>**

Study or Cohort	Frequency of Diarrhea (%)	Frequency of Severe Diarrhea (%)	Frequency of Treatment Related Diarrhea (%)	Frequency of Withdrawal due to Diarrhea (%)
SIB-0221	17.1	2.7	16.4	2.1
SIB-0431 Treatment Phase I	7.1	0.8	6.1	0.3
SIB-0431 RW	2.6	0.0	2.0	0.0
SIB-0432	6.0	0.0	4.9	0.5
Well Controlled Safety Group <sup>2</sup>	8.2	0.8	7.2	0.6
Long Term Safety Group <sup>3</sup>	8.8	1.0	4.8	1.3

<sup>1</sup>Study SIB-0221 included dose groups of Lubiprostone 32 mcg and 48 mcg; all other studies included only 16 mcg dose group

<sup>2</sup>includes data from SIB-0221 all doses of Lubiprostone, SIB-0431 Treatment Phase I, SIB-0432

<sup>3</sup>includes data from study SIB-05S1

The sponsor performed a hazard rate analysis for the occurrence of diarrhea on All Active Doses of the well-controlled safety group and found that the likelihood of experiencing a first episode of diarrhea was greatest during the first week of treatment with Lubiprostone. The hazard rate for All Active Doses in the well-controlled safety group was highest in the first 4 days of treatment (HR range: 0.006-0.015). Placebo subjects had a 5.6% (CHR 0.029) likelihood of experiencing diarrhea while Lubiprostone subjects at any dose had 8.6% (CHR 0.049) likelihood of experiencing diarrhea. The likelihood of experiencing diarrhea also increased with an escalation in dose (7.3% (CHR 0.038) 16 mcg vs. 12.5% (CHR 0.111) 32 mcg vs. 27.3% (CHR 0.190) 48 mcg).

In the randomized withdrawal treatment phase, diarrhea was observed in the P/P and the L/L group with the same likelihood of 0.7% (CHR 0.001). During the open label treatment period, the cumulative incidence rate of diarrhea in the all active doses group was 9.8% (CHR 0.031). The occurrence of diarrhea was similar in the P/P/L group (10.2%) and the L/L/L group (10.1%), but lower in the L/P/L group (8.0%) with cumulative hazard rate at 0.031 vs. 0.039 vs. 0.007, respectively. Furthermore, for the L/L/L subjects during the open label treatment, the largest observed individual hazard rate was 0.016 at day 2, a rate that represented 41% of the total risk. It should also be noted that 95% of the total risk for experiencing diarrhea was observed by Day 4 in the L/L/L group.

A Cox regression analysis that adjusted for gender and age was performed. The Cox regression analysis showed that the rate at which subjects taking any dose of Lubiprostone (after adjusting for gender and age) were to experience diarrhea was increased relative to placebo (hazard ratio= 1.547; p=0.0625). There were no significant differences in rates based on subject age or sex (HR= 0.984, p=0.9659 vs. HR=0.841, p=0.6084, respectively).

### **Medical officer comments**

***Based on Lubiprostone's mechanism of action, diarrhea is an adverse event of somewhat expected frequency. Although an average of 8.5% Lubiprostone subjects in the well-controlled safety and long-term safety populations reported diarrhea, the medical officer is less concerned that this adverse event is treatment limiting. Only 0.6% to 1.3% of patients withdrew from treatment secondary to diarrhea. It is also reassuring to note that the frequency of severe diarrhea and discontinuation due to diarrhea was highest in study SIB-0221 that utilized two higher doses, 32 mcg and 48 mcg.***

### **Abdominal Pain**

Most reported abdominal pain events were considered treatment-related by the investigator; range 1.3%-4.1%; however, relatively few subjects discontinued secondary to abdominal pain (maximum 1.4% in SIB-0221). The subjects in the long term safety group had the highest frequency of severe abdominal pain (1.2%).

**Table 41: Summary of Important Frequencies for the Adverse Event Abdominal Pain (All Active Doses)<sup>1</sup>**

Study or Cohort	Frequency of Abdominal Pain (%)	Frequency of Severe Abdominal Pain (%)	Frequency of Treatment Related Abdominal Pain (%)	Frequency of Withdrawal due to Abdominal Pain (%)
SIB-0221	6.2	0.7	4.1	1.4
SIB-0431 Treatment Phase I	5.6	0.8	4.0	0.0
SIB-0431 RW	2.6	0.7	2.0	0.0
SIB-0432	1.6	0.0	1.3	0.5
Well Controlled Safety Group <sup>2</sup>	4.0	0.4	2.9	0.4
Long Term Safety Group <sup>3</sup>	3.5	1.2	2.1	0.2

<sup>1</sup>Study SIB-0221 included dose groups of Lubiprostone 32 mcg and 48 mcg; all other studies included only 16 mcg dose group

<sup>2</sup>includes data from SIB-0221 all doses of Lubiprostone, SIB-0431 Treatment Phase I, SIB-0432

<sup>3</sup>includes data from study SIB-05S1

Placebo subjects experienced a higher likelihood of abdominal pain when compared to subjects that received Lubiprostone at any dose. Placebo subjects had a 7.1% (CHR 0.028) likelihood of experiencing abdominal pain while Lubiprostone subjects at any dose had a 6.0% (CHR 0.036) likelihood of experiencing abdominal pain. The likelihood of experiencing abdominal pain did not exhibit any dose relationship (6.0% (CHR 0.037) 16 mcg vs. 6.5% (CHR 0.045) 32 mcg vs. 4.9% (CHR 0.004) 48 mcg).

In the randomized withdrawal treatment phase, abdominal pain was observed in the L/P group with a 1.4% (CHR 0.002) likelihood whereas in the L/L group the likelihood was 0.7% (CHR 0.001). No abdominal pain events were observed in the placebo (P/P) group. During the open label treatment period, the cumulative incidence rate of abdominal pain in the all active doses group was 8.9% (CHR 0.024). The occurrence of abdominal pain was highest in the P/P/L group (11.8%, CHR 0.022) compared to the L/L/L group (8.6%, CHR 0.027) and the L/P/L group (2.6%, CHR 0.015).

Furthermore, for the L/L/L subjects during the open label treatment, the largest observed individual hazard rate was 0.016 at day 0, a rate that represented 59% of the total risk. Since the events occurred at day 0 prior to being dosed as part of the open label study, the continuing abdominal pain was probably from the prior treatment period. It should also be noted that 93% of the total risk for experiencing abdominal pain was observed by the midpoint of the 15-21 day interval in the L/L/L group.

A Cox regression analysis that adjusted for gender and age was performed. The Cox regression analysis showed that subjects taking any dose of Lubiprostone (after adjusting for gender and age) were less likely to experience abdominal pain relative to placebo subjects (hazard ratio= 0.940; p=0.7829). There were no significant differences in rates based on subject age or sex (HR=0.804, p=0.6083 vs. HR=1.045, p=0.9121, respectively).

### **Medical officer comments**

*Based on the preferred term in MedDRA, the sponsor has classified abdominal pain into 6 separate categories. The above analysis for hazard ratio and Cox regression was performed for the preferred term abdominal pain only. When all types of abdominal pain (abdominal pain, abdominal pain-upper, abdominal pain-lower, abdominal discomfort, abdominal tenderness, and stomach discomfort) are combined, placebo subjects exhibit a frequency of 7.8% and Lubiprostone 16 mcg subjects exhibit a frequency of 6.7%. As seen in the cumulative incidence rate, the likelihood of experiencing*

*abdominal pain did not exhibit a dose relationship. Likewise, when all types of abdominal pain are combined, a dose relationship could not be demonstrated in terms of adverse events for all abdominal pain. Lubiprostone 32 mcg subjects experienced all abdominal pain at a frequency of 12.2% and Lubiprostone 48 mcg subjects experienced all abdominal pain at a frequency of 4.4%. However, it appears that the frequency of abdominal distension seems to increase as dose is increased. Lubiprostone 16 mcg subjects reported abdominal distension at a 2.5% frequency rate, the 32 mcg subjects reported abdominal distension at 10.2% frequency rate and Lubiprostone 48 mcg subjects reported abdominal distension at 11.1% frequency rate. It should be noted that the 2.5% frequency rate for abdominal distension seen in the Lubiprostone 16 mcg subjects is lower than the frequency rate seen in placebo subjects (3.2%).*

## Vomiting

Unlike nausea, most reported vomiting events were not considered treatment-related by the investigator; range 0.3% - 0.8%, and there were very few subjects that discontinued secondary to vomiting (maximum 0.3% in SIB-0432). The long term safety group had the highest frequency of severe vomiting (1.0%).

**Table 42: Summary of Important Frequencies for the Adverse Event Vomiting (All Active Doses)<sup>1</sup>**

Study or Cohort	Frequency of Vomiting (%)	Frequency of Severe Vomiting (%)	Frequency of Treatment Related Vomiting (%)	Frequency of Withdrawal due to Vomiting (%)
SIB-0221	4.1	0.0	0.7	0.0
SIB-0431 Treatment Phase I	1.0	0.3	0.3	0.0
SIB-0431 RW	0.7	0.0	0.7	0.0
SIB-0432	1.6	0.5	0.5	0.3
Well Controlled Safety Group <sup>2</sup>	1.7	0.3	0.4	0.1
Long Term Safety Group <sup>3</sup>	2.9	1.0	0.8	0.2

<sup>1</sup>Study SIB-0221 included dose groups of Lubiprostone 32 mcg and 48 mcg; all other studies included only 16 mcg dose group

<sup>2</sup>includes data from SIB-0221 all doses of Lubiprostone, SIB-0431 Treatment Phase I, SIB-0432

<sup>3</sup>includes data from study SIB-05S1

Placebo subjects 1.2% (CHR 0.004) had a similar likelihood of experiencing vomiting compared to Lubiprostone subjects 1.8% (CHR 0.007) at any dose. The likelihood of experiencing vomiting increased with increasing dose (1.4% (CHR 0.006) 16 mcg vs. 2.6% (CHR 0.001) 32 mcg vs. 9.5% (CHR 0.030) 48 mcg).

In the randomized withdrawal treatment phase, vomiting was not observed in any of the treatment groups (0.000 for each). During the open label treatment period, the cumulative incidence rate of vomiting in the all active doses group is 3.6% (CHR 0.009). The occurrence of vomiting was similar in the L/L/L group (4.4%, CHR 0.010) and the P/P/L group (4.0%, CHR 0.012), and no subjects in the L/P/L group reported vomiting (0.0%, CHR 0.000).

Furthermore, for the L/L/L subjects during the open label treatment, the largest observed individual hazard rate was 0.004 at day 0 and Day 4, each represented 40% of the total risk. Since 40% of the events occurred at day 0 prior to being dosed as part of the open label study, the continued vomiting at Day 0 could probably be attributed to the prior treatment period. It should also be noted that 90% of the

total risk for experiencing vomiting was observed by the midpoint of the 22-28 day interval in the L/L/L group.

The Cox regression analysis showed that subjects taking any dose of Lubiprostone were more likely to experience vomiting relative to placebo subjects (hazard ratio= 1.506; p=0.4243).

## Headache

Most reported headache events were considered treatment-related by the investigator; range 0.7%-2.5%, except in the long term safety group. Very few subjects discontinued secondary to headache (maximum 1.4% in SIB-0221). The subjects in the dose response study SIB-0221 had the highest frequency of severe headache events (1.4%).

**Table 43: Summary of Important Frequencies for the Adverse Event Headache (All Active Doses)<sup>1</sup>**

Study or Cohort	Frequency of Headache (%)	Frequency of Severe Headache (%)	Frequency of Treatment Related Headache (%)	Frequency of Withdrawal due to Headache (%)
SIB-0221	4.8	1.4	2.1	1.4
SIB-0431 Treatment Phase I	4.3	0.5	2.5	0.0
SIB-0431 RW	0.7	0.0	0.7	0.0
SIB-0432	4.2	0.3	2.3	0.5
Well Controlled Safety Group <sup>2</sup>	4.3	0.5	2.4	0.4
Long Term Safety Group <sup>3</sup>	4.0	0.8	1.2	0.0

<sup>1</sup>Study SIB-0221 included dose groups of Lubiprostone 32 mcg and 48 mcg; all other studies included only 16 mcg dose group

<sup>2</sup>includes data from SIB-0221 all doses of Lubiprostone, SIB-0431 Treatment Phase I, SIB-0432

<sup>3</sup>includes data from study SIB-05S1

Placebo subjects 5.0% (CHR 0.029) had a similar likelihood of experiencing headache compared to Lubiprostone subjects 4.9% (CHR 0.030) at any dose. The likelihood of experiencing headache did not exhibit any dose relationship (4.7% (CHR 0.027) 16 mcg vs. 8.7% (CHR 0.064) 32 mcg vs. 4.4% (CHR 0.045) 48 mcg).

In the randomized withdrawal treatment phase, headache was not observed in the P/P and the L/P treatment groups (0.000 for each), but the L/L group exhibited a 0.7% likelihood of headache events (CHR 0.001). During the open label treatment period, the cumulative incidence rate of headache in the all active doses group was 5.8% (CHR 0.022). The occurrence of headache was similar in the P/P/L group (6.2%, CHR 0.008) and the L/L/L group (6.1%, CHR 0.030) and slightly lower in the L/P/L group (4.1%, CHR 0.027).

The CHR for Lubiprostone 16 mcg subjects experiencing headache during the double blind study was 0.027, and the CHR for the L/L/L subjects experiencing headache in the open label study was 0.030, meaning that the probability of a first headache occurring between the double blind treatment and the open label intervals increased by 11.1%.

Furthermore, for the L/L/L subjects during the open label treatment, the largest observed individual hazard rate was 0.020 at day 0 representing 67% of the total risk. Since 67% of the events occurred at day 0 prior to being dosed as part of the open label study, the continuing headache at Day 0 could

probably be attributed to the prior treatment period. It should also be noted that 93% of the total risk for experiencing headache was observed by day 5 in the L/L/L group.

The Cox regression analysis showed that subjects taking any dose of Lubiprostone were slightly more likely (after adjusting for gender and age) to experience headache relative to placebo subjects (hazard ratio= 1.018; p=0.9469).

## Dizziness

The long term safety group and the subjects from the well-controlled studies had similar frequency rates of dizziness (2.7% vs. 2.5% respectively) and also similar frequency rates of severe dizziness (0.4% vs. 0.3%), treatment-related dizziness (1.0% vs. 1.4%), and withdrawal due to dizziness (0.4% vs. 0.2%). Very few subjects discontinued secondary to dizziness (maximum 0.7% in SIB-0221). The subjects in the dose response study SIB-0221 had the highest frequency of dizziness adverse events (4.8%) and treatment-related dizziness adverse events (4.1%).

**Table 44: Summary of Important Frequencies for the Adverse Event Dizziness (All Active Doses)<sup>1</sup>**

Study or Cohort	Frequency of Dizziness (%)	Frequency of Severe Dizziness (%)	Frequency of Treatment Related Dizziness (%)	Frequency of Withdrawal due to Dizziness (%)
SIB-0221	4.8	0.0	4.1	0.7
SIB-0431 Treatment Phase I	1.8	0.0	0.5	0.0
SIB-0431 RW	0.7	0.0	0.7	0.0
SIB-0432	2.3	0.8	1.3	0.3
Well-Controlled Safety Group <sup>2</sup>	2.5	0.3	1.4	0.2
Long Term Safety Group <sup>3</sup>	2.7	0.4	1.0	0.4

<sup>1</sup>Study SIB-0221 included dose groups of Lubiprostone 32 mcg and 48 mcg; all other studies included only 16 mcg dose group

<sup>2</sup>includes data from SIB-0221 all doses of Lubiprostone, SIB-0431 Treatment Phase I, SIB-0432

<sup>3</sup>includes data from study SIB-05S1

Placebo subjects 2.2% (CHR 0.011) had a similar likelihood of experiencing dizziness compared to Lubiprostone subjects 2.6% (CHR 0.010) at any dose. The likelihood of experiencing dizziness did not exhibit any dose relationship (2.3% (CHR 0.007) 16 mcg vs. 6.3% (CHR 0.045) 32 mcg vs. 4.5% (CHR 0.026) 48 mcg).

In the randomized withdrawal treatment phase, dizziness was not observed in the P/P group (0.000) and both the L/P and L/L treatment groups exhibited the same likelihood of dizziness events (0.7% CHR 0.001). During the open label treatment period, the cumulative incidence rate of dizziness in the all active doses group is 3.2% (CHR 0.011). The occurrence of dizziness was highest in the L/P/L group (6.5%, CHR 0.041) compared to the L/L/L group (3.3%, CHR 0.006) and the P/P/L group (1.9%, CHR 0.007).

The CHR for Lubiprostone 16 mcg subjects experiencing dizziness during the double blind study was 0.007 and the CHR for the Lubiprostone 16 mcg subjects experiencing dizziness in the open label study was 0.006, meaning that the probability of a first dizziness episode occurring between the midpoints of the double blind treatment and the open label intervals did not increase during the open label treatment. Furthermore, for the L/L/L subjects during the open label treatment, the largest observed individual



hazard rate was 0.004 at day 0 representing 67% of the total risk. Since 67% of the events occurred at day 0 prior to being dosed as part of the open label, the continuing dizziness at Day 0 could probably be attributed to the prior treatment period. It should also be noted that 100% of the total risk for experiencing dizziness was observed by the midpoint of the 253-280 day interval in the L/L/L group.

The Cox regression analysis showed that subjects taking any dose of Lubiprostone were slightly more likely (after adjusting for gender and age) to experience dizziness relative to placebo subjects (hazard ratio=1.142; p=0.7253). Subjects who were 65 years old or greater were more likely to experience dizziness (HR= 2.271, p=0.0757).

## Syncope

No subject withdrew due to syncope in any of the studies (0.0%). None of the pivotal efficacy studies SIB-0431 Treatment Phase I and SIB-0432 had any subjects where the investigators reported treatment related syncope events. Very few subjects reported syncope adverse events (maximum 0.7% in SIB-0221).

**Table 45: Summary of Important Frequencies for the Adverse Event Syncope (All Active Doses)<sup>1</sup>**

Study or Cohort	Frequency of Syncope (%)	Frequency of Severe Syncope (%)	Frequency of Treatment Related Syncope (%)	Frequency of Withdrawal due to Syncope (%)
<b>SIB-0221</b>	0.7	0.0	0.7	0.0
<b>SIB-0431 Treatment Phase I</b>	0.0	0.0	0.0	0.0
<b>SIB-0431 RW</b>	0.0	0.0	0.0	0.0
<b>SIB-0432</b>	0.3	0.0	0.0	0.0
<b>Well-Controlled Safety Group<sup>2</sup></b>	0.2	0.0	0.1	0.0
<b>Long Term Safety Group<sup>3</sup></b>	0.4	0.4	0.0	0.0

<sup>1</sup>Study SIB-0221 included dose groups of Lubiprostone 32 mcg and 48 mcg; all other studies included only 16 mcg dose group

<sup>2</sup>includes data from SIB-0221 all doses of Lubiprostone, SIB-0431 Treatment Phase I, SIB-0432

<sup>3</sup>includes data from study SIB-05S1

Syncope was not observed in placebo subjects (CHR 0.000) whereas it was rarely observed in the Lubiprostone subjects 0.2% (CHR 0.000) at any dose. The likelihood of experiencing syncope did not exhibit any dose relationship (0.1% (CHR 0.000) 16 mcg vs. 0.0% (CHR 0.000) 32 mcg vs. 2.3% (CHR 0.003) 48 mcg).

In the randomized withdrawal treatment phase, syncope was not observed in any of the treatment groups (CHR 0.000 for each). During the open label treatment period, the cumulative incidence rate of syncope in the all active doses group was 0.5% (CHR 0.000). The occurrence of syncope was similar in the P/P/L group (0.6%, CHR 0.000) and the L/L/L group (0.5%, CHR 0.000), but it was not observed in the L/P/L group (0.0%, CHR 0.000).

The CHR for Lubiprostone 16 mcg subjects experiencing syncope during the double blind study and the open label study was 0.000, meaning that the probability of a first syncopal event occurring between the midpoints of the double blind treatment and the open label intervals did not increase during the open label treatment. There were no non-zero hazard rates for the open label treatment period.

The Cox regression analysis showed that subjects taking any dose of Lubiprostone were more likely to experience syncope relative to placebo subjects (hazard ratio= 1.68; p=0.9969).

## Peripheral Edema

None of the peripheral edema events were rated by the investigators as severe in any of the studies. Very few subjects withdrew due to peripheral edema (maximum 0.3% in both SIB-0431 Treatment Phase I and SIB-0432).

**Table 46: Summary of Important Frequencies for the Adverse Event Peripheral Edema (All Active Doses)<sup>1</sup>**

Study or Cohort	Frequency of Peripheral Edema (%)	Frequency of Severe Peripheral Edema (%)	Frequency of Treatment Related Peripheral Edema (%)	Frequency of Withdrawal due to Peripheral Edema (%)
SIB-0221	2.1	0.0	0.7	0.0
SIB-0431 Treatment Phase I	0.3	0.0	0.3	0.3
SIB-0431 RW	0.0	0.0	0.0	0.0
SIB-0432	1.0	0.0	0.5	0.3
Well-Controlled Safety Group <sup>2</sup>	0.8	0.0	0.4	0.2
Long Term Safety Group <sup>3</sup>	1.2	0.0	0.4	0.0

<sup>1</sup>Study SIB-0221 included dose groups of Lubiprostone 32 mcg and 48 mcg; all other studies included only 16 mcg dose group

<sup>2</sup>includes data from SIB-0221 all doses of Lubiprostone, SIB-0431 Treatment Phase I, SIB-0432

<sup>3</sup>includes data from study SIB-05S1

Lubiprostone subjects 0.8% (CHR 0.004) at any dose had a slightly higher likelihood of experiencing peripheral edema than placebo subjects 0.5% (CHR 0.002). The likelihood of experiencing peripheral edema increased as the dose increased (0.7% (CHR 0.004) 16 mcg vs. 2.2% (CHR 0.003) 32 mcg vs. 3.1% (CHR 0.001) 48 mcg).

In the randomized withdrawal treatment phase, peripheral edema was not observed in any of the treatment groups (CHR 0.000 for each). During the open label treatment period, the cumulative incidence rate of peripheral edema in the all active doses group was 1.2% (CHR 0.003). The occurrence of peripheral edema was slightly higher in the L/P/L group (1.7%, CHR 0.001) relative to the P/P/L group (1.3%, CHR 0.001) and in the L/L/L group (1.0%, CHR 0.004).

The CHR for Lubiprostone 16 mcg subjects experiencing peripheral edema during the double blind study was 0.004 and during the open label study was 0.004, meaning that the probability of a first peripheral edema event occurring between the midpoints of the double blind treatment and the open label intervals did not increase during the open label treatment.

Furthermore, for the L/L/L subjects during the open label treatment, the largest observed individual hazard rate was 0.004 at day 0 representing 100% of the total risk. Since 100% of the events occurred at day 0 prior to being dosed as part of the open label treatment period, the continuing peripheral edema at Day 0 could probably be all attributed to the prior treatment period.

The Cox regression analysis showed that subjects taking any dose of Lubiprostone were more likely to experience peripheral edema relative to placebo subjects (hazard ratio= 1.636; p=0.5390).

## Fatigue

Most of the fatigue events were considered by the investigators as unrelated to treatment (range: 0.2%-0.6%). Very few subjects withdrew due to fatigue (maximum 0.3% in SIB-0431 Treatment Phase I), and very few subjects experienced severe fatigue (maximum 0.3% in SIB-0432).

**Table 47: Summary of Important Frequencies for the Adverse Event Fatigue (All Active Doses)<sup>1</sup>**

Study or Cohort	Frequency of Fatigue (%)	Frequency of Severe Fatigue (%)	Frequency of Treatment Related Fatigue (%)	Frequency of Withdrawal due to Fatigue (%)
<b>SIB-0221</b>	0.7	0.0	0.0	0.0
<b>SIB-0431 Treatment Phase I</b>	1.3	0.0	0.3	0.3
<b>SIB-0431 RW</b>	0.7	0.0	0.0	0.0
<b>SIB-0432</b>	1.8	0.3	0.3	0.0
<b>Well-Controlled Safety Group<sup>2</sup></b>	1.4	0.1	0.2	0.1
<b>Long Term Safety Group<sup>3</sup></b>	1.7	0.0	0.6	0.0

<sup>1</sup>Study SIB-0221 included dose groups of Lubiprostone 32 mcg and 48 mcg; all other studies included only 16 mcg dose group

<sup>2</sup>includes data from SIB-0221 all doses of Lubiprostone, SIB-0431 Treatment Phase I, SIB-0432

<sup>3</sup>includes data from study SIB-05S1

Lubiprostone subjects 1.5% (CHR 0.007) at any dose had a slightly higher likelihood of experiencing fatigue than placebo subjects 0.5% (CHR 0.003). The likelihood of experiencing fatigue did not exhibit a dose relationship as the subjects that received 32 mcg of Lubiprostone did not have any fatigue events (0.000). The 16 mcg Lubiprostone subjects had a 1.5% (CHR 0.008) likelihood of experiencing fatigue while the 48 mcg Lubiprostone subjects had a 2.7% (CHR 0.001) likelihood of experiencing fatigue events.

In the randomized withdrawal treatment phase, fatigue was not observed in any of the treatment groups (CHR 0.000 for each). During the open label treatment period, the cumulative incidence rate of fatigue in the all active doses group was 1.7% (CHR 0.009). The occurrence of fatigue was almost double the frequency in the L/P/L group (3.0%, CHR 0.014) compared to both the P/P/L group (1.3%, CHR 0.006) and the L/L/L group (1.7%, CHR 0.009).

The CHR for Lubiprostone 16 mcg subjects experiencing fatigue during the double blind study was 0.008 and during the open label study was 0.009, meaning that the probability of a first fatigue event occurring between the midpoints of the double blind treatment and the open label intervals did increase by 12.5% during the open label treatment.

Furthermore, for the L/L/L subjects during the open label treatment, the largest observed individual hazard rate was 0.008 at day 0 representing 89% of the total risk. Since 89% of the events occurred at day 0 prior to being dosed as part of the open label period, the continuing fatigue at Day 0 could probably be attributed to the prior treatment period. It should also be noted that 100% of the risk of having fatigue events were observed by midpoint of the 22-28 day interval.

The Cox regression analysis showed that subjects taking any dose of Lubiprostone were more likely to experience fatigue relative to placebo subjects (hazard ratio= 3.065; p=0.1403).

## Dyspnea

Most of the dyspnea events were considered by the investigators as related to treatment (range: 0.2%-2.7%). Most of the subjects that experienced dyspnea withdrew due to dyspnea (maximum 2.1% in SIB-0221); however, only 0.2% of dyspnea events were considered severe by the investigators

**Table 48: Summary of Important Frequencies for the Adverse Event Dyspnea (All Active Doses)<sup>1</sup>**

Study or Cohort	Frequency of Dyspnea (%)	Frequency of Severe Dyspnea (%)	Frequency of Treatment Related Dyspnea (%)	Frequency of Withdrawal due to Dyspnea (%)
SIB-0221	2.7	0.0	2.7	2.1
SIB-0431 Treatment Phase I	0.3	0.0	0.0	0.3
SIB-0431 RW	0.0	0.0	0.0	0.0
SIB-0432	0.3	0.0	0.3	0.3
Well-Controlled Safety Group <sup>2</sup>	0.6	0.0	0.5	0.5
Long Term Safety Group <sup>3</sup>	0.2	0.2	0.2	0.2

<sup>1</sup>Study SIB-0221 included dose groups of Lubiprostone 32 mcg and 48 mcg; all other studies included only 16 mcg dose group

<sup>2</sup>includes data from SIB-0221 all doses of Lubiprostone, SIB-0431 Treatment Phase I, SIB-0432

<sup>3</sup>includes data from study SIB-05S1

Lubiprostone subjects 0.7% (CHR 0.004) at any dose had a slightly higher likelihood of experiencing dyspnea than placebo subjects 0.2% (CHR 0.002). The likelihood of experiencing dyspnea increased as the dose increased. The 16 mcg Lubiprostone subjects had a 0.4% (CHR 0.002) likelihood of experiencing dyspnea while the likelihood increased to 2.1% in the 32 mcg Lubiprostone subjects (CHR 0.003) and to 4.4% in the 48 mcg Lubiprostone subjects (CHR 0.045).

In the randomized withdrawal treatment phase, dyspnea was not observed in any of the treatment groups (CHR 0.000 for each). During the open label treatment period, the cumulative incidence rate of dyspnea in the all active doses group was 0.2% (CHR 0.000). The occurrence of dyspnea was not observed in both P/P/L and the L/L/L groups (0.000 for each) but was 1.3% in the L/P/L group (CHR 0.002).

The CHR for Lubiprostone 16 mcg subjects experiencing dyspnea during the double blind study was 0.002 and during the open label study was 0.000, meaning that the probability of a first dyspnea event occurring between the midpoints of the double blind treatment and the open label intervals did not increase during the open label treatment. Furthermore, only the L/P/L group during the open label treatment had non-zero hazard rates.

The Cox regression analysis showed that subjects taking any dose of Lubiprostone were more likely to experience dyspnea relative to placebo subjects (hazard ratio= 2.821; p=0.3369).

## Cardiac Disorders

Most of the cardiac disorders were considered by the investigators as unrelated to treatment except in the dose response study SIB-0221 (1.4%). There were very few subjects that discontinued due to cardiac disorders (maximum 1.4% in SIB-0221) and even fewer subjects reported cardiac disorders that were rated as severe by the investigators (maximum 0.5% in SIB-0431 Treatment Phase I).

**Table 49: Summary of Important Frequencies for the Adverse Event Cardiac Disorders (All Active Doses)<sup>1</sup>**

Study or Cohort	Frequency of Cardiac Disorders (%)	Frequency of Severe Cardiac Disorders (%)	Frequency of Treatment Related Cardiac Disorders (%)	Frequency of Withdrawal due to Cardiac Disorders (%)
SIB-0221	1.4	0.0	1.4	1.4
SIB-0431 Treatment Phase I	0.8	0.5	0.3	0.5
SIB-0431 RW	0.0	0.0	0.0	0.0
SIB-0432	1.0	0.0	0.0	0.0
Well-Controlled Safety Group <sup>2</sup>	1.0	0.2	0.3	0.4
Long Term Safety Group <sup>3</sup>	0.8	0.0	0.2	0.0

<sup>1</sup>Study SIB-0221 included dose groups of Lubiprostone 32 mcg and 48 mcg; all other studies included only 16 mcg dose group

<sup>2</sup>includes data from SIB-0221 all doses of Lubiprostone, SIB-0431 Treatment Phase I, SIB-0432

<sup>3</sup>includes data from study SIB-05S1

Lubiprostone subjects 1.0% (CHR 0.004) at any dose had a higher likelihood of experiencing cardiac disorders than placebo subjects 0.5% (CHR 0.002). The likelihood of experiencing cardiac disorders did not exhibit a dose relationship. There were no cardiac disorders observed at the highest dose of 48 mcg Lubiprostone (0.000), but the 16 mcg Lubiprostone subjects had a 1.0% (CHR 0.004) likelihood of experiencing cardiac disorders while the likelihood increased to 2.1% in the 32 mcg Lubiprostone subjects (CHR 0.003).

In the randomized withdrawal treatment phase, cardiac disorders were not observed in any of the treatment groups (CHR 0.000 for each). During the open label treatment period, the cumulative incidence rate of cardiac disorders in the all active doses group was 1.1% (CHR 0.002). The occurrence of cardiac disorders was not observed in the L/P/L group whereas the L/L/L group had 1.5% likelihood of experiencing cardiac disorders (CHR 0.004). The P/P/L group had a 0.8% likelihood (CHR 0.000) of experiencing cardiac disorders.

The CHR for Lubiprostone 16 mcg subjects experiencing cardiac disorders during the double blind study and during the open label study was 0.004, meaning that the probability of a first cardiac disorder adverse event occurring between the midpoints of the double blind treatment and the open label intervals did not increase during the open label treatment. Furthermore, the largest individual hazard rate in the L/L/L group was 0.004 at day 0 therefore 100% of the risk of cardiac events occurrence was attributed to the prior treatment period.

The Cox regression analysis showed that subjects taking any dose of Lubiprostone were more likely to experience cardiac disorders relative to placebo subjects (hazard ratio= 2.113; p=0.3387).

### 7.1.6 Laboratory Findings

As predetermined in the study protocol, blood samples for hematology, biochemistry and urine samples for urinalysis were collected at baseline, throughout the study, and at the final assessment. Clinical significance was assessed based on pre-determined clinically significant low and high values for each parameter as defined in Appendix 7 of the sponsor's Statistical Analytic Plan. In addition to the below parameters, serum pregnancy tests were performed on females of child bearing potential at screening (visit 1) and final treatment visit (week 12) and (week 16 for randomized withdrawal). Additionally, a urine pregnancy test was performed at randomization (visit 2) to rule out pregnancy. Laboratory essays were performed by an accredited central laboratory except for urine pregnancy that was performed by a local laboratory and the results were reviewed by the investigator.

#### Hematology

Hematology parameters included: White Blood Cell (WBC) count ( $\times 10^3/\mu\text{l}$ ), lymphocytes (%), Polymorphonuclear cells (%), monocytes (%), eosinophils (%), basophils (%), Absolute lymphocytes ( $\times 10^3/\mu\text{l}$ ), Absolute Polymorphonuclear ( $\times 10^3/\mu\text{l}$ ), Absolute monocytes ( $\times 10^3/\mu\text{l}$ ), Absolute basophils ( $\times 10^3/\mu\text{l}$ ), Absolute eosinophils ( $\times 10^3/\mu\text{l}$ ), hemoglobin (g/dL), hematocrit (%), RBC count ( $\times 10^6/\mu\text{l}$ ), Platelet count ( $\times 10^3/\mu\text{l}$ ), Mean Corpuscular Volume (MCV) (fL), Mean Corpuscular Hemoglobin Concentration (MCHC) (g/dL), Mean Corpuscular Hemoglobin (MCH) (pg).

- For the **well-controlled safety cohort**, the mean and median values for each parameter at baseline and final assessment for the pooled group were within clinically acceptable normal ranges. At baseline and each post-baseline time point, the observed values and the changes from baseline were similar for placebo subjects and Lubiprostone 16 mcg subjects. Dose dependent results from baseline were observed in the following cases:  
**Absolute Lymphocytes ( $\times 10^3/\mu\text{l}$ ):** at Week 8: -0.02 for Placebo, 0.00 for 16 mcg, -0.02 for 32 mcg, -0.05 for 48 mcg  
**WBC count ( $\times 10^3/\mu\text{l}$ ):** at Week 8: -0.03 for Placebo, -0.06 for 16 mcg, -0.32 for 32 mcg, -0.50 for 48 mcg  
**Polymorphonuclear cells (%):** at Week 8: 0.38 for Placebo, -0.37 for 16 mcg, -1.10 for 32 mcg, -1.56 for 48 mcg  
**Absolute Polymorphonuclear cells ( $\times 10^3/\mu\text{l}$ ):** at Week 8: -0.01 for Placebo, -0.05 for 16 mcg, -0.29 for 32 mcg, -0.46 for 48 mcg  
**Mean Corpuscular Hemoglobin (MCH) (pg):** at week 12: -0.09 for Placebo, -0.03 for 16 mcg, -0.15 for 32 mcg, -0.36 for 48 mcg  
at last value: -0.05 for Placebo, -0.02 for 16 mcg, -0.06 for 32 mcg, -0.25 for 48 mcg
- For the **well-controlled safety group**, overall, there was a shift from normal to low for **WBC count** ( $\times 10^3/\mu\text{l}$ ) in 5.7% of placebo subjects vs. 3.1% of Lubiprostone 16 mcg subjects and 6.9% of Lubiprostone 32 mcg subjects at Week 8. The shift from normal to low occurred in week 4, week 8, week 12 and at the last value time point. The proportion of subjects that demonstrated this shift at the various time points in the 16 mcg Lubiprostone treatment group (3.1% - 3.8%) was generally similar or lower than placebo group (3.5% - 5.7%). In the Lubiprostone 32 mcg group, the highest number of subjects that exhibited the shift from normal to low WBC count was 3.

- For the well-controlled safety group, there was a shift from normal to high in **hemoglobin** (g/dL) values at week 8 in 1.6% of placebo subjects vs. 2.2% of Lubiprostone 16 mcg subjects. For week 12, 1.7% of placebo subjects had a shift from normal hemoglobin to low hemoglobin while 2.9% of Lubiprostone 16 mcg subjects demonstrated that similar shift. Likewise, at the last value timepoint, 1.6% of placebo subjects and 2.2% of Lubiprostone subjects had a shift of hemoglobin from normal to low.
- The **MCV** (fL) value did exhibit a shift from normal to high in 0.8% of placebo subjects vs. 1.6% in Lubiprostone 16 mcg subjects at week 8, 0.4% vs. 2.2% at week 12 and 0.8% vs. 1.8% at last value timepoint in placebo and Lubiprostone 16 mcg subjects respectively. At the last value time point, 2.4% of subjects each in Lubiprostone 32 mcg and 48 mcg treatment dose groups exhibited a shift from normal to high MCV at the last value timepoint.
- **Monocytes** (%) shift from normal to low at week 4 in all groups as follows: 10.5% in placebo subjects vs. 10.1% Lubiprostone 16 mcg subjects, 12.9% Lubiprostone 32 mcg subjects, and 10.7% lubiprostone 48 mcg subjects. Similarly at week 8 there is a shift to low from normal in monocytes (%) as follows 16.1% placebo subjects, 11.7% Lubiprostone 16 mcg subjects, 11.1% Lubiprostone 32 mcg subjects and 20.8% Lubiprostone 48 mcg subjects. At week 12, monocytes (%) exhibit a decline from normal to low in 10.6% of placebo subjects, 11.9% of Lubiprostone 16 mcg subjects, 14.3% of Lubiprostone 32 mcg subjects and 13.0% of Lubiprostone 48 mcg subjects. At last value time point, similar decline was observed from normal to low in 10.6% of placebo subjects, 11.9% of Lubiprostone 16 mcg subjects, 14.3% of Lubiprostone 32 mcg subjects and 7.7% of Lubiprostone 48 mcg subjects.
- There was a decline in **polymorphonuclear cells** (%) in 0.3% of placebo subjects and 1.2 % of lubiprostone 16 mcg subjects at week 4 and 1.2% of placebo subjects and 1.8% of Lubiprostone 16 mcg subjects at week 8. At week 12, polymorphonuclear cells (%) exhibit a shift from low to high in 1 of 10 Lubiprostone 16 mcg subject (10%) compared to none in placebo. At the last value timepoint, 1 of 16 subjects (6.3%) in the Lubiprostone 16 mcg group exhibited a shift from low to high in the polymorphonuclear cells (%).
- At last value timepoint, **RBC count** ( $\times 10^6/\mu\text{l}$ ) displayed a shift from normal to low in 1.8% of placebo subjects vs. 3.0% of Lubiprostone 16 mcg subjects.
- The **absolute eosonophils** ( $\times 10^3/\mu\text{l}$ ), exhibited a shift from normal to high in 1.6% of placebo subjects and 3.3% of Lubiprostone 16 mcg subjects at week 12 and similarly at last value time point (1.5% placebo vs. 3.3% Lubiprostone 16 mcg).
- There was a shift from normal to high in **eosonophils** (%) in 0.8% of placebo subjects and 1.1% of Lubiprostone 16 mcg subjects, and it also occurred in last value time point (1.0% placebo vs. 1.6% Lubiprostone 16 mcg).

For the **randomized withdrawal safety group**, the mean and median values for each hematology parameter at baseline and final assessment for the P/P subjects, L/P subjects and the L/L subjects were within clinically acceptable normal ranges. At baseline, at week 16 and the last value time point, the observed values and the changes from baseline were similar among the 3 treatment groups.

- There was a shift from normal to high in **eosinophils** (%) in 2.4% of P/P subjects, 3.0% of L/P subjects and 1.9% of L/L subjects at week 16 and in 1.5% of P/P subjects, 2.9% of L/P subjects and 2.1% of L/L subjects at last value timepoint.
- The **absolute eosinophils** ( $\times 10^{-3}/\mu\text{l}$ ), exhibited a shift from normal to high in 2.4% of P/P subjects, 3.1% of L/P subjects and 3.9% of L/L subjects at week 16 and in 2.3% of P/P subjects, 3.0% of L/P subjects and 3.5% of L/L subjects at last value timepoint.
- For the randomized withdrawal safety group, there was a shift from normal to low in **hemoglobin** (g/dL) values at week 16 in 7.7% of P/P subjects, 3.5% of L/P subjects and 1.1% of L/L and a similar shift occurred at last value timepoint in 5.6% of P/P subjects, 5.7% of L/P subjects and 0.8% of L/L subjects.
- There was an increase in **lymphocytes** (%) in 1.2% of P/P subjects and 2.8% of L/L subjects at week 16 and in 2.4% of P/P subjects, 0.8% of L/P subjects and 2.8% of L/L subjects at last value time point.
- **Monocytes** (%) shifted from normal to low at week 16 in all treatment groups as follows: 9.5% in P/P subjects vs. 11.3% L/P subjects, and 13.3% L/L subjects. Similarly, at last value time point, there was a shift to low from normal in monocytes (%) as follows 6.8% P/P subjects, 10.5% L/P subjects, and 14.3% L/L subjects.
- There was a shift from normal to low in **WBC count** ( $\times 10^{-3}/\mu\text{l}$ ) in 3.9% of P/P subjects, in 2.2% of L/P subjects and 5.2% of L/L subjects at week 16.

For the **long term safety group**, the mean and median values for each hematology parameter at baseline and final assessment for the P/P/L subjects, L/P/L subjects and the L/L/L subjects were within clinically acceptable normal ranges. At baseline, weeks 4, 12, 20, 28, 36 and the last value time point, the observed values and the changes from baseline were similar among the 3 treatment groups. The L/P/L treatment group tended to show the largest magnitude of changes from baseline which could be due to the small number of subjects in that particular group (N=80). Because of the small sample size in the L/P/L enrollment group, a few outlying hematology data points could exert a larger influence.

- There was a shift from normal to high in **eosinophils** (%) in 7.1% of P/P/L subjects, 5.0% of L/P/L subjects and 3.4% of L/L/L subjects at week 36 and in 3.5% of P/P/L subjects, 3.9% of L/P/L subjects and 1.2% of L/L/L subjects at last value timepoint.
- The **absolute eosinophils** ( $\times 10^{-3}/\mu\text{l}$ ) exhibited a shift from normal to high in 3.7% of P/P/L subjects, 3.4% of L/P/L subjects and 2.6% of L/L/L subjects at week 12 and in 2.9% of P/P/L subjects, 1.3% of L/P/L subjects and 2.0% of L/L/L subjects at last value timepoint.
- For the long-term safety group, there was a shift from normal to low in **hemoglobin** (g/dL) values at week 12 in 2.9% of P/P/L subjects, 6.9% of L/P/L subjects and 1.8% of L/L/L subjects and a similar shift occurred at week 36 in 3.7% of P/P/L subjects, 10.5% of L/P/L subjects and 2.5% of L/L/L subjects. Likewise, at last value timepoint, there was a decline in hemoglobin in 1.8% of P/P/L subjects, 5.7% of L/P/L subjects and 3.8% of L/L/L subjects.



