

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 021908/S-011

Trade Name: **AMITIZA**

Generic Name: **Lubiprostone**

Sponsor: **Sucampo Pharma Americas, LLC**

Approval Date: April 19, 2013

Indications: Amitiza is a chloride channel activator indicated for:

- Treatment of chronic idiopathic constipation in adults
- Treatment of opioid-induced constipation in adults with chronic, non-cancer pain
- Treatment of irritable bowel syndrome with constipation in women ≥ 18 years old

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 021908/S-011

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
Summary Review	X
Officer/Employee List	X
Office Director Memo	
Cross Discipline Team Leader Review	X
Medical Review(s)	X
Chemistry Review(s)	X
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	X
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Other Review(s)	X
Administrative/Correspondence Document(s)	X

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021908/S-011

APPROVAL LETTER



NDA 21908/S-011

SUPPLEMENT APPROVAL

Sucampo Pharma Americas, LLC.
Attention: Jeffrey Carey
Senior Director, Regulatory Affairs
4520 East-West Highway, Suite 300
Bethesda, MD 20814

Dear Mr. Carey,

Please refer to your Supplemental New Drug Application (sNDA) dated July 20, 2012, received July 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amitiza (lubiprostone) Capsules (8 mcg, 24 mcg).

We acknowledge receipt of your amendments dated August 8, August 24, September 12, September 25, October 22, October 26, November 16, December 11, December 14, December 17, December 18, December 20, December 26, 2012, January 11, January 17, February 11, February 20 and March 1, March 21, March 27, April 8, April 17 and April 19, 2013.

This "Prior Approval" supplemental new drug application provides for the addition of the following indication:

Amitiza is indicated for the treatment of opioid-induced constipation (OIC) in adults with chronic, non-cancer pain.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling text for the package insert, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and carton and immediate container labels submitted on April 19, 2013, as soon as they are available, but no more than 30 days after they are printed.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Maureen Dewey, M.P.H.
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 5159
10903 New Hampshire Avenue
Silver Spring, Maryland
*Use zip code **20903** if shipping via United States Postal Service (USPS).*
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. Studies of pediatric patients with pain due to cancer or

advanced medical illness are also challenging to conduct due to the difficulties of studying children in a palliative care environment.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOYCE A KORVICK
04/19/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021908/S-011

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AMITIZA safely and effectively. See full prescribing information for AMITIZA.

AMITIZA (lubiprostone) capsules, for oral use
Initial U.S. Approval: 2006

RECENT MAJOR CHANGES

Indications and Usage (1.2) 04/2013
Dosage and Administration (2.1) 04/2013
Warnings and Precautions, Pregnancy (5.1) removed 11/2012

INDICATIONS AND USAGE

Amitiza is a chloride channel activator indicated for:

- Treatment of chronic idiopathic constipation in adults (1.1)
- Treatment of opioid-induced constipation in adults with chronic, non-cancer pain (1.2)
- Treatment of irritable bowel syndrome with constipation in women $\geq$ 18 years old (1.3)

Limitations of Use:

Effectiveness of Amitiza in the treatment of opioid-induced constipation in patients taking diphenylheptane opioids (e.g., methadone) has not been established (1) (14.2)

DOSAGE AND ADMINISTRATION

Capsules should be swallowed whole and should not be broken apart or chewed (2)

Chronic Idiopathic Constipation and Opioid-induced Constipation

- 24 mcg taken twice daily orally with food and water (2.1)

Reduce the dosage in patients with moderate and severe hepatic impairment (2.1)

Irritable Bowel Syndrome with Constipation

- 8 mcg taken twice daily orally with food and water (2.2)

Reduce the dosage in patients with severe hepatic impairment (2.2)

DOSAGE FORMS AND STRENGTHS

- Capsules: 8 mcg and 24 mcg (3)

CONTRAINDICATIONS

- Amitiza is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction. (4)

WARNINGS AND PRECAUTIONS

- Patients may experience nausea; concomitant administration of food may reduce this symptom (5.1)
- Do not prescribe for patients that have severe diarrhea (5.2)
- Patients taking Amitiza may experience dyspnea within an hour of first dose. This symptom generally resolves within 3 hours, but may recur with repeat dosing (5.3)
- Evaluate patients with symptoms suggestive of mechanical gastrointestinal obstruction prior to initiating treatment with Amitiza (5.4)

ADVERSE REACTIONS

- Most common adverse reactions (incidence $>$ 4%) in chronic idiopathic constipation are nausea, diarrhea, headache, abdominal pain, abdominal distension, and flatulence (6.1)
- Most common adverse reactions (incidence $>$ 4%) in opioid-induced constipation are nausea and diarrhea (6.1)
- Most common adverse reactions (incidence $>$ 4%) in irritable bowel syndrome with constipation are nausea, diarrhea, and abdominal pain (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-825-3327 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Concomitant use of diphenylheptane opioids (e.g., methadone) may interfere with the efficacy of Amitiza (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Nursing Mothers: Caution should be exercised when administering to a nursing woman (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: April 2013

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Chronic Idiopathic Constipation
- 1.2 Opioid-induced Constipation
- 1.3 Irritable Bowel Syndrome with Constipation

2 DOSAGE AND ADMINISTRATION

- 2.1 Chronic Idiopathic Constipation and Opioid-induced Constipation
- 2.2 Irritable Bowel Syndrome with Constipation

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Nausea
- 5.2 Diarrhea
- 5.3 Dyspnea
- 5.4 Bowel Obstruction

6 ADVERSE REACTIONS

- 6.1 Clinical Studies Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use

- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Chronic Idiopathic Constipation
- 14.2 Opioid-induced Constipation
- 14.3 Irritable Bowel Syndrome with Constipation

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

- 17.1 Nausea, Dyspnea, or Diarrhea
- 17.2 Nursing Mothers

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Chronic Idiopathic Constipation

Amitiza[®] is indicated for the treatment of chronic idiopathic constipation in adults.

1.2 Opioid-induced Constipation

Amitiza is indicated for the treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain.

Limitations of Use:

- Effectiveness of Amitiza in the treatment of opioid-induced constipation in patients taking diphenylheptane opioids (e.g., methadone) has not been established. [see *Clinical Studies (14.2)*]

1.3 Irritable Bowel Syndrome with Constipation

Amitiza is indicated for the treatment of irritable bowel syndrome with constipation (IBS-C) in women $\geq$ 18 years old.

2 DOSAGE AND ADMINISTRATION

Take Amitiza orally with food and water. Swallow capsules whole and do not break apart or chew. Physicians and patients should periodically assess the need for continued therapy.

2.1 Chronic Idiopathic Constipation and Opioid-induced Constipation

The recommended dose is 24 mcg twice daily orally with food and water.

Dosage in patients with hepatic impairment

For patients with moderately impaired hepatic function (Child-Pugh Class B), the recommended starting dose is 16 mcg twice daily. For patients with severely impaired hepatic function (Child-Pugh Class C), the recommended starting dose is 8 mcg twice daily. If this dose is tolerated and an adequate response has not been obtained after an appropriate interval, doses can then be escalated to full dosing with appropriate monitoring of patient response [see *Use in Specific Populations (8.7)* and *Clinical Pharmacology (12.3)*].

2.2 Irritable Bowel Syndrome with Constipation

The recommended dose is 8 mcg twice daily orally with food and water.

Dosage in patients with hepatic impairment

For patients with severely impaired hepatic function (Child-Pugh Class C), the recommended starting dose is 8 mcg once daily. If this dose is tolerated and an adequate response has not been

obtained after an appropriate interval, doses can then be escalated to full dosing with appropriate monitoring of patient response. Dosage adjustment is not required for patients with moderately impaired hepatic function (Child-Pugh Class B) [see *Use in Specific Populations* (8.7) and *Clinical Pharmacology* (12.3)].

3 DOSAGE FORMS AND STRENGTHS

Amitiza is available as an oval, gelatin capsule containing 8 mcg or 24 mcg of lubiprostone.

- 8 mcg capsules are pink and are printed with “SPI” on one side
- 24 mcg capsules are orange and are printed with “SPI” on one side

4 CONTRAINDICATIONS

Amitiza is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Nausea

Patients taking Amitiza may experience nausea. Concomitant administration of food with Amitiza may reduce symptoms of nausea [see *Adverse Reactions* (6.1)].

5.2 Diarrhea

Amitiza should not be prescribed to patients that have severe diarrhea. Patients should be aware of the possible occurrence of diarrhea during treatment. Patients should be instructed to discontinue Amitiza and inform their physician if severe diarrhea occurs [see *Adverse Reactions* (6.1)].

5.3 Dyspnea

In clinical trials, dyspnea was reported by 3%, 1%, and < 1% of the treated CIC, OIC, and IBS-C populations receiving Amitiza, respectively, compared to 0%, 1%, and < 1% of placebo-treated patients. There have been postmarketing reports of dyspnea when using Amitiza 24 mcg twice daily. Some patients have discontinued treatment because of dyspnea. These events have usually been described as a sensation of chest tightness and difficulty taking in a breath, and generally have an acute onset within 30–60 minutes after taking the first dose. They generally resolve within a few hours after taking the dose, but recurrence has been frequently reported with subsequent doses.

5.4 Bowel Obstruction

In patients with symptoms suggestive of mechanical gastrointestinal obstruction, perform a thorough evaluation to confirm the absence of an obstruction prior to initiating therapy with Amitiza.

6 ADVERSE REACTIONS

The following adverse reactions are described below and elsewhere in labeling:

- Nausea [see *Warnings and Precautions (5.1)*]
- Diarrhea [see *Warnings and Precautions (5.2)*]
- Dyspnea [see *Warnings and Precautions (5.3)*]

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

During clinical development of Amitiza for CIC, OIC, and IBS-C, 1234 patients were treated with Amitiza for 6 months and 524 patients were treated for 1 year (not mutually exclusive).

Chronic Idiopathic Constipation

Adverse reactions in dose-finding, efficacy, and long-term clinical studies: The data described below reflect exposure to Amitiza 24 mcg twice daily in 1113 patients with chronic idiopathic constipation over 3- or 4-week, 6-month, and 12-month treatment periods; and from 316 patients receiving placebo over short-term exposure (≤ 4 weeks). The placebo population (N = 316) had a mean age of 47.8 (range 21–81) years; was 87.3% female; 80.7% Caucasian, 10.1% African American, 7.3% Hispanic, 0.9% Asian; and 11.7% elderly (≥ 65 years of age). Of those patients treated with Amitiza 24 mcg twice daily (N=1113), the mean age was 50.3 (range 19-86) years; 86.9% were female; 86.1% Caucasian, 7.6% African American, 4.7% Hispanic, 1.0% Asian; and 16.7% elderly (≥ 65 years of age). Table 1 presents data for the adverse reactions that occurred in at least 1% of patients who received Amitiza 24 mcg twice daily and that occurred more frequently with study drug than placebo.

Table 1: Percent of Patients with Adverse Reactions (Chronic Idiopathic Constipation)

System/Adverse Reaction ¹	Placebo	Amitiza 24 mcg Twice Daily
	N = 316 %	N = 1113 %
Gastrointestinal disorders		
Nausea	3	29
Diarrhea	1	12
Abdominal pain	3	8
Abdominal distension	2	6
Flatulence	2	6
Vomiting	0	3
Loose stools	0	3
Abdominal discomfort ²	1	3
Dyspepsia	< 1	2
Dry mouth	< 1	1
Nervous system disorders		
Headache	5	11
Dizziness	1	3
General disorders and site administration conditions		
Edema	< 1	3
Fatigue	1	2
Chest discomfort/pain	0	2
Respiratory, thoracic, and mediastinal disorders		
Dyspnea	0	2

¹Includes only those events associated with treatment (possibly, probably, or definitely related, as assessed by the investigator).

²This term combines “abdominal tenderness,” “abdominal rigidity,” “gastrointestinal discomfort,” “stomach discomfort”, and “abdominal discomfort.”

The most common adverse reactions (incidence > 4%) in CIC were nausea, diarrhea, headache, abdominal pain, abdominal distension, and flatulence.

Nausea: Approximately 29% of patients who received Amitiza 24 mcg twice daily experienced nausea; 4% of patients had severe nausea and 9% of patients discontinued treatment due to nausea. The rate of nausea associated with Amitiza 24 mcg twice daily was lower among male (8%) and elderly (19%) patients. No patients in the clinical studies were hospitalized due to nausea.

Diarrhea: Approximately 12% of patients who received Amitiza 24 mcg twice daily experienced diarrhea; 2% of patients had severe diarrhea and 2% of patients discontinued treatment due to diarrhea.

Electrolytes: No serious adverse reactions of electrolyte imbalance were reported in clinical studies, and no clinically significant changes were seen in serum electrolyte levels in patients receiving Amitiza.

Less common adverse reactions: The following adverse reactions (assessed by investigator as probably or definitely related to treatment) occurred in less than 1% of patients receiving Amitiza 24 mcg twice daily in clinical studies, occurred in at least two patients, and occurred more frequently in patients receiving study drug than those receiving placebo: fecal incontinence, muscle cramp, defecation urgency, frequent bowel movements, hyperhidrosis, pharyngolaryngeal pain, intestinal functional disorder, anxiety, cold sweat, constipation, cough,

dysgeusia, eructation, influenza, joint swelling, myalgia, pain, syncope, tremor, decreased appetite.

Opioid-induced Constipation

Adverse reactions in efficacy and long-term clinical studies: The data described below reflect exposure to Amitiza 24 mcg twice daily in 860 patients with OIC for up to 12 months and from 632 patients receiving placebo twice daily for up to 12 weeks. The total population (N = 1492) had a mean age of 50.4 (range 20–89) years; was 62.7% female; 82.7% Caucasian, 14.2% African American, 0.8% American Indian/Alaska Native, 0.8% Asian; 5.2% were of Hispanic ethnicity; and 8.8% were elderly (≥ 65 years of age). Table 2 presents data for the adverse reactions that occurred in at least 1% of patients who received Amitiza 24 mcg twice daily and that occurred more frequently with study drug than placebo.

Table 2: Percent of Patients with Adverse Reactions (OIC Studies)

System/Adverse Reaction ¹	Placebo	Amitiza 24 mcg Twice Daily
	N = 632 %	N = 860 %
Gastrointestinal disorders		
Nausea	5	11
Diarrhea	2	8
Abdominal pain	1	4
Flatulence	3	4
Abdominal distension	2	3
Vomiting	2	3
Abdominal discomfort ²	1	1
Nervous system disorders		
Headache	1	2
General disorders and site administration conditions		
Peripheral edema	< 1	1

¹Includes only those events associated with treatment (possibly, probably, or definitely related, as assessed by the investigator).

²This term combines “abdominal tenderness,” “abdominal rigidity,” “gastrointestinal discomfort,” “stomach discomfort”, and “abdominal discomfort.”

The most common adverse reactions (incidence > 4%) in OIC were nausea and diarrhea.

Nausea: Approximately 11% of patients who received Amitiza 24 mcg twice daily experienced nausea; 1% of patients had severe nausea and 2% of patients discontinued treatment due to nausea.

Diarrhea: Approximately 8% of patients who received Amitiza 24 mcg twice daily experienced diarrhea; 2% of patients had severe diarrhea and 1% of patients discontinued treatment due to diarrhea.

Less common adverse reactions: The following adverse reactions (assessed by investigator as probably or definitely related to treatment) occurred in less than 1% of patients receiving Amitiza 24 mcg twice daily in clinical studies, occurred in at least two patients, and occurred more frequently in patients receiving study drug than those receiving placebo: fecal incontinence, blood potassium decreased.

Irritable Bowel Syndrome with Constipation

Adverse reactions in dose-finding, efficacy, and long-term clinical studies: The data described below reflect exposure to Amitiza 8 mcg twice daily in 1011 patients with IBS-C for up to 12 months and from 435 patients receiving placebo twice daily for up to 16 weeks. The total population (N = 1267) had a mean age of 46.5 (range 18–85) years; was 91.6% female; 77.5% Caucasian, 12.9% African American, 8.6% Hispanic, 0.4% Asian; and 8.0% elderly (≥ 65 years of age). Table 3 presents data for the adverse reactions that occurred in at least 1% of patients who received Amitiza 8 mcg twice daily and that occurred more frequently with study drug than placebo.

Table 3: Percent of Patients with Adverse Reactions (IBS-C Studies)

System/Adverse Reaction ¹	Placebo	Amitiza 8 mcg Twice Daily
	N = 435 %	N = 1011 %
Gastrointestinal disorders		
Nausea	4	8
Diarrhea	4	7
Abdominal pain	5	5
Abdominal distension	2	3

¹Includes only those events associated with treatment (possibly or probably related, as assessed by the investigator).

The most common adverse reactions (incidence > 4%) in IBS-C were nausea, diarrhea, and abdominal pain.

Nausea: Approximately 8% of patients who received Amitiza 8 mcg twice daily experienced nausea; 1% of patients had severe nausea and 1% of patients discontinued treatment due to nausea.

Diarrhea: Approximately 7% of patients who received Amitiza 8 mcg twice daily experienced diarrhea; <1% of patients had severe diarrhea and <1% of patients discontinued treatment due to diarrhea.

Less common adverse reactions: The following adverse reactions (assessed by investigator as probably related to treatment) occurred in less than 1% of patients receiving Amitiza 8 mcg twice daily in clinical studies, occurred in at least two patients, and occurred more frequently in patients receiving study drug than those receiving placebo: dyspepsia, loose stools, vomiting, fatigue, dry mouth, edema, increased alanine aminotransferase, increased aspartate aminotransferase, constipation, eructation, gastroesophageal reflux disease, dyspnea, erythema, gastritis, increased weight, palpitations, urinary tract infection, anorexia, anxiety, depression, fecal incontinence, fibromyalgia, hard feces, lethargy, rectal hemorrhage, pollakiuria.

6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post-approval use of Amitiza. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Voluntary reports of adverse reactions occurring with the use of Amitiza include the following: syncope, ischemic colitis, hypersensitivity/allergic-type reactions (including rash, swelling, and throat tightness), malaise, tachycardia, muscle cramps or muscle spasms, and asthenia.

7 DRUG INTERACTIONS

No *in vivo* drug–drug interaction studies have been performed with Amitiza.

Based upon the results of *in vitro* human microsome studies, there is low likelihood of pharmacokinetic drug–drug interactions. *In vitro* studies using human liver microsomes indicate that cytochrome P450 isoenzymes are not involved in the metabolism of lubiprostone. Further *in vitro* studies indicate microsomal carbonyl reductase may be involved in the extensive biotransformation of lubiprostone to the metabolite M3 [see *Clinical Pharmacology (12.3)*]. Additionally, *in vitro* studies in human liver microsomes demonstrate that lubiprostone does not inhibit cytochrome P450 isoforms 3A4, 2D6, 1A2, 2A6, 2B6, 2C9, 2C19, or 2E1, and *in vitro* studies of primary cultures of human hepatocytes show no induction of cytochrome P450 isoforms 1A2, 2B6, 2C9, and 3A4 by lubiprostone. Based on the available information, no protein binding–mediated drug interactions of clinical significance are anticipated.

Interaction potential with diphenylheptane opioids (e.g. methadone): Non-clinical studies have shown opioids of the diphenylheptane chemical class (e.g., methadone) to dose-dependently reduce the activation of CIC-2 by lubiprostone in the gastrointestinal tract. There is a possibility of a dose-dependent decrease in the efficacy of Amitiza in patients using diphenylheptane opioids.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

Risk Summary

There are no adequate and well-controlled studies with Amitiza in pregnant women. A dose dependent increase in fetal loss was observed in pregnant guinea pigs that received lubiprostone doses equivalent to 0.2 to 6 times the maximum recommended human dose (MRHD) based on body surface area (mg/m²). Animal studies did not show an increase in structural malformations. Amitiza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Current available data suggest that miscarriage occurs in 15-18% of clinically recognized pregnancies, regardless of any drug exposure. Consider the risks and benefits of available

therapies when treating a pregnant woman for chronic idiopathic constipation, opioid-induced constipation or irritable bowel syndrome with constipation.

Animal Data

In developmental toxicity studies, pregnant rats and rabbits received oral lubiprostone during organogenesis at doses up to approximately 338 times (rats) and approximately 34 times (rabbits) the maximum recommended human dose (MHRD) based on body surface area (mg/m^2). Maximal animal doses were 2000 mcg/kg/day (rats) and 100 mcg/kg/day (rabbits). In rats, there were increased incidences of early resorptions and soft tissue malformations (*situs inversus*, cleft palate) at the 2000 mcg/kg/day dose; however, these effects were probably secondary to maternal toxicity. A dose-dependent increase in fetal loss occurred when guinea pigs received lubiprostone after the period of organogenesis, on days 40 to 53 of gestation, at daily oral doses of 1, 10, and 25 mcg/kg/day (approximately 0.2, 2 and 6 times the MHRD based on body surface area (mg/m^2)). The potential of lubiprostone to cause fetal loss was also examined in pregnant Rhesus monkeys. Monkeys received lubiprostone post-organogenesis on gestation days 110 through 130 at daily oral doses of 10 and 30 mcg/kg/day (approximately 3 and 10 times the MHRD based on body surface area (mg/m^2)). Fetal loss was noted in one monkey from the 10-mcg/kg dose group, which is within normal historical rates for this species. There was no drug-related adverse effect seen in monkeys.

8.3 Nursing Mothers

It is not known whether lubiprostone is excreted in human milk. In rats, neither lubiprostone nor its active metabolites were detectable in breast milk following oral administration of lubiprostone. Because lubiprostone increases fluid secretion in the intestine and intestinal motility, human milk-fed infants should be monitored for diarrhea. Caution should be exercised when Amitiza is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Chronic Idiopathic Constipation

The efficacy of Amitiza in the elderly (≥ 65 years of age) subpopulation was consistent with the efficacy in the overall study population. Of the total number of constipated patients treated in the dose-finding, efficacy, and long-term studies of Amitiza, 15.5% were ≥ 65 years of age, and 4.2% were ≥ 75 years of age. Elderly patients taking Amitiza 24 mcg twice daily experienced a lower rate of associated nausea compared to the overall study population taking Amitiza (19% vs. 29%, respectively).

Opioid-induced Constipation

The safety profile of Amitiza in the elderly (≥ 65 years of age) subpopulation (8.8% were ≥ 65 years of age and 1.6% were ≥ 75 years of age) was consistent with the safety profile in the overall study population. Clinical studies of Amitiza did not include sufficient numbers of

patients aged 65 years and over to determine whether they respond differently from younger patients.

Irritable Bowel Syndrome with Constipation

The safety profile of Amitiza in the elderly (≥ 65 years of age) subpopulation (8.0% were ≥ 65 years of age and 1.8% were ≥ 75 years of age) was consistent with the safety profile in the overall study population. Clinical studies of Amitiza did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients.

8.6 Renal Impairment

No dosage adjustment is required in patients with renal impairment [see *Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh Class B) and severe hepatic impairment (Child-Pugh Class C) experienced markedly higher systemic exposure of lubiprostone active metabolite M3, when compared to normal subjects [see *Clinical Pharmacology (12.3)*]. Clinical safety results demonstrated an increased incidence and severity of adverse events in subjects with greater severity of hepatic impairment.

In case of chronic idiopathic constipation or opioid-induced constipation indications, the starting dosage of Amitiza should be reduced in patients with moderate hepatic impairment. The starting dose of Amitiza should be reduced in all patients with severe hepatic impairment, regardless of the indication [see *Dosage and Administration (2.1, 2.2)*]. No dosing adjustment is required in patients with mild hepatic impairment (Child-Pugh Class A).

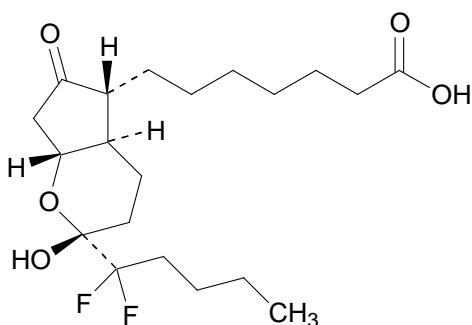
10 OVERDOSAGE

There have been two confirmed reports of overdosage with Amitiza. The first report involved a 3-year-old child who accidentally ingested 7 or 8 capsules of 24 mcg of Amitiza and fully recovered. The second report was a study patient who self-administered a total of 96 mcg of Amitiza per day for 8 days. The patient experienced no adverse reactions during this time. Additionally, in a Phase 1 cardiac repolarization study, 38 of 51 healthy volunteers given a single oral dose of 144 mcg of Amitiza (6 times the highest recommended dose) experienced an adverse event that was at least possibly related to the study drug. Adverse reactions that occurred in at least 1% of these volunteers included the following: nausea (45%), diarrhea (35%), vomiting (27%), dizziness (14%), headache (12%), abdominal pain (8%), flushing/hot flash (8%), retching (8%), dyspnea (4%), pallor (4%), stomach discomfort (4%), anorexia (2%), asthenia (2%), chest discomfort (2%), dry mouth (2%), hyperhidrosis (2%), and syncope (2%).

11 DESCRIPTION

Amitiza (lubiprostone) is a chloride channel activator for oral use.

The chemical name for lubiprostone is (-)-7-[(2*R*,4*aR*,5*R*,7*aR*)-2-(1,1-difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[*b*]pyran-5-yl]heptanoic acid. The molecular formula of lubiprostone is C₂₀H₃₂F₂O₅ with a molecular weight of 390.46 and a chemical structure as follows:



Lubiprostone drug substance occurs as white, odorless crystals or crystalline powder, is very soluble in ether and ethanol, and is practically insoluble in hexane and water. Amitiza is available as an imprinted, oval, soft gelatin capsule in two strengths. Pink capsules contain 8 mcg of lubiprostone and the following inactive ingredients: medium-chain triglycerides, gelatin, sorbitol, ferric oxide, titanium dioxide, and purified water. Orange capsules contain 24 mcg of lubiprostone and the following inactive ingredients: medium-chain triglycerides, gelatin, sorbitol, FD&C Red #40, D&C Yellow #10, and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lubiprostone is a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. Lubiprostone acts by specifically activating ClC-2, which is a normal constituent of the apical membrane of the human intestine, in a protein kinase A-independent fashion.

By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine, thereby facilitating the passage of stool and alleviating symptoms associated with chronic idiopathic constipation. Patch clamp cell studies in human cell lines have indicated that the majority of the beneficial biological activity of lubiprostone and its metabolites is observed only on the apical (luminal) portion of the gastrointestinal epithelium.

Lubiprostone, via activation of apical ClC-2 channels in intestinal epithelial cells, bypasses the antisecretory action of opiates that results from suppression of secretomotor neuron excitability.

Activation of ClC-2 by lubiprostone has also been shown to stimulate recovery of mucosal barrier function and reduce intestinal permeability via the restoration of tight junction protein complexes in *ex vivo* studies of ischemic porcine intestine.

12.2 Pharmacodynamics

Although the pharmacologic effects of lubiprostone in humans have not been fully evaluated, animal studies have shown that oral administration of lubiprostone increases chloride ion

transport into the intestinal lumen, enhances fluid secretion into the bowels, and improves fecal transit.

12.3 Pharmacokinetics

Lubiprostone has low systemic availability following oral administration and concentrations of lubiprostone in plasma are below the level of quantitation (10 pg/mL). Therefore, standard pharmacokinetic parameters such as area under the curve (AUC), maximum concentration ($C_{\max}$), and half-life ($t_{1/2}$) cannot be reliably calculated. However, the pharmacokinetic parameters of M3 (only measurable active metabolite of lubiprostone) have been characterized. Gender has no effect on the pharmacokinetics of M3 following the oral administration of lubiprostone.

Absorption

Concentrations of lubiprostone in plasma are below the level of quantitation (10 pg/mL) because lubiprostone has a low systemic availability following oral administration. Peak plasma levels of M3, after a single oral dose with 24 mcg of lubiprostone, occurred at approximately 1.10 hours. The $C_{\max}$ was 41.5 pg/mL and the mean AUC_{0-t} was 57.1 pg·hr/mL. The AUC_{0-t} of M3 increases dose proportionally after single 24-mcg and 144-mcg doses of lubiprostone.

Distribution

In vitro protein binding studies indicate lubiprostone is approximately 94% bound to human plasma proteins. Studies in rats given radiolabeled lubiprostone indicate minimal distribution beyond the gastrointestinal tissues. Concentrations of radiolabeled lubiprostone at 48 hours post-administration were minimal in all tissues of the rats.

Metabolism

The results of both human and animal studies indicate that lubiprostone is rapidly and extensively metabolized by 15-position reduction, α -chain β -oxidation, and ω -chain ω -oxidation. These biotransformations are not mediated by the hepatic cytochrome P450 system but rather appear to be mediated by the ubiquitously expressed carbonyl reductase. M3, a metabolite of lubiprostone found in both humans and animals, is formed by the reduction of the carbonyl group at the 15-hydroxy moiety that consists of both α -hydroxy and β -hydroxy epimers. M3 makes up less than 10% of the dose of radiolabeled lubiprostone. Animal studies have shown that metabolism of lubiprostone rapidly occurs within the stomach and jejunum, most likely in the absence of any systemic absorption.

Elimination

Lubiprostone could not be detected in plasma; however, M3 has a $t_{1/2}$ ranging from 0.9 to 1.4 hours. After a single oral dose of 72 mcg of ^3H -labeled lubiprostone, 60% of total administered radioactivity was recovered in the urine within 24 hours and 30% of total administered radioactivity was recovered in the feces by 168 hours. Lubiprostone and M3 are only detected in trace amounts in human feces.

Food Effect

A study was conducted with a single 72-mcg dose of ³H-labeled lubiprostone to evaluate the potential of a food effect on lubiprostone absorption, metabolism, and excretion. Pharmacokinetic parameters of total radioactivity demonstrated that C_{max} decreased by 55% while AUC_{0-∞} was unchanged when lubiprostone was administered with a high-fat meal. The clinical relevance of the effect of food on the pharmacokinetics of lubiprostone is not clear. However, lubiprostone was administered with food and water in a majority of clinical trials.

Special Populations

Renal Impairment

Sixteen subjects, 34–47 years old (8 severe renally impaired subjects [creatinine clearance (CrCl) < 20 mL/min] who required hemodialysis and 8 control subjects with normal renal function [CrCl > 80 mL/min]), received a single oral 24-mcg dose of Amitiza. Following administration, lubiprostone plasma concentrations were below the limit of quantitation (10 pg/mL). Plasma concentrations of M3 were within the range of exposure from previous clinical experience with Amitiza.

Hepatic Impairment

Twenty-five subjects, 38–78 years old (9 with severe hepatic impairment [Child-Pugh Class C], 8 with moderate impairment [Child-Pugh Class B], and 8 with normal liver function), received either 12 mcg or 24 mcg of Amitiza under fasting conditions. Following administration, lubiprostone plasma concentrations were below the limit of quantitation (10 pg/mL) except for two subjects. In moderately and severely impaired subjects, the C_{max} and AUC_{0-t} of the active lubiprostone metabolite M3 were increased, as shown in Table 4.

Table 4: Pharmacokinetic Parameters of the Metabolite M3 for Subjects with Normal or Impaired Liver Function following Dosing with Amitiza

Liver Function Status	Mean (SD) AUC _{0-t} (pg-hr/mL)	% Change vs. Normal	Mean (SD) C _{max} (pg/mL)	% Change vs. Normal
Normal (n=8)	39.6 (18.7)	n.a.	37.5 (15.9)	n.a.
Child-Pugh Class B (n=8)	119 (104)	+119	70.9 (43.5)	+66
Child-Pugh Class C (n=8)	234 (61.6)	+521	114 (59.4)	+183

These results demonstrate that there is a correlation between increased exposure of M3 and severity of hepatic impairment. [see *Use in Specific Populations (8.7)*]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two 2-year oral (gavage) carcinogenicity studies (one in Crl:B6C3F1 mice and one in Sprague-Dawley rats) were conducted with lubiprostone. In the 2-year carcinogenicity study in mice,

lubiprostone doses of 25, 75, 200, and 500 mcg/kg/day (approximately 2, 6, 17, and 42 times the highest recommended human dose, respectively, based on body surface area) were used. In the 2-year rat carcinogenicity study, lubiprostone doses of 20, 100, and 400 mcg/kg/day (approximately 3, 17, and 68 times the highest recommended human dose, respectively, based on body surface area) were used. In the mouse carcinogenicity study, there was no significant increase in any tumor incidences. There was a significant increase in the incidence of interstitial cell adenoma of the testes in male rats at the 400 mcg/kg/day dose. In female rats, treatment with lubiprostone produced hepatocellular adenoma at the 400 mcg/kg/day dose.

Mutagenesis

Lubiprostone was not genotoxic in the *in vitro* Ames reverse mutation assay, the *in vitro* mouse lymphoma (L5178Y TK^{+/−}) forward mutation assay, the *in vitro* Chinese hamster lung (CHL/IU) chromosomal aberration assay, and the *in vivo* mouse bone marrow micronucleus assay.

Impairment of Fertility

Lubiprostone, at oral doses of up to 1000 mcg/kg/day, had no effect on the fertility and reproductive function of male and female rats. However, the number of implantation sites and live embryos were significantly reduced in rats at the 1000 mcg/kg/day dose as compared to control. The number of dead or resorbed embryos in the 1000 mcg/kg/day group was higher compared to the control group, but was not statistically significant. The 1000 mcg/kg/day dose in rats is approximately 169 times the highest recommended human dose of 48 mcg/day, based on body surface area.

14 CLINICAL STUDIES

14.1 Chronic Idiopathic Constipation

Two double-blinded, placebo-controlled studies of identical design were conducted in patients with chronic idiopathic constipation. Chronic idiopathic constipation was defined as, on average, less than 3 spontaneous bowel movements (SBMs) per week (a SBM is a bowel movement occurring in the absence of laxative use) along with one or more of the following symptoms of constipation for at least 6 months prior to randomization: 1) very hard stools for at least a quarter of all bowel movements; 2) sensation of incomplete evacuation following at least a quarter of all bowel movements; and 3) straining with defecation at least a quarter of the time.

Following a 2-week baseline/washout period, a total of 479 patients (mean age 47.2 [range 20–81] years; 88.9% female; 80.8% Caucasian, 9.6% African American, 7.3% Hispanic, 1.5% Asian; 10.9% ≥ 65 years of age) were randomized and received Amitiza 24 mcg twice daily or placebo twice daily for 4 weeks. The primary endpoint of the studies was SBM frequency. The studies demonstrated that patients treated with Amitiza had a higher frequency of SBMs during Week 1 than the placebo patients. In both studies, results similar to those in Week 1 were also observed in Weeks 2, 3, and 4 of therapy (Table 5).

Table 5: Spontaneous Bowel Movement Frequency Rates¹ (Efficacy Studies)

Trial	Study Arm	Baseline Mean ± SD Median	Week 1 Mean ± SD Median	Week 2 Mean ± SD Median	Week 3 Mean ± SD Median	Week 4 Mean ± SD Median	Week 1 Change from Baseline Mean ± SD Median	Week 4 Change from Baseline Mean ± SD Median
Study 1	Placebo	1.6 ± 1.3 1.5	3.5 ± 2.3 3.0	3.2 ± 2.5 3.0	2.8 ± 2.2 2.0	2.9 ± 2.4 2.3	1.9 ± 2.2 1.5	1.3 ± 2.5 1.0
	Amitiza 24 mcg Twice Daily	1.4 ± 0.8 1.5	5.7 ± 4.4 5.0	5.1 ± 4.1 4.0	5.3 ± 4.9 5.0	5.3 ± 4.7 4.0	4.3 ± 4.3 3.5	3.9 ± 4.6 3.0
Study 2	Placebo	1.5 ± 0.8 1.5	4.0 ± 2.7 3.5	3.6 ± 2.7 3.0	3.4 ± 2.8 3.0	3.5 ± 2.9 3.0	2.5 ± 2.6 1.5	1.9 ± 2.7 1.5
	Amitiza 24 mcg Twice Daily	1.3 ± 0.9 1.5	5.9 ± 4.0 5.0	5.0 ± 4.2 4.0	5.6 ± 4.6 5.0	5.4 ± 4.8 4.3	4.6 ± 4.1 3.8	4.1 ± 4.8 3.0

¹Frequency rates are calculated as 7 times (number of SBMs) / (number of days observed for that week).

In both studies, Amitiza demonstrated increases in the percentage of patients who experienced SBMs within the first 24 hours after administration when compared to placebo (56.7% vs. 36.9% in Study 1 and 62.9% vs. 31.9% in Study 2, respectively). Similarly, the time to first SBM was shorter for patients receiving Amitiza than for those receiving placebo.

Signs and symptoms related to constipation, including abdominal bloating, abdominal discomfort, stool consistency, and straining, as well as constipation severity ratings, were also improved with Amitiza versus placebo. The results were consistent in subpopulation analyses for gender, race, and elderly patients (≥ 65 years of age).

During a 7-week randomized withdrawal study, patients who received Amitiza during a 4-week treatment period were then randomized to receive either placebo or to continue treatment with Amitiza. In Amitiza-treated patients randomized to placebo, SBM frequency rates returned toward baseline within 1 week and did not result in worsening compared to baseline. Patients who continued on Amitiza maintained their response to therapy over the additional 3 weeks of treatment.

14.2 Opioid-induced Constipation

The efficacy of Amitiza in the treatment of opioid-induced constipation in patients receiving opioid therapy for chronic, non-cancer-related pain was assessed in three randomized, double-blinded, placebo-controlled studies. In Study 1, the median age was 52 years (range 20–82) and 63.1% were female. In Study 2, the median age was 50 years (range 21–77) and 64.4% were female. In Study 3, the median age was 50 years (range 21–89) and 60.1% were female. Patients had been receiving stable opioid therapy for at least 30 days prior to screening, which was to continue throughout the 12-week treatment period. At baseline, mean oral morphine equivalent daily doses (MEDDs) were 99 mg and 130 mg for placebo-treated and Amitiza-treated patients, respectively, in Study 1. Baseline mean MEDDs were 237 mg and 265 mg for placebo-treated and Amitiza-treated patients, respectively, in Study 2. In Study 3, baseline mean MEDDs were 330 mg and 373 mg for placebo-treated and Amitiza-treated patients, respectively. The Brief Pain Inventory-Short Form (BPI-SF) questionnaire was administered to patients at baseline and monthly during the treatment period to assess pain control. Patients had documented opioid-induced constipation at baseline, defined as having less than 3 spontaneous bowel movements

(SBMs) per week, with at least 25% of SBMs associated with one or more of the following conditions: (1) hard to very hard stool consistency; (2) moderate to very severe straining; and/or (3) having a sensation of incomplete evacuation. Laxative use was discontinued at the beginning of the screening period and throughout the study. With the exception of the 48-hour period prior to first dose and for at least 72 hours (Study 1) or 1 week (Study 2 and Study 3) following first dose, use of rescue medication was allowed in cases where no bowel movement had occurred in a 3-day period. Median weekly SBM frequencies at baseline were 1.5 for placebo patients and 1.0 for Amitiza patients in Study 1 and, for both Study 2 and Study 3, median weekly SBM frequencies at baseline were 1.5 for both treatment groups.

In Study 1, patients receiving non-diphenylheptane (e.g., non-methadone) opioids (n = 431) were randomized to receive placebo (n = 217) or Amitiza 24 mcg twice daily (n = 214) for 12 weeks. The primary efficacy analysis was a comparison of the proportion of “overall responders” in each treatment arm. A patient was considered an “overall responder” if ≥ 1 SBM improvement over baseline were reported for all treatment weeks for which data were available *and* ≥ 3 SBMs/week were reported for at least 9 of 12 treatment weeks. The proportion of patients in Study 1 qualifying as an “overall responder” was 27.1% in the group receiving Amitiza 24 mcg twice daily compared to 18.9% of patients receiving placebo twice daily (treatment difference = 8.2%; p-value = 0.03). Examination of gender and race subgroups did not identify differences in response to Amitiza among these subgroups. There were too few elderly patients (≥ 65 years of age) to adequately assess differences in effects in that population.

In Study 2, patients receiving opioids (N = 418) were randomized to receive placebo (n = 208) or Amitiza 24 mcg twice daily (n = 210) for 12 weeks. Study 2 did not exclude patients receiving diphenylheptane opioids (e.g., methadone). The primary efficacy endpoint was the mean change from baseline in SBM frequency at Week 8; 3.3 vs. 2.4 for Amitiza and placebo-treated patients, respectively; treatment difference = 0.9; p-value = 0.004. The proportion of patients in Study 2 qualifying as an “overall responder,” as prespecified in Study 1, was 24.3% in the group receiving Amitiza compared to 15.4% of patients receiving placebo. In the subgroup of patients in Study 2 taking diphenylheptane opioids (baseline mean [median] MEDDs of 691 [403] mg and 672 [450] mg for placebo and Amitiza patients, respectively), the proportion of patients qualifying as an “overall responder” was 20.5% (8/39) in the group receiving Amitiza compared to 6.3% (2/32) of patients receiving placebo. Examination of gender and race subgroups did not identify differences in response to Amitiza among these subgroups. There were too few elderly patients (≥ 65 years of age) to adequately assess differences in effects in that population.

In Study 3, patients receiving opioids (N = 451) were randomized to placebo (n = 216) or Amitiza 24 mcg twice daily (n = 235) for 12 weeks. Study 3 did not exclude patients receiving diphenylheptane opioids (e.g., methadone). The primary efficacy endpoint was the change from baseline in SBM frequency at Week 8. The study did not demonstrate a statistically significant improvement in SBM frequency rates at Week 8 (mean change from baseline of 2.7 vs. 2.5 for Amitiza and placebo-treated patients, respectively; treatment difference = 0.2; p-value = 0.76). The proportion of patients in Study 3 qualifying as an “overall responder,” as prespecified in Study 1, was 15.3% in the patients receiving Amitiza compared to 13.0% of patients receiving placebo. In the subgroup of patients in Study 3 taking diphenylheptane opioids (baseline mean [median] MEDDs of 730 [518] mg and 992 [480] mg for placebo and Amitiza patients, respectively), the proportion of patients qualifying as an “overall responder” was 2.1% (1/47) in the group receiving Amitiza compared to 12.2% (5/41) of patients receiving placebo.

14.3 Irritable Bowel Syndrome with Constipation

Two double-blinded, placebo-controlled studies of similar design were conducted in patients with IBS-C. IBS was defined as abdominal pain or discomfort occurring over at least 6 months with two or more of the following: 1) relieved with defecation; 2) onset associated with a change in stool frequency; and 3) onset associated with a change in stool form. Patients were sub-typed as having IBS-C if they also experienced two of three of the following: 1) < 3 spontaneous bowel movements (SBMs) per week, 2) > 25% hard stools, and 3) > 25% SBMs associated with straining.

Following a 4-week baseline/washout period, a total of 1154 patients (mean age 46.6 [range 18–85] years; 91.6% female; 77.4% Caucasian, 13.2% African American, 8.5% Hispanic, 0.4% Asian; 8.3% ≥ 65 years of age) were randomized and received Amitiza 8 mcg twice daily (16 mcg/day) or placebo twice daily for 12 weeks. The primary efficacy endpoint was assessed weekly utilizing the patient’s response to a global symptom relief question based on a 7-point, balanced scale (“significantly worse” to “significantly relieved”): “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 primary efficacy analysis was a comparison of the proportion of “overall responders” in each arm. A patient was considered an “overall responder” if the criteria for being designated a “monthly responder” were met in at least 2 of the 3 months on study. A “monthly responder” was defined as a patient who had reported “significantly relieved” for at least 2 weeks of the month or at least “moderately relieved” in all 4 weeks of that month. During each monthly evaluation period, patients reporting “moderately worse” or “significantly worse” relief, an increase in rescue medication use, or those who discontinued due to lack of efficacy, were deemed non-responders.

The percentage of patients in Study 1 qualifying as an “overall responder” was 13.8% in the group receiving Amitiza 8 mcg twice daily compared to 7.8% of patients receiving placebo twice daily. In Study 2, 12.1% of patients in the Amitiza 8 mcg group were “overall responders” versus 5.7% of patients in the placebo group. In both studies, the treatment differences between the placebo and Amitiza groups were statistically significant.

Results in men: The two randomized, placebo-controlled, double-blinded studies comprised 97 (8.4%) male patients, which is insufficient to determine whether men with IBS-C respond differently to Amitiza from women.

During a 4-week randomized withdrawal period following Study 1, patients who received Amitiza during the 12-week treatment period were re-randomized to receive either placebo or to continue treatment with Amitiza. In Amitiza-treated patients who were “overall responders” during Study 1 and who were re-randomized to placebo, SBM frequency rates did not result in worsening compared to baseline.

16 HOW SUPPLIED/STORAGE AND HANDLING

Amitiza is available as an oval, soft gelatin capsule containing 8 mcg or 24 mcg of lubiprostone with “SPI” printed on one side. Amitiza is available as follows:

8 mcg pink capsule

- Bottles of 60 (NDC 64764-080-60)

24 mcg orange capsule

- Bottles of 60 (NDC 64764-240-60)
- Bottles of 100 (NDC 64764-240-10)

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

Protect from light and extreme temperatures.

17 PATIENT COUNSELING INFORMATION

Physicians and patients should periodically assess the need for continued therapy.

17.1 Nausea, Dyspnea or Diarrhea

Instruct patients to take Amitiza twice daily with food and water to reduce the occurrence of nausea. Patients taking Amitiza may experience dyspnea within an hour of the first dose. Dyspnea generally resolves within 3 hours, but may recur with repeat dosing. Patients on treatment who experience severe nausea, dyspnea, or diarrhea should notify their physician.

17.2 Nursing Mothers

Advise lactating women to monitor their human milk-fed infants for diarrhea while taking Amitiza [see *Use in Specific Populations* (8.3)].

Marketed by:

Sucampo Pharma Americas, LLC
Bethesda, MD 20814

and

Takeda Pharmaceuticals America, Inc.
Deerfield, IL 60015

Amitiza[®] is a registered trademark of Sucampo AG.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021908/S-011

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Joyce Korvick, MD. MPH
Subject	Division Director Summary Review
NDA/Supplement #	21908/S011
Review Type	Priority
Applicant Name	Sucampo Pharmaceuticals, Inc.
Date of Submission	July 20, 2012
PDUFA Goal Date	April 19, 2013 (clock extended due to major amendment)
Proprietary Name / Established (USAN) Name	Amitiza (lubiprostone)
Dosage Forms / Strength	24 mcg Capsules
Proposed Indication(s)	Amitiza is indicated for the treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain.
Recommended Action:	APPROVAL

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Farrokh Sohrabi
Statistical Review	Freda Cooner
Non Clinical Pharmacology/Toxicology Review	Sushanta Chakder
CMC Review	Yong Wang
Clinical Pharmacology Review	Sandhya Apparaju
DAAAP consult review	Elizabeth Kilgore
DSI	(primary review) Khairy Malek (team leader review) Susan Leibenhaut
PMHS	Jeanine Best
OSE/DMEPA	Denise Baugh
SEALD	Ann Marie Trentacosti
CDTL Review	Robert Fiorentino

OND=Office of New Drugs

CMC= Chemistry and Manufacturing

DAAAP = Division of Anesthesia, Analgesia, and Addiction Products

DSI=Division of Scientific Investigations

PMHS = Pediatric and Maternal Health Staff, Office of New Drugs

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

SEALD – Study Endpoints and Labeling Development

DPDP/OPDP= Division of Professional Drug Promotion, Office of Prescription Drug Proportion.

CDTL=Cross-Discipline Team Leader

1. Introduction

This is a supplemental application proposes a new indication to be added to the professional labeling of Amitiza (lubiprostone) for the treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain. The recommended dose is 24 mcg twice per day. An important limitation of use is listed in the label and is as follows: Effectiveness of Amitiza in the treatment of opioid-induced constipation in patients taking diphenylheptane opioids (e.g., methadone) has not been established.

Amitiza is currently indicated for treatment of Irritable Bowel Syndrome-constipation predominant (8 mcg per day) (IBS-c) and Chronic Idiopathic Constipation (24 mcg twice per day) (CIC). Lubiprostone is a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. Lubiprostone acts by specifically activating CIC-2, which is a normal constituent of the apical membrane of the human intestine, in a protein kinase A-independent fashion. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine, thereby facilitating the passage of stool.

There are currently no drugs approved for the treatment of OIC. However, a variety of medications are used off-label for this purpose. These include stool softeners, bulk-forming laxatives, stimulant laxatives, saline osmotic laxatives, osmotic laxatives, lubricants, and other agents such as polyethylene glycol (PEG) 3350.

Opioid Induced Constipation (OIC) is a frequent complication of chronic opioid use. Opioids tend to inhibit gastric emptying, increase absorption and decrease secretion in both the large and small intestines, delay small intestinal and colonic transit, and increase internal anal sphincter tone. Some of the signs and symptoms related to this effect are constipation, dry hard stools, incomplete evacuation, straining at stool and abdominal distension.

This supplemental application relies on two well controlled studies which demonstrate efficacy; one of which excluded methadone use. An additional study failed to demonstrate efficacy.

The primary areas of particular interest for this review include *in vitro* testing of methadone and lubiprostone, the primary efficacy endpoint and selected analyses (e.g. subgroup by methadone use), the DSI site inspection, labeling and the overall Risk/Benefit of this new indication.

2. Background

Sucampo pharmaceuticals Inc. submitted data from three double-blind, placebo-controlled, 12-week clinical trials in this supplemental NDA. One of these trials failed to demonstrate efficacy (OBD-0632). Two of the phase-3 trials did demonstrate efficacy (OBD-1033 and OBD-0631).

Studies OBD-1631 and OBD-1632 were identically designed to evaluate the efficacy and safety of lubiprostone for the treatment of OIC in adults with chronic non-cancer pain. The

primary efficacy endpoint for these trials was the change from baseline in spontaneous bowel movement (SBM) frequency at Week 8 in subjects without dose reduction. These studies included patients who were taking methadone.

Study OBD-1033 was designed after the completion of Study 0631 and 0632. The sponsor suspected that patients receiving methadone may react differently to lubiprostone, and therefore changed the entry criteria to exclude patients taking methadone. The primary endpoint was also different. The primary efficacy analysis was a comparison of the proportion of “overall responders” in each treatment arm. A patient was considered an “overall responder” if ≥ 1 SBM improvement over baseline were reported for all treatment weeks for which data were available and ≥ 3 SBMs/week were reported for at least 9 of 12 treatment weeks.

See the Clinical Review for an overview of the history and pre-submission regulatory activity related to this sNDA. The Sponsor developed lubiprostone under IND 77,771.

The following regulatory history relates to many of the review issues and it is outlined in the CDTL review as follows:

Meetings

April 22, 2010: pre-sNDA meeting

- The Sponsor reported that after completion of OBD-0631 and OBD-0632, they had noted an interaction between methadone and lubiprostone, in which methadone impeded the pharmacologic activity of lubiprostone. Thus, the Sponsor asked if it would be acceptable to combine data from those two trials in order to support an indication in a revised target population of non-methadone OBD patients. DGIEP indicated that this approach would not be acceptable and that at least one additional trial (OBD-1033) be performed specifically targeting the intended population.
- For future trials, DGIEP recommended that the primary endpoint be based on a responder analysis, rather than change in bowel frequency [from baseline].

March 6, 2012: Type B, pre-sNDA meeting

- DGIEP expressed concern that the results of OBD-1033 may not be adequately robust as a single phase 3 trial (e.g., per-protocol analysis did not support the results of the ITT analysis) and also suggested the following:
 - “Please note that your primary analysis should be based on the intent-to-treat population (as randomized) with early dropouts considered as treatment failures.”
- DGIEP recommended sensitivity analyses in OBD-1033 to confirm the primary analysis of the ITT population. The Sponsor agreed with these recommendations.
- DGIEP requested confirmation that the responder rate analyses conform to the Agency’s definitions of weekly responder, weekly non-responder, and monthly responder.

Advice Letters

February 03, 2011

Sponsor submitted draft protocol and statistical analysis plan (SAP) of OBD-1033 to the Agency for review. Further revisions from the Sponsor were submitted November 16, 2010. Key comments and recommendations from the statistician that reviewed the SAP and protocol, Dr. Wen-Jen Chen, follow (comments were sent to Sponsor in an advice letter dated February 3, 2011):

- The primary efficacy analysis should be based on the intent-to-treat (ITT) population defined as all patients randomized.
- To calculate the weekly SBM frequency rates, the number of days observed in a week should be used, rather than the number of observed hours in a week as defined in the SAP and protocol.

August 16, 2007 (Statistical Advice Letter for studies 631 and 632)

- “The primary efficacy analysis should be conducted for the intent to treat (ITT) population and consist of all randomized subjects who take at least one dose of study medication, regardless of the number of hours per day that data are collected.”
- “We suggest that week 8 and/or week 12 be reserved for the primary efficacy comparisons”
- “Additional supportive analyses should address the use and frequency of rescue medication and the extent of possible confounding in the analyses of efficacy for both spontaneous bowel movement (SBM) and bowel movement (BM) results. A repeated measures model based on complete case data without rescue could be used as an additional way to explore the treatment effect over the trial period.”

July 16, 2007 (Clinical Advice Letter for studies OBD-631 and OBD-632)

- From a safety perspective, the dose-reduction strategy outlined in the protocol was considered acceptable to FDA. However, FDA noted that if a patient’s dose is reduced prior to the measurement of the primary endpoint, this may confound evaluation of the drug’s efficacy for this indication. Patients who have their dose reduced can participate in the safety extension study but should be excluded from the efficacy analysis for any endpoints whose timeframes overlap two different doses. As an example, if the patient’s dose is reduced at Week 9, the number of spontaneous bowel movements (SBMs) at Week 8 could still be analyzed, but the number of SBMs at Week 12 should not be analyzed for that patient.
- At the Pre-IND meeting in October 2006, the Division recommended that the primary endpoint be assessed at either Week 8 or Week 12. The proposed primary endpoint was considered acceptable by FDA, but FDA noted that this will limit potential labeling claims for efficacy for this indication to 8 weeks.

3. CMC

The CMC review had the following comments and conclusions:

“The products are currently FDA approved drug products as 8 µg and 24 µg capsules. No changes of formulation, dosage form, manufacturing, and packaging processes are proposed in this supplement. Only the 24 µg capsule would be used for the currently proposed indication. The proposed new indication will result in an increase of drug consumption. Consequently, the applicant is required to prepare an environment assessment. Based on their calculation, Sucampo Pharma claims categorical exclusion from preparing an environmental assessment on the basis of 21 CFR 25.31(b): the estimated concentration of drug substance at the point of entry into the aquatic environment will not exceed 1 part per billion. Hence, the claim for categorical exclusion is acceptable and the supplement is recommended for approval.”

“I concur with the conclusions reached by the chemistry reviewer. There are no outstanding issues.”

4. Nonclinical Pharmacology/Toxicology

In the current submission, the following three pharmacology studies were submitted:

- Effects of combination of RU-0211 and oxycodone on oxycodone-induced constipation in mice;
- A study of the gastrointestinal effects of SPI-0211 on opioid induced constipation in male CD-1 mice;
- Methadone but not morphine Inhibits lubiprostone-stimulated Cl-currents in T84 intestinal cells and recombinant human CIC- 2, but not CFTR Cl-currents.

In addition, a published study showing a reversal by lubiprostone of the morphine induced inhibition of the human intestinal mucosal fluid secretion was submitted (Sun et al, 2011 Dig Dis Sci, 56: 330-338)

The second study showed that SPI-0211 appears to be more effective on morphine-induced constipating effects in mice than that caused by methadone.

The results of the in vitro study were summarized as follows:

“In summary, the study was conducted to determine whether methadone inhibits Cltransport by epithelial cells. Lubiprostone-stimulated Cl- currents, measured by short circuit currents (Isc) in T84 cells, were inhibited by methadone. The hCIC Cl- currents in HEK293 cells were inhibited by methadone, but not by morphine. Naloxone alone, or with methadone, had no inhibitory effect. Morphine, at a concentration of 5 µM, had no effect on Isc. The inhibition of hCIC Cl- currents was lower when lubiprostone was added before methadone as compared to that observed when lubiprostone was added after methadone, suggesting that lubiprostone does not bind to channels previously bound to methadone.”

The review concluded that “The nonclinical safety of lubiprostone has been established in previous in vitro and in vivo studies reviewed under earlier submissions. The pharmacology studies submitted in the current submission suggest that lubiprostone might be effective in improving altered gastrointestinal transit caused by certain opioids. From a nonclinical perspective, the supplemental NDA application is approvable.”

“I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding non clinical pharmacology/toxicology issues that preclude approval.”

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology studies were submitted to this application.

Sucampo selected the dosing of 24 mg BID for OIC based on the previous studies conducted for Chronic Idiopathic Constipation (CIC).

An *in vitro* pharmacology study that evaluated the interaction potential of methadone and lubiprostone has been submitted to the non-clinical sections of this NDA supplement and by the Clinical Pharmacology reviewer. The applicant concluded that the “study suggests that methadone may inhibit effect of lubiprostone on opioid-dependent constipation by inhibiting the CIC-2 chloride channel currents induced by lubiprostone.”

The reviewer concluded that “Whether this interaction with methadone that was noted *in vitro*, actually translates into reduced efficacy of lubiprostone in the clinical setting could only be determined by evaluation of the available clinical evidence in this regard.”

This issue is considered further by the clinical reviewers Drs. Sohrabi and Fiorentino (for complete information refer to these reviews). They reviewed the clinical trials for methadone use and attempted to determine if there was a clinical effect (see section 7.Clinical/Statistical-Efficacy of this review for a summary of their findings)

The clinical pharmacology reviewed proposed revisions of the currently approved Amitiza professional labeling in Sections 7.0 (drug-drug interactions), section 8.0 (specific populations), and section 12.0 (Clinical pharmacology) and recommendations have been proposed from a Clinical Pharmacology perspective. The hepatic impairment (HI) language has been reviewed and revised in the highlights and sections 2.0, 8.0 and 12.0 of the labeling as needed to ensure consistency and clarity of dose adjustment language across the labeling.

Clinical pharmacology input was considered in the negotiations of the revised labeling.

“I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.”

6. Clinical Microbiology

Not applicable, this is an oral preparation.

7. Clinical/Statistical-Efficacy

Of the three studies submitted by the sponsor in this application only two support efficacy. Because Studies 0631 and 0632 had disparate results, Sucampo Pharmaceuticals conducted a third study 1033. As the design for study 1033 was being developed several issues were considered: the results from the *in vitro* study regarding the potential for an interaction with methadone, the subgroup analysis according to methadone use from study 0631 and 0632, the evolving definition of clinical response as the primary endpoint for OIC, and the DSI site recommendations effect on the primary analysis.

Complete details regarding the various analyses that were conducted regarding the efficacy of lubiprostone for OIC can be found in the primary clinical review, the CDTL review and the statistical review.

Study 1033 was the final study conducted to support this indication. The primary efficacy analysis was a comparison of the proportion of “overall responders” in each treatment arm. A patient was considered an “overall responder” if ≥ 1 SBM improvement over baseline were reported for all treatment weeks for which data were available and ≥ 3 SBMs/week were reported for at least 9 of 12 treatment weeks. “Overall responders” is the preferred primary endpoint for OIC. As the statistical review points out, the sponsor’s intent-to-treat (ITT) analysis (All randomized subjects who took at least one dose of study medication and had at least one treatment-period diary entry) is not acceptable. The analysis should not include a qualification based upon diary entries. In either case, each of the analyses pointed to a statistically significant difference in response rate. As the statistical reviewer points out the difference in outcome response is small.