- There was an increase in **lymphocytes (%)** in 3.6% of P/P/L subjects, in 3.1% of L/P/L subjects and in 1.5% of L/L/L subjects at week 4 and in 3.7% of P/P/L subjects, 3.6% of L/P/L subjects and 1.8% of L/L/L subjects at week 12. Similarly, at last value time point, there was an increase in lymphocytes (%) in 3.0% of P/P/L subjects, in 1.4% of L/P/L subjects and in 3.7% of L/L/L subjects.
- The **MCV (fL)** value did exhibit a shift from normal to high in 7.1% of P/P/L subjects, in 16.7% of L/P/L subjects, and in 3.3% in L/L/L subjects at week 20. Similar shift trends were seen in 11.5% of P/P/L subjects, in 13.0% of L/P/L subjects, and in 11.9% in L/L/L subjects at week 28. At week 36, MCV (fL) did again shift from normal to high in 5.2% of P/P/L subjects, in 5.3% of L/P/L subjects, and in 5.1% of L/L/L subjects.
- **Monocytes (%)** shift from normal to low at week 4 in all 3 treatment groups as follows: 9.1% in P/P/L subjects vs. 3.7% in L/P/L subjects vs. 10.9% in L/L/L subjects and at week 12 as follows: 13.7% in P/P/L subjects vs. 16.7% L/P/L subjects vs. 7.8% L/L/L subjects. Similarly at week 20, there was a shift to low from normal in monocytes (%) as follows: 7.6% P/P/L subjects, 14.3% L/P/L subjects, and 5.8% L/L/L subjects and also at week 28, in 9.5% of P/P/L subjects, 20.0% in L/P/L subjects, and in 13.9% L/L/L subjects. Likewise at week 36, similar shift trends were exhibited in 6.6% of P/P/L subjects, 12.5% of L/P/L subjects, and 17.1% of L/L/L subjects, and it was also seen at last value time point in 7.3% of P/P/L subjects, 11.3% of L/P/L subjects, and 13.5% of L/L/L subjects.
- There was a decline in **absolute polymorphonuclear cells ( $\times 10^3/\mu\text{l}$ )** in 5.7% of P/P/L subjects, 3.3% of L/P/L subjects and 0.9% of L/L/L subjects at week 12 and 2.5% of P/P/L subjects, 5.0 % of L/P/L subjects and 1.1% of L/L/L subjects at week 36.
- **Polymorphonuclear cells (%)** shifted from normal to high at week 12 in all treatment groups as follows: 4.9% in P/P/L subjects vs. 3.6% L/P/L subjects vs. 5.3% L/L/L subjects. Similarly at week 36, there was a shift from normal to high in Polymorphonuclear cells (%) as follows 7.4% P/P/L subjects vs. 5.3% L/P/L subjects vs. 2.4% L/L/L subjects, and also at last value time point, similar trend existed in 5.5% P/P/L subjects vs. 6.9% L/P/L subjects vs. 2.5% L/L/L subjects.
- At week 4, **RBC count ( $\times 10^6/\mu\text{l}$ )** displayed a shift from normal to low in 5.9% of P/P/L subjects and 1.5% of L/L/L subjects. Likewise, at week 28, a similar trend was seen in 1.2% of P/P/L subjects and 7.0% of L/L/L subjects and at last value time point, in 1.8% of P/P/L subjects, 2.8 % of L/P/L subjects and 3.8% of L/L/L subjects.
- **WBC count ( $\times 10^3/\mu\text{l}$ )** shifted from normal to low at week 4 in all 3 treatment groups as follows: 8.2% in P/P/L subjects vs. 0.0% in L/P/L subjects vs. 3.0% in L/L/L subjects and at week 12 as follows: 8.7% in P/P/L subjects vs. 3.3% L/P/L subjects vs. 4.6% L/L/L subjects. Similarly at week 36, there was a shift to low from normal in WBC count ( $\times 10^3/\mu\text{l}$ ) as follows: 1.3% P/P/L subjects, 5.3% L/P/L subjects, and 1.2% L/L/L subjects.
- There was an increase in **WBC count ( $\times 10^3/\mu\text{l}$ )** in 1.5% of P/P/L subjects, 0.0% of L/P/L subjects and 6.0% of L/L/L subjects at week 4 and 1.9% of P/P/L subjects, 0.0% of L/P/L subjects and 5.5% of L/L/L subjects at week 12. Likewise, there was a similar trend at week 20 in 0.0% of P/P/L subjects, 4.0% of L/P/L subjects and 5.6% of L/L/L subjects.

### **Medical officer comments**

*The mean changes in hematology values from baseline as discussed above, are clinically acceptable for a population of subjects with irritable bowel syndrome constipation type who are otherwise generally considered healthy. Given that the majority of frequencies of newly occurring clinically significant laboratory values were very low (< 5% of subjects) for all parameters assessed in hematology, and there were no clinically meaningful sequel such as neutropenic fever secondary to declining WBCs or severe anemia, the medical officer is more confident in the safety of the recommended therapeutic dose.*

### **Biochemistry**

Biochemistry parameters included: Total cholesterol (mg/dL), triglycerides (mg/dL), glucose (mg/dL), total protein (g/dL), albumin (g/dL), alkaline phosphatase (IU/L), aspartate transaminase (AST) (IU/L), alanine transaminase (ALT) (IU/L), gamma glutamyl transferase (GGT) (IU/L), lactate dehydrogenase (IU/L), total bilirubin (mg/dL), direct bilirubin (mg/dL), blood urea nitrogen (BUN) (mg/dL), uric acid (mg/dL), creatinine (mg/dL), sodium (mmol/L), potassium (mmol/L), chloride (mmol/L), calcium (mg/dL), phosphorus (mg/dL), and magnesium (mg/dL)

- For the **well-controlled safety group**, the mean and median values for each parameter at baseline and final assessment for the pooled group were within clinically acceptable normal ranges. At baseline and each post-baseline time point, the observed values and the changes from baseline were similar for placebo subjects and Lubiprostone 16 mcg subjects. Dose dependent results from baseline were observed in the following cases:

**Alkaline phosphatase (IU/L):** at Week 4: -0.45 for Placebo, 1.28 for 16 mcg, 1.60 for 32 mcg, 3.27 for 48 mcg.

at Week 8 : 1.25 for Placebo, 1.93 for 16 mcg, 2.20 for 32 mcg, 4.07 for 48 mcg.

at Week 12 : 1.75 for Placebo, 1.53 for 16 mcg, 3.56 for 32 mcg, 5.48 for 48 mcg.

**total bilirubin (mg/dL):** at Week 4: 0.00 for Placebo, 0.00 for 16 mcg, 0.01 for 32 mcg, 0.02 for 48 mcg.

**blood urea nitrogen (BUN mg/dL):** at Week 4: -0.03 for Placebo, -0.18 for 16 mcg, -0.71 for 32 mcg, -0.79 for 48 mcg.

**Chloride (mmol/L):** at Week 12: -0.45 for Placebo, -0.10 for 16 mcg, -0.72 for 32 mcg, -0.84 for 48 mcg.

at Last Value Time point: -0.40 for Placebo, -0.11 for 16 mcg, -0.28 for 32 mcg, -0.70 for 48 mcg.

**Phosphorus (mg/dL):** at Week 12: -0.01 for Placebo, 0.03 for 16 mcg, 0.11 for 32 mcg, 0.18 for 48 mcg.

at Last Value Time point: 0.30 for Placebo, 0.04 for 16 mcg, 0.11 for 32 mcg, 0.17 for 48 mcg.

**Total Protein (g/dL):** at Week 12: -0.03 for Placebo, -0.04 for 16 mcg, -0.05 for 32 mcg, -0.12 for 48 mcg.

**Triglycerides (mg/dL):** at Week 4: -0.12 for Placebo, -2.70 for 16 mcg, -11.43 for 32 mcg, -13.55 for 48 mcg.

at week 8: -2.48 for Placebo, -1.21 for 16 mcg, -9.07 for 32 mcg, -18.96 for 48 mcg.

- For the **well-controlled safety group overall**, there was a shift from normal to high for total cholesterol (mg/dL) in 11.7% of placebo subjects vs. 13.4% of Lubiprostone 16 mcg subjects,

14.3% of Lubiprostone 32 mcg and 48 mcg subjects at Week 4. The shift from normal to high also occurred at week 8 in 16.3% of placebo subjects vs. 14.0% of Lubiprostone 16 mcg subjects, 8.3% of Lubiprostone 32 mcg subjects, and 22.2% of Lubiprostone 48 mcg subjects. Likewise at week 12, similar trends were seen in 16.7% of placebo subjects vs. 16.0% of Lubiprostone 16 mcg subjects, 11.1% of Lubiprostone 32 mcg and 48 mcg subjects. At last value time point, total cholesterol did increase from normal to high in 18.5% of placebo subjects vs. 15.8% of Lubiprostone 16 mcg subjects, 9.5% of Lubiprostone 32 mcg subjects, and 17.9% of Lubiprostone 48 mcg subjects.

- The **Phosphorus** (mg/dL) value did exhibit a shift from low to high in 20.0% of placebo subjects (1 out of 5 subjects) vs. 16.7% in Lubiprostone 16 mcg subjects (1 out of 6 subjects) at week 12 and similarly at last value time point in 12.5% of placebo subjects (1 out of 8 subjects) vs. 11.1% of Lubiprostone 16 mcg subjects (1 out of 9 subjects).
- The **Phosphorus** (mg/dL) exhibited a shift from normal to high in 5.0% of placebo subjects, 3.3% of Lubiprostone 16 mcg subjects, and 4.8% of Lubiprostone 48 mcg subjects at week 12, and likewise at last value time point in 4.1% placebo subjects vs. 3.8% Lubiprostone 16 mcg subjects, and 5.3% of Lubiprostone 48 mcg subjects.
- There was a shift from high to low in **potassium** (mmol/L) in 50% of Lubiprostone 16 mcg subjects (1 out of 2 subjects) at week 12 and a similar shift in 33.3% of Lubiprostone 16 mcg subjects (1 out of 3 subjects) at last value timepoint.
- There was an increase in **glucose** (mg/dL) in 19.4% of placebo subjects, 18.8% of Lubiprostone 16 mcg subjects, 21.4% of Lubiprostone 32 mcg subjects and 4.2% of Lubiprostone 48 mcg subjects at week 4. Likewise similar trend was seen at week 8 in 18.6% of placebo subjects, 19.8% of

Lubiprostone 16 mcg subjects, 12.0% of Lubiprostone 32 mcg subjects and 5.3% of Lubiprostone 48 mcg subjects. At week 12, glucose (mg/dL) did also shift from normal to high in 20.2% of placebo subjects, 19.1% of Lubiprostone 16 mcg subjects and 14.3% of Lubiprostone 32 mcg subjects. A similar shift occurred at last value time point in 18.0% of placebo subjects, 17.9% of Lubiprostone 16 mcg subjects, 10.5% of Lubiprostone 32 mcg subjects and 2.9% of Lubiprostone 48 mcg subjects.

- There was a shift from normal to high for **triglycerides** (mg/dL) in 12.2% of placebo subjects vs. 17.2% of Lubiprostone 16 mcg subjects, 23.8% of Lubiprostone 32 mcg subjects and 4.8% of Lubiprostone 48 mcg subjects at Week 4. The shift from normal to high also occurred at week 8 in 11.5% of placebo subjects vs. 13.8% of Lubiprostone 16 mcg subjects, 17.6% of Lubiprostone 32 mcg subjects, and 6.3% of Lubiprostone 48 mcg subjects. Likewise at week 12, similar trends were seen in 14.1% of placebo subjects vs. 15.6% of Lubiprostone 16 mcg subjects, 6.7% of Lubiprostone 32 mcg subjects and 20.0% of Lubiprostone 48 mcg subjects. At last value time point, triglycerides (mg/dL) did increase from normal to high in 14.3% of placebo subjects vs. 15.4% of Lubiprostone 16 mcg subjects, 16.7% of Lubiprostone 32 mcg subjects, and 14.3% of Lubiprostone 48 mcg subjects.

For the **randomized withdrawal safety group**, the mean and median values for each biochemistry parameter at baseline and final assessment for the P/P, L/P and the L/L subjects were within clinically acceptable normal ranges. At baseline, at week 16 and the last value time point, the observed values and the changes from baseline were similar among the 3 treatment groups.

- There was a shift from normal to high in **ALT (SGPT)** (IU/L) in 7.3% of P/P subjects, 6.2% of L/P subjects and 1.9% of L/L subjects at week 16 and in 6.4% of P/P subjects, 5.3% of L/P subjects and 1.4% of L/L subjects at last value timepoint.
- The **AST (SGOT)** (IU/L) exhibited a shift from normal to high in 1.2% of P/P subjects, 5.9% of L/P subjects and 1.8% of L/L subjects at week 16 and in 2.3% of P/P subjects, 5.1% of L/P subjects and 1.3% of L/L subjects at last value timepoint.
- **Total Cholesterol** (mg/dL) shifted from normal to high at week 16 in all treatment groups as follows: 16.4% in P/P subjects vs. 11.3% L/P subjects, and 21.9% L/L subjects. Similarly at last value time point, there was a shift to high from normal in total cholesterol (mg/dL) as follows 19.3% P/P subjects, 12.5% L/P subjects, and 19.8% L/L subjects.
- There was an increase in **gamma-glutamyl transpeptidase** (IU/L) in 6.2% of P/P subjects, 2.0% of L/P subjects and 1.9% of L/L subjects at week 16 and in 4.7% of P/P subjects, 1.4% of L/P subjects and 2.8% of L/L subjects at last value time point.
- **Glucose** (mg/dL) shifted from normal to high at week 16 in all treatment groups as follows: 7.4% in P/P subjects vs. 22.1% L/P subjects, and 17.3% L/L subjects. Similarly, at last value time point, there was a shift to high from normal in glucose (mg/dL) as follows 9.7% P/P subjects, 22.6% L/P subjects, and 16.4% L/L subjects. At last value time point, there was also a shift from high to low in 1 treatment group, 5.9% of L/P subjects (2 out of 34 subjects).
- There was a shift from normal to high in **triglycerides** (mg/dL) values at week 16 in 19.0% of P/P subjects, 19.1% of L/P subjects and 18.6% of L/L subjects. A similar shift occurred at last value timepoint in 15.7% of P/P subjects, 19.6% of L/P subjects and 16.8% of L/L subjects.

For the **long-term safety group**, the mean and median values for each biochemistry parameter at baseline and final assessment for the P/P/L, L/P/L, and the L/L/L subjects were within clinically acceptable normal ranges. At baseline, weeks 4, 12, 20, 28, 36 and the last value time point, the observed values and the changes from baseline were similar among the 3 treatment groups. The L/P/L treatment group tended to show the largest magnitude of changes from baseline which could be due to the small number of subjects in that particular group (N=80). Because of the small sample size in the L/P/L enrollment group, a few outlying biochemistry data points could exert larger influence. Triglyceride (mg/dL) levels demonstrated the largest change from baseline in all enrollment groups especially in the L/P/L group

- There was a shift from normal to high in **ALT (SGPT)** (IU/L) in 5.1% of P/P/L subjects, 2.8% of L/P/L subjects and 3.4% of L/L/L subjects at week 4 and in 3.3% of P/P/L subjects, 8.0% of L/P/L subjects and 1.0% of L/L/L subjects at week 20.

- **Total Cholesterol** (mg/dL) shifted from normal to high at week 4 in all treatment groups as follows: 16.7% in P/P/L subjects vs. 28.6% L/P/L subjects, and 21.0% L/L/L subjects. Similarly at week 12, there was a shift to high from normal in total cholesterol (mg/dL) as follows 11.6% in P/P/L subjects vs. 15.0% L/P/L subjects, and 17.6% L/L/L subjects. At week 20, a similar trend was seen in 15.0% in P/P/L subjects vs. 18.8% L/P/L subjects, and 17.3% L/L/L subjects. A similar shift occurred at week 28 in 19.2% P/P/L subjects vs. 18.8% L/P/L subjects, and 21.3% L/L/L subjects and at week 36 in 11.3% P/P/L subjects vs. 15.4% L/P/L subjects, and 21.7% L/L/L subjects. At last value timepoint, total cholesterol (mg/dL) increased in 13.5% of P/P/L subjects, 19.6% of L/P/L subjects and 21.1% of L/L/L subjects.
- The **gamma glutamyl transferase** (IU/L) exhibited a shift from normal to high in 2.9% of P/P/L subjects and 5.5% of L/L/L subjects at week 4 and in 1.2% of P/P/L subjects, 8.3% of L/P/L subjects and 2.2% of L/L/L subjects at week 28. Similar trend was seen at week 36 in 1.2% of P/P/L subjects, 5.0% of L/P/L subjects and 2.3% of L/L/L subjects.
- There was a shift from normal to high in **Phosphorus** (mg/dL) values at week 4 in 4.4% of P/P/L subjects, 5.4% of L/P/L subjects and 3.5% of L/L/L subjects and a similar shift occurred at week 28 in 7.2% of P/P/L subjects, 12.0% of L/P/L subjects and 3.4% of L/L/L subjects. At week 36, there was also an increase in phosphorus (mg/dL) in 4.7% of P/P/L subjects, 9.5% of L/P/L subjects and 1.2% of L/L/L subjects.
- A decrease in **potassium** (mmol/L) was seen in 1.8% of P/P/L subjects, 6.3% of L/P/L subjects and 5.7% of L/L/L subjects at week 12 and in 1.2% of P/P/L subjects and 6.6% of L/L/L subjects at week 28. Similar trend was seen at last value timepoint in 1.2% of P/P/L subjects, 5.1% of L/P/L subjects and 2.0% of L/L/L subjects.
- **Glucose** (mg/dL) shifted from normal to high at week 4 in all treatment groups as follows: 18.9% in P/P/L subjects vs. 20.0% L/P/L subjects, and 14.8% L/L/L subjects. Similarly at week 12, there was a shift to high from normal in glucose (mg/dL) as follows 10.2% P/P/L subjects, 14.3% L/P/L subjects, and 16.0% L/L/L subjects. At week 20, there was a similar trend in 12.2% of P/P/L subjects, 20.0% L/P/L subjects, and 21.5% L/L/L subjects, and also at week 28 in 12.9% of P/P/L subjects, 27.8% of L/P/L subjects, and 25.4% of L/L/L subjects. The increase in glucose (mg/dL) was also seen at week 36 in 17.3% of P/P/L subjects, 28.6% of L/P/L subjects, and 21.1% of L/L/L subjects and at last value time point in 16.7% of P/P/L subjects, in 21.8% of L/P/L subjects, and in 17.7% of L/L/L subjects. At week 36, there was a shift in glucose (mg/dL) from normal to low in 4.0% of P/P/L subjects and 14.3% in L/P/L subjects.
- There was a shift from normal to low in **sodium** (mmol/L) values at week 20 in 3.3% of P/P/L subjects and 7.4% of L/P/L subjects.
- **Triglycerides** (mg/dL) shifted from normal to high at week 4 in all treatment groups as follows: 10.3% in P/P/L subjects vs. 16.0% L/P/L and L/L/L subjects each. Similarly at week 12, there was a shift to high from normal in triglycerides (mg/dL) as follows 9.0% P/P/L subjects, 21.7% L/P/L subjects, and 13.4% L/L/L subjects. At week 20, there was a similar trend in 13.2% of P/P/L subjects, 17.6% of L/P/L subjects, and 13.8% L/L/L subjects, and also at week 28 in 11.7% of P/P/L subjects, 42.1% of L/P/L subjects, and 15.3% of L/L/L subjects. The increase in triglycerides (mg/dL) was also seen at week 36 in 6.6% of P/P/L subjects, 37.5% of L/P/L

subjects, and 18.6% of L/L/L subjects and at last value time point in 13.0% of P/P/L subjects, in 25.5% of L/P/L subjects, and in 13.5% of L/L/L subjects.

### **Medical officer comments**

*Most of the biochemistry laboratory values are clinically acceptable for a population of subjects with irritable bowel syndrome constipation type who are otherwise generally considered healthy. With the exception of total cholesterol, glucose and triglycerides which are difficult to interpret due to lack of dietary restrictions and non-fasting conditions during blood draws, the frequencies of newly occurring clinically significant laboratory values were very low (< 5% of subjects) for most parameters. Phosphorus and potassium were the only electrolytes that exhibited shifts in both the well-controlled safety and the long term safety groups. Phosphorus showed an increase from low and normal baselines whereas potassium demonstrated a decrease from normal or high baselines. It is difficult to infer any conclusions regarding changes in phosphorus since there were no concurrent changes that were exhibited in calcium or albumin in both the well-controlled safety and the long term safety groups. A shift to low potassium in isolation without an increase in BUN, Creatinine or changes in sodium and chloride could be attributed to multiple factors such as dietary or possibly diuretic use or other concomitant medications. When compared to the placebo cohort in the well-controlled safety group, there were similar changes from baseline that were identified in subjects treated with the 3 different doses of Lubiprostone and placebo. Therefore, no dose dependent decreases in potassium were observed in the well-controlled safety group. The medical officer is generally confident in the biochemistry laboratory safety data of the recommended therapeutic dose.*

### **Urinalysis**

Urinalysis parameters included: specific gravity and urine pH

For the **well-controlled safety group**, mean values for both specific gravity and urine pH were similar between placebo subjects and Lubiprostone 16 mcg subjects. There were also no obvious differences across the Lubiprostone dose groups. The differences that were observed between placebo and Lubiprostone 16 mcg and across the Lubiprostone dose groups in the analyses of the change from baseline are as follows:

- There was a shift from normal to high pH in 2.9% of placebo subjects, 2.1% of Lubiprostone 16 mcg subjects, 3.6% of Lubiprostone 32 mcg subjects and 10.0% of Lubiprostone 48 mcg subjects at week 4 and in 1.1% of placebo subjects, 2.3% of Lubiprostone 16 mcg subjects, 8.0% of Lubiprostone 32 mcg subjects and 4.2% of Lubiprostone 48 mcg subjects at week 8. Likewise, similar trends were seen in 2.0% of placebo subjects, 1.4% of Lubiprostone 16 mcg subjects, 5.0% of Lubiprostone 32 mcg subjects and 18.2% of Lubiprostone 48 mcg subjects at week 12. At last value timepoint, pH showed an increase in 2.4% of placebo subjects, 1.8% of Lubiprostone 16 mcg subjects, 5.1% of Lubiprostone 32 mcg subjects and 15.0% of Lubiprostone 48 mcg subjects.

For the **randomized withdrawal safety group**, the mean and median values for pH and specific gravity at baseline, week 16 and last value timepoint for the P/P subjects, L/P subjects and the L/L subjects were within clinically acceptable normal ranges. At baseline, at week 16 and the last value time point, the observed values and the changes from baseline were similar among the 3 treatment groups.

- The pH values exhibited the largest magnitude of change from normal to high in the P/P subjects at 3.8% (5 out of 133 subjects) at last value time point. Otherwise, most of the pH values showed minimal shifts in all 3 treatment groups. The specific gravity at all timepoints did not reveal any shifts in P/P, L/P, or L/L subjects.

For the **long term safety group**, there were no time-dependent trends for either parameter, with the mean pH being in the range of 6.42 to 6.47 at all time points. The specific gravity remained unchanged at a value of 1.02 at all timepoints in all the enrollment groups.

- pH exhibited a shift from normal to high at week 20 in all treatment groups as follows: 5.3% of P/P/L subjects and 3.6% L/P/L subjects. Specific gravity did not demonstrate any shifts throughout the entire 36 weeks of treatment period in any of the enrollment groups.

### **Medical officer comments**

*The urinalysis data is clinically acceptable for a population of subjects with irritable bowel syndrome constipation type who are otherwise healthy. The changes in pH that were noted fall within the acceptable normal variation of 4.6-8.0 with an average of 6.0. The specific gravity values that were observed in the well-controlled safety group, randomized withdrawal safety group and the long term safety group also reflect the normal variation in a healthy human population (SG: 1.003-1.030).*

### **7.1.7 Vital Signs**

Vital sign parameters included: heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), temperature, respiration rate, weight and body mass index (BMI).

For the **well-controlled safety group**, there was a statistically significant difference across the groups in the mean change from baseline in SBP at the last value timepoint (0.97 mmHg for placebo vs. -0.90 mmHg for Lubiprostone 16 mcg vs. -4.02 mmHg for Lubiprostone 32 mcg vs. 0.11 mmHg for Lubiprostone 48 mcg,  $p=0.046$ ). There were no other statistically significant results. For BMI (0.15 for placebo vs. 0.05 for Lubiprostone 16 mcg vs. 0.08 for Lubiprostone 32 mcg vs. 0.16 for Lubiprostone 48 mcg) and weight (0.95 for placebo vs. 0.32 for Lubiprostone 16 mcg vs. 0.51 for Lubiprostone 32 mcg vs. 0.87 for Lubiprostone 48 mcg), the mean changes from baseline at the last value timepoint increased as the Lubiprostone dose increased. The mean decrease in DBP at week 4 became larger as the Lubiprostone dose increased (-0.07 mmHg for Lubiprostone 16 mcg vs. -2.23 mmHg for Lubiprostone 32 mcg vs. -2.52 mmHg for Lubiprostone 48 mcg), but a similar trend was not seen for SBP. For body temperature at week 12, there was a mean decrease from baseline in all treatment groups including placebo, but there was no dose dependent trend observed.

For the **randomized withdrawal safety group**, the mean values for all vital signs remained essentially unchanged at week 16 and at last value time point. The mean changes from baseline were very small and were not consistently in the same direction nor did they increase over time.

For the **long term safety group**, there was minimal difference observed between the three enrollment groups throughout the 36 weeks of treatment period for any vital sign measure. The mean changes from

baseline were very small in the P/P/L, L/P/L and the L/L/L subjects at all post-baseline value time points.

### **Medical officer comments**

*The vital signs safety data appears clinically acceptable for a population of subjects with irritable bowel syndrome constipation type who are otherwise considered generally healthy. When comparing the safety data of the recommended therapeutic dose of Lubiprostone 16 mcg versus placebo, there does not appear to be an increased risk to subjects of developing vital sign or weight abnormalities when the study drug is administered for up to 52 weeks.*

### **7.1.8 Physical Examinations**

As pre-determined in the study protocol, physical examinations were performed on all subjects at baseline, throughout the study, and at final assessment. Physical examination parameters included assessment of the following body systems: abdominal, gastrointestinal, cardiovascular, chest, other, other/specify, EENT, Head/Neck, lymphatic, musculoskeletal, neurological, respiratory, and skin/extremities.

For the **well-controlled safety** cohort, across all body systems with a normal baseline evaluation, the frequencies of most shifts from normal to abnormal in the placebo and Lubiprostone 16 mcg groups were less than 5% except in the body system abdominal and musculoskeletal. There were 9.1% of placebo subjects and 7.5% of Lubiprostone 32 mcg subjects that had a shift from normal baseline abdominal body system to abnormal at week 4 and last value time point, respectively. In the musculoskeletal body system, 5.1% of placebo subjects had a shift from normal baseline to abnormal at week 4. The body system with the highest frequency of shifts from normal to abnormal was the abdominal and gastrointestinal system, for which a range of 2.7% to 9.1% of placebo subjects and a range of 2.8% to 3.5% of Lubiprostone 16 mcg subjects experienced a shift from normal to abnormal at weeks 4, 12 and last value time point. The changes in abdominal and gastrointestinal body system from normal baseline to abnormal at post baseline time points did not reveal a dose dependent trend. In fact, no subjects in the Lubiprostone 48 mcg group had a shift from normal baseline to abnormal at weeks 4, 12 and last value timepoint in the abdominal and gastrointestinal body system. In placebo and all doses of Lubiprostone in the abdominal and gastrointestinal body system, the proportion of subjects with shifts from abnormal baseline to normal at the post-baseline time points exceeded the shifts from normal to abnormal.

For the **long term safety** cohort, across most body systems, the frequency of shifts from normal to abnormal remained essentially unchanged over 36 weeks and at final assessment. With the exception of 5.1% of L/L/L subjects (5 out of 99 subjects) at week 20, in no body system did the frequency of shifts from normal to abnormal exceed 5% of subjects with normal baseline evaluations. The highest proportion of shifts from normal to abnormal at each time point was in the abdominal, EENT and musculoskeletal body system.



### **Medical officer comments**

*The physical examination data, when considered as a whole, are clinically acceptable for a population of subjects with irritable bowel syndrome constipation type who are otherwise healthy. There does not appear to be an increased risk to subjects of developing any clinically significant abnormalities in any body system, either during extended treatment with Lubiprostone or when comparing the safety of the recommended therapeutic dose of Lubiprostone (16 mcg) to placebo.*

#### **7.1.9 Electrocardiogram (ECGs)**

##### **7.1.9.1 Overview of ECG Testing in the Clinical Program**

The sponsor performed a phase I and a phase II study to evaluate the effects of Lubiprostone on ECG parameters with the initial NDA approval. No further studies were conducted to specifically evaluate ECG parameters with this supplemental NDA. The sponsor, however, performed ECGs in the dose response study SIB-0221.

The primary objective of the SIB-0221 study was to evaluate three doses of Lubiprostone for efficacy, tolerability and safety. The study was multi-center double blind placebo controlled that evaluated 16 mcg, 32 mcg and 48 mcg doses of Lubiprostone all administered as bid doses of 8 mcg, 16 mcg and 24 mcg. During this study, the investigators also obtained baseline ECGs at randomization (visit 2) and another ECG at week 12, end of treatment office visit. Abnormal ECGs were to be submitted to a central reader for additional review and analysis. Study SIB-0221 consisted of 194 subjects that were divided into treatment groups as follows: 48 Placebo subjects, 52 8 mcg bid Lubiprostone subjects, 49 32 mcg bid Lubiprostone subjects, and 45 24 mcg bid Lubiprostone subjects.

##### **ECG Analysis Plan**

ECG interval changes were based on mean changes from baseline, where baseline was the initial ECG obtained at randomization (visit 2).

**Heart Rate:** The baseline heart rate for all Lubiprostone doses (range: 66.08-68.71) was similar to placebo (66.35),  $p=0.576$ . The change from baseline in heart rate was greatest in the Lubiprostone 48 mcg group. There were minimal increases noted in the placebo group (2.17 bpm) and the active doses group (1.05 bpm increase in the Lubiprostone 32 mcg vs. a 3.16 bpm change in the Lubiprostone 48 mcg); however, the Lubiprostone 16 mcg dose revealed a decrease in heart rate (-0.98 bpm).

**PR and QRS:** For the PR interval, there was no mean change from baseline in all the Lubiprostone treatment groups and placebo. There was a 0.02 sec increase in the QRS duration in the Lubiprostone 16 mcg dose compared to baseline. No other doses of Lubiprostone exhibited any change in QRS duration.

**QT and QT<sub>c</sub>:** There was no change in the QT and QT<sub>c</sub> interval from baseline in any of the Lubiprostone treatment groups or placebo.

### **Medical officer comments**

*The study SIB-0221 was limited not only due to the inadequate number of patients in each dose group, but it was not designed specifically to assess the effects of Lubiprostone on ECG parameters. In addition, the evaluation of effects of Lubiprostone on ECG parameters was limited by single ECG analyses at baseline and end of treatment time points. Lubiprostone at the 48 mcg dose may cause a slight increase in heart rate relative to placebo over a 12 week treatment period. It is difficult to*

*establish a dose relationship in terms of heart rate effect since the number of subjects evaluated in each dose group is small and the heart rate did not seem to increase with dose escalation in study SIB-0221. Despite the limitations, Lubiprostone at doses of 16 mcg, 32 mcg, and 48 mcg per day, for 12 weeks, as studied in this protocol shows no evidence of any effect on cardiac conduction (PR and QRS duration) or cardiac repolarization (QT/QTc interval). Furthermore, Lubiprostone has already undergone a phase I study that evaluated cardiac safety in healthy volunteers. In that particular study, a 24 mcg dose and 144 mcg dose of Lubiprostone were studied. The only notable finding was a minor increase in heart rate and a QTcI change of +20 ms from baseline for Lubiprostone at 144 mcg dose. Based on the above data, at the 8 mcg bid dose, Lubiprostone does not seem to effect cardiac repolarization.*

#### **7.1.10 Immunogenicity**

The sponsor did not provide any clinical or adverse event data regarding immunogenicity in this supplemental New Drug Application

#### **7.1.11 Human Carcinogenicity**

The sponsor did not provide any clinical or adverse event data regarding human carcinogenicity in this application.

#### **7.1.12 Special Safety Studies**

Since Lubiprostone did not demonstrate a tendency to result in life-threatening side effects in the preclinical and clinical studies, no specific monitoring or testing was required during the study that would be considered outside standard of care for a clinical trial with the exception of bilateral hand X-rays. Bilateral hand X-rays were performed in the phase II study SIB-0221. The baseline bilateral hand X-rays were to be completed within 7 days of randomization (visit 2), and another set of hand X-rays were to be completed within 7 days prior to visit 6 which occurred at week 12 (final treatment visit). The radiologist read the X-rays and determined the clinical significance. Abnormal X rays indicating a change could be submitted for review by a centralized reader. The Agency had prior concerns that Lubiprostone treatment may have deleterious effect on bone density.

Tables 50 and 51 below summarize the shifts from baseline to final assessment in right and left Hand X-ray results as performed in study SIB-0221. There were no subjects that had right hand X-ray findings that shifted from normal to clinically significant abnormal. Three subjects each in the placebo group and the Lubiprostone 32 mcg and 48 mcg group had a shift from normal to abnormal but were not clinically significant. Two subjects in the Lubiprostone 16 mcg group had a shift from normal to abnormal but clinically not significant. One subject in the Lubiprostone 48 mcg group shifted from abnormal but clinically not significant at baseline to abnormal with clinical significance at final assessment. According to the sponsor, this particular subject experienced progression to clinically significant abnormality of an existing condition in the right hand that was already deemed abnormal at baseline. One subject in the Lubiprostone 16 mcg group whose X-rays were noted to be abnormal and clinically significant at baseline remained at abnormal with clinical significance at final assessment.

**Table 50: Shift Table of Right Hand X-ray Results for Study SIB-0221**

Parameter	Baseline	Final Assessment	Placebo N=48 (%)	Lubiprostone 16mcg N=52 (%)	Lubiprostone 32mcg N=49 (%)	Lubiprostone 48mcg N=45 (%)
<b>Right Hand</b>	Normal	Normal	30/34 (88.2)	27/35 (77.1)	24/31 (77.4)	28/36 (77.8)
		Abnormal 1*	3/34 (8.8)	2/35 (5.7)	3/31 (9.7)	3/36 (8.3)
		Abnormal 2**	0/34 (0.0)	0/35 (0.0)	0/31 (0.0)	0/36 (0.0)
		Missing	1/34 (2.9)	3/35 (8.6)	1/31 (3.2)	3/36 (8.3)
	Abnormal 1*	Normal	3/12 (25.0)	2/13 (15.4)	4/18 (22.2)	1/8 (12.5)
		Abnormal 1*	9/12 (75.0)	10/13 (76.9)	10/18 (55.6)	5/8 (62.5)
		Abnormal 2**	0/12 (0.0)	0/13 (0.0)	0/18 (0.0)	1/8 (12.5)
		Missing	0/12 (0.0)	1/13 (7.7)	1/18 (5.6)	1/8 (12.5)
	Abnormal 2**	Normal	0/0 (0.0)	0/1 (0.0)	0/0 (0.0)	0/0 (0.0)
		Abnormal 1*	0/0 (0.0)	0/1 (0.0)	0/0 (0.0)	0/0 (0.0)
		Abnormal 2**	0/0 (0.0)	1/1 (100)	0/0 (0.0)	0/0 (0.0)
		Missing	0/0 (0.0)	0/1 (0.0)	0/0 (0.0)	0/0 (0.0)
	Missing	Normal	1/1 (100)	0/1 (0.0)	0/0 (0.0)	0/1 (0.0)
		Abnormal 1*	0/1 (0.0)	0/1 (0.0)	0/0 (0.0)	0/1 (0.0)
		Abnormal 2**	0/1 (0.0)	0/1 (0.0)	0/0 (0.0)	0/1 (0.0)
		Missing	0/1 (0.0)	1/1 (100)	0/0 (0.0)	1/1 (100)

Reviewer's Table modified from Table 1.4.4, Integrated Summary of Safety, page 75 of 126

Abnormal 1\* = Abnormal and not clinically significant

Abnormal 2\*\* = Abnormal and clinically significant

There were no subjects that had left hand X-ray findings that shifted from normal at baseline to clinically significant abnormal at week 12. The largest number of subjects that had a shift from normal to abnormal but not clinically significant occurred in the Lubiprostone 16 mcg (3 subjects, 7.7%). Both placebo (6.5%) and Lubiprostone 48 mcg (5.9%) had 2 subjects that had a shift from normal at baseline to abnormal at week 12 but were not considered clinically significant. Three subjects in the Lubiprostone 16 mcg group had a shift from normal to abnormal but clinically not significant. One subject (11.1%) in the Lubiprostone 48 mcg group shifted from abnormal but clinically not significant at baseline to abnormal with clinical significance at final assessment (experienced a fracture of the left third finger), and one subject in the Lubiprostone 16 mcg group remained at abnormal with clinical significance at final assessment.

**Table 51: Shift Table of Left Hand X-ray Results for Study SIB-0221**

Parameter	Baseline	Final Assessment	Placebo N=48 (%)	Lubiprostone 16mcg N=52 (%)	Lubiprostone 32mcg N=49 (%)	Lubiprostone 48mcg N=45 (%)
Left Hand	Normal	Normal	28/31 (90.3)	30/39 (76.9)	25/29 (86.2)	28/34 (82.4)
		Abnormal 1 <sup>*</sup>	2/31 (6.5)	3/39 (7.7)	1/29 (3.4)	2/34 (5.9)
		Abnormal 2 <sup>**</sup>	0/31 (0.0)	0/39 (0.0)	0/29 (0.0)	0/34 (0.0)
		Missing	1/31 (3.2)	3/39 (7.7)	0/29 (0.0)	3/34 (8.8)
	Abnormal 1 <sup>*</sup>	Normal	2/15 (13.3)	1/9 (11.1)	4/20 (20.0)	0/9 (0.0)
		Abnormal 1 <sup>*</sup>	13/15 (86.7)	7/9 (77.8)	12/20 (60.0)	7/9 (77.8)
		Abnormal 2 <sup>**</sup>	0/15 (0.0)	0/9 (0.0)	0/20 (0.0)	1/9 (11.1)
		Missing	0/15 (0.0)	1/9 (11.1)	1/20 (5.0)	1/9 (11.1)
	Abnormal 2 <sup>**</sup>	Normal	0/0 (0.0)	0/1 (0.0)	0/0 (0.0)	0/1 (0.0)
		Abnormal 1 <sup>*</sup>	0/0 (0.0)	0/1 (0.0)	0/0 (0.0)	0/1 (0.0)
		Abnormal 2 <sup>**</sup>	0/0 (0.0)	1/1 (100)	0/0 (0.0)	0/1 (0.0)
		Missing	0/0 (0.0)	0/1 (0.0)	0/0 (0.0)	0/1 (0.0)
	Missing	Normal	1/1 (100)	0/1 (0.0)	0/0 (0.0)	0/1 (0.0)
		Abnormal 1 <sup>*</sup>	0/1 (0.0)	0/1 (0.0)	0/0 (0.0)	0/1 (0.0)
		Abnormal 2 <sup>**</sup>	0/1 (0.0)	0/1 (0.0)	0/0 (0.0)	0/1 (0.0)
		Missing	0/1 (0.0)	1/1 (100)	0/0 (0.0)	1/1 (100)

Reviewer's Table modified from Table 1.4.4, Integrated Summary of Safety, page 75 of 126

Abnormal 1<sup>\*</sup> = Abnormal and not clinically significant

Abnormal 2<sup>\*\*</sup> = Abnormal and clinically significant

### **Medical officer comments**

*The shifts from normal to abnormal in both right and left hand X-rays were mostly less than 10%. The shifts from abnormal to normal were proportionally greater than the shifts from normal to abnormal. Although a formal lumbar spine and hip bone densitometry analysis would provide a more accurate reflection of lubiprostone's effect on bone metabolism, given the above analyses, there does not appear to be a negative impact on bone density as measured via hand X-rays. The timing between the completion of the baseline hand X-rays and the follow-up hand X-rays was only three months which would make it difficult to accurately evaluate long term effects of Lubiprostone on bone density.*

### **7.1.13 Withdrawal Phenomena and/or Abuse Potential**

Subject safety under conditions of Lubiprostone withdrawal was studied during the Randomized Withdrawal (RW) or Treatment Phase II period of study SIB-0431. The 436 subjects that completed Treatment Phase I of SIB-0431 were randomized prior to the start of Treatment Phase I in a 1:1:1 ratio to three different treatment groups. The 139 subjects that took placebo in treatment phase I continued to receive placebo in the randomized withdrawal study (P/P). The 297 subjects that received Lubiprostone in treatment phase I were divided into 2 groups in the randomized withdrawal as follows: 146 of the subjects were switched to receive placebo treatment (L/P) and 151 subjects continued to receive Lubiprostone treatment (L/L). The 146 subjects that were initially receiving Lubiprostone in Treatment

Phase I and now receiving placebo in Treatment Phase II (L/P) provided the safety data corresponding to the withdrawal of Lubiprostone 16 mcg. When comparing the frequency of adverse events in the RW period among the treatment groups, a lower number of L/P subjects (29.9%) reported at least 1 adverse event compared to 37.1% in the Lubiprostone/Lubiprostone (L/L) group and 38.4% in the Placebo/Placebo (P/P) group. Same number of subjects in the P/P and the L/P group (4 each) reported at least one severe adverse event whereas 3 subjects in the L/L group reported severe adverse events. Although there were similar frequencies of treatment-related adverse events reported in the P/P (8.7%) and the L/P (8.2%) subjects, there was a greater number of treatment-related adverse events reported in subjects that continued to take Lubiprostone treatment (11.9%) during the RW. There were no deaths and no serious adverse events reported in Treatment Phase II by any of the treatment groups. One subject in the L/L group (0.7%) discontinued due to abdominal distension.

Upper respiratory infection (3.4% vs. 2.2% vs. 2.0%, respectively), urinary tract infection (3.4% vs. 0.7% vs. 1.3%, respectively), bronchitis (2.7% vs. 0.0% vs. 0.7%, respectively) and neck pain (2.0% vs. 0.0% vs. 0.0%, respectively) occurred more often in the L/P group than the P/P and the L/L group. Sinusitis had a higher frequency in the L/L group (4.0%) than the L/P group (2.0%) and the P/P group (1.4%); similarly, abdominal pain had a higher frequency in the L/L group (2.6%) compared to the L/P (2.0%) and the P/P (2.2%) group. Flatulence was more frequent in the P/P subjects (4.3%) than the L/P (2.7%) and the L/L (2.0%) subjects.

Severe adverse events were reported in similar frequency among the P/P (2.9%) vs. L/P (2.7%) vs. L/L (2.0%) subjects. Abdominal Pain (1 in L/P and 1 in L/L) was the only severe adverse event reported by more than 1 subject.

The L/L group (11.9%) exhibited more treatment-related adverse events compared to the P/P (8.7%) and the L/P (8.2%) group even though the differences were not statistically significant. In the SOC, the highest frequency of treatment-related adverse events was in the gastrointestinal disorders (6.5% P/P vs. 5.4% L/P vs. 8.6% L/L). Nausea and diarrhea were the most frequently reported treatment-related adverse events in the L/L group (2.6% and 2.0%, respectively) compared to the L/P (1.4% and 0.0%, respectively) and the P/P (1.4% each) groups.

The rebound phenomenon following withdrawal of Lubiprostone treatment was also examined by evaluating the frequency of AEs reported during the seven days immediately following a subject's last dose of study drug. Based on Lubiprostone's short residence in the body (specifically elimination half life is approximately 1-2 hours, with metabolites in 7-8 hours), a 7 day window after the last dose of study drug represents approximately 84-168 half lives. The sponsor compiled a summary of adverse events that were reported within 7 days after the last dose of the study drug. These AEs were consistent with the overall AE profile of lubiprostone and do not constitute new safety concerns that arise following withdrawal from treatment with Lubiprostone. In addition to the aforementioned RW study, the sponsor noted that the pharmacological profile of Lubiprostone is not consistent with a drug that would have the potential for abuse or drug dependence.

### **Medical officer comments**

*The sponsor performed a thorough randomized withdrawal analysis. Considering the lack of significant differences in frequency of AEs between the L/P and the P/P subjects, and the lack of newly occurring adverse events in the Lubiprostone subjects when switched to placebo in the RW study, there appears to be no obvious safety risks in subjects following immediate cessation or after seven days of withdrawal from Lubiprostone treatment.*

#### **7.1.14 Human Reproduction and Pregnancy Data**

Studies of Lubiprostone in pregnant or lactating women were not conducted for this supplemental NDA application. Pregnant women were excluded from all clinical trials of Lubiprostone. Any women who became pregnant during a study were immediately discontinued from study participation. Two pregnancies were reported during the clinical development of Lubiprostone under IND # 66,529.

**Subject SIB-0432-207-007** became pregnant while taking Lubiprostone as part of the study. Her last menstrual period before the pregnancy was on December 9, 2005 (Study Day -27). A gynecological exam dated (b) (6) revealed the pregnancy, and subject was immediately removed from the study. The subject was discontinued from the study after 12 days of treatment. Subject was initially lost to follow-up. When she was contacted on March 7, 2007, she reported that her baby is healthy at 4.5 months old.

41 year old subject **SIB-0221-18-R001** was diagnosed with an ectopic pregnancy on Day 85. The ectopic pregnancy was resolved the next day by an elective procedure. The subject was in the Lubiprostone 48 mcg treatment group. The subject discontinued the study medication 2 days prior to the event (Day 83), at the end of week 12, having already completed study treatments as planned. The investigator considered the event to be possibly related to the study medication.

#### **7.1.15 Assessment of Effect on Growth**

The study population in this supplemental New Drug Application included adults age 18 years and older. The application, therefore, has no information regarding the effect of Lubiprostone on growth.

#### **7.1.16 Overdose Experience**

Lubiprostone has been studied in humans up to 144 mcg/day which is nine times the recommended dose of 16 mcg (8 mcg bid) for irritable bowel syndrome constipation type. During the phase I study which involved an administration of a single dose of Lubiprostone 144 mcg/day, 39 of the 51 subjects experienced AEs. The AEs that were reported in > 1% of this group were nausea, vomiting, diarrhea, dizziness, headache, watery stools, retching, abdominal pain, dyspnea, flushing, hot flush, loose stools, pallor, stomach discomfort, syncope, abdominal pain upper, anorexia, asthenia, chest discomfort, dry mouth, hyperhidrosis, skin irritation, and syncope vasovagal. In the initial NDA review, 3 overdose cases (2 confirmed reports and 1 possible) were noted. One of the overdose cases experienced 4 episodes each of vomiting and diarrhea along with a stomach ache. The other two overdose cases did not report any adverse events. Based on the safety and tolerability profile of Lubiprostone, it is expected that an overdose could potentially be associated with the following symptoms: nausea, vomiting, headache, diarrhea, abdominal pain, dizziness, flatulence and possible dehydration. Treatment for overdose should be supportive and aimed at symptomatic therapy.