The clinical reviewer remarks that while the difference is small “comparing the treatment effect for lubiprostone to other approved drugs is limited given that there are no other drugs approved for the treatment of OIC in adults with chronic non-cancer pain. He does however point out that for lubiprostone in IBS-C, the treatment difference favoring lubiprostone over placebo in two 12-week efficacy trials was ~6% (although responder definitions were different for the IBS-C population than the OIC population). For lubiprostone in CIC, a responder definition was not used for the primary endpoint, making comparisons of treatment differences across indications impractical – a similar problem comparing lubiprostone to methylaltrexone. The reviewer also notes that linaclotide, recently approved for CIC and IBS-C, demonstrated a treatment difference of ~10% to 15% in the CIC population studied (albeit over a 12-week period, using overall complete SBM (CSBM) responders as the primary endpoint, rather than SBM responders). Dr. Sohrabi concludes that in his view, a treatment difference of 8% favoring lubiprostone represents a clinically meaningful treatment effect in adults with chronic non-cancer pain and OIC and offers another treatment option for OIC in this patient population.”

Finally, the reviewer views the various secondary analyses of SBM as clinically supportive of the overall response. The CDTL is also in agreement.

Study 0631 and 0632 had similar designs which were staggered in their conduct. As noted above, there were several discussions between Sucampo and DGIEP regarding the disparate results. Sucampo focused on the use of methadone and specifically the difference in the dosing between trials and arms of the study as one factor which might explain the differences between both studies.

The review team accepted the results from study 0631 as the second study supportive of this indication. This study was designed and conducted prior to DGIEPs current recommendations regarding endpoint evaluations for OIC. In this study the primary efficacy endpoint was the mean change from baseline in SBM frequency at Week 8. However, because there were several statistical concerns, outlined in the statistical review, the FDA agreed to use primary analysis was that stated in the protocol regarding SBMs, but an ITT analysis conducted with all randomized patients. Further, as an exploratory analysis the preferred primary endpoint for OIC as defined in study 1033 was conducted. Again, the results supported approval, although the difference was small but clinically meaningful. The statistically reviewer cautioned against using the p-value for the exploratory analysis as it was not controlled for multiplicity.

Finally, it was felt that the data from Study 0632 should be included in the labeling as the results did not demonstrate statistical significance between placebo and lubiprostone. The clinical reviewer did a thorough review and could not agree with the sponsor that the results were due to the methadone dosing. (For complete details refer to the clinical review).

The CDTL memo summarized the methadone issue as follows:

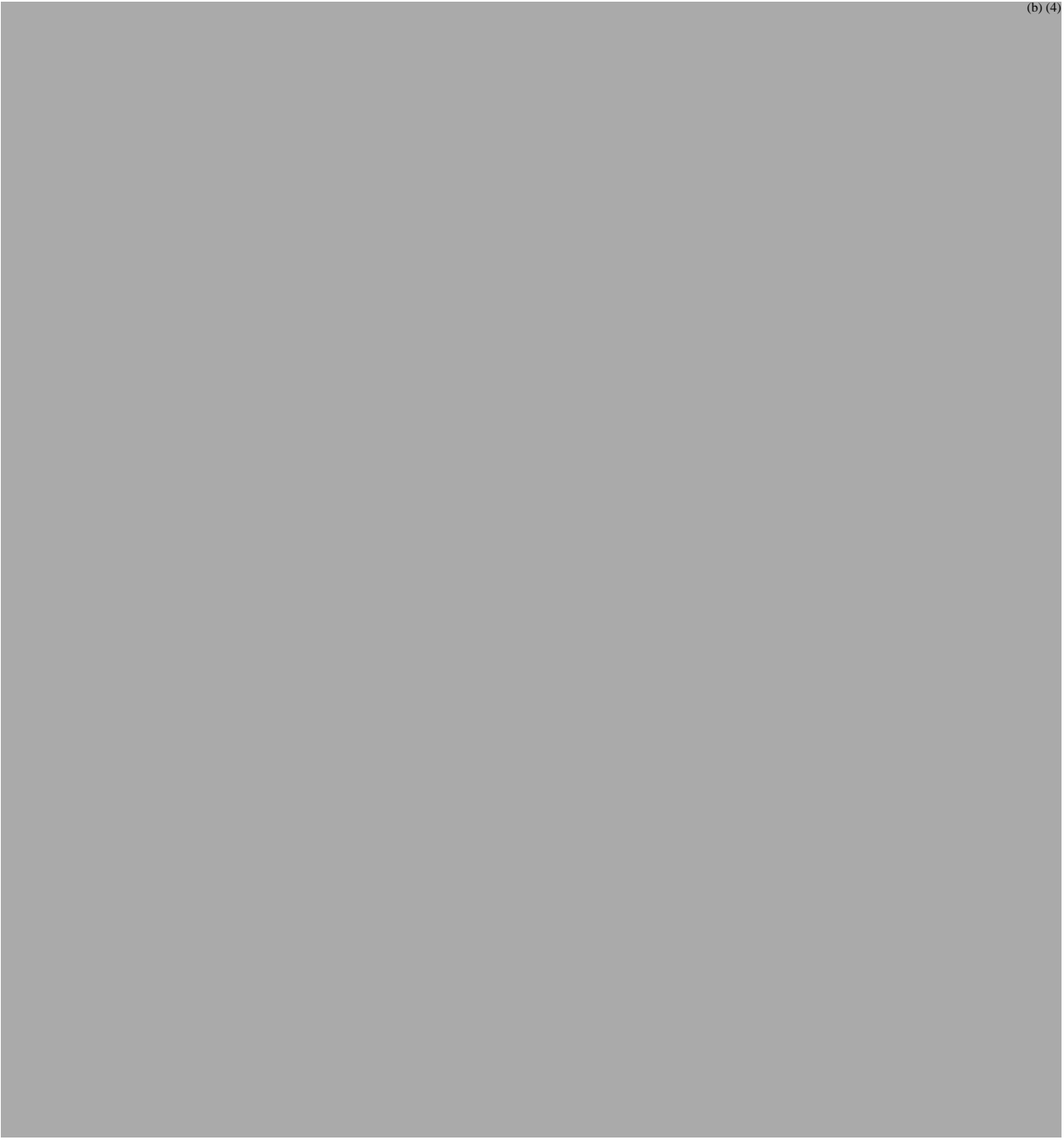
“However as Dr. Sohrabi explains in his review, the percentage of subjects on a methadone is only slightly higher in the ITT population of OBD-0632 than OBD-0631. Further, the distribution of subjects on methadone is balanced across treatment arms for both the ITT and efficacy evaluable populations in OBD-0632. As Dr. Sohrabi also notes, even if there were a significant treatment interaction with methadone, the slightly higher percentage of methadone users in OBD-0632 compared to OBD-0631 would not adequately explain the failure of trial OBD-0632 on efficacy endpoints”.

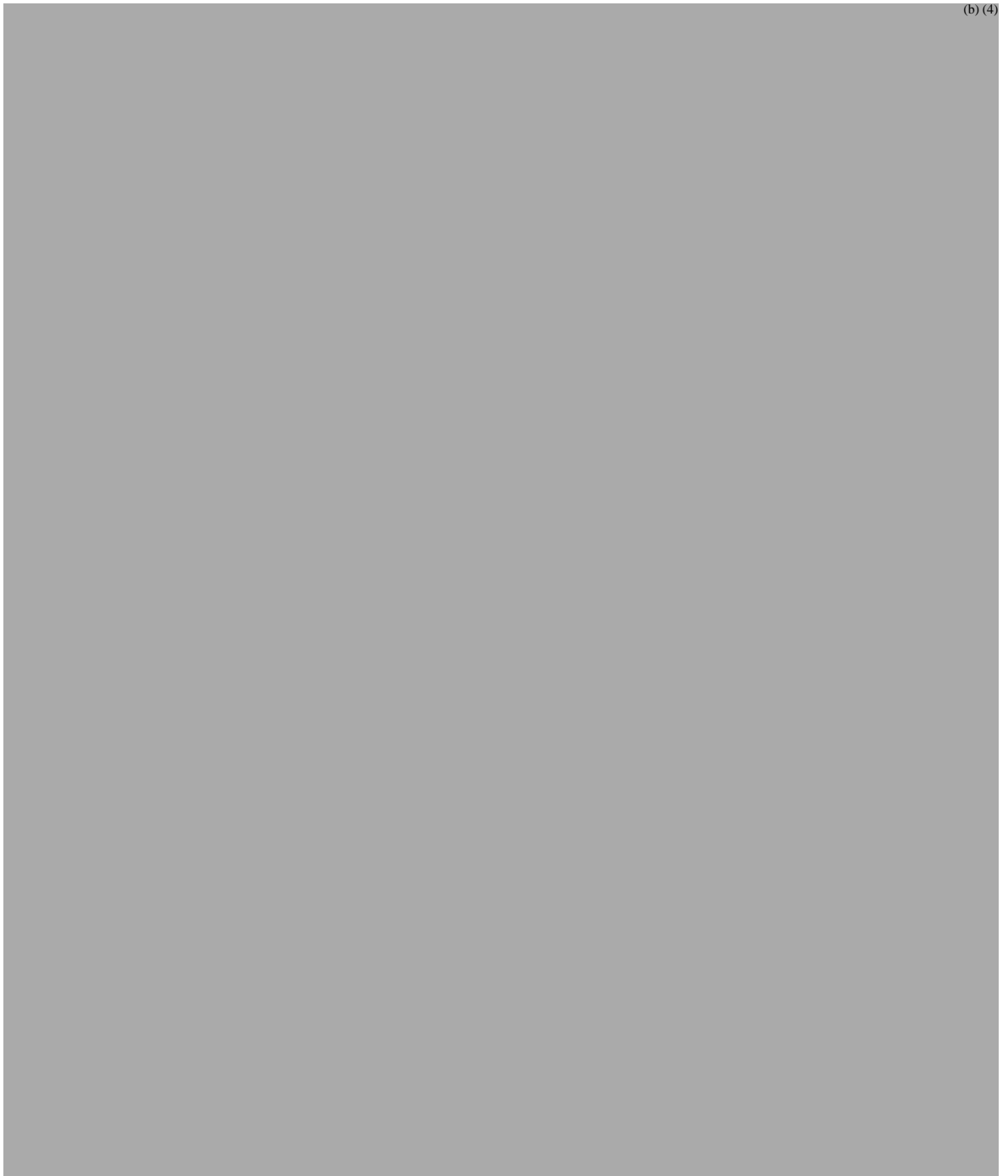
“The Sponsor also argued that because methadone inhibited chloride channels in a dose-dependent manner in the nonclinical study and because subjects on methadone in OBD-0632 had a higher average morphine equivalent daily doses (MEDD) than subjects on methadone in OBD-0631, methadone-treated subjects in OBD-0632 had a greater impact on reduction of lubiprostone efficacy in that trial than methadone-treated subjects in OBD-0631. However, as pointed out by Dr. Sohrabi in his review, the magnitude of the treatment difference favoring the lubiprostone group in OBD-0632 is smaller in the higher MEDD subgroup (1.8%) than the lower MEDD subgroup (4.4%), but this pattern is reversed in the results for OBD-0631, where the treatment effect is larger in the higher MEDD subgroup (14.7%) than the lower MEDD subgroup (8.6%). The lack of a consistent relationship between the MEDD and primary outcome made Dr. Sohrabi unable to agree with the Sponsor that the failure of trial OBD-0632 was due to the higher overall MEDD as well as the higher MEDD in the subgroup of diphenylheptane subjects in OBD-0632 as compared with OBD-0631”.

“Dr. Sohrabi’s detailed clinical review of factors that may have contributed to the failure of OBD-0632 did not find a single or consistent explanation for the trial’s failure. A detailed discussion of the elements reviewed and conclusions can be found in Appendix 4 of Dr. Sohrabi’s review (*see Discussion of Individual Trials: Trial SMR/0211 OBD-0632*)”.

The final agreed upon labeling for efficacy represents the efficacy data according to the agreed upon primary endpoint, considering FDA preferred ITT analysis, and removal of patients from suspect sites (see DSI section below).

(b) (4)





Based upon the medical officer review, CDTL memo, and statistical review of these data, I am in agreement that the data support approval of lubiprostone for the treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain.

8. Safety

No significant changes in safety were seen in this NDA compared to those seen in the previously submitted applications for IBS-d or CIC. Adverse Reactions frequently associated

with Amitiza include nausea, diarrhea, vomiting, abdominal pain, flatulence, abdominal discomfort, abdominal distension, headache, and peripheral edema compared to placebo patients. Dyspnea, also in the current drug label, had an incidence rate comparable to that seen in the clinical trial of Amitiza conducted for CIC at the labeled dose of 24mcg BID.

The medical reviewer utilized the safety data from the clinical trials OBD-1033, OBD-0631, OBD-0632, and OBD-06S1 (a long term extension trial), as well as the 120 day safety update, and the most recent Periodic Safety Update report.

As reported in Adverse Reactions section 6.1 of the label 1492 of patients with opioid-induced constipation were included in this safety analysis.

Frequent adverse reactions (ARs) remain the same, and no suggestion of withdrawn symptoms (none were expected due to mechanism of action) were noted by the reviewer.

- Sections 6.1: ARs are displayed according to indication/subpopulations in the section regarding OIC. The sites which were removed from the efficacy analysis were also removed from the safety analysis when calculating final rates (see section 11 DSI Consult below). This did not change the overall evaluation of safety.

(b) (4)

The Postmarketing section (6.2 of the professional labeling) was updated to include ischemic colitis which was reported to AERs/FAERs database since the approval of Amitiza in 2006, and listed in the sponsors most recent PSUR. This was summarized as follows in the Medical Officers review:

“As of the most recent PSUR, cumulatively (from February 31, 2006 to January 31, 2012), the Sponsor reported 12 cases of ischemic colitis (IC). A review by the Office of Surveillance and Epidemiology/Division of Pharmacovigilance-1 (OSE/DPV1), conducted in September 2008, demonstrated six postmarketing cases of IC from initiation of marketing

through August 12, 2008. Of the six cases, five patients had a serious outcome of hospitalization. Four of the six patients were female, all six patients were on lubiprostone for chronic constipation, and mean age was 62 years. Two of the patients were concomitantly on estrogen, a medication that has been associated with IC. Four patients had underlying conditions that might have predisposed them to development of IC, including hypertension, dehydration, and congestive heart failure.”

“During the current review cycle, OSE/DPV1 searched the AERS database for the period from August 13, 2008 to January 2, 2013 and identified six new cases of ischemic colitis. Of the six cases, five patients had a serious outcome of hospitalization. Four of the six patients were female, five of the six patients were on lubiprostone for chronic constipation, and mean age was 54 years. None of the patients was on concomitant medications with potential to cause ischemic colitis.”

The reviewer comments that “Although several patients in these case series had underlying medical history or were taking concomitant medications that could have contributed to the development of IC, a causal role of lubiprostone cannot be ruled. This reviewer is somewhat reassured that there have been no reports of colectomy or death in these 12 patients. Given the totality of the data from the reports by OSE/DPV-1 since lubiprostone’s first approval in January 2006, this reviewer recommends updating the labeling to include IC in the Adverse Reactions Postmarketing Experience section.”

Finally, a review of the clinical trials submitted to this application did not reveal cases of ischemic colitis.

I agree with the Medical Reviewer and the Team Leader that given the small number of cases and that the cases did not result in colectomy or death, this reaction should be placed in the Postmarketing section.

9. Advisory Committee Meeting

This application was a supplement to the NDA adding a new indication. It was not taken to an Advisory Committee.

10. Pediatrics

The Applicant requested a deferral of Pediatric Research and Equity Act (PREA) required studies in pediatric patients ages 6 months to 17 years of age and a waiver request in pediatric patients 0 to 6 months of age, both for the indication of opioid-induced constipation.

Pediatric Research Committee (PeRC) did (meeting date 2/13/13) not concur with a deferral request and instead recommended a full waiver of pediatric studies for opioid-induced constipation because studies would be impossible or highly impracticable.

The rationale for this recommendation is captured in the PMHS review as follows:
“There is a lack of consensus on the use of opioids for treatment of chronic non-cancer pain in pediatric patients. Multiple published references have noted that conducting safety and

efficacy trials in pediatric patients with opioid induced constipation remains a challenge. Studies of pediatric patients with pain due to cancer or advanced medical illness are also challenging to conduct due to the difficulties of studying children in a palliative care environment. Thus, PMHS and DGIEP both agree that a waiver for studies in all pediatric age groups should be granted because studies would be impossible or highly impracticable.”

11. Other Relevant Regulatory Issues

• Division of Scientific Investigations (DSI) Audits:

DGIEP reviewers requested inspection of sites from two phase-3 protocols which were relied upon for the demonstration of efficacy:

1. Protocol SMR/0211OBD-1033 entitled “A Multicenter, Randomized, Placebo-controlled, Double-blinded Study of the Efficacy and Safety of Lubiprostone in Subjects with Opioid- Induced Bowel Dysfunction”; conducted from December 7, 2010 to November 16, 2011 and enrolled 447 subjects at a total of 105 investigative sites.
2. Protocol SPI/0211OBD-0631 entitled “A Multicenter, Randomized, Placebo-controlled, Double-blinded Study of the Efficacy and Safety of Lubiprostone in Patients with Opioid induced Bowel Dysfunction”; conducted from August 3, 2007 to March 6, 2009, and followed by an open label extension study period from Dec 2007 to September 2009. A total of 439 subjects received study drug at 80 investigative sites.

The following sites were chosen for inspection for Protocol SPI/0211OBD-0631:

- Site 1069 (Sandoval): Large number of subjects (25 subjects) with disproportionately high responder status (~20%)
- Site 1018 (Leslie): Site with largest number of subjects (28 subjects)

The following sites were chosen for inspection for Protocol SMR/0211OBD-1033:

- Site 3098 (Wolfson): Highest % of lubiprostone responders (32%) for a site with ≥ 10 subjects (19 subjects)
- Site 3019 (Chilombo): Highest % of placebo non-responders (60%) for site with ≥ 10 subjects (10 subjects).

Two review recommendations were received by DGIEP from DSI for this sNDA; primary reviewer – Dr. Malik, and team leader – Dr. Leibenhaut. Their final recommendations differ regarding analysis of the reports from the site inspectors. For decision making purposes, the CDTL and I are both relying on the OSI team leader’s recommendations. For a full discussion of this issue, refer to these reviews.

In summary, DSI recommended that DGIEP not to rely on data from Site 3019 in study 1033, and Site 1069 in study 0631. Inspection of site 3019 showed several deficiencies, and documents from the applicant show that Sucampo was already suspicious the conduct of the study at this site. In fact, the Sponsor informed FDA that a representative from the monitoring team of the CRO vendor expressed concerns regarding source documentation at Site 3019 while the trial was ongoing.

The site inspections raised issues from a related site 3119, where these sites were administered by E.M., a clinical research associate. The field investigator had problems with E.M. on a previous inspection. We agree with DSI's recommendation not to rely on this data, and have excluded it from the analysis for study 1033.

For Study 1069, during inspection paper documentation could not be inspected because it was inadvertently shredded. While there appears that this inadvertent action taken by someone not related to the study conduct was unfortunate, we cannot confirm documentation on inspection. For this reason, DSI recommended that data from this site is unreliable. We have excluded this data from the analysis.

During the site inspections DSI recommended an inspection of Sucampo Pharmaceuticals, Inc.. The following reasons were noted in the DSI Team Leader review:

1. During the inspection of the Leslie site, FDA learned that remonitoring of the trial SMR/0211OBD-0631 had occurred after the study was closed, the database had been locked, and the study analyzed. A sponsor inspection was issued to determine the adequacy of monitoring during the trial and the adequacy of the remonitoring procedures, database lock and unlock and preservation of the blind for this study.
2. During the inspection of the clinical sites for both studies, it was determined that the primary efficacy endpoint submitted to the NDA (line listings) for both studies could not be verified at the clinical sites because a calculation was required to convert the raw eDiary data on the CDs at the clinical sites into the value that was submitted to the NDA.
3. When results of the inspection of the Chilombo (site 3019) and Dao (site 1069) sites became known, it became apparent that monitoring procedures and clinical trial conduct for both studies should be inspected and evaluated.

As noted in the EIR, after the study, the sponsor worked to resolve discrepancies regarding the safety data. The integrity of the efficacy data was not a concern because this patient reported outcome was collected via direct data capture. The DSI Team Leader review goes on to note that, "The nature of the discrepancies (adverse events [AEs], concomitant medications, abnormal physical findings that did not result in adverse events) and the eventual resolution provide evidence that the data are reliable. Additionally, the sponsor identified the issues and undertook a number of actions, including terminating their CRO, conducting audits, and instituting a remonitoring program to ensure the integrity of the data."

The summary comments of the DSI Team Leader go on to state the following: "Inspection of the sponsor observed deficiencies concerning monitoring as noted above and in Dr. Malek's review. However, the sponsor inspection also provided evidence that the sponsor took actions so that the data is considered reliable for both studies. For Protocol SMR/0211OBD-0631 the sponsor worked to mitigate issues with poor monitoring. For Protocol SMR/0211OBD-1033, there was an issue with falsification that was suspected by the sponsor but was not detected with a third party audit.

Nevertheless, the sponsor, based on suspicions, provided the information concerning questionable data integrity to FDA and conducted an analysis in which data from the Chilombo (site 3019) and Moreno (site 3119) sites were removed”.

“For both studies, the efficacy data was captured with direct patient reporting and there were no questions concerning this data. Randomized double blind controlled study designs afford additional assurance that the efficacy data generated by the studies can be used for the support of this indication. It is interesting to note that the Chilombo site, the most violative, had the highest placebo non-response. Concerning the safety issues, the sponsor identified issues late in the trial for SMR/0211OBD-0631 and, during the extension trial and after the closure of the trials, worked with the auditors and the new CRO responsible for monitoring to correct the discrepancies”.

DGIEP agrees with the DSI Team Leader assessment that the data are considered reliable for both studies based upon the site inspection of Sucampo, with the exclusion of data from the sites already outlined above.

- **Financial Disclosure, *acceptable***

Other Consults:

SEALD Consult:

DGIEP consulted SEALD for comments regarding [REDACTED] (b) (4)

[REDACTED]

“The review concludes that the applicant has not submitted [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

[REDACTED] (b) (4)

(b) (4)

These recommendations were considered during the negotiations regarding final labeling.

DEMEPA REVIEW:

The following are comments to the DGIEP from DMEPA regarding the potential for medication error and recommendations for labeling.

“DMEPA concludes that the proposed container label and sample labeling can be improved to increase the readability and prominence of important information to promote the safe use of the product and to clarify information.”

DMEPA Recommendations:

A. “Consider adding the following statement to the Dosage and Administration Subsection under the Highlights of Prescribing Information and the Full Prescribing Information Headings: “Capsules should be swallowed whole and should not be broken apart or chewed”. Addition of this statement will maintain consistency with its appearance in the Patient Counseling Information Subsection (17) of the insert labeling.”

B. Comments to the Applicant (Note these comments were sent to the sponsor during labeling negotiations and incorporated into the label)

1. All Container Labels and Professional Sample Labeling

a. Revise the presentation of the proprietary name, from all lower case “amitiza” to title case “Amitiza” to improve its readability and to further distinguish it from the active ingredient.

b. Add the following statement to all container labels and sample labeling (e.g., blister card and sample tray): “Swallow Whole – Do NOT Break Apart or Chew”. Addition of this statement may reinforce this message, which is found in the Patient Counseling Information Subsection (17) of the insert labeling and may help minimize the occurrence of wrong technique errors.

2. All Container Labels (24 mcg [60 count and 100 count] and 8 mcg [60 count])

a. Relocate the statement “Marketed by: Sucampo” to the side panel to accommodate recommendation B(1)(b)

b. Consider deleting the statement [REDACTED] (b) (4)
...” from the side panel to minimize clutter and allow room for recommendation B(2)(a).

3. Professional Sample Blister Card

- a. Add the statement “Each capsule contains XX mcg” to clearly state the amount contained in each capsule and to minimize accidental overdoses.
4. Professional Carton Labeling and Sample Tray (24 mcg)
- a. Although the established name (active ingredient and dosage form) is at least half the size of the proprietary name, it lacks prominence due to either thin font size or lack of color contrast. Improve the prominence of the established name taking into consideration the typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

In response to the request above the sponsor made the appropriate changes accept regarding b.1.a, and while Sucampo added the statement “Each capsule contains XX mcg” to the package the letter E overlaps a capsule well and might be difficult to read.

The following is the response from DMEPA reviewer:

“DMEPA acknowledges that the Applicant is unwilling to consider the recommendations to revise the presentation of the proprietary name on the container label and carton labeling from all upper case to title case letters and to revise the "Each capsule contains XX mg" statement on the blister labels such that the information is not destroyed with the removal of a capsule from the blister. We therefore find the revised labels as submitted acceptable. However, if we retrieve medication error cases post marketing due to labeling, we may recommend additional regulatory action at that time”.

I agree with this recommendation.

“There are no other unresolved relevant regulatory issues”

12. Labeling

- Proprietary name: *unchanged in this supplement*
- Physician labeling:
 - The changes in the label are primarily related to the new indication as described above.
 - The sponsor was requested to clarify the word “rebound” at the end of each section: CIC and IBS-c. The sponsor justified the response and stated it was designed to be similar to that found in the Linzess labels.
 - Limitations of Use section was added to the indication because of the potential interaction of lubiprostone with methadone and the lack of a consistent response in this subgroup between studies as described above. The new labeling includes the follow statement:
 - Effectiveness of Amitiza in the treatment of opioid-induced constipation in patients taking diphenylheptane opioids (e.g., methadone) has not been established
- Carton and immediate container labels: approved as attached to action letter.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action:** Approval

- **Risk Benefit Assessment**

Opioid induced constipation (OIC) does not result in mortality but can be associated with morbidity, such as pseudo-obstruction and fecal incontinence, and may reduce the value of effective pain relief in adult patients using opioids for chronic non-cancer pain. There may be a need for alternative options for treatment of OIC in the chronic non-cancer adult patient population, especially if the drug has demonstrated efficacy in the target population.

Lubiprostone 24 mcg BID is effective in treatment of OIC in adults with chronic non-cancer pain. This effect was demonstrated in two of three studies submitted to this supplemental NDA. The effectiveness of lubiprostone in patients with OIC taking diphenylheptane opioids (e.g., methadone) has not been established.

The overall safety profile of lubiprostone is acceptable for a laxative and comparable with the safety profile established for other approved indications (CIC and IBS-C). Adverse events associated with the gastrointestinal tract were more frequent with lubiprostone compared to placebo, but were manageable. Ischemic colitis cases have been reported in the postmarketing database since approval of lubiprostone. These cases did not result in death or colectomy. Ischemic colitis should be added to the Postmarketing Experience section of the label.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS)**

We have determined that a REMS is not necessary for this application.

- **Recommendation for other Postmarketing Requirements and Commitments (PMR/PMC):**

We have determined that PMR/PMCs are not necessary for this supplemental application.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOYCE A KORVICK
04/19/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021908/S-011

OFFICER/EMPLOYEE LIST

**Officer/Employee List
NDA 21908/S011**

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Name
Apparaju, Sandhya
Baugh, Denise
Best, Jeanine
Beitz, Julie
Bray, Jeff
Cao, Christian
Chakder, Sushanta
Delasko, Jeanne
Ishihara, Richard
Klemm, Kathleen
Korvick, Joyce
Kowblansky, Marie
Kusiak, Victoria
Leibenhaut, Susan
McEvoy, Brad
Merchant, Lubna
Sachs, Hari
Scherer, Matt
Sohrabi, Farrokh
Stockbridge, Norman
Thompson, Susan
Trentacosti, Ann Marie
Yang, Baichun

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021908/S-011

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 19, 2013
From	Robert P. Fiorentino, M.D., M.P.H.
Subject	Cross-Discipline Team Leader Review
NDA #	NDA # 21908
Supplement #	Supplement # 011
Applicant	Sucampo Pharmaceuticals, Inc.
Date of Submission	July 20, 2012
PDUFA Goal Date	April 19, 2013 (3 month extension due to 11/16/2012 major amendment)
Proprietary Name / Established (USAN) names	AMITIZA, lubiprostone
Dosage forms / Strength	24 mcg B.I.D.
Proposed Indication(s)	Opioid-induced constipation in adults with chronic non-cancer pain
Recommendation	Approval

Table of Contents

1. Introduction	2
2. Background	2
3. CMC / Device.....	4
4. Nonclinical Pharmacology/Toxicology	5
5. Clinical Pharmacology/Biopharmaceutics	6
6. Clinical / Statistical: Efficacy.....	8
Primary Efficacy Evaluation.....	10
Supportive Analyses of Primary Endpoints	15
Evaluation of Secondary and Other Proposed Claims	20
Statistical Analyses and Concerns	25
7. Safety.....	26
8. Advisory Committee Meeting	28
9. Pediatrics	28
10. Other Relevant Regulatory Issues	29
OSI Inspections	29
11. Labeling.....	33
12. Recommendations/Risk Benefit Assessment	35

1. Introduction

This review covers the sNDA (NDA 21908, Supplement 11) submitted by Sucampo Pharmaceuticals to support the approval of Amitiza for opioid induced constipation (OIC) in patients with chronic non-cancer pain. The efficacy supplement contained the data from three clinical trials and *in vitro* pharmacology studies. No new nonclinical studies were submitted to this Supplement.

The following reviews formed the primary approval basis for this sNDA (only primary reviewers listed; signatures are electronic [via DAARTS]):

- Clinical
 - Farrokh Sohrabi, M.D., signed 04/04/2013
- Statistics
 - Freda Cooner, signed 04/15/2013
- Clinical Pharmacology
 - Sandhya Apparaju, Ph.D., signed 3/06/2013
- Nonclinical
 - Sushanta Chakder Ph.D., signed 03/18/2013
- CMC / ONDQA (Division II, Branch VI)
 - Yong Wang, signed 10/01/2012
- Pediatric and Maternal Health Staff (PMHS)
 - Jeanine Best, MSN, RN, PNP, signed 3/08/2013
- Office of Prescription Drug Promotion (OPDP)
 - Meeta Patel, PharmD, sign 3/29/2013
- SEALD Endpoint Review
 - Ann Marie Trentacosti, signed 11/06/2012
- SEALD End-of-Cycle Labeling Review
 - Jeanne Delasko, signed 4/16/2013
- Division of Medication Error Prevention and Analysis (DMEPA)
 - Denise V. Baugh, PharmD, BCPS, signed 12/14/2012
- Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
 - Elizabeth Kilgore, MD., signed 03/18/2013
- Office of Scientific Investigations (OSI)
 - Primary Review: Khairy Malek, M.D., Ph.D., signed 03/27/2013
 - Team Leader Review: Susan Leibenhaut, M.D., signed 03/27/2013

2. Background

Lubiprostone (AMITIZA) activates chloride channel type 2 (ClC-2), which is located on the intestinal epithelial cell and increases chloride transport into the lumen of the intestine thereby enhancing fluid secretion into the bowels and improving fecal transit.

AMITIZA was approved in January 2006 for the treatment of chronic idiopathic constipation (CIC) in adults at the 24 mcg BID dose and in April 2008 for IBS-C in adult women at the 8 mcg BID dose.

There is currently no FDA approved drug indicated for the treatment of OIC. However there exists a wide variety of over-the-counter and prescription products that are used to treat constipation including the following: stool softeners (docusate), bulk-forming laxatives (psyllium, methylcellulose, polycarbophil), stimulant laxatives (bisacodyl, senna, and castor oil), saline osmotic laxative (sodium phosphate, magnesium citrate, and magnesium hydroxide), osmotic laxatives (lactulose and sorbitol), lubricants (mineral oil, glycerin), and other osmotic agents like polyethylene glycol (PEG)-3350 (with and without electrolytes).

See the Clinical Review for an overview of the history and presubmission regulatory activity related to this sNDA. The Sponsor developed lubiprostone under IND 77,771.

Meetings

April 22, 2010: pre-sNDA meeting

- The Sponsor reported that after completion of OBD-0631 and OBD-0632, they had noted an interaction between methadone and lubiprostone, in which methadone impeded the pharmacologic activity of lubiprostone. Thus, the Sponsor asked if it would be acceptable to combine data from those two trials in order to support an indication in a revised target population of non-methadone OBD patients. DGIEP indicated that this approach would not be acceptable and that at least one additional trial (OBD-1033) be performed specifically targeting the intended population.
- For future trials, DGIEP recommended that the primary endpoint be based on a responder analysis, rather than change in bowel frequency [from baseline].

March 6, 2012: Type B, pre-sNDA meeting

- DGIEP expressed concern that the results of OBD-1033 may not be adequately robust as a single phase 3 trial (e.g., per-protocol analysis did not support the results of the ITT analysis) and also suggested the following:
 - “Please note that your primary analysis should be based on the intent-to-treat population (as randomized) with early dropouts considered as treatment failures.”
- DGIEP recommended sensitivity analyses in OBD-1033 to confirm the primary analysis of the ITT population. The Sponsor agreed with these recommendations.
- DGIEP requested confirmation that the responder rate analyses conform to the Agency’s definitions of weekly responder, weekly non-responder, and monthly responder.

Advice Letters

February 03, 2011

- Sponsor submitted draft protocol and statistical analysis plan (SAP) of OBD-1033 to the Agency for review. Further revisions from the Sponsor were submitted November 16, 2010. Key comments and recommendations from the statistician that reviewed the SAP and protocol, Dr. Wen-Jen Chen, follow (comments were sent to Sponsor in an advice letter dated February 3, 2011):
 - The primary efficacy analysis should be based on the intent-to-treat (ITT) population defined as all patients randomized.

- To calculate the weekly SBM frequency rates, the number of days observed in a week should be used, rather than the number of observed hours in a week as defined in the SAP and protocol.

August 16, 2007 (Statistical Advice Letter for studies 631 and 632)

- “The primary efficacy analysis should be conducted for the intent to treat (ITT) population and consist of all randomized subjects who take at least one dose of study medication, regardless of the number of hours per day that data are collected.”
- “We suggest that week 8 and/or week 12 be reserved for the primary efficacy comparisons”
- “Additional supportive analyses should address the use and frequency of rescue medication and the extent of possible confounding in the analyses of efficacy for both spontaneous bowel movement (SBM) and bowel movement (BM) results. A repeated measures model based on complete case data without rescue could be used as an additional way to explore the treatment effect over the trial period.”

July 16, 2007 (Clinical Advice Letter for studies OBD-631 and OBD-632)

- From a safety perspective, the dose-reduction strategy outlined in the protocol was considered acceptable to FDA. However, FDA noted that if a patient’s dose is reduced prior to the measurement of the primary endpoint, this may confound evaluation of the drug’s efficacy for this indication. Patients who have their dose reduced can participate in the safety extension study but should be excluded from the efficacy analysis for any endpoints whose timeframes overlap two different doses. As an example, if the patient’s dose is reduced at Week 9, the number of spontaneous bowel movements (SBMs) at Week 8 could still be analyzed, but the number of SBMs at Week 12 should not be analyzed for that patient.
- At the Pre-IND meeting in October 2006, the Division recommended that the primary endpoint be assessed at either Week 8 or Week 12. The proposed primary endpoint was considered acceptable by FDA, (b) (4)

3. CMC / Device

The ONDQA review notes that the products are currently FDA approved drug products as 8 µg and 24 µg capsules. No changes of formulation, dosage form, manufacturing, and packaging processes are proposed in this supplement. Only the 24 µg capsule would be used for the currently proposed indication. The proposed new indication will result in an increase of drug consumption and the applicant is required to prepare an environment assessment. Based on its calculation, Sucampo Pharma claims categorical exclusion from preparing an environmental assessment on the basis of 21 CFR 25.31(b): the estimated concentration of drug substance at the point of entry into the aquatic environment will not exceed 1 part per billion. Hence, the claim for categorical exclusion is acceptable and the supplement is recommended for approval by the CMC reviewer.

No facilities review/inspection was performed. There are no unresolved CMC issues at the time this memo was finalized.

4. Nonclinical Pharmacology/Toxicology

In the current submission, the following three pharmacology studies were submitted:

- ‘Effects of combination of RU-0211 and oxycodone on oxycodone-induced constipation in mice.’
- “A study of the gastrointestinal effects of SPI-0211 on opioid-induced constipation in male CD-1 mice.”
- “Methadone but not morphine Inhibits lubiprostone-stimulated Cl⁻ currents in T84 intestinal cells and recombinant human ClC-2, but not CFTR Cl⁻ currents.”

In addition, a published study showing a reversal by lubiprostone of the morphine-induced inhibition of the human intestinal mucosal fluid secretion was submitted (Sun *et al*, 2011 Dig Dis Sci, 56: 330-338).

The Nonclinical Review had the following notable conclusions:

- In male mice, lubiprostone caused a dose dependent reversal of the oxycodone-induced decrease in propulsion of a graphite marker (significant at 100 µg/kg).
- Lubiprostone had no significant effect on methadone (a diphenylheptane opioid)-induced constipation in male mice, while lubiprostone, at a dose of 100 µg/kg, caused a significant reversal of the effect of morphine on the intestinal charcoal meal transit. Lubiprostone (100 µg/kg) caused a partial reversal (not significant) of the methadone or methadone plus morphine-induced reduction of the intestinal transit of the charcoal meal. The findings suggested to the nonclinical reviewer that lubiprostone may be more effective on morphine induced constipation than methadone-induced constipation. In T84 cells expressing hClC chloride channels, morphine (5 µM) had no effect on lubiprostone (250 nM)-induced short circuit current, while methadone (5 µM) caused an inhibition (88%) of the lubiprostone-stimulated short circuit current. Methadone also inhibited lubiprostone-stimulated Cl⁻ currents in HEK293 cells in a concentration-dependent manner, while morphine (5 µM) had no effect on this current. Other opioid agonists, such as oxycodone, oxymorphone and hydromorphone (at 5 µM) had no effects on lubiprostone-stimulated Cl⁻ currents in T84 cells. In addition to methadone, fentanyl and loperamide also caused an inhibition of the lubiprostone-stimulated Cl⁻ currents in T84 cells.
- Lubiprostone caused a reversal of the short circuit current (a marker for chloride secretion) in isolated segments of human jejunum, and this effect of lubiprostone was not blocked by tetrodotoxin, a blocker of enteric nerves, suggesting to the nonclinical reviewer that the effect of lubiprostone is not mediated via enteric neurons, and it acts directly by activating intestinal chloride channels.

Thus, the Nonclinical reviewer concluded that lubiprostone appears to be less effective in reversing the constipating effect of methadone than that of morphine in mice. In *in vitro* electrophysiology studies using T84 and HEK-29 cells, methadone was shown to cause an inhibition of lubiprostone-induced Cl⁻ currents, while morphine had no effect on this current.

The Nonclinical reviewer concluded that there is a possibility that methadone (or other diphenylheptane opioids) may reduce the effectiveness of lubiprostone.

In addition to methadone, fentanyl and loperamide also caused an inhibition of the lubiprostone-stimulated Cl currents in T84 cells. However, the clinical relevance of this is unclear as loperamide is used to treat diarrhea, which would not be expected to be used for a constipated patient. Interaction between fentanyl and lubiprostone is also unlikely to be clinically relevant as discussed in the Clinical Pharmacology summary (Section 5).

The nonclinical safety of lubiprostone has been established in previous *in vitro* and *in vivo* studies reviewed under earlier submissions. The pharmacology studies submitted in the current submission suggest that lubiprostone might be effective in improving altered gastrointestinal transit caused by certain opioids.

From a nonclinical perspective, the supplemental NDA application is considered approvable.

5. Clinical Pharmacology/Biopharmaceutics

The pharmacokinetics of Amitiza have been previously described and labeled.

There are no new Clinical Pharmacology studies in human subjects in this efficacy supplement. There were no dose-ranging or phase 2 trials in support of the OIC indication. A dose of 24 mcg BID has been evaluated in phase 3 trials of OIC, chosen based on its efficacy and approval for chronic idiopathic constipation (CIC).

However Clinical Pharmacology reviewed the same *in vitro* pharmacology study that evaluated the interaction potential of methadone and lubiprostone as described in the NonClinical review (Section 4). In addition, the proposed revisions to the Amitiza labeling under this sNDA, including those pertaining to the new mechanistic drug-drug interaction information with methadone, have been reviewed by Clinical Pharmacology and recommendations proposed.

The Clinical Pharmacology reviewer makes the following comments regarding the interaction between lubiprostone and methadone:

- “In vitro data suggests that the efficacy of lubiprostone could be lower in presence of methadone-type opioids (diphenylheptanes). Depending on the strength of clinical evidence from the submitted OIC clinical trials (methadone users vs. non-users), the in vitro data may support labeling language under ‘limitations of use’. If clinical efficacy was not perceived to be compromised due to concomitant methadone usage in the clinical trial data, then appropriate language could be included in the precautions and/or drug-drug interactions sections of the label. We defer the final language to the clinical review team of this NDA.”
- “The clinical relevance and rationale for the drug concentrations evaluated in these in vitro investigations is not fully understood but is addressed here briefly:
 - The observed IC₅₀ (half-maximal inhibition of lubiprostone-activated ClC₂ currents by methadone) is ~ 100 nM; concentrations of methadone up to 5 μM

were evaluated *in vitro* and produced significant (concentration-dependent) inhibition of lubiprostone-induced Cl⁻ channel currents, with 90% inhibition noted at 5 μ M concentration of methadone in the T84 cell line.

- Per Dolophine label (oral methadone), the dose for management of pain is individualized but generally the usual starting dose in opioid non-tolerant patients is 2.5 to 10 mg every 8 to 12 hours, slowly titrated to effect. Peak (C_{max}) concentrations of methadone following a 10 mg oral dose are noted to be ~124 ng/mL (~ 358 nM) and steady-state concentrations at this dose were ~ 65 ng/mL (~ 187 nM).”
- “Thus the IC₅₀ values for methadone noted in the various *in vitro* cell lines appear within the concentrations achievable following clinically relevant dose of methadone. Whether this interaction with methadone that was noted *in vitro*, actually translates into reduced efficacy of lubiprostone in the clinical setting could only be determined by evaluation of the available clinical evidence in this regard.”

Other Drug Interactions

No *in vivo* drug–drug interaction studies have been performed with Amitiza.

The Clinical Pharmacology reviewer provides the following general comments regarding the potential for DDIs with lubiprostone:

- Based upon the results of *in vitro* human microsome studies, there is low likelihood of CYP450 enzyme-mediated pharmacokinetic drug–drug interactions. *In vitro* studies using human liver microsomes indicate that cytochrome P450 isoenzymes are not involved in the metabolism of lubiprostone. Further *in vitro* studies indicate microsomal carbonyl reductase may be involved in the extensive biotransformation of lubiprostone to the metabolite M3.
- Additionally, *in vitro* studies in human liver microsomes demonstrate that lubiprostone does not inhibit cytochrome P450 isoforms 3A4, 2D6, 1A2, 2A6, 2B6, 2C9, 2C19, or 2E1, and *in vitro* studies of primary cultures of human hepatocytes show no induction of cytochrome P450 isoforms 1A2, 2B6, 2C9, and 3A4 by lubiprostone. Based on the available information, no protein binding–mediated drug interactions of clinical significance are anticipated.

The potential interaction between lubiprostone and fentanyl (based on *in vitro* data) noted in the Nonclinical review, was not addressed in the Clinical Pharmacology review. However as noted separately by the Clinical Pharmacologist, the half maximal inhibitory concentration (IC₅₀) with fentanyl (3 μ M) would translate into clinical exposures (C_{max}) many orders of magnitude higher than that expected by fentanyl (i.e., via transderm patch), which is to make any interaction clinically irrelevant.

Potential for interactions between loperamide and fentanyl are therefore not included in the label.

6. Clinical / Statistical: Efficacy

Refer to the Clinical Review by Dr. Farrokh Sohrabi for detailed discussion and analysis of the efficacy data submitted to this sNDA.

The Sponsor submitted data from three double-blind, placebo-controlled, 12-week clinical trials to this sNDA. Since one of the trials (OBD-0632) failed to demonstrate efficacy, evidence for the efficacy of lubiprostone comes from two phase 3 trials, OBD-1033 and OBD-0631. Within each of the three efficacy trials, subjects were randomized in a 1:1 ratio to receive either placebo or lubiprostone (24 mcg BID) for 12 weeks.

OBD-0631 and OBD-0632 were identically designed, multi-center, double-blind, placebo-controlled trials whose primary objective was to evaluate the efficacy and safety of lubiprostone for treatment of OIC in adults with chronic non-cancer pain. The primary efficacy endpoint for trial OBD-0631 and OBD-0632 was change from baseline in SBM frequency at Week 8 in subjects without dose reduction.

OBD-1033 was a multi-center, parallel group, double-blind, placebo-controlled trial whose primary objective was to evaluate the efficacy and safety of lubiprostone for its proposed indication, treatment of OIC in adults with chronic non-cancer pain. The primary efficacy endpoint for trial OBD-1033 was the overall SBM responder rate in ITT subjects.

Subjects eligible to participate in these 3 trials were those ≥ 18 years of age who had been treated for chronic, noncancer-related pain with opioids for ≥ 30 days prior to screening, diagnosed with OIC, capable of utilizing an eDiary to report their daily SBMs, and willing to continue opioid therapy and discontinue the use of laxatives, stool softeners, and other concomitant medications affecting gastrointestinal motility throughout the trial. The Sponsor defined an SBM as any BM that did not occur within 24 hours after rescue laxative use. OIC was defined as an average of < 3 SBMs/week and at least one of the following for $\geq 25\%$ of SBMs during each week of the screening period: (1) hard/very hard stools; (2) sensation of incomplete evacuation; and/or (3) moderate to very severe straining associated with SBMs.

The major difference between Study 1033 and 0631/0632 was that Study 1033 excluded subjects who were taking methadone (or a congener of methadone) from enrollment. A dose reduction may have been initiated by the investigator if severe nausea, severe diarrhea, or another adverse event (AE) was reported by the subject to the site and was ongoing for ≥ 3 days. Unlike OBD-1033, which permitted use of rescue laxatives beyond 72 hours following treatment initiation, in trials OBD-0631 and OBD-0632, the use of rescue laxatives was not permitted during the first week following treatment initiation.

As discussed in Dr. Sohrabi's review, at the beginning of the 3-week screening period, laxatives and other prohibited concomitant medications were stopped and recording of daily bowel habits begun via electronic diary (eDiary). For efficacy analyses, the baseline period was 14 days prior to the first dose of study drug and was used to determine disease status and other demographic factors at baseline. Constipation status at baseline was defined based on the average of diary entries for the 14 days prior to the administration of the first drug dose.

Dr. Sohrabi notes that allowing usual use of laxatives as needed while concurrently receiving lubiprostone during a clinical trial might confound efficacy assessment. In addition he notes that the discontinuation of subjects' usual laxative regimen at the onset of the screening period has the potential to create a situation that does not accurately capture each subject's true baseline constipation status.

Dr. Sohrabi notes in his review that the relatively large number of screen failures could be attributed to potential subjects not meeting the criteria for OIC during screening.

The patient populations used for analyses of the three efficacy trials were as follows:

- Safety-evaluable population: All randomized subjects who took at least one dose of study medication were in the safety population and included in safety analysis.
- Intent-to-treat (ITT) population: All randomized subjects who took at least one dose of study medication and had at least one treatment-period diary entry.
- Modified intent-to-treat (mITT) population: This population was defined only for OBD-1033. Routine monitoring and subsequent audit of data collected at Sites 3019 and 3119 led the Sponsor to question the suitability of the data. As a result, a mITT population was used that excluded data from Sites 3019 and 3119. (See Section 10, OSI Inspections, for more information)
- Per-protocol population: ITT subjects who were randomized and met the detailed inclusion and exclusion criteria
- Completer population: Subjects who completed the treatment regimen through Week 12; this population was used for supportive analyses.

Discontinuation rate across the three studies was ~28% with the most common reasons being adverse events, patient choice and lost to follow-up. Refer to Dr. Sohrabi's clinical review for a detailed account of subject disposition across the three trials. In his review, he notes that the overall dropout rates, although higher in OBD-0631 and OBD-0632 than in OBD-1033, were comparable to what the Sponsor had anticipated in the SAP for each trial. In Dr. Sohrabi's assessment, there were no clinically important differences in subject disposition between the two arms of any of the three efficacy trials that would be expected to drive efficacy in favor of lubiprostone subjects. With respect to protocol violations, Dr. Sohrabi notes that the number of violations was generally balanced across the treatment arms within each trial, with a few exceptions.

The average age of subjects across these 3 trials was approximately 50 years old and they were predominantly female (63%). As noted by Dr. Sohrabi, the trials did not directly capture medical conditions associated with opioid use and therefore there was no clear delineation of a primary pain condition for which subjects were on chronic opioids. That being said, back pain was present in approximately 48% of all subjects enrolled and was the most common condition observed that is typically associated with opioid analgesia. The median duration of opioid use across the 3 trials as estimated by this reviewer was approximately 33 months (mean ~53 months). The combined Morphine Equivalent Daily Dose (MEDD) at baseline across the 3 trials was ~244mg (median MEDD was much less). As noted by Dr. Sohrabi, the MEDD was higher in subjects on methadone (or congeners of methadone) than subjects not on

methadone (or congeners of methadone) in the placebo and lubiprostone arms of both trials (OBD-0631 and OBD-0632). Other than methadone, the types/classes of opioids used were similar across the 3 trials.

Baseline constipation status summary data is presented in Table 1.

Table 1. Constipation Status at Baseline: OBD-1033, OBD-0631, and OBD-0632 (ITT Population)

Variable	OBD-1033		OBD-0631		OBD-0632	
	Placebo	LBP	Placebo	LBP	Placebo	LBP
BM Frequency per Week,¹ N	220	219	216	219	212	222
Mean ± Standard Deviation	1.9 ± 0.91	1.9 ± 1.03	2.4 ± 1.39	2.4 ± 1.54	2.7 ± 1.73	2.8 ± 1.82
SBM Frequency per Week,² N	220	219	216	221	212	222
Mean ± Standard Deviation	1.4 ± 0.81	1.3 ± 0.81	1.5 ± 0.96	1.4 ± 1.1	1.6 ± 1.30	1.6 ± 1.34
Complete SBM Frequency per Week,³ N	220	219	216	219	212	222
Mean ± Standard Deviation	0.3 ± 0.59	0.3 ± 0.56	0.4 ± 0.59	0.4 ± 0.70	0.5 ± 0.80	0.3 ± 0.66
Using Rescue Laxatives at Baseline, N	220	219	217	222	213	224
Yes, n (%)	111 (50.5)	110 (50.2)	133 (61.3)	132 (59.5)	132 (62.3)	142 (63.4)

Abbreviations: LBP, lubiprostone

¹Number of bowel movements (BMs) per week at baseline was calculated as follows: (Number of reported BMs / Number of observed hours) x 168 hours.

² An SBM was defined as any BM that did not occur within 24 hours after use of a rescue laxative.

³ Completeness of a BM or SBM was determined based on the following question in the daily eDiary: "Did your bowels feel completely empty after the BM? Y/N."

Source: Adapted from Dr. Sohrabi's clinical review

Primary Efficacy Evaluation

Trial OBD-1033

The primary efficacy endpoint for OBD-1033 was the overall SBM response rate in ITT subjects (All randomized subjects who took at least one dose of study medication and had at least one treatment-period diary entry). An overall SBM responder was defined as a subject who had ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥ 3 SBMs per week for at least 9 of the 12 treatment weeks. The Sponsor considered subjects with < 9 weeks of weekly SBM rates as non-responders. With a week considered a 168-hour interval, if subjects had < 85 hours of observed data in a week, then the Sponsor considered the data insufficient and the rate missing for that week. Last observation carried forward (LOCF) was not used in the primary analysis.

As also discussed in Dr. Sohrabi's review, clinical site was included as a randomization stratification factor at baseline (with a pre-specified plan to pool sites with < 3 subjects per treatment group). Baseline weekly SBM frequency was also a stratification factor at randomization (SBMs < 0.6 , $0.6 \leq$ SBMs ≤ 2 , and $2 <$ SBMs < 3). In the original protocol, the Sponsor indicated that analyses would *not* be stratified by baseline SBM frequency. The Sponsor amended the protocol on October 19, 2010, indicating that analyses *would* be stratified by baseline SBM frequency. However, in a second amendment to the protocol on June 13, 2011, the Sponsor again revised the protocol, indicating that analyses *would not* be stratified by baseline SBM frequency. The Sponsor did not provide an

explanation for this change to the protocol. As Dr. Sohrabi points out in his review, in all versions of the SAP for OBD-1033, the Sponsor indicated that analyses would not additionally be stratified by baseline SBM frequency (only by site); therefore the proposed protocol revisions do not appear to ever have been incorporated into the SAP.

Table 2. Primary Analysis of Overall SBM Response in OBD-1033 (ITT Population)

Overall SBM Response ¹	Placebo (N=220) n (%)	Lubiprostone (N=219) n (%)	Difference (95%CI)	P-Value ²
Responder	41 (18.6%)	59 (26.9%)	8.3% (0.49, 16.1)	0.035

Abbreviations: CI, confidence interval.

¹Overall SBM response defined as ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥ 3 SBMs per week for at least 9 of the 12 treatment weeks.

²P-values for overall response rates comparing treatment groups were analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by pooled site.

Source: Clinical reviewer's table, modified from Sponsor's Table 2.7.3.3-8, page 39 of 119, Summary of Clinical Efficacy and Table 1.2.1.4, page 30, response to IR6.

As Dr. Sohrabi points out in his review, comparing the treatment effect for lubiprostone to other approved drugs is limited given that there are no other drugs approved for the treatment of OIC in adults with chronic non-cancer pain. He does however point out that for lubiprostone in IBS-C, the treatment difference favoring lubiprostone over placebo in two 12-week efficacy trials was ~6% (although responder definitions were different for the IBS-C population than the OIC population). For lubiprostone in CIC, a responder definition was not used for the primary endpoint, making comparisons of treatment differences across indications impractical – a similar problem comparing lubiprostone to methylnaltrexone. Dr. Sohrabi also notes that linaclotide, recently approved for CIC and IBS-C, demonstrated a treatment difference of ~10% to 15% in the CIC population studied (albeit over a 12-week period, using overall complete SBM (CSBM) responders as the primary endpoint, rather than SBM responders). Dr. Sohrabi concludes that in his view, a treatment difference of 8% favoring lubiprostone represents a clinically meaningful treatment effect in adults with chronic non-cancer pain and OIC and offers another treatment option for OIC in this patient population.

Analyses of the primary endpoint for the other analysis populations is presented in Table 3.

Table 3. Supportive Analysis of Overall SBM Response in OBD-1033 (mITT, Completer and Per-Protocol Populations)

Overall SBM Response ¹ by Population	Placebo	Lubiprostone	P-Value ²
mITT	(N=212)	(N=212)	
Responder, n (%)	41 (19.3%)	58 (27.4%)	0.034
Completer	(N=184)	(N=169)	
Responder, n (%)	40 (21.7%)	55 (32.5%)	0.018
Per-Protocol	(N=179)	(N=177)	
Responder, n (%)	37 (20.7%)	53 (29.9%)	0.065

¹Overall SBM response defined as ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥ 3 SBMs per week for at least 9 of the 12 treatment weeks.

²P-values for overall response rates comparing treatment groups were analyzed using the CMH test stratified by pooled site.

Source: Clinical Reviewer's table, modified from Sponsor's Table 2.7.3.3-9, page 39 of 119 and Table 2.7.3.3-10, page 40 of 119, Summary of Clinical Efficacy; and Table IR12, Sponsor's response to IR12.

As presented in Table 3, the size of the treatment effect is similar across all study populations. The per-protocol population is non-significant which is likely due to a smaller sample size

rather than systematic bias, since as Dr. Solhrabi has demonstrated, protocol violations were generally balanced across both treatment arms.

Trial OBD-0631

The primary endpoint for OBD-0631 was the change from baseline in SBM frequency at Week 8 in ITT subjects who did not undergo dose reduction. As with trial OBD-1033, for a bowel movement to count as an SBM, the BM could not have occurred within 24 hours after use of a rescue laxative. Unlike OBD-1033, however, in which the Sponsor considered the rate for subjects with <85 hours of weekly data as missing for that week, in OBD-0631, if ≥ 25 but <85 hours were observed during a week and ≥ 85 hours were observed during the prior week, then the Sponsor imputed data from the prior week to provide a total of 85 hours of data. If subjects had <25 hours of observed data in a week, then the Sponsor considered the data insufficient and the rate missing for that week.

Dr. Solhrabi notes, different missing data handling procedures between trials OBD-1033 and OBD-0631 might complicate comparisons of findings between the trials. At the request of the clinical statistics review team, the Sponsor performed several exploratory analyses to investigate the impact of missing data on the results. As noted in the statistical review, missing data handling strategies and daily (vs. hourly) based weekly SBM frequency were also investigated, and the results were fairly consistent with those from the primary analyses.

Table 4 presents the primary analysis of Study OBD-0631

Table 4. Primary Analysis of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-0631 (ITT Population)

Variable ¹	Placebo (N=217)	Lubiprostone (N=221)	Difference (95% CI)	P-Value ²
Baseline Observed Value				
n	216	212		
Mean $\pm$ Standard Deviation	1.5 $\pm$ 0.96	1.4 $\pm$ 1.09		
Median (Minimum, Maximum)	1.5 (0, 7)	1.5 (0, 8)		
Week 8 Observed Value				
n	169	164		
Mean $\pm$ Standard Deviation	3.8 $\pm$ 3.24	4.5 $\pm$ 3.73		
Median (Minimum, Maximum)	3.0 (0, 17)	4.0 (0, 28)		
Change from Baseline at Week 8				
n	169	164		
Mean $\pm$ Standard Deviation	2.4 $\pm$ 3.25	3.2 $\pm$ 3.35	0.76 (0.06, 1.47)	0.019
Median (Minimum, Maximum)	1.4 (-3, 16)	2.7 (-2, 21)		

Abbreviations: CI, confidence interval.

¹Weekly SBM (BM) frequency rate: (168 x number of SBMs (BMs)/number of hours observed)

²P-value is based on the treatment effect from a van Elteren test stratified by pooled site.

Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups. Additionally, Shapiro-Wilk p-value testing for normality was performed by the Sponsor and p-value was <0.001. A small p-value (<0.05) indicates non-normality.

Source: Clinical Review, originally modified from Sponsor's Table 2.7.3.3-18, page 53 of 119, Summary of Clinical Efficacy; and Table 1.2.3.1.5, page 31, response to IR6.

As with the analyses of the primary endpoint in OBD-1033, the treatment difference was similar for the ITT, completer, and per-protocol populations in OBD-0631.

DGIEP requested the Sponsor perform a supportive analysis of the overall SBM response endpoint (as defined for OBD-1033) in OBD-0631 such that the outcomes could be compared to the results of Study OBD-1033. The result of this analysis are presented in Table 5.

Table 5. Supportive Analysis of Overall SBM Response in OBD-0631 (ITT Population)

Overall SBM Response ¹ by Population	Placebo (N=217) n (%)	Lubiprostone (N=221) n (%)	Difference (95% CI)	P-Value ²
Responder	32 (14.7%)	54 (24.4%)	9.7% (2.3, 17.1)	0.010

Abbreviation: CI, confidence interval

¹Overall SBM response defined as ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥ 3 SBMs per week for at least 9 of the 12 treatment weeks.

²P-value is for informational purposes only. P-values for overall response rates comparing treatment groups were analyzed using the CMH test stratified by pooled site.

Source: Clinical Review, modified from Table 1.2.1.4, page 30, response to IR6.

As noted by Dr. Sohrabi, this supportive analysis in OBD-0631 showed a treatment difference of approximately 10% favoring lubiprostone subjects and in his assessment provides evidence of efficacy that supports the findings of the primary analysis in OBD-1033.

Impact of Dose Reduction on the Results of OBD-631

In OBD-0631 (and OBD-1033) a protocol-specified dose reduction may have occurred if severe nausea, severe diarrhea, or another AE was reported by the subject and was ongoing for 3 or more days. However the primary analysis in OBD-631 was only in subjects who *did not undergo dose reduction* (this rule was not applied in OBD-1033). As noted in Dr. Sohrabi's review, there was concern that this handling could potentially discriminate against lubiprostone subjects who underwent dose reduction. In particular, if the reason for dose reduction was severe diarrhea, then inclusion of these subjects could have potentially driven the efficacy endpoint in favor of lubiprostone.

However, as presented in Table 6, when subjects who had a dose reduction are included in the primary analysis of OBD-631, the results are very similar to the original analysis that excluded such subjects.

Table 6. Change from Baseline in SBM Frequency at Week 8 in OBD-0631 (ITT, including subjects with dose reductions)

Change from Baseline in SBM Frequency at Week 8	OBD-0631		P-Value ¹
	Placebo (N=217)	Lubiprostone (N=221)	
All Subjects			
n	169	171	0.015
Mean ± Standard Dev	2.4 ± 3.25	3.2 ± 3.33	
Median (Min, Max)	1.4 (-3, 16)	2.6 (-2, 21)	

¹P-value based on treatment effect from van Elteren test stratified by pooled site. Italicized p-values for informational purposes.

Source: Clinical Reviewer, originally adapted from Sponsor's Table 1.3.1.2, module 5.3.5.3, page 823 to 834 of 2585, Integrated Summary of Efficacy; and Table 2.7.3.3-18, page 53 of 119, Summary of Clinical Efficacy.

Trial OBD-632

OBD-632 failed to demonstrate statistically significant differences between placebo and lubiprostone in the primary efficacy endpoint (mean change from baseline in SBM frequency at Week 8 in subjects without dose reduction) in the ITT population. Trials OBD-0631 and OBD-0632 were identical with respect to design, trial protocol, and SAP, and the primary efficacy endpoint for trial OBD-0632 was identical to that for OBD-0631.

Table 7 presents the results of the pre-specified primary analysis.

Table 7. Primary Analysis of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-0632 (ITT Population)

Variable ¹	Placebo (N=212)	Lubiprostone (N=223)	Difference (95% CI)	P-Value ²
Baseline Observed Value				
n	211	215		
Mean ± Standard Deviation	1.6 ± 1.30	1.6 ± 1.33		
Median (Minimum, Maximum)	1.5 (0, 8)	1.5 (0, 9)		
Week 8 Observed Value				
n	175	168		
Mean ± Standard Deviation	4.0 ± 3.28	4.1 ± 3.22		
Median (Minimum, Maximum)	3.0 (0, 21)	3.5 (0, 17)		
Change from Baseline at Week 8				
n	175	168	0.21 (-0.47, 0.90)	0.842
Mean ± Standard Deviation	2.4 ± 3.20	2.6 ± 3.26		
Median (Minimum, Maximum)	1.8 (-4, 21)	2.0 (-3, 16)		

¹Weekly SBM (BM) frequency rate: (168 x number of SBMs (BMs)/number of hours observed)

²P-value is based on the treatment effect from a van Elteren test stratified by pooled site.

Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups. Additionally, Shapiro-Wilk p-value testing for normality was performed by the Sponsor and p-value was <0.001. A small p-value (<0.05) indicates non-normality.

Source: Clinical Reviewer's table, modified from Sponsor's Table 2.7.3.3-18, page 53 of 119, Summary of Clinical Efficacy; and Table 1.2.3.1.5, page 31, response to IR6.

Given the *in vitro* interaction of methadone with lubiprostone, the Sponsor attributed the failure of OBD-0632 on the primary endpoint to the slightly higher percentage of methadone-treated subjects in OBD-0632 than OBD-0631 and the higher baseline MEDD of subjects in OBD-0632 than OBD-0631. Citing the interaction of methadone with the receptor target of

lubiprostone, the Sponsor stated that, “as nearly 20% of subjects in this trial used methadone, with an average MEDD of approximately 1000, there was a major impact of this interaction on study results.”

However as Dr. Sohrabi explains in his review, the percentage of subjects on a methadone is only slightly higher in the ITT population of OBD-0632 than OBD-0631. Further, the distribution of subjects on methadone is balanced across treatment arms for both the ITT and efficacy evaluable populations in OBD-0632. As Dr. Sohrabi also notes, even if there were a significant treatment interaction with methadone, the slightly higher percentage of methadone users in OBD-0632 compared to OBD-0631 would not adequately explain the failure of trial OBD-0632 on efficacy endpoints.

The Sponsor also argued that because methadone inhibited chloride channels in a dose-dependent manner in the nonclinical study and because subjects on methadone in OBD-0632 had a higher average MEDD than subjects on methadone in OBD-0631, methadone-treated subjects in OBD-0632 had a greater impact on reduction of lubiprostone efficacy in that trial than methadone-treated subjects in OBD-0631. However, as pointed out by Dr. Sohrabi in his review, the magnitude of the treatment difference favoring the lubiprostone group in OBD-0632 is smaller in the higher MEDD subgroup (1.8%) than the lower MEDD subgroup (4.4%), but this pattern is reversed in the results for OBD-0631, where the treatment effect is larger in the higher MEDD subgroup (14.7%) than the lower MEDD subgroup (8.6%). The lack of a consistent relationship between the MEDD and primary outcome made Dr. Sohrabi unable to agree with the Sponsor that the failure of trial OBD-0632 was due to the higher overall MEDD as well as the higher MEDD in the subgroup of diphenylheptane subjects in OBD-0632 as compared with OBD-0631.

Dr. Sohrabi’s detailed clinical review of factors that may have contributed to the failure of OBD-0632 did not find a single or consistent explanation for the trial’s failure. A detailed discussion of the elements reviewed and conclusions can be found in Appendix 4 of Dr. Sohrabi’s review (*see Discussion of Individual Trials: Trial SMR/0211 OBD-0632*).

Supportive Analyses of Primary Endpoints

Analysis of Efficacy Endpoints Using a “True” ITT Population

The Sponsor pre-specified the ITT population as all randomized subjects who had received at least one study treatment and *had at least one post-treatment diary entry*, but the statistical review team for this sNDA noted that a true ITT population should consist of all randomized subjects. This is consistent with the advice given to the sponsor by the FDA in previous correspondence.

The statistical review team asked the Sponsor to perform exploratory analyses of the overall SBM response endpoint using all randomized subjects for both OBD-1033 and OBD-0631. The Sponsor’s analysis results are in Table 8. As noted in Dr. Sohrabi’s review, the magnitude

of the treatment effect is consistent with the primary analysis of OBD-1033 using the Sponsor’s pre-specified definition of the ITT population and the supportive analysis of the overall SBM response endpoint in OBD-0631 using the Sponsor’s definition of the ITT population.

Table 8. Overall SBM Response in OBD-1033 and OBD-0631 (True ITT Population¹)

Overall SBM Response ²	OBD-1033				OBD-0631			
	Placebo (N=226)	Lubiprostone (N=221)	Difference (95% CI)	P-value ³	Placebo (N=220)	Lubiprostone (N=223)	Difference (95% CI)	P-value ³
Responder, n (%)	41 (18.1)	59 (26.7)	8.6 (0.8, 16.3)	0.035	32 (14.5)	54 (24.2)	9.7 (2.3, 17)	0.011

¹True ITT population includes all randomized subjects. Of the 443 subjects randomized in trial OBD-0631, 4 subjects were excluded from the Sponsor’s ITT population due to being randomized but never dosed (3 placebo and 1 lubiprostone). One lubiprostone subject was randomized but had no post-baseline data. Of the 447 subjects randomized in trial OBD-1033, 8 subjects (6 placebo and 2 lubiprostone) were excluded from the Sponsor’s ITT population due to not taking any doses of study medication.

²Overall SBM response defined as ≥1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥3 SBMs per week for at least 9 of the 12 treatment weeks.

³P-value is based on the treatment effect from CMH stratified by pooled site. P-values are for informational purposes only.

Source: Clinical Review, originally taken from Sponsor’s Table E4.1.3.0, page 29, response to IR6. Confidence intervals from Dr. Freda Cooner.

See the statistical review and further discussion below for more detail on analyses using the “true” ITT population.

Durability of Response over Treatment Period

Table 9 presents the change from baseline in SBM frequency by week for both OBD-1033 and OBD-0631.

Table 9. Change from Baseline in SBM Frequency by Week - OBD-1033 and OBD-0631 (ITT)

Time Point	Change from Baseline in SBM Frequency by Week	OBD-1033		OBD-0631	
		Placebo (N=220)	Lubiprostone (N=219)	Placebo (N=217)	Lubiprostone (N=221)
	Baseline (Mean ± Standard Dev)	1.4 ± 0.81	1.3 ± 0.81	1.5 ± 0.96	1.4 ± 1.09
Week 1	n	217	212	211	214
	Mean ± Standard Dev	1.8 ± 2.45	3.1 ± 4.11	1.8 ± 2.41	2.6 ± 3.10
Week 2	n	215	206	213	210
	Mean ± Standard Dev	2.3 ± 2.73	3.0 ± 3.78	1.8 ± 2.71	2.4 ± 2.97
Week 3	n	206	200	200	204
	Mean ± Standard Dev	2.2 ± 2.94	2.8 ± 3.22	2.1 ± 2.96	2.5 ± 2.90
Week 4	n	205	195	196	193
	Mean ± Standard Dev	2.3 ± 3.07	3.3 ± 3.46	2.0 ± 2.91	2.9 ± 3.16
Week 5	n	193	190	191	184
	Mean ± Standard Dev	2.2 ± 3.08	3.1 ± 3.35	2.3 ± 3.32	3.1 ± 3.33
Week 6	n	191	190	179	180
	Mean ± Standard Dev	2.6 ± 3.16	3.0 ± 3.30	2.4 ± 3.12	3.0 ± 3.51
Week 7	n	190	186	168	173
	Mean ± Standard Dev	2.6 ± 2.98	3.2 ± 3.20	2.4 ± 3.10	2.7 ± 3.02
Week 8	n	185	178	169	171
	Mean ± Standard Dev	2.5 ± 3.07	3.1 ± 3.50	2.4 ± 3.25	3.2 ± 3.33
Week 9	n	184	173	166	168
	Mean ± Standard Dev	2.5 ± 3.11	3.3 ± 3.52	2.3 ± 3.13	3.2 ± 3.49
Week 10	n	180	166	163	163
	Mean ± Standard Dev	2.7 ± 3.15	3.2 ± 3.36	2.4 ± 3.33	3.3 ± 3.36
Week 11	n	181	166	162	158
	Mean ± Standard Dev	2.5 ± 2.95	3.1 ± 3.20	2.5 ± 2.94	3.1 ± 3.22
Week 12 [†]	n	180	159	150	150
	Mean ± Standard Dev	2.7 ± 3.34	3.1 ± 3.13	2.5 ± 3.28	3.3 ± 3.69

[†]The change from baseline in SBM frequency at Week 12 was a secondary efficacy endpoint for trials OBD-1033 and OBD-0631.

Source: Clinical Reviewer's table, originally adapted from Sponsor's Table 1.3.1.2, module 5.3.5.3, pages 823-834, Integrated Summary of Efficacy.

The results in Table 9 contrast with an analysis of weekly responders, defined as subjects with ≥ 1 additional SBM compared to baseline during a given week and ≥ 3 SBMs during that given week. The Sponsor evaluated this secondary endpoint using both LOCF analysis and non-LOCF analysis. Table 10 presents the results with non-LOCF analysis for the ITT population.

Table 10. Weekly SBM Response – Trial OBD-1033 (ITT Population, Non-LOCF Analysis)

Time Point	Responder Status ¹	Placebo (N=220)	Lubiprostone (N=219)
Week 1	n	217	212
	Responder, n (%)	107 (48.6)	128 (58.4)
Week 2	n	215	206
	Responder, n (%)	115 (52.3)	123 (56.2)
Week 3	n	206	200
	Responder, n (%)	104 (47.3)	115 (52.5)
Week 4	n	205	195
	Responder, n (%)	104 (47.3)	128 (58.4)
Week 5	n	193	190
	Responder, n (%)	109 (49.5)	123 (56.2)
Week 6	n	191	190
	Responder, n (%)	111 (50.5)	117 (53.4)
Week 7	n	190	186
	Responder, n (%)	111 (50.5)	121 (55.3)
Week 8	n	185	178
	Responder, n (%)	110 (50.0)	108 (49.3)
Week 9	n	184	173
	Responder, n (%)	108 (49.1)	113 (51.6)
Week 10	n	180	166
	Responder, n (%)	115 (52.3)	108 (49.3)
Week 11	n	181	166
	Responder, n (%)	102 (46.4)	104 (47.5)
Week 12	n	180	159
	Responder, n (%)	103 (46.8)	99 (45.2)

¹Weekly SBM responders have ≥ 1 additional SBM compared with baseline during the given week and ≥ 3 SBMs during the week.

Source: Clinical Reviewer's table, originally modified from Sponsor's Table 2.7.3.3-32, pages 75 to 76 of 119, Summary of Clinical Efficacy.

As noted in Dr. Sohrabi's clinical review, a weekly responder rate analysis does not evaluate efficacy on a continuous basis over a 12-week period, a consideration which he believes is important when evaluating efficacy for a chronic condition such as OIC. He also notes that patient dropouts and discontinuations increased as the trial progressed, and may have influenced the weekly responder rates in the last few weeks of the trial. More importantly, evidence of a persistence of effect of lubiprostone was suggested by other exploratory analyses.

See Section 6.1.9, *Discussion of Persistence of Efficacy and/or Tolerance Effects*, of Dr. Sohrabi's clinical review for a detailed analysis of durability of response. As noted in his review, given the preponderance of secondary and exploratory analyses favoring lubiprostone over placebo at later time points in the double-blind trials, Dr. Sohrabi's concluded that lubiprostone 24 mcg BID demonstrated persistence of effect over 12 weeks in the OIC population.

Other Explorations of Lubiprostone's Effect on SBM Frequency

As noted by Dr. Sohrabi, exploratory analyses were performed to determine whether lubiprostone increases SBM frequency by increasing the number of days per week in which treated subjects have SBMs or by increasing the number of SBMs subjects have each day.

The Sponsor performed an exploratory analysis of individual days per week with ≥ 1 SBM in OBD-1033. Results are summarized in Table 11.

Table 11. Summary of Individual Days per Week with at Least One SBM in OBD-1033 (ITT)

Time Point	Statistic ¹	Placebo (N=220)	Lubiprostone (N=219)
Week 1	n	195	199
	Mean $\pm$ Standard Deviation	2.9 $\pm$ 1.51	3.3 $\pm$ 1.65
Week 2	n	194	185
	Mean $\pm$ Standard Deviation	3.2 $\pm$ 1.59	3.4 $\pm$ 1.76
Week 3	n	183	180
	Mean $\pm$ Standard Deviation	3.0 $\pm$ 1.67	3.3 $\pm$ 1.78
Week 4	n	177	184
	Mean $\pm$ Standard Deviation	3.3 $\pm$ 1.67	3.5 $\pm$ 1.78
Week 5	n	163	176
	Mean $\pm$ Standard Deviation	3.3 $\pm$ 1.68	3.5 $\pm$ 1.80
Week 6	n	172	172
	Mean $\pm$ Standard Deviation	3.4 $\pm$ 1.79	3.5 $\pm$ 1.74
Week 7	n	171	170
	Mean $\pm$ Standard Deviation	3.4 $\pm$ 1.77	3.6 $\pm$ 1.80
Week 8	n	159	164
	Mean $\pm$ Standard Deviation	3.5 $\pm$ 1.79	3.4 $\pm$ 1.82
Week 9	n	168	161
	Mean $\pm$ Standard Deviation	3.4 $\pm$ 1.81	3.6 $\pm$ 1.92
Week 10	n	160	154
	Mean $\pm$ Standard Deviation	3.6 $\pm$ 1.76	3.5 $\pm$ 1.78
Week 11	n	167	152
	Mean $\pm$ Standard Deviation	3.4 $\pm$ 1.73	3.6 $\pm$ 1.93
Week 12	n	161	139
	Mean $\pm$ Standard Deviation	3.4 $\pm$ 1.79	3.6 $\pm$ 1.84

¹The median (minimum, maximum) statistic was 3.0 (1, 7) at each time point for both treatment arms.
Source: Clinical Reviewer's table, adapted from Sponsor's Table 1.14.22, module 5.3.5.3, page 2566-2568, Integrated Summary of Efficacy.

These findings suggest that subjects in both treatment arms were having, on average, SBMs between 3 and 4 days out of each 7-day week throughout the trial. As noted by Dr. Sohrabi in his review, these results do not show an appreciable increase in the mean *number of days* per week in which lubiprostone subjects were having ≥ 1 SBM as compared with placebo subjects and that it appears that lubiprostone's effect on OIC involves increasing the *number of SBMs per day* on average rather than increasing the number of days per week in which subjects are having ≥ 1 SBM.

Sub-Populations

Dr. Sohrabi did not conclude that the efficacy of lubiprostone is different in males than females. As he notes in his review, his findings are congruent with findings of analyses by gender for previously approved indications of lubiprostone.

Because subjects aged ≥ 65 years comprised only about 10% of the total population in trials OBD-1033 and OBD-0631, Dr. Sohrabi contends that the trials did not include sufficient numbers of subjects aged ≥ 65 years to determine whether they respond differently from younger subjects.

Overall, Dr. Sohrabi did not find a clear trend toward a larger treatment difference in non-white subjects than white subjects and he noted that his findings are congruent with findings of analyses by race for previously approved indications of lubiprostone.

Evaluation of Secondary and Other Proposed Claims

Table 12 summarizes the protocol-specific primary and secondary endpoints.

Table 12. Protocol-Specific Primary and Secondary Efficacy Endpoints

Classification	Endpoint	Study Number		
		OBD-1033	OBD-0631	OBD-0632
Primary	Overall SBM response rate ^{1,2}	X	--	--
	Change from baseline in SBM ¹ frequency at Week 8 for subjects with no dose reductions	--	X	X
Secondary	Change from baseline in SBM frequency at:			
	Week 8	X	--	--
	Week 12	X	X	X
	Overall	X	X	X
	Percentage of subjects with first postdose SBM ¹ within 24 hours after first dose	X	X	X
	Percentage of subjects with first postdose SBM ¹ within 48 hours after first dose	X	X	X
	Weekly responder rates ³	X	--	--
	Overall responder rates ^{3,4}	--	X	X
	Health-related quality of life	X	--	--
	Overall mean change from baseline in:			
	Straining associated with SBMs ¹	X	X	X
	Stool consistency of SBMs ¹	X	X	X
	Constipation severity	X	X	X
	Abdominal bloating	X	X	X
	Abdominal discomfort	X	X	X
Bowel habit regularity	X	X	X	
Overall treatment effectiveness	X	X	X	

¹ A spontaneous bowel movement (SBM) was defined as any bowel movement that did not occur within 24 hours after use of a rescue medication.

² To be classified as an overall responder, subjects were required to demonstrate at least a moderate response (≥ 1 SBM improvement over baseline SBM frequency) for all treatment weeks for which observed data were available and to demonstrate a full response (≥ 3 SBMs per week) for at least 9 of the 12 treatment weeks.

³ Subjects were classified as full responders, moderate responders, or non-responders based on weekly SBM frequencies. A full responder was defined as a subject whose SBM frequency was ≥ 4 for the week; and a moderate responder had a SBM frequency of ≥ 3 but < 4 . A non-responder had < 3 SBM frequencies for the week, dropped out during or before the given week due to lack of efficacy, or used rescue medication during or within 24 hours prior to the given week.

⁴ An overall responder was in the study for at least 8 weeks and achieved at least moderate response for at least 50% of the weeks on the study.

Source: SEALD review

See the previous section for discussion on primary endpoints and relevant supportive analyses. Refer to the primary reviews for detailed discussion of these endpoints.

It’s important to note that in OBD-631 inferential analysis was only to be performed if the analysis of the primary endpoint yielded a p-value < 0.05 , but there was no specified hierarchy of evaluation for these secondary endpoints.

Similarly, in OBD-1033 no hierarchy of evaluation was pre-specified, i.e., no secondary efficacy endpoints were pre-specified as key secondary endpoints, from which results of analysis would then be used to determine a stepwise hierarchy for evaluation of other secondary endpoints.

As noted by the SEALD Endpoint reviewer, “The analyses of the OIC symptom data is confounded by the fact that there was no adjustment for multiplicity in secondary endpoint statistical analyses which can inflate the probability of a Type I error.”

Bowel Function Parameters

As pre-specified secondary endpoints in all 3 trials, the Sponsor assessed overall changes from baseline in the following bowel function parameters: (1) straining; (2) stool consistency of SBMs; (3) constipation severity; (4) abdominal bloating; and (5) abdominal discomfort. (b) (4)



Study Endpoints and Labeling Development (SEALD) provided a review as a response to a request for consultation by DGIEP to review the secondary endpoints of individual signs and symptoms of OIC (b) (4)



Although statistically significant improvements relative to placebo in several OIC symptoms were observed in the Amitiza treated subjects in all three trials, SEALD concluded that it is unclear if these changes are clinically meaningful, because an *a priori* method of interpreting a treatment benefit (e.g., a responder definition) was not provided. SEALD also noted that the analyses of the OIC symptom data are confounded by the fact that there was no adjustment for multiplicity in secondary endpoint statistical analyses which can inflate the probability of a Type I error.

SEALD also makes the following comment in their review:

“For the two clinical trials in which a statistically significant improvement in the primary endpoint (Study OBD-0631: mean change from baseline in the frequency of SBMs at Week 8 in the subjects without dose reductions; and Study OBD-1033: overall SBM response rate) was observed in patients treated with lubiprostone compared with patients treated with placebo, a statistical improvement was also seen in straining, stool consistency, and constipation severity; but not in the other symptom endpoints (e.g., abdominal bloating or abdominal discomfort). The clinical protocols did not prespecify which secondary endpoints would show a statistical significance. In addition, information has not been provided concerning the interpretation of results (e.g., clinically meaningful change in score or responder). Therefore, the applicant has not justified how a statistical improvement equates with a clinically significant improvement or that that a statistically significant improvement in a few but not all

measured symptoms represents a clinically meaningful change in the overall condition for the patient.”

(b) (4)

Impact on Analgesic Effects of Opioids

(b) (4)

(b) (4)

The DAAAP consult focused on the findings of the Brief Pain Inventory-Short Form (BPISF) and the Morphine Equivalent Daily Dose (MEDD) change in opioid use to address DGIEP’s questions for DAAAP input. DAAAP reviewers also searched the submission for AEs which may have suggested increased or uncontrolled pain.

The BPI-SF is a patient-reported outcome measure that assesses the severity of pain and the impact of pain on daily functions. It has two domains: pain severity and pain interference. “Worst” pain is included in the pain severity domain. As noted by DAAAP, the Applicant modified the BPI-SF so that only the multiple-choice questions about pain were answered at baseline and at the end of each treatment month.

The DAAAP reviewers note that in studies of analgesics, the most meaningful endpoint and that which is typically used as a primary endpoint in studies is either worst pain or average pain. Pain interference and pain severity are not used to assess analgesia *per se*, as they are comprised of multiple domains in addition to pain. Therefore, DAAAP’s review focused on the results regarding “worst pain.”

DAAAP’s responded to DGIEP’s question with the following comments and recommendations:

- The effects of Amitiza on analgesia were not assessed adequately during the phase 3 clinical trials due to the following:
 - Collecting pain scores on a monthly basis is much too infrequent to adequately assess change in pain. In order to analyze the data, it would be useful to have at least weekly pain assessments.
 - Although opioid dosages were collected daily in the eDiaries, the data was presented as monthly MEDD. It is not possible to assess opioid usage as it relates to pain assessments using such infrequent intervals. Opioid usage may vary day to day based on changes in the patient’s pain, and these changes may

relate to the effect of lubiprostone on the analgesic efficacy of the opioids. Therefore, the MEDD must be analyzed by the Applicant at more frequent intervals, at least weekly, in order to provide meaningful results that can be interpreted in regards to MEDD and analgesia.

- Patients whose pain was not adequately controlled may have used additional non-opioid analgesic rescue which may confound the interpretation of MEDD usage. This was not analyzed by the Sponsor.

- [Redacted text block with (b) (4) label]

[Redacted text block with (b) (4) label]

[Redacted text block]

[Redacted text block]

Statistical Analyses and Concerns

See the statistical review by Freda Cooner, Ph.D. for a detailed discussion of her findings.

Dr. Cooner raised concerns with the sponsor-defined intent-to-treat (ITT) population for the primary analysis for all three studies since it was based on all randomized subjects who took at least one dose of double-blinded study medication *and had at least one treatment-period diary entry*. She notes that basing analysis on a post-randomization event does not preserve the randomization, and since the event is treatment related, the subgrouping is further invalidated.

Dr. Cooner presents the study results for all three trials using efficacy endpoints, overall SBM response rate and change of from baseline in SBM frequency at Week 8, in the all randomized subjects population (what she describes as the true ITT population). However, she states in her review that the results from the post-hoc analyses on the non-pre-specified efficacy endpoints (overall 12-week SBM response rate for Studies OBD-0631 and OBD-632, and change from baseline in SBM frequency at Week 8 for Study OBD-1033) should be viewed with caution.

For the efficacy endpoint of overall SBM response rate (All Randomized Subjects), the results are presented in Table 13. Note that only Study OBD-1033 pre-specified this endpoint as primary (shaded column). For this study, the results showed a statistically significant difference favoring lubiprostone over placebo using a significance level of 5% based on a CMH test stratified by pooled site. The lubiprostone group also showed benefit over placebo group on this efficacy endpoint for Study OBD-0631, but not for Study OBD-0632.

Table 13. Analysis of Overall SBM Response (All Randomized Subjects)

Study	OBD-1033		OBD-0631		OBD-0632	
	Placebo	Lubiprostone	Placebo	Lubiprostone	Placebo	Lubiprostone
N	226	221	220	223	216	235
Responder, n (%)	41 (18.1%)	59 (26.7%)	32 (14.5%)	54 (24.2%)	28 (13.0%)	36 (15.3%)
Non-responder, n (%)	185 (81.9%)	162 (73.3%)	188 (85.5%)	169 (75.8%)	188 (87.0%)	199 (84.7%)
Difference, %	8.6%		9.7%		2.3%	
95% CI^a, %	(0.9%, 16.3%)		(2.4%, 17.0%)		(-4.1%, 8.8%)	
P-value^b	0.030		0.004		0.479	

a: CI = Confidence Interval; CI based on normal approximation

b: Based on a CMH test stratified by pooled site

Source: Statistical Review, Table 3.1

For the efficacy endpoint of change from baseline in SBM frequency at Week 8, the results are presented in Table 14. This was the primary efficacy endpoint for Studies OBD-0631 and OBD-0632 only (shaded columns).

Table 14. Analysis of Change from Baseline in SBM Frequency at Week 8 (All Randomized Subjects)

Study	OBD-1033		OBD-0631		OBD-0632	
	Placebo	Lubiprostone	Placebo	Lubiprostone	Placebo	Lubiprostone
N	226	221	220	223	216	235
Baseline						
n	217	212	216	218	209	217
Mean (SD ^a)	1.42 (0.81)	1.25 (0.77)	1.46 (0.96)	1.42 (1.09)	1.59 (1.30)	1.56 (1.30)
Week 8						
n	179	173	169	171	176	174
Mean (SD)	4.06 (3.14)	4.43 (3.54)	3.81 (3.24)	4.56 (3.69)	3.97 (3.28)	4.17 (3.26)
Change from Baseline at Week 8						
n	179	173	169	171	176	174
Mean (SD)	2.58 (3.08)	3.14 (3.54)	2.39 (3.25)	3.17 (3.33)	2.46 (3.21)	2.71 (3.27)
Difference (SE ^b)	0.56 (0.35)		0.78 (0.36)		0.25 (0.35)	
95% CI ^c	(-0.13, 1.26)		(0.08, 1.48)		(-0.43, 0.93)	
P-value ^d	0.163		0.024		0.497	

a: SD = Standard Deviation

b: SE = Standard Error

c: CI = Confidence Interval

d: Based on ANCOVA model with baseline value as covariate and stratified by pooled site

Source: Statistical review, Table 3.2

Dr. Cooner also performed analyses in which she removed the problematic sites discussed elsewhere in this review (see Section 10, *OSI Inspections*). As she concludes, excluding the data from the 11 subjects randomized at Site 3019 and the 6 subjects randomized at Site 3119 did not cause notable difference in the treatment effect estimates or alter the conclusion for Study OBD-1033. Excluding the data from the 25 subjects randomized at Site 1069 did not cause notable difference in the treatment effect estimates or alter the conclusion for Study OBD-0631.

Dr. Cooner notes that neither of the Studies OBD-1033 or OBD-0631 showed sufficiently strong evidence of treatment efficacy as a single large clinical trial as they were not designed as such. She states in her review that study OBD-0631 consistently showed a strong treatment benefit of lubiprostone over placebo (both on the pre-specified primary endpoint of change from baseline in SBM frequency and on the post-hoc efficacy endpoint of overall SBM response rate), while the treatment difference in Study OBD-1033 was only marginally significant on the pre-specified primary endpoint of overall SBM response rate.

Based on these findings, she concludes that pre-specified sensitivity analyses and post-hoc exploratory analyses for all three pivotal studies support a benefit of lubiprostone over placebo in improving weekly SBM frequency.

7. Safety

As noted by the clinical reviewer, no new safety signals emerge from the AE database from OIC clinical trials, and AEs associated with lubiprostone in CIC and IBS-C trials were also the AEs most prominently associated with lubiprostone in OIC trials: nausea, diarrhea, vomiting, abdominal pain, flatulence, abdominal discomfort, abdominal distension, headache, and peripheral edema were more common among subjects receiving lubiprostone than placebo in

the OIC trials, and these AEs are all listed in the current drug label. Dyspnea, also in the current drug label, had an incidence rate in the OIC trials comparable to the incidence rate in clinical trials of lubiprostone for CIC at the 24 mcg BID dose. Chest pain, another AE that has been associated with lubiprostone in prior clinical trials, was not more common among lubiprostone subjects than placebo subjects in the OIC clinical trials. There were no AEs of opioid withdrawal or ischemic colitis clearly linked to use of lubiprostone in any of the OIC clinical trials.

Dr. Sohrabi also reviewed the most recent Periodic Safety Update Report (PSUR) for lubiprostone, which provided cumulative AE information through January 31, 2012, and noted no new safety signals.

Deaths

There were no deaths reported in OBD-0631 or OBD-0632. There was one death reported in OBD-1033 and one death reported in OBD-06S1. Both subjects were in the lubiprostone arm:

- Subject 3014015: 53 year-old female with insomnia, fibromyalgia, headache, depression, and OIC. Medications included Vicodin, Norco, Soma, Effexor, Valium, and zolpidem. The subject was found dead 2 days after she received last dose of lubiprostone. The cause of death based on autopsy report was multiple drug toxicity.
- Subject 1069031: 45 year-old female with asthma, COPD, depression, fibromyalgia, osteoarthritis, anxiety, borderline personality disorder, back pain, erosive duodenitis, tobacco use, and OIC who was taking Dilaudid, fentanyl, morphine, oxycodone, hydrocodone with acetaminophen, Advair, albuterol, ipratropium, Zolof, and Xanax. The patient was hospitalized with shortness of breath believed to be due to an unresolved case of pneumonia, at which time the study drug was discontinued. She was subsequently found to have severe pulmonary embolism, an esophageal mass, and pleural effusion. On hospital day #3, she developed severe septic shock, respiratory failure, and acute renal failure and died 3 days later. Subject had been in the lubiprostone arm of OBD-0631.

In Dr. Sohrabi's assessment, the cause of these subjects' deaths did not appear to be related to the study drug.

Non-fatal Serious Adverse Events

Dr. Sohrabi assessed non-fatal SAEs by CRFs, narratives and datasets provided by the Sponsor. As adjudicated by this reviewer, none of the non-fatal SAEs were attributed by the PI to administration of lubiprostone. Dr. Sohrabi does not note any SAEs that were clearly indicative of, or related to, opioid withdrawal. He also states in his review that there appear to be no trends or patterns in the SAEs of subjects on a diphenylheptane opioid (e.g., methadone) as compared with subjects not on an opioid from this class.

Discontinuations due to Adverse Events

As noted in Dr. Sohrabi's review, in the double-blind trials, a higher percentage of patients discontinued the trials due to AEs in the lubiprostone treatment group (6%) than in the placebo group (2%). In the open-label trial, patient choice was the most common reason for

discontinuation in both the placebo→lubiprostone (12%) and lubiprostone→lubiprostone (10%) groups.

In the double-blind trials pool, nausea (3%) and diarrhea (1%) were the most common AEs that led to discontinuation from treatment in the lubiprostone group and were the only AEs that led to discontinuation from treatment in $\geq 1\%$ of the subjects. Dr. Sohrabi also notes in his review that nausea and diarrhea are among the well-established adverse events associated with lubiprostone. All of the AEs that led to discontinuation from treatment in the double-blind trials in the placebo group were reported in $<1\%$ of the subjects.

Laboratory Data

The clinical reviewer did not note significant safety signals from his analysis of blood chemistries (including electrolytes), hepatic enzymes, triglycerides, and urinalysis.

Vital Signs

Based on the findings in subjects enrolled in the double-blind and open-label trials, Dr. Sohrabi did not identify concerns about adverse effects of lubiprostone on vital signs (BP, heart rate, respiration rate, temperature, and weight) in the adult population.

8. Advisory Committee Meeting

An Advisory Committee meeting was not held for this sNDA.

9. Pediatrics

On August 17, 2012, DGIEP requested Pediatric and Maternal Health (PMHS) to assist with the preparation of Pediatric Review Committee (PeRC) paperwork for this efficacy Supplement.

As noted by the PMHS reviewer, the Applicant has outstanding, overdue PREA requirements for the two previous approved indications of CIC and IBS-C (a deferral/extension request was submitted on January 4, 2013). ***However, these PREA requirements will be discussed and handled separately from this Efficacy Supplement (#011).***

For the current OIC supplement, the Applicant requested a deferral of PREA required studies in pediatric patients ages 6 months to 17 years of age and a waiver request in pediatric patients 0 to 6 months of age, both for the indication of opioid-induced constipation.

PeRC, PMHS, and DGIEP did not concur with the applicant's deferral request in pediatric patients ages 6 months to 17 years of age and instead recommended a full waiver of pediatric studies for opioid-induced constipation because studies would be impossible or highly impracticable. There is a lack of consensus on the use of opioids for treatment of chronic non-cancer pain in pediatric patients. Multiple published references have noted that conducting

safety and efficacy trials in pediatric patients with opioid-induced constipation remains a challenge. Studies of pediatric patients with pain due to cancer or advanced medical illness are also challenging to conduct due to the difficulties of studying children in a palliative care environment. Thus, PMHS and DGIEP both agree that a waiver for studies in all pediatric age groups should be granted because studies would be impossible or highly impracticable.

Pediatric Use labeling was revised by PMHS to reflect the appropriate regulatory statement under 21 CFR 201.57(c)(9)(iv) when safety and effectiveness have not been established.

10. Other Relevant Regulatory Issues

OSI Inspections

DGIEP consulted OSI on September 11, 2012 and requested inspection of data from studies OBD-0631 and OBD-1033. See the Primary OSI review (Dr. Malik, signed 3/27/2013) and the separate Team Leader review (Dr. Leibenhaut, signed 3/27/2013).

The following sites were chosen by DGIEP for inspection for Study 0631:

- Site 1069 (Sandoval): Large number of subjects with disproportionately high responder status (~20%)
- Site 1018 (Leslie): Site with largest number of subjects

The following sites were chosen by DGIEP for inspection for Study 1033:

- Site 3098 (Wolfson): Highest % of lubiprostone responders (32%) for a site with ≥ 10 subjects
- Site 3019 (Chilombo): Highest % of placebo non-responders (60%) for site with ≥ 10 subjects. The Sponsor informed FDA that a representative from the monitoring team of the CRO vendor expressed concerns regarding source documentation at Site 3019 while the trial was ongoing.

Based on the inspections, the primary OSI reviewer, Dr. Malik, concluded the following in his review:

“The data from sites 3098 (Wolfson) and site 1018 (Dr. Leslie) are acceptable, while the data from site 3019 (Dr. Chilombo) and site 1069 (Dr. Dao) are unacceptable and cannot be used. Since 50% of the sites were found to be un-reliable and inadequately monitored, I recommend that the Sponsor should be asked to perform a third party audit on a reasonable percentage of sites and respond directly to OND. We can evaluate the audit report and make a decision whether we will consider another cycle of inspections or accept the report.” *[sic]*

Dr. Malik had the following concerns regarding site 3019 and 1069, which he gave a final classification of OAI (OAI = Significant deviations from regulations. Data unreliable):

- Site 3019 (Chilombo): Review of the EIR showed many deficiencies: lack of supervision by the CI; electronic diaries were not available and so efficacy parameters

- could not be confirmed; numerous protocol violations; the PI failed to maintain the study records.
- Site 1069 (Sandoval / [REDACTED]^{(b) (6)}/Dao): The field investigator did not find any records at the site and was told that the records were inadvertently shredded while in storage. The FDA could not verify the data.

Dr. Malik gave a final classification of VAI (VAI = Deviation(s) from regulations) to Site 1018 (Leslie) as well as the Sponsor (Sucampo). Site 3098 (Wolfson) received an NAI (NAI = No deviation from regulations) from Dr. Malik.

As noted in the OSI Team Leader review (Dr. Leibenhaut), a sponsor inspection was not originally planned for this supplemental NDA review. However, in the course of inspections of the clinical sites, the following issues arose that in OSI's view warranted a sponsor inspection:

1. During the inspection of the Leslie site, FDA learned that "remonitoring" of the trial SMR/0211OBD-0631 had occurred after the study was closed, the database had been locked, and the study analyzed. A sponsor inspection was issued to determine the adequacy of monitoring during the trial and the adequacy of the remonitoring procedures, database lock and unlock and preservation of the blind for this study.
2. During the inspection of the clinical sites for both studies, it was determined that the primary efficacy endpoint submitted to the NDA (line listings) for both studies could not be verified at the clinical sites because a calculation was required to convert the raw eDiary data on the CDs at the clinical sites into the value that was submitted to the NDA.
3. When results of the inspection of the Chilombo and Dao sites became known, it became apparent that monitoring procedures and clinical trial conduct for both studies should be inspected and evaluated.

The OSI Team Leader, Dr. Leibenhaut, reached a different conclusion than the primary OSI reviewer, Dr. Malik, and noted these differences in her review. Her final classifications are presented in Table 15.

Table 15. Final OSI Classification

Name of clinical investigator (CI) or Sponsor	Protocol #/ # of Subjects/ Site #	Inspection Date	Final Classification
Eric Wolfson, M.D. 6803 W. Tropicana, Las Vegas, NV89106	SMR/0211OBD-1033/ 19 Subjects/ Site 3098	November 26 to 29, 2012	Pending (Preliminary classification NAI)
Karamo Chilombo, M.D. 1530 E. South Street Long Beach, CA 90805	SMR/0211OBD-1033 10 Subjects/ Site 3019	October 30 to January 10, 2013	Pending (Preliminary classification OAI)
Nelson Sandoval, M.D. 5390 E. Erickson Drive Tucson, AZ 85712	SMR/0211OBD-0631 25 Subjects/ Site 1069	January 17 and 18, 2013	Pending (Preliminary classification VAI) ^a
Harvey Leslie, M.D. 3009 Rainbow Drive Decatur, GA 30034	SMR/0211OBD-0631 26 Subjects/ Site 1018	November 19 to 20 and November 26 to 29, 2012	Pending (Preliminary classification NAI) ^b
Sucampo Pharmaceuticals, Inc. 4520 East-West Highway Bethesda, MD 20814	SMR/0211OBD-1033 and SMR/0211OBD-0631	February 21 to 28, 2013	Pending (Preliminary classification VAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field. For each of these pending classifications, the EIR has been received from the field, but complete review of EIR is pending.

- a. Dr. Dao participated in only the remonitoring, and was not responsible for the conduct of the study. While he signed a Form FDA 1572, he does not appear to meet the criteria to be a clinical investigator under FDA’s regulations and is accordingly not responsible for record-keeping. The pending classification is VAI, but OSI considers that the data are not reliable in any case.
- b. The field classification is NAI and the reclassification has not been discussed. Dr. Malik and I may not agree on a classification, but the data are considered reliable in any case.

Source: Dr. Leibenhaut’s OSI Review

Dr. Leibenhaut concludes in her review that the data from these two pivotal trials can be considered reliable, and third-party audits as recommended by the primary reviewer, are unlikely to reveal additional deficiencies that would materially impact application review. Dr. Leibenhaut also notes that while the sponsor inspection uncovered deficiencies in the conduct and monitoring of the trials, the sponsor inspection also established that, for each trial, when the sponsor detected these deficiencies, the sponsor took steps to mitigate the deficiencies. Additionally, she notes that the sponsor has already undertaken extensive re-monitoring for the OBD-0631 trial and concludes that these actions render the data reliable for both trials.

However, Dr. Leibenhaut’s notes a number of disagreements with Dr. Malik’s review and presents the following summary comments:

- Sucampo became aware of data discrepancies during the conduct of an extension study of Protocol 0631 and also of Protocol 0632. Sucampo worked with a CRO responsible for monitoring at that time and most discrepancies were resolved. Sucampo became concerned because of the large number of notes to file after audits were conducted that were related to medical history or adverse events which were not recorded for the subjects during the time in

Study 0631 [but were subsequently reported in the Extension Study 06S1]. An audit of the CRO was conducted that resulted in termination of the contract with the CRO and a new agreement between Sucampo and (b) (4) that included remonitoring of the study. There was apparently confusion on the part of the sponsor and monitor as to whether to categorize abnormal findings noted on physical examination eCRF as being either an adverse event because it had not been recorded on the medical history and was newly noted or not to categorize it as an AE because it was documented in the medical history. As noted by the OSI Team Leader, the discrepancies do not appear to involve significant adverse events, but rather an attempt to characterize an abnormal physical finding or reconcile a concomitant medication record. Many of the issues were resolved through efforts to identify and rectify discrepancies. According to the OSI Team Leader review, the sponsor also acted appropriately by auditing the CRO, replacing the CRO, and conducting additional remonitoring.

- The primary OSI reviewer noted that the investigator for Site 3019 (Chilombo) had less than one year of research experience and the investigator for Site 3119 (Dr. Moreno) was apparently arrested for practicing without proper certification. The OSI Team Leader gives Sucampo credit, in that they requested a third party audit and the auditor could not detect fraud.
- The Primary OSI reviewer was concerned that at sites 1069 and 1018, there were 3 PIs at different timepoints for each site (“one after the other”) and that “this caused improper supervision and less concentration on the different aspects of the study.” However the Team Leader notes that although the observation concerning the number of PIs is correct, this finding, in and of itself, does not raise questions concerning data integrity.
- The primary OSI reviewer also notes that the field investigator did not find any records at Site 1069 and was told that the records were inadvertently shredded while in storage. The FDA could not verify the data. Because the primary data from this site could not be verified it was deemed unacceptable (OAI) by the primary reviewer. However the OSI Team Leader classified this site as VAI. There was no indication that fraudulent or otherwise suspicious activity occurred at this site.

The DGIEP review team agreed with the Sponsor and the OSI reviewers that site data from Site 3019 should not be used. The team also also agreed that it would be appropriate to remove data from Site 3119 because of an issue with falsification that was suspected by the sponsor (but not detected with a third party audit). Nevertheless, based on these suspicions the sponsor removed Site 3119. Importantly, as noted in the OSI Team Leader review, both the Chilombo site (#3019) and Moreno site (#3119) were administered by the same clinical research associate (b) (6) who could have potentially influenced the data from Site 3119 in a manner similar to Site 3019. Dr. Chilombo’s site enrolled 10 subjects and Dr. Moreno’s site enrolled 5 subjects. These two sites only participated in Study OBD-1033.

The original analysis accepted by DGIEP includes site 1069 but excludes data from Sites 3019 and 3119.

However, at the time of finalization of this review, discussions were ongoing among the team as to whether data from Site 1069 should also be excluded from analyses presented in the label. This is primarily due to the OSI Team Leader noting in her review (see footnote “a” in Table 15 above), the following: “The pending classification is VAI, but OSI considers that the data are not reliable in any case.”

11. Labeling

DMEPA Review

DMEPA evaluated the proposed container label, carton and insert labeling for this sNDA. DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Amitiza medication error reports and also reviewed the Amitiza labels and package insert labeling submitted by the Applicant. DMEPA concluded that the proposed container label and sample labeling can be improved to increase the readability and prominence of important information to promote the safe use of the product and to clarify information. See the DMEPA review for detailed recommendations regarding the container label, which were forwarded to the applicant. Two of DMEPA's recommendations were not accepted by the sponsor: DMEPA requested that the sponsor revise the presentation of the proprietary name on all container labels and professional sample labeling, from all lower case "amitiza" to title case "Amitiza" to improve its readability and to further distinguish it from the active ingredient. However the sponsor chose to use "AMITIZA" [all caps] and DMEPA found this acceptable. In addition, the sponsor was unwilling to revise the "Each capsule contains XX mg" statement on the blister labels such that the information is not destroyed with the removal of a capsule from the blister. DMEPA ultimately did not find this unacceptable from an approval standpoint but noted that any medication errors might prompt re-evaluation.

SEALD Label Review

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, final agreed-upon prescribing information (PI) for critical format elements revealed no outstanding labeling format issues and the SEALD Director had no objection to the approval of this PI at this time.

OPDP

OPDP reviewed the proposed draft PI, agreed with the changes and had no additional comments at the time of finalization of this CDTL review.

Key Labeling Issues & Negotiations with Applicant

- Ischemic Colitis

A review by DPV 1 dated September 5, 2008 reported 6 cases of ischemic colitis (IC) associated with Amitiza use. It was recommended at that time to update the label for Amitiza to include IC in the Postmarketing Adverse Events section. However the currently approved label does not contain such language.

During this review, DGIEP requested an updated analysis of post-market cases of IC from OSE. Christian Cao, Safety Evaluator, Division of Pharmacovigilance-1 (DPV-1) provided (dated Feb. 05, 2013) a Provision of Pharmacovigilance Data with summary of cases of ischemic colitis (IC) possibly related to Amitiza (lubiprostone) as identified in the FDA Adverse Event Reporting System (FAERS) database since August 13, 2008.

The FAERS search retrieved 12 reports. After excluding duplicate cases and cases that did not meet OSE case definition, 6 new cases were identified.

The Review team decided to include IC in the postmarketing section of the label as recommended by OSE.

- Limitation of Use

A limitation of use was added to the indication for OIC primarily because of 1) the *in vitro* findings that methadone may block the MOA of lubiprostone and 2) the fact that the confirmatory study OBD-1033 specifically excluded subjects on methadone, thereby effectively failing to demonstrate that lubiprostone would be effective in OIC due to methadone.

- Study OBD-0632

The sponsor initially proposed to [REDACTED] (b) (4)

The review team, in discussion with SEALD, felt that inclusion of the “failed” trial OBD-632 was reasonable to include in the label, important to understand the effectiveness of lubiprostone and also to more broadly characterize the purported interaction between lubiprostone and methadone.

- Removal of Claims

As discussed previously in my review, the proposed label was revised to [REDACTED] (b) (4)

- Modification to Previous Approved Sections of Label

The label was modified in manner that kept presentation of efficacy and safety data separate but consistent (to the extent possible) across all sections describing trial data for each indication.

- Presentation of clinical efficacy

In Section 14 the description of the study results contains the data from the all-randomized populations, excluding Sites 3019 and 3119, (b) (4)

12. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This supplemental NDA meets statutory standards required under 21 CFR 314.105 and should be approved.

- **Risk Benefit Assessment**

OIC can be a serious condition that does not improve with continued opioid therapy, negatively affects quality of life, and can lead to patients reducing or terminating treatment with opioids. There are currently no FDA-approved therapies for this indication.

The efficacy of lubiprostone for OIC (in patients with chronic non-cancer pain) is demonstrated by two randomized, double-blind 12-week trials (OBD-1033 and OBD-0631) comparing lubiprostone 24 mcg BID with placebo. Both trials demonstrated a statistically significant treatment effect favoring lubiprostone. Based on an analysis of the overall responder definition, the observed benefit appears to be approximately 8-10% over placebo (depending on study population analyzed).

A treatment benefit for lubiprostone was not demonstrated in OBD-632 and the reason is unknown. Although the non-clinical data provides evidence for the possibility of a treatment interaction between methadone and lubiprostone, the clinical and statistical reviewers could not find convincing evidence of a clinically significant interaction.

Because OBD-1033, as the second confirmatory trial, excluded subjects on methadone, further exploration of a treatment interaction could not be investigated. However, given the non-clinical findings and the lack of further clinical evaluation of this interaction in the confirmatory trial, OBD-1033, a Limitation of Use statement is recommended for the label. In addition, the results of study OBD-632 should be described in the label to provide clinically relevant information on the observed treatment benefit of lubiprostone for OIC and context for why a Limitation of Use statement is in the label.

No new safety concerns were identified in the development program for OIC. As noted by the clinical reviewer, nausea and diarrhea are among the well-established adverse

events associated with lubiprostone. The observed treatment benefit, considered in conjunction with a lack of significant safety concern across the OIC studies, suggested that the drug could be an effective treatment for OIC with acceptable risks.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

None recommended.

- **Recommendation for other Postmarketing Requirements and Commitments**

No PMCs or PMRs are recommended. PREA mandated pediatric studies have been waived for the proposed indication (OIC).

- **Recommended Comments to Applicant**

No comments recommended.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT FIORENTINO
04/19/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021908/S-011

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type sNDA
Application Number(s) 21-908
Priority or Standard Priority

Submit Date(s) July 20, 2012
Received Date(s) July 20, 2012
PDUFA Goal Date April 19, 2013
(major amendment)

Division / Office DGIEP/ODE3

Reviewer Name(s) Farrokh Sohrabi, M.D.
Review Completion Date April 3, 2013

Established Name Lubiprostone
(Proposed) Trade Name Amitiza®
Therapeutic Class Chloride channel activator
Sponsor Sucampo Pharmaceuticals, Inc.

Formulation(s) Oral capsule
Dosing Regimen 24 mcg B.I.D.
Indication(s) Opioid-induced constipation (OIC)
Intended Population(s) Adults with chronic non-cancer
pain and OIC

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	13
1.1	Recommendation on Regulatory Action	13
1.2	Risk Benefit Assessment.....	13
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies .	13
1.4	Recommendations for Postmarket Requirements and Commitments	13
2	INTRODUCTION AND REGULATORY BACKGROUND	14
2.1	Product Information	14
2.2	Tables of Currently Available Treatments for Proposed Indications	15
2.3	Availability of Proposed Active Ingredient in the United States	15
2.4	Important Safety Issues with Consideration to Related Drugs.....	15
2.5	Summary of Presubmission Regulatory Activity Related to Submission	15
2.6	Other Relevant Background Information	17
3	ETHICS AND GOOD CLINICAL PRACTICES.....	17
3.1	Submission Quality and Integrity	17
3.2	Compliance with Good Clinical Practices	18
3.3	Financial Disclosures.....	21
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	21
4.1	Chemistry Manufacturing and Controls	22
4.2	Clinical Microbiology.....	22
4.3	Nonclinical Pharmacology/Toxicology	22
4.4	Clinical Pharmacology.....	22
4.4.1	Mechanism of Action.....	23
4.4.2	Pharmacodynamics.....	23
4.4.3	Pharmacokinetics.....	24
5	SOURCES OF CLINICAL DATA.....	24
5.1	Tables of Studies/Clinical Trials	24
5.2	Review Strategy	25
5.3	Discussion of Individual Studies/Clinical Trials.....	25
5.3.1	Trial OBD-1033	25
5.3.2	Trials OBD-0631 and OBD-0632	28
5.3.3	Trial OBD-06S1.....	29
6	REVIEW OF EFFICACY	30
6.1	Indication	30
6.1.1	Methods	30
6.1.2	Demographics.....	31
6.1.3	Subject Disposition	39

6.1.4	Analysis of Primary Endpoint(s)	45
6.1.5	Analysis of Secondary Endpoints(s).....	53
6.1.6	Other Endpoints	71
6.1.7	Subpopulations	84
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	94
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	94
6.1.10	Additional Efficacy Issues/Analyses	95
7	REVIEW OF SAFETY.....	105
7.1	Methods.....	106
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	106
7.1.2	Categorization of Adverse Events.....	107
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	108
7.2	Adequacy of Safety Assessments	108
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	108
7.2.2	Explorations for Dose Response.....	111
7.2.3	Special Animal and/or In Vitro Testing	112
7.2.4	Routine Clinical Testing	112
7.2.5	Metabolic, Clearance, and Interaction Workup	112
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class	112
7.3	Major Safety Results	112
7.3.1	Deaths.....	112
7.3.2	Nonfatal Serious Adverse Events	113
7.3.3	Dropouts and/or Discontinuations	119
7.3.4	Significant Adverse Events	122
7.3.5	Submission Specific Primary Safety Concerns	122
7.4	Supportive Safety Results	127
7.4.1	Common Adverse Events	127
7.4.2	Laboratory Findings	135
7.4.3	Vital Signs	142
7.4.4	Electrocardiograms (ECGs)	143
7.4.5	Special Safety Trials/Clinical Trials	145
7.4.6	Immunogenicity	146
7.5	Other Safety Explorations.....	146
7.5.1	Dose Dependency for Adverse Events	146
7.5.2	Time Dependency for Adverse Events.....	146
7.5.3	Drug-Demographic Interactions	148
7.5.4	Drug-Disease Interactions.....	153
7.5.5	Drug-Drug Interactions.....	153
7.6	Additional Safety Evaluations	153
7.6.1	Human Carcinogenicity	153
7.6.2	Human Reproduction and Pregnancy Data.....	153

7.6.3	Pediatrics and Assessment of Effects on Growth	153
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	154
7.7	Additional Submissions / Safety Issues	155
8	POSTMARKET EXPERIENCE.....	156
9	APPENDICES	159
	Appendix 1: Benefit-Risk Assessment.....	159
	Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033.....	161
	Appendix 3: Discussion of Individual Trials: Trial SMR/0211 OBD-0631	182
	Appendix 4: Discussion of Individual Trials: Trial SMR/0211 OBD-0632.....	194
	Appendix 5: Discussion of Individual Trials: Trial SMR/0211 OBD-06S1.....	213
	Appendix 6: Pooled Efficacy Data by Opioid Class and Subclass (OBD-1033, OBD-0631, and OBD-0632)	222
	Appendix 7: Narratives of Subjects Selected for Review Based on Adverse Events Suggestive of Possible Opioid Withdrawal	223
	Appendix 8: Laboratory Reference Ranges.....	227
	Appendix 9: Functional Living Index-Emesis (FLIE) Nausea Scores.....	227
	Appendix 10: Daily Electronic Diary	228
9.1	Literature Review/References	230
9.2	Labeling Recommendations	232
9.3	Advisory Committee Meeting.....	239

Table of Tables

Table 1. Clinical Trials Submitted to Support sNDA	24
Table 2. Demographic Characteristics at Baseline – OBD-1033, OBD-0631, and OBD-0632 (ITT Population).....	32
Table 3. Demographic Characteristics at Baseline (Continued) – OBD-1033, OBD-0631, and OBD-0632 (ITT Population).....	33
Table 4. Constipation Status at Baseline – OBD-1033, OBD-0631, and OBD-0632 (ITT Population)	36
Table 5. Constipation Status at Baseline (Continued) – OBD-1033, OBD-0631, and OBD-0632 (ITT Population*)	37
Table 6. Summary of Subjects on Each Class/Subclass of Opioids by Trial – OBD-1033, OBD-0631, and OBD-0632 (Safety-Evaluable Population)	38
Table 7. Reason for Screen Failures that Occurred in $\geq 4\%$ of Subjects in Double-blind Trials	39
Table 8. Subject Disposition – OBD-1033, OBD-0631, and OBD-0632 (Randomized Subjects)	41
Table 9. Summary of Protocol Violations (ITT Population).....	43
Table 10. Primary Analysis of Overall SBM Response in OBD-1033 (ITT Population) .	46
Table 11. Supportive Analysis of Overall SBM Response in OBD-1033 (mITT, Completer and Per-Protocol Populations).....	47
Table 12. Primary Analysis of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-0631 (ITT Population)	49
Table 13. Supportive Analysis of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-0631 (Completer Population)	50
Table 14. Supportive Analysis of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-0631 (Per-Protocol Population).....	50
Table 15. Primary Analysis of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-0632 (ITT Population)	51
Table 16. Analysis of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-0632 (Completer Population).....	52
Table 17. Analysis of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-0632 (Per-Protocol Population).....	52
Table 18. Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-1033 (ITT Population).....	54
Table 19. Summary of Change from Baseline in SBM Frequency at Week 12 in OBD-1033 (ITT, mITT, Completer, and Per-Protocol Populations)	56
Table 20. Summary of Overall Change from Baseline in SBM Frequency in OBD-1033 (ITT, mITT, Completer, and Per-Protocol Populations)	57
Table 21. Summary of SBMs within 24 and 48 Hours of First Study Medication Dose in OBD-1033 (ITT, mITT, Completer, and Per-Protocol Populations)	58
Table 22. Weekly SBM Response – Trial OBD-1033 (ITT Population, Non-LOCF Analysis).....	59

Table 23. Summary of PAC-QOL Total Score Response by Month for OBD-1033 (ITT population)	61
Table 24. Summary of End of Treatment EQ-5D Response for OBD-1033 (ITT population)	62
Table 25. Overall Change from Baseline in Bowel Function Parameters - OBD-1033 (ITT Population)	63
Table 26. Summary of Overall Treatment Effectiveness in OBD-1033 (ITT and mITT Populations)	64
Table 27. Summary of Change from Baseline in SBM Frequency at Week 12 in OBD-0631 (ITT, Completer, and Per-Protocol Populations).....	66
Table 28. Summary of Overall Change from Baseline in SBM Frequency in OBD-0631 (ITT, Completer, and Per-Protocol Populations)	67
Table 29. Summary of SBMs within 24 and 48 Hours of First Study Medication Dose in OBD-0631 (ITT, Completer, and Per-Protocol Populations).....	68
Table 30. Overall Responder Rates in OBD-0631 (ITT, Completer, and Per-Protocol Populations)	69
Table 31. Overall Change from Baseline in Bowel Function Parameters - OBD-0631 (ITT Population)	70
Table 32. Summary of Overall Treatment Effectiveness in OBD-0631 (ITT, Completer, and Per-Protocol Populations)	71
Table 33. Overall Change from Baseline in CSBM Frequency in OBD-1033 and OBD-0631 (ITT)	72
Table 34. Change from Baseline in SBM Frequency by Week - OBD-1033 and OBD-0631 (ITT)	73
Table 35. Change from Baseline in SBM Frequency by Month - OBD-1033 and OBD-0631 (ITT)	73
Table 36. Frequency of CSBMs by Week in OBD-1033 and OBD-0631 (ITT Population)	75
Table 37. Frequency of CSBMs by Month in OBD-1033 and OBD-0631 (ITT Population)	76
Table 38. Proportion of SBMs rated as Complete by Overall SBM Responders and Non-Responders in OBD-1033 and OBD-0631 (ITT Population).....	76
Table 39. Frequency of SBMs by Week in OBD-1033 and OBD-0631 (ITT Population).....	77
Table 40. Frequency of SBMs by Month in OBD-1033 and OBD-0631 (ITT Population)	78
Table 41. Frequency of Complete BMs by Week in OBD-1033 and OBD-0631 (ITT Population)	79
Table 42. Frequency of Complete BMs by Month in OBD-1033 and OBD-0631 (ITT Population)	80
Table 43. Frequency of BMs by Week in OBD-1033 and OBD-0631 (ITT Population) ..	81
Table 44. Frequency of BMs by Month in OBD-1033 and OBD-0631 (ITT Population) ..	82
Table 45. Time to First SBM and Proportion of Subjects with First SBM within 4, 8, and 12 Hours of First Dose of Study Drug in OBD-1033 (ITT Population)	83