### 7.1.17 Post-Marketing Experience

Lubiprostone was approved on January 31, 2006 at 24 mcg bid for the treatment of chronic idiopathic constipation. Since its marketing in 2006, the sponsor has supplied the agency quarterly post-marketing safety updates as part of the approval requirement. The majority of AEs reported between January 31, 2006 and April 30, 2007 were in the SOC of gastrointestinal disorders. There were 346 events reported in the gastrointestinal disorders (37.01%). Other AEs by SOC reported by at least 5% of individuals were general disorders and administration site conditions (19.25%), nervous system disorders (12.83%), respiratory, thoracic and mediastinal disorders (5.24%) and skin and subcutaneous tissue disorders (5.03%). No causality ratings were included with these AEs.

Table 52 summarizes the adverse events by preferred terms that have been reported to the sponsor since the approval of Lubiprostone 24 mcg bid until April 30, 2007. It is difficult to establish causality since causality ratings information was not available. By preferred term, AEs reported by at least 2% of individuals were nausea (9.95%), diarrhea (9.20%), drug ineffective (6.31%), Abdominal pain (4.71%), dizziness (4.06%), headache (3.10%), dyspnea (2.46%), abdominal distension (2.35%), underdone (2.35%), and syncope (2.03%).

**Table 52: Summary of Postmarketing Adverse Events by Preferred Term from January 31, 2006 to April 30, 2007**

Preferred Term	Events <sup>1</sup> n (%)
Nausea	93 (9.95)
Diarrhea	86 (9.20)
Drug Ineffective	59 (6.31)
Abdominal pain	44 (4.71)
Dizziness	38 (4.06)
Headache	29 (3.10)
Dyspnea	23 (2.46)
Abdominal distension	22 (2.35)
Underdone	22 (2.35)
Syncope	19 (2.03)
Vomiting	17 (1.82)
Edema peripheral	16 (1.71)
Drug tolerance	14 (1.50)
Muscle spasms	13 (1.39)
Rash	13 (1.39)
Asthenia	12 (1.28)
Chest discomfort	11 (1.18)
Constipation	11 (1.18)
Hyperhidrosis	10 (1.07)

Reviewer's Table modified from table 2.7.4.6-2, page 124 of 126

<sup>1</sup>Events that represent at least 1% of the total postmarketing AE reports

**Table 53: Summary of Serious Adverse Events Reported by more than 1 Individual in Postmarketing between January 31, 2006 to October 31, 2007**

Preferred Term	Number of Serious Adverse Events
Death	2
Tachycardia	3
Hypotension	2
Syncope	5
Dyspnea	3
Diarrhea	5
Drug exposure during pregnancy	2
Chest Pain	2
Nausea	3

Reviewer's Table modified from table 2.7.4.6-3, page 126 of 126

Table 53 summarizes the serious and unexpected adverse events that occurred between January 31, 2006 and October 31, 2007 in more than 1 patient since the approval of Lubiprostone 24 mcg bid for chronic idiopathic constipation. In reviewing all the serious post-marketing adverse events that were reported between January 31, 2006 and October 31, 2007, they appear to be similar to the adverse events seen during the studies for Lubiprostone 8 mcg bid. The dose of Lubiprostone (24 mcg bid) that is currently marketed for chronic idiopathic constipation is three times the dose (8 mcg bid) that the sponsor is proposing for the treatment of irritable bowel syndrome constipation type. On May 16, 2007, a labeling modification of Lubiprostone 24 mcg bid was made to include the association of the drug with syncope, malaise, increased heart rate, muscle cramps, muscle spasms, rash and asthenia.

The postmarketing experience of Lubiprostone 24 mcg bid as it is used to treat chronic idiopathic constipation in adult patients was reviewed. The post-marketing safety data collected and submitted by the sponsor during the periods from January 31, 2006 to April 30, 2007, from May 1, 2007 until July 31, 2007, and from August 1, 2007 to October 31, 2007 were reviewed. Recently, the sponsor provided another post-marketing safety update from November 1, 2007 to January 31, 2008, and they are proposing a labeling change to reflect (b) (4)

All the spontaneous AE reports have been compiled from information gathered in the United States. Lubiprostone currently is only marketed in the United States; therefore, there is no data from any other countries' experience.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

Among the well-controlled safety group, long term safety group and randomized withdrawal safety cohorts, there was adequate subject exposure in terms of appropriate drug dosages, duration of treatment, and total number of patients. The demographic subsets of subjects were slightly limited as for lack of diversity, lack of geriatric subjects and male subjects; however, consistency therein was well maintained across the study groups. The overall clinical efficacy and safety tests were applicable and potentially important findings were adequately explored.

### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

A graphic description of the primary clinical data sources for this supplemental New Drug Application is shown in table 54. Efficacy was the primary objective for the two Phase III, well-controlled studies



(SIB-0431 Treatment Phase I; SIB-0432) and the one Phase II study (SIB-0221). Safety was the primary objective for one phase III long term safety study (SIB-05S1). The effects of Lubiprostone withdrawal and lasting efficacy were examined during the 4-week randomized withdrawal study or Treatment Phase II of SIB-0431.

**Table 54: Clinical Trials: Primary Clinical Data and Populations Exposed**

Study	Design	Study Objective	Duration	Group, Dose, # of Subjects Treated/Completed
<b>SIB-0221</b>	Double blind, randomized multicenter, placebo	Safety and Efficacy	12 weeks	Lubiprostone 16 mcg 52/42 Lubiprostone 32 mcg 49/33 Lubiprostone 48 mcg 45/30 Placebo 48/41
<b>SIB-0431 Treatment Phase I</b>	Double blind, randomized multicenter, placebo	Efficacy and Safety	12 weeks	Lubiprostone 16 mcg 395/297 Placebo 193/139
<b>SIB-0431 Treatment Phase II</b>	Randomized Withdrawal	Withdrawal and Lasting Efficacy	4 weeks	Lubiprostone 16mcg/Lubiprostone 16mcg 151/146 Lubiprostone 16mcg/Placebo 146/143 Placebo/Placebo 139/131
<b>SIB-0432</b>	Double blind, randomized multicenter, placebo	Efficacy and Safety	12 weeks	Lubiprostone 16 mcg 385/303 Placebo 194/151
<b>SIB-05S1</b>	Open label, multicenter	Safety	36 weeks	Lubiprostone 16 mcg 520/304

Reviewer's Table modified from table 2.7.4.1-1, page 9 of 126

For ease of safety evaluation, the study populations were categorized into unique patient cohorts. The three patient cohorts which will be emphasized throughout the safety review include: the well-controlled safety group, the randomized withdrawal safety cohort, and the long term safety cohort.

The **Well-controlled safety cohort** included the safety evaluable population from studies SIB-0221, SIB-0431 Treatment Phase I and SIB-0432. Safety evaluable population was defined as any subject who took a double blind medication. In the event that these subjects took a medication that differs from what they were randomized to, subjects represented the treatment group corresponding to the study drug they actually received. In studies SIB-0431 Treatment Phase I and SIB-0432, Lubiprostone 16 mcg and placebo were compared in double-blind trials. Study SIB-0221 consisted of 4 treatment arms, all with bid dosing: placebo, Lubiprostone 16 mcg (8 mcg plus 2 placebo capsules in the morning and evening), Lubiprostone 32 mcg (two 8 mcg plus 1 placebo capsules in the morning and evening) and Lubiprostone 48 mcg (three 8 mcg capsules in the morning and evening). The Lubiprostone 16 mcg treatment group was combined from the three studies (SIB-0221, SIB-0431 Treatment Phase I and SIB-0432) whereas the Lubiprostone 32 mcg and 48 mcg were presented separately.

The **Long-term safety cohort** included the safety evaluable population from the open label study SIB-05S1 of 36 weeks duration. The only dose group presented in this cohort was the 16 mcg although the safety data in which the dose was decreased during this study were also reported in the 16 mcg group.

The **Randomized Withdrawal safety cohort** included the safety evaluable subjects in study SIB-0431 Treatment Phase II. The exposure during randomized withdrawal was as follows: 151 subjects took Lubiprostone during both treatment phases, 146 subjects took Lubiprostone in treatment phase I and placebo during Treatment phase II, and 139 subjects took placebo in both treatment phases.

**Table 55: Summary of Subject Disposition/Extent of Exposure for All Randomized Subjects in Well-Controlled studies and Open Label study**

Variable	Well-Controlled Studies (SIB-0221 + SIB-0431 Treatment Phase I + SIB-0432)		Open Label Study SIB-05S1
	Placebo N=436 n (%)	Lubiprostone 16 mcg N=835 n (%)	Lubiprostone 16 mcg N=522 n (%)
Subjects Randomized	436 (100)	835 (100)	522 (100)
Treated <sup>1</sup>	435 (99.8)	832 (99.6)	520 (99.6)
Not Treated <sup>1</sup>	1 (0.2)	3 (0.4)	2 (0.4)
Completed Subjects	331 (75.9)	642 (76.9)	304 (58.2)
<b>Reasons for Discontinuation</b>			
Voluntary Withdrawal	38 (8.7)	68 (8.1)	71 (13.6)
Adverse Events	25 (5.7)	41 (4.9)	21 (4.0)
Lack of Efficacy	22 (5.0)	31 (3.7)	70 (13.4)
Non-Compliance	6 (1.4)	21 (2.5)	20 (3.8)
Lost to F/U	10 (2.3)	14 (1.7)	26 (5.0)
Other	2 (0.5)	14 (1.7)	7 (1.3)
Protocol Violation	1 (0.2)	4 (0.5)	3 (0.6)
Did not meet entry Criteria	1 (0.2)	0 (0.0)	0 (0.0)
<b>Duration of Exposure<sup>2</sup></b>			
Month 1	385/436 (88.3)	769/835 (92.1)	
Month 2	339/436 (77.8)	694/835 (83.1)	
Month 3	305/436 (70.0)	645/835 (77.2)	
Treatment Phase	385/436 (88.3)	769/835 (92.1)	
<b>Number of Days in Treatment Period</b>			
N	433 (99.3)	829 (99.3)	505 (96.7)
Mean (SD)	74.9 (23.75)	75.7 (22.98)	253.5 (100.97)
Median	84	84	254
Range	1.0-112.0	1.0-128.0	5.0-433

Reviewer's Table modified from table 2.7.4.1-2, page 15 of 126 and Table 2.7.4.1-4, page 18 of 126

<sup>1</sup>Percentages are total which fall into the particular category divided by the number of subjects randomized

<sup>2</sup>Percentages are calculated as the number of subjects on study drug divided by the number of randomized subjects who were expected to remain on study drug based on the respective study design

As graphically illustrated above, in the well-controlled studies, 436 placebo subjects were assessed, 435 were treated, and 331 subjects (75.9%) completed their respective studies; 835 Lubiprostone 16 mcg subjects were assessed, 832 were treated, and 642 subjects (76.9%) completed their respective studies. Both placebo and Lubiprostone 16 mcg group had similar reasons for discontinuation. In the placebo group, the most common reasons for discontinuation were as follows: subject voluntary withdrawal (8.7%), adverse events (5.7%), and lack of efficacy (5.0%). Similarly in the Lubiprostone 16 mcg group, the most common reasons for discontinuation were subjects voluntary withdrawal (8.1%),

adverse events (4.9%), and lack of efficacy (3.7%). The mean number of days on study drug was 74.9 for placebo subjects and 75.7 for Lubiprostone 16 mcg subjects. In the placebo group, 88.3% of assessed subjects were on the study drug for at least 1 month, 77.8% of subjects were on study drug for at least 2 months, and 70.0% of those expected to be on study at 3 months were on the study drug for at least 3 months. In the Lubiprostone 16 mcg group, 92.1% of assessed subjects were on the study drug for at least 1 month, 83.1% of subjects were on study drug for at least 2 months, and 77.2% of subjects were on study drug for at least 3 months. Note that at each time point, the percentage was based on the number of subjects expected to be on study drug at that time.

As noted above in table 55, for the open label phase, a placebo group did not exist, and all subjects were assigned to take Lubiprostone 16 mcg. There were 522 subjects assessed, 520 were treated and 304 subjects (58.2%) completed the study. The most common reasons for discontinuation were subjects voluntary withdrawal (13.6%) and lack of efficacy (13.4%). The mean number of days on study drug was 253.5.

For the well-controlled safety group, the mean daily medication exposure for subjects in the Lubiprostone 16 mcg dose group and placebo was the same for the treatment phase at 1.62 capsules per day. It was similar in treatment months 1 and 2 except month 3 (1.80 capsules per day Placebo vs. 1.76 capsules per day Lubiprostone 16 mcg),  $p=0.045$ . The mean percent compliance for the treatment period based on CRF for the well-controlled safety group was 93.69% for placebo subjects, 93.34% for Lubiprostone 16 mcg subjects, 89.79% for Lubiprostone 32 mcg subjects, and 89.24% for Lubiprostone 48 mcg subjects. Similar proportion of subjects were at least 70% compliant in the placebo and the Lubiprostone 16 mcg group (93.3% vs. 93.2%, respectively) based on the CRF.

**Table 56: Summary of Subject Disposition/Extent of Exposure for All Randomized Subjects in Study SIB-0431 Treatment Phase II**

Variable	Treatment Group			Total N=436 n (%)
	Placebo/Placebo N=139 n (%)	Lubiprostone/Placebo N=146 n (%)	Lubiprostone/ Lubiprostone N=151 n (%)	
Subjects who completed Phase I	139 (100)	146 (100)	151 (100)	436 (100)
Subjects who entered Phase II	139 (100)	146 (100)	151 (100)	436 (100)
Subjects Treated <sup>1</sup>	139 (100)	146 (100)	151 (100)	436 (100)
Subjects Not Treated <sup>1</sup>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Completed Subjects	131 (94.2)	143 (97.9)	146 (96.7)	420 (96.3)
<b>Reasons for Discontinuation</b>				
Voluntary Withdrawal	1 (0.7)	1 (0.7)	0 (0.0)	2 (0.5)
Adverse Events	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
Lack of Efficacy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-Compliance	1 (0.7)	1 (0.7)	0 (0.0)	2 (0.5)
Lost to F/U	4 (2.9)	1 (0.7)	2 (1.3)	7 (1.6)
Unknown	2 (1.4)	0 (0.0)	1 (0.7)	3 (0.7)
Protocol Violation	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
Did not meet entry Criteria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Duration of Exposure<sup>2</sup></b>				
Month 4	135/139 (97.1)	142/146 (97.3)	149/151 (98.7)	426/436 (97.7)
<b>Number of Days in Treatment Period</b>				
N	139 (100)	144 (98.6)	151 (100)	434 (99.5)
Mean (SD)	115.2 (6.34)	114.9 (6.92)	114.0 (5.86)	114.7 (6.39)
Median	113.0	113.0	113.0	113.0
Range	102.0-147.0	101.0-164.0	92.0-146.0	92.0-164.0

Reviewer's Table modified from table 2.7.4.1-3, page 16 of 126

<sup>1</sup>Percentages are total which fall into the particular category divided by the number of subjects who entered Treatment Phase II

<sup>2</sup>Percentages are calculated as the number of subjects on study drug divided by the number of subjects who entered Treatment Phase II and were expected to remain on study drug based on the respective study design

As illustrated in table 56 above, in the 4 week randomized withdrawal study, 139 placebo/placebo (P/P) subjects who completed treatment phase I were treated in treatment phase II and 131 of them completed the study. The 297 Lubiprostone subjects who completed treatment phase I were divided as follows into 2 treatment groups: 146 of the subjects were switched to be treated with placebo and 151 continued to receive Lubiprostone. Of the 146 L/P subjects that were treated in Treatment phase II, 143 subjects completed the study, and of the 151 L/L subjects that were treated in treatment phase II, 146 subjects completed the study.

Lost to follow-up was the most common reason for discontinuation in the P/P (2.9%) and the L/L (1.3%) groups. No subject reported lack of efficacy as a reason for discontinuation in any of the treatment groups. Only 1 subject in the L/L treatment group reported adverse event as a reason for discontinuation. There were 1 subject each in P/P (0.7%) and L/P (0.7%) groups that discontinued due to voluntary withdrawal and non-compliance. Likewise in the L/L treatment group, one subject each discontinued treatment phase II due to adverse events (0.7%), unknown reasons (0.7%) and protocol violation (0.7%).

For the randomized withdrawal safety group, the mean daily medication exposure for subjects in the L/P and L/L group was the same for treatment phase II at 1.79 capsules per day. The P/P group also had similar total daily dose at 1.81 capsules per day,  $p=0.776$ . The mean percent compliance based on CRF was 97.02% for P/P subjects, 95.30% for L/P subjects, and 96.42% for L/L subjects. The proportion of subjects that were at least 70% compliant were as follows: 97.1% in the P/P group, 94.5% in the L/P group, 96.0% in the L/L group. A larger proportion of subjects required a dose decrease in the L/P group (7.5%) than the L/L (6.6%) and the P/P (2.2%) groups.

## 7.2.2 Demographics

The overall summary of demographics for the well-controlled safety population is presented below in table 57. As graphically depicted, the median subject age was 47 years (range: 18-85 years); 92.0% of subjects were aged  $\geq 18$  and  $< 65$  years and 8.0% of subjects were  $\geq 65$  years old. Of the 1361 safety evaluable subjects overall, 1245 (91.5%) were female and 1058 (77.7%) were Caucasian.

**Table 57: Summary of Demographics for the Well-Controlled Safety Population**

Variable	Statistic	Placebo	Lubiprostone 16 mcg	Total <sup>1</sup>
Age (years)	n (%)	435 (100)	832 (100)	1361 (100)
	Mean	47.3	46.1	46.5
	SD	12.80	12.68	12.67
	Median	48.0	46.0	47.0
	Range	18.0-85.0	19.0-83.0	18.0-85.0
Age Group n (%)	$18 \leq \text{Age} < 65$	395 (90.8)	771 (92.7)	1252 (92.0)
	$\text{Age} \geq 65$	40 (9.2)	61 (7.3)	109 (8.0)
Gender n (%)	Female	404 (92.9)	757 (91.0)	1245 (91.5)
	Male	31 (7.1)	75 (9.0)	116 (8.5)
Race n (%)	Caucasian	339 (77.9)	642 (77.2)	1058 (77.7)
	African-American	53 (12.2)	111 (13.3)	171 (12.6)
	Hispanic/Latino	36 (8.3)	74 (8.9)	120 (8.8)
	Other	5 (1.1)	1 (0.1)	6 (0.4)
	Asian	2 (0.5)	3 (0.4)	5 (0.4)
	American Indian/ Alaska Native	0 (0.0)	1 (0.1)	1 (0.1)

Reviewer's Table modified from table 2.7.4.1-5, page 21 of 126

<sup>1</sup>This column includes Lubiprostone 32 mcg and 48 mcg subjects in addition to placebo and Lubiprostone 16 mcg subjects

## Medical officer comments

*Comparisons of demographic characteristics across the different Lubiprostone dose groups reveal similar populations in terms of age, sex and race. The majority of patients in the Lubiprostone 32 mcg dose (87.8%) and 48 mcg dose (95.6%) were  $18 \leq \text{age} < 65$ . In Lubiprostone 32 mcg and 48 mcg dose groups, the majority of subjects were females (93.9% and 84.4%, respectively) and Caucasian (81.6% and 82.2%, respectively). Since the subjects in the open label study had to complete either SIB-0431 or SIB-0432 prior to enrolling into the open label study SIB-05S1, the demographics in the long term safety group are similar to the well-controlled safety population. Additionally, the randomized withdrawal safety group is also similar to the well-controlled safety group in terms of demographics since the subjects that completed treatment phase I of SIB-0431 are the ones that were treated in treatment phase II.*

### **7.2.3 Description of Secondary Clinical Data Sources Used to Evaluate Safety**

The Agency's review of the Lubiprostone 24 mcg bid was used as a source of clinical data to evaluate safety for the supplemental New Drug Application. The adverse events that were reported by at least 1% of subjects taking Lubiprostone 24 mcg bid and its frequency was at least twice the frequency reported in the placebo group were as follows: nausea, diarrhea, abdominal pain, flatulence, abdominal discomfort, loose stools, vomiting, abdominal pain-lower, dry mouth, stomach discomfort, dizziness, peripheral edema, chest discomfort, dyspnea, hyperhidrosis, and palpitations.

### **7.2.4 Adequacy of Overall Clinical Experience**

According to the ICH Guidance (E1) on extent and duration of exposure needed to assess clinical exposure for a drug, this supplemental New Drug Application had an adequate number of subjects exposed to Lubiprostone. To characterize a pattern of adverse drug events over time, the ICH Guidance (E1) also recommends that a select number of subjects should be treated for 6 months at the dosage levels intended for clinical use. This supplemental New Drug Application for Lubiprostone had an adequate exposure duration ranging from 12 weeks to 52 weeks. The well-controlled efficacy trials were adequately and appropriately designed in that they were randomized, double blinded, placebo-controlled, parallel-grouped, and multi-centered and also able to provide adequate safety data for up to 16 weeks.

There are several limitations in this supplemental New Drug Application. It is the medical officer's opinion that Lubiprostone's safety in pregnant women or women who could become pregnant has not been fully explored and adequately defined. Additionally, the medical officer doesn't think these limitations hinder the approvability of the supplemental NDA rather subject the application to further post-marketing commitments. The subject data base is reflective of the truly intended market population of Lubiprostone since the diagnosis of IBS and IBS-C is unusual after the age of 50. However, the limited number of males and geriatric subjects studied in the clinical trials limits the safety and efficacy conclusions that can be applied to these particular populations.

### **7.2.5 Adequacy of Special Animal and/or In Vitro Testing**

There were no pharmacology or animal studies submitted as part of this supplemental New Drug Application.

### **7.2.6 Adequacy of Routine Clinical Testing**

It is the reviewer's opinion that the routine clinical testing of subjects in this supplemental New Drug Application was adequate. The sponsor performed adequate monitoring of safety parameters including laboratory values, vital signs, and physical assessments. The safety parameters were performed with appropriate frequency and scrutiny.

### **7.2.7 Adequacy of Metabolic, Clearance, and Interaction Workup**

There were no pharmacodynamics or pharmacokinetics studies of Lubiprostone submitted with this supplemental New Drug Application.

### **7.2.8 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study**

It is the reviewer's opinion that the adequacy of the risk/benefit profile of Lubiprostone has been adequately studied except for the following outstanding issues discussed within this review: Lubiprostone use in subjects with renal impairment and Lubiprostone use in subjects with hepatic impairment. Although not completely optimal, the submitted data were adequate for this reviewer to perform a safety review and make recommendations.

### **7.2.9 Assessment of Quality and Completeness of Data**

The overall safety and efficacy data supplied within this supplemental New Drug Application was thorough and well organized. The sponsor provided an adequate database within this application from which to review the proposed indication. There were, however, some important data, as mentioned above that were not adequately explored.

### **7.2.10 Additional Submissions, including Safety Update**

The sponsor submitted a one time required 4 month safety update covering the time frame from 30 June 2007 to 31 October 2007. There was no new safety information found during this reporting period for Lubiprostone 8 mcg bid dose.

## **8. ADDITIONAL CLINICAL ISSUES**

### **8.1 Dosing Regimen and Administration**

In this reviewer's opinion the adequacy of dose finding in this supplemental New Drug Application was appropriate, but limited due to lack of exploration of certain findings. The dose response study SIB-0221 evaluated dose levels of 16 mcg/day (8 mcg bid), 32 mcg/day (16 mcg bid), and 48 mcg/day (24 mcg bid) over a 12 week period. The results of this study showed that all 3 doses of Lubiprostone were more effective than placebo in relieving symptoms of IBS-C; however, the Lubiprostone 16 mcg and 32 mcg dose revealed similar results. In general, the likelihood of experiencing most treatment-related gastrointestinal AEs in this study did appear to increase with increasing Lubiprostone dose. The treatment-related AE for which frequency increased most dramatically with Lubiprostone dose was nausea and diarrhea. Nausea was experienced by 6.3% of placebo subjects, 17.3% of Lubiprostone 16 mcg subjects, 18.4% of Lubiprostone 32 mcg subjects and 22.2% of Lubiprostone 48 mcg subjects. Similarly, diarrhea was experienced by 4.2% of placebo subjects, 11.5% of Lubiprostone 16 mcg subjects, 12.2% of Lubiprostone 32 mcg subjects, and 26.7% of Lubiprostone 48 mcg subjects. As indicated, there was nearly one and half times the events of nausea and at least twice the events of diarrhea in the 48 mcg dose group compared to the 16 mcg dose group. Abdominal distension as a treatment-related AE was reported in higher frequency in the 32 mcg and the 48 mcg dose group; however, abdominal pain-upper was reported only in the 16 mcg dose group. Despite Lubiprostone 48 mcg subjects rating treatment effectiveness higher than the Lubiprostone 16 mcg subjects in all 3 months, the Lubiprostone 48 mcg subjects did not have a higher responder rate than the 16 mcg subjects at months 2 and 3. The 32 mcg dose subjects had a higher treatment effectiveness rating than the 16 mcg group at all three months and exhibited a better responder rate in all months except month 2. The responder rate for month 2 in the 16 mcg dose group was 62.2% whereas the responder rate for the 32

mcg dose group was 61.5% in month 2. The 32 mcg dose revealed similar results to the 16 mcg dose in most of the endpoints; however, the subjects in the 32 mcg dose group had higher rates of discontinuation. There were 16.2% of subjects in the Lubiprostone 32 mcg group that discontinued the study due to an AE compared to 5.8% of subjects in the Lubiprostone 16 mcg group.

According to the sponsor, the 16 mcg/day dose was the minimum effective dose with the most desirable safety profile. The 48 mcg dose group produced a statistically significant effect in the primary efficacy analysis and most secondary efficacy analysis in study SIB-0221 since it was powered to detect a difference between placebo and the 48 mcg dose group. An argument can be made that the sponsor should have chosen the 32 mcg/day dose as it exhibited some treatment-related gastrointestinal AEs (such as dry mouth, vomiting, eructation, abdominal pain-upper, abdominal pain-lower) that were lower in frequency than the 16 mcg/day dose. This reviewer believes that the Lubiprostone 32 mcg dose should have been further explored in the phase III studies because it was also found to be more efficacious than placebo. The sponsor had concerns since the discontinuation rates and the frequency of abdominal pain adverse events were greater in the higher doses of Lubiprostone. In the sponsor's cumulative incidence rate analysis, abdominal pain did not seem to exhibit a dose relationship. Abdominal distension was reported as an adverse event in 5 subjects in the Lubiprostone 32 mcg dose group as compared to 1 subject in the Lubiprostone 16 mcg dose group. Despite the imbalance of abdominal distension as an adverse event in the Lubiprostone 32 mcg dose group, the 16 mcg dose group (7 subjects, 13.5%) was just as likely as the Lubiprostone 32 mcg group (6 subjects, 12.2%) to report all abdominal pain (abdominal pain, abdominal pain-lower, abdominal pain-upper, abdominal tenderness) as an adverse event. There were 4 subjects (7.7%) in the Lubiprostone 16 mcg dose group that reported treatment-related all abdominal pain (abdominal pain, abdominal pain-upper) compared to 3 subjects (6.1%) in the 32 mcg dose group. Furthermore, abdominal distension was also reported in 5 subjects (10.4%) in the placebo group, and all abdominal pain was reported by 3 subjects (6.3%) in the placebo group. One subject discontinued from the Lubiprostone 32 mcg dose group due to abdominal pain whereas two subjects discontinued due to abdominal distension; similarly, one subject in the placebo group discontinued due to abdominal pain and another subject discontinued due to abdominal distension. Thus, the sponsor could have further explored the conflicting adverse events and unexplained discontinuation rates with a larger number of patients using placebo, 16 mcg (8 mcg bid) and 32 mcg (16 mcg bid) dose groups in phase III trials.

This reviewer has doubts in regards to the appropriate dose selection for this supplemental New Drug Application because the 32 mcg group (16 mcg bid) seems to exhibit similar adverse events and reasons for discontinuation as the 16 mcg (8 mcg bid) and placebo groups. The 32 mcg (16 mcg bid) dose can also ultimately be individually tapered to avoid such assumed pharmacodynamic effects as nausea, diarrhea, possibly abdominal pain and distension.

Lubiprostone has not been adequately tested in subjects with renal or hepatic impairment; therefore, recommendations on dose modifications in such special populations cannot be made. The effects of food were not evaluated in this supplemental application.



## 8.2 Drug-Drug Interactions

Drug-drug interactions assessment was not performed as part of the supplemental drug application. The sponsor did perform these studies with the initial application for Lubiprostone 24 mcg bid for chronic idiopathic constipation treatment.

## 8.3 Special Populations

- Safety and effectiveness of Lubiprostone in pediatric patients has not been established.
- The clinical studies for lubiprostone included a somewhat limited proportion of subjects aged 65 and older (8.1% in pooled cohort). The results for the primary efficacy endpoint between Lubiprostone and placebo in this age group were similar but not statistically significant. The actual observed values of effectiveness did not provide evidence that Lubiprostone 16 mcg was better than placebo in the 65 and older subgroup. The overall responder rate which was the primary efficacy variable was 10.3% in the Lubiprostone 16 mcg group and 10.5% in the placebo group. In the monthly responder rates, Lubiprostone 16 mcg group (range: 8.6%-19.0%) demonstrated a higher rate than placebo group (range: 7.9%-10.5%) at all monthly time points. In the age group  $\geq 65$ , the difference in the monthly responder rates between placebo and Lubiprostone 16 mcg subjects did not increase as the months progressed (Months 1, 2, and 3: 0.7%, 8.5% and 4.2%, respectively). The difference in the monthly responder rates between placebo and Lubiprostone 16 mcg subjects in the age group  $\geq 65$  years old had more variation and was lower than that seen in the general study population especially in months 1 and 3.
- Lubiprostone has not yet been adequately studied in subjects who have **renal impairment**.
- Lubiprostone has not yet been adequately studied in subjects who have **hepatic impairment**.
- There have been no adequate and well-controlled studies of Lubiprostone in **pregnant women**.
- The excretion of Lubiprostone or its metabolite in the milk of **nursing mothers** has not been evaluated.

## 8.4 Pediatrics

The safety and effectiveness of Lubiprostone in pediatric patients has not been established.

## 8.5 Advisory Committee Meeting

There was no Advisory Committee Meeting required for this supplemental New Drug Application.

## 8.6 Literature Review

The sponsor provided 24 pieces of literature as references to support this supplemental New drug Application. Of the 24 listed references, five were cited from peer reviewed journals dating from 2002 to 2007. Two of the references were press releases, one was FDA's review of Zelnorm, one was an abstract, one was a chapter from a book, two were appendices from a book and twelve were actual sponsor trials. The five peer reviewed journal articles discussed various topics including chloride channels, irritable bowel syndrome and chronic constipation. The sponsor's literature review was not ideal in that it did not contain any articles or independent (not sponsor supported) research describing the use of Lubiprostone in chronic idiopathic constipation or any current or potential off-label use. The

medical reviewer performed an additional literature search utilizing the Agency's databases and on-line resources to support this supplemental New Drug Application review.

## **8.7 Post-Marketing Risk Management Plan**

The sponsor has not submitted a Post-marketing risk management plan for this supplemental New Drug Application.

### **Medical officer comments**

*After a thorough safety review and analysis, the medical officer does not believe a post-marketing risk management plan is needed for Lubiprostone. A post-marketing management plan beyond the standard 4-month safety update is not indicated for this supplemental application since there are no major serious safety concerns with the 8 mcg bid dose. Additionally, Lubiprostone is currently used for a different indication at the higher dose of 24 mcg bid.*

## **9. OVERALL ASSESSMENT**

### **9.1 Conclusions**

The clinical program with Lubiprostone 16 mcg (8 mcg bid), consisting of two adequate and well-controlled Phase III efficacy studies, one 4 week randomized withdrawal study, and one phase III long term safety and efficacy study demonstrates that administration of Lubiprostone 8 mcg bid provides some relief of symptoms associated with constipation predominant irritable bowel syndrome. Statistical significance was attained in both pivotal studies up to 12 weeks for the primary efficacy endpoint: the overall responder rate. Overall and monthly responder definitions were based on the weekly assessments of global symptom relief obtained as part of the subject's electronic diary responses. Global symptom relief was assessed based on the 7 point balanced scale associated with the following weekly 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? The 7 point balanced scale incorporated the following ratings: **3** significantly relieved, **2** moderately relieved, **1** a little bit relieved, **0** unchanged, **-1** a little bit worse, **-2** moderately worse, and **-3** significantly worse. An overall responder was defined as a monthly responder for at least 2 out of the 3 months during the 12 week treatment period. In the study SIB-0431 Treatment Phase I, Lubiprostone subjects had 13.8% overall responder rate while placebo subjects had a 7.8% overall responder rate. In the second pivotal study, SIB-0432, Lubiprostone subjects had 12.1% overall responder rate whereas the placebo subjects had 5.7% overall responder rate. In both individual studies (SIB-0431 Treatment Phase I and SIB-0432), the difference in the overall responder rate between Lubiprostone and placebo subjects were 6% and 6.4% respectively, and the difference was statistically significant. In the pooled group, Lubiprostone subjects had 13.0% overall responder rate and placebo subjects had 6.8% overall responder rate. The difference in the overall responder rate between Lubiprostone subjects and placebo subjects was 6.2%, and it was statistically significant.

Monthly responder rate during the 12 week treatment period was a key secondary efficacy endpoint in the 2 pivotal studies. A monthly responder was defined as a subject whose symptoms were rated as "Moderately relieved" for all 4 weeks within a month or "Significantly relieved" for at least 2 weeks

within a month provided the three conditions were met: 1. the percent of days of rescue medication use did not increase during the month as compared to baseline, 2. the subject did not discontinue the study during the month due to lack of efficacy, 3. the subject had no ratings of “Moderately worse” or “Significantly worse” during the month. In each of the pivotal studies (SIB-0431 Treatment Phase I and SIB-0432), the Lubiprostone 16 mcg group (range: 9.8%-16.1%) demonstrated a higher monthly responder status than placebo (range: 5.7%-10.4%) at all monthly timepoints. The difference between placebo and Lubiprostone 16 mcg group in the study SIB-0431 Treatment Phase I (months 1, 2, and 3: 3.8%, 6.6%, and 5.5%, respectively) was similar to the difference that was seen in study SIB-0432 (months 1, 2, and 3: 3%, 6.2%, 7.8%, respectively) except at month 3. The pooled group also revealed similar results in the monthly responder rates (months 1, 2, and 3: 3.4%, 6.4%, and 6.6% respectively). Statistically significant differences were observed in Month 2 for the pooled population and SIB-0431 Treatment Phase I study.

Study SIB-0431 Treatment Phase I enrolled 590 subjects (396-Lubiprostone 16 mcg, 194-Placebo) throughout 65 centers in the United States and randomly allocated them to either Lubiprostone 8 mcg bid or placebo. In study SIB-0431 Treatment Phase I efficacy analysis, the overall responder rate was significantly higher ( $p=0.029$ ) in the Lubiprostone 16 mcg group (13.8%) than in the placebo group (7.8%). Statistical significance in study SIB-0431 Treatment Phase I was also seen for monthly responder rate for month 2 which was a key secondary efficacy endpoint. Study SIB-0431 Treatment Phase I also demonstrated statistical significance over placebo in two other secondary endpoints such as stool consistency at months 2 and 3 and degree of straining at months 1 and 2. Although study SIB-0431 Treatment Phase I did not show statistical significance in many of the secondary endpoints including monthly abdominal discomfort/pain, monthly abdominal bloating, monthly spontaneous bowel movement frequency rates, monthly bowel movement frequency rates, monthly severity of constipation, monthly symptom relief, and overall IBS-QOL, the results for these secondary efficacy variables were not worse than placebo and trended slightly in favor of Lubiprostone. Based on the secondary endpoints, an assertion can be made that Lubiprostone may benefit some patients with constipation predominant irritable bowel syndrome.

Study SIB-0432 enrolled 581 (387-Lubiprostone 16 mcg, 194-Placebo) throughout 65 centers in the United States and randomly allocated them to either Lubiprostone 8 mcg bid or placebo. In study SIB-0432 efficacy analysis, the overall responder rate was significantly higher ( $p=0.023$ ) in the Lubiprostone 16 mcg group (12.1%) than in the placebo group (5.7%). Statistical significance in study SIB-0432 was also seen for symptom relief at month 2 and overall IBS-QOL at last visit. Although study SIB-0432 did not show statistical significance in many of the secondary endpoints including monthly responder rate, monthly abdominal discomfort/pain, monthly abdominal bloating, monthly spontaneous bowel movement frequency rates, monthly bowel movement frequency rates, monthly stool consistency, monthly degree of straining, and monthly severity of constipation, the results for these secondary efficacy variables were not worse than placebo and trended slightly in favor of Lubiprostone 16 mcg/day. Based on the secondary endpoints, an assertion can be made that Lubiprostone may benefit some patients with constipation predominant irritable bowel syndrome.

The 4 week Randomized Withdrawal study (SIB-0431 Treatment Phase II) enrolled 436 subjects that completed SIB-0431 Treatment Phase I. The 436 subjects were divided as follows: 139 placebo subjects in Treatment Phase I continued to take Placebo, 297 subjects that were receiving Lubiprostone in treatment phase I were either switched to placebo (146 subjects) or continued on Lubiprostone

treatment (151 subjects). At month 4, the Placebo/Placebo subjects had a responder rate of 7.9% and the Lubiprostone/Lubiprostone subjects had a responder rate of 11.3%. The difference between subjects that received placebo throughout the 16 weeks (Treatment Phase I and II) and the subjects that received Lubiprostone for 16 weeks in responder rate was 3.4%, and it was not statistically significant,  $p=0.415$ . However, efficacy of 3.4% over placebo and its clinical meaningfulness is difficult to judge in the face of a disease that tends to exhibit fluctuations. Furthermore, the comparison of subjects who took Lubiprostone in Treatment Phase I and then switched to placebo in treatment phase II (40.0%) to the subjects that took Lubiprostone in treatment phase I and II (38.1%) revealed a responder rate difference of 1.9%. The subjects who were switched to placebo demonstrated a higher responder rate by 1.9% ( $p=0.971$ ) which indicates that Lubiprostone subjects are less likely to have relapse of their symptoms when treatment is discontinued. This could lead one to question whether Lubiprostone 8 mcg bid dose exerts any effect let alone a meaningful clinical effect. Since a withdrawal trial is an enrichment design that excludes non-responders, one would expect an overestimate of the effect size which did not occur in this case.

The long term efficacy of Lubiprostone 8 mcg bid was evaluated during the conduct of the study SIB-05S1, 36 week open label period. Due to the open label design of this study, the efficacy evaluation did not provide direct comparison with placebo; rather, it provided only comparative results with the same assessments performed in the double-blind randomized studies. Study SIB-05S1 was an open label, long term safety and efficacy study which enrolled 522 subjects with constipation predominant irritable bowel syndrome who were treated with 16 mcg/day (8 mcg bid) of Lubiprostone administered over a 36 week period. The monthly responder rate range was 12.3% to 57.9% during the 13 month study period. A monthly responder was defined as a subject whose symptoms were rated as “Moderately relieved” for all 4 weeks within a month or “Significantly relieved” for at least 2 weeks within a month provided the two conditions were met: the subject did not discontinue the study during the month due to lack of efficacy, and the subject had no ratings of “Moderately worse” or “Significantly worse” during the month. The same global symptom relief question and rating scale were utilized as the well-controlled trials; however, this study did not assess rescue medication usage as one of the conditions for being a monthly responder. Since the primary objective of the study was to demonstrate long term safety and tolerability of Lubiprostone 8 mcg bid, no inferential statistics were performed on the monthly responder rates. The results of study SIB-05S1 do support the results of the pivotal efficacy studies; but caution must be used in interpreting the degree of efficacy. Various literature have identified that the symptoms of irritable bowel syndrome seem to respond to placebo; therefore, some of the response could be due to the known 20% to > 50% placebo effect.

The overall efficacy of Lubiprostone 8 mcg bid reveals marginal benefit in some patients. However, given the fact that there are no FDA approved treatments for constipation predominant irritable bowel syndrome, it may prove to be beneficial in women under the age of 65. The reduction in symptoms of constipation predominant irritable bowel syndrome was demonstrated in the short term studies (up to 12 weeks) and the long term study (up to 52 weeks). In age  $\geq 65$  years old, the overall responder rate of Lubiprostone subjects was the same as placebo subjects; therefore, efficacy has not been established in this particular sub-group. Furthermore, the 2 pivotal studies did not include adequate number of male subjects which makes it difficult to make any efficacy conclusions.

There were a total of 1361 subjects (1366 randomized/enrolled – 5 subjects never received any drug) treated in the safety population of which 1105 subjects received active drug and 256 received placebo.

Of the 1105 subjects that received Lubiprostone, 779 subjects received only Lubiprostone and 326 subjects received both placebo and Lubiprostone. One thousand and eleven subjects received Lubiprostone 16 mcg/day (8 mcg bid) in all the studies combined (SIB-0221, SIB-0431 Treatment Phase I and II, SIB-0432 and SIB-05S1). In the long term safety study, SIB-05S1, 520 subjects were treated with Lubiprostone 8 mcg bid for 36 weeks but were exposed to Lubiprostone for longer durations due to their previous treatment assignments in the well-controlled studies (SIB-0431 Treatment phase I and II and SIB-0432): 179 subjects received Lubiprostone for 36 weeks, 80 subjects received Lubiprostone for 48 weeks, and 261 subjects received Lubiprostone for 52 weeks.

A male subject age 71 years old who was randomized to the Lubiprostone/Placebo group and was receiving Lubiprostone died of sudden cardiac arrest. He was enrolled in the study SIB-0431 Treatment Phase I, and the last dose of Lubiprostone was taken on study day 72. No autopsy report was provided.

The occurrence of serious adverse events in the studied population was relatively low. Four placebo subjects (0.9%) reported 7 serious adverse events (SAEs) with no preferred term SAE being reported by more than one subject. Seven subjects taking Lubiprostone 16 mcg (0.8%) reported 9 treatment emergent SAEs. Two Lubiprostone subjects reported 4 SAEs (cardiac arrest, atrial fibrillation, coronary artery disease and mitral valve incompetence) in the cardiac disorders SOC. One SAE of chest pain that was reported as non-cardiac in nature was considered treatment-related. In the open label treatment period, 10 subjects reported 11 treatment emergent SAEs. Syncope was the only SAE preferred term reported by more than 1 subject.

Across all active doses of Lubiprostone (N=926) in the well-controlled safety group, the most commonly reported adverse event preferred terms were nausea (12.3%), diarrhea (8.2%), headache (4.3%), Upper respiratory tract infection (4.1%), abdominal pain (4.0%), and urinary tract infection (4.0%). Comparatively for placebo (N=435), the corresponding reports of adverse events in the above preferred terms were: nausea (6.4%), diarrhea (5.3%), headache (4.4%), Upper respiratory tract infection (2.3%), abdominal pain (5.3%), and urinary tract infection (3.4%). In the open label treatment period, the most commonly reported adverse events were similar to the ones reported in the well-controlled trials: diarrhea (8.8%), nausea (6.5%), urinary tract infection (6.5%), headache (4.0%), abdominal pain (3.5%) and upper respiratory tract infection (2.9%).

An analysis of cumulative adverse event incidence rates, time to first adverse events and a Cox proportional hazard analysis for the occurrence of any adverse event (nausea, diarrhea, vomiting, headache, dizziness, syncope, peripheral edema, fatigue, dyspnea, cardiac disorders) indicated that subjects taking Lubiprostone were more likely than placebo subjects to experience most adverse events with the exception of abdominal pain. The risk of experiencing nausea, diarrhea, and headache was greatest within the first few days of treatment (2-5 days), and it did not increase over time to any appreciable degree. However, the risk of experiencing vomiting and fatigue was greatest three weeks into treatment (Day 22-28). Even though peripheral edema, syncope, dyspnea, and cardiac disorders were more likely to occur in Lubiprostone subjects, it was difficult to predict the timing of occurrence during treatment. Dizziness, on the other hand, was more likely to be experienced by subjects  $\geq 65$  years old (hazard ratio=2.271,  $p=0.0757$ ) and also more likely to occur later in the treatment period (Day 253-280). According to the Cox regression analysis, the adverse event that was more likely to occur in females was nausea (hazard ratio=1.970;  $p=0.0826$ ).

The frequency of withdrawal for Lubiprostone 16 mcg (8 mcg bid) subjects in the well-controlled safety group was lower than for the placebo subjects. Overall 2.3% of placebo subjects and 1.9% of Lubiprostone 16 mcg subjects withdrew because of gastrointestinal adverse events. The breakdown of gastrointestinal adverse events in the well-controlled safety group that led to withdrawal for at least 1% of subjects was nausea (1.2%) for the Lubiprostone 16 mcg group and abdominal pain (1.4%) for the placebo group. The types and frequencies of the individual AEs that led to withdrawal were generally similar across the long term and randomized withdrawal studies, and these results were similar to those observed in the well-controlled trials. Gastrointestinal disorders were once again the most common System Organ Class for AEs leading to withdrawal. Adverse events that led to withdrawal in the open label long term safety study for at least 1% of subjects was diarrhea (1.3%). Only one subject discontinued in the randomized withdrawal study due to abdominal distension (0.7%).