Table 46. Time to First SBM and Proportion of Subjects with First SBM within 4, 8, and 12 hours of First Dose of Study Drug in OBD-0631 (ITT Population).....	83
Table 47. Overall Change from Baseline in Bowel Habit Regularity - OBD-1033 and OBD-0631 (ITT)	84
Table 48. Overall SBM Response by Gender in OBD-1033 (ITT Population)	85
Table 49. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Gender in OBD-0631 (ITT Population)	85
Table 50. Overall SBM Response by Gender in OBD-0631 (ITT Population)	85
Table 51. Overall SBM Response by Age in OBD-1033 (ITT Population).....	86
Table 52. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Age in OBD-0631 (ITT Population).....	86
Table 53. Overall SBM Response by Age in OBD-0631 (ITT Population).....	87
Table 54. Overall SBM Response by Race in OBD-1033 (ITT Population).....	87
Table 55. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Race in OBD-0631 (ITT Population)	88
Table 56. Overall SBM Response by Race in OBD-0631 (ITT Population).....	88
Table 57. Overall SBM Response by Opioid Class in OBD-1033 (ITT Population).....	89
Table 58. Overall SBM Response by Phenanthrene Subclass in OBD-1033 (ITT Population)	90
Table 59. Overall SBM Response by Opioid Use Duration at Baseline in OBD-1033 (ITT Population)	90
Table 60. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Opioid Class in OBD-0631 (ITT Population)	91
Table 61. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Phenanthrene Opioid Subclass in OBD-0631 (ITT Population)	92
Table 62. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Opioid Use Duration at Baseline in OBD-0631 (ITT Population)	93
Table 63. Summary of Overall SBM Response (Modified Definition) in OBD-1033 (ITT, Completer, and Per-Protocol Populations)	94
Table 64. Summary of Subjects with Rescue Laxative Use at Baseline, Each Month, and Overall – OBD-1033 and OBD-0631 (Safety-Evaluable Population).....	96
Table 65. Percent of Days of Rescue Laxative Use by Month – OBD-1033 and OBD-0631 (Safety-Evaluable Population).....	97
Table 66. Supportive Analysis of Overall SBM Response in OBD-0631 (ITT Population)	98
Table 67. Change from Baseline in SBM Frequency at Week 8 in OBD-0631 (ITT) and OBD-0631 Excluding Site #1069 ¹	99
Table 68. Overall SBM Response in OBD-0631 (ITT) and OBD-0631 Excluding Site #1069	99
Table 69. Overall SBM Response in OBD-1033 and OBD-0631 (True ITT Population ¹)	99

Table 70. Change from Baseline in SBM Frequency at Week 8 in OBD-1033 and OBD-0631 (ITT)	100
Table 71. Overall SBM Response in Subjects without Dose Reduction in OBD-1033 and OBD-0631 (ITT Population).....	101
Table 72. Summary of Individual Days per Week with at Least One SBM in OBD-1033 (ITT)	102
Table 73. Overall SBM Response by Daily-Based Calculation of Weekly SBM Frequency in OBD-1033 and OBD-0631 (ITT) – All Multiple Daily BMs Count Towards Weekly Average	103
Table 74. Overall SBM Response by Daily-Based Calculation of Weekly SBM Frequency in OBD-1033 and OBD-0631 (ITT) – Multiple BMs Per Day Contributing One BM Towards Weekly Average	103
Table 75. Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in Pooled Trials OBD-0631 and OBD-0632 (ITT Population)	104
Table 76. Overall Change from Baseline in SBM Frequency in Pooled Trials OBD-0631 and OBD-0632 (ITT Population).....	104
Table 77. Time to First SBM in Pooled Trials OBD-1033, OBD-0631, and OBD-0632 (ITT Population)	105
Table 78. Analysis Groups for Review of Safety	107
Table 79. Summary of Duration of Exposure for Subjects in Double-blind Trials and Open-label Trial (Treated Subjects)	109
Table 80. Demographic Characteristics at Baseline – Double-blind Trials and Open-label Trial (Safety Evaluable Subjects).....	110
Table 81. Constipation Status at Baseline – Double-blind and Open-label Trials (Safety Evaluable Subjects)	111
Table 82. Brief Narratives of Deaths in Double-blind Trial and Open-label Trial	113
Table 83. Summary of All Nonfatal Serious Adverse Events for the Double-blind Trials Pool.....	114
Table 84. Summary of All Nonfatal Serious Adverse Events for the Open-label Trial OBD-06S1	117
Table 85. Subject Discontinuation in Pooled Double-blind Trials and Open-label Trial – Randomized Subjects	120
Table 86. Adverse Events Leading to Discontinuation from Treatment in 1% or More of Lubiprostone Subjects – Double-blind Trials Pool (Safety Evaluable Subjects)	121
Table 87. Adverse Events Leading to Discontinuation from Treatment in 1% or More of Lubiprostone Subjects – Overall Safety Pool (Safety Evaluable Subjects).....	121
Table 88. Change from Baseline in Opioid Dose by Month in Double-blind Trials Pool – OBD-1033, OBD-0631, and OBD-0632 (ITT Population).....	123
Table 89. Incidence of Most Common Adverse Events – Overall Safety Pool (Safety Evaluable Subjects).....	129
Table 90. Incidence of Most Common Adverse Events – Double-blind Trials Pool and Open-label Long-Term Trial (Safety Evaluable Subjects).....	130
Table 91. Incidence of Severe Cases of Most Common Adverse Events – Overall Safety Pool (Safety Evaluable Subjects)	133

Table 92. Incidence of Severe Cases of Most Common Adverse Events – Double-blind Trials Pool and Open-label Trial (Safety Evaluable Subjects)	134
Table 93. Shift Table of Key Hematology Lab Values – Double-blind Pool and Open-label Trial.....	135
Table 94. Shift Table of Serum Chemistry Lab Values – Double-blind Pool and Open-label Trial (Safety Evaluable Subjects)	136
Table 95. Trends in Serum ALT Level in Lubiprostone Subjects with ALT Greater than or Equal to 120 IU/L at Any Laboratory Time Point in Double-blind and Open-label Trials	138
Table 96. Incidence of Adverse Events Relating to Liver Tests – Overall Safety Pool	139
Table 97. Trends in Serum Potassium Level in Subjects with Potassium Less than 3.0 mmol/L While Exposed to Lubiprostone in Double-blind and Open-label Trials	140
Table 98. Subjects with ECG Shifts to Abnormal / Clinically Significant in Double-blind Trials Pool	144
Table 99. Subjects with ECG Shifts to Abnormal / Clinically Significant in OBD-06S1	145
Table 100. Incidence of Most Common Adverse Events by Age – Double-blind Trials Pool and Open-label Long-Term Trial (Safety Evaluable Subjects)	149
Table 101. Incidence of Most Common Adverse Events by Gender – Double-blind Trials Pool and Open-label Long-Term Trial (Safety Evaluable Subjects)	150
Table 102. Incidence of Most Common Adverse Events by Race – Double-blind Trials Pool and Open-label Trial (Safety Evaluable Subjects).....	151
Table 103. Incidence of Most Common Adverse Events by Opioid Class (Diphenylheptane Versus Other Opioid Classes) – Double-blind Trials Pool and Open-label Trial (Safety Evaluable Subjects).....	152
Table 104. Postmarketing Adverse Events from February 1, 2006 to January 31, 2012	157
Table 105. Primary Fatal Events from February 1, 2006 to January 31, 2012 in Postmarket Setting.....	158
Table 106. Schedule of Visits – Trial OBD-1033	164
Table 107. Change from Baseline in Opioid Dose by Month in OBD-1033 (ITT Population)	175
Table 108. Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-1033 (mITT Population)	176
Table 109. Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-1033 (Completer Population)	177
Table 110. Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-1033 (Per-Protocol Population).....	177
Table 111. Change from Baseline in PAC-QOL Subscale Scores by Month for OBD-1033 (ITT)	178
Table 112. Treatment Effectiveness by Week in OBD-1033 (ITT Population).....	179
Table 113. Treatment Effectiveness by Month in OBD-1033 (ITT Population).....	179
Table 114. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Opioid Class in OBD-1033 (ITT Population)	180

Table 115. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Phenanthrene Opioid Subclass in OBD-1033 (ITT Population)	180
Table 116. Schedule of Visits – Trials OBD-0631 and OBD-0632	184
Table 117. Change from Baseline in Opioid Dose by Month in OBD-0631 (ITT Population)	189
Table 118. Treatment Effectiveness by Week in OBD-0631 (ITT Population).....	191
Table 119. Treatment Effectiveness by Month in OBD-0631 (ITT Population).....	191
Table 120. Analysis of Overall SBM Response by Opioid Class in OBD-0631 (ITT Population)	192
Table 121. Overall SBM Response by Phenanthrene Opioid Subclass in OBD-0631 (ITT Population)	192
Table 122. Monthly Summary of Subjects with Rescue Laxative Use - OBD-0632 (Safety-Evaluable).....	195
Table 123. Percent Days of Rescue Laxative Use by Month - OBD-0632 (Safety-Evaluable)	195
Table 124. Change from Baseline in Opioid Dose by Month in OBD-0632 (ITT Population)	196
Table 125. Summary of Change from Baseline in SBM Frequency at Week 12 in OBD-0632 (ITT, Completer, and Per-Protocol Populations).....	197
Table 126. Summary of Overall Change from Baseline in SBM Frequency in OBD-0632 (ITT, Completer, and Per-Protocol Populations)	197
Table 127. Summary of SBMs within 24 and 48 Hours of First Study Medication Dose in OBD-0632 (ITT, Completer, and Per-Protocol Populations).....	198
Table 128. Overall Responder Rates in OBD-0632 (ITT, Completer, and Per-Protocol Populations)	198
Table 129. Overall Change from Baseline in Bowel Parameters – OBD-0632 (ITT Population)	199
Table 130. Summary of Overall Treatment Effectiveness in OBD-0632 (ITT, Completer, and Per-Protocol Populations)	200
Table 131. Time to First SBM and Proportion of Subjects with First SBM within 4, 8, and 12 Hours of First Dose of Study Drug in OBD-0632 (ITT Population)	200
Table 132. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Gender in OBD-0632 (ITT Population).....	201
Table 133. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Age in OBD-0632 (ITT Population)	201
Table 134. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Race in OBD-0632 (ITT Population)	202
Table 135. Summary of Subjects Using a Diphenylheptane at Baseline in OBD-0631 and OBD-0632	203
Table 136. Baseline MEDD of Subjects by Opioid Class in OBD-0631 and OBD-0632 (ITT)	204
Table 137. Overall SBM Response by Baseline MEDD in OBD-0631 and OBD-0632 (ITT Population)	204

Table 138. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Baseline MEDD in OBD-0631 and OBD-0632 (ITT Population)	205
Table 139. Subjects in Violation of Inclusion Criteria for OIC in OBD-0631 and OBD-0632	206
Table 140. Overall SBM Response by Baseline Percentage of Days of Rescue Laxative Use in OBD-0631 and OBD-0632 (ITT Population).....	207
Table 141. Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Baseline Percent Days of Rescue Laxative Use – OBD-0631 and OBD-0632 (ITT)	207
Table 142. Overall SBM Response by Opioid Use Duration at Baseline in OBD-0631 and OBD-0632 (ITT Population).....	208
Table 143. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Opioid Use Duration at Baseline in OBD-0631 and OBD-0632 (ITT Population).....	209
Table 144. Medical Diagnoses Potentially Associated with Opioid Use in OBD-0631 and OBD-0632 (ITT Population).....	210
Table 145. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Opioid Class in OBD-0631 and OBD-0632 (ITT Population)	211
Table 146. Overall SBM Response by Opioid Class in OBD-0631 and OBD-0632 (ITT Population)	211
Table 147. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Phenanthrene Subclass in OBD-0631 and OBD-0632 (ITT Population).....	212
Table 148. Overall SBM Response by Phenanthrene Subclass in OBD-0631 and OBD-0632 (ITT)	212
Table 149. Schedule of Visits – Trial OBD-06S1.....	215
Table 150. Change from Baseline in Opioid Dose by Month in OBD-06S1.....	220
Table 151. Change from Baseline in SBM Frequency by Month in OBD-06S1 (ITT Population)	221
Table 152. Laboratory Reference Ranges	227

Table of Figures

Figure 1. Brief Pain Inventory Pain Interference, Pain Severity, and Worst Pain Scores – Double-blind Trials Pool (Safety-Evaluable Subjects)	124
Figure 2. Brief Pain Inventory Pain Interference, Pain Severity, and Worst Pain Scores – Open-label Trial (Safety-Evaluable Subjects).....	125
Figure 3. Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Opioid Class – Trials OBD-1033, OBD-0631, OBD-0632 (ITT Population)	222
Figure 4. Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Phenanthrene Subclass – Trials OBD-1033, OBD-0631, OBD-0632 (ITT Population)	223
Figure 5. FLIE Scores – Double-blind Trials Pool (Safety Evaluable Subjects).....	228
Figure 6. FLIE Scores – Open-label Trial OBD-06S1 (Safety Evaluable Subjects).....	228

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of Amitiza® (lubiprostone) 24 mcg orally twice daily for the treatment of opioid-induced constipation in adult patients with chronic non-cancer pain based on the Sponsor's demonstration of an acceptable safety and efficacy profile, contingent on the pending finalization of the statistical review of this sNDA. Approval of lubiprostone 24 mcg orally twice daily for the treatment of opioid-induced constipation in adults with chronic non-cancer pain is also contingent upon the Sponsor incorporating the Agency's recommended changes to the lubiprostone drug label.

1.2 Risk Benefit Assessment

The expansion of the indication for Amitiza® 24 mcg orally (PO) twice daily (BID) to include the treatment of adult patients with opioid-induced constipation (OIC) and chronic non-cancer pain provides patients with an alternative to other available products used "off label" to treat the same condition. In this reviewer's assessment, Amitiza® 24 mcg BID can be an effective and safe option. In this reviewer's assessment, the clinical trials of Amitiza® 24 mcg BID demonstrate efficacy up to 12 weeks and an acceptable safety profile up to 48 weeks duration in a population of adult patients with OIC and chronic non-cancer pain when compared with no FDA-approved treatment. [Appendix 1: Benefit-Risk Assessment](#) provides a more detailed benefit-risk assessment.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

After a thorough safety review and analysis, this clinical reviewer believes that a postmarketing risk evaluation and mitigation strategy is not needed for lubiprostone.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommendations for postmarket requirements or commitments.

The Agency has granted the Sponsor a full waiver for pediatric studies for all pediatric age groups required under the Pediatric Research Equity Act (PREA) for the indication of OIC in pediatric patients with chronic non-cancer pain. The Pediatric Research Committee (PeRC) PREA subcommittee meeting was held on February 13, 2013, and the committee agreed with DGIEP in granting the Sponsor a full waiver. The Sponsor was granted a full waiver for pediatric patients of all age groups because there is inadequate number of pediatric patients who receive opioid therapy for non-life limiting

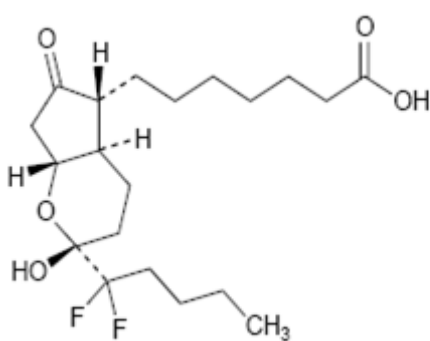
illnesses for greater than 4 weeks. Section 7.6.3 [Pediatrics and Assessment of Effects on Growth](#) provides further discussion.

2 Introduction and Regulatory Background

Opioid-induced bowel dysfunction (OBD) is a term used to describe the adverse effects on the gastrointestinal system due to opioid therapy. OIC is a frequent and one of the many symptoms reported by patients thought to have OBD. Opioids exert their analgesic effects via opioid receptors (μ , δ , and κ). The majority of the opioids used in clinical practice have their primary activity at μ receptors, which are expressed in the central and peripheral nervous system and the myenteric and submucosal plexi of the gastrointestinal system. Activation of μ receptors by exogenous opioids leads to analgesia as well as major side effects such as sedation, bowel dysfunction, respiratory depression, and dependence. In the gastrointestinal system, opioid therapy tends to inhibit gastric emptying, increase absorption and decrease secretion in both the large and small intestine, delay small intestinal and colonic transit, and increase internal anal sphincter tone. Consequently, the combined effects of exogenous opioids result in increased gastroesophageal reflux, hard dry stools, incomplete evacuation, straining, and abdominal distension.

2.1 Product Information

Trade Name (established name): Amitiza® (lubiprostone)



Molecular Formula: $C_{20}H_{32}O_5F_2$

Molecular Weight: 390.46

Chemical Name: (-)-7-[(2R,4aR,5R,7aR)-2-(1,1-difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[b]pyran-5-yl]heptanoic acid

Route of Administration, Description, and Formulation: Lubiprostone occurs as white, odorless crystals or crystalline powder. Amitiza® is orally administered and available as an imprinted, oval, soft gelatin capsule in two strengths. Pink capsules contain 8 mcg of lubiprostone and the following inactive ingredients: medium-chain triglycerides, gelatin, sorbitol, ferric oxide, titanium dioxide, and purified water. Orange capsules contain 24 mcg of lubiprostone and the following inactive ingredients: medium-chain triglycerides, gelatin, sorbitol, FD&C Red #40, D&C Yellow #10, and purified water.

2.2 Tables of Currently Available Treatments for Proposed Indications

Treatment for OIC includes non-pharmacologic therapies such as dietary changes (e.g., increased fluid intake), manual evacuation, behavioral treatment (e.g., increased activity), and stress reduction. There is one FDA-approved drug for OIC in patients with advanced illness receiving palliative care (methylnaltrexone); however, medications used to treat constipation and colon cleansing products are used “off-label” to treat OIC.

Multiple medications (over-the-counter and prescription) are available for treatment of OIC, including: stool softeners such as docusate; bulk-forming laxatives such as psyllium, methylcellulose, and polycarbophil; stimulant laxatives such as bisacodyl, senna, and castor oil; saline osmotic laxatives such as sodium phosphate, magnesium citrate, and magnesium hydroxide; osmotic laxatives such as lactulose and sorbitol; lubricants such as mineral oil and glycerin; and other osmotic agents like polyethylene glycol (PEG) 3350 with electrolytes and PEG 3350 without electrolytes.

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 (CIC) in adults at the 24 mcg BID dose. Market approval was granted for lubiprostone in irritable bowel syndrome with constipation (IBS-C) in adult women at the 8 mcg BID dose in April 2008.

2.4 Important Safety Issues with Consideration to Related Drugs

No important safety issues with consideration to related drugs emerged during the review of this sNDA.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- April 22, 2010: **Type B, pre-sNDA meeting** between DGIEP and Sponsor to discuss the results of trials OBD-0631 and OBD-0632.
 - The Sponsor reported that after completion of OBD-0631 and OBD-0632, it had noted an interaction between methadone and lubiprostone, in which methadone impeded the pharmacologic activity of lubiprostone. Thus, the Sponsor asked if it would be acceptable to combine data from those two

trials in order to support an indication in a revised target population of non-methadone OBD patients. DGIEP indicated that this approach would not be acceptable and that at least one additional trial (OBD-1033) be performed specifically targeting the intended population.

- For future trials, DGIEP recommended that the primary endpoint be based on a responder analysis, rather than change in bowel frequency. The Agency indicated that trial OBD-1033, with a primary endpoint based on a responder analysis, would be weighed more heavily than trial OBD-0631 and that OBD-0631 would be considered supportive.
 - The Sponsor was asked to provide safety information for each new proposed indication separately by indication, as well as combined.
- August 24, 2010: Sponsor submitted a draft protocol and statistical analysis plan (SAP) of OBD-1033 to Agency for review. Further revisions from the Sponsor were submitted November 16, 2010. Key comments and recommendations from the statistician that reviewed the SAP and protocol, Dr. Wen Jen Chen, follow (comments were sent to Sponsor in an Advice Letter dated February 3, 2011):
- The primary efficacy analysis should be based on the intent-to-treat (ITT) population, defined as all patients randomized. Any patient who is randomized but has no efficacy assessment should be considered a failure.
 - To calculate the weekly SBM frequency rates, the number of days observed in a week should be used, rather than the number of observed hours in a week as defined in the SAP and protocol.
 - In the SAP, a multiplicity adjustment method was proposed only for an individual secondary endpoint with multiple comparisons and cannot control the overall type I error rate for all of the proposed secondary endpoints. Therefore, if the Sponsor planned to make additional claims of treatment benefits based on the secondary endpoint analyses, then the Sponsor must provide a multiplicity adjustment method to control the overall type I error rate at the two-sided significance level of 5% in the strong sense for the primary and secondary endpoint analyses. In this regard, the gate keeping approach may be useful.
 - For the primary endpoint analysis based on the ITT population, subjects with <4 days of data observed for a week should be considered missing and classified as non-responders for that week. For analyses of secondary endpoints, missing data should be treated as failures / non-responders.
 - Instead of applying Kaplan-Meier life table estimates and Cox proportional hazards regression model to analyze the proportion of subjects in each treatment group with their first SBM reported within 24 hours (48 hours) of first dose administration, the Cochran-Mantel-Haenszel procedure should be used, stratifying by clinical site to analyze such data.

- March 6, 2012: **Type B, pre-sNDA meeting** between DGIEP and Sponsor to discuss a planned efficacy supplement submission for the OIC indication. The preliminary results of trial OBD-1033 were also discussed.
 - DGIEP expressed concern that the results of OBD-1033 may not be adequately robust as a single phase 3 trial (e.g., per-protocol analysis did not support the results of the ITT analysis) and suggested that the primary analysis be based on the ITT population (as randomized) with early dropouts considered treatment failures. DGIEP recommended sensitivity analyses in OBD-1033 to confirm the primary analysis of the ITT population. The Sponsor agreed with these recommendations.
 - DGIEP requested confirmation that the responder rate analyses conform to the Agency's definitions of weekly responder, weekly non-responder, and monthly responder.
 - DGIEP requested safety data from each controlled trial for the OIC indication individually and pooled integrated analyses of safety data from the three controlled trials.
 - DGIEP indicated that review priority would be determined at the time of filing and that if the Sponsor desired a priority designation, the Sponsor's formal request should include a rationale for why it believes Amitiza® offers a significant improvement compared to products currently marketed.
 - DGIEP recommended that the Sponsor should address the drug-drug interaction potential between lubiprostone and commonly used opioids.
 - DGIEP recommended that in all phase 3 trials conducted and to be conducted, the Sponsor provide analyses of the primary and key secondary endpoints using opioid dose converted to morphine equivalent daily doses (MEDD) to evaluate if efficacy is confounded by the MEDD.
 - DGIEP clarified that although the primary efficacy endpoints used in OBD-0631, OBD-0632, and OBD-1033 assess OIC, these endpoints do not evaluate other opioid-induced gastrointestinal symptoms that define OBD. The Agency advised the Sponsor that in the event the Sponsor wished to pursue an OBD indication, the Sponsor would need to define an appropriately selected and validated endpoint that captures the signs and symptoms that define an OBD population.

2.6 Other Relevant Background Information

The Sponsor developed lubiprostone under IND 77,771.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Methods used to evaluate data quality and integrity included:

- Review of possible bias based on financial ties
- Seeking source documentation for efficacy analyses
- Evaluation of safety data by reviewing JMP datasets, case report forms, narratives, and verbatim terms
- Review of Sponsor's compliance with Good Clinical Practices

The Sponsor submitted the application in electronic modular format. The application was generally well organized and navigable. There were, however, several issues with incomplete or missing analyses/datasets. JMP datasets, for example, were submitted with several poorly defined dataset variables (including variables corresponding to baseline MEDD and the primary efficacy variable for trials OBD-0631 and OBD-0632). DGIEP sent two separate information requests to the Sponsor to clarify dataset variables and to provide well-commented and organized software programming code for each primary analysis dataset and efficacy table. Additionally, the Sponsor did not submit detailed listings of protocol violations for OBD-0631 and OBD-0632 as part of the original electronic sNDA. Further, the Sponsor did not provide results from explorations of treatment effects in age, gender, and racial subgroups, as required by 21 CFR 314.50(d)(5)(v), for the primary endpoint for OBD-0631 and OBD-0632 in the original submission. The Sponsor subsequently provided these subgroup analyses in response to information requests from DGIEP.

Given the failure of one of the three efficacy trials submitted as part of this sNDA and the use of different primary endpoints between the two trials used to support efficacy of lubiprostone for the proposed indication, extensive additional analyses were performed to evaluate the Sponsor's efficacy claims. Many of these additional analyses were requested in the 74-Day Letter. The Sponsor's response to information requested in the 74-Day Letter exceeded 1000 pages and given the voluminous data therein, this response triggered a major amendment that extended the review clock by 3 months.

3.2 Compliance with Good Clinical Practices

According to the Sponsor, all of the trials were conducted in accordance with U.S. Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR 50), Institutional Review Boards (21 CFR 56), and the obligations of clinical investigators (21 CFR 312). Per the Sponsor, the four trials submitted for this sNDA were conducted in accordance with U.S. Title 21 CFR on Good Clinical Practices (GCPs), which is consistent with the ethical principles set forth in the Declaration of Helsinki, the International Conference on Harmonisation, and the FDA.

A request for Office of Scientific Investigations (OSI) audit was placed for this sNDA. OSI inspected four separate clinical sites at the request of DGIEP: site # 1018, trial OBD-0631 (site with a large number of subjects); site # 1069, trial OBD-0631 (site with a large number of subjects and a higher than average responder status); site # 3019, trial OBD-1033 (site where suitability of data was initially questioned by Sponsor); and

site # 3098, trial OBD-1033 (site with a large number of subjects (>10) and a higher than average percentage of lubiprostone responders). Highlights of OSI's preliminary findings are discussed below. At the time of completion of this medical officer's review, OSI's recommendations are pending finalization. For details, please see Clinical Inspection Summary (CIS) by OSI medical officer Dr. Khairy Malek and OSI acting team leader Dr. Susan Leibenhaut (both reviews dated March 27, 2013). In her review, Dr. Leibenhaut indicated that an addendum to her CIS would be issued if conclusions change when the classifications for the inspections have been finalized.

OBD-0631

According to OSI, although the listed principal investigator (PI) at site # 1069 was Dr. Nelson Sandoval, three PIs participated at this site, one after the other. OSI, upon completion of inspection, noted that source documents from site # 1069 had been destroyed (presumably due to inadvertent shredding while in storage). OSI concluded that the data from site # 1069 could not be verified and are thus considered unreliable. Dr. Leibenhaut's preliminary classification of site # 1069 noted deviation(s) from regulations, but Dr. Leibenhaut did not agree with Dr. Malek, who classified the site as objectionable action indicated (OAI). For completeness, this clinical reviewer performed an analysis of the primary endpoint (mean change from baseline in spontaneous bowel movement (SBM) frequency at Week 8 in subjects without dose reduction) for OBD-0631 and the overall SBM responder rate for OBD-0631 excluding all the data generated from site # 1069. Results are in [Table 67](#) and [Table 68](#), but briefly, the treatment difference with subjects from site # 1069 excluded was similar to the treatment difference with subjects from site # 1069 included.

Additionally, in the study report for OBD-0631, the Sponsor noted (in Section 9.6) that:

"A re-monitoring of this study was completed [REDACTED] (b) (4) [REDACTED]. On-site monitoring visits were performed to complete source data verification and to confirm eCRFs, essential regulatory documents, drug accountability, and informed consent were adequately completed and documented. The database was locked and unlocked appropriately, and the endpoints were not changed. No subject efficacy data were changed during the re-monitoring process. As there may have been adjustments to the exposure window due to imputations of first/last dose, as well as additions to the violator listing based on re-monitoring findings, there are slight differences in the efficacy outputs versus the original lock."

OSI asked the Sponsor to explain the re-monitoring process and findings. The Sponsor indicated that based upon findings from Sponsor review of data at six investigative sites wherein adverse events noted in source documents were in some cases not reported in the electronic data capture system, the Sponsor, in conjunction with partner Takeda, decided to procure a third party contract research organization (CRO), [REDACTED] (b) (4) Research to re-monitor all site data. Of the 80 sites that enrolled subjects for OBD-

0631, 3 sites (representing 5 enrolled patients in total) did not respond to contact attempts by the Sponsor to gain access to trial files for re-monitoring.

The Sponsor noted that no changes to patient efficacy data, as collected in the electronic diary, could be made during the course of re-monitoring. The Sponsor explained two scenarios where a data correction made during re-monitoring could result in a change in efficacy endpoint: (1) a change to the exposure window; or (2) adjustment of patient inclusion in ITT for the primary endpoint. Re-monitoring of data from three subjects (1051003, 1052005, and 1072018) identified source discrepancies that led to addition of, or correction to, dose reduction dates. Because the primary endpoint analysis for OBD-0631 only included subjects that did not dose reduce prior to Week 8 of treatment, these three subjects were not included in the primary efficacy analysis. The Sponsor noted that mean change from baseline values for lubiprostone and placebo groups remained the same regardless of the inclusion of these patients, with no meaningful impact on the treatment effect.

Reviewer comments: *This reviewer's recommendation on regulatory action is not changed by the inability to verify source data from site # 1069 or the re-monitoring process in OBD-0631.*

OBD-1033

In the clinical study report (CSR) for OBD-1033, the Sponsor indicated that routine monitoring and subsequent audit of data collected at sites # 3019 and 3119 led the Sponsor to question the suitability of the data from these two sites. As a result, the modified ITT population excluded data from sites # 3019 and 3119 (note the original CSR referred to site # 3019 as "3109." The Sponsor corrected this error in a subsequent communication to the sNDA). DGIEP asked for more information on the nature of the issue at sites # 3019 and 3119. The Sponsor responded as follows:

"During the study, a representative from the monitoring team of the CRO vendor expressed concerns regarding source documentation at Site 3019. Improvement in the site's organization and record keeping was noted during subsequent monitoring visits to the site. The CRO vendor conducted a routine audit at Site 3019 on 19 and 20 October 2011. Although one major issue (maintenance of inadequate case histories) and some minor issues were identified, the auditor had no concerns about the integrity of the data collected at the site. Corrective action was taken to address the issues identified during the audit. Despite the results of the audit report, the Sponsor decided to have an independent third party vendor (b) (4) perform "for-cause audits" at Sites 3019 and 3119 (these sites shared the same Study Coordinator). These audits were conducted on 23 November 2011 (Site 3119) and 12-13 December 2011 (Site 3019). Because of the pending database lock (08 December 2011), the Sponsor decided to include the analysis of a modified ITT population in the event major GCP violations indicative of compromised data were confirmed at

the two sites. Again, the independent auditor concluded that there were no concerns related to the integrity of the data collected at the two sites.”

After inspecting site # 3019, OSI deemed data obtained from that site unacceptable (OAI). Although DGIEP had not requested an inspection of site # 3119, Dr. Malek’s review noted that the PI at site # 3119, Dr. Shura Moreno, was arrested for practicing without proper certification.

Reviewer comments: As noted above, the Sponsor, based on suspicions, performed efficacy analyses in an mITT population that excluded all subjects from sites # 3019 and 3119. These results are in section 6.1.4 Analysis of Primary Endpoint(s) and 6.1.5 Analysis of Secondary Endpoints(s), but in summary, analysis results with subjects from site # 3019 and 3119 excluded were similar to analysis results with subjects from site # 3019 and 3119 included. Thus, this reviewer’s recommendation on regulatory action is not changed by the possible data integrity issues at these two sites.

A Sponsor inspection was not originally planned for this sNDA review. However, in the course of clinical site inspections, several issues, including the re-monitoring of OBD-0631 and results of inspections at site # 3019 and site # 1069, prompted OSI to conduct a Sponsor inspection. From the totality of inspection results, Dr. Leibenhaut indicated that the data from trials OBD-1033 and OBD-0631, aside from the exceptions discussed above, could be used in support of this sNDA.

3.3 Financial Disclosures

The Sponsor provided a signed copy of FDA Form 3454 certifying that it has not entered into any financial arrangements with its clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the trial 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 54.2(f), the Sponsor certified that no clinical investigator received any significant payments of any sorts.

Reviewer comments: This officer reviewed results of OSI site inspections and financial disclosures statements from previous submissions by the Sponsor for the CIC and IBS-C indications. Investigators identified on previous site inspections as problematic (Edward Sargent) and investigators previously identified as receiving substantive monetary compensation from the Sponsor (John Johanson and Douglas Drossman) were not listed as investigators for any of the clinical trials for this submission.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Sponsor submitted no new quality data for review with this sNDA. Please refer to the quality review dated September 28, 2012 by Dr. Yong Wang for details.

4.2 Clinical Microbiology

The Sponsor submitted no microbiology data for review.

4.3 Nonclinical Pharmacology/Toxicology

Lubiprostone underwent extensive animal testing for general pharmacologic, toxicologic, genotoxic, and antigenic effects in various species as part of the original marketing application. Since approval of lubiprostone for IBS-C in April 2008, the Sponsor has conducted several additional nonclinical studies. In relation to the current sNDA, three nonclinical studies were submitted. The first two of these studies are briefly summarized below. The third study, which evaluated the interaction potential of methadone and lubiprostone, was reviewed by both Dr. Chakder and clinical pharmacologist Dr. Sandhya Apparaju. Therefore, this third study is discussed in section [4.4.2 Pharmacodynamics](#). For Dr. Chakder's detailed reviews of these three studies, please see pharmacology review dated March 18, 2013.

Study 050627 (dated January 31, 2008), studied the effect of lubiprostone in oxycodone-induced constipation in mice. A dose-finding test of oxycodone, by which constipation was induced in mice, was initially performed. The severity of constipation was assessed using the graphite marker propulsion ratio (the presence or absence of arrival of a graphite marker at the cecum 150 minutes after administration). Once the dose-finding model was complete, mice were treated with lubiprostone at doses of 0, 0.1, 1, 10, and 100 mcg/kg and oxycodone 5 mg/kg simultaneously. Lubiprostone increased the graphite marker propulsion ratio in a dose-dependent manner; this effect was statistically significant at a dose of 100 mcg/kg compared to the control group.

Study 8222133 (dated March 11, 2010), evaluated the gastrointestinal effects of lubiprostone on OIC in male mice. Lubiprostone was orally administered at doses of 0, 10, or 100 mcg/kg, immediately followed by intraperitoneal administration of morphine (5 mg/kg) or methadone (10 mg/kg), followed 15 minutes later by an orally administered charcoal meal. The mice were euthanized 20 minutes following the meal and the total distance the charcoal meal travelled was measured. The 100 mcg/kg dose of lubiprostone produced an increase in charcoal meal transit in the morphine dose group relative to the control group, but not in the methadone dose group. The study concluded that lubiprostone 100 mcg/kg antagonized the constipating gastrointestinal effects of morphine, but not methadone.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

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

4.4.2 Pharmacodynamics

There were no new clinical pharmacology studies in human subjects in this efficacy supplement. An *in vitro* pharmacology study that evaluated the interaction potential of methadone and lubiprostone was submitted to the nonclinical section of this sNDA. The study was reviewed by pharmacologist Dr. Sushanta Chakder and clinical pharmacologist Dr. Sandhya Apparaju. In this medical officer's assessment, Dr. Chakder's review findings concurred with Dr. Apparaju's (see Dr. Chakder's pharmacology review, dated March 18, 2013, for further details). Below, this medical officer summarizes Dr. Apparaju's review findings, focusing in particular on the clinical implications of the findings. For additional details, please refer to clinical pharmacology review by Dr. Apparaju dated March 6, 2013.

Study report number NSR0211-12-003-01, dated June 22, 2012, examined the effects of several opioid classes, including diphenylheptane opioids (e.g., methadone), on ClC-2. Cl⁻ currents were measured by short circuit current (I_{sc}) across T84 cells, and by whole cell patch clamp of recombinant human ClC-2 in stably transfected HEK293 cells in the presence and absence of methadone and morphine. The study showed that methadone inhibits lubiprostone-stimulated Cl⁻ currents in T84 intestinal cells and recombinant human ClC-2 (hClC-2). The Sponsor suggested that this action of diphenylheptane opioids (e.g., methadone), may serve as the basis for the possible reduced efficacy of lubiprostone in methadone-treated patients.

Dr. Apparaju's review of the study noted that prior addition of 5 μ M methadone caused major (~88%) inhibition of lubiprostone-stimulated I_{sc} in the T84 cell line. Additionally, in the HEK293 cell line, methadone added before or after 100 nM lubiprostone inhibited ClC-2 Cl⁻ currents in a concentration-dependent manner. Methadone exhibited half-maximal inhibition at approximately 0.1 μ M. When methadone was added before lubiprostone, greater inhibition (~90% at 1 μ M) was observed compared to when methadone was added after lubiprostone (~60% at 1 μ M). Norpropoxyphene (another diphenylheptane opioid) exhibited half-maximal inhibition at 0.075 μ M. A survey of other commonly used opioids showed lack of inhibition of T84 cell lubiprostone-stimulated I_{sc} by morphine, oxycodone, oxymorphone, and hydromorphone at 5 μ M.

In summary, the data from this *in vitro* pharmacology study suggest that co-administration with diphenylheptane opioids (e.g., methadone) may reduce the effects of lubiprostone on intestinal secretion and transit. Dr. Apparaju noted that clinically relevant oral doses of methadone used in chronic pain management (e.g., 2.5 mg to 10 mg every 8 to 12 hours, slowly titrated to effect) would yield local (gastrointestinal) concentrations high enough to interact with activity of lubiprostone at CIC-2.

4.4.3 Pharmacokinetics

The Sponsor conducted no further pharmacokinetics studies for this sNDA.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1. Clinical Trials Submitted to Support sNDA

Trial ID	Trial Design	Product Dose, Route, and Regimen	Total N ¹	No. of Subjects Treated / Completed	Key Inclusion Criteria
OBD-1033 Efficacy & Safety US/Europe (105)	Phase 3, DB, R, PC Multicenter 12 weeks	LBP 24 mcg PO BID	447	219/169	Age ≥18 y, OIC, ² chronic non-cancer pain treated consistently with any opioid (except methadone or congener of methadone³) for ≥30 d and throughout trial
		Placebo PO BID		220/184	
OBD-0631 Efficacy & Safety US/Canada (80)	Phase 3, DB, R, PC Multicenter 12 weeks	LBP 24 mcg PO BID	443	222/152	Age ≥18 y, OIC, chronic non-cancer pain treated consistently with any opioid for ≥30 d and throughout trial
		Placebo PO BID		217/154	
OBD-0632 Efficacy & Safety US/Canada (88)	Phase 3, DB, R, PC Multicenter 12 weeks	LBP 24 mcg PO BID	451	224/152	Age ≥18 y, OIC, chronic non-cancer pain treated consistently with any opioid for ≥30 d and throughout trial
		Placebo PO BID		213/153	
OBD-06S1 Long Term Safety US/Canada (137)	OL, Multicenter, Extension 36 weeks	LBP 24 mcg PO BID as needed	443	439/286	Completed 12 weeks of treatment in trial OBD-0631 or OBD-0632, required continued treatment with opioids for non-cancer pain

Abbreviations: BID, twice daily; d, days; DB, double-blind; LBP, lubiprostone; OBD, opioid-induced bowel dysfunction; OIC, opioid-induced constipation; OL, open-label; PC, placebo-controlled; R, randomized; y, years.

¹N=Number of patients who were randomized into OBD-1033, OBD-0631, and OBD-0632. For OBD-06S1, N=number of patients who completed OBD-0631 or OBD-0632 and subsequently enrolled in OBD-06S1.

²OIC was defined as an average of <3 SBMs per week during the last 2 weeks of the screening period and at least one of the following for ≥25% of SBMs during each week of the screening period: hard or very hard stools, sensation of incomplete evacuation, and/or moderate to very severe straining associated with SBMs.

³Congener of methadone included propoxyphene (frequently administered as Darvocet).

Source: Reviewer's table adopted from Sponsor's Table 2.7.3.6-1, page 112 of 119, Summary of Clinical Efficacy.

5.2 Review Strategy

The phase 3, double-blind trials OBD-1033, OBD-0631, and OBD-0632 are the principal source of data supporting the determination of efficacy of lubiprostone. The clinical review of efficacy is discussed in detail in section 6 [Review of Efficacy](#). These three 12-week efficacy trials also gathered safety data, which in conjunction with the safety data obtained in the open-label extension trial OBD-06S1, will be reviewed in detail in section 7 [Review of Safety](#).

5.3 Discussion of Individual Studies/Clinical Trials

See [Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033](#), [Appendix 3: Discussion of Individual Trials: Trial SMR/0211 OBD-0631](#), [Appendix 4: Discussion of Individual Trials: Trial SMR/0211 OBD-0632](#), and [Appendix 5: Discussion of Individual Trials: Trial SMR/0211 OBD-06S1](#) for detailed discussion of each of the clinical trials submitted for this sNDA. A brief overview of the trials follows.

5.3.1 Trial OBD-1033

OBD-1033 was a multicenter, randomized, placebo-controlled, double-blinded, parallel-group phase 3 trial of the efficacy and safety of lubiprostone in adults (age ≥ 18 years) with chronic non-cancer pain and OIC not taking a diphenylheptane opioid. The trial consisted of a screening visit 3 weeks prior to first dose of medication, a double-blind period of 12 weeks, and a follow up visit at week 14.

Key inclusion criteria included: (1) treatment for chronic non-cancer-related pain with any full agonist opioid other than methadone or congener of methadone (propoxyphene or other combination opioid containing propoxyphene) for ≥ 30 days prior to screening; (2) OIC, defined as having an average of < 3 spontaneous bowel movements (SBMs) per week during the screening period (with “spontaneous” defined as bowel movements not occurring within 24 hours after use of a rescue laxative) and ≥ 1 of 3 associated signs/symptoms (hard or very hard stools, sensation of incomplete evacuation, and/or moderate to very severe straining associated with SBMs) for $\geq 25\%$ of SBMs during each week of the screening period (as reported in the daily diary); and (3) discontinuation of laxatives and stool softeners from the screening visit through the completion of the trial.

Key exclusion criteria included: (1) use of methadone or a congener of methadone; (2) changes to opioid regimen (including adjustment of MEDD by $\geq 30\%$) within 30 days of screening; (3) known or suspected disorders of the large or small bowel (including ulcerative colitis or Crohn’s disease), gastrointestinal surgery within 90 days prior to screening visit, or history of bowel resection at any time; and (4) history of clinically significant cardiovascular or other systemic disease (as judged by investigator), unless the investigator felt the condition would not interfere with study assessments or result in

increased risk to the subject. Subjects not meeting eligibility criteria at the screening visit or randomization visit were considered screen failures (see schedule of trials for OBD-1033 in [Table 106](#) and for OBD-0631/OBD-0632 in [Table 116](#)).

At the beginning of the 3-week screening period, laxatives and other prohibited concomitant medications (listed in detail in [Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033](#)) were stopped and recording of daily bowel habits begun via electronic diary (eDiary). The diary prompted subjects to provide information each evening prior to bedtime about the constipation events during the preceding day. The entry window was since the prior night's entry, if available, or for the entire previous day, if a diary entry was not completed the prior night (48-hour entry window). For efficacy analyses, the baseline period was 14 days prior to the first dose of study drug and was used to determine disease status and other demographic factors at baseline. For example, constipation status at baseline was defined based on the average of diary entries for the 14 days prior to the administration of the first drug dose.

Reviewer comments: Although this reviewer acknowledges that allowing usual use of laxatives as needed while concurrently receiving lubiprostone during a clinical trial might confound efficacy assessment, the discontinuation of subjects' usual laxative regimen at the onset of the screening period has the potential to create a situation that does not accurately capture each subject's true baseline constipation status.

For instance, if a subject was using a laxative 3 times weekly and with such a regimen, was having an average of 5 BMs/week and 3 SBMs/week, discontinuation of the laxative at the onset of screening would be expected to reduce that subject's BM and SBM frequency. Thus, the "baseline" constipation status that would be determined based on diary entries for the 14 days prior to the first dose of study drug might instead document a BM frequency of 3 BMs/week and 0 SBMs/week (the BMs were not "spontaneous" because they were produced following laxative use). Then, if that subject was randomized to receive twice daily lubiprostone and subsequently had an average of 5 BMs/week and 3 SBMs/week for the trial's duration, the study drug would be deemed efficacious, when in actuality, the subject would be having the same BM and SBM frequency whether taking "usual" laxative 3 times weekly or lubiprostone twice daily.

Based on the discussion above, it remains unclear to this reviewer whether in such a subject, the study drug has demonstrated an advantage over the usual laxative regimen used prior to trial enrollment. To explore this issue further, DGIEP asked the Sponsor to provide, for each efficacy trial, the mean BM frequency and complete BM frequency for subjects prior to the screening visit, at which time the subjects' usual laxative regimen was stopped. The Sponsor responded that this information had not been captured and confirmed that any BM frequency data captured in daily diaries from screening onward reflected patient bowel habits without use of laxative medications. Baseline BM, complete BM, SBM, and complete SBM frequency data are presented in [Table 4](#), but

because true baseline bowel habit data were not collected, the provided data may fail to capture patient bowel habits prior to screening.

The treatment period began with the first dose of study medication (randomization visit) and ended upon completion of the end of treatment visit or upon administration of the last dose. Eligible subjects were randomly assigned to blinded doses of lubiprostone (24 mcg) twice daily (BID) or matching placebo in a 1:1 ratio. A dose reduction may have been initiated by the investigator if severe nausea, severe diarrhea, or another adverse event (AE) was reported by the subject to the site and was ongoing for ≥ 3 days. In these cases the investigator, in consultation with the subject and/or medical monitor, may have reduced study medication to once daily (QD) dosing. Once a dose reduction occurred, the subject could resume the BID regimen at the investigator's discretion. Rescue laxatives (principally bisacodyl suppositories and if needed, a saline enema) were allowed during the trial in the event that no BM occurred within a 3-day period; however, the use of rescue laxatives was not allowed within 24 hours prior to the first dose of the study drug or during the first 72 hours following treatment initiation.

During the 12-week double-blind period, subjects had three telephone assessments (at week 1, week 6, and week 10) and three clinic assessments (at week 4, week 8, and week 12). A final follow-up assessment occurred 2 weeks following the end of the double-blind period. The patient populations used for efficacy and safety analyses were:

- Safety-evaluable population: All randomized subjects who took at least one dose of study medication were included in the safety analysis.
- Intent-to-treat (ITT) population: All randomized subjects who took at least one dose of study medication and had at least one treatment-period diary entry were used for efficacy, demographic, and baseline characteristics data analysis. Subjects in the ITT population were grouped with the treatment group to which they were randomized, regardless of which treatment they actually received.
- Modified intent-to-treat (mITT) population: Defined only for trial OBD-1033. Routine monitoring and subsequent audit of data collected at sites # 3019 and 3119 led the Sponsor to question the suitability of the data. As a result, a mITT population was used that excluded data from sites # 3019 and 3119. See section [3.2 Compliance with Good Clinical Practices](#) for additional details.
- Per-protocol population: ITT subjects who were randomized and met the detailed inclusion and exclusion criteria. The determination of the per-protocol population was made during the blinded, "frozen" data review.
- Completers population: Subjects who completed the treatment regimen through Week 12; this population was used for supportive analyses.

Reviewer comments: Although the Sponsor pre-defined the ITT population in the SAP as all randomized subjects who had received at least one study treatment and had at least one post-treatment diary entry, a true ITT population should consist of all randomized subjects. Thus, the Sponsor was asked to perform analyses on the primary

endpoints in the true ITT population (all randomized subjects) for each of the efficacy trials. The results for OBD-1033 and OBD-0631 are presented in [Table 69](#).

The primary efficacy endpoint was the overall SBM response rate in ITT subjects. A responder was defined as a subject who had ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥ 3 SBMs per week for at least 9 of the 12 treatment weeks. Weekly SBM frequency rate was calculated on an hourly basis ($168 \times \text{number of SBMs} / \text{number of hours observed}$). The Sponsor's hourly-based assessment was discordant with the Agency's recommendation in the Advice Letter dated February 3, 2011 (see section 2.5 Summary of Presubmission Regulatory Activity Related to Submission). In that Advice Letter, the Agency advised the Sponsor to calculate the weekly SBM frequency rates using the number of days observed in a week rather than the number of observed hours in a week. During the review of this sNDA, the Sponsor was asked to perform exploratory analyses using a daily-based assessment for SBM frequency calculation. Results of these exploratory analyses are summarized in section 6.1.10 Additional Efficacy Issues/Analyses.

There were multiple secondary endpoints, but the Sponsor did not pre-specify a hierarchy of evaluation for all of these endpoints in the SAP. A list of all secondary and exploratory efficacy endpoints is in [Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033](#). Handling of missing data is discussed in detail in the efficacy sections, [6.1.4 Analysis of Primary Endpoint\(s\)](#) and [6.1.5 Analysis of Secondary Endpoints\(s\)](#), and in [Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033](#). Safety evaluations during the trial involved reporting of AEs coded to Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms, physical examination and clinical laboratory tests at pre-specified clinic visits, and assessment of nausea, pain, opioid dose adjustment, and rescue laxative usage. Detailed listings of safety evaluations are also in [Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033](#).

5.3.2 Trials OBD-0631 and OBD-0632

OBD-0631 and OBD-0632 were also multicenter, randomized, placebo-controlled, double-blinded, parallel-group phase 3 trials of the efficacy and safety of lubiprostone in adults (age ≥ 18 years) with chronic non-cancer pain and OIC. OBD-0631 and OBD-0632 were identical in trial design and were conducted prior to OBD-1033. As in OBD-1033, OBD-0631 and OBD-0632 consisted of a screening visit 3 weeks prior to first dose of medication, a double-blind period of 12 weeks, and a follow up visit at week 14.

Key inclusion and exclusion criteria were similar to OBD-1033, with the major exception that trials OBD-0631 and OBD-0632 also included subjects who were on methadone (or congener of methadone) for treatment of chronic non-cancer-related pain. The principal reasons for exclusion of subjects on methadone from trial OBD-1033 related to: (1)

failure of trial OBD-0632, which is discussed at length in section [6.1.4 Analysis of Primary Endpoint\(s\)](#) and [Appendix 4: Discussion of Individual Trials: Trial SMR/0211 OBD-0632](#); and (2) nonclinical studies that demonstrated an inhibitory interaction between methadone and lubiprostone (see section [4.4.2 Pharmacodynamics](#)).

Screening procedures, treatment procedures and timelines for trials OBD-0631 and OBD-0632 were identical to those for OBD-1033. As in OBD-1033, a dose reduction may have been initiated by the investigator if severe nausea, severe diarrhea, or another AE was reported by the subject to the site and was ongoing for ≥ 3 days. In these cases the investigator, in consultation with the subject and/or medical monitor, may have reduced study medication to QD dosing. Unlike OBD-1033, which allowed resumption of the BID regimen at the investigator's discretion in subjects who had undergone dose reduction, subjects in trials OBD-0631 and OBD-0632 who had undergone dose reduction continued the reduced dose until the end of the treatment period. Procedures regarding use of rescue laxatives were similar to those used in OBD-1033. However, unlike OBD-1033, which permitted use of rescue laxatives beyond 72 hours following treatment initiation, in trials OBD-0631 and OBD-0632, the use of rescue laxatives was not permitted during the first week following treatment initiation. The patient populations used for efficacy and safety analyses in OBD-0631 and OBD-0632 were identical to those used in OBD-1033, except that there was no mITT population in OBD-0631 and OBD-0632.

In contrast to OBD-1033, trials OBD-0631 and OBD-0632 did not use the overall SBM response as the primary efficacy endpoint. Instead, the primary efficacy endpoint was the change in frequency of SBMs from baseline at Week 8 in subjects without dose reduction. Weekly SBM frequency rate was calculated on an hourly basis ($168 \times$ number of SBMs / number of hours observed). As with OBD-1033, there were multiple secondary endpoints, for which a hierarchy of evaluation was either not pre-specified or poorly described in the SAP. A list of all secondary and exploratory efficacy endpoints is in [Appendix 3: Discussion of Individual Trials: Trial SMR/0211 OBD-0631](#). Handling of missing data is discussed in detail in the efficacy sections, [6.1.4 Analysis of Primary Endpoint\(s\)](#) and [6.1.5 Analysis of Secondary Endpoints\(s\)](#) and in [Appendix 3: Discussion of Individual Trials: Trial SMR/0211 OBD-0631](#). Safety evaluations were essentially identical to those of OBD-1033 and are described in [Appendix 3: Discussion of Individual Trials: Trial SMR/0211 OBD-0631](#).

5.3.3 Trial OBD-06S1

OBD-06S1 was a 36-week multicenter, open-label phase 3 trial of the safety of lubiprostone 24 mcg BID as needed in adults with chronic non-cancer pain and OIC. Subjects who had completed the 12-week efficacy trials OBD-0631 and OBD-0632 were eligible to enroll in OBD-06S1. Details of eligibility criteria, trial procedures and conduct, and outcome measures in OBD-06S1 are in [Appendix 5: Discussion of Individual Trials: Trial SMR/0211 OBD-06S1](#).

6 Review of Efficacy

Efficacy Summary

Reviewer comments: It should be noted that at the time of completion of this medical officer's primary review, the statistical team's review of efficacy is still pending. As such, the analysis results (e.g., p-values, ITT population as defined by the Sponsor versus ITT population consisting of all randomized patients) presented in this review may differ somewhat from the analysis results presented by the statistical review team.

6.1 Indication

The proposed indication is "for the treatment of opioid-induced constipation (b) (4)

[REDACTED]

6.1.1 Methods

The Sponsor submitted three double-blind, placebo-controlled, 12-week clinical trials for this sNDA. Evidence for the efficacy of lubiprostone comes from two phase 3 trials, OBD-1033 and OBD-0631. OBD-1033 was a multi-center, parallel group, double-blind, placebo-controlled trial whose primary objective was to evaluate the efficacy and safety of lubiprostone for its proposed indication, treatment of OIC in adults with chronic non-cancer pain.

Subjects eligible to participate were those ≥ 18 years of age who had been consistently treated for chronic, noncancer-related pain with any opioid (except methadone or a congener of methadone) for ≥ 30 days prior to screening, diagnosed with OIC, capable of utilizing an eDiary to report their daily SBMs, and willing to continue opioid therapy and discontinue the use of laxatives, stool softeners, and other concomitant medications affecting gastrointestinal motility throughout the trial. Detailed inclusion and exclusion criteria are in [Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033](#). The Sponsor defined an SBM as any BM that did not occur within 24 hours after rescue laxative use. OIC was defined as an average of < 3 SBMs/week and at least one of the following for $\geq 25\%$ of SBMs during each week of the screening period: (1) hard/very hard stools; (2) sensation of incomplete evacuation; and/or (3) moderate to very severe straining associated with SBMs. The primary efficacy endpoint for trial OBD-1033 was the overall SBM responder rate in ITT subjects.

OBD-0631 was also a multi-center, double-blind, placebo-controlled trial whose primary objective was to evaluate the efficacy and safety of lubiprostone for treatment of OIC in adults with chronic non-cancer pain. Trial design and inclusion/exclusion criteria were similar to those of trial OBD-1033, but trial OBD-0631 included subjects taking

methadone or a congener of methadone for chronic non-cancer pain. The primary efficacy endpoint for trial OBD-0631 was change from baseline in SBM frequency at Week 8 in subjects without dose reduction. The detailed protocol of trial OBD-0631 is in [Appendix 3: Discussion of Individual Trials: Trial SMR/0211 OBD-0631](#).

A third trial, OBD-0632, identical in design, inclusion/exclusion criteria, and endpoints, to trial OBD-0631, was also conducted, but this trial failed on the primary endpoint. The findings of OBD-0632 with respect to baseline demographics, subject disposition, and the primary efficacy endpoint are discussed alongside the findings of OBD-1033 and OBD-0631, but the focus of this review of efficacy will be on trials OBD-1033 and OBD-0631. Results of secondary and exploratory analyses of trial OBD-0632 are presented separately in [Appendix 4: Discussion of Individual Trials: Trial SMR/0211 OBD-0632](#).

6.1.2 Demographics

[Table 2](#) and [Table 3](#) present baseline demographic data for the three efficacy trials, excluding cases for which information is not available or is unknown.

Table 2. Demographic Characteristics at Baseline – OBD-1033, OBD-0631, and OBD-0632 (ITT Population)

Variable	OBD-1033		OBD-0631		OBD-0632	
	Placebo (N=220)	Lubiprostone (N=219)	Placebo (N=217)	Lubiprostone (N=221)	Placebo (N=212)	Lubiprostone (N=223)
Sex, n (%)						
Male	82 (37.3)	81 (37.0)	73 (33.6)	85 (38.5)	86 (40.6)	83 (37.2)
Female	138 (62.7)	138 (63.0)	144 (66.4)	136 (61.5)	126 (59.4)	140 (62.8)
Race, n (%)						
American Indian/Alaska Native	0 (0.0)	1 (0.5)	2 (0.9)	3 (1.4)	3 (1.4)	4 (1.8)
Asian	1 (0.5)	1 (0.5)	3 (1.4)	3 (1.4)	1 (0.5)	1 (0.4)
Black/African American	38 (17.3)	35 (16.0)	35 (16.2)	42 (19.0)	17 (8.1)	20 (9.0)
White	176 (80.0)	182 (83.1)	175 (81.0)	170 (76.9)	185 (87.7)	194 (87.0)
Other	5 (2.3)	0 (0.0)	1 (0.5)	3 (1.4)	5 (2.4)	4 (1.8)
Age (years)						
Mean ± Standard Deviation	51.5 ± 11.68	51.9 ± 9.01	49.9 ± 11.94	50.1 ± 9.89	49.8 ± 10.44	48.9 ± 9.85
Median (Minimum, Maximum)	52.0 (22, 80)	52.0 (20, 82)	50.0 (21, 77)	(19, 77)	50.0 (22, 86)	49.0 (21, 79)
Age Group, n (%)						
<50 Years	89 (40.5)	77 (35.2)	108 (49.8)	113 (51.1)	103 (48.6)	112 (50.2)
≥50 Years and <65 Years	99 (45.0)	128 (58.4)	87 (40.1)	89 (40.3)	95 (44.8)	99 (44.4)
≥65 Years	32 (14.5)	14 (6.4)	22 (10.1)	19 (8.6)	14 (6.6)	12 (5.4)

Note: There was one subject in the placebo arm of OBD-0631 and one subject in the placebo arm of OBD-0632 whose race information was missing.
 Source: Reviewer's table, adapted from Sponsor's Table 2.7.3.3-4, page 26 to 27 of 119, Summary of Clinical Efficacy.

Table 3. Demographic Characteristics at Baseline (Continued) – OBD-1033, OBD-0631, and OBD-0632 (ITT Population)

Variable	OBD-1033		OBD-0631		OBD-0632	
	Placebo (N=220)	Lubiprostone (N=219)	Placebo (N=217)	Lubiprostone (N=221)	Placebo (N=212)	Lubiprostone (N=223)
Baseline Observed Combined Morphine Equivalent Daily Dose (mg)						
Mean ± Standard Deviation	96.5 ± 118.80	126.7 ± 223.71	250.7 ± 456.26	285.6 ± 473.79	331.6 ± 444.63	372.7 ± 787.00
Median (Minimum, Maximum)	43.5 (5, 750)	52.5 (5, 2271)	113.8 (5, 3656)	150.0 (8, 4000)	171.9 (5, 2736)	180.0 (4, 7605)
Baseline Duration of Opioid Use (Months)¹						
Mean ± Standard Deviation	55.5 ± 61.12	50.1 ± 57.63	54.9 ± 59.61	52.7 ± 55.79	49.4 ± 52.40	52.9 ± 52.66
Median (Minimum, Maximum)	33.6 (2, 399)	27.7 (2, 360)	33.2 (2, 490)	35.8 (2, 393)	35.3 (2, 321)	37.7 (2, 280)
Medical Conditions That May Have Been Associated with Opioid Use,^{1,2} n (%)						
Arthralgia	25 (11.4)	32 (14.6)	27 (12.4)	28 (12.7)	26 (12.3)	23 (10.3)
Arthritis	24 (10.9)	23 (10.5)	23 (10.6)	40 (18.1)	32 (15.1)	34 (15.2)
Back pain	110 (50)	118 (53.9)	96 (44.2)	115 (52)	91 (42.9)	103 (46.2)
Fibromyalgia	25 (11.4)	26 (11.9)	35 (16.2)	27 (12.2)	22 (10.4)	32 (14.3)
Intervertebral Disc Degeneration ³	53 (24.1)	58 (26.5)	69 (31.8)	81 (36.7)	70 (33)	91 (40.8)
Muscle Spasms	27 (12.3)	26 (11.9)	38 (17.5)	34 (15.4)	30 (14.2)	28 (12.6)
Musculoskeletal Pain	13 (5.9)	14 (6.4)	8 (3.7)	13 (5.9)	9 (4.2)	7 (3.1)
Neck Pain	32 (14.5)	31 (14.2)	24 (11.1)	25 (11.3)	20 (9.4)	21 (9.4)
Osteoarthritis	53 (24.1)	68 (31.1)	49 (22.6)	68 (30.8)	60 (28.3)	61 (27.4)
Spinal Column Stenosis ⁴	37 (16.8)	48 (21.9)	51 (23.5)	57 (25.8)	58 (27.4)	52 (23.3)

¹These were post hoc analyses performed by the Sponsor at the request of DGIEP.

²Trials did not directly capture medical conditions associated with opioid use. In some cases, subjects may be captured in multiple analysis sets due to medical history inclusive of multiple pain conditions. The table reflects the Sponsor's identification of potential medical conditions that may have been associated with opioid use.

³Includes intervertebral disc degeneration / intervertebral disc disorder / intervertebral disc protrusion.

⁴Includes spinal column stenosis / spinal cord injury / spinal fusion surgery / spinal osteoarthritis.

Source: Reviewer's table, adapted from Sponsor's Table 2.7.3.3-4, page 27 of 119, Summary of Clinical Efficacy; Table 11.1.1.1.1, page 736; Table 11.1.1.2.1, page 794; Table 12.1.1.2.1, page 851; and Table 13.1.1.2.1, page 908 from response to 74-Day Letter IR.

Reviewer comments: *The placebo and lubiprostone arms within each of the three double-blind trials were generally well matched with regard to gender, race, and age. When comparing baseline demographics across trials, OBD-0632 enrolled fewer black/African-American subjects than OBD-0631 and OBD-1033. Age groups were balanced across both arms of each trial, with the exception of OBD-1033, in which the number of subjects 65 years or older in the placebo arm was more than twice that in the lubiprostone arm. Given what is known about the mechanism of action of lubiprostone, no significant differences in efficacy findings would be expected based on these demographic differences between the three trials. Overall, the demographic subsets of subjects were limited by the inadequate percentage of geriatric subjects; however, consistency therein was generally well maintained across the study groups.*

Regarding principal diagnoses underlying chronic pain, the Sponsor noted that trials did not directly capture medical conditions associated with opioid use. Therefore, there was no clear delineation of a primary pain condition for which subjects were on chronic opioids. [Table 3](#) reflects the Sponsor's identification of potential medical conditions that may have been associated with opioid use. Overall, back pain was the most common potential medical condition associated with opioid use in all three trials, and incidence of back pain was comparable across the two treatment groups in each trial.

Mean duration of opioid use at baseline was generally similar across treatment arms for the three efficacy trials. The baseline MEDD was higher in both the placebo and lubiprostone arms of trial OBD-0632 than the treatment arms of trial OBD-0631. Subgroup analyses, in which baseline demographics were stratified by subjects on methadone (or congeners of methadone) and subjects not on methadone (or congeners of methadone), are presented in [Table 136](#) of [Appendix 4: Discussion of Individual Trials: Trial SMR/0211 OBD-0632](#). This subgroup analysis revealed that the MEDD was higher in subjects on methadone (or congeners of methadone) than subjects not on methadone (or congeners of methadone) in the placebo and lubiprostone arms of both trials (OBD-0631 and OBD-0632).

Baseline Constipation Status

Baseline constipation status was determined by responses to constipation-related diary questions for the 2 weeks prior to administration of the first dose of study drug. At the screening visit (Day -24 to -21), subjects' laxatives and other prohibited medications were stopped and the eDiary distributed (discussed in section [5.3 Discussion of Individual Studies/Clinical Trials](#), and described in detail in [Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033](#)). Parameters used to determine baseline constipation status included:

- SBM frequency per week: An SBM was defined as any BM that did not occur within 24 hours after use of a rescue laxative
- Average stool consistency of SBMs: 0 (very loose), 1 (loose), 2 (normal), 3 (hard), 4 (very hard)
- Hard or very hard stool consistency in $\geq 25\%$ SBMs

- Severity of constipation: 0 (absent), 1 (mild), 2 (moderate), 3 (severe), 4 (very severe)
- Average degree of straining associated with SBMs: 0 (absent), 1 (mild), 2 (moderate), 3 (severe), 4 (very severe)
- Moderate or worse straining $\geq 25\%$ SBMs
- Sensation of incomplete evacuation $\geq 25\%$ SBMs
- Abdominal discomfort: 0 (absent), 1 (mild), 2 (moderate), 3 (severe), 4 (very severe)
- Abdominal bloating: 0 (absent), 1 (mild), 2 (moderate), 3 (severe), 4 (very severe)
- Bowel habit regularity: 1 (very regular) to 7 (very irregular)
- Percent days of rescue laxative use

In an information request to the Sponsor, DGIEP also asked the Sponsor to provide the BM frequency and complete BM frequency for subjects at baseline. [Table 4](#) and [Table 5](#) summarize constipation status at baseline for the three trials.

Table 4. Constipation Status at Baseline – OBD-1033, OBD-0631, and OBD-0632 (ITT Population)

Variable	OBD-1033		OBD-0631		OBD-0632	
	Placebo	LBP	Placebo	LBP	Placebo	LBP
BM Frequency per Week,¹ N	220	219	216	219	212	222
Mean ± Standard Deviation	1.9 ± 0.91	1.9 ± 1.03	2.4 ± 1.39	2.4 ± 1.54	2.7 ± 1.73	2.8 ± 1.82
Median (Minimum, Maximum)	2.0 (0, 6)	2.0 (0, 6.1)	2.1 (0, 8.0)	2.2 (0, 12)	2.5 (0, 11)	2.3 (0, 12)
Complete BM Frequency per Week,² N	220	219	216	219	212	222
Mean ± Standard Deviation	0.5 ± 0.67	0.5 ± 0.70	0.6 ± 0.84	0.8 ± 1.23	0.8 ± 1.02	0.7 ± 1.13
Median (Minimum, Maximum)	0 (0, 3.5)	0 (0, 3.5)	0.50 (0, 4.3)	0.50 (0, 11)	0.54 (0, 7)	0 (0, 6.5)
SBM Frequency per Week,³ N	220	219	216	221	212	222
Mean ± Standard Deviation	1.4 ± 0.81	1.3 ± 0.81	1.5 ± 0.96	1.4 ± 1.1	1.6 ± 1.30	1.6 ± 1.34
Median (Minimum, Maximum)	1.5 (0, 4.2)	1.0 (0, 5)	1.5 (0, 6.5)	1.5 (0, 7.5)	1.5 (0, 7.5)	1.5 (0, 8.5)
Complete SBM Frequency per Week, N	220	219	216	219	212	222
Mean ± Standard Deviation	0.3 ± 0.59	0.3 ± 0.56	0.4 ± 0.59	0.4 ± 0.70	0.5 ± 0.80	0.3 ± 0.66
Median (Minimum, Maximum)	0 (0, 3)	0 (0, 3)	0 (0, 3)	0 (0, 5)	0 (0, 7)	0 (0, 5)
Hard or Very Hard Stool Consistency in ≥25% SBMs, N	220	219	217	221	212	223
Yes, n (%)	178 (80.9)	178 (81.3)	163 (75.1)	167 (75.6)	162 (76.4)	163 (73.1)
Sensation of Incomplete Evacuation ≥25% of SBMs, N	220	219	217	221	212	223
Yes, n (%)	177 (80.5)	167 (76.3)	169 (77.9)	155 (70.1)	157 (74.1)	165 (74.0)
Moderate or Worse Straining ≥25% of SBMs, N	220	219	217	221	212	223
Yes, n (%)	193 (87.7)	190 (86.8)	180 (82.9)	179 (81.0)	166 (78.3)	177 (79.4)

Abbreviations: LBP, lubiprostone

¹Number of bowel movements (BMs) per week at baseline was calculated as follows: (Number of reported BMs / Number of observed hours) x 168 hours.

²Completeness of a BM or SBM was determined based on the following question in the daily eDiary: "Did your bowels feel completely empty after the BM? Y/N."

³An SBM was defined as any BM that did not occur within 24 hours after use of a rescue laxative.

Source: Reviewer's table, adapted from Sponsor's Table 2.7.3.3-5, pages 29 to 31 of 119, Summary of Clinical Efficacy; Table 1.1.5.1.1, page 32, response to IR6; and Table 1.3.19.9, module 5.3.5.3, pages 2227 to 2228 of 2585, Integrated Summary of Efficacy.

Table 5. Constipation Status at Baseline (Continued) – OBD-1033, OBD-0631, and OBD-0632 (ITT Population*)

Variable	OBD-1033		OBD-0631		OBD-0632	
	Placebo	Lubiprostone	Placebo	Lubiprostone	Placebo	Lubiprostone
Average Consistency,¹ N	200	199	197	187	183	195
Mean ± Standard Deviation	2.9 ± 0.83	3.0 ± 0.73	3.0 ± 0.83	3.0 ± 0.86	2.9 ± 0.85	3.0 ± 0.83
Median (Minimum, Maximum)	3.0 (0, 4)	3.0 (0.5, 4)	3.0 (0.5, 4)	3.0 (0, 4)	3.0 (0, 4)	3.00 (0, 4)
Severity of Constipation,² N	220	219	217	221	212	223
Mean ± Standard Deviation	2.3 ± 0.73	2.4 ± 0.76	2.3 ± 0.75	2.3 ± 0.77	2.3 ± 0.74	2.4 ± 0.77
Median (Minimum, Maximum)	2.3 (0, 4)	2.4 (0.1, 4)	2.3 (0.4, 4)	2.4 (0.3, 4)	2.2 (0.1, 4)	2.4 (0.1, 4)
Average Degree of Straining,² N	200	199	197	187	183	195
Mean ± Standard Deviation	2.6 ± 0.81	2.7 ± 0.80	2.6 ± 0.84	2.7 ± 0.90	2.5 ± 0.87	2.7 ± 0.91
Median (Minimum, Maximum)	2.7 (0, 4)	3.0 (0.5, 4)	2.8 (0, 4)	3.0 (0, 4)	2.6 (0, 4)	2.8 (0, 4)
Abdominal Discomfort,² N	220	219	217	221	212	223
Mean ± Standard Deviation	2.2 ± 0.70	2.2 ± 0.71	2.2 ± 0.70	2.2 ± 0.72	2.1 ± 0.74	2.2 ± 0.74
Median (Minimum, Maximum)	2.1 (0.2, 3.9)	2.1 (0, 3.8)	2.1 (0.4, 3.9)	2.2 (0.1, 4)	2.1 (0.1, 4)	2.2 (0, 3.9)
Abdominal Bloating,² N	220	219	217	221	212	223
Mean ± Standard Deviation	2.2 ± 0.75	2.2 ± 0.74	2.2 ± 0.77	2.2 ± 0.76	2.1 ± 0.78	2.3 ± 0.82
Median (Minimum, Maximum)	2.2 (0, 4)	2.2 (0, 4)	2.1 (0, 4)	2.2 (0, 4)	2.1 (0, 4)	2.3 (0, 4)
Bowel Habit Regularity,³ N	220	219	216	221	212	223
Mean ± Standard Deviation	4.7 ± 1.63	4.7 ± 1.60	4.7 ± 1.57	4.5 ± 1.71	4.6 ± 1.68	4.8 ± 1.60
Median (Minimum, Maximum)	5.0 (1, 7)	5.0 (1, 7)	5.0 (1, 7)	5.0 (1, 7)	5.0 (1, 7)	5.0 (1, 7)
Percent Days of Rescue Laxative Use, N	220	219	217	221	212	223
Mean ± Standard Deviation	7.5 ± 11.0	9.3 ± 13.4	15.1 ± 18.6	13.6 ± 18.2	15.5 ± 19.7	15.6 ± 19.8
Median (Minimum, Maximum)	7.1 (0, 79)	7.1 (0, 79)	8.3 (0, 100)	7.1 (0, 100)	9.1 (0, 100)	8.3 (0, 93)
Using Rescue Laxatives at Baseline, N	220	219	217	222	213	224
Yes, n (%)	111 (50.5)	110 (50.2)	133 (61.3)	132 (59.5)	132 (62.3)	142 (63.4)

*The Sponsor calculated percent subjects using rescue laxatives at baseline using the safety-evaluable population as the denominator.

¹Consistency scale: 0 (very loose), 1 (loose), 2 (normal), 3 (hard), 4 (very hard)

²Straining, severity, abdominal discomfort, and abdominal bloating scales: 0 (absent), 1 (mild), 2 (moderate), 3 (severe), 4 (very severe)

³Bowel habit regularity scale: 1 (Very regular) to 7 (Very irregular)

Source: Reviewer's table, adapted from Sponsor's Table 2.7.3.3-5, pages 29 to 31 of 119, Summary of Clinical Efficacy; and module 5.3.5.3, Table 1.1.10, pages 415 to 416 of 2585, Integrated Summary of Efficacy.

Reviewer comments: The design of the three trials, which only counted an SBM if the BM did not occur within 24 hours after use of a rescue laxative, may lead to exaggeration of baseline constipation severity (underestimation of true baseline BM frequency). Nonetheless, baseline constipation status was generally comparable across both treatment arms in the three efficacy trials. Although baseline rescue laxative use was generally balanced across both treatment arms in the three trials, the mean percent of days of rescue laxative use at baseline and the percent of subjects using rescue laxatives at baseline were higher in OBD-0631 and OBD-0632 than in OBD-1033. Based on this finding, one might surmise that subjects in OBD-0631 and OBD-0632 were more constipated at baseline than subjects in OBD-1033. This hypothesis, however, is not supported by the other parameters that measured constipation status at baseline (e.g., SBM frequency, straining, constipation severity, etc.) because these other parameters were quite similar across the three trials.

Opioid Use

The Sponsor categorized opioids into three classes: (1) diphenylheptanes, which include methadone and propoxyphene; (2) phenanthrenes, which include the subclasses of hydrocodones, morphines, and oxycodones; and (3) phenylpiperidines, which include fentanyl and meperidine. At DGIEP's request, the Sponsor provided a tabular presentation of the number and percentage of subjects on each class and subclass of opioids, and [Table 6](#) summarizes the results.

Table 6. Summary of Subjects on Each Class/Subclass of Opioids by Trial – OBD-1033, OBD-0631, and OBD-0632 (Safety-Evaluable Population)

Variable	OBD-1033		OBD-0631		OBD-0632	
	Placebo (N=220)	Lubiprostone (N=219)	Placebo (N=218)	Lubiprostone (N=221)	Placebo (N=214)	Lubiprostone (N=223)
Opioid Class						
Diphenylheptane, n (%)	0	1 (0.5) [†]	36 (16.5)	45 (20.4)	41 (19.2)	44 (19.7)
Phenanthrene, n (%)	215 (97.7)	211 (96.3)	202 (92.7)	195 (88.2)	183 (85.5)	196 (87.9)
Phenylpiperidine, n (%)	13 (5.9)	17 (7.8)	21 (9.6)	25 (11.3)	34 (15.9)	30 (13.5)
Phenanthrene Subclass						
Hydrocodones, n (%)	137 (62.3)	131 (59.8)	90 (41.3)	106 (48)	96 (44.9)	90 (40.4)
Morphines, n (%)	37 (16.8)	37 (16.9)	68 (31.2)	58 (26.2)	50 (23.4)	64 (28.7)
Oxycodones, n (%)	59 (26.8)	66 (30.1)	80 (36.7)	78 (35.3)	78 (36.4)	75 (33.6)

Note: If subjects were taking more than one opioid, they are counted once in each category.

[†]Subject 1033-3022-001 was prescribed methadone by a provider during the trial. The subject reported he was unaware methadone was a prohibited medication and discontinued methadone after three doses due to nausea.

Source: Reviewer's table, modified from Sponsor's Table 52, pages 96-97, Response to 74-Day Letter.

The percentage of subjects using diphenylheptane opioids was similar between OBD-0631 and OBD-0632 and generally balanced across the two treatment arms in each trial. This issue is discussed further in [Table 135](#) in the context of discussion of the failure of trial OBD-0632. The percentage of subjects using phenanthrenes and phenylpiperidines was also generally balanced across the treatment arms of all three trials, although the overall percentage of subjects on phenylpiperidines was higher in OBD-0632 than OBD-1033 or OBD-0631.

6.1.3 Subject Disposition

In trial OBD-1033, a total of 927 subjects were screened, of whom 480 subjects were screen failures. Thus, 447 subjects were randomized at 105 sites in the USA and Europe (91 sites in the USA and 14 sites in Europe). European countries with trial sites were Belgium, the Czech Republic, Germany, Poland, Sweden, the United Kingdom, and Northern Ireland. In trial OBD-0631, a total of 942 subjects were screened, of whom 499 subjects were screen failures. Thus, 443 subjects were randomized at 80 sites in the USA and Canada. In trial OBD-0632, a total of 890 subjects were screened, of whom 439 subjects were screen failures. Thus, 451 subjects were randomized at 88 sites in the USA and Canada.

Screen failures were determined at the time of the screening visit and at the end of the 3-week screening period (see schedule for OBD-1033 in [Table 106](#) and for OBD-0631/OBD-0632 in [Table 116](#)). The major reasons provided for the 1418 screen failures in the three efficacy trials were as follows: (1) did not meet criteria for OBD (61%); (2) less than 70% compliant with the daily diary (34%); and (3) potential for noncompliance with the trial protocol (17%). [Table 7](#) summarizes reasons for screen failures.

Table 7. Reason for Screen Failures that Occurred in ≥4% of Subjects in Double-blind Trials

Category	Reasons for Screen Failures *	OBD-1033 (N=480) n (%)	OBD-0631 (N=499) n (%)	OBD-0632 (N=439) n (%)	Total (N=1418) n (%)
Not met inclusion criteria	Has opioid-induced bowel dysfunction (OBD) ¹	220 (45.8)	334 (66.9)	307 (69.9)	861 (60.7)
	Daily diary compliance ≥70% for the last 2 weeks of screening period	131 (27.3)	192 (38.5)	166 (37.8)	489 (34.4)
	Discontinued prohibited concomitant medications from screening visit onward ²	25 (5.2)	48 (9.6)	42 (9.6)	115 (8.1)
	Willing to fill out diary/comply with data collection	24 (5)	26 (5.2)	17 (3.9)	67 (4.7)
Met exclusion criteria	Potential for noncompliance with trial protocol ³	64 (13.3)	108 (21.6)	65 (14.8)	237 (16.7)
	Increased/decreased opioid dosage by >30%, changed opioid or route of administration within 30 days of screening, or was likely to discontinue or adjust dosage by >30% over course of trial	21 (4.4)	26 (5.2)	26 (5.9)	73 (5.1)
Other	SBM eligibility failure ⁴	64 (13.3)	5 (1)	18 (4.1)	87 (6.1)

*A subject might have multiple screen failure reasons.

¹OBD: average of <3 SBMs/week during screening period and ≥1 of following for ≥25% of SBMs each week of screening period: (1) hard/very hard stools; (2) sensation of incomplete evacuation; and/or (3) moderate/very severe straining associated with SBMs.

²Prohibited medications included anticholinergics, laxative agents, and tricyclic antidepressants. A complete list is provided in [Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033](#).

³Potential for noncompliance with dosing schedule, visit schedule, diary completion, or trial procedures

⁴Includes those subjects for whom inclusion/exclusion CRFs were not completed, but who failed to meet baseline SBM criteria of <3 weekly SBMs on average according to diary entries and eligibility calculations.

Source: Reviewer's table, adapted from Sponsor's Table 7.3, pages 9 to 11, response to IR7.

Reviewer comments: *It initially appears that a smaller proportion of subjects who failed screening did so due to not meeting criteria for OBD in OBD-1033 (46%) than OBD-0631 (67%) or OBD-0632 (70%). However, on closer examination, this officer noted that the proportion of subjects with SBM eligibility failure is higher in OBD-1033 (13%) than OBD-0631 (1%) or OBD-0632 (4%). Thus, it may be that more subjects in OBD-1033 did not have inclusion/exclusion CRFs completed at the screening visit than the other*

two efficacy trials and subsequent examination of SBM eligibility based on diary entries revealed that 13% of these subjects were not eligible for randomization. When the screen failures due to not meeting OBD inclusion criteria and not meeting SBM eligibility are combined, the proportion of screen failures due to not meeting OBD criteria (based on SBM frequency and/or associated signs/symptoms) in OBD-1033 increases to 59%, a proportion more comparable to that for OBD-0631 (68%) and OBD-0632 (74%).

Within each of the three efficacy trials, subjects were randomized in a 1:1 ratio to receive either placebo or lubiprostone (24 mcg BID) for 12 weeks. This produced comparable numbers of subjects randomized to each treatment in trials OBD-1033 (226 subjects randomized to placebo and 221 subjects randomized to lubiprostone), OBD-0631 (220 subjects randomized to placebo and 223 subjects randomized to lubiprostone), and OBD-0632 (216 subjects randomized to placebo and 235 subjects randomized to lubiprostone). The patient populations used for analyses of the three efficacy trials were as follows:

- Safety-evaluable population: All randomized subjects who took at least one dose of study medication were in the safety population and included in safety analysis.
- Intent-to-treat (ITT) population: All randomized subjects who took at least one dose of study medication and had at least one treatment-period diary entry.
- Modified intent-to-treat (mITT) population: This population was defined only for OBD-1033. Routine monitoring and subsequent audit of data collected at Sites 3019 and 3119 led the Sponsor to question the suitability of the data. As a result, a mITT population was used that excluded data from Sites 3019 and 3119. See section 3.2 [Compliance with Good Clinical Practices](#) for additional discussion.
- Per-protocol population: ITT subjects who were randomized and met the detailed inclusion and exclusion criteria (discussed in detail in [Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033](#)).
- Completer population: Subjects who completed the treatment regimen through Week 12; this population was used for supportive analyses.

Table 8 summarizes subject disposition for trials OBD-1033, OBD-0631, and OBD-0632.

Table 8. Subject Disposition – OBD-1033, OBD-0631, and OBD-0632 (Randomized Subjects)

Disposition	OBD-1033		OBD-0631		OBD-0632	
	Placebo (N=226)	Lubiprostone (N=221)	Placebo (N=220)	Lubiprostone (N=223)	Placebo (N=216)	Lubiprostone (N=235)
Randomized subjects, n (%)	226 (100.0%)	221 (100.0%)	220 (100.0%)	223 (100.0%)	216 (100.0%)	235 (100.0%)
Safety evaluable subjects, n (%)	220 (97.3%)	219 (99.1%)	218 (99.1%)	221 (99.1%)	214 (99.1%)	223 (94.9%)
Intent-to-treat subjects, n (%)	220 (97.3%)	219 (99.1%)	217 (98.6%)	221 (99.1%)	212 (98.1%)	223 (94.9%)
Modified intent-to-treat subjects, ¹ n (%)	213 (94.2%)	211 (95.5%)				
Completed subjects, n (%)	184 (81.4%)	169 (76.5%)	154 (70.0%)	152 (68.2%)	153 (70.8%)	152 (64.7%)
Per-protocol subjects, n (%)	179 (79.2%)	177 (80.1%)	156 (70.1%)	153 (68.6%)	147 (68.1%)	150 (63.8%)
Discontinued subjects, n (%)	42 (18.6%)	52 (23.5%)	66 (30.0%)	71 (31.8%)	63 (29.2%)	83 (35.3%)
Reason for Discontinuation, n (%)						
Adverse event	4 (1.8%)	13 (5.9%)	7 (3.2%)	16 (7.2%)	5 (2.3%)	9 (3.8%)
Lack of efficacy	6 (2.7%)	5 (2.3%)	7 (3.2%)	6 (2.7%)	2 (0.9%)	5 (2.1%)
Discontinuation of opioids	0 (0.0%)	3 (1.4%)	1 (0.5%)	5 (2.2%)	0 (0.0%)	3 (1.3%)
Patient choice	15 (6.6%)	12 (5.4%)	18 (8.2%)	10 (4.5%)	21 (9.7%)	19 (8.1%)
Lost to follow-up	5 (2.2%)	3 (1.4%)	6 (2.7%)	13 (5.8%)	10 (4.6%)	14 (6.0%)
Noncompliance	4 (1.8%)	7 (3.2%)	7 (3.2%)	2 (0.9%)	3 (1.4%)	4 (1.7%)
Investigator decision ²	0	0	1 (0.5%)	3 (1.3%)	1 (0.5%)	3 (1.3%)
Sponsor request ³	3 (1.3%)	1 (0.5%)	2 (0.9%)	1 (0.4%)	2 (0.9%)	2 (0.9%)
Other ⁴	5 (2.2%)	8 (3.6%)	17 (7.7%)	15 (6.7%)	19 (8.8%)	24 (10.2%)

¹ Modified intent-to-treat was defined only for trial OBD-1033 and excluded subjects at sites 3019 and 3119 due to internal audits that led Sponsor to question the suitability of data collected at those sites.

² "Investigator decision" includes the following reasons for discontinuation: adverse event, opioid adjustment, patient non-compliance, prohibited medication, and unknown.

³ "Sponsor request" includes the following reasons for discontinuation: enrollment closed, improper contract research organization (CRO) instruction, opioid adjustment, patient non-compliance, randomization error, and protocol violation (OBD status or prohibited medication).

⁴ "Other" includes the following reasons for discontinuation: adverse event, enrollment closed, lack of efficacy, opioid adjustment, patient choice, patient completed but did not rollover to extension trial, primary care physician request, randomization error, subject relocation, protocol violation (drug addiction, multiple violations, OBD status, prohibited medication, renal function criteria, screening diary compliance), and unknown.

Note: Randomization errors include out-of-window randomization, interactive voice response (IVR) error, and incorrect kit assignment (i.e., improper treatment allocation).

Source: Reviewer's table, adapted from Sponsor's Table 2.7.3.3-2, page 21 of 119, Summary of Clinical Efficacy; Table 2.7.4.1-1, page 10 of 167, Summary of Clinical Safety; and Table 2, response to IR1.

In determining the sample size for each trial, the SAP for trials OBD-0631 and OBD-0632 assumed that 30% of patients would drop out of the trial by Week 8 (at which time the primary efficacy endpoint would be evaluated) and the SAP for trial OBD-1033 assumed that 20% of patients would drop out of the trial by Week 9. Out of all subjects in each trial, as summarized in [Table 8](#), 137 (31%) had dropped out by the end of Week 12 in trial OBD-0631, 146 (32%) had dropped out by the end of Week 12 in trial OBD-0632, and 94 (21%) had dropped out by the end of Week 12 in trial OBD-1033. Overall discontinuation rates were higher in the lubiprostone arm than the placebo arm in all three double-blind trials. Discontinuation due to lack of efficacy was generally balanced in the two treatment arms of each trial, with rates ranging from 1% to 3% among placebo subjects and 2% to 3% among lubiprostone subjects.

Reviewer comments: On initial review of the Sponsor's table detailing reasons for discontinuation, specific reasons that were lumped under the headings of "investigator decision," "Sponsor's request," and "other" were not clear to this medical officer. In response to an information request (IR) from DGIEP, the Sponsor provided a table detailing the reasons that comprised each of these categories. The specific reasons that had been originally lumped under "investigator decision," "Sponsor's request," and "other" are delineated in the legend of [Table 8](#) and this table reflects re-categorization by this reviewer where appropriate to reflect the addition details provided in the IR. The re-categorization did not notably change the balance of discontinuation reasons between the treatment arms in any of the trials.

A higher percentage of placebo subjects than lubiprostone subjects discontinued OBD-0631 (8% versus 5%) due to patient choice, but the overall discontinuation rate was similar for both treatment groups in OBD-0631 and in the other two trials. Further, the overall dropout rates, although higher in OBD-0631 and OBD-0632 than in OBD-1033, were comparable to what the Sponsor had anticipated in the SAP for each trial. In this reviewer's assessment, there were no clinically important differences in subject disposition between the two arms of any of the three efficacy trials that would be expected to drive efficacy in favor of lubiprostone subjects.

Determination of Per-Protocol Population

ITT subjects who were determined to be protocol violators were excluded from the per-protocol analyses. Criteria used to determine protocol violations included:

- Subjects not meeting inclusion criteria numbers 1, 2, 3, 4, 5, 6, and/or 7 (see [Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033](#), and [Appendix 3: Discussion of Individual Trials: Trial SMR/0211 OBD-0631](#))
- In OBD-1033, subjects not meeting exclusion criteria numbers 1, 2, 5, 6, 9, 10, 11, 16, 17, 18, and/or 19. In OBD-0631 and OBD-0632, subjects not meeting exclusion criteria 1, 4, 5, 8, 9, 10, 15, 16, 17, and/or 18 were considered to be in violation of protocol. The differences in numbering of exclusion criteria among the three trials were due to the additional exclusion of subjects using methadone or a congener of methadone in trial OBD-1033.

- Those who received the wrong treatment or incorrect dose based on the randomization code
- Subjects who demonstrated inconsistent use of potentially confounding concomitant medication during the trial
- Dose of fiber supplement was not stable from Day –21 through Day 60
- Change from baseline MEDD of $\pm 30\%$ between 7 days before screening visit and end of treatment, with duration of adjusted dose lasting >7 consecutive days
- Less than 65% dosing compliance (with exception for subjects who reduced dose due to an AE), or $>120\%$ dosing compliance
- Diary completion rate $<50\%$ for eligibility determination

Table 9 lists the protocol violations for each efficacy trial.

Table 9. Summary of Protocol Violations (ITT Population)

Protocol Violation*	OBD-1033		OBD-0631		OBD-0632	
	Placebo (N=220) n (%)	Lubiprostone (N=219) n (%)	Placebo (N=217) n (%)	Lubiprostone (N=221) n (%)	Placebo (N=212) n (%)	Lubiprostone (N=223) n (%)
Key eligibility criteria ¹ not met	10 (4.5%)	7 (3.2%)	35 (16.1%)	37 (16.7%)	47 (22.2%)	48 (21.5%)
Misrandomized ²	8 (3.6%)	8 (3.7%)	1 (0.5%)	2 (0.9%)	0	1 (0.4%)
Prohibited/inconsistent medication use and/or inconsistent use of confounding medication ³	10 (4.5%)	13 (5.9%)	13 (6.0%)	13 (5.9%)	11 (5.2%)	6 (2.7%)
Opioid dose increase of $>30\%$ from baseline MEDD ⁴	6 (2.7%)	6 (2.7%)	9 (4.1%)	7 (3.2%)	6 (2.8%)	7 (3.1%)
Opioid dose decrease of $>30\%$ from baseline MEDD ⁴	2 (0.9%)	0	5 (2.3%)	10 (4.5%)	5 (2.4%)	2 (0.9%)
$<65\%$ dosing compliance ⁵	7 (3.2%)	5 (2.3%)	11 (5.1%)	17 (7.7%)	13 (6.1%)	23 (10.3%)
$>120\%$ dosing compliance ⁵	0	3 (1.4%)	1 (0.5%)	0	0	1 (0.4%)
Other ⁶	2 (0.9%)	1 (0.5%)	2 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	45 (20.5%)	43 (19.6%)	77 (35.5%)	86 (38.9%)	82 (38.7%)	88 (39.5%)

*A subject might have multiple protocol violations. Subjects who met multiple violations were counted once in each category.

¹For OBD-0631 and OBD-0632, defined as inclusion criteria (IC) #s 1, 3, 4, 7, and exclusion criteria (EC) #s 1, 4, 5, 8, 9, 10, 16, 17, 18. For OBD-1033, defined as IC #s 1, 2, 3, 4, 7, and EC #s 1, 2, 5, 6, 9, 10, 11, 16, 17, 18, 19.

²Subject received wrong treatment/incorrect dose (misrandomized), or assigned to wrong baseline SBM strata upon randomization.

³Includes subjects not meeting IC #s 5 and/or 6, those whose dose of fiber was not stable from Day -21 through end of treatment, or those subjects who inconsistently administered a potentially confounding medication.

⁴MEDD: morphine equivalent daily dose. Applies to subjects not meeting IC #2, EC #3 (trials OBD-0631 and OBD-0632) or EC #4 (trial OBD-1033), or whose opioid dose was adjusted for >7 consecutive days from randomization through end of treatment.

⁵Except for those subjects who dose reduced due to adverse event (AE).

⁶Includes patients whose screening diary completion rate was $<50\%$ (the two placebo subjects in OBD-0631) or subjects who had confounding concurrent medical history diagnosis (the three subjects in OBD-1033 had irritable bowel syndrome-mixed (one placebo, one lubiprostone) or irritable bowel syndrome-unconfirmed subtype (one placebo)).

Note: Source: Reviewer's Table, adapted from Table 14.1.3, CSR of OBD-0631; Table 14.1.3, CSR of OBD-0632; Table 14.1.3, CSR of OBD-0631; and Sponsor's response to IR4.

Misrandomization occurred in 3 subjects in OBD-0631, 1 subject in OBD-0632, and 16 subjects in OBD-1033 (balanced across the treatment arms, with 8 placebo subjects and 8 lubiprostone subjects).

Reviewer comments: *This medical officer independently reviewed protocol violations for the ITT population in each trial. The most common violation categorized as “key eligibility criteria not met” was weekly SBM frequency ≥ 3 during screening period or absence of at least one of the following for $\geq 25\%$ of SBMs during each week of the screening period: (1) hard or very hard stools; (2) sensation of incomplete evacuation; and/or (3) moderate to very severe straining associated with SBMs.*

In OBD-1033, more placebo subjects had baseline weekly SBM frequency ≥ 3 than lubiprostone subjects (seven versus three), and this would not be expected to favor lubiprostone subjects in terms of efficacy. In OBD-0631, there were four placebo subjects with baseline weekly SBM frequency ≥ 3 as compared with seven lubiprostone subjects. In OBD-0632, there were 11 placebo subjects with baseline weekly SBM frequency ≥ 3 as compared with 12 lubiprostone subjects. Although the Sponsor proposed that higher overall number of subjects with baseline weekly SBM frequency ≥ 3 in OBD-0632 than OBD-0631 “negatively influenced the possibility for lubiprostone to demonstrate normalization of SBM frequency in OBD-0632,” this reviewer notes that the distribution of subjects with baseline weekly SBM frequency ≥ 3 was balanced across the placebo and lubiprostone arms in OBD-0632. This issue is discussed further in [Table 139 of Appendix 4: Discussion of Individual Trials: Trial SMR/0211 OBD-0632](#).

Regarding prohibited/inconsistent medication use and/or inconsistent use of confounding medication, the most common violation involved use of a prohibited medication that could potentially increase BM frequency (e.g., metoclopramide) or decrease BM frequency (e.g., tricyclic antidepressants). The use and potential impact of prohibited and/or confounding medications was more difficult to adjudicate and interpret, because several subjects were on more than one prohibited medication, one of which might be expected to increase BM frequency and another that might decrease BM frequency. As such, protocol violations relating to use of prohibited or potentially confounding medications were difficult to separate based on expected effect of the medication on BM frequency, but overall, no notable imbalances across treatment arms were present with respect to use of such medications.

Overall, protocol violations were less frequent in OBD-1033 than OBD-0631 or OBD-0632. The number of violations was generally balanced across the treatment arms within each trial, with a few exceptions. In OBD-0632, 23 lubiprostone subjects (10%) were excluded from the per-protocol population due to $<65\%$ dosing compliance as compared with 13 placebo subjects (6%). This imbalance between the treatment groups theoretically might favor the placebo group on efficacy in the ITT population.

In OBD-0631, 5 subjects (2%) were excluded from the per-protocol population for decreasing opioid dose beyond 30% from baseline, as compared with 10 lubiprostone subjects (5%). In theory, this imbalance could favor the lubiprostone group because one could expect that reduction in opioid dose might reduce OIC and improve response to lubiprostone. This imbalance potentially favoring the lubiprostone arm in OBD-0631 is countered by the imbalance across treatment arms in subjects with $<65\%$ dosing

compliance (11 subjects (5%) in placebo arm and 17 (8%) in lubiprostone arm). The latter imbalance would be expected to favor placebo subjects.

6.1.4 Analysis of Primary Endpoint(s)

Because the three efficacy trials (OBD-0631, OBD-0632, and OBD-1033) submitted as part of this sNDA did not all use the same primary endpoint, analysis of the primary endpoint will be discussed separately for each trial. As indicated by the Sponsor in the final version of the SAP for each of three efficacy trials, all inferential analyses of efficacy were based on the principle of two-tailed tests at a significance level of $\alpha=0.05$. For each of the three efficacy trials, there was only one primary endpoint, and as such, the Sponsor indicated that no adjustment for multiplicity would be needed. The Sponsor calculated weekly SBM frequency rates using hours (instead of days), with the number of hours defined as the number of hours observed in the eDiary during the week (168-hour interval) that the subject was actively enrolled in the trial and taking study medication. For a bowel movement to count as an SBM, the BM could not have occurred within 24 hours after use of a rescue laxative.

Reviewer comments: *It should be noted that at the time of completion of this medical officer's primary review, the statistical team's review of efficacy is still pending.*

OBD-1033

Proportion of subjects who were overall SBM responders is a binary endpoint. An overall SBM responder was defined as a subject who had ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥ 3 SBMs per week for at least 9 of the 12 treatment weeks. The primary efficacy endpoint for OBD-1033 was the overall SBM response rate in ITT subjects. The information used to determine the overall SBM response rate was based on subject responses to daily diary questions. The Sponsor considered subjects with < 9 weeks of weekly SBM rates as non-responders. With a week considered a 168-hour interval, if subjects had < 85 hours of observed data in a week, then the Sponsor considered the data insufficient and the rate missing for that week. Last observation carried forward (LOCF) was not used in the primary analysis.

Clinical site was a baseline stratification factor at randomization. Baseline weekly SBM frequency was also a stratification factor at randomization (SBMs < 0.6 , $0.6 \leq$ SBMs ≤ 2 , and $2 <$ SBMs < 3). The Sponsor indicated that this stratification by baseline SBM frequency would provide balance by treatment arm. Although clinical site was always reported as a stratification factor in the primary analysis, the Sponsor modified (in the protocol, not the SAP) its plan on whether or not the primary analysis would be additionally stratified by baseline SBM frequency. In the original protocol, the Sponsor indicated that analysis would not be stratified by baseline SBM frequency. The Sponsor amended the protocol on October 19, 2010, indicating that analysis would be stratified by baseline SBM frequency. In a second amendment to the protocol on June 13, 2011, the Sponsor again revised the protocol, indicating that analysis would not be stratified by baseline SBM frequency. OBD-1033 ended on November 16, 2011. The Sponsor did

not provide an explanation for this change to the protocol. In all versions of the SAP for OBD-1033, the Sponsor indicated that analysis would not additionally be stratified by baseline SBM frequency. Baseline constipation status was determined by responses to constipation-related diary questions for the 2 weeks prior to administration of the first dose of study drug. At the screening visit (Day -24 to -21), subjects' laxatives and other prohibited medications (described in detail in [Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033](#)) were stopped and the eDiary distributed.

Reviewer comments: *Because laxatives and other prohibited medications were discontinued prior to assessment of baseline constipation status, the calculated baseline SBM frequency may not represent subjects' actual baseline, but rather reflects baseline SBM frequency during a controlled run-in which subjects' usual laxative regimen was prohibited. This issue was discussed previously in section 5.3 Discussion of Individual Studies/Clinical Trials.*

Table 10 shows results of the pre-specified primary efficacy analysis in OBD-1033.

Table 10. Primary Analysis of Overall SBM Response in OBD-1033 (ITT Population)

Overall SBM Response ¹	Placebo (N=220) n (%)	Lubiprostone (N=219) n (%)	Difference (95%CI)	P-Value ²
Responder	41 (18.6%)	59 (26.9%)	8.3% (0.49, 16.1)	0.035

Abbreviations: CI, confidence interval.

¹Overall SBM response defined as ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥ 3 SBMs per week for at least 9 of the 12 treatment weeks.

²Sponsor's p-values for overall response rates comparing treatment groups were analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by pooled site.

Source: Reviewer's table, modified from Sponsor's Table 2.7.3.3-8, page 39 of 119, Summary of Clinical Efficacy and Table 1.2.1.4, page 30, response to IR6.

In the ITT population of OBD-1033, there was an absolute treatment difference between lubiprostone and placebo of 8.3% and the treatment effect favored the lubiprostone group by a statistically significant margin ($p=0.035$).

Reviewer comments: *Evaluation of the clinical meaningfulness of the treatment effect for lubiprostone via comparison to the treatment effect for other approved drugs is limited for two reasons. First, there are no other drugs approved for treatment of OIC in adults with chronic non-cancer pain. Second, there are no other drugs approved for constipation that are in the same drug class as lubiprostone.*

Despite these limitations, review of the treatment effect for lubiprostone in other indications and other drugs approved for constipation is informative. For lubiprostone in IBS-C, the treatment difference favoring lubiprostone over placebo in two 12-week efficacy trials was ~6%. However, direct comparison of treatment differences is limited by the fact that overall responder definitions were different for the IBS-C population and the OIC population. For lubiprostone in CIC, a responder definition was not used for the primary endpoint, making comparisons of treatment differences across indications impractical. Methylnaltrexone was approved in 2008 for treatment of OIC in adults with advanced illness receiving palliative care. The two trials used to support approval,

however, used rescue-free laxation within 4 hours of the double-blind dose of study medication as the primary endpoint. Because these trials did not evaluate efficacy in a controlled, double-blinded manner over 12 weeks, comparison of treatment effect with lubiprostone in the OIC trials submitted to the current sNDA is not instructive.

Linaclotide, recently approved for CIC and IBS-C, demonstrated a treatment difference of ~10% to 15% in the CIC population studied. The two trials used to support approval for CIC did assess efficacy over a 12-week period, but the linaclotide trials used overall complete SBM (CSBM) responders as the primary endpoint, rather than SBM responders. Given that many symptomatic disease conditions (e.g., OIC, IBS-C) commonly have a large placebo response rate, this reviewer would not anticipate large treatment differences between placebo and lubiprostone for OIC. In this reviewer's opinion, a treatment difference of 8% favoring lubiprostone represents a clinically meaningful treatment effect in adults with chronic non-cancer pain and OIC and offers another treatment option for OIC in this patient population.

The Sponsor also performed secondary analyses of the primary efficacy endpoint (overall SBM response) in the mITT, completer and per-protocol populations, and these findings are summarized in [Table 11](#). Due to a question of the suitability of the data collected at sites # 3019 and 3119, the Sponsor excluded those sites from the mITT population (see section [3.2 Compliance with Good Clinical Practices](#) for additional discussion). The per-protocol population consisted of ITT subjects who were randomized and met inclusion and exclusion criteria (as discussed in section [6.1.3](#)

[Subject Disposition](#) and detailed in [Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033](#)). The completer population included subjects who completed the treatment regimen through Week 12.

Table 11. Supportive Analysis of Overall SBM Response in OBD-1033 (mITT, Completer and Per-Protocol Populations)

Overall SBM Response ¹ by Population	Placebo	Lubiprostone	P-Value ²
mITT	(N=212)	(N=212)	
Responder, n (%)	41 (19.3%)	58 (27.4%)	0.034
Completer	(N=184)	(N=169)	
Responder, n (%)	40 (21.7%)	55 (32.5%)	0.018
Per-Protocol	(N=179)	(N=177)	
Responder, n (%)	37 (20.7%)	53 (29.9%)	0.065

¹Overall SBM response defined as ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥ 3 SBMs per week for at least 9 of the 12 treatment weeks.

²Sponsor's p-values for overall response rates comparing treatment groups analyzed using the CMH test stratified by pooled site. Source: Reviewer's table, modified from Sponsor's Table 2.7.3.3-9, page 39 of 119 and Table 2.7.3.3-10, page 40 of 119, Summary of Clinical Efficacy; and Table IR12, Sponsor's response to IR12.

In the mITT population, the treatment difference was 8%. In the completer population, the treatment difference was 11%, and in the per-protocol population, the treatment difference was 9%.

Reviewer comments: Reporting of results for the mITT population for this trial are valid, because exclusions from the ITT population decrease the sample size in the mITT population by <5%. Larger decreases in sample size occurred in the completer and per-

protocol populations, though protocol violations were generally balanced across both treatment arms in trial OBD-1033. The Sponsor attributed the p-value >0.05 in the per-protocol population to “the combination of a decrease in the sample size and the difference in distribution of data as compared to the completer population.” In this reviewer’s assessment, the numerical magnitude of the absolute difference in treatment effect is similar for the ITT, mITT, completer, and per-protocol populations, providing supportive evidence for the primary efficacy analysis.

OBD-0631

The primary endpoint for OBD-0631 was the change from baseline in SBM frequency at Week 8 in ITT subjects who did not undergo dose reduction. The information used to determine the results of the primary endpoint was based on subject responses to the daily eDiary questions and periodic assessments (by telephone and in person).

As with trial OBD-1033, for a bowel movement to count as an SBM, the BM could not have occurred within 24 hours after use of a rescue laxative. Unlike OBD-1033, however, in which the Sponsor considered the rate for subjects with <85 hours of weekly data as missing for that week, in OBD-0631, if ≥ 25 but <85 hours were observed during a week and ≥ 85 hours were observed during the prior week, then the Sponsor imputed data from the prior week to provide a total of 85 hours of data. If subjects had <25 hours of observed data in a week, then the Sponsor considered the data insufficient and the rate missing for that week.

Reviewer comments: *This reviewer notes that different missing data handling procedures between trials OBD-1033 and OBD-0631 might complicate comparisons of findings between the trials. At the request of the statistical review team, the Sponsor performed several exploratory analyses to investigate the impact of missing data on the results. At this time, the statistical reviewer’s final review is pending.*

Table 12 shows results of the pre-specified primary efficacy analysis in OBD-0631.

Table 12. Primary Analysis of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-0631 (ITT Population)

Variable ¹	Placebo (N=217)	Lubiprostone (N=221)	Difference (95% CI)	P-Value ²
Baseline Observed Value				
n	216	212		
Mean ± Standard Deviation	1.5 ± 0.96	1.4 ± 1.09		
Median (Minimum, Maximum)	1.5 (0, 7)	1.5 (0, 8)		
Week 8 Observed Value				
n	169	164		
Mean ± Standard Deviation	3.8 ± 3.24	4.5 ± 3.73		
Median (Minimum, Maximum)	3.0 (0, 17)	4.0 (0, 28)		
Change from Baseline at Week 8				
n	169	164		
Mean ± Standard Deviation	2.4 ± 3.25	3.2 ± 3.35	0.76 (0.06, 1.47)	0.019
Median (Minimum, Maximum)	1.4 (-3, 16)	2.7 (-2, 21)		

Abbreviations: CI, confidence interval.

¹Weekly SBM (BM) frequency rate: (168 x number of SBMs (BMs)/number of hours observed)

²Sponsor's p-value is based on the treatment effect from a van Elteren test stratified by pooled site.

Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups. Additionally, Shapiro-Wilk p-value testing for normality was performed by the Sponsor and p-value was <0.001. A small p-value (<0.05) indicates non-normality.

Source: Reviewer's table, modified from Sponsor's Table 2.7.3.3-18, page 53 of 119, Summary of Clinical Efficacy; and Table 1.2.3.1.5, page 31, response to IR6.

In the ITT population of OBD-0631, placebo subjects demonstrated a mean increase from baseline of 2.4 in SBM frequency at Week 8, as compared with lubiprostone subjects, who showed a mean increase from baseline of 3.2 in SBM frequency at Week 8. The difference between the two groups reached statistical significance (p=0.019).

Reviewer comments: In OBD-0631 and OBD-1033, a protocol-specified dose reduction may have occurred if severe nausea, severe diarrhea, or another AE was reported by the subject and was ongoing for 3 or more days. By including only subjects who did not undergo dose reduction, the primary endpoint of OBD-0631 potentially discriminates against lubiprostone subjects who underwent dose reduction. In particular, if the reason for dose reduction was severe diarrhea, then inclusion of these subjects could have potentially driven the efficacy endpoint in favor of lubiprostone. Exploratory analyses presented later in this efficacy review (see [Table 70](#)) address the potential impact of excluding subjects with dose reduction from efficacy evaluation.

The Sponsor also performed supportive analyses of the primary endpoint (change from baseline in SBM frequency at Week 8) in the completer and per-protocol populations, and these findings are summarized in [Table 13](#) and [Table 14](#), respectively. The Sponsor's p-values in these tables are provided for informational purposes only.

Table 13. Supportive Analysis of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-0631 (Completer Population)

Variable ¹	Placebo (N=154)	Lubiprostone (N=152)	P-Value ²
Baseline Observed Value			
n	154	146	
Mean ± Standard Deviation	1.4 ± 0.82	1.3 ± 1.07	
Median (Minimum, Maximum)	1.5 (0, 4)	1.3 (0, 8)	
Week 8 Observed Value			
n	152	143	
Mean ± Standard Deviation	3.8 ± 3.13	4.7 ± 3.86	
Median (Minimum, Maximum)	3.0 (0, 17)	4.0 (0, 28)	
Change from Baseline at Week 8			
n	152	143	
Mean ± Standard Deviation	2.3 ± 3.15	3.4 ± 3.42	0.013
Median (Minimum, Maximum)	1.4 (-3, 16)	2.9 (-2, 21)	

¹Weekly SBM (BM) frequency rate: (168 x number of SBMs (BMs)/number of hours observed)

²Sponsor's p-value is based on the treatment effect from a van Elteren test stratified by pooled site.

Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups. Additionally, Shapiro-Wilk p-value testing for normality was performed by the Sponsor and p-value was <0.001. A small p-value (<0.05) indicates non-normality.

Source: Reviewer's table, modified from Sponsor's Table 2.7.3.3-19, page 54 of 119, Summary of Clinical Efficacy.

Table 14. Supportive Analysis of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-0631 (Per-Protocol Population)

Variable ¹	Placebo (N=156)	Lubiprostone (N=153)	P-Value ²
Baseline Observed Value			
n	156	146	
Mean ± Standard Deviation	1.4 ± 0.77	1.2 ± 0.87	
Median (Minimum, Maximum)	1.5 (0, 4)	1.2 (0, 4)	
Week 8 Observed Value			
n	126	120	
Mean ± Standard Deviation	3.7 ± 3.05	4.4 ± 3.26	
Median (Minimum, Maximum)	3.0 (0, 17)	4.0 (0, 21)	
Change from Baseline at Week 8			
n	126	120	
Mean ± Standard Deviation	2.3 ± 3.10	3.1 ± 3.06	0.064
Median (Minimum, Maximum)	1.4 (-3, 16)	2.7 (-1, 19)	

¹Weekly SBM (BM) frequency rate: (168 x number of SBMs (BMs)/number of hours observed)

²Sponsor's p-value is based on the treatment effect from a van Elteren test stratified by pooled site.

Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups. Additionally, Shapiro-Wilk p-value testing for normality was performed by the Sponsor and p-value was <0.001. A small p-value (<0.05) indicates non-normality.

Source: Reviewer's table, modified from Sponsor's Table 2.7.3.3-20, page 55 of 119, Summary of Clinical Efficacy.

In the completer population, placebo subjects demonstrated a mean increase from baseline of 2.3 in SBM frequency at Week 8, as compared with lubiprostone subjects, who showed a mean increase from baseline of 3.4 in SBM frequency at Week 8. In the per-protocol population, placebo subjects demonstrated a mean increase from baseline of 2.3 in SBM frequency at Week 8, as compared with lubiprostone subjects, who showed a mean increase from baseline of 3.1 in SBM frequency at Week 8.

The Sponsor also performed a pre-specified supportive analysis using ITT subjects with ≥85 hours of data each week for all 8 weeks and no dose reductions prior to Week 8.

Results were similar to the primary analysis, with placebo subjects showing a mean increase from baseline of 2.2 in SBM frequency at Week 8, and lubiprostone subjects showing a mean increase from baseline of 3.2 in SBM frequency at Week 8 (p=0.013).

Reviewer comments: *As with the analyses of the primary endpoint in OBD-1033, the treatment difference was similar for the ITT, completer, and per-protocol populations in OBD-0631. The Sponsor acknowledged that the pre-specified primary endpoint used in OBD-0631, by assessing change in SBM frequency at an arbitrarily chosen point in time (Week 8), was not as rigorous an indicator of continuous treatment effect as the overall SBM response endpoint subsequently selected as the primary endpoint in OBD-1033. DGIEP requested the Sponsor perform a supportive analysis of the overall SBM response endpoint in OBD-0631. Results are presented in Table 66. Briefly, this supportive analysis in OBD-0631 showed a treatment difference of approximately 10% favoring lubiprostone subjects and in this reviewer’s assessment, provides evidence of efficacy that supports the findings of the primary analysis in OBD-1033.*

OBD-0632

Trials OBD-0631 and OBD-0632 were identical with respect to design, trial protocol, and SAP, and the primary efficacy endpoint for trial OBD-0632 was identical to that for OBD-0631. Table 15 shows the results of the pre-specified primary analysis.

Table 15. Primary Analysis of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-0632 (ITT Population)

Variable ¹	Placebo (N=212)	Lubiprostone (N=223)	Difference (95% CI)	P-Value ²
Baseline Observed Value				
n	211	215		
Mean ± Standard Deviation	1.6 ± 1.30	1.6 ± 1.33		
Median (Minimum, Maximum)	1.5 (0, 8)	1.5 (0, 9)		
Week 8 Observed Value				
n	175	168		
Mean ± Standard Deviation	4.0 ± 3.28	4.1 ± 3.22		
Median (Minimum, Maximum)	3.0 (0, 21)	3.5 (0, 17)		
Change from Baseline at Week 8				
n	175	168		
Mean ± Standard Deviation	2.4 ± 3.20	2.6 ± 3.26	0.21 (-0.47, 0.90)	0.842
Median (Minimum, Maximum)	1.8 (-4, 21)	2.0 (-3, 16)		

¹Weekly SBM (BM) frequency rate: (168 x number of SBMs (BMs)/number of hours observed)

²Sponsor’s p-value is based on the treatment effect from a van Elteren test stratified by pooled site.

Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups. Additionally, Shapiro-Wilk p-value testing for normality was performed by the Sponsor and p-value was <0.001. A small p-value (<0.05) indicates non-normality.

Source: Reviewer’s table, modified from Sponsor’s Table 2.7.3.3-18, page 53 of 119, Summary of Clinical Efficacy; and Table 1.2.3.1.5, page 31, response to IR6.

In the ITT population of OBD-0632, placebo subjects demonstrated a mean increase from baseline of 2.4 in SBM frequency at Week 8, as compared with lubiprostone subjects, who showed a mean increase from baseline of 2.6 in SBM frequency at Week 8. The difference between the two groups did not reach statistical significance (p=0.842). The Sponsor also performed analyses of the change from baseline in SBM

frequency at Week 8 in the completer and per-protocol populations, and these findings are in [Table 16](#) and [Table 17](#). P-values are provided for informational purposes only.

Table 16. Analysis of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-0632 (Completer Population)

Variable ¹	Placebo (N=153)	Lubiprostone (N=152)	P-Value ²
Baseline Observed Value			
n	153	147	
Mean ± Standard Deviation	1.5 ± 1.14	1.5 ± 0.97	
Median (Minimum, Maximum)	1.5 (0, 8)	1.5 (0, 4)	
Week 8 Observed Value			
n	153	144	
Mean ± Standard Deviation	4.0 ± 3.38	4.2 ± 3.29	
Median (Minimum, Maximum)	3.5 (0, 21)	4.0 (0, 17)	
Change from Baseline at Week 8			
n	153	144	0.838
Mean ± Standard Deviation	2.5 ± 3.30	2.7 ± 3.31	
Median (Minimum, Maximum)	2.0 (-4, 21)	2.0 (-3, 16)	

¹Weekly SBM (BM) frequency rate: (168 x number of SBMs (BMs)/number of hours observed)

²Sponsor's p-value is based on the treatment effect from a van Elteren test stratified by pooled site.

Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups. Additionally, Shapiro-Wilk p-value testing for normality was performed by the Sponsor and p-value was <0.001. A small p-value (<0.05) indicates non-normality.

Source: Reviewer's table, modified from Sponsor's Table 2.7.3.3-19, page 54 of 119, Summary of Clinical Efficacy.

Table 17. Analysis of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-0632 (Per-Protocol Population)

Variable ¹	Placebo (N=147)	Lubiprostone (N=150)	P-Value ²
Baseline Observed Value			
n	146	144	
Mean ± Standard Deviation	1.5 ± 1.03	1.4 ± 0.95	
Median (Minimum, Maximum)	1.5 (0, 5)	1.5 (0, 4)	
Week 8 Observed Value			
n	129	125	
Mean ± Standard Deviation	4.0 ± 3.35	4.2 ± 3.45	
Median (Minimum, Maximum)	3.0 (0, 21)	3.5 (0, 17)	
Change from Baseline at Week 8			
n	129	125	0.824
Mean ± Standard Deviation	2.5 ± 3.29	2.8 ± 3.41	
Median (Minimum, Maximum)	1.6 (-4, 21)	1.9 (-3, 16)	

¹Weekly SBM (BM) frequency rate: (168 x number of SBMs (BMs)/number of hours observed)

²Sponsor's p-value is based on the treatment effect from a van Elteren test stratified by pooled site.

Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups. Additionally, Shapiro-Wilk p-value testing for normality was performed by the Sponsor and p-value was <0.001. A small p-value (<0.05) indicates non-normality.

Source: Reviewer's table, modified from Sponsor's Table 2.7.3.3-20, page 55 of 119, Summary of Clinical Efficacy.