The clinical and laboratory data presented in this application including biochemistry, hematology, urinalysis, vital signs and physical examination data appeared clinically acceptable for a population of subjects with constipation predominant irritable bowel syndrome who are otherwise considered generally healthy. ECG and bilateral hand X-rays were evaluated in the dose response study SIB-0221 at baseline and at final assessment. Lubiprostone at doses of 16 mcg, 32 mcg, and 48 mcg per day for 12 weeks showed no evidence of effect on heart rate, cardiac conduction, cardiac repolarization or morphological changes. Although formal lumbar and hip bone densitometry analysis would have provided a more accurate reflection of Lubiprostone's effect on bone metabolism, Lubiprostone did not appear to cause a negative impact on bone density.

The pharmacological profile of Lubiprostone is not consistent with a drug that would have the potential for abuse or drug dependence. The overall safety profile in the sponsor's randomized withdrawal study indicated that there appears to be no obvious safety risks following immediate cessation of Lubiprostone. When a comparison was performed between the subjects that received placebo in treatment phase I and II (P/P) and subjects that received Lubiprostone in treatment phase I and then switched to placebo (L/P), the responder rate was significantly higher in the L/P subjects (40.0%) compared to 7.9% in the P/P subjects,  $p < 0.001$ . This reveals that Lubiprostone does not exhibit a rebound phenomenon.

To date, no adequate and well-controlled studies of Lubiprostone in pregnant or lactating women have been conducted. In fact, pregnant women were excluded from all clinical trials of Lubiprostone and any woman who became pregnant during a study was immediately discontinued from study participation. Two pregnancies were reported during the development of Lubiprostone. Of the 2 pregnancies, one woman had a healthy baby and the other woman was diagnosed with an ectopic pregnancy. The ectopic pregnancy was resolved by an elective procedure. Given the lack of controlled human pregnancy data from the clinical trials, the labeling of Lubiprostone should reflect the absence of efficacy and safety data for pregnant women or women who could become pregnant.

The addition of Lubiprostone 8 mcg bid for the treatment of constipation predominant irritable bowel syndrome provides a much safer alternative than the only available product at this time. Zelnorm was initially approved on July 24, 2002 and then withdrawn from the market on March 30, 2007 due to cardiovascular adverse event findings. It can be obtained from the sponsor through a treatment IND for adult females under the age of 55 who are identified to be appropriate candidates for Zelnorm by their physicians. Therefore, Lubiprostone with its marginal efficacy in some subjects under the age of 65 can

be a viable and definitely safer alternative. The results of the clinical studies of Lubiprostone 8 mcg bid provide marginal efficacy but considerable safety and tolerability data up to 52 weeks duration in a population of patients with constipation predominant irritable bowel syndrome when compared to no treatment at all. Lubiprostone like most prescription medications is accompanied by some mild and often short-lived side effects, however; these effects are balanced by sustained relief of symptoms of constipation predominant irritable bowel syndrome.

## **9.2 Recommendation on Regulatory Action**

The medical officer recommends an approval action be taken for oral Lubiprostone 16 mcg/day (8 mcg capsules bid) for treatment of constipation predominant irritable bowel syndrome in women  $\geq 18$  years old. Approval of Lubiprostone 16 mcg/day (8 mcg capsules bid) for the treatment of constipation predominant irritable bowel syndrome is contingent upon the sponsor incorporating the Food and Drug Administration's recommended changes to the Lubiprostone drug label and adhering to the required Phase IV commitment studies.

## **9.3 Recommendation on Post-marketing Actions**

The medical officer recommends that the sponsor perform a Phase IV commitment study to determine the safety and efficacy of Lubiprostone in the pediatric population. This study should be conducted in accordance with the Pediatric Research Equity Act of 2007. The sponsor has requested a waiver for the age group 0-5 years old and a deferral for ages 6-17 years old. A pediatric plan along with the deferral has been submitted for the age group 6-17. The medical officer has reviewed the pediatric waiver and agrees with the waiver. The pediatric plan has been reviewed by the medical officer and will be reviewed by PeRC.

Lubiprostone has not been adequately studied in subjects with renal impairment. The medical officer recommends that the sponsor perform a Phase IV study to assess the need for potential dose adjustment in such subjects.

## **9.4 Risk Management Activity**

No new risk management activity required with this supplemental NDA.

## **9.5 Other Phase 4 Requests**

The sponsor should consider conducting studies to establish efficacy and safety of Lubiprostone at the 16 mcg bid dose in constipation predominant irritable bowel syndrome.

## **9.6 Comments to Applicant**

The medical officer has no additional comments for the applicant

## **10 APPENDICES**

### **10.1 Review of Individual Study Reports**

#### **Study SPI/0211SIB-0221**

**Title: A 12-Week, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Phase II Study of safety and efficacy of Oral SPI-0211 for the Treatment of Constipation-predominant Irritable Bowel Syndrome.**

##### **10.1.1 Objectives**

The objectives of this study were to evaluate the safety and efficacy of 3 doses of Lubiprostone in constipation-predominant Irritable Bowel Syndrome (IBS-C). Irritable Bowel Syndrome (IBS) was defined using the Rome II Criteria. According to the Rome II criteria for a diagnosis of IBS one needs: at least 12 weeks or more, which need not be consecutive, in the preceding 12 months, of abdominal discomfort or pain that has 2 out of the 3 features: 1. relieved with defecation; and/or 2. onset associated with a change in frequency of stool; and/or 3. onset associated with a change in form (appearance) of stool. Constipation predominant IBS (IBS-C) is associated with 1 or more of the following symptoms: fewer than 3 bowel movements (BMs) per week, hard or lumpy stools, and/or straining during a bowel movement.

##### **Study Design**

This was a multi-center, parallel-group, double-blind, placebo-controlled study approximately 126 days in duration including baseline and follow-up periods. One hundred and Ninety five subjects (52 to 16 mcg of SPI-0211, 49 to 32 mcg of SPI-0211, 46 to 48 mcg SPI-0211 and 48 to Placebo) were enrolled at 20 centers in the United States. Following initial assessments, including a 4 week baseline period, subjects received 12 weeks of double-blind medication. The study consisted of the screening visit (visit 1), randomization visit (visit 2), 3 interim visits (Visit 3, telephone contact 1 week after randomization; Visit 4, office visit conducted 4 weeks after randomization; Visit 5, office visit conducted 8 weeks after randomization), and an end of treatment (visit 6) at week 12. A final phone interview was conducted 14 days after Visit 6. Subjects completed Irritable Bowel Syndrome-Quality of Life (IBS-QOL) questionnaire at Visits 2, 4, and 6.

In order to qualify for randomization into the double-blind treatment phase, evidence of constipation predominant IBS must have been demonstrated and recorded in the daily diary during the baseline period. Study drug was administered orally for a total treatment period of 12 weeks. It was taken at breakfast and dinner with food and at least 8 ounces of water. Subjects documented abdominal symptoms and bowel activity in a daily diary. The daily and monthly ratings of abdominal discomfort/pain, bloating, and constipation, daily counts of spontaneous bowel movements, bowel movements and use of rescue medications, degree of straining and stool consistency of spontaneous bowel movements, weekly ratings of treatment effectiveness, responder rates at each month and global assessments using IBS-QOL questionnaire and safety and tolerability of administered doses relative to placebo were evaluated to determine efficacy and safety of SPI-0211. The study was conducted between April 2003 and June 2004. Treatment medications were given in one of the following combinations:



Group 1: Three Placebo capsules (Three 0 mcg capsules taken b.i.d) with food at breakfast and dinner with at least 8 ounces of water

Group 2: Two Placebo capsules and one 8 mcg SPI-0211 capsule (Two 0 mcg capsules and one 8 mcg SPI-0211 capsule taken bid) with food at breakfast and dinner with at least 8 ounces of water

Group 3: One Placebo capsule and two 8mcg SPI-0211 capsules (One 0 mcg capsule and Two 8 mcg SPI-0211 capsules taken bid) with food at breakfast and dinner with at least 8 ounces of water

Group 4: Three 8 mcg SPI-0211 capsules (Three 8 mcg SPI-0211 capsules taken bid) with food at breakfast and dinner with at least 8 ounces of water

### **Statistical Methods of Analysis**

The primary efficacy variable was the change from baseline in mean abdominal discomfort/pain ratings during month 1. The change from baseline was calculated as the average of all diary ratings during the baseline period subtracted from the average of all diary ratings during Month 1. Each month represented a 28 day interval beginning with the day of the first dose of study medication (Day 1). Therefore, for the diary assessments, Month 1 started with the daily ratings on Day 1 and ended with the daily ratings on Day 28. Baseline period was defined with respect to diary data as the 28 days prior to the randomization visit (visit 2) for which diary data was recorded. Skipped days were assumed missing and not factored into the baseline period.

The analysis of the primary and secondary efficacy variables were based on 3 subsets: Intent to treat (ITT) subjects with Last observation carried forward (LOCF), ITT subjects without LOCF and per protocol (PP) subjects. No interim analysis was performed. To assess improvement from baseline within each treatment group, the Wilcoxon signed rank tests were performed for most efficacy endpoints at the end of each week and/or month. Results were analyzed by a van Elteren test stratified by pooled center. Small centers (those that consist of  $\leq 8$  ITT subjects) were pooled.

Demographic data (age, gender, height, and race) were summarized for each treatment group and overall. The descriptive statistics included mean for continuous variables and numbers and percentages for categorical variables. Baseline disease status was assessed by IBS history characteristics and evaluation of subjects' ratings of abdominal discomfort/pain, abdominal bloating, constipation severity, spontaneous bowel movement frequency rate, degree of straining, stool consistency, and baseline IBS-QOL questionnaire results at screening/baseline period. The comparability between the treatment groups and between pooled centers was evaluated by separate one way analysis of variance test (ANOVA) for age and height and by chi square tests for nominal categorical variables. These analyses were performed for ITT subjects. Physical examination, medical history and surgical history were summarized by the treatment group and overall, but no inferential statistics was done.

The "last observation carried forward" (LOCF) technique was used to impute missing values. For a given subject, the most recent non-missing treatment-period data point was carried forward to subsequent week or month where data was missing.

**Table 58: Study SIB-0221: Study Schedule**

	Baseline Period		Treatment Period				Follow-up Period
Visit	1 Screening <sup>1</sup>	2 Randomization	3 Interim	4 Interim	5 Interim	6 Final	7 Follow-up
Study Week (Day)	Week – 4 (-31 to -28)	Day 0	Week 1 (7 ± 2)	Week 4 (28 ± 3)	Week 8 (56 ± 3)	Week 12 (84 ± 3)	Week 14 (96 ± 2)
Location	Office	Office	Phone	Office	Office	Office	Phone
Informed Consent	X						
Bowel Symptom Survey	X <sup>2</sup>						
IBS-QOL		X		X		X	
Medical History	X	X					
Inclusion/Exclusion Criteria	X	X					
Weight	X	X		X	X	X	
Vital Signs	X	X		X	X	X	
Physical Exam	X	X		X		X	
Laboratory Tests	X	X		X	X	X	
Serum Pregnancy	X					X	
Urine Dipstick Pregnancy		X					
Sigmoidoscopy or Colonoscopy	X <sup>3</sup>						
12 Lead ECG		X				X	
X-Ray (Hand)		X <sup>4</sup>				X <sup>5</sup>	
Electronic Diary	X <sup>6,7</sup>	X		X	X	X	
Adverse Events			X	X	X	X	X
Concomitant Therapy	X <sup>8</sup>	X	X	X	X	X	X
Study Medication Distribution		X		X	X		
Study Medication Collection				X	X	X	

Reviewer's Table modified from Table 9-1, page 16 of 106 Final Study Report

<sup>1</sup>The timeline for subjects undergoing a sigmoidoscopy or colonoscopy was up to Day -54

<sup>2</sup>Survey is based upon the Rome II Modular Questionnaire for IBS

<sup>3</sup>Procedure necessary if previous results are unavailable or procedure was completed more than 5 years ago

<sup>4</sup>To be completed within 7 days following the Baseline/Randomization Visit

<sup>5</sup>To be completed within 7 days prior to Visit 6

<sup>6</sup>Diary is distributed and data collected for the 4 weeks prior to the subsequent visit

<sup>7</sup>Subjects undergoing a sigmoidoscopy or colonoscopy will begin the diary not less than one week after the completion of the procedure

<sup>8</sup>Concomitant therapy included a history of medications used within 90 days of the screening visit (Visit 1)

As noted in table 58, subjects were screened at Visit 1 to determine their eligibility to enroll in the trial. This visit took place approximately 28 days prior to the subject being placed on double blind study drug. Subjects who had been routinely taking a daily fiber supplement such as Metamucil or Per Diem, etc., for at least 3 months preceding Visit 1 were allowed to remain on the supplement throughout the study and were instructed not to change dosage or schedule. The sponsor did not allow usage of rescue

medications during baseline and treatment periods except under certain conditions. After 3 consecutive days of not having a spontaneous bowel movement (SBM), if a subject needed relief, the investigator could prescribe 10 mg of bisacodyl (Dulcolax) suppository. If this was not effective, Fleet enema was prescribed. If both rescue medications failed, additional rescue medications were prescribed after further discussion with the investigator. All rescue medications administered were recorded and the usage documented in the subject daily diary.

Subjects were instructed to return 28 days after the first day of screening for visit 2 evaluation. Subjects were instructed to return completed daily diaries. Visit 2 occurred approximately 28 days after the screening visit. Before any assessments were performed, subjects were asked to complete the IBS-QOL questionnaire. Baseline ECG was also obtained.

Visit 3 was a telephone interview to ensure compliance, completion of hand X-rays and evaluation of any adverse events. It took place after the subject had completed 1 week of double blind treatment. Subjects were instructed to complete daily diaries and to return their diaries along with the study container at the next visit.

Subjects then returned after approximately 28 days of double blind treatment for visit 4. Subjects completed IBS-QOL questionnaire during this visit. All returned medications were inventoried and subjects were re-dispensed new study medication. Subjects were instructed to complete the diaries and return them to visit 5.

Visit 5 occurred approximately after 56 days of double blind treatment. No physical exam or IBS-QOL questionnaire was performed during this visit. Hand X-rays were scheduled to occur 7 days prior to visit 6.

Subjects returned after approximately 84 days of double blind treatment for visit 6. IBS-QOL questionnaire was completed during this visit. ECGs were performed. Clinical investigators ensured that hand X-rays were performed 7 days prior to this visit. Hand X-rays were compared to baseline hand X-rays. Diaries were then collected and returned to the sponsor.

Visit 7 (Day 98) was a follow-up telephone interview that occurred approximately 14 days after the completion of visit 6.

### **Inclusion/Exclusion Criteria**

For **inclusion criteria** in this study, the patient must:

- be a male or non-pregnant (as per negative serum pregnancy test), non-breast feeding female subject between the ages of 18 and 80.
- had a diagnosis of IBS according to the Rome II Criteria
- Met the criteria for constipation predominant IBS evaluated by the Bowel Symptom Survey
- had 2 or more of the following symptoms during the baseline period as indicated in the subject's electronic daily diary
  - Fewer than 3 SBMs/week at least 25% of the time
  - At least 25% of the SBMs recorded a straining assessment of moderate or greater severity

- At least 25% of the SBMs recorded a stool consistency assessment of hard or very hard stools
- be willing and able to complete his/her own diary and questionnaires
- had read and understood the IRB approved informed consent form

**Exclusion Criteria** for this study encompassed subjects who:

- had diarrhea predominant or alternating (diarrhea and constipation cycling or diarrhea and normal cycling) IBS
- had gastrointestinal or abdominal surgery (except appendectomy, cholecystectomy, fundal plication, hemorrhoidectomy, hysterectomy, and polypectomy)
- had a known or suspected organic disorders of the large or small bowel such as Ulcerative Colitis, Crohn's Disease, mechanical bowel obstruction, and pseudo-obstruction. Subjects under 50 years of age were to have results of flexible sigmoidoscopy or colonoscopy within the last 5 years and following the onset of IBS. If the subject was age 50 or over, results of colonoscopy was required.
- had a history or current diagnosis of medical condition associated with constipation (other than IBS)
- had evidence of unexplained weight loss or rectal bleeding
- had clinically significant cancer within the last 5 years
- had history of any medical/surgical condition that might significantly interfere with the absorption, distribution, metabolism or excretion of the study drug
- had, per the investigator's discretion, clinically significant cardiovascular, liver, or lung disease, neurologic or psychiatric disorders (including active alcohol or drug abuse), other systemic disease, impaired renal function (serum creatinine concentration greater than 1.8 mg/dL)
- had clinically significant abnormalities of hematology, urinalysis or biochemistry per the investigator's discretion
- had taken medication approved for IBS (Zelnorm, etc.) within 4 weeks of the randomization visit (Visit 2)
- had demonstrated a potential for non-compliance with study protocol (i.e., dosing schedule, visit schedule or study procedures)
- was a female of child bearing potential without adequate contraceptive protection during the trial. Oral contraceptives, Depo Provera, or Norplant must have been used for at least 3 months prior to screening visit. Intra uterine devices, sterilization or double barrier methods were to be used during the trial.
- was unwilling to stop administration of disallowed medications 4 weeks preceding randomization and during the treatment periods
- had received an investigational drug within 30 days preceding the screening visit and was a prior participant in a study that involved SPI-0211

### **Demography and Disease History**

A total of 195 subjects were enrolled in this study to receive either 3 different doses of SPI-0211 (8 mcg bid, 16 mcg bid, 24 mcg bid) or Placebo bid at 20 centers in the United States. Of the 195 enrolled subjects, 1 subject in the 48 mcg dose group who was randomized was not treated due to abnormal baseline ECG and another subject in the 16 mcg dose group who was dosed withdrew voluntarily prior to any assessments being complete. Therefore, 193 subjects constituted the Intent to Treat (ITT) population which was defined as any subjects who were randomized, treated with study medication and had an outcome for at least 1 efficacy endpoint. Overall, the study population was predominantly female (175 of 193 subjects, 90.7%) and Caucasian (157 of 193, 81.3%). The mean age of subjects was

45.9 years (range: 19-74 years) and all subjects had a confirmed diagnosis of constipation predominant IBS. Variables like age, height, gender, race, baseline constipation status, baseline IBS disease status, history of medical procedures like Flexible sigmoidoscopy, barium enema and colonoscopy did not differ significantly ( $p > 0.05$ ) between the treatment groups. The 48 mcg SPI-0211 treatment group had slightly more subjects with  $< 3$  SBMs/wk  $\geq 25\%$  of the time as compared to the placebo group, the 16 mcg SPI-0211 and the 32 mcg SPI-0211 treatment groups; however, this was not significantly different ( $p=0.0876$ ). Table 59 below graphically depicts subject demographic information and disease history.

**Table 59: Summary of Demographics Information and Disease History (ITT Subjects)**

Variable	Category	Placebo	Lubiprostone 16 mcg	Lubiprostone 32 mcg	Lubiprostone 48 mcg	Total	P- Value*
<b>Subject Number</b>	<b>N (%)</b>	48 (%)	51 (%)	49 (%)	45 (%)	193 (%)	
<b>Age (years)</b>	Mean	44.6	46.5	48.3	43.9	45.9	0.2083
	SD	11.08	10.14	11.85	11.61	11.22	
	Median	46.0	47.0	47.0	44.0	46.0	
	Range	24.0-69.0	23.0-72.0	24.0-74.0	19.0-72.0	19.0-74.0	
<b>Height (inches)</b>	Mean	65.33	64.42	64.91	65.73	65.08	0.2295
	SD	3.357	3.148	2.963	3.250	3.192	
	Median	66.0	64.0	64.8	65.8	65.0	
	Range	54.0-73.0	58.0-76.0	59.0-71.0	59.0-73.0	54.0-76.0	
<b>Gender</b>	Male	4 (8.3)	4 (7.8)	3 (6.1)	7 (15.6)	18 (9.3)	0.4143
	Female	44 (91.7)	47 (92.2)	46 (93.9)	38 (84.4)	175 (90.7)	
<b>Race</b>	Caucasian	40 (83.3)	40 (78.4)	40 (81.6)	37 (82.2)	157 (81.3)	0.9566
	African-American	2 (4.2)	5 (9.8)	3 (6.1)	4 (8.9)	14 (7.3)	
	Hispanic	6 (12.5)	5 (9.8)	6 (12.2)	4 (8.9)	21 (10.9)	
	Other	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.5)	
Flexible Sigmoidoscopy	NO	34 (70.8)	35 (68.6)	36 (73.5)	32 (71.1)	137 (71.0)	0.9566
	YES	14 (29.2)	16 (31.4)	13 (26.5)	13 (28.9)	56 (29.0)	
Barium Enema	NO	48 (100.0)	50 (98.0)	47 (95.9)	43 (95.6)	188 (97.4)	0.5116
	YES	0 (0.0)	1 (2.0)	2 (4.1)	2 (4.4)	5 (2.6)	
Colonoscopy	NO	13 (27.1)	15 (29.4)	13 (26.5)	13 (28.9)	54 (28.0)	0.9844
	YES	35 (72.9)	36 (70.6)	36 (73.5)	32 (71.1)	139 (72.0)	
<b>Screening Period</b>							
< 3 SBMs/Week $\geq 25\%$ of the time	NO	20 (41.7)	17 (33.3)	14 (28.6)	8 (17.8)	59 (30.6)	0.0876
	YES	28 (58.3)	34 (66.7)	35 (71.4)	37 (82.2)	134 (69.4)	
Straining $\geq$ Moderate $\geq 25\%$ of the Time	NO	4 (8.3)	3 (5.9)	4 (8.2)	2 (4.4)	13 (6.7)	0.8740
	YES	44 (91.7)	48 (94.1)	45 (91.8)	43 (95.6)	180 (93.3)	
Consistency $\geq$ Hard $\geq 25\%$ of the Time	NO	6 (12.5)	6 (11.8)	7 (14.3)	6 (13.3)	25 (13.0)	0.9907
	YES	42 (87.5)	45 (88.2)	42 (85.7)	39 (86.7)	168 (87.0)	

Reviewer's table, modified from Table 11-1, page 48 of 106, Final Study Report

\*p-values are based on one-way ANOVA for age and height, and on Pearson exact chi-square tests for categorical variables

### 10.1.2 Adverse Events

An adverse event (AE) was any undesirable event occurring to a subject during the clinical study, whether or not it was considered related to the study product(s). Events that were absent at baseline and developed after the initiation of double-blind treatment and events that were present at baseline and worsened after the initiation of double blind treatment were to be recorded as AEs. Events with onset dates before randomization or after the last day of treatment plus 14 days were considered to have fallen outside the safety evaluation window. These events were reported in the Adverse events listing and excluded from the summaries. Analyses include all safety data from the date of first dose intake of study medication through the date of last dose plus 14 days.

The principal investigator was required to assess severity of the event and the relationship to the study drug for all AEs, according to the criteria below.

#### **Severity:**

- **Mild:** Transient symptoms, no interference with the subject's daily activities; acceptable
- **Moderate:** Marked symptoms, moderate interference with the subject's daily activities, but still acceptable.
- **Severe:** considerable interference with the subject's daily activities; unacceptable

#### **Relationship to Study Drug:**

- **Unrelated:** Concurrent illness, concurrent medication, or other known cause was clearly responsible for the AE, OR based upon available information regarding subject history, disease process, relationship of the AE to dosing and drug pharmacology, a relationship between the study drug and the AE was unlikely.
- **Possible:** The AE followed a reasonable sequence from the time of study drug administration, but could also have been produced by the subject's clinical state or by other drugs administered to the subject.
- **Probable:** The AE followed a reasonable sequence from the time of study drug administration, followed a known response pattern of the drug class, was confirmed by improvement on stopping the study drug, and the suspect drug was the most likely of all causes.
- **Definite:** The AE followed a reasonable sequence from the time of study drug administration, followed a known response pattern of the drug class, was confirmed by improvement on stopping the study drug, and no other reasonable cause existed.

A serious adverse event (SAE) was any experience that suggested a medical hazard, including any event that:

- was fatal;
- was life-threatening (an event in which the subject was at risk of death at the time of the event; it did not refer to an event that might have caused death had it been more severe);
- required hospitalization or prolonged the existing hospitalization;
- resulted in persistent or significant disability/incapacity;
- was a congenital anomaly; or
- was an important medical event (an event that may not fit the other criteria for a SAE listed above, but based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes listed above)

All SAEs that occurred on or after the day of the first dose of study drug until 14 days after the final dosing with double blind study drug was to be reported immediately to (b) (4).

The original terms used in the case report form by the investigators to identify AEs were coded to MedDRA preferred terms. The incidence of an AE was defined as the number of subjects who experienced at least 1 episode during the study. AEs with onset dates prior to randomization or more than 14 days after the last day of treatment were considered as falling outside the treatment period, and were excluded from the summaries. Events with completely or partially missing onset dates were included in the tabulations, unless the partial date information available clearly indicated that the event happened out of the treatment period.

Of the 195 subjects randomized to Study SIB-0221, 194 subjects were treated with at least 1 dose of double-blind study medication. One subject in the 48 mcg dose group was randomized and not treated with study medication due to abnormal baseline ECG. Therefore, the safety evaluable subjects which was defined as all randomized subjects who took at least 1 dose of double-blind study medication was composed of 194 subjects. Of the 194 subjects, 125 (64.4%) subjects reported at least one adverse event during the study. At least one AE was reported by 67.3% of the subjects in the 16 mcg SPI-0211 treatment group, 61.2% of subjects in the 32 mcg SPI-0211, 71.1% of subjects in the 48 mcg SPI-0211 and 58.3% of subjects in the placebo treatment group.

Adverse events resulted in study discontinuation in a total of 18 subjects (9.3%), 3 subjects (5.8%) in the 16 mcg SPI-0211 group, 8 subjects (16.3%) in the 32 mcg SPI-0211 group, 6 subjects (13.3%) in the 48 mcg SPI-0211 and 1 (2.1%) subject in the placebo group ( $p=0.0175$ ). Vomiting, abdominal pain and distension caused one placebo subject to discontinue the study. One subject each in the 16 mcg SPI-0211 group, 32 mcg SPI-0211 group and 48 mcg SPI-0211 experienced dyspnea which led to study discontinuation. 1 subject each in the 16 mcg and the 32 mcg Lubiprostone groups, but 2 subjects in the 48 mcg group reported nausea as a reason for discontinuing the study. More subjects in the 48 mcg group experienced diarrhea which led them to discontinue the study drug (2 subjects 48 mcg SPI-0211 group vs. 1 subject 32 mcg SPI-0211 vs. 0 in both placebo and 16 mcg SPI-0211 groups).

No subjects died in the study, but there were 3 serious AEs that occurred: 1 subject in the 32 mcg SPI-0211 group had a perforated appendix, 1 subject in the 48 mcg SPI-0211 group had an ectopic pregnancy and another subject in the 48 mcg group had worsening cholecystitis.

A total of 12 subjects (6.2%) had AEs that were considered severe, 5 (9.6%) in the 16 mcg SPI-0211, 5 (10.2%) in the 32 mcg SPI-0211, 2 (4.4%) in the 48 mcg SPI-0211 treatment groups and none in the placebo group,  $p=0.3606$ . In the gastrointestinal disorders, 2 subjects each in the 32 mcg (4.1%) and 48 mcg (4.4%) SPI-0211 groups experienced severe diarrhea. In terms of severity, no other preferred term adverse event was reported by more than one subject.

The most common body system AEs, at the Systems Order Class (SOC) level, were gastrointestinal disorders (overall 82 subjects, 42.3%), infections and infestations (overall 40 subjects, 20.6%), nervous system disorders (overall 26 subjects, 13.4%), and musculoskeletal and connective tissue disorders (overall 12 subjects, 6.2%).

Of the 82 subjects, reporting AEs in the gastrointestinal body system 13 were placebo subjects, 22 were 16 mcg SPI-0211 subjects, 25 were 32 mcg SPI-0211 subjects, and 22 were 48 mcg SPI-0211 subjects. The difference was statistically significant ( $p=0.0204$ ). Same number of subjects (5 subjects) reported abdominal distension in placebo, 32 mcg SPI-0211, and 48 mcg SPI-0211 treatment groups; however, only one subject in the 16 mcg SPI-0211 reported abdominal distension. Equal number of subjects (3 subjects) reported abdominal pain in the placebo and the 32 mcg Lubiprostone groups, but 4 subjects in the 16 mcg SPI-0211 and 2 subjects in the 48 mcg SPI-0211 groups reported abdominal pain. The 16 mcg SPI-0211 group reported abdominal pain-lower (1 subject) and abdominal pain-upper (2 subjects). However, 2 subjects reported abdominal pain-lower in the 32 mcg SPI-0211 group. Diarrhea (12 subjects, 26.7% in 48 mcg vs. 7 subjects, 13.5% in 16 mcg vs. 6 subjects, 12.2% in 32 mcg vs. 2 subjects, 4.2% in placebo) and nausea (14 subjects, 31.1% in 48 mcg vs. 10 subjects, 19.2% in 16 mcg vs. 9 subjects, 18.4% in 32 mcg vs. 6 subjects, 12.5% in placebo) were reported in higher frequency in the varying doses of SPI-0211. Vomiting occurred with the same frequency in the 16 mcg and 32 mcg group (1 subject each) but was higher in placebo (3 subjects, 6.3%) and 48 mcg SPI-0211 groups (4 subjects, 8.9%).

Of the 40 subjects, reporting AEs in the infections and infestations organ class 6 were placebo subjects, 13 were 16 mcg SPI-0211 subjects, 9 were 32 mcg SPI-0211 subjects, and 12 were in the 48 mcg SPI-0211 subjects,  $p=0.1835$ . The overall frequency of the events were similar except for upper respiratory tract infection (4 subjects in 48 mcg, 8.9% vs. 5 subjects in 16 mcg, 9.6% vs. 3 subjects in 32 mcg, 6.1% vs. 1 subject in placebo, 2.1%) and urinary tract infection (5 subjects in 48 mcg, 11.1% vs. 4 subjects in 16 mcg, 7.7% vs. 0 subjects in 32 mcg and in placebo, 0.0%). There were a higher proportion of subjects in the 16 mcg and the 48 mcg SPI-0211 dose groups that reported upper respiratory tract and urinary tract infections.

Of the 26 subjects, reporting AEs in the nervous system disorders 8 were placebo subjects, 4 were 16 mcg SPI-0211 subjects, 8 were 32 mcg SPI-0211 subjects, and 6 were 48 mcg SPI-0211 subjects,  $p=0.9700$ . At the adverse event level, dizziness (3 subjects in 32 mcg vs. 2 subjects each in 16 mcg, 48 mcg SPI-0211 and in placebo) and headache (4 subjects in placebo, 8.3% vs. 3 subjects in 32 mcg, 6.1% vs. 2 subjects each in 16 mcg and 48 mcg) were reported in highest frequency among subjects.



**Table 60: Summary of Subject Disposition: All Randomized Subjects**

<b>Variable</b>	<b>Placebo N=48 n (%)</b>	<b>Lubiprostone 16mcg N=52 n (%)</b>	<b>Lubiprostone 32mcg N=49 n (%)</b>	<b>Lubiprostone 48mcg N=46 n (%)</b>	<b>Total N=195 n (%)</b>
Subjects Randomized	48 (100)	52 (100)	49 (100)	46 (100)	195 (100)
Subjects Randomized but not Treated	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.5)
Subjects Treated	48 (100)	52 (100)	49 (100)	45 (97.8)	194 (99.5)
Subjects Completed	41 (85.4)	42 (80.8)	33 (67.3)	30 (65.2)	146 (74.9)
Subjects Discontinued	7 (14.6)	10 (19.2)	16 (32.7)	16 (34.8)	49 (25.1)
<b>Reason for Discontinuation</b>					
Adverse Events	1 (2.1)	3 (5.8)	8 (16.3)	6 (13.0)	18 (9.2)
Lack of Efficacy	6 (12.5)	3 (5.8)	4 (8.2)	4 (8.7)	17 (8.7)
Voluntary Withdrawal	0 (0.0)	4 (7.7)	3 (6.1)	3 (6.5)	10 (5.1)
Non-Compliance	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.5)
Lost to F/U	0 (0.0)	0 (0.0)	1 (2.0)	1 (2.2)	2 (1.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.5)
<b>Timing of Early Discontinuation</b>					
Week 1	0 (0.0)	3 (5.8)	2 (4.1)	3 (6.5)	8 (4.1)
Week 2	1 (2.1)	2 (3.8)	2 (4.1)	1 (2.2)	6 (3.1)
Week 3	1 (2.1)	1 (1.9)	3 (6.1)	2 (4.3)	7 (3.6)
Week 4	0 (0.0)	1 (1.9)	4 (8.2)	4 (8.7)	9 (4.6)
Week 5-8	3 (6.3)	3 (5.8)	4 (8.2)	4 (8.7)	14 (7.2)
Week 9-12	2 (4.2)	0 (0.0)	1 (2.0)	2 (4.3)	5 (2.6)
<b>Number of days on Study Drug*</b>					
Mean (Std Dev)	75.88 (19.039)	72.87 (26.156)	66.27 (29.095)	66.58 (28.600)	70.48 (26.133)

Reviewer's table, modified from Table 10-1, page 46 of 106, Final Study Report

\*Number of Days on Study Drug = (Date of Last Dose – Date of First Dose + 1)

### 10.1.3 Withdrawals, Compliance, and Protocol Violations

A total of 195 subjects were randomized into the study. 48 subjects into the placebo group, 52 into the 16 mcg SPI-0211 group, 49 into the 32 mcg SPI-0211 group, and 46 into the 48 mcg SPI-0211 group. One subject in the 48 mcg SPI-0211 group was randomized but not treated, making a total of 45 subjects who were treated with 48 mcg SPI-0211, 49 subjects treated with 32 mcg SPI-0211, 52 subjects treated with 16 mcg SPI-0211, and 48 subjects treated with placebo. A total of 146 subjects completed the study. The percentage of subjects completing the study was 85.4% in the placebo group, 80.8% in the 16 mcg SPI-0211 group, 67.3% in the 32 mcg group, and 65.2% in the 48 mcg SPI-0211 group. The mean

number of days the subjects were on the study drug was 75.88 in the placebo group, 72.87 in the 16 mcg SPI-0211 group, 66.27 in the 32 mcg SPI-0211 group, and 66.58 in the 48 mcg SPI-0211 group. A total of 49 subjects (14.6%, 7 Placebo; 19.2%, 10 16 mcg SPI-0211; 32.7%, 16 32 mcg SPI-0211; 34.8%, 16 48 mcg SPI-0211) discontinued the study. The reasons for discontinuation were AEs (18 subjects, 9.2%), lack of efficacy (17 subjects, 8.7%), voluntary withdrawal (10 subjects, 5.1%), lost to follow-up (2 subjects, 1.0%) and non-compliance (1 subject, 0.5%). The majority of the 32 mcg and 48 mcg SPI-0211 subjects that discontinued the study discontinued due to adverse events while in the placebo group only 1 (2.1%) subject discontinued due to an adverse event. The most common reason for withdrawal in the placebo group was lack of efficacy; whereas, there was an equal number of patients in the 16 mcg SPI-0211 who withdrew for adverse events (3, 5.8%) and lack of efficacy (3, 5.8%). The number of subjects discontinuing in the first week was higher for all the treatment groups of SPI-0211 (3 subjects in 16 mcg, 2 subjects in 32 mcg, 3 subjects in the 48 mcg) than placebo (0 subjects). At week 4, none of the subjects in the placebo group dropped out of the study whereas 1 (1.9%) subject in 16 mcg, 4 (8.2%) subjects in the 32 mcg, and 4 (8.7%) subjects in the 48 mcg treatment group discontinued the study.

## Compliance

Treatment compliance was estimated by using the study drug administration record in the subject's daily diary and case report form (CRF). The percent compliance was calculated by dividing the actual cumulative exposure to study drug by the exposure the subject should have received (based on the number of days the subject was on the study drug). The percent compliance was the lowest in the 32 mcg (85.3% - 95.2%) and 48 mcg (86.4% - 93.1%) SPI-0211 treatment group in all three months compared to Placebo (91.4% - 97.0%). The 16 mcg (90.3% - 98.2%) treatment group had similar compliance percent as Placebo. 8 subjects in the 32 mcg SPI-0211 treatment group and 7 subjects in the 48 mcg SPI-0211 treatment group required dose reductions compared to 1 subject each in Placebo and 16 mcg SPI-0211 treatment groups. By month 3, the  $\geq 70\%$  compliance had decreased (79.2% Placebo, 78.4% 16 mcg SPI-0211, 57.1% 32 mcg SPI-0211, 60.0% 48 mcg SPI-0211) significantly more than month 1 (100% Placebo, 100% 16 mcg SPI-0211, 89.8% 32 mcg SPI-0211, 84.4% 48 mcg SPI-0211) for all treatment groups. The  $< 70\%$  study drug compliance was highest in month 3 (8.3%) relative to months 1 (4.7%) and 2 (5.2%) which had similar rates. Overall, a total of 14 subjects, 1 in placebo group, 0 in 16 mcg SPI-0211, 4 in 32 mcg SPI-0211, 9 in 48 mcg SPI-0211, had treatment compliance of  $< 70\%$ ,  $p=0.001$ .

## Protocol Deviations

The following protocol violations were determined and entered into the database after "soft lock" and before "hard lock" and unblinding. Data of the protocol violators were removed from the per protocol subset for the applicable month. Protocol violators were identified using the following criteria:

- Any subject who took at least 1 of the prohibited concomitant medications listed in the protocol (anticholinergics, anti-spasmodics, prokinetic agents, cholinesterase inhibitors, laxatives such as MiraLax, ExLax, etc.) that was not prescribed as a rescue medication by the investigator, was a protocol violator during the month(s) in which the medication was taken.
- A subject who took fewer than 70% of the required double-blind doses for a given month was considered a protocol violator for that month.

Across all 3 months, the most frequent protocol violations were use of prohibited concomitant medications and < 70% study drug compliance. In the baseline period, however, protocol violations were due to prohibited concomitant medication use and inclusion/exclusion criteria violations or misrandomization. The use of prohibited concomitant medications was highest in the baseline period and then decreased during months 1-3 in each treatment group except the 16 mcg group. In the 16 mcg dose group, the use of prohibited concomitant medications was lowest during the baseline period (62.7% at Month 0, 66.7% at Month 1, 64.7% at Month 2, 66.7% at Month 3). The 48 mcg SPI-0211 (51.1%-55.6%) had the least use of prohibited concomitant medication relative to Placebo (66.7%-75.0%), the 16 mcg (64.7%-66.7%) and 32 mcg SPI-0211 (77.6%-79.6%) treatment groups. Contact laxatives were used by more subjects in the 16 mcg SPI-0211 (33 subjects), in the 32 mcg SPI-0211 (26 subjects) and the 48mcg SPI-0211 (24 subjects) than in the placebo (21 subjects) treatment group. Likewise, the use of fleet enema in the 16 mcg (29 subjects), the 32 mcg (21 subjects) and the 48 mcg (20 subjects) SPI-0211 dose groups was higher than placebo (17 subjects) treatment group. 9 subjects in the placebo group used bulk producers whereas 14 subjects each used them in the 16 mcg and 32 mcg SPI-0211 treatment groups.

The rescue medication usage was higher than Placebo in 16 mcg and 32 mcg SPI-0211 treatment groups across all months. However, in the 48 mcg SPI-0211 dose group, rescue medication usage was lower than Placebo in month 1 but higher than placebo in months 2 and 3. For Month 1, 13 subjects in the placebo group used rescue medications whereas 16 subjects in the 16 mcg SPI-0211 and 19 subjects in the 32 mcg SPI-0211 treatment groups. Similarly, 8 subjects in month 2 and 7 subjects in month 3 in the placebo treatment group used rescue medications compared to 19 subjects in month 2 and 17 subjects in month 3 in the 16 mcg SPI-0211 group. The 32 mcg SPI-0211 treatment group had 10 subjects in both months 2 and 3 that used rescue medications. Overall, all doses of SPI-0211 had higher rates of rescue medication usage compared to placebo subjects, but the 48 mcg dose was the only dose group that used rescue medication for less percent of days than placebo group (48 days Placebo, 51 days 16 mcg, 49 days 32 mcg, 45 days 48 mcg).

#### **10.1.4 Efficacy Results**

##### **Primary Efficacy Endpoint**

The primary efficacy was the change from baseline in mean abdominal discomfort/pain ratings during treatment month 1. The baseline value was defined as the average value obtained from the diary data during the course of the baseline period. The change from baseline was calculated as the average of all diary ratings during the 4 week baseline period subtracted from the average of all diary ratings during treatment month 1. For these diary assessments, each month represented a 28 day interval beginning with the day of the first dose of study drug (Day 1). Therefore, month 1 started with the daily assessment on Day 1 and ended with the daily assessment on Day 28. The assessment of abdominal pain was based on the daily question: How would you rate your abdominal discomfort/pain today? Abdominal discomfort/pain was rated by the subjects each evening based on the scale: 0 (absent), 1 (mild), 2 (moderate), 3 (severe), and 4 (very severe).

For the ITT subjects with LOCF, the mean abdominal discomfort/pain ratings at baseline was 2.02 for placebo, 2.18 for 16 mcg SPI-0211, 2.17 for 32 mcg SPI-0211 and 2.10 for 48 mcg SPI-0211 groups. During Month 1, the mean decrease in abdominal pain was greater in the SPI-0211 (0.40-0.46) treated

groups compared to placebo (0.19). The greatest mean decrease in abdominal pain ratings occurred in the 48 mcg SPI-0211 (0.46) and the 16 mcg SPI-0211 (0.45). All SPI-0211 treatment groups showed statistically significant difference from baseline,  $p < 0.0001$ . The difference from placebo in mean change from baseline in abdominal discomfort/pain was significant in the 48 mcg SPI-0211 dose group,  $p = 0.0226$  using the multiple comparisons step-down procedure. Based on this analysis, it was deduced that SPI-0211 treatment with 48 mcg SPI-0211 dose produced statistically significant improvement in abdominal discomfort/pain in subjects with constipation predominant IBS. Although the 16 mcg dose group did produce a mean change of 0.45 in abdominal pain/ discomfort rating, the difference was not statistically significant relative to placebo using the multiple comparisons step-down procedure.

### **Study SPI/0211SIB-0431**

**Title: 12 Week Multi-Center, Double-Blind, Randomized, Placebo-Controlled Phase III Study of Efficacy and Safety of Lubiprostone for the Treatment of Constipation-predominant Irritable Bowel Syndrome.**

#### **10.1.1 Objectives**

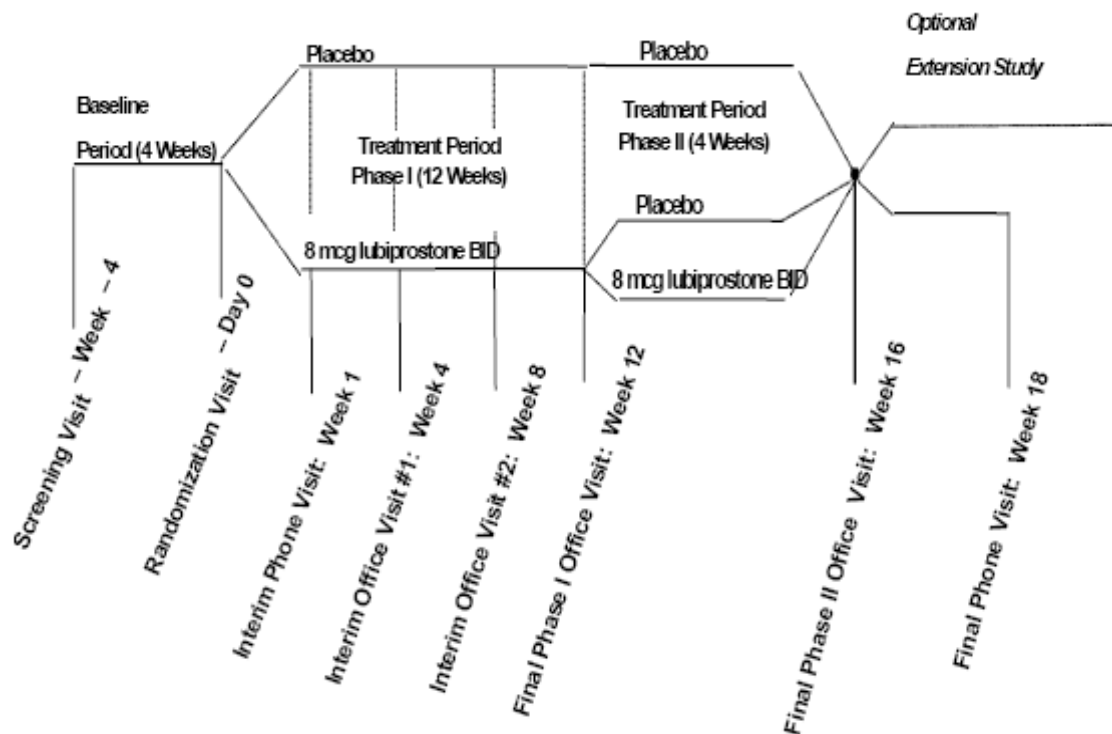
The primary objective of this study was to assess the efficacy and safety of oral 16 mcg Lubiprostone compared to placebo for the treatment of constipation predominant irritable bowel syndrome. IBS is defined using the Rome II Criteria. According to the Rome II criteria for a diagnosis of IBS one needs: at least 12 weeks or more, which need not be consecutive, in the preceding 12 months, of abdominal discomfort or pain that has 2 out of the 3 features: 1. relieved with defecation; and/or 2. onset associated with a change in frequency of stool; and/or 3. onset associated with a change in form (appearance) of stool. Constipation-predominant IBS is associated with 1 or more of the following symptoms: fewer than 3 BMs per week, hard or lumpy stools, and/or straining during a bowel movement.