In the completer population, placebo subjects demonstrated a mean increase from baseline of 2.5 in SBM frequency at Week 8, as compared with lubiprostone subjects, who showed a mean increase from baseline of 2.7 in SBM frequency at Week 8. In the per-protocol population, placebo subjects demonstrated a mean increase from baseline of 2.5 in SBM frequency at Week 8, as compared with lubiprostone subjects, who showed a mean increase from baseline of 2.8 in SBM frequency at Week 8.

Reviewer comments: *Although there was a numerical difference in mean change in SBM frequency from baseline at Week 8 that favored the lubiprostone group in the ITT, completer, and per-protocol populations in OBD-0632, the magnitude of the treatment effect was smaller than in analyses of the primary endpoint in OBD-0631. Further, the treatment difference between lubiprostone and placebo subjects in the primary analysis of the ITT population in OBD-0632 failed to reach statistical significance.*

In light of the subsequently demonstrated in vitro interaction of methadone with lubiprostone, the Sponsor attributed the failure of OBD-0632 to win on the primary endpoint to the slightly higher percentage of methadone-treated subjects in OBD-0632 than OBD-0631 and the higher baseline MEDD of subjects in OBD-0632 than OBD-0631. Citing the interaction of methadone with the receptor target of lubiprostone, the Sponsor stated that “as nearly 20% of subjects in this trial used methadone, with an average MEDD of approximately 1000, there was a major impact of this interaction on study results.” This medical officer’s detailed review of factors that may have contributed to the failure of OBD-0632 did not find a single or consistent explanation for the trial’s failure. A detailed discussion of the elements reviewed and conclusions is in [Appendix 4: Discussion of Individual Trials: Trial SMR/0211 OBD-0632](#).

6.1.5 Analysis of Secondary Endpoints(s)

The list of secondary efficacy endpoints evaluated for each double-blind trial is presented in [Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033](#) and [Appendix 3: Discussion of Individual Trials: Trial SMR/0211 OBD-0631](#). Results of analysis of these secondary endpoints, discussed below, are presented individually for OBD-1033 and OBD-0631. Results for the failed trial, OBD-0632, are presented in [Appendix 4: Discussion of Individual Trials: Trial SMR/0211 OBD-0632](#).

OBD-1033

In OBD-1033, there were multiple endpoints within the secondary analyses. The final version of the SAP did not specify a hierarchy for evaluation of the *entire set* of secondary efficacy endpoints. The Sponsor indicated in the SAP that multiple secondary endpoints would “require adjustment to the p-value to maintain the family-wise significance level.” The Sponsor used Hommel’s stagewise rejective method to adjust for multiple comparisons within a group for several secondary endpoints, but this officer notes that the Sponsor did not provide appropriate multiplicity adjustment for the entire list of secondary endpoints. The Sponsor’s missing data procedures, use of LOCF, and approach to multiplicity adjustment are briefly discussed below and described in [Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033](#).

Imputation of missing SBM data depended upon the amount of data observed. The Sponsor defined a week as a 168-hour interval. If ≥ 85 hours were observed during a week then the missing data within that week were imputed with the average SBM data for that week. If ≥ 25 , but < 85 hours were observed during a week, and ≥ 85 hours were observed during the prior week, then data were imputed from the prior week to provide

a total of 85 hours of data. The Sponsor used LOCF to impute missing values for weeks with no data. For a given subject, the most recent non-missing treatment period questionnaire domain value was carried forward to subsequent time points where data were missing. The Sponsor also conducted supportive analyses of the secondary endpoints by not performing any missing value imputation.

Reviewer comments: Given the absence of a pre-specified hierarchy by the Sponsor for evaluation of the entire set of secondary endpoints, this medical officer questions the statistical validity of the comparisons. In particular, for those secondary endpoints for which there was no hierarchy and no multiplicity adjustment, statistical significance should not be claimed.

Change from Baseline in SBM Frequency at Week 8 without Dose Reduction

The Sponsor analyzed mean change from baseline in SBM frequency at Week 8 in subjects without dose reduction (the primary endpoint in OBD-0631 and OBD-0632) as a secondary endpoint in OBD-1033. [Table 18](#) presents results for the ITT population. The Sponsor's p-values are included for informational purposes only.

Table 18. Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-1033 (ITT Population)

Variable ¹	Placebo (N=220)	Lubiprostone (N=219)	P-Value ²
Baseline Observed Value			
n	217	207	
Mean ± Standard Deviation	1.4 ± 0.80	1.3 ± 0.82	
Median (Minimum, Maximum)	1.5 (0, 4)	1.0 (0, 5)	
Week 8 Observed Value			
n	182	168	
Mean ± Standard Deviation	4.0 ± 3.09	4.2 ± 3.14	
Median (Minimum, Maximum)	4.0 (0, 20)	3.8 (0, 14)	
Change from Baseline at Week 8			
n	182	168	
Mean ± Standard Deviation	2.5 ± 3.03	2.9 ± 3.18	
Median (Minimum, Maximum)	2.0 (-3, 20)	2.4 (-3, 13)	0.076

¹Weekly SBM (BM) frequency rate: (168 x number of SBMs (BMs)/number of hours observed)

²Sponsor's p-value is based on the treatment effect from a van Elteren test stratified by pooled site.

Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups. Additionally, Shapiro-Wilk p-value testing for normality was performed by the Sponsor and p-value was <0.001. A small p-value (<0.05) indicates non-normality.

Source: Reviewer's table, modified from Sponsor's Table 2.7.3.3-18, page 53 of 119, Summary of Clinical Efficacy.

The difference between the lubiprostone and placebo groups numerically favored the lubiprostone group (2.9 versus 2.5, p=0.076). The Sponsor also performed supportive analyses of this endpoint (change from baseline in SBM frequency at Week 8 in subjects without dose reduction) in the mITT, completer and per-protocol populations, the results of which were similar to the results for the ITT population. The findings for the mITT, completer and per-protocol populations are summarized in [Table 108](#), [Table 109](#) and [Table 110](#), respectively, of [Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033](#). Using the missing data procedures that were summarized at the beginning of this section (section [6.1.5 Analysis of Secondary Endpoints\(s\)](#)), the Sponsor also conducted pre-specified supportive analyses of the ITT and mITT

population using only subjects with ≥ 85 hours of data each week for all 8 weeks and no dose reductions prior to Week 8. LOCF was not used. Results showed that differences between treatment groups were numerically superior for the lubiprostone group in both the ITT (3.0 versus 2.6, $p=0.297$) and mITT population (3.0 versus 2.6, $p=0.279$).

The Sponsor indicated that the mean change from baseline in SBM frequency at Week 8 endpoint was more limited as an efficacy endpoint than overall SBM response because Week 8 was a somewhat arbitrarily chosen time point for efficacy analysis and did not permit as complete an assessment of continuous efficacy throughout the entire trial period as the overall SBM response endpoint. The Sponsor also pointed out that this analysis only included subjects who did not undergo dose reduction, possibly eliminating subjects who experienced efficacy even at a reduced dose.

Reviewer comments: Using the primary efficacy endpoint of OBD-0631 and OBD-0632 for analysis of data in OBD-1033 yielded results that numerically favored the lubiprostone subjects in the ITT, mITT, completer, and per-protocol populations. This reviewer agrees that Week 8 is a somewhat arbitrarily chosen time point for analysis of efficacy in a condition (OIC) with considerable variation in natural disease course. Further, by including only subjects that did not undergo dose reduction, this efficacy endpoint potentially discriminates against lubiprostone subjects who underwent dose reduction. In particular, if the reason for dose reduction was severe diarrhea, then inclusion of these subjects could have potentially driven the efficacy endpoint in favor of lubiprostone. This issue is further discussed in section 6.1.10 Additional Efficacy Issues/Analyses, specifically in Table 70 and Table 71.

Mean Change from Baseline in SBM Frequency at Week 12

The difference between treatment groups in change from baseline SBM frequency at Week 12 was evaluated as a secondary endpoint in OBD-1033. For the ITT population, as pre-specified in the SAP, Hommel's stagewise rejective method was used to determine if Week 8, Week 12, and overall time points were statistically significant. This method to adjust for multiple comparisons within a group was also used in analyses of the completer and per-protocol populations. The results for the ITT, mITT, completer, and per-protocol populations are summarized in Table 19.

Table 19. Summary of Change from Baseline in SBM Frequency at Week 12 in OBD-1033 (ITT, mITT, Completer, and Per-Protocol Populations)

Change from Baseline in SBM Frequency ¹ at Week 12	Placebo	Lubiprostone	P-Value
ITT	(N=220)	(N=219)	
n	180	159	
Mean ± Standard Deviation	2.7 ± 3.34	3.1 ± 3.13	0.120 ²
Median (Minimum, Maximum)	2.0 (-2, 19)	2.5 (-3, 14)	
mITT	(N=213)	(N=211)	
n	173	152	
Mean ± Standard Deviation	2.7 ± 3.38	3.1 ± 3.17	0.089 ³
Median (Minimum, Maximum)	1.9 (-2, 19)	2.5 (-3, 14)	
Completer	(N=184)	(N=169)	
n	175	153	
Mean ± Standard Deviation	2.7 ± 3.36	3.1 ± 3.14	0.235 ²
Median (Minimum, Maximum)	2.0 (-2, 19)	2.5 (-3, 14)	
Per-Protocol	(N=179)	(N=177)	
n	153	136	
Mean ± Standard Deviation	2.7 ± 3.25	3.1 ± 3.24	0.324 ²
Median (Minimum, Maximum)	1.9 (-2, 19)	2.5 (-3, 14)	

¹Weekly SBM (BM) frequency rate: (168 x number of SBMs (BM)/number of hours observed)

²Sponsor's p-value was initially based on the treatment effect from a van Elteren test stratified by pooled site and then adjusted using Hommel's stagewise rejective method for Week 8, Week 12, and overall.

³Sponsor's p-value is based on the treatment effect from a van Elteren test stratified by pooled site.

Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups. Additionally, Shapiro-Wilk p-value testing for normality was performed by the Sponsor and p-value was <0.001. A small p-value (<0.05) indicates non-normality

Source: Reviewer's table, adapted from Sponsor's Table 14.2.4.4 page 158 of 785, CSR for OBD-1033 and module 5.3.5.3; Tables 1.2.4.1, 1.2.4.2, and 1.2.4.3, pages 531 to 541 of 2585, Integrated Summary of Efficacy.

The difference between the lubiprostone and placebo groups numerically favored the lubiprostone group in the ITT population (3.1 versus 2.7, p=0.120), the mITT population (3.1 versus 2.7, p=0.089), the completer population (3.1 versus 2.7, p=0.235), and the per-protocol population (3.1 versus 2.7, p=0.324).

Reviewer comments: *In this reviewer's assessment, Week 12 is a less arbitrary time point for analysis of efficacy than Week 8 because Week 12 marked the end of treatment in the double-blind trials. Nonetheless, in a condition such as OIC, which is marked by considerable variation in natural disease course, mean change from baseline in SBM frequency at Week 12 does not assess efficacy in as continuous a manner as the overall SBM response endpoint used in OBD-1033. Notably, the analysis of mean change from baseline in SBM frequency at Week 12, unlike the Week 8 analysis that was used as the primary endpoint for trial OBD-0631, does include subjects who had dose reductions. As a result, the Week 12 analysis would not be expected to discriminate against lubiprostone subjects who might be more likely to undergo dose reduction than placebo subjects. Given the lack of pre-specified analysis hierarchies and lack of complete multiplicity adjustment for secondary endpoints, the Sponsor's p-values are of limited interpretability and provided for informational purposes only. In this reviewer's assessment, the numerical trend favoring the lubiprostone group in all four populations does support the primary analysis of efficacy findings.*

Overall Change from Baseline in SBM Frequency

As a secondary endpoint in OBD-1033, the Sponsor evaluated overall difference between treatment groups in change from baseline SBM frequency. The Sponsor defined the overall endpoint as the average weekly SBM frequency rate while on study medication. Missing data procedures described earlier (see top of section 6.1.5

[Analysis of Secondary Endpoints\(s\)](#)) were used and LOCF was not employed.

For the ITT population, as pre-specified in the SAP, Hommel's stagewise rejective method was used to determine if Week 8, Week 12, and overall time points were statistically significant. The results for the ITT, mITT, completer, and per-protocol populations are in [Table 20](#). Due to absence of pre-specified hierarchy for evaluation of secondary endpoints, the Sponsor's p-values are for informational purposes only.

Table 20. Summary of Overall Change from Baseline in SBM Frequency in OBD-1033 (ITT, mITT, Completer, and Per-Protocol Populations)

Overall Change from Baseline in SBM Frequency ¹	Placebo	Lubiprostone	P-Value ²
ITT	(N=220)	(N=219)	
n	218	213	
Mean ± Standard Deviation	2.3 ± 2.45	3.1 ± 2.94	0.005 ²
Median (Minimum, Maximum)	1.8 (-1, 17)	2.5 (-2, 17)	
mITT	(N=213)	(N=211)	
n	211	205	
Mean ± Standard Deviation	2.3 ± 2.46	3.1 ± 2.95	0.001 ³
Median (Minimum, Maximum)	1.8 (-1, 17)	2.5 (-2, 17)	
Completer	(N=184)	(N=169)	
n	184	169	
Mean ± Standard Deviation	2.4 ± 2.45	3.2 ± 2.88	0.010 ²
Median (Minimum, Maximum)	1.9 (-1, 17)	2.7 (-2, 15)	
Per-Protocol	(N=179)	(N=177)	
n	177	174	
Mean ± Standard Deviation	2.3 ± 2.46	3.2 ± 3.06	0.026 ²
Median (Minimum, Maximum)	1.8 (-1, 17)	2.5 (-2, 17)	

¹Weekly SBM (BM) frequency rate: (168 x number of SBMs (BMs)/number of hours observed)

²Sponsor's p-value was initially based on the treatment effect from a van Elteren test stratified by pooled site and then adjusted using Hommel's stagewise rejective method for Week 8, Week 12, and overall.

³Sponsor's p-value is based on the treatment effect from a van Elteren test stratified by pooled site.

Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups. Additionally, Shapiro-Wilk p-value testing for normality was performed by the Sponsor and p-value was <0.001. A small p-value (<0.05) indicates non-normality.

Source: Reviewer's table, adapted from Sponsor's Tables 14.2.5.1, 14.2.5.2, 14.2.5.3, and 14.2.5.4 pages 159 to 163 of 785, CSR for OBD-1033; and module 5.3.5.3, Tables 1.2.5.2 and 1.2.5.3, pages 560 to 565 of 2585, Integrated Summary of Efficacy.

The difference between the lubiprostone and placebo groups in the ITT population (3.1 versus 2.3, p=0.005), the mITT population (3.1 versus 2.3, p=0.001), the completer population (3.2 versus 2.4, p=0.010) and the per-protocol population (3.2 versus 2.3, p=0.026) consistently favored the lubiprostone group.

Reviewer comments: *In this reviewer's assessment, overall change in SBM frequency may be a better secondary efficacy endpoint than change from baseline in SBM frequency at Week 8 or at Week 12 because overall change better considers the continuity of treatment effect over time. On the other hand, the overall change from baseline endpoint only captures change in SBM frequency rate while subjects were on*

study medication, rather than for a well-defined and consistent time period. Further, multiplicity adjustment was not made for the entire set of secondary endpoints. As such, reliance on statistical significance of findings alone to support efficacy is limited. In this reviewer's assessment, however, the consistent numerical trend favoring lubiprostone subjects in all four populations does provide some supportive evidence of efficacy.

SBMs within 24 and 48 Hours after First Dose of Study Medication

The Sponsor evaluated SBMs within 24 and 48 hours after first dose of study medication as secondary endpoints. The Sponsor considered subjects that received a rescue laxative within 1 day prior to first dose as censored if their first SBM occurred during the rescue laxative period, which was defined as the 24 hours post first dose of study medication. The proportion of subjects in each treatment group with their first SBM reported within 24 hours of first dose administration was obtained from the Kaplan-Meier life table estimates and Cox proportional hazards regression model. The treatment groups were compared using the likelihood-ratio chi-square test and if the Sponsor's p-value for 24 hours was ≤ 0.05 , then the groups were also compared at 48 hours (pre-specified hierarchy). The significance level was set at 0.05 for both comparisons (no multiplicity adjustment). Results are presented for trial OBD-1033 in Table 21, and the Sponsor's p-values are provided for supportive purposes only.

Table 21. Summary of SBMs within 24 and 48 Hours of First Study Medication Dose in OBD-1033 (ITT, mITT, Completer, and Per-Protocol Populations)

Time to First SBM	Number at Risk (% with SBM) ¹		P-Value ²
	Placebo	Lubiprostone	
ITT	(N=220)	(N=219)	
24 Hours, n (%)	136 (37.8)	109 (49.0)	0.016
48 Hours, n (%)	86 (60.4)	62 (70.7)	0.022
mITT	(N=213)	(N=211)	
24 Hours, n (%)	132 (37.6)	101 (50.8)	0.005
48 Hours, n (%)	83 (60.5)	56 (72.5)	0.008
Completer	(N=184)	(N=169)	
24 Hours, n (%)	112 (38.7)	81 (50.5)	0.023
48 Hours, n (%)	72 (60.6)	44 (73.1)	0.012
Per-Protocol	(N=179)	(N=177)	
24 Hours, n (%)	114 (35.8)	86 (49.9)	0.007
48 Hours, n (%)	73 (58.5)	45 (73.8)	0.002

Note: Proportions determined using Kaplan-Meier estimates in a time-to-event analysis. Subjects with no SBMs or with first SBM during the first 24 hours of the rescue laxative phase are censored; if no SBM, time to first SBM set to trial duration.

¹Number at risk (i.e., not yet achieving first SBM and not censored) prior to specified time and Kaplan-Meier estimate for percent already experiencing first SBM prior to specified time.

²Treatment groups were compared using a likelihood-ratio chi-square test.

Source: Reviewer's table, adapted from Tables 14.2.9.1, 14.2.9.2, 14.2.9.3, and 14.2.9.4 pages 170 to 173, CSR of OBD-1033.

In the ITT population, 38% of placebo subjects had their first SBM within 24 hours of study drug as compared with 49% of lubiprostone subjects. At 48 hours after first dose of study drug, 60% of placebo subjects had experienced their first SBM, as compared with 71% of lubiprostone subjects. Results for the mITT, completer, and per-protocol populations were similar to those of the ITT population. In all four patient populations, a greater percentage of lubiprostone subjects had SBMs within 24 and 48 hours of first study medication dose than placebo subjects. (b) (4)

Reviewer comments: *Placebo subjects had a notably high response rate, with nearly 40% of placebo subjects having an SBM within 24 hours of first dose. In this reviewer's assessment, evaluation of SBMs within 24 and 48 hours after first dose of study medication does not strongly inform overall efficacy of lubiprostone in the OIC population because OIC is a chronic condition. Assessment of efficacy over a treatment period of hours, rather than weeks, is not necessarily indicative of overall efficacy in this population. Endpoints that assess continuous response over a period of weeks (rather than hours or days) are more relevant to evaluating efficacy in the OIC patient population.*

(b) (4)

Weekly Responder Rates

Weekly SBM response rate was evaluated as a pre-specified secondary endpoint in trial OBD-1033, but not in trial OBD-0631. Weekly responders were defined as subjects with ≥ 1 additional SBM compared to baseline during a given week and ≥ 3 SBMs during the given week. The Sponsor evaluated this secondary endpoint using both LOCF analysis and non-LOCF analysis. Table 22 presents the results with non-LOCF analysis for the ITT population. The Sponsor analyzed weekly rates using CMH tests stratified by clinical site, but made no adjustment for multiple comparisons. Thus, these comparisons are not statistically valid and p-values provided by the Sponsor are not presented.

Table 22. Weekly SBM Response – Trial OBD-1033 (ITT Population, Non-LOCF Analysis)

Time Point	Responder Status ¹	Placebo (N=220)	Lubiprostone (N=219)
Week 1	n	217	212
	Responder, n (%)	107 (48.6)	128 (58.4)
Week 2	n	215	206
	Responder, n (%)	115 (52.3)	123 (56.2)
Week 3	n	206	200
	Responder, n (%)	104 (47.3)	115 (52.5)
Week 4	n	205	195
	Responder, n (%)	104 (47.3)	128 (58.4)
Week 5	n	193	190
	Responder, n (%)	109 (49.5)	123 (56.2)
Week 6	n	191	190
	Responder, n (%)	111 (50.5)	117 (53.4)
Week 7	n	190	186
	Responder, n (%)	111 (50.5)	121 (55.3)
Week 8	n	185	178
	Responder, n (%)	110 (50.0)	108 (49.3)
Week 9	n	184	173
	Responder, n (%)	108 (49.1)	113 (51.6)
Week 10	n	180	166
	Responder, n (%)	115 (52.3)	108 (49.3)
Week 11	n	181	166
	Responder, n (%)	102 (46.4)	104 (47.5)
Week 12	n	180	159
	Responder, n (%)	103 (46.8)	99 (45.2)

¹Weekly SBM responders have ≥ 1 additional SBM compared with baseline during the given week and ≥ 3 SBMs during the week. Source: Reviewer's table, modified from Sponsor's Table 2.7.3.3-32, pages 75 to 76 of 119, Summary of Clinical Efficacy.

In the ITT population, a greater percentage of lubiprostone subjects were weekly responders at Week 1 through Week 7 than placebo subjects. Although a numerical trend favoring lubiprostone subjects was present at all weeks except for Week 8, Week 10, and Week 12, the treatment effect decreased in the last five weeks of the trial (Week 8 through 12). By Week 8, weekly responder rates were similar between the placebo and lubiprostone groups and remained comparable through Week 12. Analysis of weekly responder rates in the mITT, completer, and per-protocol populations produced similar results. As with the ITT population, in the mITT population, a numerical trend favoring lubiprostone subjects was present at all weeks except for Week 8, Week 10, and Week 12. In the completer and per-protocol populations, a numerical trend in favor of lubiprostone subjects was present at all weeks except for Weeks 10 and 12.

The Sponsor used LOCF in a supportive analysis, and these results favored the lubiprostone group more consistently than results without LOCF. A greater percentage of lubiprostone subjects were weekly responders at each week (Week 1 through Week 12) than placebo subjects in all populations (ITT, mITT, completer, and per-protocol).

Reviewer comments: *Given the previous discussion about the potential weaknesses of endpoints that evaluate response rate at the end of a specific week rather than on a continuous basis, this reviewer's assessment of the weekly responder rate endpoint is that it does not provide strong supportive evidence of the results of the primary analysis for OBD-1033. Additionally, the finding of a higher weekly responder rate in the placebo group than the lubiprostone group of the ITT population for 3 of the last 5 weeks of the trial does not support durability of efficacy response.*

Because the Sponsor used LOCF to impute missing values primarily caused by early withdrawal from the trial (as pre-specified in the SAP), it is not surprising that LOCF analyses would more strongly favor the lubiprostone group than non-LOCF analyses. In general, the validity of imputation methods such as LOCF hinges on frequently unrealistic assumptions. Thus, such imputation methods have not been recommended.¹ In this officer's assessment, the more consistent numerical trend favoring lubiprostone subjects in LOCF analyses than non-LOCF analyses does not translate to supportive evidence of durability of efficacy response. This reviewer notes, however, that the non-LOCF analyses were also not statistically valid due to lack of adjustment for multiple comparisons. Further, because of the expected fluctuation in the disease course of OIC, the weekly responder rate analysis is not as appropriate an approach to evaluating persistence of efficacy as an overall responder analysis. An overall responder analysis more completely assesses efficacy on a continuous basis. In fact, the persistence of effect of lubiprostone was demonstrated by an exploratory analysis using a modified definition of an overall SBM responder recommended by DGIEP (see [Table 63](#)).

Health-Related Quality of Life: PAC-QOL and EQ-5D

The Sponsor analyzed health-related quality of life measures for the ITT population in OBD-1033 (pre-specified), but not in OBD-0631. Subjects in OBD-1033 rated their

¹ Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. *N Engl J Med.* 2012;367(14):1355-1360.

general health-related quality of life using the Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaire before starting treatment and at the end of Months 1, 2, and 3. The PAC-QOL is an instrument used to measure patients' experience of constipation. This instrument is internally consistent, valid, reproducible, and responsive to treatment over time in patients with chronic constipation.²

The PAC-QOL comprises four subscales (dissatisfaction, physical discomfort, psychosocial discomfort, and worries and concerns), each scored on a 5-point Likert scale (from 0 to 4) and a total score. A lower score indicates better quality of life. Citing a validation study of the PAC-QOL in chronic constipation,³ the Sponsor chose a 1-point improvement from baseline as clinically meaningful in subjects with chronic constipation. [Table 23](#) summarizes results of change from baseline by month in PAC-QOL total score. Due to lack of a pre-specified analysis hierarchy and incomplete multiplicity adjustments, the Sponsor's p-values are for informational purposes only.

Table 23. Summary of PAC-QOL Total Score Response by Month for OBD-1033 (ITT population)

Change from Baseline in PAC-QOL Total Score Response at:	Placebo (N=220)	Lubiprostone (N=219)	P-Value ¹
Month 1			0.206
n	207	210	
Mean ± Standard Deviation	-0.60 ± 0.794	-0.76 ± 0.847	
Median (Minimum, Maximum)	-0.40 (-3.0, 1.2)	-0.58 (-3.4, 1.0)	
Month 2			0.417
n	194	191	
Mean ± Standard Deviation	-0.80 ± 0.870	-0.91 ± 0.941	
Median (Minimum, Maximum)	-0.61 (-3.4, 1.8)	-0.79 (-3.6, 1.1)	
Month 3			0.801
n	150	132	
Mean ± Standard Deviation	-0.90 ± 0.929	-0.94 ± 0.968	
Median (Minimum, Maximum)	-0.71 (-3.4, 1.0)	-0.87 (-3.6, 0.8)	

¹Sponsor's p-value was initially based on the treatment effect from a van Elteren test stratified by pooled site and then adjusted using Hommel's stagewise rejective method for Month 1, Month 2, and Month 3.

Note: Shapiro-Wilk p-value testing for normality was also performed by the Sponsor and p-value was <0.001. A small p-value (<0.05) indicates non-normality.

Source: Reviewer's table, adapted from Sponsor's Table 14.2.16, pages 208 to 210 of 785, CSR of OBD-1033.

Changes from baseline in PAC-QOL total scores were not notably different between lubiprostone and placebo groups at Month 1 (-0.76 versus -0.60), Month 2 (-0.91 versus -0.80), or Month 3 (-0.94 versus -0.90). Further, the mean numerical change in total PAC-QOL score was less than 1 point in lubiprostone subjects at each month.

Therefore, using the Sponsor's threshold for clinical meaningfulness (change of 1 point or more in total score), the change reported in lubiprostone subjects was not clinically meaningful. Similarly, changes from baseline in scores for the four PAC-QOL subscales (see [Table 111](#) of [Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033](#)) were not notably different between treatment groups at any time point.

² Marquis P, De La Loge C, Dubois D, McDermott A, Chassany O. Development of the Patient Assessment of Constipation Quality of Life Questionnaire. *Scand J Gastroenterol.* 2005;40:540-551.

³ Dubois D, Gilet H, Viala-Danten M, Tack J. Psychometric performance and clinical meaningfulness of the Patient Assessment of Constipation-Quality of Life questionnaire in prucalopride (RESOLOR) trials for chronic constipation. *Neurogastroenterol Motil.* 2010;22(2):e54-63.

The EuroQuol Health State Index (EQ-5D) is a standardized measure of health status. The questionnaire consists of two components, the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). The descriptive system, also referred to as the summary index, is a weighted index of five health states (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of which has three dimensions (from 1 = no problem to 3 = extreme problems). The EQ-VAS asks subjects to rate how well or bad their health is today and records the respondent's self-rated health on a vertical, visual analogue scale (from 0 = worst imaginable health state to 100 = best imaginable health state). Table 24 presents differences between treatment groups in mean change from baseline in the EQ-5D summary index and EQ-VAS score at the end of treatment. As there was no pre-specified hierarchy for evaluation of these secondary endpoints, the Sponsor's p-values in the table are for informational purposes only.

Table 24. Summary of End of Treatment EQ-5D Response for OBD-1033 (ITT population)

Change from Baseline in:	Placebo (N=220)	Lubiprostone (N=219)	P-Value ¹
EQ-5D Summary Index			
n	203	202	0.860
Mean ± Standard Deviation	-0.01 ± 0.204	-0.01 ± 0.223	
Median (Minimum, Maximum)	0.00 (-0.5, 0.5)	0.00 (-0.6, 0.6)	
EQ-VAS			
n	203	202	0.438
Mean ± Standard Deviation	1.24 ± 21.6	2.45 ± 23.0	
Median (Minimum, Maximum)	1.00 (-66, 79)	2.50 (-90, 82)	

¹Sponsor's p-value was initially based on the treatment effect from a van Elteren test stratified by pooled site and then adjusted using Hommel's stagewise rejective method for the two domains (EQ Summary Index and EQ-VAS).

Note: Shapiro-Wilk p-value testing for normality was also performed by the Sponsor and p-value was <0.001. A small p-value (<0.05) indicates non-normality.

Source: Reviewer's table, adapted from Sponsor's Table 14.2.17, pages 223 to 226 of 785, CSR of OBD-1033.

Differences between treatment groups in mean change from baseline were not notably different at the end of treatment between the lubiprostone and placebo groups for the EQ-5D summary index (-0.01 versus -0.01) or the EQ-VAS score (2.45 versus 1.24).

Reviewer comments: *From a clinical standpoint, the overall treatment effect suggested by the primary efficacy endpoint of overall SBM response in the ITT population of trial OBD-1033 should translate to relief of constipation, which in turn would be expected to positively affect quality of life. In this reviewer's assessment, the minimal differences in change in quality of life (as measured by PAC-QOL, EQ-5D summary index, and EQ-VAS) between lubiprostone and placebo subjects do not support the primary analysis findings for OBD-1033. Appropriately, the Sponsor is not seeking to include findings from the PAC-QOL or EQ-5D questionnaires in drug labeling.*

Overall Mean Change from Baseline in Bowel Function Parameters

As pre-specified secondary endpoints, the Sponsor assessed overall changes from baseline in the following bowel function parameters: (1) straining; (2) stool consistency of SBMs; (3) constipation severity; (4) abdominal bloating; and (5) abdominal discomfort. (b) (4)

Table 25

presents results of analysis of overall change from baseline in these bowel function parameters for the ITT population. The Sponsor used Hommel's stagewise rejective method to adjust for multiple comparisons, but not for the entire set of bowel function parameter endpoints. Further, there was no pre-specified hierarchy for evaluation of the endpoints, so the Sponsor's p-values in the table are for informational purposes only.

Table 25. Overall Change from Baseline in Bowel Function Parameters - OBD-1033 (ITT Population)

Overall Change from Baseline in:	Statistic	Placebo (N=220)	Lubiprostone (N=219)	P-Value
Straining ¹	n	197	193	0.002 ³
	Mean ± Standard Deviation	-0.8 ± 0.90	-1.1 ± 1.03	
	Median	-0.8	-1.1	
Stool consistency of SBMs ²	n	197	193	<0.001 ³
	Mean ± Standard Deviation	-0.6 ± 0.83	-1.0 ± 0.88	
	Median	-0.6	-1.0	
Constipation severity ¹	n	220	216	0.007 ⁴
	Mean ± Standard Deviation	-0.6 ± 0.75	-0.7 ± 0.80	
	Median	-0.5	-0.6	
Abdominal bloating ¹	n	220	216	0.208 ³
	Mean ± Standard Deviation	-0.4 ± 0.72	-0.6 ± 0.76	
	Median	-0.3	-0.4	
Abdominal discomfort ¹	n	220	216	0.095 ³
	Mean ± Standard Deviation	-0.4 ± 0.67	-0.6 ± 0.77	
	Median	-0.4	-0.5	

¹Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe

²Scale: 0 = very loose, 1 = loose, 2 = normal, 3 = hard, 4 = very hard (little balls)

³Sponsor's p-value was initially based on the treatment effect from a van Elteren test stratified by pooled site and then adjusted using Hommel's stagewise rejective method for straining, stool consistency, abdominal bloating, and abdominal discomfort.

⁴Sponsor's p-value is based on the treatment effect from a van Elteren test stratified by pooled site.

Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups.

Source: Reviewer's table, modified from Sponsor's Table 2.7.3.3-33, page 79 of 119, Summary of Clinical Efficacy.

Lubiprostone subjects showed a numerical overall improvement from baseline compared with placebo subjects with respect to straining (-1.1 versus -0.8), stool consistency (-1.0 versus -0.6), constipation severity (-0.7 versus -0.6), abdominal bloating (-0.6 versus -0.4), and abdominal discomfort (-0.6 versus -0.4). Results for the mITT, completer, and per-protocol populations were similar to those for the ITT group.

Reviewer comments: The scales used to evaluate these bowel function parameters are not validated. The Sponsor did not use the Bristol Stool Form Scale to assess changes in stool consistency. For all the parameters assessed, the actual numerical magnitude of the difference favoring the lubiprostone group was small. Further, there was incomplete adjustment for multiplicity in secondary endpoint statistical analyses. The

Overall Treatment Effectiveness

A global evaluation of overall treatment effectiveness was assessed at all post-treatment weeks via the eDiary, using scores ranging from 0 for not at all effective to a score of 4 for extremely effective. Results for the ITT and mITT populations are summarized in Table 26. Because there was no pre-specified hierarchy for evaluation of this endpoint, the Sponsor's p-values are presented for informational purposes only.

Table 26. Summary of Overall Treatment Effectiveness in OBD-1033 (ITT and mITT Populations)

Overall Treatment Effectiveness ¹	Placebo (N=220)	Lubiprostone (N=219)	P-Value ²
ITT			
n	217	212	0.046
Mean ± Standard Deviation	1.6 ± 1.01	1.8 ± 1.05	
Median (Minimum, Maximum)	1.6 (0.0, 3.7)	1.8 (0.0, 4.0)	
mITT			
n	210	204	0.041
Mean ± Standard Deviation	1.6 ± 1.01	1.8 ± 1.06	
Median (Minimum, Maximum)	1.6 (0.0, 3.7)	1.8 (0.0, 4.0)	

¹Overall treatment effectiveness: 0 = Not at all, 1 = A little bit, 2 = Moderately, 3 = Quite a bit, 4 = Extremely

²Sponsor's p-value is based on the treatment effect from a van Elteren test stratified by pooled site.

Note: Shapiro-Wilk p-value testing for normality was also performed by the Sponsor and p-value was <0.001. A small p-value (<0.05) indicates non-normality.

Source: Reviewer's table, adapted from Sponsor's Tables 14.2.15.1 and 14.2.15.2, pages 206 to 207 of 785, CSR of OBD-1033.

Reviewer comments: *Lubiprostone subjects had higher mean values for overall treatment effectiveness than did placebo subjects in both the ITT and mITT populations. As with the scales used to assess change from baseline in bowel function parameters, the scale used to assess overall treatment effectiveness is not validated. Though the p-values are <0.05 for both populations, statistical significance should not be claimed in the absence of a pre-specified hierarchy for secondary endpoints. Further, the small numerical magnitude of the difference favoring the lubiprostone group does not clearly translate to clinical significance, especially in the absence of an a priori method of interpreting a treatment benefit with respect to this secondary endpoint. The Sponsor is not seeking to include overall treatment effectiveness as a PRO endpoint in labeling.*

⁴ FDA guidance for industry, 2009, Patient-Reported Outcome Measures – Use in Medical Product Development to Support Labeling Claims. Available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>.

OBD-0631

In OBD-0631, there were multiple endpoints within the secondary analyses. The Sponsor indicated in the final version of the SAP that the primary endpoint was the gatekeeper and that inferential analyses for secondary endpoints related to the primary endpoint (e.g., SBM frequencies at Week 12 and overall) would only be performed if the primary endpoint was significant ($p \leq 0.05$). The Sponsor did not specify a hierarchy for evaluation of these two secondary endpoints (change from baseline in SBM frequency at Week 12 and overall). The SAP noted that Hommel's stagewise rejective method would be used to adjust for multiple comparisons within a group for several secondary endpoints, but appropriate multiplicity adjustment was not provided for the entire list of secondary endpoints. The Sponsor's missing data procedures are briefly discussed below and in [Appendix 3: Discussion of Individual Trials: Trial SMR/0211 OBD-0631](#).

As in OBD-1033, imputation of missing SBM data in OBD-0631 depended upon the amount of data observed. If ≥ 85 hours were observed during a week then the missing data within that week were imputed with the average SBM data for that week. If ≥ 25 , but < 85 hours were observed during a week, and ≥ 85 hours were observed during the prior week, then data were imputed from the prior week to provide a total of 85 hours of data. LOCF was used to impute missing values for weeks with no data.

Reviewer comments: Unlike the SAP for OBD-1033, the SAP for OBD-0631 did state that "there are hierarchies within the secondary analyses." Nonetheless, this reviewer notes that there was no pre-specified hierarchy for evaluation of the entire set of secondary endpoints. As such, this medical officer questions the statistical validity of the comparisons. In particular, for those secondary endpoints for which there was no hierarchy and no multiplicity adjustment, (b) (4)

Mean Change from Baseline in SBM Frequency at Week 12

As pre-specified in the SAP, the Sponsor performed inferential analysis because the Sponsor's primary endpoint p-value was ≤ 0.05 . Unlike analysis of this secondary endpoint for OBD-1033, which was performed only without LOCF, analysis of mean change from baseline in SBM frequency at Week 12 in OBD-0631 was performed with and without LOCF. [Table 27](#) presents non-LOCF results for the ITT, completer, and per-protocol populations.

Table 27. Summary of Change from Baseline in SBM Frequency at Week 12 in OBD-0631 (ITT, Completer, and Per-Protocol Populations)

Change from Baseline in SBM Frequency at Week 12	Placebo	Lubiprostone	P-Value ¹
ITT	(N=217)	(N=221)	0.140
n	150	150	
Mean ± Standard Deviation	2.5 ± 3.28	3.3 ± 3.69	
Median (Minimum, Maximum)	2.2 (-3.0, 22.4)	2.6 (-2.0, 18.8)	
Completer	(N=154)	(N=152)	0.263
n	141	142	
Mean ± Standard Deviation	2.5 ± 3.31	3.3 ± 3.70	
Median (Minimum, Maximum)	2.1 (-3.0, 22.4)	2.8 (-2.0, 18.8)	
Per-Protocol	(N=156)	(N=153)	0.228
n	113	113	
Mean ± Standard Deviation	2.2 ± 2.77	3.1 ± 3.56	
Median (Minimum, Maximum)	1.9 (-3.0, 10.9)	2.4 (-2.0, 18.8)	

¹Sponsor's p-value was initially based on the treatment effect from a van Elteren test stratified by pooled site and then adjusted using Hommel's stagewise rejective method for Week 8, Week 12, and overall.

Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups. Additionally, Shapiro-Wilk p-value testing for normality was performed by the Sponsor and p-value was <0.001. A small p-value (<0.05) indicates non-normality.

Source: Reviewer's table, adapted from Sponsor's Tables 14.2.2.1.2, 14.2.2.2.2, 14.2.2.3.2, pages 127-131, CSR for OBD-0631.

As with the findings for OBD-1033, there was a numerical trend in favor of lubiprostone subjects in the ITT population (3.3 versus 2.5, p=0.140), the completer population (3.3 versus 2.5, p=0.263), and the per-protocol population (3.1 versus 2.2, p=0.228). The results of the LOCF analysis of this endpoint were similar to the non-LOCF analysis, with a numerical trend favoring the lubiprostone group in the ITT population (2.8 versus 2.2, p=0.214), completer population (3.3 versus 2.5, p=0.208), and per-protocol population (2.9 versus 2.0, p=0.127).

Reviewer comments: Analysis of mean change from baseline in SBM frequency at Week 12 in OBD-0631 produced results similar to analysis of the same endpoint in OBD-1033 (see [Table 19](#)). In both trials, the treatment effect numerically favored lubiprostone subjects in all populations.

Overall Change from Baseline in SBM Frequency

As in OBD-1033, the overall endpoint in OBD-0631 was defined as the average weekly SBM frequency rate while on study medication. As pre-specified in the SAP, the Sponsor performed inferential analysis because the Sponsor's primary endpoint p-value was ≤0.05. The SAP did not describe a hierarchy for evaluation of the overall change endpoint with respect to results of inferential analysis of the Week 12 endpoint. For the ITT, completer, and per-protocol populations, the Sponsor used Hommel's stagewise rejective method to determine if Week 8, Week 12, and overall time points were statistically significant. [Table 28](#) summarizes results for the ITT, completer, and per-protocol populations.

Table 28. Summary of Overall Change from Baseline in SBM Frequency in OBD-0631 (ITT, Completer, and Per-Protocol Populations)

Overall Change from Baseline in SBM Frequency ¹	Placebo	Lubiprostone	P-Value ²
ITT	(N=217)	(N=221)	
n	216	218	0.014
Mean ± Standard Deviation	2.1 ± 2.35	2.7 ± 2.59	
Median (Minimum, Maximum)	1.6 (-3.8, 11.5)	2.3 (-2.2, 17.4)	
Completer	(N=154)	(N=152)	
n	154	152	0.008
Mean ± Standard Deviation	2.3 ± 2.26	3.1 ± 2.60	
Median (Minimum, Maximum)	1.8 (-1.7, 10.6)	2.8 (-0.9, 17.4)	
Per-Protocol	(N=156)	(N=153)	
n	156	152	0.027
Mean ± Standard Deviation	2.1 ± 2.29	2.7 ± 2.46	
Median (Minimum, Maximum)	1.5 (-1.7, 11.5)	2.6 (-1.5, 17.4)	

¹Weekly SBM (BM) frequency rate: (168 x number of SBMs (BMs)/number of hours observed)

²Sponsor's p-value was initially based on the treatment effect from a van Elteren test stratified by pooled site and then adjusted using Hommel's stagewise rejective method for Week 8, Week 12, and overall.

Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups. Additionally, Shapiro-Wilk p-value testing for normality was performed by the Sponsor and p-value was <0.001. A small p-value (<0.05) indicates non-normality.

Source: Reviewer's table, adapted from Sponsor's Tables 14.2.3.1, 14.2.3.2, and 14.2.3.3, pages 133 to 135, CSR of OBD-0631.

As with the findings for OBD-1033, the difference between the lubiprostone and placebo groups in the ITT population (2.7 versus 2.1, p=0.014), the completer population (3.1 versus 2.3, p=0.008), and the per-protocol population (2.7 versus 2.1, p=0.027) favored the lubiprostone group in OBD-0631.

Reviewer comments: As previously discussed in comments regarding the analysis of this endpoint in trial OBD-1033, reliance on statistical significance of findings to support efficacy is limited. Nonetheless, the consistent numerical trend favoring lubiprostone subjects in both trials does provide some supportive evidence of efficacy.

SBMs within 24 and 48 Hours after First Dose of Study Medication

The Sponsor evaluated SBMs within 24 and 48 hours after first dose of study medication as pre-specified secondary endpoints. The proportion of subjects in each treatment group with their first SBM reported within 24 hours of first dose administration was obtained from the Kaplan-Meier life table estimates. As with the analysis of this endpoint in OBD-1033, the Sponsor compared the treatment groups using the likelihood-ratio chi-square test and if the Sponsor's p-value for 24 hours was ≤0.05, then the groups were also compared at 48 hours (pre-specified hierarchy). The significance level was set at 0.05 for both comparisons. Results for OBD-0631 are in [Table 29](#). Due to lack of multiplicity adjustment, the Sponsor's p-values are for informational purposes.

Table 29. Summary of SBMs within 24 and 48 Hours of First Study Medication Dose in OBD-0631 (ITT, Completer, and Per-Protocol Populations)

Time to First SBM	Number at Risk (% with SBM) ¹		P-Value ²
	Placebo	Lubiprostone	
ITT	(N=217)	(N=221)	
24 Hours, n (%)	152 (30.0)	132 (40.3)	0.024
48 Hours, n (%)	101 (53.5)	83 (62.4)	0.057
Completer	(N=154)	(N=152)	
24 Hours, n (%)	111 (27.9)	94 (38.2)	0.057
48 Hours, n (%)	77 (50.0)	60 (60.5)	
Per-Protocol	(N=156)	(N=153)	
24 Hours, n (%)	108 (30.8)	98 (35.9)	0.334
48 Hours, n (%)	69 (55.8)	61 (60.1)	

Note: Proportions determined using Kaplan-Meier estimates in a time-to-event analysis. Subjects with no SBMs or with first SBM during the first 24 hours of the rescue laxative phase are censored; if no SBM, time to first SBM set to trial duration.

¹Number at risk (i.e., not yet achieving first SBM and not censored) prior to specified time and Kaplan-Meier estimate for percent already experiencing first SBM prior to specified time.

²Treatment groups were compared using a likelihood-ratio chi-square test.

Source: Reviewer's table, adapted from Sponsor's Tables 14.2.4.1, 14.2.4.2, and 14.2.4.3, pages 136 to 138, CSR of OBD-0631.

In the ITT population, 30% of placebo subjects had their first SBM within 24 hours of study drug as compared with 40% of lubiprostone subjects. At 48 hours after first dose of study drug, 54% of placebo subjects had experienced their first SBM, as compared with 62% of lubiprostone subjects. Results in the completer and per-protocol populations were similar to those of the ITT population. In all three patient populations, a greater percentage of lubiprostone subjects had SBMs within 24 and 48 hours of first study medication dose than placebo subjects. (b) (4)

Reviewer comments: As previously discussed, in this reviewer's assessment, evaluation of SBMs within 24 and 48 hours after first dose of study medication does not strongly inform overall efficacy of lubiprostone in the OIC population. OIC is a chronic condition, and assessment of efficacy over a treatment period of hours, rather than weeks, is not necessarily indicative of overall efficacy in this population. (b) (4)

Overall Responder Rates

The Sponsor analyzed overall responder rates as a pre-specified secondary endpoint in OBD-0631 (but not in OBD-1033). The Sponsor classified subjects as full responders, moderate responders, or non-responders based on weekly SBM frequencies. A full responder had an SBM frequency ≥ 4 for the week. A moderate responder had an SBM frequency of ≥ 3 but < 4 . A non-responder had SBM frequency < 3 for the week or dropped out during or prior to the given week due to lack of efficacy, or used rescue laxative during or within 24 hours prior to the given week. An overall responder was in the trial for ≥ 8 weeks and achieved at least moderate response for at least 50% of the weeks in the trial. The Sponsor performed analysis with and without LOCF. Table 30 presents non-LOCF results. The Sponsor's p-values are for informational purposes.

Table 30. Overall Responder Rates in OBD-0631 (ITT, Completer, and Per-Protocol Populations)

Overall Responder ¹ Rates	Placebo	Lubiprostone	P-Value ²
ITT	(N=217)	(N=221)	
Responder, n (%)	85 (39.2%)	101 (45.7%)	0.087
Completer	(N=154)	(N=152)	
Responder, n (%)	79 (51.3%)	92 (60.5%)	0.037
Per-Protocol	(N=156)	(N=153)	
Responder, n (%)	64 (41.0%)	74 (48.4%)	0.126

¹An overall responder had at least moderate response for at least 50% of weeks on study, and was on study for at least 8 weeks.

²Sponsor's p-values are from Cochran-Mantel-Haenszel test stratified by site.

Source: Reviewer's table, adapted from Sponsor's Tables 14.2.5.1.2, 14.2.5.2.2, and 14.2.5.3.2, pages 140-144, CSR of OBD-0631.

A higher percentage of lubiprostone subjects than placebo subjects were overall responders in the ITT population (46% versus 39%), the completer population (61% versus 51%), and the per-protocol population (48% versus 41%). The Sponsor's analysis of the overall response rate endpoint with LOCF, though not presented in [Table 30](#), produced similar results in the ITT population (47% versus 40%), the completer population (62% versus 52%), and the per-protocol population (50% versus 41%).

Reviewer comments: *In this reviewer's assessment, the overall responder endpoint used in OBD-0631 assesses efficacy on a more continuous basis than endpoints that assess change from baseline in SBM frequency at a specific time point (e.g., Week 8 or Week 12). In defining an overall responder as a subject who has an SBM frequency ≥ 3 for at least 50% of the weeks on study, and is on study for at least 8 weeks, this endpoint is reminiscent of the overall SBM response endpoint used as the primary endpoint in OBD-1033. The two endpoints differ, however, in that the primary endpoint in OBD-1033 defined an overall responder as a subject who had ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥ 3 SBMs per week for at least 9 of the 12 treatment weeks. Based on these differences, the overall responder endpoint in OBD-0631 is less rigorous than the overall SBM response endpoint in OBD-1033. Further, the lack of a pre-specified hierarchy for this secondary endpoint limits statistical validity. Nonetheless, the numerical trend favoring lubiprostone subjects in the ITT, completer, and per-protocol populations does provide some supportive evidence of efficacy.*

Overall Mean Change from Baseline in Bowel Function Parameters

As a pre-specified secondary endpoint, the Sponsor assessed overall changes from baseline in the following bowel function parameters: (1) straining; (2) stool consistency of SBMs; (3) constipation severity; (4) abdominal bloating; and (5) abdominal discomfort. (b) (4)

[Table 31](#) presents results for the ITT population of OBD-0631. The Sponsor did not pre-specify a hierarchy for evaluation of these secondary endpoints in the SAP. Although the Sponsor presented the data with p-value results using Hommel's stagewise rejective method to adjust for multiple comparisons, this approach to multiplicity adjustment was *not* pre-specified in the final SAP for OBD-0631. P-values (those derived by the Sponsor using the van Elteren test, which was pre-specified in the SAP) are for informational purposes only.

Table 31. Overall Change from Baseline in Bowel Function Parameters - OBD-0631 (ITT Population)

Overall Change from Baseline in:	Statistic	Placebo (N=217)	Lubiprostone (N=221)	P-Value ³
Straining ¹	n	194	186	<0.001
	Mean ± Standard Deviation	-0.6 ± 0.88	-1.0 ± 1.00	
	Median	-0.6	-0.9	
Stool consistency ²	n	194	186	<0.001
	Mean ± Standard Deviation	-0.5 ± 0.77	-0.8 ± 0.91	
	Median	-0.5	-0.8	
Constipation severity ¹	n	217	221	0.002
	Mean ± Standard Deviation	-0.4 ± 0.71	-0.6 ± 0.74	
	Median	-0.3	-0.5	
Abdominal bloating ¹	n	217	221	0.126
	Mean ± Standard Deviation	-0.4 ± 0.63	-0.4 ± 0.63	
	Median	-0.2	-0.3	
Abdominal discomfort ¹	n	217	221	0.012
	Mean ± Standard Deviation	-0.3 ± 0.63	-0.5 ± 0.62	
	Median	-0.2	-0.4	

¹Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe

²Scale: 0 = very loose, 1 = loose, 2 = normal, 3 = hard, 4 = very hard (little balls)

³Sponsor's p-value is based on the treatment effect from a van Elteren test stratified by pooled site.

Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups.

Source: Reviewer's table, modified from Sponsor's Table 2.7.3.3-33, page 79 of 119, Summary of Clinical Efficacy.

In the ITT population, lubiprostone subjects showed a numerical overall improvement from baseline compared with placebo subjects with respect to straining (-1.0 versus -0.6), stool consistency (-0.8 versus -0.5), constipation severity (-0.6 versus -0.4), and abdominal discomfort (-0.5 versus -0.3). There was no measurable treatment difference for abdominal bloating (-0.4 versus -0.4). The Sponsor also performed analyses of changes from baseline in bowel function parameters for the completer and per-protocol populations with results similar to results for the ITT group.

Reviewer comments: *As previously discussed for these secondary endpoints in OBD-1033, the presence of a numerical change favoring lubiprostone in specific PRO endpoints does not translate to clinical meaningfulness. Further, although the Sponsor's p-values are included in Table 31 for completeness, this reviewer emphasizes that the lack of proper multiplicity adjustment for these secondary endpoints renders the p-values statistically invalid.*

(b) (4)

Overall Treatment Effectiveness

As in OBD-1033, overall treatment effectiveness was assessed in OBD-0631 using scores ranging from 0 for not at all effective to a score of 4 for extremely effective. Results for the ITT, completer, and per-protocol populations in OBD-0631 are summarized in Table 32. The Sponsor's p-values are for informational purposes only.

Table 32. Summary of Overall Treatment Effectiveness in OBD-0631 (ITT, Completer, and Per-Protocol Populations)

Overall Treatment Effectiveness ¹	Placebo	Lubiprostone	P-Value ²
ITT	(N=217)	(N=221)	
n	214	211	
Mean ± Standard Deviation	1.3 ± 0.99	1.6 ± 1.04	0.001
Median (Minimum, Maximum)	1.2 (0.0, 4.0)	1.7 (0.0, 4.0)	
Completer	(N=154)	(N=152)	
n	154	151	
Mean ± Standard Deviation	1.4 ± 1.02	1.8 ± 1.01	0.002
Median (Minimum, Maximum)	1.3 (0.0, 4.0)	1.8 (0.0, 4.0)	
Per-Protocol	(N=156)	(N=153)	
n	155	148	
Mean ± Standard Deviation	1.3 ± 0.92	1.7 ± 1.04	0.002
Median (Minimum, Maximum)	1.2 (0.0, 3.8)	1.6 (0.0, 4.0)	

¹Overall treatment effectiveness: 0 = Not at all, 1 = A little bit, 2 = Moderately, 3 = Quite a bit, 4 = Extremely

²Sponsor's p-values are from Wilcoxon rank-sum test.

Source: Reviewer's table, adapted from Sponsor's Tables 14.2.11.1, 14.2.11.2, and 14.2.11.3, pages 160-162, CSR of OBD-0631.

Reviewer comments: *Lubiprostone subjects had higher mean values for overall treatment effectiveness than did placebo subjects in the ITT, completer, and per-protocol populations, findings similar to those in OBD-1033. As discussed previously for OBD-1033, this endpoint is not validated. Statistical significance should not be claimed in the absence of a pre-specified hierarchy for secondary endpoints. Further, the numerical differences favoring lubiprostone subjects are small and not clinically meaningful. The Sponsor is not seeking to include this endpoint in labeling.*

6.1.6 Other Endpoints

The Sponsor performed analyses of exploratory endpoints without a pre-specified hierarchy of evaluation. Thus, this reviewer will mostly present results without p-values to emphasize numerical trends. For those exploratory endpoints that the Sponsor is seeking to include in labeling, listed p-values are for informational purposes only.

Overall Change from Baseline in Complete SBM Frequency

The Sponsor evaluated mean overall change from baseline in complete SBM (CSBM) frequency as an exploratory endpoint in OBD-1033 and OBD-0631, but did not pre-specify this endpoint in the final SAP of either trial. Data on CSBMs were based on diary responses to the question, “did your bowels feel completely empty after the BM?” [Table 33](#) presents results for the ITT populations in the two trials.

Table 33. Overall Change from Baseline in CSBM Frequency in OBD-1033 and OBD-0631 (ITT)

Overall Change from Baseline in CSBM Frequency ¹	OBD-1033		OBD-0631	
	Placebo (N=220)	Lubiprostone (N=219)	Placebo (N=217)	Lubiprostone (N=221)
Baseline Value				
n	220	219	216	219
Mean ± Standard Deviation	0.3 ± 0.59	0.3 ± 0.56	0.4 ± 0.59	0.4 ± 0.70
Median (Min, Max)	0.0 (0, 3)	0.0 (0, 3)	0.0 (0, 3)	0.0 (0, 5)
Observed Value				
n	218	213	217	218
Mean ± Standard Deviation	1.8 ± 2.20	2.3 ± 2.64	1.5 ± 1.88	2.1 ± 2.12
Median (Min, Max)	1.1 (0, 13)	1.4 (0, 13)	0.8 (0, 10)	1.5 (0, 8)
Change from Baseline				
n	218	213	216	216
Mean ± Standard Deviation	1.5 ± 2.07	2.0 ± 2.59	1.2 ± 1.83	1.7 ± 1.94
Median (Min, Max)	0.8 (-2, 13)	1.1 (-1, 13)	0.4 (-2, 10)	1.1 (-2, 8)

¹Weekly complete SBM frequency rate: (168 x number of complete SBMs/number of hours observed)

Source: Reviewer's table, adapted from Sponsor's Table 1.3.19.9, module 5.3.5.3, page 2227, Integrated Summary of Efficacy.

Reviewer comments: A numerical trend favoring lubiprostone subjects was present in overall change from baseline in CSBM frequency for both OBD-1033 and OBD-0631. Based on the findings, this reviewer suggests that in future trials of patients with OIC, CSBM frequency could potentially be used in the primary and supportive efficacy analyses instead of SBM frequency.

Change from Baseline in SBM Frequency by Week and Month

The change from baseline in SBM frequency was evaluated at each week and month using both LOCF analysis and non-LOCF analysis. The non-LOCF results by week and month, respectively, are presented in [Table 34](#) and [Table 35](#). The change from baseline in SBM frequency at Week 12 was also a secondary efficacy endpoint for OBD-1033 and OBD-0631 and although presented in [Table 34](#) for completeness, is separately presented with detailed discussion in [Table 19](#) (OBD-1033) and [Table 27](#) (OBD-0631).

Table 34. Change from Baseline in SBM Frequency by Week - OBD-1033 and OBD-0631 (ITT)

Time Point	Change from Baseline in SBM Frequency by Week	OBD-1033		OBD-0631	
		Placebo (N=220)	Lubiprostone (N=219)	Placebo (N=217)	Lubiprostone (N=221)
Week 1	n	217	212	211	214
	Mean ± Standard Dev	1.8 ± 2.45	3.1 ± 4.11	1.8 ± 2.41	2.6 ± 3.10
	Median (Min, Max)	1.5 (-3, 13)	2.0 (-3, 29)	1.4 (-4, 14)	2.0 (-3, 19)
Week 2	n	215	206	213	210
	Mean ± Standard Dev	2.3 ± 2.73	3.0 ± 3.78	1.8 ± 2.71	2.4 ± 2.97
	Median (Min, Max)	1.5 (-2, 17)	2.0 (-3, 22)	1.3 (-5, 12)	1.5 (-3, 15)
Week 3	n	206	200	200	204
	Mean ± Standard Dev	2.2 ± 2.94	2.8 ± 3.22	2.1 ± 2.96	2.5 ± 2.90
	Median (Min, Max)	1.5 (-3, 14)	2.0 (-3, 16)	1.7 (-4, 14)	2.0 (-4, 13)
Week 4	n	205	195	196	193
	Mean ± Standard Dev	2.3 ± 3.07	3.3 ± 3.46	2.0 ± 2.91	2.9 ± 3.16
	Median (Min, Max)	1.5 (-2, 18)	2.5 (-2, 17)	1.4 (-2, 14)	2.0 (-3, 19)
Week 5	n	193	190	191	184
	Mean ± Standard Dev	2.2 ± 3.08	3.1 ± 3.35	2.3 ± 3.32	3.1 ± 3.33
	Median (Min, Max)	1.5 (-3, 18)	2.5 (-2, 21)	1.8 (-4, 21)	2.5 (-2, 20)
Week 6	n	191	190	179	180
	Mean ± Standard Dev	2.6 ± 3.16	3.0 ± 3.30	2.4 ± 3.12	3.0 ± 3.51
	Median (Min, Max)	2.0 (-3, 19)	2.1 (-2, 17)	1.9 (-3, 15)	2.1 (-3, 19)
Week 7	n	190	186	168	173
	Mean ± Standard Dev	2.6 ± 2.98	3.2 ± 3.20	2.4 ± 3.10	2.7 ± 3.02
	Median (Min, Max)	2.0 (-2, 19)	2.5 (-3, 14)	1.5 (-3, 18)	2.5 (-4, 20)
Week 8	n	185	178	169	171
	Mean ± Standard Dev	2.5 ± 3.07	3.1 ± 3.50	2.4 ± 3.25	3.2 ± 3.33
	Median (Min, Max)	2.0 (-3, 20)	2.5 (-3, 21)	1.4 (-3, 16)	2.6 (-2, 21)
Week 9	n	184	173	166	168
	Mean ± Standard Dev	2.5 ± 3.11	3.3 ± 3.52	2.3 ± 3.13	3.2 ± 3.49
	Median (Min, Max)	2.0 (-2, 23)	2.5 (-2, 15)	1.5 (-3, 22)	2.4 (-2, 20)
Week 10	n	180	166	163	163
	Mean ± Standard Dev	2.7 ± 3.15	3.2 ± 3.36	2.4 ± 3.33	3.3 ± 3.36
	Median (Min, Max)	2.0 (-2, 18)	2.5 (-3, 15)	1.8 (-3, 21)	3.0 (-2, 18)
Week 11	n	181	166	162	158
	Mean ± Standard Dev	2.5 ± 2.95	3.1 ± 3.20	2.5 ± 2.94	3.1 ± 3.22
	Median (Min, Max)	1.6 (-2, 18)	2.4 (-3, 14)	1.8 (-3, 14)	2.5 (-2, 19)
Week 12 [†]	n	180	159	150	150
	Mean ± Standard Dev	2.7 ± 3.34	3.1 ± 3.13	2.5 ± 3.28	3.3 ± 3.69
	Median (Min, Max)	2.0 (-2, 19)	2.5 (-3, 14)	2.2 (-3, 22)	2.6 (-2, 19)

[†]The change from baseline in SBM frequency at Week 12 was a secondary efficacy endpoint for trials OBD-1033 and OBD-0631. Source: Reviewer's table, adapted from Sponsor's Table 1.3.1.2, module 5.3.5.3, pages 823-834, Integrated Summary of Efficacy.

Table 35. Change from Baseline in SBM Frequency by Month - OBD-1033 and OBD-0631 (ITT)

Time Point	Change from Baseline in SBM Frequency by Month	OBD-1033		OBD-0631	
		Placebo (N=220)	Lubiprostone (N=219)	Placebo (N=217)	Lubiprostone (N=221)
Month 1	n	218	213	216	218
	Mean ± Standard Dev	2.1 ± 2.43	3.0 ± 3.19	1.8 ± 2.27	2.5 ± 2.51
	Median (Min, Max)	1.5 (-1, 14)	2.3 (-2, 19)	1.5 (-4, 11)	2.1 (-3, 14)
Month 2	n	198	195	191	186
	Mean ± Standard Dev	2.5 ± 2.77	3.1 ± 2.99	2.3 ± 2.84	3.0 ± 2.97
	Median (Min, Max)	2.0 (-2, 19)	2.5 (-2, 17)	1.7 (-4, 14)	2.7 (-1, 19)
Month 3	n	187	175	167	168
	Mean ± Standard Dev	2.6 ± 2.65	3.2 ± 2.94	2.4 ± 2.72	3.2 ± 3.01
	Median (Min, Max)	2.0 (-1, 17)	2.7 (-2, 14)	1.7 (-3, 15)	2.6 (-2, 19)

Source: Reviewer's table, adapted from Sponsor's Table 1.3.2.2, module 5.3.5.3, page 1042-1044, Integrated Summary of Efficacy.

Reviewer comments: When compared with placebo subjects, lubiprostone subjects showed a greater change from baseline in SBM frequency for all 12 weeks and at Month 1, Month 2, and Month 3. No statistically valid comparisons can be made, but in this reviewer's assessment, these findings do provide supportive evidence for the efficacy of lubiprostone in OIC. The caveat, however, is that the subjects were placed under the constraints of the protocol, which prohibited them from using their usual laxative regimen and which imposed limitations on use of rescue laxatives. This issue was previously discussed in section 5.3 Discussion of Individual Studies/Clinical Trials.

Frequency of CSBMs and SBMs by Week and Month and Proportion of SBMs Rated as Complete by Overall SBM Responders

The Sponsor evaluated the frequency of CSBMs and SBMs by week and by month using both LOCF and non-LOCF analysis. The non-LOCF results for frequency of CSBMs by week and month, respectively, are presented in [Table 36](#) and [Table 37](#). The proportion of SBMs rated as complete by overall responders (overall responders were subjects who had ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥ 3 SBMs per week for at least 9 of the 12 treatment weeks) in OBD-1033 and OBD-0631 is presented in [Table 38](#). The non-LOCF results for frequency of SBMs by week and month, respectively, are presented in [Table 39](#) and [Table 40](#).

Table 36. Frequency of CSBMs by Week in OBD-1033 and OBD-0631 (ITT Population)

Time Point	CSBM Frequency by Week	OBD-1033		OBD-0631	
		Placebo (N=220)	LBP (N=219)	Placebo (N=217)	LBP (N=221)
Baseline	n	220	219	216	219
	Mean ± Standard Dev	0.3 ± 0.59	0.3 ± 0.56	0.4 ± 0.59	0.4 ± 0.70
	Median (Min, Max)	0 (0, 3)	0 (0, 3)	0 (0, 3)	0 (0, 5)
Week 1	n	217	212	212	214
	Mean ± Standard Dev	1.2 ± 1.88	2.1 ± 3.18	1.0 ± 1.60	1.9 ± 2.72
	Median (Min, Max)	0.0 (0, 11)	0.0 (0, 20)	0.0 (0, 9)	1.0 (0, 16)
Week 2	n	215	206	214	210
	Mean ± Standard Dev	1.6 ± 2.19	2.1 ± 3.14	1.5 ± 2.16	1.9 ± 2.49
	Median (Min, Max)	1.0 (0, 15)	1.0 (0, 21)	1.0 (0, 12)	1.0 (0, 12)
Week 3	n	206	200	201	204
	Mean ± Standard Dev	1.6 ± 2.25	2.0 ± 2.73	1.4 ± 2.11	1.9 ± 2.39
	Median (Min, Max)	1.0 (0, 12)	1.0 (0, 14)	1.0 (0, 11)	1.0 (0, 10)
Week 4	n	205	195	197	193
	Mean ± Standard Dev	1.8 ± 2.62	2.4 ± 2.93	1.4 ± 2.17	2.2 ± 2.63
	Median (Min, Max)	1.0 (0, 13)	1.2 (0, 14)	0.0 (0, 12)	1.2 (0, 11)
Week 5	n	193	190	192	184
	Mean ± Standard Dev	1.9 ± 2.57	2.4 ± 3.15	1.8 ± 2.58	2.4 ± 2.86
	Median (Min, Max)	1.0 (0, 14)	1.0 (0, 17)	1.0 (0, 17)	1.3 (0, 15)
Week 6	n	191	190	180	180
	Mean ± Standard Dev	2.0 ± 2.74	2.4 ± 3.13	1.7 ± 2.68	2.3 ± 2.71
	Median (Min, Max)	1.0 (0, 14)	1.0 (0, 18)	0.0 (0, 15)	1.2 (0, 17)
Week 7	n	190	186	168	173
	Mean ± Standard Dev	2.2 ± 2.83	2.6 ± 3.04	1.9 ± 2.65	2.3 ± 2.33
	Median (Min, Max)	1.0 (0, 13)	2.0 (0, 15)	1.0 (0, 12)	2.0 (0, 9)
Week 8	n	185	178	169	171
	Mean ± Standard Dev	2.1 ± 2.64	2.5 ± 2.99	1.8 ± 2.69	2.5 ± 2.61
	Median (Min, Max)	1.0 (0, 11)	2.0 (0, 13)	1.0 (0, 14)	2.0 (0, 11)
Week 9	n	184	173	166	168
	Mean ± Standard Dev	2.2 ± 2.92	2.6 ± 3.13	1.8 ± 2.45	2.6 ± 3.12
	Median (Min, Max)	1.1 (0, 22)	1.2 (0, 15)	1.0 (0, 13)	1.4 (0, 18)
Week 10	n	180	166	163	163
	Mean ± Standard Dev	2.3 ± 2.92	2.7 ± 3.11	2.0 ± 2.92	2.4 ± 2.66
	Median (Min, Max)	1.0 (0, 15)	2.0 (0, 16)	1.0 (0, 15)	1.3 (0, 10)
Week 11	n	181	166	162	158
	Mean ± Standard Dev	2.2 ± 3.01	2.7 ± 3.12	1.9 ± 2.61	2.4 ± 2.54
	Median (Min, Max)	1.0 (0, 18)	2.0 (0, 14)	1.0 (0, 14)	2.0 (0, 14)
Week 12	n	180	159	150	150
	Mean ± Standard Dev	2.3 ± 3.07	2.9 ± 2.97	1.9 ± 2.43	2.7 ± 3.14
	Median (Min, Max)	1.0 (0, 15)	2.0 (0, 14)	1.0 (0, 12)	2.0 (0, 15)

Source: Reviewer's table, from Sponsor's Table 1.3.18.2, module 5.3.5.3, pages 2035-2038, Integrated Summary of Efficacy.

Table 37. Frequency of CSBMs by Month in OBD-1033 and OBD-0631 (ITT Population)

Time Point	CSBM Frequency by Month	OBD-1033		OBD-0631	
		Placebo (N=220)	LBP (N=219)	Placebo (N=217)	LBP (N=221)
Baseline	Mean ± Standard Dev	0.3 ± 0.59	0.3 ± 0.56	0.4 ± 0.59	0.4 ± 0.70
	Median (Min, Max)	0 (0, 3)	0 (0, 3)	0 (0, 3)	0 (0, 5)
Month 1	n	218	213	217	218
	Mean ± Standard Dev	1.5 ± 1.89	2.1 ± 2.68	1.3 ± 1.70	1.9 ± 2.11
	Median (Min, Max)	0.8 (0, 11)	1.5 (0, 16)	0.8 (0, 9)	1.1 (0, 10)
Month 2	n	198	195	192	186
	Mean ± Standard Dev	2.0 ± 2.51	2.5 ± 2.86	1.8 ± 2.34	2.4 ± 2.35
	Median (Min, Max)	1.0 (0, 12)	1.5 (0, 14)	0.8 (0, 11)	1.7 (0, 10)
Month 3	n	187	175	167	168
	Mean ± Standard Dev	2.2 ± 2.67	2.7 ± 2.84	1.9 ± 2.34	2.6 ± 2.57
	Median (Min, Max)	1.5 (0, 16)	2.0 (0, 15)	1.0 (0, 14)	1.9 (0, 12)

Source: Reviewer's table, adapted from Sponsor's Table 1.3.19.2, module 5.3.5.3, page 2060, Integrated Summary of Efficacy.

Reviewer comments: *In this reviewer's assessment, it appears that subjects with OIC can reliably distinguish a complete bowel movement from one that is not complete, as evidenced by the finding of a sustained higher CSBM frequency in lubiprostone subjects compared with placebo subjects (Table 36 and Table 37). Qualitatively, on average, it appears that ~40 to 50% of SBMs were rated as complete by placebo subjects and ~50% to 60% of SBMs were rated as complete by lubiprostone subjects.*

Table 38. Proportion of SBMs rated as Complete by Overall SBM Responders and Non-Responders in OBD-1033 and OBD-0631 (ITT Population)

Group	Statistic	OBD-1033		OBD-0631	
		Placebo (N=41)	Lubiprostone (N=59)	Placebo (N=32)	Lubiprostone (N=54)
Responders	n	41	59	32	54
	Mean ± Standard Dev	57.9 ± 31.2	61 ± 32.4	56.2 ± 34.0	61 ± 29.0
	Median (Min, Max)	61.8 (0, 100)	71.4 (0, 100)	58.9 (0, 100)	63.3 (1.2, 100)
Non-responders	n	173	151	181	162
	Mean ± Standard Dev	39.9 ± 34.0	43.4 ± 33.7	34.9 ± 30.0	42.8 ± 33.9
	Median (Min, Max)	34.1 (0, 100)	41.6 (0, 100)	31 (0, 100)	39 (1.2, 100)

Source: Reviewer's table, adapted from Sponsor's Table 7.2.1 and Table 7.2.2, pages 7 to 8, response to IR7.

Reviewer comments: *As shown in Table 38, overall SBM responders rated, on average, nearly 60% of their SBMs as complete, as compared with non-responders, who rated ~35 to 40% of their SBMs as complete. On the other hand, placebo responders reported nearly as many of their SBMs as complete as did lubiprostone responders in OBD-1033 (mean 58% versus 61%) and in OBD-0631 (mean 56% versus 61%). This finding suggests that lubiprostone may treat OIC primarily by increasing number of SBMs and not the proportion of SBMs felt by subjects to be complete (further discussed following Table 72).*

Frequency of SBMs by Week and Month

The Sponsor evaluated the frequency of SBMs by week and by month using both LOCF and non-LOCF analysis. The non-LOCF results for frequency of SBMs by week and month, respectively, are presented in Table 39 and Table 40.

Table 39. Frequency of SBMs by Week in OBD-1033 and OBD-0631 (ITT Population)

Time Point	SBM Frequency by Week	OBD-1033		OBD-0631	
		Placebo (N=220)	LBP (N=219)	Placebo (N=217)	LBP (N=221)
Baseline	n	220	219	216	221
	Mean ± Standard Dev	1.4 ± 0.81	1.3 ± 0.81	1.5 ± 0.96	1.4 ± 1.09
	Median (Min, Max)	1.5 (0, 4)	1.0 (0, 5)	1.5 (0, 7)	1.5 (0, 8)
Week 1	n	217	212	212	214
	Mean ± Standard Dev	3.2 ± 2.50	4.4 ± 4.14	3.2 ± 2.37	4.1 ± 3.24
	Median (Min, Max)	3.0 (0, 13)	3.0 (0, 29)	3.0 (0, 16)	3.4 (0, 20)
Week 2	n	215	206	214	210
	Mean ± Standard Dev	3.7 ± 2.83	4.2 ± 3.82	3.2 ± 2.74	3.8 ± 3.25
	Median (Min, Max)	3.0 (0, 18)	3.5 (0, 24)	3.0 (0, 14)	3.0 (0, 22)
Week 3	n	206	200	201	204
	Mean ± Standard Dev	3.6 ± 2.98	4.1 ± 3.21	3.6 ± 3.05	3.9 ± 3.06
	Median (Min, Max)	3.0 (0, 15)	3.1 (0, 18)	3.0 (0, 18)	3.2 (0, 16)
Week 4	n	205	195	197	193
	Mean ± Standard Dev	3.7 ± 3.10	4.6 ± 3.50	3.4 ± 2.92	4.3 ± 3.38
	Median (Min, Max)	3.0 (0, 19)	4.0 (0, 19)	3.0 (0, 15)	3.5 (0, 21)
Week 5	n	193	190	192	184
	Mean ± Standard Dev	3.7 ± 3.11	4.4 ± 3.34	3.8 ± 3.27	4.5 ± 3.54
	Median (Min, Max)	3.0 (0, 18)	4.0 (0, 23)	3.0 (0, 22)	4.0 (0, 22)
Week 6	n	191	190	180	180
	Mean ± Standard Dev	4.0 ± 3.20	4.3 ± 3.32	3.8 ± 3.11	4.4 ± 3.74
	Median (Min, Max)	3.6 (0, 19)	4.0 (0, 18)	3.0 (0, 16)	4.0 (0, 22)
Week 7	n	190	186	168	173
	Mean ± Standard Dev	4.1 ± 3.02	4.4 ± 3.20	3.8 ± 3.18	4.1 ± 3.21
	Median (Min, Max)	3.1 (0, 19)	4.0 (0, 15)	3.0 (0, 20)	3.8 (0, 22)
Week 8	n	185	178	169	171
	Mean ± Standard Dev	4.0 ± 3.12	4.4 ± 3.51	3.8 ± 3.24	4.6 ± 3.69
	Median (Min, Max)	4.0 (0, 20)	4.0 (0, 23)	3.0 (0, 17)	4.0 (0, 28)
Week 9	n	184	173	166	168
	Mean ± Standard Dev	4.0 ± 3.14	4.6 ± 3.59	3.7 ± 3.19	4.5 ± 3.77
	Median (Min, Max)	3.1 (0, 25)	4.0 (0, 17)	3.0 (0, 23)	3.8 (0, 22)
Week 10	n	180	166	163	163
	Mean ± Standard Dev	4.2 ± 3.23	4.5 ± 3.33	3.8 ± 3.36	4.7 ± 3.67
	Median (Min, Max)	4.0 (0, 18)	4.0 (0, 16)	3.0 (0, 22)	4.0 (0, 20)
Week 11	n	181	166	162	158
	Mean ± Standard Dev	3.9 ± 3.03	4.4 ± 3.25	3.9 ± 2.94	4.5 ± 3.44
	Median (Min, Max)	3.0 (0, 18)	3.8 (0, 14)	3.0 (0, 16)	3.8 (0, 21)
Week 12	n	180	159	150	150
	Mean ± Standard Dev	4.1 ± 3.43	4.4 ± 3.21	3.9 ± 3.30	4.7 ± 3.96
	Median (Min, Max)	3.1 (0, 20)	4.0 (0, 15)	3.5 (0, 24)	4.0 (0, 22)

Source: Reviewer's table, from Sponsor's Table 1.3.3.2, module 5.3.5.3, pages 1122-1125, Integrated Summary of Efficacy.

Table 40. Frequency of SBMs by Month in OBD-1033 and OBD-0631 (ITT Population)

Time Point	SBM Frequency by Month	OBD-1033		OBD-0631	
		Placebo (N=220)	LBP (N=219)	Placebo (N=217)	LBP (N=221)
Baseline	Mean ± Standard Dev	1.4 ± 0.81	1.3 ± 0.81	1.5 ± 0.96	1.4 ± 1.09
	Median (Min, Max)	1.5 (0, 4)	1.0 (0, 5)	1.5 (0, 7)	1.5 (0, 8)
	n	218	213	217	218
Month 1	Mean ± Standard Dev	3.5 ± 2.49	4.3 ± 3.23	3.3 ± 2.29	3.9 ± 2.72
	Median (Min, Max)	3.0 (0, 15)	3.6 (0, 21)	2.8 (0, 13)	3.3 (0, 19)
	n	198	195	192	186
Month 2	Mean ± Standard Dev	3.9 ± 2.83	4.4 ± 2.99	3.7 ± 2.81	4.4 ± 3.23
	Median (Min, Max)	3.5 (0, 19)	3.9 (0, 19)	3.0 (0, 15)	3.8 (0, 23)
	n	187	175	167	168
Month 3	Mean ± Standard Dev	4.0 ± 2.73	4.5 ± 2.97	3.8 ± 2.76	4.6 ± 3.29
	Median (Min, Max)	3.6 (0, 17)	4.0 (0, 15)	3.1 (0, 16)	3.9 (0, 21)
	n	187	175	167	168

Source: Reviewer's table, adapted from Sponsor's Table 1.3.4.2, module 5.3.5.3, page 1147, Integrated Summary of Efficacy.

In both trials OBD-1033 and OBD-0631, lubiprostone subjects had more frequent complete SBMs and more frequent SBMs than placebo subjects at each week between Week 1 and Week 12 and at each month between Month 1 and Month 3.

Reviewer comments: The fact that the greater CSBM and SBM frequency among lubiprostone subjects compared with placebo subjects was maintained through the end of the two double-blind trials provides some reassurance of the durability of response to lubiprostone. Additionally, baseline CSBM and SBM frequencies were similar across treatment arms in both trials, suggesting that the sustained increase in CSBM and SBM frequency among lubiprostone subjects compared with placebo subjects is real and not a reflection of imbalances in baseline bowel habits across the treatment arms. Although conclusions about efficacy are limited by the restrictions placed on laxative use (see discussion in section 5.3 Discussion of Individual Studies/Clinical Trials) and by the lack of statistical validity for comparisons, it is this reviewer's assessment that the overall pattern of weekly CSBM and SBM frequency in lubiprostone subjects provides supportive evidence for the efficacy of lubiprostone in OIC.

Frequency of Complete BMs by Week and Month

The frequency of complete BMs was evaluated by week and by month using both LOCF analysis and non-LOCF analysis. The non-LOCF results for frequency of complete BMs by week and month, respectively, are presented in [Table 41](#) and [Table 42](#).

Table 41. Frequency of Complete BMs by Week in OBD-1033 and OBD-0631 (ITT Population)

Time Point	Complete BM Frequency by Week	OBD-1033		OBD-0631	
		Placebo (N=220)	LBP (N=219)	Placebo (N=217)	LBP (N=221)
Baseline	n	220	219	216	219
	Mean ± Standard Dev	0.5 ± 0.67	0.5 ± 0.70	0.6 ± 0.84	0.8 ± 1.23
	Median (Min, Max)	0 (0, 4)	0 (0, 4)	0.5 (0, 4)	0.5 (0, 11)
Week 1	n	217	212	212	214
	Mean ± Standard Dev	1.2 ± 1.88	2.2 ± 3.19	1.1 ± 1.86	2.1 ± 2.88
	Median (Min, Max)	0.0 (0, 11)	1.0 (0, 20)	0.0 (0, 10)	1.0 (0, 16)
Week 2	n	215	206	214	210
	Mean ± Standard Dev	1.7 ± 2.19	2.2 ± 3.19	1.8 ± 2.43	2.1 ± 2.54
	Median (Min, Max)	1.0 (0, 15)	1.0 (0, 21)	1.0 (0, 18)	1.0 (0, 12)
Week 3	n	206	200	201	204
	Mean ± Standard Dev	1.7 ± 2.26	2.1 ± 2.73	1.6 ± 2.16	2.1 ± 2.53
	Median (Min, Max)	1.0 (0, 12)	1.1 (0, 14)	1.0 (0, 11)	1.2 (0, 13)
Week 4	n	205	195	197	193
	Mean ± Standard Dev	1.9 ± 2.61	2.4 ± 2.92	1.5 ± 2.19	2.3 ± 2.79
	Median (Min, Max)	1.0 (0, 13)	2.0 (0, 14)	1.0 (0, 12)	1.2 (0, 14)
Week 5	n	193	190	192	184
	Mean ± Standard Dev	1.9 ± 2.55	2.5 ± 3.12	2.0 ± 2.68	2.7 ± 2.96
	Median (Min, Max)	1.0 (0, 14)	1.2 (0, 17)	1.0 (0, 17)	2.0 (0, 15)
Week 6	n	191	190	180	180
	Mean ± Standard Dev	2.1 ± 2.76	2.5 ± 3.12	1.9 ± 2.74	2.4 ± 2.71
	Median (Min, Max)	1.0 (0, 14)	1.0 (0, 18)	1.0 (0, 15)	1.4 (0, 17)
Week 7	n	190	186	168	173
	Mean ± Standard Dev	2.3 ± 2.81	2.7 ± 3.04	2.1 ± 2.76	2.4 ± 2.37
	Median (Min, Max)	1.0 (0, 13)	2.0 (0, 15)	1.0 (0, 15)	2.0 (0, 9)
Week 8	n	185	178	169	171
	Mean ± Standard Dev	2.2 ± 2.63	2.5 ± 2.98	2.0 ± 2.69	2.6 ± 2.73
	Median (Min, Max)	1.0 (0, 11)	2.0 (0, 13)	1.0 (0, 14)	2.0 (0, 12)
Week 9	n	184	173	166	168
	Mean ± Standard Dev	2.2 ± 2.91	2.7 ± 3.11	1.9 ± 2.45	2.7 ± 3.11
	Median (Min, Max)	1.2 (0, 22)	1.5 (0, 15)	1.0 (0, 13)	2.0 (0, 18)
Week 10	n	180	166	163	163
	Mean ± Standard Dev	2.4 ± 2.91	2.7 ± 3.1	2.2 ± 3.00	2.5 ± 2.66
	Median (Min, Max)	1.5 (0, 15)	2.0 (0, 16)	1.0 (0, 15)	1.4 (0, 10)
Week 11	n	181	166	162	158
	Mean ± Standard Dev	2.3 ± 3.00	2.7 ± 3.12	2.1 ± 2.67	2.5 ± 2.53
	Median (Min, Max)	1.0 (0, 18)	2.0 (0, 14)	1.0 (0, 14)	2.0 (0, 14)
Week 12	n	180	159	150	150
	Mean ± Standard Dev	2.3 ± 3.06	2.9 ± 2.96	2.0 ± 2.46	2.8 ± 3.10
	Median (Min, Max)	1.0 (0, 15)	2.0 (0, 14)	1.2 (0, 12)	2.0 (0, 15)

Source: Reviewer's table, from Sponsor's Table 1.3.20.2, module 5.3.5.3, pages 2252-2255, Integrated Summary of Efficacy.

Table 42. Frequency of Complete BMs by Month in OBD-1033 and OBD-0631 (ITT Population)

Time Point	Complete BM Frequency by Month	OBD-1033		OBD-0631	
		Placebo (N=220)	LBP (N=219)	Placebo (N=217)	LBP (N=221)
Baseline	Mean ± Standard Dev	0.5 ± 0.67	0.5 ± 0.70	0.6 ± 0.84	0.8 ± 1.23
	Median (Min, Max)	0 (0, 4)	0 (0, 4)	0.5 (0, 4)	0.5 (0, 11)
Month 1	n	218	213	217	218
	Mean ± Standard Dev	1.6 ± 1.88	2.2 ± 2.70	1.5 ± 1.82	2.1 ± 2.25
	Median (Min, Max)	1.0 (0, 11)	1.5 (0, 16)	1.0 (0, 9)	1.3 (0, 13)
Month 2	n	198	195	192	186
	Mean ± Standard Dev	2.1 ± 2.50	2.5 ± 2.85	2.0 ± 2.41	2.6 ± 2.45
	Median (Min, Max)	1.2 (0, 12)	1.5 (0, 14)	1.2 (0, 12)	2.0 (0, 13)
Month 3	n	187	175	167	168
	Mean ± Standard Dev	2.3 ± 2.66	2.7 ± 2.83	2.0 ± 2.38	2.7 ± 2.55
	Median (Min, Max)	1.6 (0, 16)	2.0 (0, 15)	1.3 (0, 14)	2.1 (0, 12)

Source: Reviewer's table, adapted from Sponsor's Table 1.3.21.2, module 5.3.5.3, page 2277, Integrated Summary of Efficacy.

Frequency of BMs by Week and Month

The frequency of BMs was evaluated by week and by month using both LOCF analysis and non-LOCF analysis. The non-LOCF results for frequency of BMs by week and month, respectively, are presented in [Table 43](#) and [Table 44](#).

Table 43. Frequency of BMs by Week in OBD-1033 and OBD-0631 (ITT Population)

Time Point	BM Frequency by Week	OBD-1033		OBD-0631	
		Placebo (N=220)	LBP (N=219)	Placebo (N=217)	LBP (N=221)
Baseline	n	220	219	216	219
	Mean ± Standard Dev	1.9 ± 0.91	1.9 ± 1.03	2.4 ± 1.39	2.4 ± 1.54
	Median (Min, Max)	2.0 (0, 6)	2.0 (0, 6)	2.1 (0, 8)	2.2 (0, 12)
Week 1	n	217	212	212	214
	Mean ± Standard Dev	3.4 ± 2.42	4.6 ± 4.10	3.7 ± 2.56	4.6 ± 3.19
	Median (Min, Max)	3.0 (0, 13)	3.2 (0, 29)	3.0 (0, 16)	4.0 (0, 20)
Week 2	n	215	206	214	210
	Mean ± Standard Dev	3.9 ± 2.77	4.5 ± 3.75	4.0 ± 4.22	4.4 ± 3.11
	Median (Min, Max)	3.1 (0, 18)	4.0 (0, 24)	3.0 (0, 51)	3.5 (0, 22)
Week 3	n	206	200	201	204
	Mean ± Standard Dev	3.9 ± 2.85	4.3 ± 3.12	4.2 ± 3.02	4.5 ± 2.98
	Median (Min, Max)	3.0 (0, 15)	3.8 (0, 18)	3.5 (0, 18)	4.0 (0, 16)
Week 4	n	205	195	197	193
	Mean ± Standard Dev	4.0 ± 2.95	4.9 ± 3.30	3.9 ± 2.76	4.7 ± 3.45
	Median (Min, Max)	3.5 (0, 19)	4.0 (0, 19)	3.0 (0, 15)	4.0 (0, 21)
Week 5	n	193	190	192	184
	Mean ± Standard Dev	3.9 ± 3.00	4.6 ± 3.30	4.3 ± 3.29	4.9 ± 3.48
	Median (Min, Max)	3.1 (0, 18)	4.0 (0, 23)	4.0 (0, 22)	4.4 (0, 22)
Week 6	n	191	190	180	180
	Mean ± Standard Dev	4.2 ± 3.13	4.5 ± 3.22	4.3 ± 3.00	4.7 ± 3.67
	Median (Min, Max)	4.0 (0, 19)	4.0 (0, 18)	3.9 (0, 16)	4.0 (0, 22)
Week 7	n	190	186	168	173
	Mean ± Standard Dev	4.3 ± 2.89	4.6 ± 3.10	4.2 ± 3.13	4.5 ± 3.11
	Median (Min, Max)	3.8 (0, 19)	4.0 (0, 15)	3.5 (0, 20)	4.0 (0, 22)
Week 8	n	185	178	169	171
	Mean ± Standard Dev	4.2 ± 3.01	4.5 ± 3.41	4.3 ± 3.27	4.9 ± 3.67
	Median (Min, Max)	4.0 (0, 20)	4.0 (0, 23)	3.8 (0, 22)	4.5 (0, 28)
Week 9	n	184	173	166	168
	Mean ± Standard Dev	4.2 ± 3.03	4.8 ± 3.44	4.3 ± 2.96	4.9 ± 3.69
	Median (Min, Max)	3.6 (0, 25)	4.0 (0, 17)	3.7 (0, 23)	4.0 (0, 22)
Week 10	n	180	166	163	163
	Mean ± Standard Dev	4.3 ± 3.13	4.7 ± 3.21	4.4 ± 3.39	5.1 ± 3.49
	Median (Min, Max)	4.0 (0, 18)	4.0 (0, 16)	3.2 (0, 22)	4.7 (0, 20)
Week 11	n	181	166	162	158
	Mean ± Standard Dev	4.0 ± 2.95	4.6 ± 3.13	4.4 ± 3.04	4.8 ± 3.29
	Median (Min, Max)	3.0 (0, 18)	3.8 (0, 14)	4.0 (0, 16)	4.0 (0, 21)
Week 12	n	180	159	150	150
	Mean ± Standard Dev	4.3 ± 3.29	4.6 ± 3.07	4.4 ± 3.25	5.0 ± 3.82
	Median (Min, Max)	3.3 (0, 20)	4.0 (0, 15)	4.0 (0, 24)	4.0 (0, 22)

Source: Reviewer's table, from Sponsor's Table 1.3.5.2, module 5.3.5.3, pages 1172-1175, Integrated Summary of Efficacy.

Table 44. Frequency of BMs by Month in OBD-1033 and OBD-0631 (ITT Population)

Time Point	BM Frequency by Month	OBD-1033		OBD-0631	
		Placebo (N=220)	LBP (N=219)	Placebo (N=217)	LBP (N=221)
Baseline	n	220	219	216	219
	Mean ± Standard Dev	1.9 ± 0.91	1.9 ± 1.03	2.4 ± 1.39	2.4 ± 1.54
	Median (Min, Max)	2.0 (0, 6)	2.0 (0, 6)	2.1 (0, 8)	2.2 (0, 12)
Month 1	n	218	213	217	218
	Mean ± Standard Dev	3.8 ± 2.36	4.5 ± 3.16	4.0 ± 2.79	4.4 ± 2.66
	Median (Min, Max)	3.3 (0, 15)	4.0 (0, 21)	3.5 (0, 27)	3.8 (0, 19)
Month 2	n	198	195	192	186
	Mean ± Standard Dev	4.1 ± 2.72	4.6 ± 2.90	4.2 ± 2.78	4.8 ± 3.20
	Median (Min, Max)	3.6 (0, 19)	4.0 (0, 19)	3.7 (0, 17)	4.3 (0, 23)
Month 3	n	187	175	167	168
	Mean ± Standard Dev	4.2 ± 2.61	4.7 ± 2.82	4.3 ± 2.75	4.9 ± 3.16
	Median (Min, Max)	3.7 (1, 17)	4.0 (1, 15)	3.7 (1, 18)	4.2 (0, 21)

Source: Reviewer's table, adapted from Sponsor's Table 1.3.6.2, module 5.3.5.3, page 1197, Integrated Summary of Efficacy.

In both OBD-1033 and OBD-0631, lubiprostone subjects had more frequent complete BMs and more frequent BMs than placebo subjects at each week between Week 1 and Week 12 and at each month between Month 1 and Month 3.

Reviewer comments: In this reviewer's assessment, the greater complete BM and BM frequency among lubiprostone subjects compared with placebo subjects throughout the span of the two double-blind trials supports durability of response to lubiprostone. Although conclusions about efficacy are limited by the restrictions placed on use of laxatives and the inability to make statistically valid comparisons, numerical trends were in favor of the lubiprostone subjects for all BM and SBM types at all evaluated time points for both trials. These findings provide supportive evidence for the efficacy and durability of efficacy of lubiprostone in OIC.

Weekly and Monthly Assessment of Treatment Effectiveness

Treatment effectiveness (a PRO) was assessed using scores ranging from 0 for not at all effective to a score of 4 for extremely effective, using both LOCF analysis and non-LOCF analysis. The non-LOCF results by week and month, respectively, are summarized in [Table 112](#) and [Table 113](#) of the Appendix for OBD-1033 and in [Table 118](#) and [Table 119](#) of the Appendix for OBD-0631. Briefly, lubiprostone subjects rated overall treatment effectiveness higher than placebo subjects at all observed time points (by week and month) for both trials. Differences between the two treatment groups favoring lubiprostone subjects appeared consistently larger in OBD-0631 than OBD-1033, though the overall magnitude of the difference between the two treatment groups did not exceed 0.5 points (on a 4-point scale) at any evaluated time point.

Reviewer comments: This reviewer does not find the overall treatment effectiveness PRO to be a particularly useful subjective measure of treatment benefit. The PRO is not validated and the results, in this reviewer's assessment, are not clinically meaningful. The Sponsor is not seeking to include findings of this PRO endpoint in drug labeling.

Median Time to First SBM and SBMs within 4, 8, and 12 Hours of First Drug Dose

As pre-specified exploratory endpoints, the Sponsor analyzed median time to first SBM and proportion of subjects in each treatment group with their first SBM at 4, 8, and 12

hours. These results are presented for OBD-1033 in [Table 45](#) and for OBD-0631 in [Table 46](#). There were no multiplicity adjustments and no pre-specified hierarchy for evaluation, so comparisons are not statistically valid.

Table 45. Time to First SBM and Proportion of Subjects with First SBM within 4, 8, and 12 Hours of First Dose of Study Drug in OBD-1033 (ITT Population)

Time to First SBM	Number at Risk (% with SBMs) ¹		P-Value ²
	Placebo (N=220)	Lubiprostone (N=219)	
0 Hours	220 (0)	219 (0)	
4 Hours	209 (5.0)	189 (13.3)	0.002
8 Hours	201 (8.6)	183 (16.0)	0.017
12 Hours	189 (14.1)	168 (22.5)	0.021
Median (95% Confidence Interval)	38.5 (27.2, 42.1)	24.3 (21.5, 29.0)	0.019

Note: Proportions and median times estimated using Kaplan-Meier estimates in a time-to-event analysis. Subjects with no SBMs or with first SBM during the first 24 hour rescue laxative phase were censored; if no SBM, time to first SBM set to trial duration.

¹Number at risk (i.e., not yet achieving first SBM and not censored) prior to specified time and Kaplan-Meier estimate for percent already experiencing first SBM prior to specified time.

²Proportions were compared using a likelihood-ratio chi-square test. Median times were compared using the Cox proportional hazards regression model. **Sponsor's p-values are for informational purposes only.**

Source: Reviewer's table, adapted from Sponsor's Tables 11-8, page 57 of 785, CSR of OBD-1033.

In OBD-1033, a greater percentage of lubiprostone subjects than placebo subjects had their first SBM within 4 hours (13% versus 5%), 8 hours (16% versus 9%), and 12 hours (23% versus 14%) of first dose of study drug. Median time to first SBM was ~14 hours less for lubiprostone subjects than placebo subjects (24.3 hours versus 38.5 hours).

Table 46. Time to First SBM and Proportion of Subjects with First SBM within 4, 8, and 12 hours of First Dose of Study Drug in OBD-0631 (ITT Population)

Time to First SBM	Number at Risk (% with SBMs) ¹		P-Value ²
	Placebo (N=217)	Lubiprostone (N=221)	
0 Hours	217 (0)	221 (0)	
4 Hours	196 (9.7)	188 (14.9)	0.093
8 Hours	184 (15.2)	169 (23.5)	0.027
12 Hours	175 (19.4)	152 (31.2)	0.004
Median (95% Confidence Interval)	46.0 (36.4, 50.5)	28.0 (25.3, 34.0)	0.030

Note: Proportions and median times estimated using Kaplan-Meier estimates in a time-to-event analysis. Subjects with no SBMs or with first SBM during the first 24 hour rescue laxative phase were censored; if no SBM, time to first SBM set to trial duration.

¹Number at risk (i.e., not yet achieving first SBM and not censored) prior to specified time and Kaplan-Meier estimate for percent already experiencing first SBM prior to specified time.

²Proportions were compared using a likelihood-ratio chi-square test. Median times were compared using the Cox proportional hazards regression model. **Sponsor's p-values are for informational purposes only.**

Source: Reviewer's table, adapted from Sponsor's Table 1.3.7.1, module 5.3.5.3, page 1202, Integrated Summary of Efficacy.

In OBD-0631, a greater percentage of lubiprostone subjects than placebo subjects had their first SBM within 4 hours (15% versus 10%), 8 hours (24% versus 15%), and 12 hours (31% versus 19%) of first dose of study drug. Median time to first SBM was ~18 hours less for lubiprostone subjects than placebo subjects (28 hours versus 46 hours).

Reviewer comments: *Similar to the findings of the secondary endpoint which assessed SBMs within the first 24 and 48 hours of first study medication administration (summarized in [Table 21](#) for OBD-1033 and in [Table 29](#) for OBD-0631), a greater percentage of lubiprostone subjects had a first SBM within 4, 8, and 12 hours of first*

study medication dose than placebo subjects in both trials. The median time to first SBM also demonstrates a more rapid time to first laxation in the lubiprostone group for both trials. However, in this reviewer’s assessment, median time to first SBM and SBMs within 4, 8, and 12 hours of first dose of study medication do not strongly inform overall efficacy of lubiprostone in the OIC population. OIC is a chronic condition, and assessment of efficacy over a treatment period of hours, rather than weeks, is not necessarily indicative of overall efficacy in this population.

Bowel Habit Regularity

Bowel habit regularity was an exploratory endpoint for OBD-1033 and OBD-0631 and results of change from baseline analysis are presented in Table 47. This PRO endpoint was based on a weekly assessment of the following question: “During the past week how would you rate the regularity of your bowel habits?” Bowel habit regularity was rated on a 7-point scale with 1 indicating “very regular” and 7 indicating “very irregular.”

Table 47. Overall Change from Baseline in Bowel Habit Regularity - OBD-1033 and OBD-0631 (ITT)

Overall Change from Baseline in Bowel Habit Regularity:	OBD-1033		OBD-0631	
	Placebo (N=220)	Lubiprostone (N=219)	Placebo (N=217)	Lubiprostone (N=221)
n	218	213	216	218
Mean ± Standard Deviation	-0.7 ± 1.54	-0.8 ± 1.66	-0.5 ± 1.63	-0.6 ± 1.45
Median	-0.5	-0.6	-0.4	-0.5

Source: Sponsor’s Table 2.7.3.3-33, page 79 of 119, Summary of Clinical Efficacy.

Reviewer comments: *Although the Sponsor listed bowel habit regularity as a secondary endpoint in the final clinical study report and final clinical protocol for OBD-0631, bowel habit regularity was listed as an exploratory endpoint in the final SAP for both trials, and thus is not discussed in the secondary endpoints section of this sNDA review. This PRO endpoint is not validated and in this reviewer’s assessment, of little clinical meaningfulness. This reviewer questions whether a subject could reliably discriminate between seven levels of bowel habit regularity in order to determine how to rank regularity on a 7-point scale. The differences between placebo and lubiprostone subjects were small and the Sponsor is not seeking to include this endpoint in labeling.*

6.1.7 Subpopulations

The Sponsor performed subgroup analyses by gender, race, and age on the primary endpoint for each trial. Findings are discussed below for OBD-1033 and OBD-0631. These analyses were pre-specified in the SAP for OBD-1033 (provided $p \leq 0.05$ for the primary endpoint in the ITT population), and are therefore presented with the Sponsor’s p-values. Subgroup analyses by gender, race, and age were not pre-specified in the SAP for OBD-0631 (or OBD-0632) and were not provided as part of the original sNDA submission. Rather, the Sponsor performed these subgroup analyses for OBD-0631 in response to an Information Request from DGIEP. Because these subgroup analyses were not pre-specified in the SAP of OBD-0631, statistical significance of findings should not be claimed and p-values are not included in the tables for OBD-0631. Because OBD-0631 used a different primary endpoint than OBD-1033, subgroup

analyses for OBD-0631 are first presented using the primary endpoint for OBD-0631 (mean change from baseline in SBM frequency at Week 8). To facilitate comparison with results from subgroup analyses in OBD-1033, results using the overall SBM response endpoint are also presented for OBD-0631.

Gender

For OBD-1033, as shown in Table 48, the overall SBM response rate was higher in male lubiprostone subjects than female lubiprostone subjects (33% versus 23%).

Table 48. Overall SBM Response by Gender in OBD-1033 (ITT Population)

Overall SBM Response ¹	Female			Male		
	Placebo (N=138)	Lubiprostone (N=138)	P-Value ²	Placebo (N=82)	Lubiprostone (N=81)	P-Value ²
Responder, n (%)	26 (18.8%)	32 (23.2%)	0.333	15 (18.3%)	27 (33.3%)	0.146

¹Overall SBM response defined as ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥ 3 SBMs per week for at least 9 of the 12 treatment weeks.

²Sponsor's p-values for overall response rates comparing treatment groups analyzed using the CMH test stratified by pooled site. Source: Reviewer's table, modified from Table 2.7.3.3-42, page 93 of 119, Summary of Clinical Efficacy. Percentages in original Table 2.7.3.3-42 were not correct and subsequently corrected by Sponsor after DGIEP notified Sponsor of error (response to IR10).

Reviewer comments: Numerically, the lubiprostone group was favored for both genders, but male subjects appeared to respond better to lubiprostone (treatment difference of 15%) than female subjects (treatment difference of 4%). The sample size, however, was smaller in the male group, making the results more difficult to interpret.

For OBD-0631, as shown in Table 49, mean change from baseline in SBM frequency at Week 8 was lower among male lubiprostone subjects than female lubiprostone subjects (2.7 versus 3.5). The numerical differences between female lubiprostone and female placebo subjects (3.5 versus 2.6) and between male lubiprostone and male placebo subjects (2.7 versus 2.0) favored the lubiprostone group in both genders.

Table 49. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Gender in OBD-0631 (ITT Population)

Change From Baseline at Week 8	Female		Male	
	Placebo (N=112)	Lubiprostone (N=98)	Placebo (N=57)	Lubiprostone (N=66)
Mean	2.6	3.5	2.0	2.7
Median	2.0	3.2	0.9	2.0

Source: Reviewer's table, modified from Sponsor's Response to 74-Day Letter, Table 17, page 28.

Table 50 presents the overall SBM response by gender in OBD-0631.

Table 50. Overall SBM Response by Gender in OBD-0631 (ITT Population)

Overall SBM Response	Female		Male	
	Placebo (N=144)	Lubiprostone (N=136)	Placebo (N=73)	Lubiprostone (N=85)
Responder, n (%)	23 (16%)	33 (24.3%)	9 (12.3%)	21 (24.7%)

Source: Reviewer's table, modified from Sponsor's Response to 74-Day Letter, Table 16, page 27.

Reviewer comments: As in OBD-1033, the treatment difference favoring lubiprostone is larger among males (12%) than females (8%), but by a smaller margin than in OBD-

1033. Rigorous conclusions are difficult to make in the setting of imbalances in sample size between the genders and the post hoc nature of the analyses for OBD-0631, but overall, this reviewer does not believe that the efficacy of lubiprostone is different in males than females. This reviewer's findings are congruent with findings of analyses by gender for previously approved indications of lubiprostone. The medical officer that reviewed lubiprostone for the CIC indication (Dr. Kristen Buck) noted "no appreciable differences in the effectiveness of lubiprostone among male and female subjects." For the IBS-C indication, there were not enough male subjects enrolled in the IBS-C trials to permit a determination regarding differences in efficacy between genders.

Age

For OBD-1033, as shown in Table 51, the treatment difference favored lubiprostone in subjects aged <65 years (10%) and favored placebo in subjects aged ≥65 years (11%), but there were only 46 subjects aged ≥65 years (~10% of total study population).

Table 51. Overall SBM Response by Age in OBD-1033 (ITT Population)

Overall SBM Response	<65 Years			≥65 Years		
	Placebo (N=188)	Lubiprostone (N=205)	P-Value	Placebo (N=32)	Lubiprostone (N=14)	P-Value
Responder, n (%)	33 (17.6%)	57 (27.8%)	0.019	8 (25%)	2 (14.3%)	0.257

Sponsor's p-values for overall response rates comparing treatment groups analyzed using the CMH test stratified by pooled site. Source: Reviewer's table, modified from Table 2.7.3.3-37, page 88 of 119, Summary of Clinical Efficacy. Percentages in original Table 2.7.3.3-37 were not correct and subsequently corrected by Sponsor after DGIEP notified Sponsor of error (response to IR10).

Reviewer comments: *The percentage of subjects aged ≥65 years in OBD-1033 (10%) was probably too small to draw any meaningful conclusions.*

For OBD-0631, as shown in Table 52, mean change from baseline in SBM frequency at Week 8 was higher in lubiprostone subjects than placebo subjects aged <65 years (3.1 versus 2.3) and in lubiprostone subjects than placebo subjects aged ≥65 years (3.7 versus 2.9).

Table 52. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Age in OBD-0631 (ITT Population)

Change From Baseline at Week 8	<65 Years		≥65 Years	
	Placebo (N=154)	Lubiprostone (N=153)	Placebo (N=15)	Lubiprostone (N=11)
Mean	2.3	3.1	2.9	3.7
Median	1.4	2.5	2.0	3.5

Source: Reviewer's table, adapted from Sponsor's Response to 74-Day Letter, Table 19, page 32 and efficacy datasets.

Table 53 presents the overall SBM response by age in OBD-0631. The treatment difference favoring lubiprostone was larger in subjects aged <65 years (10%) than subjects aged ≥65 years (2%), but there were only 41 subjects aged ≥65 years.

Table 53. Overall SBM Response by Age in OBD-0631 (ITT Population)

Overall SBM Response	<65 Years		≥65 Years	
	Placebo (N=195)	Lubiprostone (N=202)	Placebo (N=22)	Lubiprostone (N=19)
Responder, n (%)	29 (14.9%)	51 (25.2%)	3 (13.6%)	3 (15.8%)

Source: Reviewer's table, modified from Sponsor's Response to 74-Day Letter, Table 18, page 30.

Reviewer comments: *As was the case for OBD-1033, the percentage of subjects aged ≥65 years in OBD-0631 (9%) was probably too small to draw meaningful conclusions. This reviewer's findings are congruent with findings of analyses by age for a previously approved indication of lubiprostone. In the IBS-C clinical trials of lubiprostone, subjects aged ≥65 years comprised 8% of the total study population. The medical officer that reviewed lubiprostone for the IBS-C indication (Dr. Helen Sile) noted that due to the small sample size, "it is difficult to derive any meaningful conclusions regarding lack of efficacy in this particular age group." In summary, because subjects aged ≥65 years comprised only about 10% of the total population in trials OBD-1033 and OBD-0631, this reviewer contends that the trials did not include sufficient numbers of subjects aged ≥65 years to determine whether they respond differently from younger subjects.*

Race

For OBD-1033, as shown in [Table 54](#), the treatment difference favoring lubiprostone was larger among non-white subjects (21%) than among white subjects (6%).

Table 54. Overall SBM Response by Race in OBD-1033 (ITT Population)

Overall SBM Response	White			Non-White*		
	Placebo (N=176)	Lubiprostone (N=182)	P-Value	Placebo (N=44)	Lubiprostone (N=37)	P-Value
Responder, n (%)	31 (17.6%)	43 (23.6%)	0.192	10 (22.7%)	16 (43.2%)	0.247

* 38 of the 44 non-white placebo subjects and 35 of the 37 non-white lubiprostone subjects were black/African-American.

Sponsor's p-values for overall response rates comparing treatment groups analyzed using the CMH test stratified by pooled site.

Source: Reviewer's table, modified from Table 2.7.3.3-47, page 98 of 119, Summary of Clinical Efficacy. Percentages in original Table 2.7.3.3-47 were not correct and subsequently corrected by Sponsor after DGIEP notified Sponsor of error (response to IR10).

Reviewer comments: *Black/African-American subjects constituted an adequate proportion (17%) of the overall ITT population in OBD-1033. Nonetheless, imbalances in sample size between white subjects and non-white subjects may account for the larger treatment effect among non-white subjects than white subjects.*

For OBD-0631, as shown in [Table 55](#), mean change from baseline in SBM frequency at Week 8 was higher in non-white lubiprostone subjects than white lubiprostone subjects (3.6 versus 3). The mean treatment difference between white lubiprostone and placebo subjects (0.7), however, was comparable to the treatment difference between non-white lubiprostone and placebo subjects (0.9).

Table 55. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Race in OBD-0631 (ITT Population)

Change From Baseline at Week 8	White		Non-White	
	Placebo (N=135)	Lubiprostone (N=123)	Placebo (N=34)	Lubiprostone (N=41)
Mean	2.3	3	2.7	3.6
Median	1.4	2.5	1.8	3.2

Source: Reviewer's table, modified from Sponsor's Response to 74-Day Letter, Table 21, page 37, and efficacy datasets.

Table 56 presents the overall SBM response by race in OBD-0631. The treatment difference favoring lubiprostone was larger in white subjects (10%) than non-white subjects (6%).

Table 56. Overall SBM Response by Race in OBD-0631 (ITT Population)

Overall SBM Response	White		Non-White*	
	Placebo (N=175)	Lubiprostone (N=170)	Placebo (N=42)	Lubiprostone (N=51)
Responder, n (%)	22 (12.6%)	39 (22.9%)	10 (23.8%)	15 (29.4%)

* 35 of the 42 non-white placebo subjects and 42 of the 51 non-white lubiprostone subjects were black/African-American.

Source: Reviewer's table, modified from Sponsor's Response to 74-Day Letter, Table 20, page 35.

Reviewer comments: Similar to OBD-1033, black/African-American subjects constituted an adequate proportion (18%) of the overall ITT population in OBD-0631. Unlike OBD-1033, however, in OBD-0631, non-white subjects did not appear to have a more favorable response to lubiprostone than white subjects. Although results of overall SBM response analyses by race are somewhat different between the two trials, the smaller sample sizes for the non-white subjects and post hoc nature of the analyses for OBD-0631 make rigorous conclusions difficult. Overall, this reviewer does not find a clear trend toward a larger treatment difference in non-white subjects than white subjects.

This reviewer's findings are congruent with findings of analyses by race for previously approved indications of lubiprostone. The medical officer that reviewed lubiprostone for the CIC indication (Dr. Kristen Buck) noted "no appreciable differences in the effectiveness of lubiprostone among white and non-white subjects." Additionally, in the IBS-C studies of lubiprostone, the analyses of the primary endpoint by race showed that the treatment difference favoring lubiprostone was larger among non-white subjects (8%) than white subjects (6%). Notably, however, the medical officer that reviewed lubiprostone for the IBS-C indication (Dr. Helen Sile) concluded that "despite the non-white subjects revealing a greater response than white subjects, the difference is not statistically significant."

Other Subpopulation Analyses

Although not pre-specified in the SAP for any of the 12-week efficacy trials, as part of the Summary of Clinical Efficacy submitted with the sNDA, the Sponsor presented pooled subgroup analyses of mean change from baseline in SBM frequency at Week 8 by opioid class and subclass. The Sponsor categorized opioids into three classes: (1) diphenylheptanes, which include methadone and propoxyphene; (2) phenanthrenes, which include the subclasses of hydrocodones, morphines, and oxycodones; and (3) phenylpiperidines, which include fentanyl and meperidine. These post hoc results,

which pooled data from the three efficacy trials, are shown in [Figure 3](#) and [Figure 4](#) of [Appendix 6: Pooled Efficacy Data by Opioid Class and Subclass \(OBD-1033, OBD-0631, and OBD-0632\)](#). The Sponsor analyzed these pooled results such that subjects taking more than one opioid from different classes or subclasses were included in *each* class/subclass. Review of results showed possible imbalances in efficacy across opioid classes and subclasses. Thus, DGIEP asked the Sponsor for subgroup analyses based on opioid class and phenanthrene subclass for each efficacy trial *individually*.

In response to this request, given the nonclinical study findings of the inhibitory action of methadone on lubiprostone, the Sponsor noted that the imbalances shown in the pooled results may have been due to the inclusion of patients who were concomitantly taking diphenylheptanes (e.g., methadone) and opioids from other classes or subclasses. As such, the Sponsor performed the requested analyses for each individual trial by segregating diphenylheptane-using subjects from analyses with the other opioid classes. Results for analyses by opioid class/subclass are presented below for OBD-1033 and OBD-0631. Because the subgroup analyses by opioid class and subclass were not pre-specified in the SAP for any of the efficacy trials, p-values are not included in the corresponding tables. Results for OBD-0632 are discussed separately in [Table 145](#), [Table 146](#), [Table 147](#), and [Table 148](#) of [Appendix 4: Discussion of Individual Trials: Trial SMR/0211 OBD-0632](#).

DGIEP also asked the Sponsor to perform analyses of the primary endpoint by duration of opioid use at baseline for each trial. Results are presented below for OBD-1033 and OBD-0631 and in [Table 143](#) for OBD-0632.

OBD-1033 – Other Subpopulation Analyses Opioid Class and Subclass

As shown in [Table 57](#), the overall SBM response rate was numerically higher in the lubiprostone group for the phenylpiperidine and phenanthrene opioid classes. As shown in [Table 58](#), the treatment difference between arms for hydrocodones (6%), morphines (3%), and oxycodones (11%) favored the lubiprostone arm in each case.

Table 57. Overall SBM Response by Opioid Class in OBD-1033 (ITT Population)

Overall SBM Response	Placebo (N=220)	Lubiprostone (N=219)
Phenylpiperidines		
n	13	17
Responder, n (%)	2 (15.4)	3 (17.6)
Phenanthrenes		
n	215	210
Responder, n (%)	41 (19.1)	57 (27.1)

Source: Reviewer's table, modified from Sponsor's Response to 74-Day Letter, Table 4, page 10 and Table 6, page 14.

Table 58. Overall SBM Response by Phenanthrene Subclass in OBD-1033 (ITT Population)

Overall SBM Response	Placebo (N=220)	Lubiprostone (N=219)
Hydrocodones		
n	137	131
Responder, n (%)	32 (23.4)	38 (29)
Morphines		
n	37	37
Responder, n (%)	6 (16.2)	7 (18.9)
Oxycodones		
n	59	65
Responder, n (%)	9 (15.3)	17 (26.2)

Source: Reviewer's table, modified from Response to 74-Day Letter, Table 10, page 20; Table 12, page 22; and Table 14, page 24.

Reviewer comments: *The number of subjects taking phenylpiperidine opioids was probably too small to draw any meaningful conclusions. Similarly, the treatment difference between arms was smallest for the morphine subclass, but among the three phenanthrene subclasses, the morphine subclass also had the smallest sample size. Although the analyses of overall SBM response by opioid class/subclass were all post hoc and comparisons not statistically valid, this clinical reviewer finds no clear trend to suggest that lubiprostone's efficacy is different between the phenylpiperidine and phenanthrene classes or between the three phenanthrene subclasses.*

Duration of Opioid Use

As presented in [Table 59](#), the majority of subjects had been on opioids for ≥ 12 months at baseline in both treatment arms, and the distribution of subjects by duration of opioid use was generally balanced across the two treatment arms.

Table 59. Overall SBM Response by Opioid Use Duration at Baseline in OBD-1033 (ITT Population)

Overall SBM Response by Opioid Use Duration at Baseline	Placebo (N=220)	Lubiprostone (N=219)
<3 Months		
n	7	7
Responder, n (%)	2 (28.6)	1 (14.3)
≥ 3 Months and <6 Months		
n	14	24
Responder, n (%)	4 (28.6)	7 (29.2)
≥ 6 Months and <12 Months		
n	27	27
Responder, n (%)	4 (14.8)	10 (37)
≥ 12 Months and <60 Months		
n	104	100
Responder, n (%)	12 (11.5)	26 (26)
≥ 60 Months		
n	68	61
Responder, n (%)	19 (27.9)	15 (24.6)

Source: Reviewer's table, modified from Sponsor's Response to 74-Day Letter, Table I3.2.1.1.1, page 775.

Reviewer comments: *The number of subjects in the subgroup with baseline opioid use duration <3 months, ≥ 3 months and <6 months, and ≥ 6 months and <12 months was*

too small to draw any meaningful conclusions. The treatment difference favoring lubiprostone was substantial (15%) in the subgroup with baseline opioid use duration ≥ 12 months and < 60 months (the largest subgroup). Of note, in the subgroup with baseline opioid use duration ≥ 60 months, the treatment difference actually favored the placebo group by a small margin (3%). The smaller sample size in this subgroup (baseline use duration ≥ 60 months) makes comparison with the treatment difference for the largest subgroup (baseline use duration ≥ 12 months and < 60 months) difficult.

OBD-0631 – Other Subpopulation Analyses

Opioid Class and Subclass

As shown in Table 60, the mean change from baseline in SBM frequency at Week 8 was higher in the lubiprostone group than the placebo group for both the phenanthrene class (3.3 versus 2.5) and the diphenylheptane class (2.5 versus 1.6), but not for the phenylpiperidine class (2.5 in both groups). Given the large standard deviation (3.04) in the phenylpiperidine placebo group (which might be driving up the mean value), the median may be a more appropriate descriptive statistic for comparison between arms in the phenylpiperidine class. Indeed, the median change from baseline in SBM frequency at Week 8 is higher in the lubiprostone group than the placebo group (2.9 versus 1.4).

As shown in Table 61, the mean change from baseline in SBM frequency at Week 8 was higher in the lubiprostone group than the placebo group for the hydrocodone subclass (3.6 versus 2.9), but not for the morphine subclass (2.4 versus 2.5) or the oxycodone subclass (2.6 versus 2.5). As with the phenylpiperidine class analysis, however, the standard deviation was larger in the placebo group than the lubiprostone group in both the morphine and oxycodone subclasses. In fact, when median values are compared, the difference favoring lubiprostone subjects is more sizeable for both the morphine subclass (2 versus 1) and the oxycodone subclass (2.2 versus 1.7).

Table 60. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Opioid Class in OBD-0631 (ITT Population)

Change from Baseline at Week 8	Placebo (N=217)	Lubiprostone (N=221)
Phenylpiperidines		
n	13	14
Mean $\pm$ Standard Deviation	2.5 $\pm$ 3.04	2.5 $\pm$ 1.81
Median	1.4	2.9
Phenanthrenes		
n	141	133
Mean $\pm$ Standard Deviation	2.5 $\pm$ 3.38	3.3 $\pm$ 3.48
Median	1.4	2.8
Diphenylheptanes		
n	25	29
Mean $\pm$ Standard Deviation	1.6 $\pm$ 2.25	2.5 $\pm$ 2.75
Median	0.9	2.4

Source: Reviewer's table, modified from Response to 74-Day Letter, Table 5, page 11, Table 7, page 15, and Table 9, page 18.