The secondary objective of the study was to investigate the rebound phenomenon associated with the withdrawal of Lubiprostone treatment.

#### **Study Design**

This was a multi-center, parallel group, double blinded, placebo controlled study of approximately 154 days duration including randomized withdrawal phase and follow-up. For treatment phase I, five hundred and ninety subjects (396 subjects in the Lubiprostone treatment arm and 194 in the placebo group) were enrolled in 65 centers in the United States. For the Randomized withdrawal (treatment phase II), the 396 subjects in the Lubiprostone treatment group were pre-randomized in a 1:1 ratio to either receive placebo or continue treatment with Lubiprostone. The 194 subjects assigned to placebo in treatment phase I remained in placebo in treatment phase II. Following initial assessments, including a 4 week baseline period, subjects received 12 weeks of double-blind medication. The study consisted of the screening visit (visit 1), randomization visit (visit 2), 3 interim visits (visit 3, telephone contact 1 week after randomization; visit 4, office visit conducted 4 weeks after randomization; visit 5, office visit conducted 8 weeks after randomization), an end of treatment phase I (visit 6) at week 12 and an end of treatment phase II (visit 7) at week 16. A final phone interview was conducted 14 days after visit 7. Subjects completed Irritable Bowel Syndrome-Quality of Life (IBS-QOL) questionnaire at Visits 2, 4, 6 and 7.

**Figure 1: Study SIB-0431 Treatment Phase I and II Schematic**



Sponsor's Figure, Clinical Study Report-SIB-0431 Final Version, page 18 of 89

In order to qualify for randomization into the double-blind treatment phase, evidence of constipation predominant IBS must have been demonstrated and recorded in the daily diary during the baseline period. Study drug was administered orally for a total treatment period of 12 weeks for treatment phase I and 4 weeks for treatment phase II; it was taken at breakfast and dinner with food and at least 8 ounces of water. Subjects documented abdominal symptoms and bowel activity in a daily diary. The daily ratings of abdominal discomfort/pain, bloating, constipation, daily counts of spontaneous bowel movements, bowel movements and use of rescue medications, degree of straining and stool consistency of spontaneous bowel movements, weekly ratings of global symptom relief, and IBS-QOL questionnaire and the safety and tolerability of administered doses relative to placebo were evaluated to determine the efficacy and safety of Lubiprostone. The study was conducted between May 2005 and July 2006. Treatment medication was given in one of the following combinations:

#### **Treatment Phase 1**

Group 1: 194 control subjects: Two Placebo capsules (one 0 mcg capsule taken b.i.d) with food at breakfast and dinner with at least 8 ounces of water

Group 2: 396 treatment subjects: Two 8 mcg Lubiprostone capsules (One 8 mcg Lubiprostone capsule taken bid) with food at breakfast and dinner with at least 8 ounces of water

#### **Treatment Phase II**

Placebo subjects (Group 1) from Treatment Phase I continued to receive Placebo

Subjects assigned to Lubiprostone (Group 2 from treatment Phase I, 396 subjects) are pre-randomized in a 1:1 ratio to receive the following:

Group 2a: 198 withdrawal subjects: Two Placebo capsules (one 0 mcg capsule taken b.i.d) with food at breakfast and dinner with at least 8 ounces of water

Group 2b: 198 treatment subjects: Two 8 mcg Lubiprostone capsules (One 8 mcg Lubiprostone capsule taken bid) with food at breakfast and dinner with at least 8 ounces of water.

### **Statistical Methods of Analysis**

The primary efficacy variable was the overall responder rate during the 12 week treatment period of phase I. An overall responder was defined as a monthly responder for at least 2 out of the 3 months during the Treatment Phase I. A Monthly responder was defined as a subject whose symptoms were rated as moderately relieved for all 4 weeks within a month or significantly relieved for at least 2 weeks within a month provided the three conditions were met:

1. The percent of days of rescue medication use did not increase during the month as compared to baseline.
2. The subject did not discontinue the study during the month due to lack of efficacy.
3. The subject had no ratings of moderately worse or significantly worse during the month.

Monthly and overall responder definitions were based on the weekly assessments of global symptom relief obtained as part of the subject's electronic diary responses. Global symptom relief was assessed from the 7 point balanced scale associated with the following weekly 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?

- 3 Significantly relieved
- 2 Moderately relieved
- 1 A little bit relieved
- 0 Unchanged
- 1 A little bit worse
- 2 Moderately Worse
- 3 Significantly Worse

A Cochran-Mantel-Haenszel (CMH) test, stratified by pooled center was used to test the null hypothesis of equal rates between the 2 treatment groups vs. the alternate hypothesis of non-equality. Small centers (i.e. those that consisted of < 9 ITT subjects) were pooled.

Monthly responder rates were calculated for each month (months 1, 2 and 3) during the 12 week treatment period. Diary data were summarized by week and month. In treatment phase I, Week 1 and Month 1 started with the day of the first dose of study medication (Day 1). Week 1 ended 6 days later (Day 7) and Month 1 ended 27 days later (Day 28). Each subsequent treatment phase I week represented a 7 day interval and a month represented a 28 day interval following the previous week and month respectively. Treatment Phase II started at Week 13, Month 4 beginning with the first dose date (Day 1) for phase II. Week 13 ended 6 days later and month 4 ended 27 days later. Each subsequent treatment phase II week represented a 7 day interval following the previous week.

The subject had to answer a maximum of 9 daily questions and 1 weekly question. The previously discussed weekly question was the basis for the monthly responder rates. The other 9 daily assessments recorded in the diary were used as secondary endpoints. For the monthly responder rate, missing symptom relief ratings during the month were treated as ratings of “unchanged” relief. In treatment phase I, multiple efficacy variables were controlled in the monthly responder analyses via further testing procedures. Once the primary analysis of overall responder rate was significant, the 3 step testing procedure was utilized to test at the  $\alpha = 0.05$  level for each month individually and simultaneously and in a combined manner. The 3 step testing process is explained in detail in the Agency’s statistical review.

The analysis of the primary and secondary efficacy variables were based on 4 subsets: Intent to treat (ITT) subjects with last observation carried forward (LOCF), ITT subjects without LOCF, per protocol (PP) subjects and study completers without LOCF. No interim analysis was performed.

Demographic data (age, gender, height, and race) was summarized for each treatment. The descriptive statistics included mean for continuous variables and numbers and percentages for categorical variables. Baseline disease status was assessed by Bowel Symptom Survey (BSS) administered during the screening visit (visit 1), the baseline period evaluation of subjects’ ratings of abdominal discomfort/pain, abdominal bloating, constipation severity, spontaneous bowel movement frequency rate, straining, stool consistency, and baseline IBS-QOL questionnaire results. The comparability between the treatment groups and between pooled centers was evaluated by separate one way analysis of variance test (ANOVA) for age and by chi square tests for categorical variables such as race and gender. These analyses were for ITT subjects. Physical examination, medical history and surgical history were summarized by the treatment group and overall, but no inferential statistics was done.

The “last observation carried forward” (LOCF) technique was used to impute missing values. For a given subject, the most recent non-missing treatment-period data point was carried forward to subsequent week or month where data were missing. The LOCF technique was applied to weekly and monthly averages and not to data from daily ratings. In treatment phase I, LOCF was used for the non-key secondary efficacy endpoints with the exception of IBS-QOL. Likewise, the LOCF method was performed for non-key secondary efficacy endpoints in Treatment Phase II and only data from Treatment Phase II can be carried forward in Treatment Phase II. No LOCF method was applied to the follow-up period.

**Table 61: Study SIB-0431 Treatment Phase I and Treatment Phase II  
Study Schedule**

Period	Baseline		Treatment Phase I				Treatment Phase II	Follow-up
Visit	1 Screening	2 Randomization	3 Interim	4 Interim	5 Interim	6 Phase I Final	7 Phase II Final	8 Follow-up <sup>1</sup>
Study Week (Day)	Week – 4 (-28+3)	Week 0 Day 0	Week 1 (7 ± 2)	Week 4 (28 ± 3)	Week 8 (56 ± 3)	Week 12 (84 ± 2)	Week 16 (112 ± 3)	Week 18 (126 ± 2)
Location	Office	Office	Phone	Office	Office	Office	Office	Phone
Informed Consent	A <sup>2</sup>							
Bowel Symptom Survey <sup>3</sup>	A <sup>2</sup>							
IBS-QOL		X		X		X	X	
Medical History	B <sup>2</sup>	X						
Inclusion/ Exclusion Criteria	B <sup>2</sup>	X						
Height	B <sup>2</sup>							
Weight	B <sup>2</sup>	X		X	X	X	X	
Vital Signs	B <sup>2</sup>	X		X	X	X	X	
Physical Exam	B <sup>2</sup>	X				X		
Laboratory Tests	B <sup>2</sup>	X		X	X	X	X	
Serum Pregnancy Test	B <sup>2</sup>					X	X	
Urine Dipstick Pregnancy Test		X						
Adverse Events			X	X	X	X	X	X
Concomitant Therapy	B <sup>2, 4, 5</sup>	X	X	X	X	X	X	X
Sigmoidoscopy or Colonoscopy <sup>6</sup>	C <sup>2, 7, 8</sup>							
Electronic Diary	C <sup>2, 9</sup>	X	X	X	X	X	X	
Study Medication Distribution		X		X	X	X		
Study Medication Collection				X	X	X	X	

Reviewer's Table modified from Table 9-1, page 16 of 106 Final Study Report: SIB-0431

<sup>1</sup>Subjects enrolling into the extension study skipped this visit.

<sup>2</sup>The screening visit was divided into Segments A, B, C, all of which were completed on the same day unless the subject needed a colonoscopy or flexible sigmoidoscopy.

<sup>3</sup>Survey based upon the Rome II Modular Questionnaire (Investigator Form) for IBS.

<sup>4</sup>Included a history of medications used within 90 days of Screening Visit (Visit 1).

<sup>5</sup>Updated to include any new therapy used during screening and for completion of the colonoscopy.

<sup>6</sup>A flexible sigmoidoscopy could be completed instead of a colonoscopy for a subject less than 50 years of age.

<sup>7</sup>Subjects needing a colonoscopy/flexible sigmoidoscopy were given an additional 28 days to complete up to Day -54

<sup>8</sup>Procedure necessary if previous results were unavailable or procedure was completed more than 5 years ago or prior to the onset of IBS.

<sup>9</sup>Subjects who underwent a colonoscopy or flexible sigmoidoscopy began the diary at least 1 week (and the bowel habits return to prior status) following the completion of the procedure.

As noted in table 61, subjects were screened in 3 segments: A, B, C at visit 1. Subjects were screened at Visit 1 to determine their eligibility to enroll in the trial. This visit took place approximately 28 days prior to the subject being placed on double blind study drug. Subjects who had been routinely taking a daily fiber supplement such as Metamucil or Per Diem, etc., for at least 2 months preceding Visit 2 were allowed to remain on the supplement throughout the study and were instructed not to change dosage or



schedule. The sponsor did not provide rescue medications. However, after 3 consecutive days of not having a SBM, if a subject needed relief, the investigator could prescribe 10 mg of bisacodyl (Dulcolax) suppository. If this was not effective, Fleet enema was prescribed. If both rescue medication failed, additional rescue medications were prescribed after further discussion with the investigator. All rescue medications administered were recorded and the usage documented in the subject daily diary.

Subjects were instructed to return 28 days after the first day of the baseline period for Visit 2 evaluation. Subjects were instructed to return completed daily diary. Visit 2 occurred approximately 28 days after the screening visit. Before any assessments were performed, subjects were asked to complete the IBS-QOL questionnaire.

Visit 3 was a telephone interview to ensure compliance and to evaluate any adverse events. It took place after the subject had completed 1 week of double blind treatment. Subjects were instructed to complete daily diary and to return the diary along with the study container at the next visit.

Subjects then returned after approximately 28 days of double blind treatment for Visit 4. Subjects completed IBS-QOL questionnaire during this visit. All returned medications were inventoried and subjects were re-dispensed new study medication. Subjects were instructed to complete the diary and return them to Visit 5.

Visit 5 occurred after approximately 56 days of double blind treatment. No physical exam or IBS-QOL questionnaire was performed during this visit.

Subjects returned after approximately 84 days of double blind treatment for Visit 6. IBS-QOL questionnaire and a physical examination was completed during the visit. Since visit 6 was the end of phase I treatment, some subjects were dispensed study drug that might have been different from the previous 12 weeks. This visit was conducted not only for subjects that were involved in the study, but also, for subjects that withdrew early during treatment phase I.

Visit 7 was the end of phase II treatment and occurred after approximately 112 days of double blind treatment. During this visit, IBS-QOL questionnaire was completed. Returned study medications were inventoried, diaries were reviewed to verify completion and they were returned to the sponsor. The subjects were given the option to enroll in an open label extension study. Subjects not enrolling in open label study were scheduled for follow-up phone interview to occur in 2 weeks.

A follow-up telephone interview occurred approximately 14 days after the completion of Visit 7 (Day 126). This visit included subjects who withdrew from the study.

### **Inclusion/Exclusion Criteria**

For **inclusion** criteria in this study, the patient must:

- be a male or non-pregnant (as per negative serum pregnancy test), non-breast feeding female subject at least 18 years of age.
- had a diagnosis of IBS according to the Rome II Criteria
- met the criteria for constipation predominant IBS evaluated by the Bowel Symptom Survey

- had a monthly average assessment of mild or greater severity for rating of abdominal discomfort/pain as indicated in the subject's electronic diary.
- had any 2 of the following symptoms during the baseline period as indicated in the subject's electronic daily diary
  1. Fewer than 3 SBMs/week at least 25% of the time (a subject not experiencing a single SBM during the baseline period was required to meet only the first criteria)
  2. At least 25% of the SBMs recorded a straining assessment of moderate or greater severity
  3. At least 25% of the SBMs recorded a stool consistency assessment of hard or very hard stools
- was willing and able to fill out his/her own diary and IBS-QOL questionnaires
- had read and understood the IRB approved informed consent form

**Exclusion** Criteria for this study encompassed subjects who:

- had diarrhea-predominant or alternating (diarrhea and constipation cycling) IBS
- had gastrointestinal or abdominal surgery (except appendectomy, cholecystectomy, fundal plication, hemorrhoidectomy, hysterectomy, polypectomy, tubal ligation and Caesarean section)
- had a known or suspected organic disorders of the large or small bowel such as Ulcerative Colitis, Crohn's Disease, mechanical bowel obstruction, and pseudo-obstruction. Subjects under 50 years of age were to have results of flexible sigmoidoscopy or colonoscopy within the last 5 years following the onset of IBS. If the subject was age 50 or over, results of colonoscopy was required.
- had a history or current diagnosis of medical condition associated with constipation (other than IBS)
- had evidence of unexplained weight loss or rectal bleeding
- had clinically significant cancer within the last 5 years
- had history of any medical/surgical condition that might significantly interfere with the absorption, distribution, metabolism or excretion of the study drug
- had, per the investigator's discretion clinically significant cardiovascular, liver, or lung disease, neurologic or psychiatric disorders (including active alcohol or drug abuse), other systemic disease, impaired renal function (serum creatinine concentration greater than 1.8mg/dl)
- had clinically significant abnormalities of hematology, urinalysis or biochemistry per the investigator's discretion
- had taken medication approved for IBS (Zelnorm, etc.) within 4 weeks of the randomization visit (Visit 2)
- had demonstrated a potential for non-compliance with study protocol (i.e., dosing schedule, visit schedule or study procedures)
- was a female of child bearing potential without adequate contraceptive protection during the trial. Oral contraceptives, Depo Provera, or Norplant must have been used for at least 3 months prior to screening visit (visit 1). Intra uterine devices, sterilization or double barrier methods were to be used during the trial.
- was unwilling to stop administration of disallowed medications 4 weeks preceding randomization and during the treatment periods
- had received an investigational drug within 30 days preceding the screening visit and was a prior participant in a study that involved Lubiprostone

## **Demography and Disease History**

In treatment phase I, a total of 590 subjects were enrolled in this study to receive either 8 mcg bid of Lubiprostone or Placebo bid at 65 centers in the United States. Of the 590 subjects, 583 subjects (193 Placebo, 390 Lubiprostone) made up the ITT population. The ITT population was defined as the set of all randomized subjects who took at least 1 dose of double blind study medication and had at least 1 treatment-period diary entry. The overall study population was predominately female (535 of 583 subjects, 91.8%) and Caucasian (435 of 583, 74.6%). The mean age of subjects was 47.2 years (range: 19-85 years), and all subjects had a confirmed diagnosis of constipation predominant IBS. Variables like age, height, gender, and race did not differ significantly ( $p > 0.05$ ) between the treatment groups.

The responses to the Bowel Symptom Survey did not differ significantly between placebo and Lubiprostone groups but no statistical analysis was performed. The 16 mcg Lubiprostone treatment group had slightly more subjects than placebo with abdominal discomfort/pain that rarely improved after BMs (21 subjects, 5.4% vs. 4 subjects, 2.1%); more subjects that had abdominal discomfort/pain that was rarely associated with stool consistency (7 subjects, 1.8% vs. 0 subjects, 0.0%), and more subjects who report hard or lumpy stools (7 subjects, 1.8% vs. 1 subject 0.5%). Despite more subjects in the 16 mcg Lubiprostone treatment group reporting loose, mushy, or watery stools (20 subjects, 5.2% vs. 6 subjects, 3.1%), there were similar percentages of subjects in both treatment groups (Lubiprostone and Placebo) that reported rushing to the toilet (39 subjects, 10.1% vs. 20 subjects, 10.5%).

As per table 62, both placebo subjects and Lubiprostone subjects had similar baseline period IBS disease status,  $p > 0.05$ . History of medical procedures like colonoscopy occurred in more placebo subjects than 16 mcg Lubiprostone treated subjects (4 subjects, 2.1% vs. 0 subjects, 0.0%). More subjects in the Lubiprostone treatment group compared to placebo treatment group list dyspepsia (51 subjects, 13.1% vs. 22 subjects, 11.4%), nausea (13 subjects, 3.3% vs. 3 subjects, 1.6%) and abdominal distension (9 subjects, 2.3% vs. 3 subjects, 1.6%) as an active medical problem. A greater percentage of subjects in the placebo treatment group (59, 30.6% vs. 92, 23.6%) reported drug sensitivity as an active medical problem. Headache (63 subjects, 16.2% vs. 27 subjects, 14.0%), migraine headache (50 subjects, 12.8% vs. 21 subjects, 10.9%), tension headache (10 subjects, 2.6% vs. 3 subjects, 1.6%) and cluster headache (2 subjects, 0.5% vs. 0 subjects, 0.0%) were reported by more subjects in the Lubiprostone treatment group than in placebo. No statistical analysis was performed on the medical history, history of procedures or active medical problems.

**Table 62: Summary of Demographics and Disease History**  
**Study SIB-0431 Treatment Phase I (ITT Population)**

Study 312-0101 Treatment Phase 1 (ITT Population)					
Variable	Statistic	Placebo	Lubiprostone 16 mcg	Total	p-Value <sup>3</sup>
Age (years)	n (%)	193	390	583	0.198
	Mean	48.1	46.7	47.2	
	SD	12.55	12.74	12.69	
	Median	48.0	47.0	47.0	
	Range	20.0-85.0	19.0-83.0	19.0-85.0	
Height (inches)	Mean	64.8	64.9	64.9	0.626
	SD	3.09	2.90	2.96	
	Median	64.0	64.5	64.5	
	Range	56.2-74.0	57.0-75.0	56.2-75.0	
Gender n (%)	Female	180 (93.3)	355 (91.0)	535 (91.8)	0.355
	Male	13 (6.7)	35 (9.0)	48 (8.2)	
Race n (%)	Caucasian	142 (73.6)	293 (75.1)	435 (74.6)	0.103
	African-American	29 (15.0)	53 (13.6)	82 (14.1)	
	Hispanic	18 (9.3)	43 (11.0)	61 (10.5)	
	Other	3 (1.6)	0 (0.0)	3 (0.5)	
	American Indian/ Alaska Native	0 (0.0)	1 (0.3)	1 (0.2)	
	Asian	1 (0.5)	<b>0 (0.0)</b>	1 (0.2)	
Bowel Symptom Survey Results					
Abdominal Discomfort/Pain? n (%)	Yes	191 (100)	387 (100)	578 (100)	
	NO	0 (0.0)	0 (0.0)	0 (0.0)	
	Rarely	0 (0.0)	0 (0.0)	0 (0.0)	
Discomfort/Pain improves after BMs? n (%)	Yes	181 (94.8)	352 (91.0)	533 (92.2)	
	NO	6 (3.1)	14 (3.6)	20 (3.5)	
	Rarely	4 (2.1)	21 (5.4)	25 (4.3)	
Discomfort/Pain associated with BM Frequency? n (%)	Yes	159 (83.2)	341 (88.1)	500 (86.5)	
	NO	24 (12.6)	37 (9.6)	61 (10.6)	
	Rarely	8 (4.2)	9 (2.3)	17 (2.9)	
Discomfort/Pain associated with Stool Consistency? n (%)	Yes	188 (98.4)	372 (96.1)	560 (96.9)	
	NO	3 (1.6)	8 (2.1)	11 (1.9)	
	Rarely	0 (0.0)	7 (1.8)	7 (1.2)	
< 3 BMs per week?* n (%)	Yes	175 (91.6)	371 (95.9)	546 (94.5)	
	NO	16 (8.4)	16 (4.1)	32 (5.5)	
	Rarely	0 (0.0)	0 (0.0)	0 (0.0)	
> 3 BMs per day?* n (%)	Yes	8 (4.2)	16 (4.1)	24 (4.2)	
	NO	183 (95.8)	371 (95.9)	554 (95.8)	
	Rarely	0 (0.0)	0 (0.0)	0 (0.0)	
Hard or Lumpy stools?* n (%)	Yes	190 (99.5)	380 (98.2)	570 (98.6)	
	NO	1 (0.5)	7 (1.8)	8 (1.4)	
	Rarely	0 (0.0)	0 (0.0)	0 (0.0)	
Loose, mushy or watery stools?* n (%)	Yes	6 (3.1)	20 (5.2)	26 (4.5)	
	NO	185 (96.9)	367 (94.8)	552 (95.5)	
	Rarely	0 (0.0)	0 (0.0)	0 (0.0)	

Straining during BMs? <sup>*</sup> n (%)	Yes	190 (99.5)	385 (99.5)	575 (99.5)	
	NO	1 (0.5)	2 (0.5)	3 (0.5)	
	Rarely	00 (0.0)	0 (0.0)	00 (0.0)	
Rushing to the toilet? <sup>*</sup> n (%)	Yes	20 (10.5)	39 (10.1)	59 (10.2)	
	NO	171 (89.5)	348 (89.9)	519 (89.8)	
	Rarely	0 (0.0)	0 (0.0)	0 (0.0)	
Baseline Period Disease Status					
Abdominal Discomfort/Pain? <sup>1</sup>	N	193	390	583	0.885
	Mean	2.09	2.08	2.08	
	SD	0.693	0.665	0.674	
	Median	2.07	2.02	2.04	
	Range	0.46-4.00	0.71-3.96	0.46-4.00	
Abdominal Bloating <sup>1</sup>	Mean	2.28	2.27	2.27	0.877
	SD	0.735	0.686	0.702	
	Median	2.19	2.19	2.19	
	Range	0.57-4.00	0.68-4.00	0.57-4.00	
Constipation Severity <sup>1</sup>	Mean	2.29	2.24	2.26	0.441
	SD	0.643	0.652	0.649	
	Median	2.23	2.19	2.21	
	Range	0.32-4.00	0.61-3.96	0.32-4.00	
Weekly SBM Frequency	Mean	3.69	3.76	3.74	0.814
	SD	3.324	3.185	3.229	
	Median	3.11	3.25	3.25	
	Range	0.00-28.81	0.00-36.50	0.00-36.50	
SBM Stool Consistency <sup>2</sup>	N	187	375	562	0.581
	Mean	2.74	2.78	2.77	
	SD	0.661	0.640	0.647	
	Median	2.71	2.80	2.78	
	Range	0.88-4.00	0.00-4.00	0.00-4.00	
SBM Bowel Straining <sup>1</sup>	Mean	2.41	2.38	2.39	0.673
	SD	0.733	0.721	0.724	
	Median	2.30	2.33	2.33	
	Range	0.00-4.00	0.00-4.00	0.00-4.00	
Overall IBS-QOL	N	183	376	559	0.488
	Mean	54.79	56.15	55.71	
	SD	22.311	21.590	21.818	
	Median	56.62	58.09	57.35	
	Range	0.00-99.26	2.94-97.06	0.00-99.26	
Percent Rescue Med Usage	N	193	390	583	0.550
	Mean	14.05	12.96	13.32	
	SD	20.922	20.666	20.739	
	Median	4.55	3.77	3.85	
	Range	0.00-100.0	0.00-100.0	0.00-100.0	

<b>&lt; 3SBMs/week ≥ 25% of the time n (%)</b>	Yes	151 (78.2)	293 (75.1)	444 (76.2)	0.532
	NO	42 (21.8)	93 (23.8)	135 (23.2)	
	Missing	0 (0.0)	4 (1.0)	4 (0.7)	
<b>Straining ≥ Moderate ≥ 25% of the Time n (%)</b>	Yes	179 (92.7)	354 (90.8)	533 (91.4)	0.904
	NO	9 (4.7)	20 (5.1)	29 (5.0)	
	Exempt	5 (2.6)	12 (3.1)	17 (2.9)	
	Missing	0 (0.0)	4 (1.0)	4 (0.7)	
<b>Consistency ≥ Hard ≥ 25% of the Time n (%)</b>	Yes	185 (95.9)	371 (95.1)	556 (95.4)	0.648
	NO	3 (1.6)	3 (0.8)	6 (1.0)	
	Exempt	5 (2.6)	12 (3.1)	17 (2.9)	
	Missing	0 (0.0)	4 (1.0)	4 (0.7)	

Reviewer's table modified from Table 11-1, page 59 of 89, Table 14.1.5, page 60 of 89, and Table 14.1.6, page 61 of 89  
Clinical Study Report-SIB-0431

\*At least ¼ of the time in the last 3 months

<sup>1</sup>Scale: 0 (Absent), 1 (Mild), 2 (Moderate), 3 (Severe), 4 (Very Severe)

<sup>2</sup>Scale: 0 (Very Loose), 1 (Loose), 2 (Normal), 3 (Hard), 4 (Very Hard)

<sup>3</sup>p-value is from a 2-sample t-test for continuous variables and a chi-square test for categorical variables

The 436 subjects that completed treatment phase I continued onto treatment phase II. The Treatment phase II enrolled 436 subjects into three treatment groups: 139 subjects continued to receive placebo (placebo/placebo group), 146 subjects changed from Lubiprostone to Placebo (Lubiprostone/Placebo group), and 151 subjects continued to receive Lubiprostone (Lubiprostone/Lubiprostone group). As noted in table 63, overall, the study population continued to be predominantly female (401 of 436 subjects, 92%) and Caucasian (333 of 436, 76.4%). The mean age of subjects was 47.0 years (range: 20-83 years) and all subjects had a confirmed diagnosis of constipation predominant IBS. Variables like age, height, gender, race, and baseline period IBS disease status did not differ significantly ( $p > 0.05$ ) between the treatment groups. The responses to the Bowel Symptom Survey did not differ significantly between placebo/placebo group, Lubiprostone/Placebo group, and the Lubiprostone/Lubiprostone group but no statistical analysis was performed. The history of medical procedures, medical history and active medical problems of the three treatment groups in Treatment phase II did not differ significantly between the treatment groups, and they were similar to the medical histories and problems of the two treatment groups (Placebo and Lubiprostone 16 mcg) in Treatment Phase I. However, no statistical analysis was performed on the medical history, procedures or active medical problems in either Treatment Phase I or II.

**Table 63: Summary of Demographics and Disease History**  
**Study SIB-0431 Treatment Phase II (Randomized Withdrawal Population)**

Variable	Category	Placebo/Placebo	Lubiprostone/Placebo	Lubiprostone/Lubiprostone	Total	p-Value <sup>1</sup>
Subject Number	N	139	146	151	436	0.087
Age (years)	Mean	47.9	45.1	47.9	47.0	
	SD	12.77	10.90	13.76	12.59	
	Median	48.0	45.0	48.0	47.0	
	Range	21.0-82.0	20.0-73.0	20.0-83.0	20.0-83.0	
Height (inches)	Mean	65.0	64.8	65.0	64.9	0.722
	SD	3.11	2.79	2.96	2.95	
	Median	64.5	64.3	65.0	64.8	
	Range	56.2-74.0	57.0-74.0	57.0-75.0	56.2-75.0	
Gender n (%)	Female	128 (92.1)	137 (93.8)	136 (90.1)	401 (92.0)	0.489
	Male	11 (7.9)	9 (6.2)	15 (9.9)	35 (8.0)	
Race n (%)	Caucasian	105 (75.5)	107 (73.3)	121 (80.1)	333 (76.4)	0.117
	African-American	19 (13.7)	21 (14.4)	13 (8.6)	53 (12.2)	
	Hispanic	11 (7.9)	18 (12.3)	17 (11.3)	46 (10.6)	
	Asian	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)	
	Other	3 (2.2)	0 (0.0)	0 (0.0)	3 (0.7)	

Reviewer's table, modified from Table 11-2, page 60 of 89, Clinical Study Report-SIB-0431

<sup>1</sup>p-value is from a 1-way ANOVA for continuous variables and a chi-square test for categorical variables

### 10.1.2 Adverse Events

An adverse event (AE) was any undesirable event occurring to a subject during the clinical study, whether or not it was considered related to the study product(s). Events that were absent at baseline and developed after the initiation of double-blind treatment and events that were present at baseline and worsened after the initiation of double blind treatment were to be recorded as AEs.

Events with onset dates before randomization were considered to be part of the subject's medical history. Events with onset after 7 days of the last day of the 12 week treatment phase I period were considered falling outside of treatment phase I period. The safety window for treatment phase I and II overlapped. Therefore, for subjects who continued into treatment phase II, adverse events that occurred in the first 7 days after the date of the last dose of phase I treatment were counted in both treatment phases of the study. Events with onset more than 7 days and within 14 days after the last day of the treatment phase II period were included in the listings, but the events with onset within 7 days of the last day of phase II treatment were included in the AE tabulations and analysis. The subjects who enrolled in the open label extension study did not have the 14 day follow-up period. Hence, the safety window for these subjects ended on the date of the last dose of the study drug to prevent events associated with lubiprostone use in the open label trial from being attributed to placebo use during Treatment Phase II.

The principal investigator was required to assess severity of the event and the relationship to the study drug for all AEs, according to the criteria below.

#### Severity

- **Mild:** Transient symptoms, no interference with the subject's daily activities; acceptable
- **Moderate:** Marked symptoms, moderate interference with the subject's daily activities, but still acceptable.
- **Severe:** considerable interference with the subject's daily activities; unacceptable

#### Relationship to Study Drug:

- **Unrelated:** Concurrent illness, concurrent medication, or other known cause was clearly responsible for the AE, OR based upon available information regarding subject history, disease process, relationship of the AE to dosing and drug pharmacology, a relationship between the study drug and the AE was unlikely.
- **Possible:** The AE followed a reasonable sequence from the time of study drug administration, but could also be produced by the subject's clinical state or by other drugs administered to the subject.
- **Probable:** The AE followed a reasonable sequence from the time of study drug administration, followed a known response pattern of the drug class, was confirmed by improvement on stopping the study drug, and the suspect drug was the most likely of all causes.
- **Definite:** The AE followed a reasonable sequence from the time of study drug administration, followed a known response pattern of the drug class, was confirmed by improvement on stopping the study drug, and no other reasonable cause existed.

#### Frequency of Adverse Event

- **Once:** a one-time event with distinct start and stop dates. Events lasted less than 24 hours.
- **Intermittent:** event with multiple start and stop times and with fluctuations in symptoms during the course of the event. Events lasted several days or weeks.
- **Continuous:** events that were non-stop throughout the course of the event. Event lasted several days.

A serious adverse event (SAE) was any experience that suggested a medical hazard, including any event that:

- was fatal;
- was life-threatening (an event in which the subject was at risk of death at the time of the event; it did not refer to an event that might have caused death had it been more severe); required hospitalization or prolonged the existing hospitalization;
- resulted in persistent or significant disability/incapacity;
- was a congenital anomaly; or
- was an important medical event (an event that may not fit the other criteria for a SAE listed above, but based upon appropriate medical judgment, might jeopardize the subject or might require intervention to prevent one of the outcomes listed above)

All SAEs that occurred on or after the day the subject signed the consent form (screening visit, visit 1) until 7 days after the final dosing with double blind study drug was to be reported immediately to (b) (4)



The original terms used in the case report form by the investigators to identify AEs were coded to MedDRA preferred terms. The incidence of an AE was defined as the number of subjects who experienced at least 1 episode during the study. The incidence rate of an AE was calculated as the number of subjects who experienced the event during the safety window divided by the number of subjects at risk (multiplied by 100). Events with completely or partially missing onset dates were included in the tabulations, unless the partial date information available clearly indicated that the event happened outside of the treatment period.

Of the 590 subjects that were randomized, 588 subjects were considered part of the safety evaluable population. The safety evaluable population was defined as any subject who took at least 1 dose of study medication. 2 subjects (1 Placebo subject, 1 Lubiprostone 16 mcg subject) were randomized but did not receive any double blind medication. Of the 588 subjects in treatment phase I of study SIB-0431, 312 (53.1%) experienced at least one adverse event during the course of the study. Of these subjects, 106 were in the placebo group (55.2%) and 206 were in the Lubiprostone group (52.0%). The difference was not statistically significant,  $p=0.468$ .

One hundred and thirty four subjects overall (22.8%) reported at least 1 treatment-related AE; of these subjects 42 were in the placebo group (21.9%) and 92 were in the Lubiprostone 16 mcg group (23.2%). These treatment-related adverse events were also not statistically significant,  $p=0.713$ . Most frequent treatment-related adverse events were reported in the System Organ Class (SOC) of gastrointestinal disorders (112 subjects, 19.0%). Of the 112 subjects that reported AEs in the gastrointestinal disorders, 81 were in the Lubiprostone treatment group (20.5%) and 31 were in the placebo group (16.1%).

Thirty subjects (5.1%) withdrew from the study because of an AE. Of those subjects who withdrew, 10 were in the placebo group (5.2%) and 20 were in the Lubiprostone 16 mcg group (5.1%), but the difference was not statistically significant,  $p=0.935$ .

There were 7 AEs that were classified as serious, of those 2 were in the placebo group and 5 were in the Lubiprostone group. One of the placebo subjects sustained a fall that led to back injury whereas the other placebo subject experienced rhabdomyolysis secondary to Voltaren. 2 subjects in the Lubiprostone group were diagnosed with cancers, breast and thyroid gland. 1 subject in the Lubiprostone group developed dysuria post-operatively; she was undergoing an Exploratory laparotomy to repair enterocele, paravaginal defect and rectocele. Another subject in the Lubiprostone group had recurrence of her Atrial Fibrillation complicated by pulmonary edema and mitral valve incompetence. The other serious AE was the death that occurred in subject 104-011.

One subject in the Lubiprostone group died during treatment phase I.

**Subject 104-011:** The subject was a 71 year old male in the Lubiprostone/placebo group whose past medical history was significant for GERD, Dysphagia, Abdominal hernia, Hepatic Steatosis, Diabetes Mellitus, Hyperlipidemia, Obesity, Asthma and Cholecystectomy. Concomitant medications were fluticasone propionate, Fluvastatin, Glibenclamide, metformin, and Salbutamol. On study day 74, the subject experienced severe cardiac arrest and he expired. The last dose of study medication was taken on Study day 72.

Overall, 30 subjects (10 placebo; 20 Lubiprostone) experienced a total of 34 AEs for which the drug was permanently discontinued. Adverse events that led to permanent drug discontinuation in the

Lubiprostone group were mostly reported by only 1 or 2 subjects. Besides nausea (3 Lubiprostone subjects, 2 Placebo subjects), dyspepsia (2 Lubiprostone subjects, 0 Placebo subjects) and weight increased (2 Lubiprostone subjects, 0 Placebo subjects), all other AEs that led to discontinuations occurred in only 1 Lubiprostone subject.

In terms of severity, a total of 33 subjects (11 Placebo, 22 Lubiprostone) reported at least one severe adverse event. Most of the severe AEs were in the System Organ Class (SOC) of gastrointestinal disorders (15 subjects, 2.6%). However, similar number of subjects reported severe adverse events in the SOC of infections and infestations (8 subjects, 1.4%) and musculoskeletal and connective tissue disorders (7 subjects, 1.2%). At the event level, most severe AEs were reported by 1 or 2 subjects with the exception of nausea, diarrhea, abdominal pain, and sinusitis (3 Lubiprostone subjects each).

The most frequent AEs, at the System Order Class (SOC) level, were gastrointestinal disorders (overall 151 subjects, 25.7%), infections and infestations (overall 128 subjects, 21.8%), nervous system disorders (overall 40 subjects, 6.8%) and musculoskeletal and connective tissue disorders (overall 38 subjects, 6.5%). Of the 151 subjects reporting AEs in the gastrointestinal body system, 41 were placebo subjects and 110 were Lubiprostone 16 mcg subjects, but the difference was not statistically significant,  $p=0.095$ . More proportion of subjects in the Lubiprostone treatment group than placebo treatment group reported: nausea (47 subjects, 11.9% vs. 11 subjects 5.7%), diarrhea (28 subjects, 7.1% vs. 11 subjects, 5.7%), vomiting (4 subjects, 1.0% vs. 1 subject, 0.5%), dry mouth (3 subjects, 0.8% vs. 1 subject, 0.5%), loose stools (3 subjects, 0.8% vs. 0 subject, 0.0%), constipation (4 subjects, 1.0% vs. 0 subject, 0.0%) and abdominal distension (10 subjects, 2.5% vs. 3 subjects, 1.6%).

Overall, greater proportion of subjects in Placebo (48 subjects, 25.0%) than Lubiprostone (80 subjects, 20.2%) reported AEs in the infections and infestations body system, and the difference was not statistically significant,  $p=0.186$ . However, there were larger percentage of Lubiprostone subjects than placebo subjects that reported bronchitis (9 subjects, 2.3% vs. 3 subjects, 1.6%), Influenza (5 subjects, 1.3% vs. 0 subject, 0.0%).

Of the 40 total subjects that reported AEs in the nervous system disorders, 32 (8.1%) were in the Lubiprostone group and 8 (4.2%) were in the placebo group,  $p=0.077$ . More subjects in the Lubiprostone group reported headaches (17 Lubiprostone subjects, 4.3% vs. 4 placebo subjects, 2.1%), dizziness (7 Lubiprostone subjects, 1.8% vs. 5 placebo subjects, 2.6%), and lethargy (2 Lubiprostone subjects, 0.5% vs. 0 placebo subjects, 0.0%).

Of the 38 subjects that reported AEs in the musculoskeletal and connective tissue disorders, 24 (6.1%) were in the Lubiprostone group and 14 (7.3%) were in the placebo group,  $p=0.569$ . Higher percentage of subjects in the placebo group reported back pain (4 placebo subjects, 2.1% vs. 6 Lubiprostone subjects, 1.5%) and arthralgia (3 placebo subjects, 1.6% vs. 5 Lubiprostone subjects, 1.3%).

7 subjects reported AEs in the vascular disorders that were statistically significant,  $p=0.028$ . Of the 7 subjects, 5 (2.6%) were in the placebo group and 2 subjects (0.5%) were in the Lubiprostone group. The frequency of hypertension was higher among the placebo group (4 subjects, 2.1%) compared to the Lubiprostone group (1 subject, 0.3%).

Of the 436 subjects that completed phase I treatment of SIB-0431 study and were treated in treatment phase II, 153 (35.1%) experienced at least one adverse event during phase II treatment. Of these subjects, 53 were in the placebo/placebo (P/P) group, 44 were in the Lubiprostone/placebo (L/P) group, and 56 were in the Lubiprostone/Lubiprostone (L/L) group.

Forty two subjects overall (9.6%) reported at least 1 treatment-related AE; of these subjects 12 each were in the placebo/placebo and the Lubiprostone/placebo group, and 18 were in the Lubiprostone/Lubiprostone group.

There were no serious AEs reported and no deaths occurred in treatment phase II.

Overall, 1 subject (0 placebo/placebo; 0 Lubiprostone/placebo; 1 Lubiprostone/Lubiprostone) experienced a total of 1 AE for which the drug was permanently discontinued. The Adverse event that led to permanent drug discontinuation occurred in the Lubiprostone/Lubiprostone group. One subject (0.7%) experienced abdominal distension in the Lubiprostone/Lubiprostone group.

The most frequent AEs, at the SOC level were infections and infestations (overall 54 subjects, 12.4%), gastrointestinal disorders (overall 49 subjects, 11.2%), and musculoskeletal and connective tissue disorders (overall 22 subjects, 5.0%).

Of the 49 subjects reporting AEs in the gastrointestinal disorders, 16 were P/P subjects, 10 were L/P subjects, and 23 were L/L subjects. More proportion of subjects in the P/P (6 subjects, 4.3%) and the L/P (4 subjects, 2.7%) treatment groups reported flatulence compared to the L/L (3 subjects, 2.0%) treatment group. A higher percentage of subjects in the L/L group reported: abdominal pain (4 subjects, 2.6% L/L vs. 3 subjects each in the P/P (2.2%) and L/P (2.0%)), nausea (5 subjects L/L, 3.3% vs. 2 subjects L/P, 1.4% vs. 3 subjects P/P, 2.2%), diarrhea (4 subjects L/L, 2.6% vs. 0 subjects L/P, 0.0% vs. 3 subjects P/P, 2.2%), vomiting (1 subject L/L, 0.7% vs. 0 subject in L/P and P/P, 0.0%), and dry mouth (1 subject L/L, 0.7% vs. 0 subject in L/P and P/P, 0.0%).

Overall, similar proportion of subjects in L/P (17 subjects, 11.6%) and the L/L group (18 subjects, 11.9%) reported AEs in the infections and infestations body system but a higher percentage of subjects in the P/P (19 subjects, 13.8%) reported AEs. However, there were larger percentage of L/P subjects that reported Bronchitis (4 subjects L/P, 2.7% vs. 1 subject L/L, 0.7% vs. 0 subject P/P, 0.0%), Urinary Tract Infection (5 subjects L/P, 3.4% vs. 2 subjects L/L, 1.3% vs. 1 subject P/P, 0.7%), and Upper Respiratory Tract Infection (5 subjects L/P, 3.4% vs. 3 subjects L/L, 2.0% vs. 3 subjects P/P, 2.2%). A higher percentage of subjects in the L/L group reported: sinusitis (6 subjects L/L, 4.0% vs. 3 subjects L/P, 2.0% vs. 2 subjects P/P, 1.4%) and Influenza (3 subjects L/L, 2.0% vs. 0 subject L/P, 0.0% vs. 2 subjects P/P, 1.4%). Nasopharyngitis (3 subjects P/P, 2.2% vs. 1 subject in both L/P and L/L, 0.7%) occurred in a higher frequency in the P/P treatment group.

Of the 22 subjects that reported musculoskeletal and connective tissue disorders, same number of subjects were in the L/L and the P/P group (8 subjects each) whereas 6 subjects (4.1%) were in the L/P group. Back pain was reported by the same number of subjects in the L/L and P/P group (3 subjects each, 2.0% and 2.2%, respectively). Arthralgia (2 subjects L/P, 1.4%, 1 subject, 0.7% in both L/L and P/P) and neck pain (3 subjects L/P, 2.0% and 0 subjects each in L/L and P/P) were reported by higher proportion of L/P subjects compared to P/P and L/L subjects.

### **10.1.3 Withdrawals, Compliance, and Protocol Violations**

#### **Subject Disposition/Withdrawals**

A total of 590 subjects were randomized in a 2:1 ratio into the treatment phase I. 194 subjects into the placebo group, 396 into the Lubiprostone 16 mcg group. Of the 590 subjects randomized, 2 (1 Placebo, 1 Lubiprostone) did not receive any study treatment. Out of the remaining 588 safety evaluable subjects, 2 Lubiprostone subjects received study drug but no post-baseline diary data was available, another 2 Lubiprostone subjects had no dosing data and 1 other Lubiprostone subject did not have post-baseline diary data. Therefore, 5 subjects were excluded from the Lubiprostone group and a total of 583 subjects consisted of the ITT population.

A total of 436 subjects completed treatment phase I out of 590 randomized subjects (73.9%). The percentage of subjects completing phase I treatment was 71.6% in the placebo group, 75.0% in the 16 mcg Lubiprostone group. The mean number of days the subjects were on the study drug was 72.7 in the placebo group and 75.5 in the 16 mcg Lubiprostone group. A total of 154 subjects (28.4%; 55 Placebo, 25.0%; 99 Lubiprostone 16 mcg) discontinued the study.

Overall, the reasons for discontinuation were voluntary withdrawal (67 subjects, 11.4%), AEs (29 subjects, 4.9%), lack of efficacy (18 subjects, 3.1%), non-compliance (16 subjects, 2.7%), and lost to follow-up (12 subjects, 2.0%) In the placebo (28 subjects, 14.4%) and the 16 mcg Lubiprostone (39 subjects, 9.8%) treatment groups, the majority of the subjects voluntarily withdrew. 20 subjects (5.1%) in the 16 mcg Lubiprostone group relative to 9 subjects (4.6%) in the placebo group discontinued the treatment phase I due to adverse events. Similarly, there were more subjects in the Lubiprostone group that discontinued due to non-compliance than placebo (13 subjects, 3.3 % vs. 3 subjects, 1.5%). A higher proportion of placebo subjects (8 subjects, 4.1%) withdrew due to lack of efficacy than Lubiprostone subjects (10 subjects, 2.5%).

The 436 subjects that completed Treatment phase I were continued into treatment phase II. 139 of the placebo subjects in Treatment phase I continued to receive placebo in Treatment phase II (placebo/placebo, P/P). Of the 297 subjects that were receiving Lubiprostone and completed treatment phase I, 146 subjects were assigned to placebo in the treatment phase II (Lubiprostone/Placebo, L/P) and 151 subjects were continued on Lubiprostone in treatment phase II (Lubiprostone/Lubiprostone, L/L).

A total of 420 subjects completed treatment phase II. The percentage of subjects completing the treatment phase II was 94.2% in the P/P group, 97.9% in the L/P group and 96.7% in L/L group. The mean number of days the subjects were on the study drug was 114.2 in the placebo/placebo group, 113.9 in the Lubiprostone/Placebo group, and 113.0 in the Lubiprostone/Lubiprostone group. A total of 16 subjects (8 P/P, 5.8%; 3 L/P, 2.1%; 5 L/L, 3.3%) discontinued phase II treatment. The reasons for discontinuation were lost to follow-up (7 subjects, 1.6%), voluntary withdrawal and non-compliance (2 subjects each, 0.5%), unknown (3 subjects, 0.7%) and AEs (1 subject, 0.2%). The majority of the P/P group (4 subjects, 2.9%) and the L/L group (2 subjects, 1.3%) that discontinued were lost to follow-up. The one subject (0.2%) that withdrew due to adverse event was in the L/L group. The number of subjects who discontinued due to non-compliance was the same in the P/P and the L/P group (1 subject each, 0.7%).

## Compliance

Treatment compliance was estimated by using the study drug administration record in the subject's daily diary and case report form (CRF) data. The percent compliance was calculated by dividing the actual cumulative exposure to study drug by the exposure the subject should have received (based on the number of days the subject was on the study drug). In general, percent compliance was similar for the 2 treatment groups in treatment phase I based on CRF data but not diary data. In the placebo group, the compliance was 82.37% (diary based) and 93.11% (CRF based) and in the Lubiprostone 16 mcg group it was 84.87% (diary based) and 92.89% (CRF based). More subjects in the Lubiprostone 16 mcg group required dose reduction compared to placebo (28 subjects, 7.2% vs. 3 subjects, 1.6%, respectively),  $p=0.004$ . In month 3, more subjects in the Lubiprostone 16 mcg treatment group (31 subjects, 9.4%) had less than 70% compliance (diary based) relative to placebo (10 subjects, 6.8%),  $p=0.358$ . Month 1 had the highest number of subjects (49 Placebo subjects, 25.4% vs. 103 Lubiprostone subjects, 26.4%) with less than 70% compliance (diary based),  $p=0.752$ . There was a discrepancy in the number of subjects that had overall treatment compliance of  $< 70\%$  based on diary data (37 Placebo, 19.2% vs. 79 Lubiprostone, 20.3%) compared to the data from CRF (10 Placebo, 5.2% vs. 21 Lubiprostone, 5.4%).

In treatment phase II, the overall percent compliance (diary based) was similar between the L/P (93.92%) and the L/L treatment groups (93.05%) but was lower in the P/P (91.23%) treatment group,  $p=0.291$ . The CRF based percent compliance was noted to be higher than the diary based percent compliance across all treatment groups (96.86% P/P, 95.44% L/P, 96.42% L/L),  $p=0.754$ . Based on the CRF data, the P/P group (2 subjects, 1.5%) had the least number of subjects that were  $< 70\%$  compliant (6 subjects L/P, 4.2% and 5 subjects L/L, 3.3%),  $p=0.400$ . However, the diary based data reflected different proportion of subjects with treatment compliance  $< 70\%$  (8 subjects, 5.9% P/P group; 5 subjects, 3.5% L/P; 9 subjects, 6.0% L/L, ),  $p=0.564$ . The L/P (11 subjects, 7.5%) and the L/L groups (10 subjects, 6.6%) had more subjects that needed dose reduction relative to the P/P group (3 subjects, 2.2%),  $p=0.105$ .

## Protocol Deviations

The following protocol violations were determined and entered into the database after "soft lock" and before "hard lock" and unblinding. Data of the protocol violators were removed from the per protocol subset for the applicable month. If more than 5% of all subjects were protocol violators, then monthly responder and overall responder analyses were based on the per protocol (PP) population. Protocol violators were identified using the following criteria:

- Any subject who took at least 1 of the prohibited concomitant medications listed in the protocol (anticholinergics, anti-spasmodics, prokinetic agents, anti-constipation, cholinesterase inhibitors, laxatives such as MiraLax, ExLax, etc.) that was not prescribed as a rescue medication by the investigator, was a protocol violator during the month(s) in which the medication was taken.
- A subject who took any medication known to cause constipation, bloating or other IBS symptoms and/or a medication approved or intended for the treatment of IBS-C
- A subject who took fewer than 70% of the required double-blind doses for a given month was considered a protocol violator for that month.

Across all 3 months, the most frequent protocol violations were  $< 70\%$  study drug compliance and inclusion/exclusion criteria violator or misrandomized. The percentage of subjects that were considered inclusion/exclusion criteria violator or misrandomized was higher in the Lubiprostone treatment group relative to placebo at all 3 months (9 subjects, 2.3% vs. 2 subjects, 1.0% in each month). For the

Lubiprostone treatment group, the number of subjects with < 70% treatment compliance declined over the 3 months, 17 subjects, 4.4%; 13 subjects, 3.3%; 11 subjects, 2.8% for months 1, 2 and 3 respectively. For the placebo group, month 2 (9 subjects, 4.7%) had the highest number of subjects with < 70% treatment compliance (7 subjects, 3.6% in month 1 and 3 subjects, 1.6% in Month 3). The proportion of subjects with < 70% treatment compliance was higher in the Lubiprostone group than the placebo group at months 1 and 3. A greater percentage of subjects in the Lubiprostone treatment group had use of prohibited concomitant medications in months 2 and 3 (7 subjects, 1.8% vs. 2 subjects, 1.0% in month 2 and 7 subjects, 1.8% vs. 3 subjects, 1.6% in month 3) compared to placebo treatment group.

### 10.1.4 Efficacy Results

#### Primary Efficacy Analysis

The primary efficacy analysis was the overall responder rate during the 12 week treatment period. An overall responder was a subject who was a responder for at least 2 out of the 3 months during treatment phase I. Besides the daily questions that the subject answered in the diary entries each evening, the subject had to also provide weekly assessments based on one global symptom relief question. Global symptom relief was assessed from the 7 point balanced scale associated with the following electronic diary weekly 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?

- 3 Significantly relieved
- 2 Moderately relieved
- 1 A little bit relieved
- 0 Unchanged
- 1 A little bit worse
- 2 Moderately Worse
- 3 Significantly Worse

**Monthly responder** was defined as a subject who rated his/her symptoms as “**moderately relieved**” for all 4 weeks within a month or “**significantly relieved**” for at least 2 weeks within a month period provided all 3 conditions were met:

1. The percent of days of rescue medication use did not increase during the month compared to baseline
2. The subject did not discontinue during the month due to lack of efficacy
3. The subject did not have ratings of “**moderately worse**” or “**significantly worse**” during the month.

If a subject had a missing symptom relief rating for a particular week, the missing symptom relief was designated as “**unchanged**” relief. If the number of ratings were less than 4 for a month, all the missing data received a rating of “**unchanged**” in order to bring the total number of ratings up to 4 for a month. Study drop outs were handled in the same manner. Therefore, all ITT subjects had a non-missing responder status for all months. Consequently, subjects who discontinued the study also had a non-missing overall responder status. For statistical analysis, 4 populations were derived for the overall and monthly responder rates: Intent to treat (ITT) subjects with last observation carried forward (LOCF), ITT subjects without LOCF, per protocol (PP) subjects, and ITT subjects who were study completers. The PP population for the overall responder analysis excluded subjects who had at least 1 protocol violation.

**Table 64: Overall Responder Rates in 4 Populations**

Study Population	Study Arm	Overall	N (%)	Responder Difference	p-Value
<b>ITT Subjects without LOCF</b>	Placebo N=193	Responder	<b>15 (7.8)</b>	6%	0.029*
		Non-Responder	178 (92.2)		
	Lubiprostone 16 mcg N=390	Responder	<b>54 (13.8)</b>		
		Non-Responder	336 (86.2)		
<b>ITT Subjects with LOCF</b>	Placebo N=193	Responder	<b>19 (9.8)</b>	8.4%	0.009*
		Non-Responder	174 (90.2)		
	Lubiprostone 16 mcg N=390	Responder	<b>71 (18.2)</b>		
		Non-Responder	319 (81.8)		
<b>Per Protocol Subjects without LOCF</b>	Placebo N=172	Responder	<b>13 (7.6)</b>	7%	0.014*
		Non-Responder	159 (92.4)		
	Lubiprostone 16 mcg N=350	Responder	<b>51 (14.6)</b>		
		Non-Responder	299 (85.4)		
<b>Study Completer Subjects without LOCF</b>	Placebo N=139	Responder	<b>14 (10.1)</b>	7.1%	0.061
		Non-Responder	125 (89.9)		
	Lubiprostone 16 mcg N=296	Responder	<b>51 (17.2)</b>		
		Non-Responder	245 (82.8)		

Reviewer's table modified from Tables 14.2.1.1, 14.2.1.2, 14.2.1.3, 14.2.1.4, page 65 of 89, Clinical Study Report SIB-0431

\*p-value is from a CMH test stratified by pooled-center

In treatment phase I, the ITT population without LOCF, the overall responder status for placebo was 7.8% (15 out of 193 subjects) and the 16 mcg Lubiprostone group was 13.8% (54 out of 390 subjects),  $p=0.029$ . The overall responder status was slightly higher in the ITT population with LOCF (9.8%, 19/193 Placebo vs. 18.2%, 71/390 Lubiprostone),  $p=0.009$  and the per protocol population (7.6%, 13/172 placebo vs. 14.6%, 51/350),  $p=0.014$ . In the ITT population who were study completers, 14 subjects out of 139 (10.1%) were overall responders in the placebo group whereas 51 subjects out of 296 (17.2%) were overall responders in the Lubiprostone treatment group,  $p=0.061$ . Based on these analysis, it was deduced that the Lubiprostone treatment using the 16 mcg dose produced statistically significant improvement in global IBS symptoms. The only population that failed to achieve statistical significance in treatment phase I was study completers.

**Secondary Efficacy Analysis: Table 65: Monthly Responder Rates in 4 Populations**

Study Population	Treatment period	Study Arms	Status	N (%)	Responder Difference	p-Value <sup>1</sup>
ITT Subjects without LOCF	Month 1	Placebo N=193	Responder	<b>12 (6.2)</b>	3.8%	0.098
			Non-Responder	181 (93.8)		
		Lubiprostone 16 mcg N=390	Responder	<b>39 (10.0)</b>		
			Non-Responder	351 (90.0)		
	Month 2	Placebo N=193	Responder	<b>18 (9.3)</b>	6.6%	0.028*
			Non-Responder	175 (90.7)		
		Lubiprostone 16 mcg N=390	Responder	<b>62 (15.9)</b>		
			Non-Responder	328 (84.1)		
	Month 3	Placebo N=193	Responder	<b>20 (10.4)</b>	5.5%	0.069
			Non-Responder	173 (89.6)		
		Lubiprostone 16 mcg N=390	Responder	<b>62 (15.9)</b>		
			Non-Responder	328 (84.1)		
ITT Subjects with LOCF	Month 1	Placebo N=193	Responder	<b>15 (7.8)</b>	3.2%	0.174
			Non-Responder	178 (92.2)		
		Lubiprostone 16 mcg N=390	Responder	<b>43 (11.0)</b>		
			Non-Responder	347 (89.0)		
	Month 2	Placebo N=193	Responder	<b>21 (10.9)</b>	7.8%	0.016*
			Non-Responder	172 (89.1)		
		Lubiprostone 16 mcg N=390	Responder	<b>73 (18.7)</b>		
			Non-Responder	317 (81.3)		
	Month 3	Placebo N=193	Responder	<b>28 (14.5)</b>	6.8%	0.053
			Non-Responder	165 (85.5)		
		Lubiprostone 16 mcg N=390	Responder	<b>83 (21.3)</b>		
			Non-Responder	307 (78.7)		
Per Protocol Subjects without LOCF	Month 1	Placebo N=187	Responder	<b>12 (6.6)</b>	3.9%	0.097
			Non-Responder	169 (93.4)		
		Lubiprostone 16 mcg N=375	Responder	<b>38 (10.5)</b>		
			Non-Responder	325 (89.5)		
	Month 2	Placebo N=187	Responder	<b>16 (8.9)</b>	7.4%	0.015*
			Non-Responder	163 (91.1)		
		Lubiprostone 16 mcg N=375	Responder	<b>59 (16.3)</b>		
			Non-Responder	303 (83.7)		
	Month 3	Placebo N=187	Responder	<b>17 (9.2)</b>	7.2%	0.019
			Non-Responder	167 (90.8)		
		Lubiprostone 16 mcg N=375	Responder	<b>60 (16.4)</b>		
			Non-Responder	306 (83.6)		
Study Completer Subjects without LOCF	Month 1	Placebo N=139	Responder	<b>11 (7.9)</b>	4.6%	0.160
			Non-Responder	128 (92.1)		
		Lubiprostone 16 mcg N=296	Responder	<b>37 (12.5)</b>		
			Non-Responder	259 (87.5)		
	Month 2	Placebo N=139	Responder	<b>17 (12.2)</b>	6%	0.149
			Non-Responder	122 (87.8)		
		Lubiprostone 16 mcg N=296	Responder	<b>54 (18.2)</b>		
			Non-Responder	242 (81.8)		
	Month 3	Placebo N=139	Responder	<b>19 (13.7)</b>	6.9%	0.081
			Non-Responder	120 (86.3)		
		Lubiprostone 16 mcg N=296	Responder	<b>61 (20.6)</b>		
			Non-Responder	235 (79.4)		

Reviewer's table modified from Tables 14.2.2.1, 14.2.2.2, 14.2.2.3, 14.2.2.4, page 65 of 89, Clinical Study Report SIB-0431

<sup>1</sup>p-values were from CMH tests stratified by pooled-center

\*p-value is significant according to the 3- step testing procedure



### **Monthly Responder Rates: key secondary efficacy**

In treatment phase I, the monthly responder status at months 1, 2, and 3 were considered key secondary endpoints. Once the primary analysis of overall responder was found to be significant, a step wise testing procedure described in the statistical analytical protocol was utilized for a given month to declare significance while keeping the type I error rate of  $\alpha=0.05$ . The monthly responder rate was based not only on the weekly global question but also the three prespecified conditions being satisfied. In the ITT subjects without LOCF, the responder rate was higher in the 16 mcg Lubiprostone group (10.0%-15.9%) for all months compared to the placebo group (6.2%-10.4%). At Month 2 in ITT subjects without LOCF, 18 subjects (9.3%) in the placebo group were responders compared to 62 subjects (15.9%) Lubiprostone group,  $p=0.028$ . The ITT population with LOCF and the PP population had slightly higher responder rates across all 3 months for Lubiprostone treatment group. Lubiprostone subjects (10.5%-16.4%) in the PP population had a higher responder rate than placebo (6.6%-9.2%). The Lubiprostone treatment responder rate increased from Month 1 to 2 in both the ITT without LOCF (10.0%, month 1 vs. 15.9%, month 2) and the PP population (10.5%, month 1 vs. 16.3%, month 2), but the responder rate in month 3 (15.9% in ITT without LOCF and 16.4% in PP) remained the same as month 2. In ITT population who were subject completers the 16 mcg Lubiprostone (12.5%, month 1 vs. 18.2%, month 2 vs. 20.6% in month 3) did show higher responder rates than placebo (7.9%, month 1 vs. 12.2%, month 2 vs. 13.7%, month 3) at all months. Month 2 responder rate was statistically significant ( $p = 0.028$  ITT without LOCF,  $p= 0.016$  ITT with LOCF,  $p=0.015$  PP) for all populations except ITT who are study completers according to the 3 step testing procedure. The 16 mcg Lubiprostone provided global IBS symptom relief at all months better than placebo but was only statistically significant at Month 2. Despite statistical significance varying between months, the Lubiprostone data exhibited a positive trend in relieving IBS global symptoms throughout the 12 weeks.

### **Other Secondary Efficacy Endpoints**

Subjects had to answer a maximum of 9 daily questions presented in their electronic diary each evening which served as the basis for the secondary endpoints. To decrease the variation that could occur from observed data, the sponsor decided to use change from baseline as the variable for comparison. Change from baseline was calculated as baseline value subtracted from post baseline value.

Change from baseline = (post-baseline value) - (baseline value)

The baseline value represented the average of the entries from the 28 days prior to randomization, visit 2. The post baseline value was the average of all diary ratings during the given month. To assess improvement from baseline and if the data were not normally distributed, the Wilcoxon signed-rank test was performed within treatment group for each study month.

### **Change From Baseline in Abdominal Symptoms (abdominal discomfort/pain and bloating) during Months 1, 2 and 3**

The diary question that was used to assess abdominal discomfort/pain each evening was as follows: How would you rate your abdominal discomfort/pain today? Abdominal pain/discomfort was recorded by each subject in a diary each evening and was scored as: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very Severe.

Compared to the respective baseline values, the abdominal discomfort/pain had decreased significantly ( $p < 0.001$ ) at all 3 months in the placebo and Lubiprostone treated groups in all populations. In the ITT without LOCF population, at all post-baseline evaluation time points, the mean level of abdominal discomfort reported in the Lubiprostone 16 mcg group (range: 1.60-1.78) was lower than that in the placebo group (1.67-1.81), but the difference did not approach statistical significance. The Lubiprostone treated subjects in the ITT without LOCF population had a slightly larger (0.02-0.06) decrease in abdominal pain/discomfort relative to the placebo treated subjects. Overall, in the ITT population without LOCF, the change from baseline in abdominal discomfort in the placebo group was 0.35 vs. 0.38 in the Lubiprostone treated group. Similar results were observed for ITT subjects with LOCF and PP subjects. These analyses suggested that, compared to their respective baseline, the 16 mcg Lubiprostone and placebo treatment groups demonstrated similar improvements in abdominal pain/discomfort in all 3 months.

Abdominal bloating was recorded using the same 5 point scale as abdominal discomfort/pain. The diary question that was used to assess abdominal bloating was as follows: How would you rate your abdominal bloating today? Compared to the respective baseline values, the abdominal bloating had decreased significantly ( $p < 0.001$ ) at all 3 months in the placebo and Lubiprostone treated groups in all populations. In the ITT without LOCF population, at all post-baseline evaluation time points, the mean level of abdominal bloating reported in the Lubiprostone 16 mcg group (range: 1.79-1.97) was lower than that in the placebo group (1.84-2.04), but the difference did not approach statistical significance. The Lubiprostone treated subjects in the ITT without LOCF population had a slightly larger (0.03 to 0.07) decrease in abdominal bloating than those observed among placebo subjects. Overall, in the ITT population without LOCF, the change from baseline in the placebo group was 0.33 vs. 0.39 in the Lubiprostone treated group. Similar results were observed for ITT subjects with LOCF and PP subjects. These analyses suggested that, compared to their respective baseline, the 16 mcg Lubiprostone demonstrated similar improvements in abdominal bloating as placebo in all 3 months.

#### **Change from Baseline in Spontaneous Bowel Movement and Bowel Movement Frequency Rates During Months 1, 2 and 3**

Spontaneous bowel movements (SBMs) were bowel movements that occurred independent of rescue medication usage. The subject determined whether a bowel movement on any given day was the result of rescue medication use on that particular day. The subject recorded in a diary each evening the number of bowel movements and classified it as spontaneous based on the above criteria. The diary question associated with spontaneous bowel movement assessment was as follows: How many of your bowel movements occurred before you used any rescue medication (i.e. spontaneous bowel movements)?

Monthly SBM frequency rate =  $(28 \times \text{Number of SBMs}) / (\text{Number of days})$

where the number of days was the number of days during the month that the subject was in the study and taking the study drug. For SBM rate calculations for the month that began the treatment phase I (month 1) required at least 4 days of data. If less than 4 days of data were available for months 2 and 3, then the most recent data from days during the previous month were combined with days from the current month in order to bring the number of days up to 4.

The mean baseline number of SBMs during a 28 day interval was 3.69 for placebo and 3.76 for Lubiprostone treatment group,  $p=0.660$ . Compared to the respective baseline values, frequency of SBMs significantly increased ( $p<0.001$ ) at all 3 months in the placebo and Lubiprostone treated groups in all populations. In the ITT without LOCF population, at all post-baseline evaluation time points except Month 3, the change from baseline in SBM frequency rate was larger in the Lubiprostone group than in the placebo group, but the difference did not reach statistical significance. At month 3, placebo subjects demonstrated a 1.67 change from baseline in SBM frequency rates whereas Lubiprostone subjects had 1.62 change,  $p=0.547$ . The Lubiprostone treated subjects in the ITT without LOCF population had a (0.22-0.33) increase in SBMs frequency rate relative to the placebo group except in month 3 where placebo treated subjects had a 0.05 improvement in frequency of SBMs. Overall, in the ITT population without LOCF, the change from baseline in the placebo group is 1.33 vs. 1.55 in the Lubiprostone treated group. For ITT subjects with LOCF and PP subjects at all post-baseline evaluation time points, the change from baseline in SBM frequency was larger in the Lubiprostone treated group than placebo group but statistical significance was not approached. These analyses suggested that, compared to baseline, the 16 mcg Lubiprostone demonstrated a slight improvement in frequency of SBM relative to placebo in Months 1 and 2, but was no better (maybe slightly worse than placebo) in Month 3.

Unlike SBMs, bowel movements (BM) were categorized as BMs if they resulted from the use of rescue medications as determined by the subjects in their diary each evening. Monthly BMs are calculated by the same method as SBMs. The mean baseline number of BMs during a 28 day interval was 4.48 for placebo and 4.61 for Lubiprostone treatment groups,  $p=0.798$ . Compared to the respective baseline values, frequency of BMs have significantly increased ( $p<0.001$ ) at all times in the placebo and Lubiprostone treated groups. In the ITT without LOCF population, at all post-baseline evaluation time points except Month 3, the change from baseline in BM frequency rate was larger in the Lubiprostone group than in the placebo group, but the difference did not reach statistical significance. In the ITT without LOCF population, the Lubiprostone treated subjects had a (0.17-0.34) increase in BMs relative to the placebo group except in month 3 where placebo treated subjects had a 0.05 improvement relative to Lubiprostone treated subjects. Overall, in the ITT population without LOCF, the change from baseline in the placebo group was 1.00 vs. 1.19 in the Lubiprostone treated group. For ITT subjects with LOCF and PP subjects at all post-baseline evaluation time points, the change from baseline in BM frequency was larger in the Lubiprostone treated group than placebo group but statistical significance was not approached. These analyses suggested that, compared to baseline, the 16 mcg Lubiprostone demonstrated a slight increase in BM frequency relative to placebo in Months 1 and 2. However, in month 3, Lubiprostone treated subjects did not have any improvement (maybe slightly worse) in the frequency of BMs compared to placebo.

### **Change from baseline in Stool Consistency during Months 1, 2 and 3**

Stool consistency of SBMs was recorded by each subject in a diary each evening and was scored as 0 = Very Loose, watery, 1= Loose, 2 = Normal, 3 = Hard or 4 = Very Hard, little balls. The question that was used to assess stool consistency was as follows: What was the average stool consistency of your spontaneous bowel movements? The average was calculated by summing the scores for a given month and dividing by the number of SBMs in that month. The change from baseline in stool consistency at Months 1-3 between treatment groups was analyzed by the van Elteren's test stratified by pooled center.

Mean baseline stool consistency ratings in the placebo (2.74) and the Lubiprostone (2.78) subjects were similar,  $p=0.644$ . Change in stool consistency compared to the respective baseline was statistically significant ( $p<0.001$ ) at all 3 months in the placebo and Lubiprostone treatment groups in all 3 populations. For the ITT subjects without LOCF, at all post baseline evaluation time points, the mean stool consistency reported in the Lubiprostone group (range: 2.24-2.26) was lower than that in the placebo group (2.30-2.42), and the difference was statistically significant at Month 1 ( $p=0.006$ ), and Overall ( $p=0.015$ ). Overall, in the ITT population without LOCF, the change from baseline in stool consistency in the placebo group was 0.40 vs. 0.54 in the Lubiprostone treated group,  $p=0.015$ . In all 3 populations, the change in stool consistency for month 3 was not statistically significant; however, the Lubiprostone treated group showed a 0.09 to 0.11 improvement in stool consistency. Months 1 and 2 demonstrated statistically ( $p=0.006$ -0.030) significant improvement in stool consistency for ITT subjects with LOCF and PP subjects. These analyses suggested that, compared to baseline, the 16 mcg Lubiprostone treatment demonstrated a significant softening of the stool especially in Month 1.

### **Change from Baseline in Constipation Severity during Months 1, 2, and 3**

For all randomized subjects, severity of constipation was recorded using a 5 point scale: Absent (0), Mild (1), Moderate (2), Severe (3), Very Severe (4) at baseline and for months 1, 2 and 3. The diary question that was used to assess constipation was as follows: How would you rate your constipation today?

Mean baseline constipation severity was similar in both treatment groups (2.29 for placebo; 2.24 for Lubiprostone),  $p=0.514$ . Compared to the respective baseline values, constipation severity significantly decreased ( $p<0.001$ ) at all times in the placebo and Lubiprostone treated groups. For the ITT subjects without LOCF, at all post-baseline evaluation time points, the mean severity of constipation reported in the Lubiprostone group (range: 1.68-1.83) was lower than that in the placebo group (1.79-1.99), but the difference was not statistically significant. In the ITT without LOCF population, the Lubiprostone treated subjects had a 0.07 to 0.12 decrease in constipation severity relative to the placebo group. Overall, in the ITT population without LOCF, the change from baseline in the placebo group is 0.38 vs. 0.48 in the Lubiprostone treated group. Similar results were observed for ITT subjects with LOCF and PP subjects. Although statistical significance was not achieved, this analysis demonstrated a positive trend that suggested the 16 mcg Lubiprostone treatment provided a slight decrease in constipation severity.

### **Change from Baseline in Degree of Straining during Months 1, 2 and 3**

The degree of straining was recorded in a diary each evening and was scored as Absent (0), Mild (1), Moderate (2), Severe (3), Very Severe (4). The subject was to apply the above rating to any SBM that occurred during the day. The question that the subjects used to assess degree of straining was as follows: How would you rate your average straining with your spontaneous bowel movements? The average was calculated by summing the scores for a given month and dividing by the number of SBMs in that month. Analyses were based on the change from baseline, where the baseline value represented the average degree of straining rating from all SBMs during the 28 day baseline period. The mean change in baseline of degree of straining for Months 1-3 between treatment groups was analyzed by the van Elteren's test stratified by pooled center.

For the ITT subjects without LOCF, mean baseline degree of straining was similar in both treatment groups (2.41 for placebo; 2.38 for Lubiprostone),  $p=0.789$ . Compared to the respective baseline values, change in degree of straining was statistically significant ( $p<0.001$ ) at all 3 months in the placebo and Lubiprostone treatment groups in all 3 populations. For the ITT subjects without LOCF, at all post baseline evaluation time points, the mean degree of straining reported in the Lubiprostone group (range: 1.79-1.86) was lower than that in the placebo group (1.91-2.04), and the difference was statistically significant at Month 1 ( $p=0.050$ ). Overall, in the ITT population without LOCF, the change from baseline in degree of straining in the placebo group is 0.43 vs. 0.57 in the Lubiprostone treated group,  $p=0.139$ . In all 3 populations, the change in degree of straining for month 3 was not statistically significant; however, the Lubiprostone treated group showed (0.11 to 0.17) improvement in degree of straining relative to placebo. Months 1 and 2 demonstrated statistically significant ( $p=0.022$ -0.050) improvement in degree of straining for ITT subjects with LOCF and PP subjects. This analysis indicated Lubiprostone treatment significantly decreased straining in subjects especially in Month 1.

### **Symptom Relief by Month**

Global assessment of symptom relief for all subjects was recorded using a 7 point scale; Significantly Worse (-3), Moderately Worse (-2), A little bit worse (-1), Unchanged (0), A little bit relieved (1), Moderately relieved (2), Significantly relieved (3). Subjects answered a weekly question in their diary in order to assess global symptom relief. The weekly diary question that subjects answered was the same as the primary endpoint 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? The CMH tests, stratified by pooled center did not show significant differences between the treatment groups across months 1, 2 and 3. In the ITT without LOCF population, the Lubiprostone treated subjects had (0.09-0.2) better rating in their global symptom relief relative to the placebo group. Overall, in the ITT subjects without LOCF, the symptom relief in the placebo group was 0.59 vs. 0.73 in the Lubiprostone treated group,  $p=0.163$ . Similar results were observed for ITT subjects with LOCF and PP subjects. This analysis indicated that subjects suffering from constipation predominant IBS had similar scores for global symptom relief with Lubiprostone treatment compared to placebo treatment.

### **Irritable Bowel Syndrome Quality of Life (IBS-QOL)**

Irritable Bowel Syndrome Quality of Life (IBS-QOL) questionnaire was developed by Dr. D A Drossman and colleagues as a series of 34 questions. These questions were analyzed in sub-categories: dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual and relationship. Subjects completed IBS-QOL at the study site at randomization (visit 2), Week 4 (visit 4), and Week 12 (visit 6). The baseline value was the score obtained during the randomization (visit 2). The scores were based on changes from baseline and missing values were not imputed. There was a "Last Value" timepoint, which represented the last value recorded during Treatment phase I.

Between Lubiprostone and placebo groups, comparisons did not show any differences ( $p>0.359$ ) in the change from baseline IBS-QOL score to Weeks 4, 12 and Last Phase I Value in the ITT subjects without LOCF. However, during treatment at weeks 4, 12 and Last phase I value, the IBS-QOL score was always significantly ( $p<0.001$ ) better than baseline in the 16 mcg Lubiprostone group and placebo group. At week 4, the Lubiprostone treated group showed a 0.8 improvement from placebo group in the

change from baseline IBS-QOL overall score; however, at week 12 and Last phase I value, placebo showed a 0.1 improvement in the change from baseline overall IBS-QOL score compared to the Lubiprostone group. In the body image sub-category analysis, the Lubiprostone treated subjects showed a 2-3 point improvement in their change from baseline IBS-QOL score than the placebo group. At week 4, in the body image sub-category, there was a significant difference ( $p=0.038$ ) in the scores between placebo and Lubiprostone treatment groups. Subjects had conflicting results in all the other sub-categories, at times the changes from baseline IBS-QOL scores were the same in both the Lubiprostone and the placebo groups, greater in the placebo group than the Lubiprostone group or greater in the Lubiprostone group than the placebo group. For example, in the sub-category of health worry, at week 4, Lubiprostone treatment group had a change from baseline IBS-QOL score of 16.7 vs. 14.4 in the placebo group,  $p=0.120$ , at week 12, 19.7 Lubiprostone vs. 19.1 placebo,  $p=0.513$ , and Last phase I value, 18.4 Lubiprostone vs. 18.7 placebo,  $p=0.839$ . No clear trend was established favoring Lubiprostone treatment in the sub-category scores over placebo treatment.

### **SIB-0431, Treatment Phase II**

The secondary objective of the SIB-0431 study was to investigate the rebound phenomenon associated with the withdrawal of Lubiprostone treatment. This portion of the study was a 4 week randomized withdrawal period that occurred after the 12 week Treatment phase I in which subjects who were originally randomized to Lubiprostone were switched to placebo while the remaining Lubiprostone subjects were continued on Lubiprostone treatment.

#### **Treatment Phase 1**

Group 1: 194 control subjects: Placebo

Group 2: 396 treatment subjects: Lubiprostone 8 mcg bid

#### **Treatment phase II**

Placebo/Placebo (P/P): Placebo subjects (Group 1) from Treatment Phase I continued to receive Placebo

Subjects assigned to Lubiprostone (Group 2 from treatment Phase I, 396 subjects) were pre-randomized in a 1:1 ratio to receive the following:

Group 2a: Lubiprostone/ Placebo (L/P): 198 withdrawal subjects: Placebo

Group 2b: Lubiprostone/Lubiprostone (L/L): 198 treatment subjects: Lubiprostone

The randomization of the 590 subjects in a 1:1:1 ratio occurred prior to Treatment phase I. However, the 436 subjects that completed Treatment Phase I were the subjects that were enrolled and treated in the treatment phase II: P/P: 139 subjects, L/P: 146 subjects, and L/L: 151 subjects. The analysis of Month 4 responder rates relied on 2 population subsets: randomized withdrawal (RW) and phase I responders (PIR) subjects. The RW population was defined as all subjects who took at least 1 dose of the study drug dispensed at Visit 6 (week 12). Phase I responders (PIR) population was defined as a portion of RW subjects who were overall responders during treatment phase I. The comparisons were made using a CMH test stratified by pooled center.

### **Responder Rates at Month 4**

Table 66: Summary of Responder Rates at Month 4  
Phase I Responder Population

Treatment Group			
Timepoint Status	Lubiprostone/ Placebo	Lubiprostone/ Lubiprostone	p-Value <sup>1</sup>
	(N=30)	(N=21)	
Month 4 Responder	12 40.0%	8 38.1%	0.971
Non-Responder	18 60.0%	13 61.9%	

Copied from sponsor Table 14.2.18.1, page 71 of 89

<sup>1</sup>p-Value was from a CMH test stratified by pooled-center

Table 66 addressed whether subjects who were changed to placebo were more likely to relapse after 1 month compared to subjects who continued to take Lubiprostone. This analysis indicated Lubiprostone treated group was less likely to relapse when the medication was stopped, p=0.971.

Table 67: Summary of Responder Rates at Month 4  
Phase I Responders and Randomized Withdrawal Populations

Treatment Group			
Timepoint Status	Placebo/Placebo (Randomized Withdrawal)	Lubiprostone/Placebo (Phase I Responders)	p-Value <sup>1</sup>
	(N=139)	(N=30)	
Month 4 Responder	11 7.9%	12 40.0%	<0.001*
Non-responder	128 92.1%	18 60.0%	

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<sup>1</sup>p-Value was from a CMH test stratified by pooled-center

Table 67 addressed the issue of rebound. This comparison indicated that subjects who discontinue Lubiprostone treatment without a tapering schedule did not experience a worsening of their IBS symptoms, p<0.001.

Table 68: Summary of Responder Rates at Month 4  
Randomized Withdrawal Population

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

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<sup>1</sup>p-Value was from a CMH test stratified by pooled-center

Table 68 addressed the effectiveness of Lubiprostone after 4 months of treatment. Lubiprostone treatment was 3.4% better than placebo even though not statistically significant, p=0.415.

### **Changes from Baseline in Abdominal Discomfort/Pain and Bloating during Month 4**

In the RW subjects, mean baseline abdominal discomfort was similar in both treatment groups (2.09 for P/P; 2.07 for L/L). At month 4, the mean level of abdominal discomfort reported in the L/L group (1.59) was lower than that in the P/P group (1.71), but the difference was not statistically significant,  $p=0.387$ . Compared with baseline, mean month 4 abdominal discomfort did decrease at post-baseline evaluation time point for subjects in the P/P and L/L treatment group. In both treatment groups, all observed mean changes from baseline were statistically significant from zero ( $p<0.001$  for P/P and L/L subjects). In month 4, the mean decreases observed among the Lubiprostone 16 mcg (L/L) subjects was 0.10 larger than those observed among the placebo (P/P) subjects.

In the RW subjects, mean baseline abdominal bloating was similar in both treatment groups (2.29 for P/P; 2.26 for L/L). At month 4, the mean level of abdominal bloating reported in the L/L group (1.76) was lower than that in the P/P group (1.90), but the difference was not statistically significant,  $p=0.257$ . Compared with baseline, mean month 4 abdominal bloating did decrease at post-baseline evaluation time point for subjects in the P/P and L/L treatment group. In both treatment groups, all observed mean changes from baseline were statistically significant from zero ( $p<0.001$  for P/P and L/L subjects). In month 4, the mean decreases observed among the Lubiprostone 16 mcg (L/L) subjects was 0.10 larger than those observed among the placebo (P/P) subjects.

For the PIR subjects, mean abdominal discomfort was similar in both treatment groups (1.96 for L/P; 2.04 for L/L). At post-baseline evaluation time point, the mean level of abdominal discomfort reported in the Lubiprostone 16 mcg group, L/L (1.11) was slightly higher than that in the L/P group (0.97), but the difference was not statistically significant,  $p=0.823$ . In both treatment groups, the observed mean change from baseline was statistically significant from zero ( $p<0.001$  for L/P and L/L subjects). Therefore, the Lubiprostone subjects who were changed to placebo were less likely to have a relapse of their abdominal discomfort than subjects who were continued on Lubiprostone treatment.

For the PIR subjects, mean abdominal bloating was similar in both treatment groups (2.26 for L/P; 2.21 for L/L). At post-baseline evaluation time point, the mean level of abdominal bloating reported in the Lubiprostone 16 mcg group, L/L (1.21) was similar to that in the L/P group (1.19),  $p=0.761$ . In both treatment groups, the observed mean change from baseline was statistically significant from zero ( $p<0.001$  for L/P and L/L subjects). Therefore, the Lubiprostone subjects who were changed to placebo were less likely to have a relapse of their abdominal bloating than subjects who were continued on Lubiprostone treatment.

In the P/P of the RW population and the L/P of PIR population, mean abdominal discomfort was similar in both treatment groups (1.96 for L/P; 2.09 for P/P). At post-baseline evaluation time point, the mean level of abdominal discomfort reported in the L/P group, (0.97) was lower than that in the P/P group (1.71) and the difference was statistically significant,  $p=0.001$ . In both treatment groups, the observed mean changes from baseline were statistically significant from zero ( $p<0.001$  for P/P and L/P subjects). This indicated that the Lubiprostone subjects who were changed to placebo did not experience any worsening of their abdominal discomfort when the medication was withdrawn immediately.

In the P/P of the RW population and the L/P of PIR population, mean abdominal bloating was similar in both treatment groups (2.26 for L/P; 2.29 for P/P). At post-baseline evaluation time point, the mean level of abdominal bloating reported in the L/P group, (1.19) was lower than that in the P/P group (1.90)



and the difference was statistically significant,  $p < 0.001$ . In both treatment groups, the observed mean change from baseline was statistically significant from zero ( $p < 0.001$  for P/P and L/P subjects). This indicated that the Lubiprostone subjects who were changed to placebo did not experience any worsening of their abdominal bloating when the medication was withdrawn immediately.

#### **Changes From Baseline in Spontaneous Bowel Movement and Bowel Movement Frequency Rates During Month 4**

Compared to their respective baseline values, frequencies of SBMs and BMs were significantly increased at month 4 for subjects in the P/P and L/L treatment group,  $p < 0.001$ . At Month 4, the mean frequency of SBMs reported in the P/P group, (5.74) was higher than that in the L/L group (5.29) but the difference was not statistically significant,  $p = 0.909$ . Similarly, at month 4, the mean frequency of BMs reported in the P/P group, (5.97) was higher than that in the L/L group (5.68) but the difference was not statistically significant,  $p = 0.739$ . This analysis suggested that treatment with the 16 mcg dose of Lubiprostone did not provide an increase in SBM and BM frequency rates compared to placebo throughout a 4 week period.

For the PIR subjects, mean baseline frequencies of SBMs (3.94 for L/P; 4.41 for L/L,  $p = 0.100$ ) and BMs (4.77 for L/P; 5.45 for L/L,  $p = 0.951$ ) was similar in both treatment groups. The observed mean change from baseline was statistically significant from zero ( $p < 0.001$ ) for L/P in SBM and BM frequencies and for L/L subjects in the SBM frequency rate but was  $p = 0.005$  for L/L subjects in BM frequency rate. At month 4, the mean frequency of SBMs reported in the L/P group, (7.78) was higher than that in the L/L group (6.94), but the difference was not statistically significant,  $p = 0.529$ . Similarly, at month 4, the mean frequency of BMs reported in the L/P group, (7.90) was higher than that in the L/L group (7.29) but the difference was not statistically significant,  $p = 0.730$ . Therefore, the Lubiprostone subjects who were changed to placebo were less likely to have a decrease in SBM and BM frequencies than subjects who were continued on Lubiprostone treatment.

In the P/P of the RW population and the L/P of PIR population, mean baseline frequencies of SBMs (3.94 for L/P; 3.75 for P/P,  $p = 0.537$ ) and BMs (4.77 for L/P; 4.42 for P/P,  $p = 0.320$ ) was similar in both treatment groups. In both treatment groups, the observed mean change from baseline was statistically significant from zero ( $p < 0.001$  for P/P and L/P subjects). At month 4, the mean frequency of SBMs reported in the L/P group, (7.78) was higher than that in the P/P group (5.74), and the difference was statistically significant,  $p = 0.001$ . Similarly, at month 4, the mean frequency of BMs reported in the L/P group, (7.90) was higher than that in the P/P group (5.97) and the difference was statistically significant,  $p = 0.004$ . This indicated that the Lubiprostone subjects who were changed to placebo do not experience a significant decrease in SBM and BM frequencies when the drug was withdrawn immediately.

#### **Change From Baseline in Stool Consistency During Month 4**

In the RW subjects, mean baseline stool consistency was similar in both treatment groups (2.78 for P/P; 2.83 for L/L,  $p = 0.335$ ). At month 4, the mean stool consistency reported in the P/P group, (2.35) was significantly higher than that in the L/L group (2.21),  $p = 0.034$ . The lower mean stool consistency represented an overall softening of the stool throughout the 4 week period in subjects taking Lubiprostone.

For the PIR subjects, mean baseline stool consistency was similar in both treatment groups (2.64 for L/P; 2.71 for L/L,  $p=0.291$ ). The observed mean change from baseline was statistically significant from zero ( $p<0.001$ ) for L/P and L/L subjects. At month 4, the mean stool consistency reported in the L/P group, (2.03) was higher than that in the L/L group (1.87), but the difference was not statistically significant,  $p=0.161$ . Therefore, the Lubiprostone subjects whose treatment was stopped were more likely to have firmer stools than subjects who were continued on Lubiprostone treatment.

In the P/P of the RW population and the L/P of PIR population, mean baseline stool consistency was similar in both treatment groups (2.64 for L/P; 2.78 for P/P,  $p=0.432$ ). In both treatment groups, the observed mean change from baseline was statistically significant from zero ( $p<0.001$  for P/P and L/P subjects). At month 4, the mean stool consistency reported in the L/P group, (2.03) was significantly lower than that in the P/P group (2.35),  $p=0.012$ . The lower mean stool consistency indicated that the Lubiprostone subjects who were withdrawn immediately from treatment did not experience harder stools.

#### **Change From Baseline in Degree of Straining During Month 4**

In the RW subjects, mean average degree of straining at baseline was similar in both treatment groups (2.42 for P/P; 2.36 for L/L,  $p=0.838$ ). At month 4, the mean degree of straining reported in the P/P group, (1.93) was higher than that in the L/L group (1.71), but the difference was not statistically significant,  $p=0.163$ . Despite the differences between placebo and Lubiprostone groups not achieving statistical significance, Lubiprostone treatment did slightly decrease the straining in subjects over a 4 week period.

For the PIR subjects, mean baseline degree of straining was similar in both treatment groups (2.20 for L/P; 2.18 for L/L,  $p=0.703$ ). The observed mean change from baseline was statistically significant from zero ( $p<0.001$ ) for L/P and ( $p=0.001$ ) for L/L subjects. At month 4, the mean degree of straining reported in the L/P group, (1.11) was lower than that in the L/L group (1.29), but the difference was not statistically significant,  $p=0.556$ . Therefore, the subjects whose Lubiprostone treatment was stopped were more likely to continue to have decreased straining relative to subjects who were continued on Lubiprostone treatment.

In the P/P of the RW population and the L/P of PIR population, mean baseline degree of straining was similar in both treatment groups (2.20 for L/P; 2.42 for P/P,  $p=0.165$ ). In both treatment groups, the observed mean change from baseline was statistically significant from zero ( $p<0.001$  for P/P and L/P subjects). At month 4, the mean degree of straining reported in the L/P group, (1.11) was significantly lower than that in the P/P group (1.93),  $p=0.022$ . The lower mean degree of straining indicated that the Lubiprostone subjects who were withdrawn immediately from treatment did not experience worsening degree of straining.

#### **Change From Baseline in Constipation Severity During Month 4**

In the RW subjects, mean baseline constipation severity was the same in both treatment groups (2.29 for P/P and L/L  $p=0.892$ ). The observed mean change from baseline was statistically significant from zero ( $p<0.001$ ) for P/P and L/L subjects. At month 4, the mean constipation severity reported in the P/P group, (1.84) was higher than that in the L/L group (1.70), but the difference was not statistically

significant,  $p=0.481$ . Although this result was not statistically significant, the mean severity of constipation did decrease in favor of subjects taking Lubiprostone over the 4 week period.

For the PIR subjects, mean baseline constipation severity was similar in both treatment groups (2.12 for L/P; 2.22 for L/L,  $p=0.597$ ). The observed mean change from baseline was statistically significant from zero ( $p<0.001$ ) for L/P and L/L subjects. At month 4, the mean constipation severity reported in the L/P group, (0.96) was lower than that in the L/L group (1.22), but the difference was not statistically significant,  $p=0.761$ . Therefore, the subjects whose Lubiprostone treatment was stopped were more likely to experience less severe constipation than subjects who were continued on Lubiprostone treatment.

In the P/P of the RW population and the L/P of PIR population, mean baseline constipation severity was similar in both treatment groups (2.12 for L/P; 2.29 for P/P,  $p=0.312$ ). In both treatment groups, the observed mean change from baseline was statistically significant from zero ( $p<0.001$  for P/P and L/P subjects). At month 4, the mean constipation severity reported in the L/P group, (0.96) was significantly lower than that in the P/P group (1.84),  $p=0.001$ . The lower mean constipation severity indicated that the Lubiprostone subjects who were withdrawn immediately from treatment did not experience increased constipation severity.

#### **Symptom Relief During Month 4**

In the RW subjects at month 4, the mean symptom relief rating reported in the P/P group, (0.61) was lower than that in the L/L group (0.81), but the difference was not statistically significant,  $p=0.194$ . Although this result was not statistically significant, subjects with constipation predominant IBS reported better symptom relief when on Lubiprostone treatment.

For the PIR subjects, at month 4, the mean symptom relief rating reported in the L/P and the L/L group was the same (2.08),  $p=0.898$ . This analysis indicated that the subjects whose Lubiprostone treatment was stopped did not seem to notice any difference in their symptoms compared to subjects who were continued on Lubiprostone treatment.

In the P/P of the RW population and the L/P of PIR population, at month 4, the mean symptom relief rating reported in the L/P group, (2.08) was significantly higher than that in the P/P group (0.61),  $p<0.001$ . The higher mean symptom relief rating suggested that the Lubiprostone subjects who were withdrawn immediately from treatment did not experience worsening IBS symptoms.

#### **Irritable Bowel Syndrome Quality of Life (IBS-QOL) During Month 4**

In the RW subjects, mean baseline IBS-QOL score was similar in both treatment groups (55.3 for P/P; 57.1 for L/L),  $p=0.475$ . The observed mean change from baseline was statistically significant from zero ( $p<0.001$ ) for P/P and L/L subjects. At week 16, the mean IBS-QOL score reported in the P/P group, (71.3) was lower than that in the L/L group (75.0), but the difference was not statistically significant,  $p=0.557$ . The last phase II mean IBS-QOL score reported in the P/P group, (71.0) was lower than that in the L/L group (74.1), but the difference was not statistically significant,  $p=0.460$ . Although these results were not statistically significant, the mean overall IBS-QOL score did improve in favor of subjects taking Lubiprostone over the 4 week period.

The sub-category analysis demonstrated variability in the results: in dysphoria, health worry, social reaction, and relationship the L/L group reported greater change from baseline IBS-QOL scores than the P/P group at all post-baseline evaluation timepoints. However, in interference with activity and body image, the L/L group reported greater change from baseline IBS-QOL scores than the P/P group at only last phase II value timepoints. In food avoidance and sexual, the P/P group reported greater change from baseline IBS-QOL scores than the L/L group at all post-baseline evaluation timepoints; whereas, in interference with activity and body image, the P/P group reported greater change from baseline IBS-QOL scores than the L/L group at week 16. Of note, the mean baseline IBS-QOL score in sexual sub-category was significantly different in both treatment groups (64.9 for P/P; 72.7 for L/L  $p=0.028$ ).

In the PIR subjects, mean baseline IBS-QOL score was similar in both treatment groups (54.5 for L/P; 58.3 for L/L),  $p=0.573$ . The observed mean change from baseline was statistically significant from zero ( $p<0.001$ ) for L/P and L/L subjects. At week 16, the change from baseline mean IBS-QOL score in the L/P group, (28.0) was higher than that in the L/L group (27.5), but the difference was not statistically significant,  $p=0.560$ . The change from baseline in the last phase II IBS-QOL score in the L/P group (29.8) was lower than that in the L/L group (31.6), but the difference was not statistically significant,  $p=0.636$ . From this analysis, it was difficult to infer whether the subjects whose Lubiprostone treatment was stopped were more likely to have their IBS symptoms recur when compared to subjects who were continued on Lubiprostone treatment.

The sub-category analysis demonstrated variability in the results: in dysphoria, social reaction, and food avoidance, the L/L group reported greater change from baseline IBS-QOL scores than the L/P group at all post-baseline evaluation timepoints. However, in interference with activity and relationship, the L/L group reported greater change from baseline IBS-QOL scores than the L/P group at last phase II value timepoints and for body image at week 16. In health worry and sexual, the L/P group reported greater change from baseline IBS-QOL scores than the L/L group at all post-baseline evaluation timepoints; whereas, in interference with activity and relationship, the L/P group reported greater change from baseline IBS-QOL scores than the L/L group at week 16 and for body image at last phase II value timepoint.

In the P/P of the RW population and the L/P of PIR population, mean baseline IBS-QOL score was similar in both treatment groups (55.3 for P/P; 54.5 for L/P),  $p=0.867$ . The observed mean change from baseline was statistically significant from zero ( $p<0.001$ ) for P/P and L/P subjects. At week 16, the change from baseline mean IBS-QOL score in the P/P group, (17.6) was lower than that in the L/P group (28.0), but the difference was not statistically significant,  $p=0.163$ . The change from baseline in the last phase II IBS-QOL score in the P/P group (17.1) was significantly lower than that in the L/P group (29.8),  $p=0.003$ . The higher IBS-QOL score rating suggested that the Lubiprostone subjects who were withdrawn immediately from treatment did not experience significant worsening of their IBS symptoms.

The sub-category analysis demonstrated that the L/P group showed greater change from baseline IBS-QOL scores than the P/P group at all post-baseline evaluation timepoints. In dysphoria, social reaction, health worry, sexual, interference with activity, and body image, the L/P group showed significantly greater change from baseline IBS-QOL scores than the P/P group at last phase II value timepoints, (range  $p<0.001$  to  $p=0.024$ ). Despite the L/P group showing greater change from baseline IBS-QOL scores than the P/P group in relationship and food avoidance, the difference was not statistically significant at last phase II value timepoints. In both L/P and P/P treatment groups, the observed mean

change from baseline for the 8 sub-categories was statistically significant from zero (range:  $p < 0.001$  to  $p = 0.002$ ). This analysis further demonstrated that sudden withdrawal of Lubiprostone did not exacerbate IBS symptoms.

### **Use of Rescue Medication**

For treatment phase I, overall, of the 583 ITT subjects, 54.7% (319 subjects) took rescue medication (54.4%, 105 placebo; 54.9%, 214 Lubiprostone,  $p = 0.915$ ). In the placebo group, 39.9%, 43.5%, and 35.9% of subjects used rescue medication at month 1, month 2, and month 3, respectively. In the Lubiprostone 16 mcg group, 40.3%, 33.5% and 35.9% of subjects used rescue medication during the same months. In month 2, the percent of subjects using rescue medication was significantly lower in the Lubiprostone treatment group,  $p = 0.028$ . The mean percent of days rescue medication was used was higher in the Lubiprostone group (7.2-9.9) compared to placebo (4.1-8.6) in all 3 months, but the difference did not reach statistical significance. Bisacodyl (38.3% placebo; 36.9% Lubiprostone) and Fleet enema (10.9% Placebo; 9.7% Lubiprostone) were the most common rescue medications used by subjects.

In treatment phase II, the L/L group (59 subjects, 39.6%) had the highest proportion of subjects using rescue medications (46 subjects, 33.8% P/P; 40 subjects, 28.4% L/P),  $p = 0.131$ . The mean percent days of rescue medication use was also highest in the L/L group (6.4) compared to P/P (4.1) and L/P (5.4) treatment groups,  $p = 0.350$ . The use of fleet enema (6 subjects P/P, 4.3%; 7 subjects L/P, 4.8%; 7 subjects L/L, 4.6%) was similar in all treatment groups, but the L/L group (33 subjects, 21.9%) had higher usage of Bisacodyl than P/P (27 subjects, 19.4%) and L/P (28 subjects, 19.2%).

### **Study SPI/0211SIB-0432**

**Title: A 12 Week Multi-Center, Double-Blind, Randomized, Placebo-Controlled Phase III Study of Efficacy and Safety of Oral Lubiprostone for the Treatment of Constipation-predominant Irritable Bowel Syndrome.**

#### **10.1.1 Objectives**

The objective of this study was to assess the efficacy and safety of oral 16 mcg Lubiprostone compared to placebo for the treatment of constipation predominant irritable bowel syndrome.

#### **Study Design**

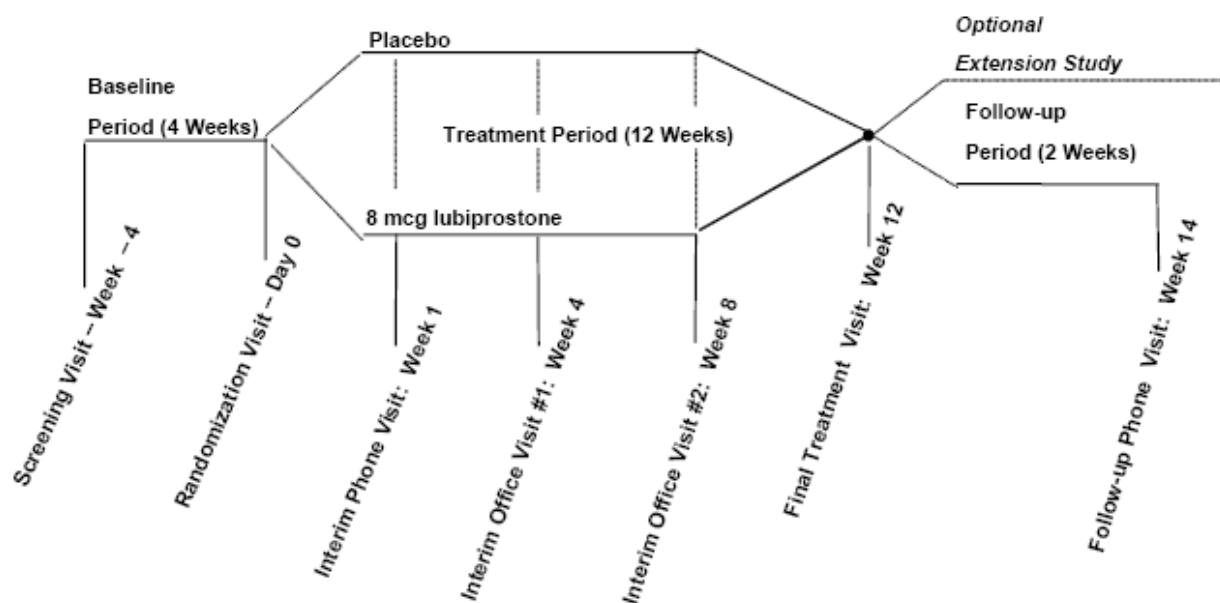
This was a multi-center, parallel group, double blinded, placebo controlled study of approximately 126 days duration including baseline and follow-up periods. Five hundred and eighty one subjects (387 subjects in the Lubiprostone treatment arm and 194 in the placebo group) were enrolled in 65 centers in the United States. Following initial assessments, including a 4 week baseline period, subjects received 12 weeks of double-blinded medication. The study consisted of the screening visit (visit 1), randomization visit (visit 2), 3 interim visits (Visit 3, telephone contact 1 week after randomization, Visit 4, office visit conducted 4 weeks after randomization and Visit 5, office visit conducted 8 weeks after randomization), a end of treatment (visit 6) at week 12 and a follow-up phone interview (visit 7) conducted 14 days after Visit 6. Subjects completed Irritable Bowel Syndrome-Quality of Life (IBS-

QOL) questionnaire at Visits 2, 4, and 6. The study design of SIB-0432 was similar to the study design of SIB-0431 Treatment Phase I without the 4 week randomized withdrawal Treatment phase II portion. The study was conducted between May 2005 and August 2006. Treatment medication was given in one of the following combinations:

Group 1: Two Placebo capsules (one 0 mcg capsule taken b.i.d) with food at breakfast and dinner with at least 8 ounces of water

Group 2: Two 8 mcg Lubiprostone capsules (one 8 mcg Lubiprostone capsule taken bid) with food at breakfast and dinner with at least 8 ounces of water

**Figure 2: Schematic of Study Visits**



Copied from sponsor's Figure 9-1, page 17 of 89 Clinical Study Report SIB-0432

## Statistical Methods of Analysis

The statistical analytical plan was also similar to study SIB-0431 Treatment Phase I. The primary efficacy variable was the overall responder rate during the 12 week treatment period, and the same definition was utilized in this study as SIB-0431 Treatment phase I. The monthly responder rates were calculated for each month (months 1, 2 and 3) during the 12 week treatment period. The same definition for a monthly responder was utilized in study SIB-0432 as study SIB-0431 Treatment Phase I.

**Table 69: Study SIB-0432 Study Schedule**

Period	Baseline		Treatment				Follow-up
Visit	1 Screening	2 Randomization	3 Interim	4 Interim	5 Interim	6 Final	8 Follow-up <sup>1</sup>
Study Week (Day)	Week – 4 (-28+ -3)	Week 0 Day 0	Week 1 (7 ± 2)	Week 4 (28 ± 3)	Week 8 (56 ± 3)	Week 12 (84 ± 2)	Week 14 (98 ± 2)
Location	Office	Office	Phone	Office	Office	Office	Phone
Procedure							
Informed Consent	A <sup>2</sup>						
Bowel Symptom Survey <sup>3</sup>	A <sup>2</sup>						
IBS-QOL		X		X		X	
Medical History	B <sup>2</sup>	X					
Inclusion/ Exclusion Criteria	B <sup>2</sup>	X					
Height	B <sup>2</sup>						
Weight	B <sup>2</sup>	X		X	X	X	
Vital Signs	B <sup>2</sup>	X		X	X	X	
Physical Exam	B <sup>2</sup>	X				X	
Laboratory Tests	B <sup>2</sup>	X		X	X	X	
Serum Pregnancy Test	B <sup>2</sup>					X	
Urine Dipstick Pregnancy Test		X					
Adverse Events			X	X	X	X	X
Concomitant Therapy	B <sup>2, 4, 5</sup>	X	X	X	X	X	X
Sigmoidoscopy or Colonoscopy <sup>6</sup>	C <sup>2, 7, 8</sup>						
Electronic Diary	C <sup>2, 9</sup>	X	X	X	X	X	
Study Medication Distribution		X		X	X	X	
Study Medication Collection				X	X	X	

Reviewer's Table modified from Table 9-1, page 15 of 75 Final Study Report: SIB-0432

<sup>1</sup>Subjects enrolling into the extension study skipped this visit.

<sup>2</sup>The screening visit was divided into Segments A, B, C, all of which were completed on the same day unless the subject needed a colonoscopy or flexible sigmoidoscopy.

<sup>3</sup>Survey based upon the Rome II Modular Questionnaire (Investigator Form) for IBS.

<sup>4</sup>Included a history of medications used within 90 days of Screening Visit (Visit 1).

<sup>5</sup>Updated to include any new therapy used during screening and for completion of the colonoscopy.

<sup>6</sup>A flexible sigmoidoscopy could be completed instead of a colonoscopy for a subject less than 50 years of age.

<sup>7</sup>Subjects needing a colonoscopy/flexible sigmoidoscopy were given an additional 28 days to complete up to Day -54

<sup>8</sup>Procedure necessary if previous results were unavailable or procedure was completed more than 5 years ago or prior to the onset of IBS.

<sup>9</sup>Subjects who underwent a colonoscopy or flexible sigmoidoscopy began the diary at least 1 week (and the bowel habits return to prior status) following the completion of the procedure.

As noted in table 69, the study schedule was similar to the schedule of study SIB-0431 Treatment Phase I. The difference occurred at the final visit 6 which was the final treatment visit for study SIB-0432. In study SIB-0431 treatment Phase I, the subjects that completed the treatment phase I were enrolled in Treatment phase II. The morning after visit 6, the subjects began to take their first study drug of treatment phase II. Therefore the subjects in Treatment phase II (or randomized withdrawal) had an extra office visit known as visit 7 (final Treatment phase II visit). The visit 7 was followed by a 2 week phone follow-up if the subjects did not enroll in the open label study SIB-05S1. Since visit 6 was the end of treatment for study SIB-0432, all electronic diaries and returned study drugs were collected and returned to the sponsor. This visit was conducted not only for subjects that were involved in the study, but also, for subjects that withdrew early during the treatment period. At this visit, the subjects were given the option to enroll in an open label extension study. Subjects not enrolling in the open label study were scheduled for follow-up phone interview to occur in 2 weeks. Visit 7 is a follow-up telephone interview that occurred approximately 14 days after the completion of Visit 6 (Day 84). Unlike study SIB-0431 Treatment Phase I and II which lasted 16 weeks, study SIB-0432 was 12 weeks in duration. They were both preceded by a 4 week baseline period and had a 2 week follow-up period that was scheduled after the treatment period. All the office visits were the same in both studies except for visit 6 at week 12 and visit 7 which occurred as an office visit at week 16 for study SIB-0431 and occurred as a phone call at week 14 for study SIB-0432.

### **Inclusion/Exclusion Criteria**

The inclusion and exclusion criteria utilized in study SIB-0432 were the same as that outlined for study SIB-0431.

### **Demography and Disease History**

Total of 581 subjects were enrolled in study SIB-0432 to receive either 8 mcg bid of Lubiprostone or Placebo bid at 65 centers in the United States. Of the 581 subjects that were randomized (194 Placebo, 387 Lubiprostone), 2 Lubiprostone subjects did not receive any treatments. Of the 579 safety evaluable subjects remaining, 1 placebo subject had no dosing data, another placebo subject had no dosing or diary data, 5 Lubiprostone subjects received treatment but had no post-baseline diary data and 1 Lubiprostone subject had no dosing data or diary data. Therefore, the ITT population consisted of 571 subjects.

The overall study population was predominately female (522 of 571 subjects, 91.4%) and Caucasian (458 of 571, 80.2%). The mean age of subjects was 46.1 years (range: 18-79 years) and all subjects had a confirmed diagnosis of constipation predominant IBS. Variables like age, height, gender, and race did not differ significantly ( $p > 0.05$ ) between the treatment groups. Baseline period disease status in terms of abdominal discomfort/pain and bloating, constipation severity, weekly SBM frequency, SBM stool consistency and bowel straining, percentage of subjects with  $< 3$  SBMs per week, and IBS overall quality of life did not differ significantly ( $p > 0.05$ ). However, subjects in the placebo treatment had a significantly higher percentage of rescue medication usage (15.23%, placebo vs. 11.72% Lubiprostone),  $p=0.030$ . Furthermore, significantly more subjects in the Lubiprostone treatment group reported at least moderate straining (92.9% vs. 85.4%),  $p=0.004$  and stool consistency that was at least hard  $\geq 25\%$  of the time (97.4% vs. 89.6%),  $p<0.001$ .



The responses to the Bowel Symptom Survey did not differ significantly between placebo and Lubiprostone group but no statistical analysis was performed. One subject (0.3%) in the 16 mcg Lubiprostone treatment group reported abdominal discomfort/pain occurring rarely. There was a larger percentage of subjects (8.9%, 17 subjects) in the placebo group than in the 16 mcg Lubiprostone group (6.7%, 25 subjects) that did not associate their abdominal discomfort/pain with their BM frequency. More subjects in the 16 mcg Lubiprostone treatment group (3.2%, 12 subjects) reported > 3 BMs per day relative to subjects in the placebo group (2.1%, 4 subjects). There was a higher percentage of subjects in Lubiprostone treatment group who reported rushing to the toilet (45 subjects, 12.0% vs. 21 subjects, 10.9%), but less percentage that reported loose, mushy, or watery stools (11 Lubiprostone subjects, 2.9%; 6 Placebo subjects, 3.1%).

History of medical problems and procedures were similar in both treatment groups. More subjects in the Lubiprostone treatment group compared to placebo treatment group listed dyspepsia (42 subjects, 11.1% vs. 17 subjects, 8.9%), nausea (7 subjects, 1.8% vs. 1 subject, 0.5%) and abdominal pain (5 subjects, 1.3% vs. 1 subject, 0.5%) as an active medical problem. A greater percentage of subjects in the placebo treatment group (68, 35.4% vs. 104, 27.4%) reported drug sensitivity as an active medical problem. Migraine headache (56 subjects, 14.8% vs. 20 subjects, 10.4%), sinus headache (13 subjects, 3.4% vs. 2 subjects, 1.0%) and dizziness (5 subjects, 1.3% vs. 0 subjects, 0.0%) were reported by more subjects in the Lubiprostone treatment group than in placebo. No statistical analysis was performed on the medical history, history of procedures or the active medical problems.

**Table 70: Summary of Demographics and Disease History: Study SIB-0432 (ITT Population)**

Table 7b: Summary of Demographics and Disease History: Study SIB 012 (ITT Population)					
Variable	Statistic	Placebo	Lubiprostone 16 mcg	Total	p-Value <sup>3</sup>
Age (years)	N (%)	192	379	571	0.132
	Mean	47.3	45.5	46.1	
	SD	13.34	12.93	13.08	
	Median	48.0	46.0	47.0	
	Range	18.0-79.0	19.0-79.0	18.0-79.0	
Height (inches)	Mean	65.0	64.7	64.8	0.388
	SD	3.34	3.15	3.21	
	Median	64.7	64.0	64.5	
	Range	59.0-85.0	53.8-76.0	53.8-85.0	
Gender n (%)	Female	179 (93.2)	343 (90.5)	522 (91.4)	0.272
	Male	13 (6.8)	36 (9.5)	49 (8.6)	
Race n (%)	Caucasian	156 (81.3)	302 (79.7)	458 (80.2)	0.336
	African-American	21 (10.9)	49 (12.9)	70 (12.3)	
	Hispanic	12 (6.3)	25 (6.6)	37 (6.5)	
	Other	2 (1.0)	0 (0.0)	2 (0.4)	
	Asian	1 (0.5)	3 (0.8)	4 (0.7)	
Bowel Symptom Survey Results					
Abdominal Discomfort/Pain? n (%)	Yes	192 (100)	373 (99.7)	565 (99.8)	
	NO	0 (0.0)	0 (0.0)	0 (0.0)	
	Rarely	0 (0.0)	1 (0.3)	1 (0.2)	

Discomfort/Pain improves after BMs? n (%)	Yes	184 (95.8)	355 (95.2)	539 (95.4)	
	NO	4 (2.1)	8 (2.1)	12 (2.1)	
	Rarely	4 (2.1)	10 (2.7)	14 (2.5)	
Discomfort/Pain associated with BM Frequency? n (%)	Yes	164 (85.4)	336 (90.1)	500 (88.5)	
	NO	17 (8.9)	25 (6.7)	42 (7.4)	
	Rarely	11 (5.7)	12 (3.2)	23 (4.1)	
Discomfort/Pain associated with Stool Consistency? n (%)	Yes	186 (96.9)	360 (96.5)	546 (96.6)	
	NO	5 (2.6)	11 (2.9)	16 (2.8)	
	Rarely	1 (0.5)	2 (0.5)	3 (0.5)	
< 3 BMs per week? * n (%)	Yes	186 (96.9)	360 (96.5)	546 (96.6)	
	NO	5 (2.6)	11 (2.9)	16 (2.8)	
	Rarely	1 (0.5)	2 (0.5)	3 (0.5)	
> 3 BMs per day? * n (%)	Yes	4 (2.1)	12 (3.2)	16 (2.8)	
	NO	188 (97.9)	362 (96.8)	550 (97.2)	
	Rarely	0 (0.0)	0 (0.0)	0 (0.0)	
Hard or Lumpy stools? * n (%)	Yes	188 (97.9)	371 (99.2)	559 (98.8)	
	NO	4 (2.1)	3 (0.8)	7 (1.2)	
	Rarely	0 (0.0)	0 (0.0)	0 (0.0)	
Loose, mushy or watery stools? * n (%)	Yes	6 (3.1)	11 (2.9)	17 (3.0)	
	NO	186 (96.9)	363 (97.1)	549 (97.0)	
	Rarely	0 (0.0)	0 (0.0)	0 (0.0)	
Straining during BMs? * n (%)	Yes	190 (99.0)	370 (98.9)	560 (98.9)	
	NO	2 (1.0)	4 (1.1)	6 (1.1)	
	Rarely	0 (0.0)	0 (0.0)	0 (0.0)	
Rushing to the toilet? * n (%)	Yes	21 (10.9)	45 (12.0)	66 (11.7)	
	NO	171 (89.1)	329 (88.0)	500 (88.3)	
	Rarely	0 (0.0)	0 (0.0)	0 (0.0)	
Baseline Period Disease Status					
Abdominal Discomfort/Pain? <sup>1</sup>	N	192	379	571	0.849
	Mean	2.08	2.07	2.07	
	SD	0.642	0.652	0.648	
	Median	2.04	2.04	2.04	
	Range	1.00-4.00	0.36-4.00	0.36-4.00	
Abdominal Bloating <sup>1</sup>	Mean	2.24	2.24	2.24	0.932
	SD	0.651	0.682	0.671	
	Median	2.21	2.19	2.19	
	Range	0.86-4.00	0.62-4.00	0.62-4.00	
Constipation Severity	Mean	2.21	2.20	2.21	0.820
	SD	0.646	0.669	0.661	
	Median	2.18	2.19	2.19	
	Range	0.54-4.00	0.00-3.96	0.00-4.00	
Weekly SBM Frequency	Mean	3.98	4.05	4.03	0.823
	SD	3.806	3.451	3.571	
	Median	3.11	3.37	3.25	
	Range	0.00-25.41	0.00-36.50	0.00-36.50	

<b>SBM Stool Consistency<sup>2</sup></b>	N	177	370	547	0.816
	Mean	2.76	2.75	2.75	
	SD	0.721	0.677	0.691	
	Median	2.74	2.75	2.74	
	Range	0.57-4.00	0.67-4.00	0.57-4.00	
<b>SBM Bowel Straining<sup>1</sup></b>	Mean	2.39	2.39	2.39	0.978
	SD	0.753	0.676	0.701	
	Median	2.35	2.29	2.33	
	Range	0.02-4.00	0.67-4.00	0.02-4.00	
<b>Overall IBS-QOL</b>	N	184	364	548	0.837
	Mean	57.58	57.97	57.84	
	SD	21.240	21.052	21.097	
	Median	58.82	60.29	59.93	
	Range	6.62-93.38	0.74-97.06	0.74-97.06	
<b>Percent Rescue Med Usage</b>	N	192	379	571	0.030
	Mean	15.23	11.72	12.91	
	SD	19.528	17.514	18.274	
	Median	7.41	3.70	4.00	
	Range	0.00-100.0	0.00-100.0	0.00-100.0	
<b>&lt; 3 SBMs/week ≥ 25% of the time n (%)</b>	Yes	144 (75.0)	282 (74.4)	426 (74.6)	0.918
	NO	48 (25.0)	96 (25.3)	144 (25.2)	
	Missing	0 (0.0)	1 (0.3)	1 (0.2)	
<b>Straining ≥ Moderate ≥ 25% of the Time n (%)</b>	Yes	164 (85.4)	352 (92.9)	516 (90.4)	0.004
	NO	13 (6.8)	17 (4.5)	30 (5.3)	
	Exempt	15 (7.8)	9 (2.4)	24 (4.2)	
	Missing	0 (0.0)	1 (0.3)	1 (0.2)	
<b>Consistency ≥ Hard ≥ 25% of the Time n (%)</b>	Yes	172 (89.6)	369 (97.4)	541 (94.7)	<0.001
	NO	5 (2.6)	0 (0.0)	5 (0.9)	
	Exempt	15 (7.8)	9 (2.4)	24 (4.2)	
	Missing	0 (0.0)	1 (0.3)	1 (0.2)	

Reviewer's table modified from Table 11-1, page 53 of 75, Table 14.1.5, page 53 of 75, and Table 14.1.6, page 54 of 75

Clinical Study Report-SIB-0432

\*At least ¼ of the time in the last 3 months

<sup>1</sup>Scale: 0 (Absent), 1 (Mild), 2 (Moderate), 3 (Severe), 4 (Very Severe)

<sup>2</sup>Scale: 0 (Very Loose), 1 (Loose), 2 (Normal), 3 (Hard), 4 (Very Hard)

<sup>3</sup>p-value is from a 2-sample t-test for continuous variables and a chi- square test for categorical variables

### 10.1.2 Adverse Events

The method in which adverse events (AE) were reported and analyzed in this clinical study was the same as that used in study SIB-0431 Treatment phase I. The one difference was the reporting of adverse events at the end of the 12 week treatment period since study SIB-0431 Treatment phase I had a treatment phase II (randomized withdrawal) portion. Events with onset dates before randomization were considered to be part of the subject's medical history. Events with onset within 7 days of the last day of the treatment period were included in the AE tabulations and analysis. Events with onset more than 7 days and within 14 days after the last day of treatment were considered falling outside of the treatment period and were excluded from the tabulations but were included in the listings. The subjects who enrolled in the open label extension study did not have the 14 day follow-up period. Hence, the AE reporting time frame for these subjects ended on the date of the last dose of the study drug.

Of the 579 safety evaluable subjects in the SIB-0432 study, 276 (47.7%) experienced at least one adverse event during the course of the study. Of these subjects, 91 were in the placebo group and 185 were in the Lubiprostone group. The difference was not statistically significant,  $p=0.731$ .

One hundred and sixteen subjects overall (20.0%) reported at least 1 treatment-related AE; of these subjects 39 were in the placebo group and 77 were in the Lubiprostone 16 mcg group. These treatment-related adverse events were also not statistically significant,  $p=0.988$ .

Thirty one subjects (5.4%) withdrew from the study because of an AE. Of those subjects who withdrew, 15 were in the placebo group and 16 were in the Lubiprostone 16 mcg group, but the difference was not statistically significant,  $p=0.075$ .

There were 4 AEs that were classified as serious. Both treatment groups had 2 subjects that experienced serious adverse events.

**Subject 215-003** (AE: Non-cardiac chest pain): This particular subject was receiving Lubiprostone 8 mcg bid. She was a 69 year old female with past medical history significant for Idiopathic Thrombocytopenic Purpura (ITP), Diastolic Dysfunction, Cerebral Hemorrhage due to ITP, Myocardial Infarction (MI), Hypothyroidism, Hyperlipidemia, Asthma, Pulmonary Embolism (PE), Splenectomy due to ITP, Parathyroidectomy, Hysterectomy and Appendectomy. Concomitant medications included: acetylsalicylic acid, amitriptyline, Atorvastatin, B-Komplex, Glyceryl Trinitrate, Heparin, Levothyroxine sodium, Lisinopril, Metoprolol succinate, morphine, psyllium hydrophilic, mucilloid, salbutamol, and seretide. The subject was hospitalized on study day 2 for chest pain radiating to her right side. She had negative cardiac enzymes and her echo revealed EF of 65% without discrete wall motion abnormalities. The subject did have a CT scan that was negative for PE and a SPECT scan that revealed abnormal dobutamine stress SPECT Radiopharmaceutical Myocardial Scan. The Dobutamine Stress test revealed a fixed moderate inferior and inferolateral wall MI but no evidence of active ischemia. The subject was treated with heparin and morphine during the hospitalization, and her chest pain was relieved. She was discharged on study day 3. The study drug was initiated on study day 1, last dose taken was study day 2, and subject discontinued the study on study day 6.

**Subject 217-017** (AE: Cholecystitis): This subject was in the 16 mcg Lubiprostone group. She was a 40 year old female with a past medical history significant for headache, nephrolithiasis, cholelithiasis, and Cholecystectomy. On study day 13, the subject woke up with abdominal cramps and fever of 102°F. She did experience vomiting. The subject was observed in the ER, and she did have an Ultrasound that revealed gallstones. The subject was scheduled to have a cholecystectomy in 2 weeks. The medical history was confusing since the subject supposedly had a previous cholecystectomy listed as part of her past medical history. The study drug was started on study day 1, subject was hospitalized on study day 13, and subject took the last dose of study drug on study day 88. However, she did complete the study.

The other 2 subjects were in the placebo group. 1 subject had an Ex-Lap for small bowel obstruction and the other subject had an abnormal surveillance mammogram after a lumpectomy

No subjects died during study SIB-0432. Overall, 31 subjects (15 placebo; 16 Lubiprostone) experienced a total of 33 AEs for which the drug was permanently discontinued. Adverse events that led to permanent drug discontinuation in more than 1 Lubiprostone subjects were nausea (6 subjects), abdominal pain (2 subjects), diarrhea (2 subjects), and headache (2 subjects).

The 2 most frequent system organ class for AEs were gastrointestinal disorders (overall 134 subjects, 23.1%) and infections and infestations (overall 96 subjects, 16.6%). Of the 134 subjects reporting AEs in the gastrointestinal body system, 41 were placebo subjects and 93 were Lubiprostone 16 mcg subjects, but the difference was not statistically significant,  $p=0.389$ . More proportion of subjects in the Lubiprostone treatment group reported: nausea (34 subjects, 8.9% vs. 11 subjects 5.6%), diarrhea (23 subjects, 6.0% vs. 10 subjects, 5.1%), vomiting (6 subjects, 1.6% vs. 1 subject, 0.5%), dry mouth (4 subjects, 1.0% vs. 0 subject, 0.0%) than placebo subjects. It should be noted that more subjects also reported abdominal pain upper in the Lubiprostone treatment group (9 subjects, 2.3% vs. 2 subjects, 1.0%), and there were more subjects who reported gastroesophageal reflux disease in the Lubiprostone group than in the placebo group (5 subjects, 1.3% vs. 0 subjects, 0.0%).

Overall, similar proportion of subjects in the Lubiprostone (64 subjects, 16.7%) and placebo (32 subjects, 16.4%) reported AEs in the infections and infestations system organ class. However, there were larger percentage of Lubiprostone subjects that reported upper respiratory tract infection (11 subjects, 2.9% vs. 2 subjects, 1.0%), bronchitis (6 subjects, 1.6% vs. 1 subject, 0.5%) and tooth infection (4 subjects, 1.0% vs. 0 subjects, 0.0%). There were no statistically significant differences between the treatment groups for the number of subjects reporting AEs in any system organ class.

The overall frequency of most adverse events was low. The AEs reported by at least 5% of subjects (Placebo and Lubiprostone) overall were nausea (45 subjects, 7.8%), diarrhea (33 subjects, 5.7%) and headache (27 subjects, 4.7%). Both the frequency of nausea and diarrhea was higher among Lubiprostone subjects compared to placebo subjects, but the frequency of headache was higher in the placebo group (11 subjects, 5.6%) than the Lubiprostone group (16 subjects, 4.2%).

Thirty four subjects (5.9%) had at least 1 severe AE; of these subjects 14 were in the placebo group and 20 were in the Lubiprostone 16 mcg group. Overall, the frequency of severe AEs were similar in both groups,  $p=0.340$ . Severe dizziness (3 subjects), vomiting, arthralgia, and back pain (2 subjects each) were the severe AEs reported by more than 1 Lubiprostone subject whereas severe abdominal pain (3 subjects) was the severe AE reported by more than 1 placebo subject.

### **10.1.3 Withdrawals, Compliance, and Protocol Violations**

#### **Subject Disposition/Withdrawals**

A total of 581 subjects were randomized in a 2:1 ratio in study SIB-0432. 194 subjects into the placebo group and 387 into the 16 mcg Lubiprostone group. 2 subjects (226-006 and 231-004) in the Lubiprostone group were randomized but not treated, making a total of 194 subjects who were treated with placebo and 385 subjects treated with Lubiprostone. A total of 454 subjects completed the study. The percentage of subjects completing the study in the placebo group was 77.8% and 78.3% in the 16 mcg Lubiprostone group. The mean number of days the subjects were on the study drug was 74.8 in the placebo group and 74.3 in the 16 mcg Lubiprostone group. A total of 127 subjects (21.9%; 43 Placebo; 84 16 mcg Lubiprostone) discontinued the study. The reasons for discontinuation were voluntary withdrawal (35 subjects, 6.0%), AEs (33 subjects, 5.7%), lack of efficacy (26 subjects, 4.5%), lost to follow-up (12 subjects, 2.1%) and non-compliance (11 subjects, 1.9%). The most common reason for withdrawal in the placebo subjects was AEs (15 subjects, 7.7%) whereas in 16 mcg Lubiprostone subjects most of them voluntarily withdrew (25 subjects, 6.5%). In the 16 mcg Lubiprostone group, the

same number of subjects discontinued the study for adverse events and lack of efficacy (18 subjects, 4.7%). Ten subjects (5.2%) voluntarily withdrew and 8 subjects (4.1%) discontinued due to lack of efficacy in the placebo group. More subjects in the Lubiprostone treatment group (8 subjects, 2.1%) had non-compliance as a reason for discontinuation than subjects in the placebo group (3 subjects, 1.5%).

## Compliance

Treatment compliance was estimated by using the study drug administration record in the subject's daily diary and case report form (CRF) data. Monthly compliance was based on the diary data, but the overall compliance was based on both the diary and the drug accountability data. At each office visit post randomization (visits 4, 5 and 6), all returned study drugs were inventoried for compliance. Diary based calculations involved the number of doses administered divided by the number of days between the first and last dose dates (per the diary) X 2. Calculation based on drug accountability data involved the number of capsules taken (the difference between the total number dispensed and the total number returned) divided by the number of days on the study drug X 2. The percent compliance was calculated by dividing the actual cumulative exposure to study drug by the exposure the subject should have received (based on the number of days the subject was on the study drug).

In general, overall percent compliance was similar for the 2 treatment groups based on CRF and the diary data. Based on diary data, the placebo group overall percent compliance was 83.99% and 84.83% in the 16 mcg Lubiprostone group,  $p=0.652$ . The CRF data did demonstrate not only similar but also higher percent of overall compliance in both treatment groups (mean: 94.18% placebo and 94.03% Lubiprostone). In month 1, mean compliance was higher among Lubiprostone subjects than placebo subjects (mean: 81.23% vs. 78.86%),  $p=0.294$ , but at month 3, more Lubiprostone subjects were less than 70% compliant compared to placebo (19 subjects, 6.0% vs. 8 subjects, 5.0%),  $p=0.657$ . Of the 558 subjects for whom overall treatment compliance data was available, 535 were at least 70% compliant and 23 were less than 70% compliant. Of the 23 subjects who were less than 70% compliant, 16 (4.2%) were 16 mcg Lubiprostone subjects and 7 (3.7%) were placebo subjects. There was a discrepancy between the diary and the CRF data in terms of subjects who were < 70% compliant for the overall treatment period. Diary based data demonstrated a greater number of subjects were less than 70% compliant in the placebo group (35 subjects, 18.2%) than the Lubiprostone group (57 subjects, 15.0%),  $p=0.327$ . Similar proportion of subjects in the 16 mcg Lubiprostone group (16 subjects, 4.2%) as the placebo group (8 subjects, 4.2%) required dose reduction,  $p=0.975$ .

## Protocol Deviations

Across all 3 months, the most frequent protocol violations were inclusion/exclusion criteria violations or misrandomization and < 70% study drug compliance in both treatment groups. The proportion of subjects who were declared inclusion/exclusion criteria violators or considered misrandomized was higher in the Lubiprostone treatment group (11 subjects, 2.9%) at all treatment months relative to placebo group (1 subject, 0.5% for all 3 months). The use of prohibited concomitant medications was higher in the Lubiprostone group than placebo group at all 3 months (3 subjects, 0.8% vs. 0 subjects, 0.00%). Month 1 has the same number of subjects in both treatment groups that were less than 70% compliant (6 subjects). The proportion of subjects with < 70% treatment compliance was higher in the Lubiprostone group than the placebo group at month 2 (10 subjects, 2.6% vs. 3 subjects, 1.6%) and month 3 (7 subjects, 1.8% vs. 3 subjects, 1.6%).

## 10.1.4 Efficacy Results

### Primary Efficacy Analysis

The primary efficacy analysis was the overall responder rate during the 12 week treatment period.

**Table 71: Overall Responder Rates in 4 Populations**

Study Population	Study Arm	Overall	N (%)	Responder Difference	p-Value
ITT Subjects without LOCF	Placebo N=192	<b>Responder</b>	<b>11 (5.7)</b>	6.4%	0.023 <sup>*</sup>
		Non-Responder	181 (94.3)		
	Lubiprostone 16 mcg N=379	<b>Responder</b>	<b>46 (12.1)</b>		
		Non-Responder	333 (87.9)		
ITT Subjects with LOCF	Placebo N=192	<b>Responder</b>	<b>20 (10.4)</b>	7.3%	0.031 <sup>*</sup>
		Non-Responder	172 (89.6)		
	Lubiprostone 16 mcg N=379	<b>Responder</b>	<b>67 (17.7)</b>		
		Non-Responder	312 (82.3)		
Per Protocol Subjects without LOCF	Placebo N=179	<b>Responder</b>	<b>11 (6.1)</b>	6.7%	0.024 <sup>*</sup>
		Non-Responder	168 (93.9)		
	Lubiprostone 16 mcg N=351	<b>Responder</b>	<b>45 (12.8)</b>		
		Non-Responder	306 (87.2)		
Study Completer Subjects without LOCF	Placebo N=151	<b>Responder</b>	<b>11 (7.3)</b>	6.9%	0.039 <sup>*</sup>
		Non-Responder	140 (92.7)		
	Lubiprostone 16 mcg N=302	<b>Responder</b>	<b>43 (14.2)</b>		
		Non-Responder	259 (85.8)		

Reviewer's table modified from Tables 14.2.1.1, 14.2.1.2, 14.2.1.3, 14.2.1.4, page 57 of 75, Clinical Study Report SIB-0432

<sup>\*</sup>p-value is from a CMH test stratified by pooled-center

In the ITT population without LOCF, the overall responder status for placebo was 5.7% (11 out of 192 subjects) and the 16 mcg Lubiprostone group was 12.1% (46 out of 379 subjects), p=0.023. The overall responder status was slightly higher in the ITT population with LOCF (10.4%, 20/192 placebo vs. 17.7%, 67/379 Lubiprostone), p=0.031 and the ITT population who are study completers (7.3%, 11/151 placebo vs. 14.2%, 43/302 Lubiprostone), p=0.039. The per protocol subjects (6.1%, 11/179 placebo vs. 12.8%, 45/351), p=0.024 had similar overall responder rate as the ITT subjects without LOCF. All populations achieved statistical significance for the overall responder rate. Based on this analysis, it was deduced that the Lubiprostone treatment with 16 mcg dose produced statistically significant improvement in IBS symptoms.

**Secondary Efficacy Analysis: Table 72: Monthly Responder Rates in 4 Populations**

Study Population	Treatment period	Study Arms	Status	N (%)	Responder Difference	p-Value <sup>1</sup>
ITT Subjects without LOCF	Month 1	Placebo N=192	Responder	<b>13 (6.8)</b>	3%	0.303
			Non-Responder	179 (93.2)		
		Lubiprostone 16 mcg N=379	Responder	<b>37 (9.8)</b>		
			Non-Responder	342 (90.2)		
	Month 2	Placebo N=192	Responder	<b>19 (9.9)</b>	6.2%	0.047
			Non-Responder	173 (90.1)		
		Lubiprostone 16 mcg N=379	Responder	<b>61 (16.1)</b>		
			Non-Responder	318 (83.9)		
	Month 3	Placebo N=192	Responder	<b>11 (5.7)</b>	7.8%	0.008
			Non-Responder	181 (94.3)		
		Lubiprostone 16 mcg N=379	Responder	<b>51 (13.5)</b>		
			Non-Responder	328 (86.5)		
ITT Subjects with LOCF	Month 1	Placebo N=192	Responder	<b>14 (7.3)</b>	3.3%	0.278
			Non-Responder	178 (92.7)		
		Lubiprostone 16 mcg N=379	Responder	<b>40 (10.6)</b>		
			Non-Responder	339 (89.4)		
	Month 2	Placebo N=192	Responder	<b>23 (12.0)</b>	5.9%	0.074
			Non-Responder	169 (88.0)		
		Lubiprostone 16 mcg N=379	Responder	<b>68 (17.9)</b>		
			Non-Responder	311 (82.1)		
	Month 3	Placebo N=192	Responder	<b>28 (14.6)</b>	8.1%	0.026
			Non-Responder	164 (85.4)		
		Lubiprostone 16 mcg N=379	Responder	<b>86 (22.7)</b>		
			Non-Responder	293 (77.3)		
Per Protocol Subjects without LOCF	Month 1	Placebo N=191	Responder	<b>13 (7.0)</b>	2.7%	0.366
			Non-Responder	172 (93.0)		
		Lubiprostone 16 mcg N=364	Responder	<b>35 (9.7)</b>		
			Non-Responder	324 (90.3)		
	Month 2	Placebo N=191	Responder	<b>19 (10.1)</b>	6.4%	0.044
			Non-Responder	169 (89.9)		
		Lubiprostone 16 mcg N=364	Responder	<b>59 (16.5)</b>		
			Non-Responder	298 (83.5)		
	Month 3	Placebo N=191	Responder	<b>11 (5.9)</b>	7.2%	0.016
			Non-Responder	177 (94.1)		
		Lubiprostone 16 mcg N=364	Responder	<b>47 (13.1)</b>		
			Non-Responder	313 (86.9)		
Study Completer Subjects without LOCF	Month 1	Placebo N=151	Responder	<b>12 (7.9)</b>	3.4%	0.355
			Non-Responder	139 (92.1)		
		Lubiprostone 16 mcg N=302	Responder	<b>34 (11.3)</b>		
			Non-Responder	268 (88.7)		
	Month 2	Placebo N=151	Responder	<b>18 (11.9)</b>	6.6%	0.066
			Non-Responder	133 (88.1)		
		Lubiprostone 16 mcg N=302	Responder	<b>56 (18.5)</b>		
			Non-Responder	246 (81.5)		
	Month 3	Placebo N=151	Responder	<b>11 (7.3)</b>	9.3%	0.009
			Non-Responder	140 (92.7)		
		Lubiprostone 16 mcg N=302	Responder	<b>50 (16.6)</b>		
			Non-Responder	252 (83.4)		

Reviewer's table modified from Tables 14.2.2.1, 14.2.2.2, 14.2.2.3, 14.2.2.4, page 57 of 75, Clinical Study Report SIB-0432

<sup>1</sup>p-values were from CMH tests stratified by pooled-center

<sup>2</sup>p-value is significant according to the 3- step testing procedure



### **Monthly Responder Rates at Months 1, 2, and 3: key secondary efficacy**

The monthly responder status at months 1, 2, and 3 were considered key secondary endpoints. A monthly responder had the same definition as the one in study SIB-0431 Treatment Phase I. In the ITT subjects without LOCF, the responder rate was higher in the 16 mcg Lubiprostone group (9.8%-16.1%) for all months compared to the placebo group (5.7%-9.9%). Despite months 2 and 3 having statistically significant p-values (month 2:  $p=0.047$ ; month 3:  $p=0.008$ ), they were not considered statistically significant due to the failure of step 1 of the 3 step testing procedure. Month 1 had the lowest monthly responder rate and was not statistically significant across all 4 populations. The ITT subjects without LOCF and the PP subjects had similar monthly responder rates. The monthly responder rates were slightly higher in the ITT subjects with LOCF and the ITT subjects who were study completers. The 16 mcg Lubiprostone provided global IBS symptom relief at all months better than placebo. Despite statistical significance varying between months, the Lubiprostone data exhibited a positive trend in relieving IBS symptoms throughout the 12 weeks.

### **Other Secondary Efficacy Endpoints**

#### **Change From Baseline in Abdominal Symptoms (abdominal discomfort/pain and bloating) during Months 1, 2 and 3**

Abdominal pain/discomfort was recorded by each subject in a diary each evening and was scored as Absent (0), Mild (1), Moderate (2), Severe (3), Very Severe (4). For the ITT subjects without LOCF, the mean baseline abdominal discomfort/pain was similar in both treatment groups (2.08 for placebo; 2.07 for Lubiprostone). Compared to the respective baseline values, the abdominal discomfort/pain had decreased significantly ( $p<0.001$ ) at all 3 months in the placebo and Lubiprostone treated groups in all populations. At all post-baseline evaluation time points, the mean level of abdominal discomfort reported in the Lubiprostone 16 mcg group (range: 1.54-1.75) was lower than that in the placebo group (1.69-1.79), but the difference did not approach statistical significance. The Lubiprostone treated subjects in the ITT without LOCF population had a slightly larger (0.03-0.14) decrease in abdominal pain/discomfort relative to placebo. Overall, in the ITT population without LOCF, the change from baseline in abdominal discomfort in the placebo group was 0.33 vs. 0.41 in the Lubiprostone treated group. Similar results were observed for ITT subjects with LOCF and PP subjects. These analyses suggested that, compared to baseline, the 16 mcg Lubiprostone demonstrated similar improvement in abdominal pain/discomfort as placebo in all 3 months.

Abdominal bloating was recorded using the same 5 point scale as abdominal discomfort/pain. Each evening the subject recorded a rating based on the above scale in the electronic diary. Compared to the respective baseline values, the abdominal bloating had decreased significantly ( $p<0.001$ ) at all 3 months in the placebo and Lubiprostone treated groups in all populations. For the ITT subjects without LOCF, the mean baseline abdominal bloating was the same in both treatment groups (2.24). At all post-baseline evaluation time points, the mean level of abdominal bloating reported in the Lubiprostone 16 mcg group (range: 1.73-1.93) was lower than that in the placebo group (1.84-1.95), but the difference did not approach statistical significance. The Lubiprostone treated subjects in the ITT without LOCF population had a slightly larger (0.03 to 0.12) decrease in abdominal bloating than those observed among placebo subjects. Overall, in the ITT population without LOCF, the change from baseline in the placebo group was 0.33 vs. 0.39 in the Lubiprostone treated group. Similar results were observed for

ITT subjects with LOCF and PP subjects. These analyses suggested that, compared to baseline, the 16 mcg Lubiprostone demonstrated similar improvement in abdominal bloating as placebo in all 3 months.

### **Change from Baseline in Spontaneous Bowel Movement and Bowel Movement Frequency Rates During Months 1, 2 and 3**

Spontaneous bowel movements (SBMs) were bowel movements that occur independent of rescue medication usage. The calculation and analysis of SBMs and BMs frequency were performed in the same manner as study SIB-0431 Treatment Phase I. The mean baseline number of SBMs during a 28 day interval was 3.98 for placebo and 4.05 for Lubiprostone treatment group,  $p=0.254$ . Compared to the respective baseline values, frequency of SBMs had significantly increased ( $p<0.001$ ) at all 3 months in the placebo and Lubiprostone treated groups in all 3 populations. In the ITT subjects without LOCF, at Month 1, the change from baseline in SBM frequency rate was larger in the Lubiprostone group (1.55) than in the placebo group (1.29), but the difference did not reach statistical significance. Placebo subjects showed a larger change from baseline in SBM frequency rates than Lubiprostone subjects at month 2 (1.68 vs. 1.63),  $p=0.791$  and month 3 (1.64 vs. 1.50),  $p=0.829$ . Overall, in the ITT population without LOCF, the change from baseline in the placebo group was 1.35 vs. 1.53 in the Lubiprostone treated group,  $p=0.807$ . Unlike the ITT subjects without LOCF, in the ITT subjects with LOCF and PP subjects at all post-baseline evaluation time points, the change from baseline in SBM frequency was larger in the Lubiprostone treated group than placebo group but statistical significance was not approached. The Lubiprostone data at times did not exhibit a positive trend in increasing the frequency of SBMs. Thus, compared to baseline, the 16 mcg Lubiprostone demonstrated similar improvement in frequency of SBM as placebo, but at times it was worse than placebo.

Unlike SBMs, BMs were categorized as BMs that resulted from use of rescue medications. The determination of SBMs vs. BMs was made by the subject in their diary each evening. Monthly BMs were calculated by the same method as SBMs. The mean baseline number of BMs during a 28 day interval was 5.14 for placebo and 4.82 for Lubiprostone treatment group,  $p=0.368$ . Compared to the respective baseline values, frequency of BMs had significantly increased ( $p<0.001$ ) at all times in the placebo and Lubiprostone treated groups. In the ITT without LOCF population, at all post-baseline evaluation time points the change from baseline in BM frequency rate was larger in the Lubiprostone group than in the placebo group, but the difference did not reach statistical significance. In the ITT without LOCF population, the Lubiprostone treated subjects had a (0.17-0.43) increase in BMs relative to the placebo group. Overall, in the ITT population without LOCF, the change from baseline in the placebo group was 0.91 vs. 1.24 in the Lubiprostone treated group,  $p=0.373$ . For ITT subjects with LOCF and PP subjects at all post-baseline evaluation time points, the change from baseline in BM frequency was larger in the Lubiprostone treated group than placebo group but statistical significance was not approached. These analyses suggested that, compared to baseline, the 16 mcg Lubiprostone demonstrated a similar increase in frequency of BM as placebo.

### **Change from baseline in Stool Consistency during Months 1, 2 and 3**

Stool consistency of SBMs was recorded by each subject in a diary each evening and was scored as Very Loose, watery (0), Loose (1), Normal (2), Hard (3) or Very Hard, little balls (4). Mean baseline stool consistency ratings in the placebo (2.76) and the Lubiprostone (2.75) subjects were similar,  $p=0.597$ . Change in stool consistency compared to the respective baseline was statistically significant

( $p < 0.001$ ) at all 3 months in the placebo and Lubiprostone treatment groups in all 3 populations. For the ITT subjects without LOCF, at all post baseline evaluation time points, the mean stool consistency reported in the Lubiprostone group (range: 2.24-2.27) was lower than that in the placebo group (2.33-2.38), but the difference was not statistically significant. Overall, in the ITT population without LOCF, the change from baseline in stool consistency in the placebo group was 0.40 vs. 0.51 in the Lubiprostone treated group,  $p = 0.136$ . For ITT subjects with LOCF and PP subjects at all post-baseline evaluation time points, the change from baseline in stool consistency was lower in the Lubiprostone treated group than placebo group, and the difference was statistically significant at month 3 ( $p = 0.041$ ) for PP subjects. Despite statistical significance varying between populations, the 16 mcg Lubiprostone data exhibited a positive trend in softening the stool.

### **Change from Baseline in Constipation Severity during Months 1, 2, and 3**

For all ITT subjects, severity of constipation was recorded using a 5 point scale; Absent (0), Mild (1), Moderate (2), Severe (3), Very Severe (4) at baseline and for Months 1, 2 and 3. Mean baseline constipation severity was similar in both treatment groups (2.21 for placebo; 2.20 for Lubiprostone),  $p = 0.577$ . Compared to the respective baseline values, constipation severity had significantly decreased ( $p < 0.001$ ) at all times in the placebo and Lubiprostone treated groups. For the ITT subjects without LOCF, at all post-baseline evaluation time points, the mean severity of constipation reported in the Lubiprostone group (range: 1.63-1.79) was lower than that in the placebo group (1.76-1.88), but the difference was not statistically significant. In the ITT without LOCF population, the Lubiprostone treated subjects have a 0.08 to 0.10 decrease in constipation severity relative to the placebo group. Overall, in the ITT population without LOCF, the change from baseline in the placebo group was 0.39 vs. 0.48 in the Lubiprostone treated group. Similar results were observed for ITT subjects with LOCF and PP subjects. Although statistical significance was not achieved, this analysis demonstrated a positive trend that suggested the 16 mcg Lubiprostone treatment provided a slight decrease in constipation severity.

### **Change from Baseline in Degree of Straining during Months 1, 2 and 3**

The degree of straining was recorded in a diary each evening and was scored as Absent (0), Mild (1), Moderate (2), Severe (3), Very Severe (4). The subject was to apply the above rating to any SBM that occurred during the day. For the ITT subjects without LOCF, mean baseline constipation severity was the same in both treatment groups (2.39),  $p = 0.668$ . Compared to the respective baseline values, change in degree of straining was statistically significant ( $p < 0.001$ ) at all 3 months in the placebo and Lubiprostone treatment groups in all 3 populations. For the ITT subjects without LOCF, at all post baseline evaluation time points, the mean degree of straining reported in the Lubiprostone group (range: 1.73-1.85) was lower than that in the placebo group (1.85-1.96), but the difference was not statistically significant. Overall, in the ITT population without LOCF, the change from baseline in degree of straining in the placebo group was 0.48 vs. 0.61 in the Lubiprostone treated group,  $p = 0.104$ . In the ITT subjects without LOCF, Lubiprostone treated subjects showed (0.08 to 0.13) improvement in degree of straining relative to placebo subjects. Similar results were observed for ITT subjects with LOCF and PP subjects. This analysis indicated Lubiprostone treatment slightly decreased straining in subjects during a 12 week period.

### **Symptom Relief by Month**

Global assessment of symptom relief for all ITT subjects was recorded using a 7 point scale; Significantly Worse (-3), Moderately Worse (-2), A little bit worse (-1), Unchanged (0), A little bit relieved (1), Moderately relieved (2), Significantly relieved (3). Subjects answered a weekly question in their diary in order to assess global symptom relief. In the ITT without LOCF population, the Lubiprostone treated subjects had (0.09-0.25) better rating in their global symptom relief relative to the placebo group. Overall, in the ITT subjects without LOCF, the symptom relief in the placebo group was 0.58 vs. 0.75 in the Lubiprostone treated group,  $p=0.060$ . Similar results were observed for ITT subjects with LOCF and PP subjects. In month 2, Lubiprostone subjects in all 3 populations reported significantly better symptom relief than placebo subjects,  $p=0.011$  to  $0.031$ . This analysis indicated that subjects suffering from constipation predominant IBS had better global symptom relief with Lubiprostone treatment than placebo especially in Month 2.

### **Irritable Bowel Syndrome Quality of Life (IBS-QOL)**

Irritable Bowel Syndrome Quality of Life (IBS-QOL) questionnaire was developed by Dr. D A Drossman and colleagues as a series of 34 questions. These questions were analyzed in sub-categories: dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual and relationship. Subjects completed IBS-QOL at the study site at randomization (visit 2), Week 4 (visit 4), and Week 12 (visit 6). The baseline value was the score obtained during the randomization (visit 2). The scores were based on changes from baseline and missing values were not imputed. There was a “Last Value” timepoint, which represented the last value recorded during the study.

The mean baseline for the overall score was similar in both the placebo and Lubiprostone treatment groups (57.6 for placebo; 58.0 for Lubiprostone),  $p=0.837$ . During treatment at week 4, week 12 and end of study value, the IBS-QOL score was always significantly ( $p<0.001$ ) better than baseline in the 16 mcg Lubiprostone and placebo groups. Subjects in the Lubiprostone group showed larger changes in the IBS-QOL scores than placebo at week 4 (13.0 vs. 12.7), week 12 (17.3 vs. 13.4) and at end of study value (15.3 vs. 11.5), and the difference was significant at end of study timepoint,  $p=0.008$ .

In the sub-category of health worry, the Lubiprostone subjects showed significant changes in IBS-QOL score at Week 12 ( $p=0.016$ ) and end of study value timepoint ( $p=0.001$ ). Likewise, in the sub-category dysphoria, the Lubiprostone subjects showed significant changes in IBS-QOL score at Week 12 ( $p=0.031$ ) and end of study value timepoint ( $p=0.012$ ). In both Interference with activity ( $p=0.023$ ) and body image ( $p=0.008$ ) sub-categories, there were significant changes in IBS-QOL scores at the end of study value timepoint between the treatment groups. In all other sub-categories, there were conflicting results. At times Lubiprostone exhibited positive trends in the changes of the IBS-QOL scores, and at other times, placebo subjects had greater changes in their IBS-QOL scores than Lubiprostone subjects.

### **Use of Rescue Medication**

Overall, of the 571 ITT subjects, 58.5% (334 subjects) took rescue medication (71.4%, 137 placebo; 52.0%, 197 Lubiprostone),  $p<0.001$ . In the placebo group, 54.5%, 44.4%, and 48.4% of subjects used rescue medication at month 1, month 2, and month 3, respectively. In the Lubiprostone 16 mcg group, 38.9%, 36.1% and 33.2% of subjects used rescue medication during the same months. The percent of subjects using rescue medication was significantly lower in the Lubiprostone treatment group in months

1 ( $p<0.001$ ) and 3 ( $p=0.001$ ). The mean percent of days rescue medication used was lower in the Lubiprostone group (6.2-7.6) compared to placebo (7.0-11.0) in all 3 months, and the difference did reach statistical significance at month 1 ( $p=0.036$ ) and overall ( $p=0.019$ ). Bisacodyl (54.7% placebo; 39.6% Lubiprostone) and Fleet enema (7.3% Placebo; 5.8% Lubiprostone) were the most common rescue medications used by subjects.

### **Study SPI/0211SIB-05S1**

#### **Title: A Phase III, Multi-Center, Open-Label Safety Study of Oral Lubiprostone for the Treatment of Constipation-predominant Irritable Bowel Syndrome.**

##### **10.1.1 Objectives**

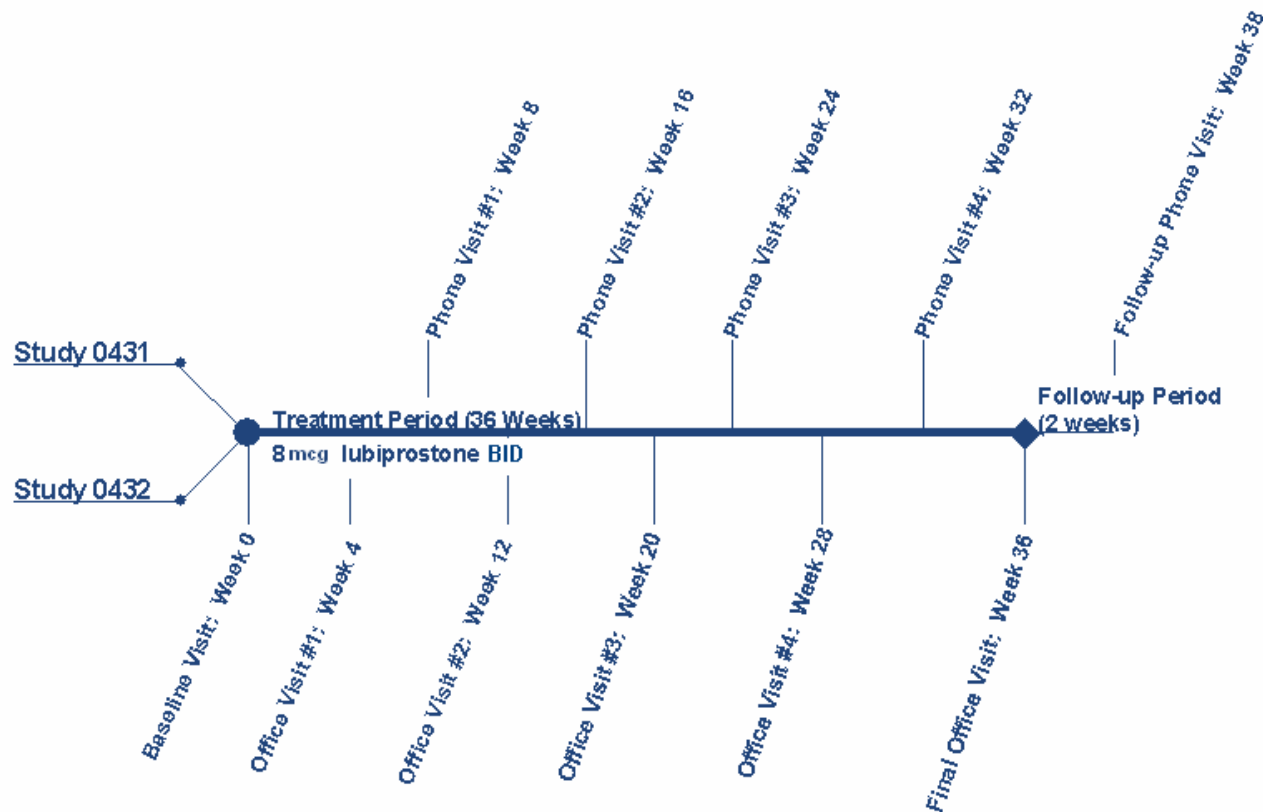
This was a multi-center open-label, Phase III study conducted to assess the long term safety of oral 16 mcg Lubiprostone for the treatment of constipation predominant irritable bowel syndrome. After completing either study SIB-0431 or SIB-0432, subjects had the option of enrolling in the open-label study. 522 subjects were enrolled in 104 centers in the United States. This study was conducted from September 2005 through November 2006.

##### **Study Design**

This was a multi-center open label study of approximately 38 weeks duration including follow-up. Subjects who completed either study SIB-0431 or SIB-0432 with  $\geq 70\%$  study medication compliance and were willing to enroll in the open label study were immediately enrolled to receive Lubiprostone 8 mcg bid for 36 weeks.

The final treatment visit of SIB-0431 and SIB-0432 study served as the baseline period for the open label study. Following final assessments in studies SIB-0431 and SIB-0432, subjects received 36 weeks of 8 mcg Lubiprostone bid medication. The study consisted of a baseline period which was also the final visit of either study SIB-0431 or SIB-0432 (visit 1), 8 interim visits (Visit 2, 4, 6, and 8 office visits and telephone contacts at Visit 3, 5, 7, and 9), an end of treatment office visit at week 36 (visit 10), and a follow-up phone interview (visit 11) conducted 14 days after Visit 10. Subjects completed Irritable Bowel Syndrome-Quality of Life (IBS-QOL) questionnaire at baseline and Visits 2, 4, 6, 8, and 10.

**Figure 3: Schematic of Study Visits**



Copied figure from sponsor's Figure 9-1, page 15 of 61 Clinical Study Report-SIB-05S1

In order to qualify for the open label study, subjects had to complete either the 16 weeks of blinded treatment in SIB-0431 or the 12 week of blinded treatment in SIB-0432. Study drug was administered orally for a total treatment period of 36 weeks; it was taken at breakfast and dinner with food and at least 8 ounces of water. Subjects documented abdominal symptoms and bowel activity in a weekly diary. The weekly ratings of abdominal discomfort/pain, bloating, severity of constipation, weekly counts of spontaneous bowel movements, degree of straining and stool consistency of spontaneous bowel movements, weekly ratings of global symptom relief, and IBS-QOL questionnaire and the safety and tolerability of administered doses were evaluated to determine the long term safety of Lubiprostone. Treatment medication was given to all subjects as two 8 mcg Lubiprostone capsules (One 8 mcg Lubiprostone capsule taken bid) with food at breakfast and dinner with at least 8 ounces of water. Subjects who underwent a dose reduction in studies SIB-0431 and SIB-0432 began the open label study taking 8 mcg Lubiprostone bid.

### Statistical Methods of Analysis

Efficacy assessment was a secondary objective of the open label study and no inferential statistics was performed. The efficacy endpoints were derived from the seven questions in the weekly diary and the IBS-QOL questionnaire completed at each office visit. Monthly responder definitions were based on the weekly assessments of global symptom relief obtained as part of the subjects' electronic diary responses. Global symptom relief was assessed from the 7 point balanced scale associated with the following weekly 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?

**3** Significantly relieved

**2** Moderately relieved

**1** A little bit relieved

**0** Unchanged

**-1** A little bit worse

**-2** Moderately Worse

**-3** Significantly Worse

A Monthly responder was defined as a subject whose symptoms were rated as “**moderately relieved**” for all 4 weeks within a month or “**significantly relieved**” for at least 2 weeks within a month provided the two conditions were met:

1. The subject did not discontinue the study during the month due to lack of efficacy.
2. The subject had no ratings of “**moderately worse**” or “**significantly worse**” during the month.

Efficacy endpoints were summarized for each month. No attempt was made to control for multiple efficacy assessments as this was an open label trial. For the endpoints of abdominal discomfort/pain and bloating, bowel movement frequency, stool consistency, bowel straining, and constipation severity, the change from baseline in mean ratings during all months was analyzed using paired t-tests.

Table 73: Schedule of Study SIB-05S1 Procedures

PERIOD	BASELINE <sup>1</sup>	TREATMENT									FOLLOW-UP
VISIT # Type	Final Treatment Visit SIB-0431 or SIB-0432	2 Interim	3 Interim	4 Interim	5 Interim	6 Interim	7 Interim	8 Interim	9 Interim	10 Final	11 Follow-up
STUDY WEEK	0	4	8	12	16	20	24	28	32	36	38
LOCATION	Office	Office	Phone	Office	Phone	Office	Phone	Office	Phone	Office	Phone
Informed Consent	X										
Medical History	X										
Inclusion/Exclusion Criteria	X										
Height	X										
Vital signs/Weight	X	X		X		X		X		X	
Physical Examination	X					X				X	
Laboratory Tests	X	X		X		X		X		X	
Serum Pregnancy	X					X				X	
Urine Pregnancy		X		X				X			
Weekly Diary	X	X	X	X	X	X	X	X	X	X	
Quality of Life	X	X		X		X		X		X	
Adverse Events		X	X	X	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X
Study Medication Distribution	X	X		X		X		X			
Study Medication Collection		X		X		X		X		X	

<sup>1</sup>Study visit was to coincide with the Final Visit of the previous study. Information from the previous study was to be utilized as history and/or baseline for this study. Study procedures outline identify information gathered for this extension study only. Additional procedures may have applied to the previous study.

Copied from Table 9-1 Sponsor's table, page 14 of 61 Clinical Study Report-SIB-05S



As noted in table 73, subjects were screened at baseline visit to determine their eligibility to enroll in the trial. This visit took place at the final treatment visit of either study SIB-0431 or SIB-0432 prior to the subject being dispensed open label drug. Subjects who had been routinely taking a daily fiber supplement such as Metamucil or Per Diem, etc., were allowed to remain on the supplement throughout the study. They were allowed to change dosage or schedule to minimize the effects of excessive fiber use. The sponsor did not provide rescue medications. However, after 3 consecutive days of not having a SBM, if a subject needed relief, the investigator could prescribe 10 mg of bisacodyl (Dulcolax) suppository. If this was not effective, Fleet enema was prescribed. If both rescue medication failed, additional rescue medications were prescribed after further discussion with the investigator. All rescue medications administered were recorded and the usage documented in the source document and CRF.

After the final treatment visit in study SIB-0431 or SIB-0432, subjects meeting the eligibility criteria were dispensed open label drug and a weekly electronic diary. Subjects were instructed to return 28 days after the first day of baseline period for Visit 2 evaluation. Subjects were instructed to return completed weekly diary and all unused medications. Visit 2 occurred approximately 28 days after the baseline visit. Before any assessments were performed, subjects were asked to complete the IBS-QOL questionnaire.

Visit 3 was a telephone interview to ensure compliance and to evaluate any adverse events. It took place after the subject had completed 8 weeks of open label treatment. Subjects were instructed to complete weekly diary and to return the diary along with the study container at the next visit.

Subjects then returned after approximately 84 days of open label treatment for Visit 4. Subjects completed IBS-QOL questionnaire during this visit. All returned medications were inventoried and subjects were re-dispensed new study medication. Subjects were instructed to complete the diaries and return them to Visit 6.

Visit 5 was a telephone interview that occurred after approximately 112 days of open label treatment. Subjects were instructed to complete weekly diary and to return the diary along with the study container at the next visit.

Subjects returned after approximately 140 days of open label treatment for Visit 6. IBS-QOL questionnaire and physical examinations were completed during the visit.

Visit 7 was a telephone interview that occurred after approximately 168 days of open label treatment. As with all phone interviews, subjects were reminded to be compliant with diary entries and open label drug. Adverse events were also assessed during the phone interview.

Subjects then returned to the office at week 28 for visit 8. During this visit like all office visits, returned medication was inventoried and diary was reviewed for compliance. IBS-QOL questionnaire was completed during the visit.

Visit 9 was similar to all other phone interviews and occurred after approximately 224 days of open label drug. Visit 10 that occurred at week 36 was the final treatment visit, and at this visit, all study medications and weekly diaries were collected and sent back to the sponsor. Final assessment of subjects in terms of vital signs, physical exams and laboratories were performed in the office. The

follow-up phone call (visit 11) was scheduled for 14 days after visit 10. When possible, visit 10 and 11 were conducted not only for subjects that completed the study, but also, for subjects that withdrew early during the study

### **Inclusion/Exclusion Criteria**

For inclusion criteria in this study, the subject:

- had completed the 16 weeks of double blind treatment in study SIB-0431 or the 12 weeks of double blind treatment in study SIB-0432
- had to be a male or non-pregnant (as per negative serum pregnancy test), non-breast feeding female subject.
- had read and understood the IRB approved informed consent form

Exclusion Criteria for this study encompassed subjects who:

- had demonstrated a potential for non-compliance with study protocol (i.e., dosing schedule, visit schedule or study procedures)
- were female of child bearing potential without adequate contraceptive protection during the trial.
- were unwilling to discontinue prohibited medications such as anti-cholinergics, anti-spasmodics, anti-constipation, cholinesterase inhibitors, prokinetic agents, laxative agents (MirLax, Ex-Lax), or medications approved for the treatment of IBS-C during the treatment period.

### **Efficacy Summary**

Total of 522 subjects were enrolled in the open label study. Of the 522 subjects, 520 received 8 mcg Lubiprostone bid treatment. In this study, subjects were evaluated based on the enrollment group to which they were randomized in either SIB-0431 or SIB-0432 study regardless of treatment they actually received.

Placebo rollover subjects: subjects who took placebo in SIB-0431 or SIB-0432 before enrolling in the open label study. These subjects were referred to as placebo/lubiprostone (P/L) subjects.

Lubiprostone/placebo rollover subjects: subjects who took Lubiprostone in SIB-0431 treatment phase I and placebo in treatment phase II before enrolling in the open label study. These subjects were referred to lubiprostone/placebo/lubiprostone (L/P/L) subjects.

Lubiprostone rollover subjects: subjects who took Lubiprostone in SIB-0431 in treatment phase I and II and Lubiprostone during SIB-0432 before enrolling in the open label study (L/L/L).

A total of 476 subjects (167 P/L, 71 L/P/L, 238 Lubiprostone) consisted of the Intent-to-Treat (ITT) population. The ITT population was defined (included all safety evaluable subjects) as all subjects who had at least 1 treatment period weekly diary entry.

**Table 74: Monthly Responder Rates for 13 months**

<b>Timepoint</b>	<b>Status</b>	<b>Placebo/ Lubiprostone (N=167)</b>	<b>Lubiprostone/ Placebo/Lubiprostone (N=71)</b>	<b>Lubiprostone (N=238)</b>
<b>Month 1</b>				
	Responder	30 ( 19.1% )	<b>14 ( 20.3% )</b>	<b>28 ( 12.3% )</b>
	Non-responder	127 ( 80.9% )	55 ( 79.7% )	199 ( 87.7% )
<b>Month 2</b>				
	Responder	39 ( 26.2% )	20 ( 28.6% )	47 ( 20.3% )
	Non-responder	110 ( 73.8% )	50 ( 71.4% )	185 ( 79.7% )
<b>Month 3</b>				
	Responder	28 ( 19.7% )	19 ( 26.8% )	56 ( 24.0% )
	Non-responder	114 ( 80.3% )	52 ( 73.2% )	177 ( 76.0% )
<b>Month 4</b>				
	Responder	40 ( 29.4% )		48 ( 21.7% )
	Non-responder	96 ( 70.6% )		173 ( 78.3% )
<b>Month 5</b>				
	Responder	38 ( 29.2% )	15 ( 24.2% )	65 ( 29.5% )
	Non-responder	92 ( 70.8% )	47 ( 75.8% )	155 ( 70.5% )
<b>Month 6</b>				
	Responder	40 ( 31.7% )	28 ( 43.1% )	67 ( 31.6% )
	Non-responder	86 ( 68.3% )	37 ( 56.9% )	145 ( 68.4% )
<b>Month 7</b>				
	Responder	32 ( 26.7% )	23 ( 39.7% )	66 ( 33.2% )
	Non-responder	88 ( 73.3% )	35 ( 60.3% )	133 ( 66.8% )
<b>Month 8</b>				
	Responder	33 ( 29.5% )	26 ( 45.6% )	58 ( 30.2% )
	Non-responder	79 ( 70.5% )	31 ( 54.4% )	134 ( 69.8% )
<b>Month 9</b>				
	Responder	34 ( 30.6% )	26 ( 50.0% )	59 ( 33.1% )
	Non-responder	77 ( 69.4% )	26 ( 50.0% )	119 ( 66.9% )
<b>Month 10</b>				
	Responder		26 ( 54.2% )	<b>62 ( 37.3% )</b>
	Non-responder		22 ( 45.8% )	104 ( 62.7% )
<b>Month 11</b>				
	Responder		25 ( 55.6% )	55 ( 34.8% )
	Non-responder		20 ( 44.4% )	103 ( 65.2% )
<b>Month 12</b>				
	Responder		22 ( 52.4% )	49 ( 32.7% )
	Non-responder		20 ( 47.6% )	101 ( 67.3% )
<b>Month 13</b>				
	Responder		<b>22 ( 57.9% )</b>	14 ( 31.8% )
	Non-responder		16 ( 42.1% )	30 ( 68.2% )

Reviewer's table modified from Table 14.2.1, page 47 of 61, Clinical Study Report-SIB-05S1

As noted in table 74, the range of responder rate was 12.3% to 57.9%. In all months, except for month 5, the L/P/L group showed the highest responder rate (20.3%-57.9%), but it also had the smallest number of subjects in the group at 71 and showed the most variation in response. The P/L group had data for treatment with Lubiprostone only for 36 weeks since this group of subjects received placebo prior to enrolling in the open label treatment. No inferential statistical analysis was performed. For the subjects that received Lubiprostone for 52 weeks (longest treatment period), the responder rate range was from 12.3% to 37.3%. Starting at month 6, the responder rate in the Lubiprostone group remained  $\geq$  30%. Efficacy endpoints for this particular study included assessments for abdominal discomfort/pain and bloating, spontaneous bowel movement frequency rates, stool consistency, degree of straining, constipation severity, symptom relief and IBS-QOL.

### **Safety Summary**

Total of 520 subjects received 8 mcg Lubiprostone bid: 179 subjects were in the P/L group, 80 subjects were in the L/P/L group and 261 subjects were in the Lubiprostone group which consisted of the safety evaluable population. The safety evaluable group was defined as any subject who took study medication in the open-label study. These subjects were evaluated based on treatment they actually received during study SIB-0431 or SIB-0432 regardless of randomization, and they were used for primary safety analysis.

357 subjects (68.7%) experienced at least 1 AE during the study. Of the 357 subjects that experienced AEs, the subjects that previously received Lubiprostone in study SIB-0431 or SIB-0432, had a higher percentage of subjects that reported AEs (58 subjects in L/P/L, 72.5% vs. 189 subjects in L/L/L, 72.4% vs. 110 subjects in P/L, 61.5%).

Twenty six subjects (5.0%) withdrew from the study because of an AE. Of those subjects who withdrew, 14 were in the P/L group (7.8%) and 2 were in the L/P/L group (2.5%) and 10 were in the Lubiprostone group (3.8%). Most adverse events that led to permanent drug discontinuation in the 3 treatment groups were reported by no more than 1 subject except for diarrhea, nausea, abdominal distension. 6 subjects in the P/L group and 1 subject in the Lubiprostone group reported diarrhea as a cause for discontinuation. 2 subjects each reported nausea and abdominal distension as cause for discontinuing the open label drug in the P/L group whereas 1 subject each reported the same AEs in the Lubiprostone group.

There were 10 AEs that were classified as serious, but none were classified as treatment-related SAEs, of those 1 was in the P/L group, 3 were in the L/P/L group and 6 were in the Lubiprostone group. One P/L and one Lubiprostone subject experienced syncopal episode. One subject in the L/P/L group experienced dysfunctional uterine bleeding, another experienced severe upper gastrointestinal hemorrhage, another one experienced severe dysmenorrhea and another subject experienced dyspnea, fatigue and sinus tachycardia. In the Lubiprostone group, the following adverse events were experienced by 1 subject each: moderate tendonitis of left shoulder, severe adnexa uteri mass, moderate osteoarthritis and underwent a right hip replacement due to degenerative joint disease, severe intentional overdose, severe urethral calculus, severe fatigue and moderate non-cardiac chest pain.

No subject died during the open label study.

Total of 132 subjects (25.4%) reported at least 1 treatment-related AE. Of those 132 subjects, 44 subjects (24.6%) were in the P/L group, 21 (26.3%) were in the L/P/L group, and 67 (25.7%) were in the Lubiprostone group. The frequencies of the most common treatment-related AEs include diarrhea (6.5%), nausea (6.3%), abdominal distension (3.7%), abdominal pain (2.9%), flatulence (2.1%), abdominal pain upper (1.9%) headache (1.5%), dizziness (1.3%), and vomiting (1.2%).

There were no clinically significant trends in the assessment of laboratory values (hematology, biochemistry, and urinalysis), vital signs, body mass index (BMI) and physical examinations.

The results of study SIB-05S1 demonstrated that Lubiprostone 8 mcg bid appeared to be safe and tolerable in subjects with IBS-C when administered twice daily for 13 months.

## **10.2 Line-by-Line Labeling Review**

### **14.2 Irritable Bowel Syndrome with Constipation**

#### **Efficacy Studies**

The percentage of patients in Study 1 qualifying as an overall responder was 18.2% in the group receiving Amitiza 8 mcg twice daily compared to 9.8% of patients receiving placebo twice daily. In Study 2, 17.7% of patients in the Amitiza 8 mcg group were overall responders versus 10.4% of patients in the placebo group.

#### **Medical officer comments**

*The medical officer does not think that the treatment difference obtained using the ITT population with LOCF imputation method should be the percentage reflected in labeling. In both pooled data and individual studies when the ITT population without LOCF method is used the treatment difference between placebo and Lubiprostone is 6% in study 1 and 6.4% in study 2. As per the sponsor's statistical analytical plan, the primary efficacy analysis was based on ITT without LOCF imputation method, and the analyses with LOCF imputation method was considered supportive. Therefore, it is misleading to use the higher percentages in the labeling especially when practicing physicians may not have access to all the clinical studies data evaluated by the Agency.*

With respect to specific symptoms, Amitiza 8 mcg twice daily was effective at improving abdominal discomfort or pain, abdominal bloating, bowel movement frequency, constipation severity, stool consistency, straining, and quality of life scores.

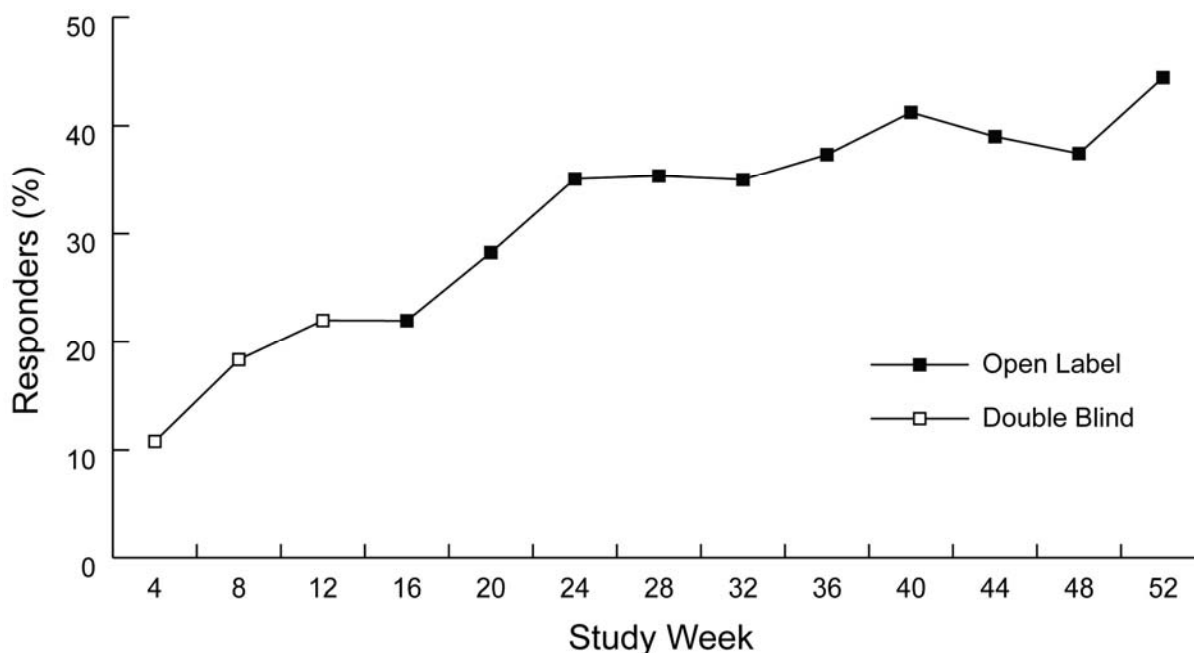
#### **Medical officer comments**

*In both pivotal efficacy studies, most of the secondary endpoints were not statistically significant. Of those secondary endpoints that were statistically significant, none of them were replicated in both studies. Each study had a different secondary endpoint that was statistically significant. Also, in this clinical program for Lubiprostone 8 mcg bid, the sponsor has failed to demonstrate 1 SBM difference above placebo; therefore, the medical officer is not certain that they can use the statement "effective at improving bowel movement frequency". Furthermore, it is a contradiction to state in one section*

*that Lubiprostone 8 mcg bid has been reported to cause abdominal pain (5% rate as an adverse event) and in another section state that the drug has been demonstrated to be “effective at improving abdominal discomfort”.*

### Long-term Studies

One open-labeled, long-term clinical safety and efficacy study was conducted in patients with IBS-C receiving Amitiza 8 mcg twice daily. This study comprised 476 intent-to-treat patients (mean age 47.5 [range 21–82] years; 93.5% female; 79.2% Caucasian, 11.6% African American, 8.6% Hispanic, 0.2% Asian; 7.8%  $\geq 65$  years of age) who were treated for an additional 36 weeks following an initial 12–16-week, double-blinded treatment period. Figure 2 depicts the percent of patients treated with Amitiza 8 mcg twice daily who qualified as overall responders (see above) over the course of the double-blinded and open-labeled treatment periods. This study demonstrated that Amitiza 8 mcg twice daily provides effective relief of global symptoms of IBS-C for up to 52 weeks.



**Figure 2: Overall Responder Rate over Long-term Treatment (Pooled Analysis)**

### Medical officer comments

*The open label study did not utilize the overall responder definition that was used in the 2 pivotal efficacy studies (SIB-0431 Treatment Phase I and SIB-0432). The open label study used a monthly responder definition for efficacy evaluation. From the above depiction, it implies that the overall responder rate was also used in the open label trial to assess efficacy. The sponsor should consider using two different graphic depiction to display results. The 2 separate figures would provide a true reflection of the results in the double blind study in which the treatment difference of the overall responder rate between Lubiprostone and placebo was 6.2% in the pooled group (6.8% Placebo*

*responders vs. 13.0% Lubiprostone responders). Since the open label did not use an overall responder rate for efficacy analyses instead used a modified definition of monthly responder rate (one that did not control for rescue medication usage), the figure should be depicted separately. The monthly responder rate for the 52 weeks in the open label trial ranged from 12.3% to 57.9%.*

*The results of the double blind studies that were depicted in this figure appear to be derived from the monthly responder rate using the ITT subjects with LOCF. It is inaccurate to state that these were the results of the overall responder rate which was the primary endpoint when the percentages were derived from the monthly responder rate which was a key secondary endpoint. The definition of monthly responder differs from that of the overall responder in the double blind studies. Additionally, in the open label study, the monthly responder definition was a modified version of the monthly responder definition utilized in the pivotal studies. Per the sponsor's statistical analytical plan, the monthly responder rate was analyzed using the ITT population without LOCF. The ITT population with LOCF was part of a supportive analysis, and it seems to overestimate the effect of Lubiprostone by imputing missing data. This figure tends to overestimate the effects of Lubiprostone since rescue medication usage was a confounding factor that was not controlled for in the open label phase.*

## **8 USE IN SPECIFIC POPULATIONS**

### **Irritable Bowel Syndrome with Constipation**

The safety profile of Amitiza in the elderly ( $\geq 65$  years of age) subpopulation (8.0% were  $\geq 65$  years of age and 1.8% were  $\geq 75$  years of age) was consistent with the safety profile in the overall study population.

#### **Medical officer comments**

*The sponsor should consider adding the efficacy results in the age group 2 (age  $\geq 65$ ) where there was no treatment difference between placebo and Lubiprostone 16 mcg subjects. The overall responder rate in subjects  $\geq 65$  was 10.3% in the Lubiprostone 16 mcg treatment group and was 10.5% in the placebo group.*

## REFERENCES

1. Longstreth GF, et al. Functional Bowel Disorders. *Gastroenterology* 2006; 130: 1480-1491.
2. Drossman DA. Introduction. The Rome Foundation and Rome III. *Neurogastroenterology Motility* 2007; 19: 783-786.
3. Irvine EJ. Design of Treatment Trials for Functional Gastrointestinal Disorders. *Gastroenterology* 2006; 130: 1538-1551.
4. Mertz HR. Irritable Bowel Syndrome. *New England Journal of Medicine* 2003; 349: 2136-46.
5. Lembo AJ. Clinical Crossroads: A 54-year-old Woman with Constipation-Predominant Irritable Bowel Syndrome. *JAMA* 2006; 295: 925-933.
6. Horwitz BJ. The Irritable Bowel Syndrome. *New England Journal of Medicine* 2001; 344: 1846-1850.





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