Table 61. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Phenanthrene Opioid Subclass in OBD-0631 (ITT Population)

Change from Baseline at Week 8	Placebo (N=217)	Lubiprostone (N=221)
Hydrocodones		
n	64	73
Mean ± Standard Deviation	2.9 ± 3.65	3.6 ± 3.85
Median	2.0	3.0
Morphines		
n	47	45
Mean ± Standard Deviation	2.5 ± 3.72	2.4 ± 2.65
Median	1.0	2.0
Oxycodones		
n	56	56
Mean ± Standard Deviation	2.5 ± 3.58	2.6 ± 2.65
Median	1.7	2.2

Source: Reviewer's table, modified from Response to 74-Day Letter, Table 11, page 21, Table 13, page 23, and Table 15, page 25.

Reviewer comments: *Although the number of subjects taking an opioid in the diphenylheptane class in OBD-0631 was probably too small to draw any meaningful conclusions, it is noteworthy that despite a nonclinical study demonstrating a negative treatment interaction between methadone and lubiprostone, the treatment effect in this class still favored the lubiprostone group. As with the findings for OBD-1033 (see [Table 57](#)), the number of subjects taking a phenylpiperidine opioid was probably too small to draw any meaningful conclusions. Similarly, as with the findings for OBD-1033 (see [Table 58](#)), the mean treatment difference between arms was negligible for the morphine subclass, but as discussed above, the median treatment difference may be a more appropriate statistic for comparison in this subclass than the mean. Further, among the opioid subclasses, the morphine subclass also had the smallest sample size. Additionally, although the mean treatment difference between arms favoring lubiprostone was minimal for the oxycodone subclass in OBD-0631, this finding was not corroborated by subclass analysis in OBD-1033. In that trial, the treatment difference favoring lubiprostone was sizeable for the oxycodone subclass (see [Table 58](#)).*

Meaningful conclusions are difficult to draw in light of the fact that these subgroup analyses by opioid class/subclass were post hoc and not powered to demonstrate significance. Conclusions are also limited because the subgroup analyses for OBD-1033 used a different primary endpoint than subgroup analyses for OBD-0631. In response to an Information Request, the Sponsor included exploratory analyses in which the overall SBM response endpoint was analyzed by opioid class/subclass for OBD-0631 and the mean change from baseline at Week 8 endpoint was analyzed by opioid class/subclass for OBD-1033. These results are in [Table 114](#) and [Table 115](#) of [Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033](#) and in [Table 120](#) and [Table 121](#) of [Appendix 3: Discussion of Individual Trials: Trial SMR/0211 OBD-0631](#). Taken in conjunction with the above discussion, this reviewer finds no trend to suggest that lubiprostone's efficacy is consistently different between phenylpiperidine and phenanthrene classes or between the three phenanthrene subclasses. Regarding the diphenylheptane class, despite the larger treatment effect in the lubiprostone group

than the placebo group in OBD-0631, given the limitations of these post hoc analyses, this reviewer cannot conclude that lubiprostone is efficacious in subjects taking diphenylheptane opioids. Further, in light of the nonclinical findings and the failure of a clinical trial (OBD-0632) that enrolled patients taking diphenylheptane opioids, it is this medical officer's assessment that the effectiveness of lubiprostone in the treatment of OIC in patients taking diphenylheptane opioids (e.g., methadone) has not been established. See [Appendix 4: Discussion of Individual Trials: Trial SMR/0211 OBD-0632](#) for a more detailed discussion.

Duration of Opioid Use

As presented in [Table 62](#), the majority of subjects had been on opioids for ≥ 12 months at baseline in both the placebo and lubiprostone arms and the distribution of subjects by duration of opioid dose was generally balanced across the two treatment arms.

Table 62. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Opioid Use Duration at Baseline in OBD-0631 (ITT Population)

Change from Baseline at Week 8 by Opioid Use Duration at Baseline	Placebo (N=169)	Lubiprostone (N=164)
<3 Months		
n	2	3
Mean $\pm$ Standard Deviation	1.5 $\pm$ 0.89	-0.6 $\pm$ 1.62
Median (Min, Max)	1.5 (1, 2)	-0.5 (-2, 1)
≥ 3 Months and <6 Months		
n	10	16
Mean $\pm$ Standard Deviation	2.6 $\pm$ 3.36	3.6 $\pm$ 2.97
Median (Min, Max)	1.9 (-2, 10)	2.9 (1, 11)
≥ 6 Months and <12 Months		
n	19	21
Mean $\pm$ Standard Deviation	2.2 $\pm$ 2.58	3.6 $\pm$ 2.83
Median (Min, Max)	1.0 (-2, 8)	3.5 (-2, 9)
≥ 12 Months and <60 Months		
n	85	72
Mean $\pm$ Standard Deviation	2.3 $\pm$ 3.17	2.5 $\pm$ 2.70
Median (Min, Max)	1.4 (-3, 16)	2.0 (-2, 10)
≥ 60 Months		
n	53	52
Mean $\pm$ Standard Deviation	2.6 $\pm$ 3.66	4.0 $\pm$ 4.19
Median (Min, Max)	1.5 (-2, 15)	3.5 (-1, 21)

Source: Reviewer's table, modified from Sponsor's Response to 74-Day Letter, Table I1.2.2.1.1, pages 742 to 746.

Reviewer comments: *The number of subjects in the subgroup with baseline opioid use duration <3 months, ≥ 3 months and <6 months, and ≥ 6 months and <12 months was too small to draw any meaningful conclusions. In the subgroup with baseline use duration ≥ 12 months and <60 months (largest subgroup), the mean change from baseline in SBM frequency at Week 8 was only marginally higher in the lubiprostone arm than the placebo arm (2.5 versus 2.3). In the subgroup with baseline use duration ≥ 60 months, the mean change from baseline in SBM frequency at Week 8 was notably higher in the lubiprostone arm than the placebo arm (4 versus 2.6). This finding is counter to the analysis of overall SBM response in the subgroup with baseline use*

duration ≥ 60 months in OBD-1033 (see [Table 59](#)), which showed no treatment benefit in the lubiprostone arm. Given the small subgroup sample sizes, the post hoc nature of these subgroup analyses, and the lack of consistent findings between the two trials (OBD-0631 and OBD-1033), this medical officer cannot surmise a clear association between opioid use duration at baseline and the primary endpoint in either trial.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

None was performed as part of this sNDA. Lubiprostone is approved for treatment of CIC at a dose of 24 mcg BID, the same dose evaluated in the OIC population in the trials submitted for this sNDA. The Sponsor indicated that the treatment duration and selection of doses for OIC trials were primarily based on safety and efficacy data collected from clinical trials of lubiprostone for treatment of CIC.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Based on discussions with DGIEP prior to submission of this sNDA, the Sponsor performed additional exploratory analyses to assess the durability of response.

Modified Definition of Overall SBM Response

DGIEP recommended an exploratory analysis in which the overall SBM response primary endpoint was modified to examine persistence of efficacy in the last 4 weeks of OBD-1033. The modified primary endpoint defined overall responders as subjects with ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥ 3 SBMs per week for at least 9 weeks *and* for at least 3 of the last 4 weeks. Results are summarized in [Table 63](#).

Table 63. Summary of Overall SBM Response (Modified Definition) in OBD-1033 (ITT, Completer, and Per-Protocol Populations)

Overall SBM Response ¹ by Population	Placebo	Lubiprostone	P-Value ²
ITT, n	220	219	
Responder, n (%)	40 (18.2%)	55 (25.1%)	0.074
Completer, n	184	169	
Responder, n (%)	39 (21.2%)	51 (30.2%)	0.045
Per-Protocol, n	179	177	
Responder, n (%)	36 (20.1%)	50 (28.2%)	0.117

¹Overall SBM response defined as ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥ 3 SBMs per week for at least 9 weeks *and* for at least 3 of the last 4 weeks.

²Sponsor's p-values for overall response rates comparing treatment groups were analyzed using the CMH test stratified by pooled site. **Sponsor's p-values are for informational purposes only.**

Source: Reviewer's table, adapted from Sponsor's Table 2.7.3.3-13, page 48 of 119, Summary of Clinical Efficacy.

Reviewer comments: *The DGIEP-recommended modified definition of overall SBM response is more stringent than the Sponsor's pre-specified primary endpoint definition because it incorporates the response for at least 3 out of the last 4 weeks of the double-blind trial. Based on this modified definition, in all three patient populations, the percentage of overall responders was higher in the lubiprostone group than the placebo group. Although the Sponsor's p-values are presented in [Table 63](#) for completeness, this endpoint was not pre-specified and statistical comparisons are not valid. The*

numerical magnitude of the treatment difference between lubiprostone and placebo subjects is consistent in the three populations (approximately 7% to 9%) and is congruent with the results of analyses on the pre-specified primary endpoint for OBD-1033 (see [Table 10](#) and [Table 11](#)). In this reviewer's assessment, the above analysis supports the durability of response relative to placebo over the 12 weeks of OBD-1033.

This reviewer finds that several other exploratory analyses support durability of response. Given the lack of multiplicity adjustment in these analyses, this reviewer can only comment on numerical trends and not statistical trends. Change from baseline in SBM frequency by week was numerically greater in the lubiprostone group than the placebo group for all 12 weeks of both OBD-1033 and OBD-0631 (see [Table 34](#)). A similar trend existed with analysis of change from baseline in SBM frequency by month (see [Table 35](#)). Summaries of frequency of complete SBMs by week and month (see [Table 36](#) and [Table 37](#)), frequency of SBMs by week and by month (see [Table 39](#) and [Table 40](#)), frequency of complete BMs by week and by month (see [Table 41](#) and [Table 42](#)), and frequency of BMs by week and by month (see [Table 43](#) and [Table 44](#)) also showed numerical trends favoring the lubiprostone group over the placebo group at all evaluated time points (through Week 12 or Month 3) in both OBD-1033 and OBD-0631.

Not all analyses, however, consistently supported durability of response. In the non-LOCF analysis of weekly SBM response in OBD-1033 ([Table 22](#)), for example, the weekly responder rate was higher in the placebo group than the lubiprostone group of the ITT population for 3 of the last 5 weeks of the trial. However, this analysis was not statistically valid (due to lack of adjustment for multiplicity), thus precluding rigorous conclusions. Additionally, a weekly responder rate analysis does not evaluate efficacy on a continuous basis over a 12-week period, a consideration which this reviewer believes is important when evaluating efficacy for a chronic condition such as OIC. Finally, patient dropouts and discontinuations increased as the trial progressed, and may have influenced the weekly responder rates in the last few weeks of the trial. More importantly, persistence of effect of lubiprostone was shown by the exploratory analysis using the modified definition of overall SBM response as defined by DGIEP ([Table 63](#)).

Overall, given the preponderance of secondary and exploratory analyses favoring lubiprostone over placebo at later time points in the double-blind trials, it is this reviewer's assessment that lubiprostone 24 mcg BID demonstrated persistence of effect over 12 weeks in the OIC population. The open-label trial OBD-06S1, although not designed primarily to assess efficacy, also examined the change from baseline in SBM frequency by month over 9 months (see [Table 151](#)). The numerical data demonstrates that the increase in SBM frequency over baseline is generally maintained at each month through the end of the trial. These findings from OBD-06S1 should be interpreted with caution, however, because there was no comparator arm and because subjects were using lubiprostone on an as needed basis.

6.1.10 Additional Efficacy Issues/Analyses

Rescue Laxatives

In OBD-1033, the use of rescue laxatives was not allowed within 24 hours prior to the first dose of the study drug or during the first 72 hours following treatment initiation. In OBD-0631 and OBD-0632, the use of rescue laxatives was not allowed within 24 hours prior to the first dose of the study drug or during the first week of treatment. Beyond these restrictions, in the event that no BM occurred within a 3-day period, use of rescue laxatives was permitted at the investigator's discretion as described below:

- Rescue laxative 1: the investigator may have instructed the subject to administer the clinically recommended dose (10 mg) of bisacodyl (Dulcolax) suppository.
- Rescue laxative 2: if the first rescue laxative failed to induce a BM, the investigator instructed the subject to administer a repeat dose of bisacodyl suppository or administer a saline enema.

In OBD-1033, if both rescue laxatives failed, the investigator may have prescribed another medication for immediate short-term use, including a medication from the excluded medication list other than MiraLax, Relistor, and Resolor. In OBD-0631 and OBD-0632, if both rescue laxatives failed, the investigator may have prescribed another medication for immediate short-term use, including a medication from the excluded medication list other than MiraLax or Zelnorm. The excluded medication list is detailed in [Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033](#). Baseline rescue laxative use in the three efficacy trials was summarized in [Table 5](#).

The Sponsor tabulated the number and percent of subjects who used any rescue laxative medication at baseline, at each month in the double-blind efficacy trials, and overall. Results for OBD-1033 and OBD-0631 are in [Table 64](#). Percent days of rescue laxative use by month was also analyzed and results are summarized in [Table 65](#).

Table 64. Summary of Subjects with Rescue Laxative Use at Baseline, Each Month, and Overall – OBD-1033 and OBD-0631 (Safety-Evaluable Population)

Time Point	OBD-1033		OBD-0631	
	Placebo	Lubiprostone	Placebo	Lubiprostone
Baseline, N	220	219	217	222
Rescue laxative used, n (%)	111 (50.5)	110 (50.2)	133 (61.3)	132 (59.5)
Month 1, N	220	216	217	221
Rescue laxative used, n (%)	82 (37.3)	74 (34.3)	106 (48.8)	104 (47.1)
Month 2, N	207	199	194	189
Rescue laxative used, n (%)	53 (25.6)	45 (22.6)	81 (41.8)	67 (35.4)
Month 3, N	190	183	168	170
Rescue laxative used, n (%)	40 (21.1)	37 (20.2)	69 (41.1)	54 (31.8)
Overall, N	220	219	218	220
Rescue laxative used, n (%)	101 (45.9)	91 (42.1)	128 (58.7)	120 (54.5)

Source: Reviewer's table, generated from Sponsor's data, module 5.3.5.3, Table 1.1.10, pages 415 to 416 of 2585, Integrated Summary of Efficacy; Table 14.3.15, pages 494 to 497, CSR OBD-1033; and Table 14.3.16, pages 455 to 456, CSR of OBD-0631.

When compared with baseline, by the end of Month 1, the percentage of subjects using rescue laxatives decreased by similar amounts in both the lubiprostone and placebo

arms of both trials. This decrease in rescue laxative use plateaued at Month 2 and remained generally unchanged at the end of Month 3. In OBD-1033, 50% of lubiprostone subjects used rescue laxatives at baseline, as compared with 20% at Month 3. In OBD-0631, 60% of lubiprostone subjects used rescue laxatives at baseline, as compared with 32% at Month 3.

Table 65. Percent of Days of Rescue Laxative Use by Month – OBD-1033 and OBD-0631 (Safety-Evaluable Population)

Time Point	Statistic	OBD-1033		OBD-0631	
		Placebo	Lubiprostone	Placebo	Lubiprostone
Month 1	n	82	74	106	104
	Mean ± Standard Dev	9.8 ± 8.13	8.9 ± 6.90	8.7 ± 15.94	8.6 ± 16.59
	Median (Min, Max)	7.1 (3.6, 46.4)	7.1 (3.6, 28.6)	0 (0, 100)	0 (0, 100)
Month 2	n	53	45	81	67
	Mean ± Standard Dev	12.9 ± 11.19	11.0 ± 7.05	8.2 ± 17.02	6.1 ± 15.35
	Median (Min, Max)	10.7 (3.6, 57.1)	10.7 (3.6, 28.6)	0 (0, 100)	0 (0, 100)
Month 3	n	40	37	69	54
	Mean ± Standard Dev	11.4 ± 8.41	12.6 ± 10.33	6.5 ± 12.00	5.8 ± 15.67
	Median (Min, Max)	10.7 (3.6, 42.9)	7.1 (3.6, 35.7)	0 (0, 76)	0 (0, 100)
Overall	n	101	91	128	120
	Mean ± Standard Dev	6.4 ± 7.48	6.0 ± 6.66	8.2 ± 13.94	7.8 ± 15.69
	Median (Min, Max)	3.6 (1.2, 48.8)	2.4 (1.2, 28.6)	1.5 (0, 95.8)	1.3 (0, 100)

Source: Reviewer's table, from Table 14.3.15, page 494-497, CSR OBD-1033 and Table 14.3.16, page 455-456, CSR OBD-0631.

In OBD-1033, placebo subjects had a slightly higher mean percent of days of rescue laxative use than lubiprostone subjects overall (6.4% versus 6%). The percent days of rescue laxative use increased among both placebo and lubiprostone subjects at Month 2 as compared with Month 1. Of note, the percent days of rescue laxative use in Month 3 was actually slightly higher in the lubiprostone group than the placebo group (12.6% versus 11.4%). In OBD-0631, placebo subjects had a slightly higher mean percent of days of rescue laxative use than lubiprostone subjects overall and at Month 1, Month 2, and Month 3. Overall, the mean percent of days of rescue laxative use was 8.2% for placebo and 7.8% for lubiprostone. Differences between treatment groups at Month 1, Month 2, and Month 3 were small, and there was a general trend toward decrease in mean percent of days of rescue laxative use by month as OBD-0631 progressed.

Reviewer comments: *It is expected that subjects in the lubiprostone arm should have less rescue laxative use if lubiprostone provides relief of OIC. Although the percentage of subjects using rescue laxatives was lower in the lubiprostone group than the placebo group at most evaluated time points in both trials, the magnitude of the difference between the two treatment arms was generally small. Further, the decline in percentage of subjects using rescue laxatives overall as compared with baseline was small. As a result, in this reviewer's assessment, it is unclear whether lubiprostone is providing enough subjective relief of OIC symptoms among subjects in the clinical trials to reliably reduce use of rescue laxatives.*

Supportive Evidence of Efficacy for Results from Primary Analysis of Overall SBM Response in Trial OBD-1033

The Sponsor performed additional post hoc sensitivity analyses and exploratory analyses on efficacy endpoints as requested by DGIEP, as discussed below.

Overall SBM Response Analysis of Trial OBD-0631

Results of post hoc analysis of the overall SBM response endpoint in the ITT population of trial OBD-0631 are summarized in [Table 66](#).

Table 66. Supportive Analysis of Overall SBM Response in OBD-0631 (ITT Population)

Overall SBM Response¹ by Population	Placebo (N=217) n (%)	Lubiprostone (N=221) n (%)	Difference (95% CI)	P-Value²
Responder	32 (14.7%)	54 (24.4%)	9.7% (2.3, 17.1)	0.010

Abbreviation: CI, confidence interval

¹Overall SBM response defined as ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥ 3 SBMs per week for at least 9 of the 12 treatment weeks. **P-value is for informational purposes only.**

²Sponsor's p-values for overall response rates comparing treatment groups analyzed using the CMH test stratified by pooled site. Source: Reviewer's table, modified from Table 1.2.1.4, page 30, response to IR6.

The treatment effect favored the lubiprostone group in all three patient populations, with a treatment difference of 9.7% in the ITT population, 11.4% in the completer population (19.5% placebo responders versus 30.9% lubiprostone responders, $p=0.010$), and 10.7% in the per-protocol population (14.1% placebo responders versus 24.8% lubiprostone responders, $p=0.012$). The treatment effect is comparable to those obtained in OBD-1033 for the three patient populations (see [Table 10](#) and [Table 11](#)).

Reviewer comments: Although evaluation of the overall SBM response endpoint in OBD-0631 is post hoc and statistical significance of findings should not be claimed, based on the numerical trends, it is this reviewer's assessment that the findings do support the results of the primary analysis of efficacy in OBD-1033 and OBD-0631. As discussed previously (see discussion below [Table 10](#)), in this reviewer's opinion, a treatment difference of 8% to 10% favoring lubiprostone represents a clinically meaningful treatment effect in adults with chronic non-cancer pain and OIC and offers another treatment option for OIC in this patient population.

Other Analyses

Analysis of Efficacy Endpoints in Trial OBD-0631 with Exclusion of Site # 1069

As discussed in section [3.1 Submission Quality and Integrity](#), during an OSI inspection, it was revealed that source records from clinical site # 1069 (trial OBD-0631) could not be verified. Therefore, this reviewer performed post hoc analyses of the primary endpoint (mean change from baseline in SBM frequency at Week 8 in subjects without dose reduction) and the overall SBM responder rate for OBD-0631 excluding all the data generated from site # 1069. Results are in [Table 67](#) and [Table 68](#) and overall, demonstrate little impact from exclusion of data of subjects from site # 1069.

Table 67. Change from Baseline in SBM Frequency at Week 8 in OBD-0631 (ITT) and OBD-0631 Excluding Site #1069¹

Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction	OBD-0631		OBD-0631 Excluding Site #1069	
	Placebo (N=217)	Lubiprostone (N=221)	Placebo (N=205)	Lubiprostone (N=208)
n	169	164	159	151
Mean ± Standard Dev	2.4 ± 3.25	3.2 ± 3.35	2.4 ± 3.28	3.3 ± 3.42
Median (Min, Max)	1.4 (-3, 16)	2.7 (-2, 21)	1.4 (-3, 16)	2.9 (-2, 21)

¹There were 25 ITT subjects at site #1069, 12 in the placebo arm and 13 in the lubiprostone arm.

Source: Reviewer's table, generated from efficacy datasets.

Table 68. Overall SBM Response in OBD-0631 (ITT) and OBD-0631 Excluding Site #1069

Overall SBM Response ¹	OBD-0631		OBD-0631 Excluding Site #1069	
	Placebo (N=217)	Lubiprostone (N=221)	Placebo (N=205)	Lubiprostone (N=208)
Responder, n (%)	32 (14.7%)	54 (24.4%)	32 (15.6%)	51 (24.5%)

¹Overall SBM response defined as ≥1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥3 SBMs per week for at least 9 of the 12 treatment weeks.

Source: Reviewer's table, generated from efficacy datasets.

Analysis of Efficacy Endpoints Using a True ITT Population

The Sponsor pre-specified the ITT population as all randomized subjects who had received at least one study treatment and had at least one post-treatment diary entry, but the statistical review team for this sNDA noted that a true ITT population should consist of all randomized subjects. The statistical review team asked the Sponsor to perform exploratory analyses of the overall SBM response endpoint using the true ITT population (all randomized subjects) for OBD-1033 and OBD-0631. The Sponsor's analysis results are in [Table 69](#). Overall, the magnitude of the treatment effect is consistent with the primary analysis of OBD-1033 using the Sponsor's pre-specified definition of the ITT population (8.6% versus 8.3%; see [Table 10](#)) and the supportive analysis of the overall SBM response endpoint in OBD-0631 using the Sponsor's definition of the ITT population (9.7% in both analyses; see [Table 66](#)). Randomized subjects that did not receive any study drug and discontinued immediately after randomization did not contribute data at Week 8. Therefore, the Sponsor's analysis of the mean change from baseline in SBM frequency at Week 8 in subjects without dose reduction using a true ITT population produced the same results as for the pre-specified ITT population in OBD-0631 and OBD-1033 (see [Table 12](#) and [Table 18](#), respectively).

Table 69. Overall SBM Response in OBD-1033 and OBD-0631 (True ITT Population¹)

Overall SBM Response ²	OBD-1033				OBD-0631			
	Placebo (N=226)	Lubiprostone (N=221)	Difference (95% CI)	P-Value ³	Placebo (N=220)	Lubiprostone (N=223)	Difference (95% CI)	P-value ³
Responder, n (%)	41 (18.1)	59 (26.7)	8.6 (0.8, 16.3)	0.035	32 (14.5)	54 (24.2)	9.7 (2.3, 17)	0.011

¹True ITT population includes all randomized subjects. Of the 443 subjects randomized in trial OBD-0631, 4 subjects were excluded from the Sponsor's ITT population due to being randomized but never dosed (3 placebo and 1 lubiprostone). One lubiprostone subject was randomized but had no post-baseline data. Of the 447 subjects randomized in trial OBD-1033, 8 subjects (6 placebo and 2 lubiprostone) were excluded from the Sponsor's ITT population due to not taking any doses of study medication.

²Overall SBM response defined as ≥1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥3 SBMs per week for at least 9 of the 12 treatment weeks.

³Sponsor's p-value is based on the treatment effect from CMH stratified by pooled site. **P-values for informational purposes only.** Source: Reviewer's table, from Sponsor's Table E4.1.3.0, page 29, response to IR6. Confidence intervals from Dr. Freda Cooner.

Reviewer comments: *This medical officer is reassured by the fact that conclusions of the key efficacy analyses do not change when a true ITT population is substituted for the Sponsor's pre-defined ITT population.*

Role of Dose Reduction in Efficacy Analyses

Change from baseline in SBM frequency at Week 8 in subjects without dose reduction was the primary endpoint for OBD-0631. As previously summarized in [Table 12](#), OBD-0631 won on this primary endpoint in the ITT population. This endpoint was evaluated as a secondary endpoint in OBD-1033 (see [Table 18](#)), where the differences between lubiprostone and placebo subjects, though favoring lubiprostone subjects, did so by a smaller numerical margin than in OBD-0631 (2.9 versus 2.5 in OBD-1033; 3.2 versus 2.4 in OBD-0631). As discussed previously (see below [Table 18](#) in section 6.1.5

[Analysis of Secondary Endpoints\(s\)](#)), exclusion of subjects who had undergone dose reduction might potentially discriminate more against lubiprostone subjects than placebo subjects. The Sponsor also evaluated change from baseline in SBM frequency at Week 8 in all ITT subjects (regardless of dose reduction) as an exploratory analysis for both trials. These results are in [Table 70](#).

Table 70. Change from Baseline in SBM Frequency at Week 8 in OBD-1033 and OBD-0631 (ITT)

Change from Baseline in SBM Frequency at Week 8	OBD-1033		P-Value ¹	OBD-0631		P-Value ¹
	Placebo (N=220)	Lubiprostone (N=219)		Placebo (N=217)	Lubiprostone (N=221)	
Subjects without Dose Reduction						
n	182	168	<i>0.076</i>	169	164	0.019
Mean ± Standard Dev	2.5 ± 3.03	2.9 ± 3.18		2.4 ± 3.25	3.2 ± 3.35	
Median (Min, Max)	2.0 (-3, 20)	2.4 (-3, 13)		1.4 (-3, 16)	2.7 (-2, 21)	
All Subjects						
n	185	178	<i>0.044</i>	169	171	<i>0.015</i>
Mean ± Standard Dev	2.5 ± 3.07	3.1 ± 3.50		2.4 ± 3.25	3.2 ± 3.33	
Median (Min, Max)	2.0 (-3, 20)	2.5 (-3, 21)		1.4 (-3, 16)	2.6 (-2, 21)	

¹Sponsor's p-value based on treatment effect from van Elteren test stratified by pooled site. **Italicized p-values are for informational purposes only.**

Source: Reviewer's table, adapted from Sponsor's Table 1.3.1.2, module 5.3.5.3, page 823 to 834 of 2585, Integrated Summary of Efficacy; and Table 2.7.3.3-18, page 53 of 119, Summary of Clinical Efficacy.

The table demonstrates that as compared to the analysis in which subjects with dose reduction were excluded, when subjects who had dose reduction are included in the analysis, the differences between lubiprostone and placebo subjects are slightly more strongly in favor of lubiprostone subjects in OBD-1033 (3.1 versus 2.5) and essentially unchanged in OBD-0631 (3.2 versus 2.4). The Sponsor also evaluated overall SBM response in ITT subjects without dose reduction as an exploratory analysis for both trials. These results are in [Table 71](#).

Table 71. Overall SBM Response in Subjects without Dose Reduction in OBD-1033 and OBD-0631 (ITT Population)

Overall SBM Response ¹	OBD-1033				OBD-0631			
	Placebo (N=217)	LBP (N=204)	Difference	P-Value ²	Placebo (N=216)	LBP (N=212)	Difference	P-value ²
Responder, n (%)	41 (18.9)	51 (25)	6.1%	0.099	32 (14.8)	50 (23.6)	8.8%	0.020

Abbreviations: LBP, lubiprostone

¹Overall SBM response defined as ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥ 3 SBMs per week for at least 9 of the 12 treatment weeks.

²Sponsor's p-value is based on treatment effect from CMH stratified by pooled site. **P-values are for informational purposes only.**

Source: Reviewer's table, adapted from Sponsor's Table 7.1, page 6, response to IR7.

Reviewer comments: *With regard to the overall response endpoint, the treatment difference favoring lubiprostone decreased from 8% to 6% in OBD-1033 when subjects who dose reduced were excluded. This finding does support the hypothesis that exclusion of subjects with dose reduction (as was done in the primary endpoint for OBD-0631) may discriminate against lubiprostone subjects. The Sponsor noted that in OBD-1033, 15 lubiprostone subjects dose reduced during the 12 weeks of treatment, as compared with only 3 placebo subjects. Of the 15 lubiprostone subjects who dose reduced, 8 were overall SBM responders, and 5 of these 8 subjects dose reduced because of diarrhea. Thus, with respect to the overall SBM response endpoint, lubiprostone subjects are more favored in terms of efficacy when subjects with dose reduction are included in the analysis than when they are excluded.*

On the other hand, Table 70 shows that inclusion of subjects with dose reduction only marginally affected efficacy findings with respect to the mean change from baseline in SBM frequency at Week 8 endpoint. In this reviewer's assessment, it is appropriate to include subjects with dose reduction in the primary efficacy analysis, particularly when the primary endpoint is a binary responder endpoint.

Weekly Distribution of SBMs

Based on the results of analyses of the primary endpoint in OBD-1033 (see Table 10) and OBD-0631 (see Table 12), it appears that when compared with placebo, lubiprostone treats OIC by increasing SBM frequency. It is less clear, however, whether lubiprostone increases SBM frequency by increasing the number of days per week in which treated subjects have SBMs or by increasing the number of SBMs subjects have each day. The Sponsor performed an exploratory analysis of individual days per week with ≥ 1 SBM in OBD-1033. Results are summarized in Table 72, and findings suggest that subjects in both treatment arms were having SBMs between 3 and 4 days out of each 7-day week throughout the trial.

Table 72. Summary of Individual Days per Week with at Least One SBM in OBD-1033 (ITT)

Time Point	Statistic ¹	Placebo (N=220)	Lubiprostone (N=219)
Week 1	n	195	199
	Mean ± Standard Deviation	2.9 ± 1.51	3.3 ± 1.65
Week 2	n	194	185
	Mean ± Standard Deviation	3.2 ± 1.59	3.4 ± 1.76
Week 3	n	183	180
	Mean ± Standard Deviation	3.0 ± 1.67	3.3 ± 1.78
Week 4	n	177	184
	Mean ± Standard Deviation	3.3 ± 1.67	3.5 ± 1.78
Week 5	n	163	176
	Mean ± Standard Deviation	3.3 ± 1.68	3.5 ± 1.80
Week 6	n	172	172
	Mean ± Standard Deviation	3.4 ± 1.79	3.5 ± 1.74
Week 7	n	171	170
	Mean ± Standard Deviation	3.4 ± 1.77	3.6 ± 1.80
Week 8	n	159	164
	Mean ± Standard Deviation	3.5 ± 1.79	3.4 ± 1.82
Week 9	n	168	161
	Mean ± Standard Deviation	3.4 ± 1.81	3.6 ± 1.92
Week 10	n	160	154
	Mean ± Standard Deviation	3.6 ± 1.76	3.5 ± 1.78
Week 11	n	167	152
	Mean ± Standard Deviation	3.4 ± 1.73	3.6 ± 1.93
Week 12	n	161	139
	Mean ± Standard Deviation	3.4 ± 1.79	3.6 ± 1.84

¹The median (minimum, maximum) statistic was 3.0 (1, 7) at each time point for both treatment arms.

Source: Reviewer's table, adapted from Sponsor's Table 1.14.22, module 5.3.5.3, page 2566-2568, Integrated Summary of Efficacy.

Reviewer's comments: Results do not show an appreciable increase in the number of days per week in which lubiprostone subjects were having ≥1 SBM as compared with placebo subjects. Thus, based on this analysis, it appears that lubiprostone's effect on OIC involves increasing the number of SBMs per day rather than increasing the number of days per week in which subjects are having ≥1 SBM. However, the slightly higher mean number of days per week with an SBM in the lubiprostone group might be sufficient to account for the higher overall SBM responder rate in the lubiprostone group. Moreover, the results suggest that lubiprostone is not exerting its effect by creating a brisk laxation response with multiple SBMs for 1 or 2 days per week and then no SBMs for the remainder of the week. A previous discussion of proportion of SBMs that were felt as complete by overall SBM responders in OBD-1033 and OBD-0631 (see [Table 38](#)) also supported the hypothesis that lubiprostone treats OIC primarily by increasing SBM frequency.

Hourly- Versus Daily-Based Assessment for Weekly SBM Frequency Calculation

In both OBD-1033 and OBD-0631, the Sponsor calculated weekly SBM frequency rate on an hourly basis (168 x number of SBMs / number of hours observed). The Sponsor's hourly-based assessment was discordant with the Agency's recommendation in an Advice Letter that pertained to the protocol of OBD-1033 (see section 2.5 [Summary of Presubmission Regulatory Activity Related to Submission](#)). In that Advice Letter, the Agency advised the Sponsor to calculate the weekly SBM frequency rates using the number of days observed in a week rather than the number of observed hours in a week. During the review of this sNDA, DGIEP asked the Sponsor to perform exploratory

analyses using a daily-based assessment for weekly SBM frequency calculation. In the analysis in [Table 73](#), all multiple daily BMs count towards the weekly average. In the analysis in [Table 74](#), multiple BMs per day only contributed one BM towards the weekly average. The Sponsor's p-values in both tables are for informational purposes only.

Table 73. Overall SBM Response by Daily-Based Calculation of Weekly SBM Frequency in OBD-1033 and OBD-0631 (ITT) – All Multiple Daily BMs Count Towards Weekly Average

Overall SBM Response	OBD-1033			OBD-0631		
	Placebo (N=220)	Lubiprostone (N=219)	P-Value	Placebo (N=217)	Lubiprostone (N=221)	P-Value
Responder, n (%)	40 (18.2%)	59 (26.9%)	0.034	36 (16.6%)	48 (21.7%)	0.133

Note 1: For this analysis, all multiple daily BMs count towards the weekly average. Additionally, a minimum of 4 days of diary entries for a week had to be present in order for data to be considered non-missing for the week.

Note 2: P-values for overall response rates comparing treatment groups were analyzed using the CMH test stratified by pooled site.

Source: Reviewer's table, modified from Table E4.5.1.1 from Sponsor's Response to IR6.

Table 74. Overall SBM Response by Daily-Based Calculation of Weekly SBM Frequency in OBD-1033 and OBD-0631 (ITT) – Multiple BMs Per Day Contributing One BM Towards Weekly Average

Overall SBM Response	OBD-1033			OBD-0631		
	Placebo (N=220)	Lubiprostone (N=219)	P-Value	Placebo (N=217)	Lubiprostone (N=221)	P-Value
Responder, n (%)	34 (15.5%)	54 (24.7%)	0.018	30 (13.8%)	39 (17.6%)	0.217

Note 1: For this analysis, multiple BMs per day only contributed one BM towards the weekly average. Additionally, a minimum of 4 days of diary entries for a week had to be present in order for data to be considered non-missing for the week.

Note 2: P-values for overall response rates comparing treatment groups were analyzed using the CMH test stratified by pooled site.

Source: Reviewer's table, modified from Table E4.5.1.2 from Sponsor's Response to IR6.

Reviewer comments: *For OBD-1033, using a daily-based assessment for weekly SBM frequency calculation, the treatment difference favoring lubiprostone was ~9%, consistent with the primary analysis using an hourly-based assessment. For OBD-0631, using a daily-based assessment for weekly SBM frequency calculation, the treatment difference favoring lubiprostone is ~4% to 5%, smaller than the treatment difference using an hourly-based assessment for weekly SBM frequency (~10%, see [Table 66](#)). However, the overall SBM response endpoint was not the primary endpoint for OBD-0631, so the findings for OBD-0631 on this endpoint using a daily-based assessment instead of an hourly-based assessment are less interpretable than findings for OBD-1033. In this officer's assessment, with respect to the overall SBM response endpoint, the treatment effect favors the lubiprostone group in OBD-1033 and OBD-0631, both with hourly- and daily-based assessment for weekly SBM frequency calculation.*

Efficacy Analyses from Pooled Trials

Change from Baseline in SBM Frequency at Week 8 – Pooled Trials

Change from baseline in SBM frequency at Week 8 in subjects without dose reduction was the primary endpoint for OBD-0631 and OBD-0632. Although the analysis for OBD-0631 won on this primary endpoint in the ITT population (see [Table 12](#)), OBD-0632 failed on this primary endpoint in the ITT population (see [Table 15](#)). The Sponsor performed a post hoc analysis of the primary endpoint based on pooled efficacy data from OBD-0631 and OBD-0632. Results are in [Table 75](#), and discussed below because the Sponsor is seeking to include the results of this analysis in drug labeling.

Table 75. Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in Pooled Trials OBD-0631 and OBD-0632 (ITT Population)

Change from Baseline at Week 8 in SBM Frequency ¹	Placebo (N=429)	Lubiprostone (N=444)	P-Value ²
n	344	332	0.023
Mean ± Standard Deviation	2.4 ± 3.22	2.9 ± 3.31	
Median (Minimum, Maximum)	1.5 (-4, 21)	2.4 (-3, 21)	

¹Weekly SBM (BM) frequency rate: (168 x number of SBMs (BMs)/number of hours observed)

²Sponsor's p-value based on the treatment effect from van Elteren test stratified by pooled site. **P-values are informational only.** Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups. Additionally, Shapiro-Wilk p-value testing for normality was performed by the Sponsor and p-value was 0.01. A small p-value (<0.05) indicates non-normality.

Source: Reviewer's table, modified from Sponsor's Table 2.7.3.3-23, page 58 of 119, Summary of Clinical Efficacy.

Reviewer comments: *In this medical officer's assessment, pooling of efficacy data from one failed trial and one trial that won on the primary endpoint is not a valid or scientifically appropriate way of demonstrating efficacy. Further, the comparison between placebo and lubiprostone subjects is not statistically valid (analysis was not pre-specified and trial OBD-0632 failed to demonstrate a statistically significant difference between the treatment groups with respect to the primary endpoint).* (b) (4)

Overall Change from Baseline in SBM Frequency – Pooled Trials

Overall change from baseline in SBM frequency was a secondary endpoint for OBD-0631 and OBD-0632. The Sponsor performed a post hoc analysis of this endpoint based on pooled efficacy data from OBD-0631 and OBD-0632. (b) (4)

Table 76. Overall Change from Baseline in SBM Frequency in Pooled Trials OBD-0631 and OBD-0632 (ITT Population)

Overall Change from Baseline in SBM Frequency ¹	Placebo (N=429)	Lubiprostone (N=444)	P-Value ²
n	425	435	0.014
Mean ± Standard Deviation	2.2 ± 2.46	2.7 ± 2.66	
Median (Minimum, Maximum)	1.6 (-6, 16)	2.2 (-7, 17)	

¹Weekly SBM (BM) frequency rate: (168 x number of SBMs (BMs)/number of hours observed)

²Sponsor's p-value was initially based on the treatment effect from a van Elteren test stratified by pooled site and then adjusted using Hommel's stagewise rejective method for Week 8, Week 12, and overall. **P-values are for informational purposes only.** Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups. Additionally, Shapiro-Wilk p-value testing for normality was performed by the Sponsor and p-value was 0.01. A small p-value (<0.05) indicates non-normality.

Source: Reviewer's table, modified from Sponsor's Table 2.7.3.3-23, page 58 of 119, Summary of Clinical Efficacy.

Reviewer comments: *As previously mentioned, in this medical officer's assessment, the comparison between placebo and lubiprostone subjects is not statistically valid.* (b) (4)

Time to First SBM – Pooled Trials

SBM within 24 and 48 hours of first study medication dose was a secondary endpoint in all three efficacy trials. SBM within 4, 8, and 12 hours of first study medication dose and

median time to first SBM were exploratory endpoints in all three efficacy trials. The results for these endpoints are presented separately for each trial (Table 21 and Table 45 for OBD-1033, Table 29 and Table 46 for OBD-0631, and Table 127 and Table 131 for OBD-0632). The Sponsor performed a post hoc analysis of these endpoints based on pooled efficacy data from OBD-1033, OBD-0631, and OBD-0632. (b) (4)

The Sponsor's p-values are for informational purposes.

Table 77. Time to First SBM in Pooled Trials OBD-1033, OBD-0631, and OBD-0632 (ITT Population)

Time to First SBM	Number at Risk (% with SBMs) ¹		P-Value ²
	Placebo (N=649)	Lubiprostone (N=663)	
4 Hours	596 (8.2)	563 (15.1)	<0.001
8 Hours	563 (13.3)	527 (20.5)	<0.001
12 Hours	533 (17.9)	491 (25.9)	<0.001
24 Hours	440 (32.2)	393 (40.7)	0.001
48 Hours	287 (55.7)	236 (64.3)	0.001
Median (95% Confidence Interval)	39.5 (35.9, 46.0)	28.7 (26.0, 33.3)	0.003

Note: Proportions and median times estimated using Kaplan-Meier estimates in a time-to-event analysis. Data for subjects with no SBMs were censored and time to first SBM was set to trial duration.

¹Number at risk (i.e., not yet achieving first SBM and not censored) prior to specified time and Kaplan-Meier estimate for percent already experiencing first SBM prior to specified time.

²Proportions were compared using a likelihood-ratio chi-square test. Median times were compared using the Cox proportional hazards regression model.

Source: Reviewer's table, adapted from Sponsor's Table 2.7.3.3-31, page 73 of 119, Summary of Clinical Efficacy.

Reviewer comments: *In this reviewer's assessment, evaluation of SBMs within 4, 8, 12, 24, and 48 hours after first dose of study medication does not strongly inform overall efficacy of lubiprostone in the OIC population, because OIC is a chronic condition and assessment of efficacy over a treatment period of hours, rather than weeks, is not necessarily indicative of overall efficacy in this population. Further, the comparison between placebo and lubiprostone subjects is not statistically valid.* (b) (4)

7 Review of Safety

Safety Summary

Based on the safety data submitted from four trials (OBD-1033, OBD-0631, OBD-0632, and OBD-06S1) and available postmarket data, this medical reviewer finds that the safety of lubiprostone 24 mcg BID is adequate for the treatment of adults with OIC and chronic non-cancer pain.

In this reviewer's assessment, no new safety signals emerge from the AE database from OIC clinical trials, and AEs associated with lubiprostone in CIC and IBS-C trials were also the AEs most prominently associated with lubiprostone in OIC trials. Namely, nausea, diarrhea, vomiting, abdominal pain, flatulence, abdominal discomfort, abdominal distension, headache, and peripheral edema were more common among subjects receiving lubiprostone than placebo in the OIC trials, and these AEs are all

listed in the current drug label. Dyspnea, also in the current drug label, had an incidence rate in the OIC trials comparable to the incidence rate in clinical trials of lubiprostone for CIC at the 24 mcg BID dose. Chest pain, another AE that has been associated with lubiprostone in prior clinical trials, was not more common among lubiprostone subjects than placebo subjects in the OIC clinical trials. There were no AEs of opioid withdrawal or ischemic colitis clearly linked to use of lubiprostone in any of the OIC clinical trials.

This medical officer reviewed the recent Periodic Safety Update Report (PSUR) for lubiprostone, which provided cumulative AE information through January 31, 2012, and noted no new safety signals. DGIEP asked the Sponsor to submit a 120-day safety update as described in 21 CFR 314.50(d)(5)(vi)(b). In a response dated December 26, 2012, the Sponsor noted that no clinical trials in patients with OIC have been conducted other than those already submitted in support of this sNDA. The Sponsor reported “no changes to the exposure data since the time of the supplemental NDA submission for OIC which would warrant submission of a safety update at this time.” The Sponsor also noted that through November 2012, “there have been no clinically significant changes in incidence of AEs reported from postmarketing use globally.”

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The pooled database from three double-blind trials (OBD-1033, OBD-0631, and OBD-0632) and database from the open-label trial OBD-06S1 were used to evaluate safety.

Safety evaluable subjects consisted of all enrolled subjects who took at least one dose of study treatment. In the event that subjects took a medication that differed from what they should have been randomized to, subjects in this population represented the treatment group corresponding to the study drug they actually received. In the double-blind trials pool, 12 of the 662 subjects who were randomized to receive placebo never received treatment, resulting in 650 subjects who were treated. A total of 14 of the 679 subjects who were randomized to receive lubiprostone never received treatment, resulting in 665 subjects who were treated. In the double-blind trials pool, one subject had been randomized to placebo, but received lubiprostone instead, and three subjects had been randomized to lubiprostone, but received placebo instead. These cases of misrandomization resulted in 652 safety evaluable placebo subjects and 663 safety evaluable lubiprostone subjects.

[Table 78](#) summarizes the safety evaluable subjects in the databases.

Table 78. Analysis Groups for Review of Safety

12-Week Double-blind Trials	Trials Included	Number of Safety Evaluable Subjects		
		Placebo	Lubiprostone	Total
Double-blind Trials Pool	OBD-1033 OBD-0631 OBD-0632	652	663	1315
Open-label Long-term Trial	Trials Included	Number of Safety Evaluable Subjects ¹		
		Placebo-Lubiprostone	Lubiprostone-Lubiprostone	All Subjects Lubiprostone
Trial OBD-06S1	OBD-06S1	225	214	439
All Trials	Trials Included	Number of Safety Evaluable Subjects ²		
		Placebo	Lubiprostone	Total
Overall Safety Pool	OBD-1033 OBD-0631 OBD-0632 OBD-06S1	652	889	1541

¹The placebo-lubiprostone group comprises subjects who received placebo in the 12-week double-blind trial (OBD-0631 or OBD-0632) and lubiprostone in the open-label extension trial (OBD-06S1) and the lubiprostone-lubiprostone group comprises subjects who received lubiprostone both in the 12-week double blind trial and in the open-label extension trial.

²Subjects who received treatment with placebo in OBD-0631 or OBD-0632 and then with lubiprostone in OBD-06S1 are counted in both the placebo group and the lubiprostone group.

Source: Reviewer's table, modified from Sponsor's Table 2.7.4.1-2, page 13 of 167, Summary of Clinical Safety.

7.1.2 Categorization of Adverse Events

The Sponsor coded adverse events (AEs) using the Medical Dictionary of Regulatory Activities (MedDRA) (version 13.1) and classified by MedDRA system organ class (SOC) and preferred term (PT). All AEs observed by the investigator, spontaneously reported by subjects, or volunteered during open-ended questioning of subjects from the time the first dose of study drug was taken through the end of the follow-up period were to be recorded on the electronic case report forms (eCRFs), regardless of whether or not the events were considered to be related to the study drug. The Sponsor defined treatment-emergent adverse events (TEAEs) as events not present at baseline that occurred after treatment with the study drug or an event present at baseline and worsened after treatment with the study drug. TEAEs with onset dates on or after the first dose of study drug, but no later than follow up, were documented.

Reviewer comments: *This reviewer evaluated the appropriateness of the Sponsor's coding by comparing preferred terms to verbatim terms recorded by investigators. Coding was reasonably accurate and exceptions are described below.*

For this reviewer's analysis of TEAEs, an AE incidence count was generated from the provided AE dataset for the overall safety pool, the double-blind trials pool and the open-label extension trial. The safety evaluable patient population served as the denominator for all incidence count calculations. Although the Sponsor's system of AE categorization and coding was comprehensive and generally accurate, this reviewer noted a few incorrect translations of AEs from verbatim term to PTs and also noted a potential for splitting of several AEs due to separation of closely related PTs. As a

result, in generating the AE incidence count, this medical officer modified PTs in the Sponsor's AE dataset in the following ways:

- Combined “abdominal pain,” “abdominal pain lower,” “abdominal pain upper,” and “gastrointestinal pain” as the same AE (PT “abdominal pain”).
- Combined “abdominal discomfort” and “abdominal tenderness” as the same AE (PT “abdominal discomfort”) instead of two different AEs.
- Combined “hepatic enzyme increased,” “alanine aminotransferase increase,” and “aspartate aminotransferase increased” as the same AE (PT “hepatic enzyme increased”) instead of three different AEs. The PT “liver function tests abnormal” was kept separate as the verbatim terms for this PT did not clearly delineate whether the liver function tests abnormal were the hepatic enzymes or not.
- Combined “gastroenteritis viral” and “gastrointestinal viral infection” as the same AE (PT “gastroenteritis viral”) instead of two different AEs.
- Combined “rash,” “rash erythematous,” “rash macular,” “rash maculo-papular,” “rash papular,” and “rash pustular” as the same AE (PT “rash”).
- Recoded a case of “blood carbon monoxide” (verbatim: c/o gas) to “flatulence.”
- Recoded a case of “gastrointestinal disorder” (verbatim: bloating/gas) to “flatulence.”
- Recoded a case “sinus operation” (verbatim: nasal drainage) to “rhinorrhea.”
- Recoded four cases of “edema” in which verbatim terms clearly referred to peripheral or extremity edema to “edema peripheral.”

Reviewer's comment: The safety data tables presented in this review of safety reflect the recoding of AEs described above. For completeness, however, this officer did also generate AE tables using the Sponsor's original version of the AE dataset to ensure accuracy of the AE data tables as presented by the Sponsor in the Summary of Clinical Safety. This reviewer's findings were generally congruent with the AE data tables presented in the Summary of Clinical Safety.

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

Data from trials OBD-1033, OBD-0631, OBD-0632, and OBD-06S1 were combined and analyzed for the integrated safety evaluation, as presented in [Table 78](#).

Reviewer comments: The pooling of data as presented in the Sponsor's integrated summary of safety (ISS) appears acceptable.

7.2 Adequacy of Safety Assessments

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

Assessments of the actual exposure to study medication were based on the medication usage recorded in the daily diary. For the double-blind trials, exposure ended at either

the date of last dose or Week 14 visit date, whichever occurred earlier. If the number of capsules taken per the diary was greater than the number of capsules in the bottle return counts or the percentage of diary entries during the treatment period was <70% (total diary entries divided by the number of days), then bottle return counts were used to calculate exposure. If bottle counts were not available in the above instances, then diary data were used for exposure.

Table 79. Summary of Duration of Exposure for Subjects in Double-blind Trials and Open-label Trial (Treated Subjects)

Duration of Exposure ¹	Double-blind Trials (OBD-1033, OBD-0631, OBD-0632)		Open-label Trial OBD-06S1	
	Placebo N=650 n (%)	Lubiprostone N=665 n (%)	Placebo N=225 n (%)	Lubiprostone N=214 n (%)
≥1 Day	650 (100)	665 (100)	225 (100)	214 (100)
≥1 Week	639 (98.3)	642 (96.5)	221 (98.2)	212 (99.1)
≥4 Weeks	581 (89.4)	577 (86.8)	211 (93.8)	209 (97.7)
≥8 Weeks	521 (80.2)	514 (77.3)	196 (87.1)	196 (91.6)
≥12 Weeks			186 (82.7)	186 (86.9)
≥24 Weeks			159 (70.7)	160 (74.8)

¹Percentages are the number of subjects in the category divided by the number of subjects who were treated.

Source: Reviewer's Table modified from Table 2.7.4.1-3, page 15 of 167 and 2.7.4.1-5, page 18 of 167, Summary of Clinical Safety.

A total of 514 (77%) subjects were exposed to lubiprostone for ≥8 weeks in the 12-week double-blind trials pool. The Sponsor also assessed extent of exposure. For the double-blind trials pool, the mean total daily dose among subjects receiving placebo was 43.2 ± 9.8 mcg and 40.8 ± 8.4 mcg among subjects receiving lubiprostone. For the 9-month open-label trial, the mean total daily dose among placebo-lubiprostone subjects was 33.7 ± 12.2 mcg and 31.8 ± 13.0 mcg among lubiprostone-lubiprostone subjects.

Reviewer Comments: *The lower mean total daily dose among subjects in the open-label trial as compared with the double-blind trials pool is not unexpected given the longer duration of 36 weeks for the open-label trial and given the fact that dosing was 24 mcg BID as needed for signs and symptoms in the open-label trial, as opposed to 24 mcg BID scheduled in the double-blind trials.*

Table 80 presents baseline demographic characteristics of safety evaluable subjects.

Table 80. Demographic Characteristics at Baseline – Double-blind Trials and Open-label Trial (Safety Evaluable Subjects)

Variable	Double-blind Trials Pool (OBD-1033, OBD-0631, OBD-0632)		Open-label Trial OBD-06S1	
	Placebo (N=652)	LBP (N=663)	Placebo-LBP (N=225)	LBP-LBP (N=214)
Sex, n (%)				
n	652	663	225	214
Male	244 (37.4)	247 (37.3)	86 (38.2)	90 (42.1)
Female	408 (62.6)	416 (62.7)	139 (61.8)	124 (57.9)
Race, n (%)				
n	650	663	224	214
American Indian/Alaska Native	5 (0.8)	8 (1.2)	0	4 (1.9)
Asian	5 (0.8)	5 (0.8)	2 (0.9)	1 (0.5)
Black/African American	90 (13.8)	98 (14.8)	26 (11.6)	29 (13.6)
White	539 (82.9)	545 (82.2)	193 (86.2)	174 (81.3)
Other	11 (1.7)	7 (1.1)	3 (1.3)	6 (2.8)
Age (years)				
n	652	663	225	214
Mean ± Standard Dev	50.5 ± 11.47	50.3 ± 9.67	50.1 ± 10.81	49.6 ± 9.07
Median	51.0	50.0	50.0	49.0
Minimum, Maximum	21, 89	19, 82	22, 85	26, 73

Abbreviations: LBP, lubiprostone

Note: The placebo-lubiprostone group comprises subjects who received placebo in the 12-week, double-blind trial (OBD-0631 or OBD-0632) and lubiprostone in the open-label extension trial (OBD-06S1) and the lubiprostone-lubiprostone group comprises subjects who received lubiprostone both in the 12-week, double-blind trial and in the open-label extension trial.

Source: Reviewer's table modified from Table 2.7.4.1-7, page 21, and Table 2.7.4.1-11, page 26, Summary of Clinical Safety.

Table 81. Constipation Status at Baseline – Double-blind and Open-label Trials (Safety Evaluable Subjects)

Variable	Double-blind Trials		Open-label Trial OBD-06S1	
	Placebo (N=652)	Lubiprostone (N=663)	Placebo-LBP (N=225)	LBP-LBP (N=214)
SBM Frequency per Week, n	650	662	225	214
Mean ± Standard Deviation	1.5 ± 1.04	1.4 ± 1.11	1.4 ± 1.01	1.4 ± 0.94
Median (Min, Max)	1.5 (0, 8)	1.5 (0, 9)	1.5 (0, 8)	1.5 (0, 4)
Average Consistency, n	581	582	197	186
Mean ± Standard Deviation	2.9 ± 0.83	3.0 ± 0.81	3.0 ± 0.83	3.0 ± 0.86
Median (Min, Max)	3.0 (0, 4)	3.0 (0, 4)	3.0 (1, 4)	3.0 (0, 4)
Hard or Very Hard Stool Consistency in ≥25% SBMs, n	652	663	225	214
Yes, n (%)	504 (77.3%)	508 (76.6%)	167 (74.2%)	166 (77.6%)
Severity of Constipation	651	663	225	214
Mean ± Standard Deviation	2.3 ± 0.74	2.4 ± 0.76	2.3 ± 0.74	2.4 ± 0.70
Median (Min, Max)	2.3 (0,4)	2.4 (0,4)	2.3 (0,4)	2.4 (0,4)
Average Degree of Straining, n	581	582	197	186
Mean ± Standard Deviation	2.6 ± 0.84	2.7 ± 0.87	2.6 ± 0.87	2.8 ± 0.85
Median (Min, Max)	2.7 (0,4)	3.0 (0,4)	2.7 (0,4)	3.0 (0,4)
Moderate or Worse Straining ≥25% of SBMs, n	652	663	225	214
Yes, n (%)	540 (82.8%)	546 (82.4%)	177 (78.7%)	176 (82.2%)
Sensation of Incomplete Evacuation ≥25% SBMs, n	652	663	225	214
Yes, n (%)	504 (77.3%)	488 (73.6%)	167 (74.2%)	163 (76.2%)
Abdominal Discomfort, n	651	663	225	214
Mean ± Standard Deviation	2.1 ± 0.71	2.2 ± 0.72	2.1 ± 0.69	2.3 ± 0.64
Median (Min, Max)	2.1 (0,4)	2.2 (0,4)	2.1 (0,4)	2.2 (0,4)
Abdominal Bloating, n	651	663	225	214
Mean ± Standard Deviation	2.2 ± 0.76	2.2 ± 0.77	2.2 ± 0.74	2.3 ± 0.73
Median (Min, Max)	2.2 (0, 4)	2.2 (0, 4)	2.2 (0, 4)	2.3 (0, 4)
Bowel Habit Regularity, n	650	663	225	214
Mean ± Standard Deviation	4.7 ± 1.62	4.7 ± 1.64	4.6 ± 1.63	4.8 ± 1.54
Median (Min, Max)	5.0 (1, 7)	5.0 (1, 7)	5.0 (1, 7)	5.0 (1, 7)
Percent Days of Rescue Laxative Use	651	663	225	214
Mean ± Standard Deviation	12.6 ± 17.22	12.9 ± 17.53	13.2 ± 16.15	13.1 ± 16.22
Median (Min, Max)	7.1 (0, 100)	7.1 (0, 100)	7.7 (0, 100)	7.4 (0, 100)

Abbreviations: LBP, lubiprostone

Note 1: The Double-blind trials pool includes trials OBD-1033, OBD-0631, and OBD-0632.

Note 2: Baseline for the open-label trial is the baseline of the preceding 12-week double-blind trial (OBD-0631 or OBD-0632).

Source: Sponsor's Table 2.7.4.1-8, page 22 to 23 of 167; Table 2.7.4.1-12, page 27 to 28 of 167, Summary of Clinical Safety.

7.2.2 Explorations for Dose Response

The Sponsor evaluated lubiprostone as 24 mcg BID in three double-blind trials (OBD-0631, OBD-0632, OBD-1033) and as a 24 mcg BID as needed dosing regimen in the 36-week open-label trial OBD-06S1. No dose response explorations were performed as part of this sNDA.

Reviewer Comments: Because the Sponsor did not perform any dose-response trials in subjects with OIC, this reviewer is unable to make any definitive statements on whether total dosage was optimal.

7.2.3 Special Animal and/or In Vitro Testing

None was conducted or initiated to support this sNDA.

7.2.4 Routine Clinical Testing

The Sponsor performed adequate monitoring of safety parameters including vital signs, physical exams, and laboratory testing. See section [7.4.2 Laboratory Findings](#), section [7.4.3 Vital Signs](#), and section [7.4.4 Electrocardiograms \(ECGs\)](#).

Reviewer comments: *In this reviewer's assessment, the routine clinical testing of subjects in this sNDA was adequate.*

7.2.5 Metabolic, Clearance, and Interaction Workup

There were no safety-related pharmacodynamics or pharmacokinetics trials of lubiprostone submitted with this sNDA.

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

None was conducted.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in OBD-0631 or OBD-0632. There was one death reported in OBD-1033 and one death reported in OBD-06S1. Both subjects were in the lubiprostone arm. The Sponsor reported that neither death was related to study drug. [Table 82](#) provides brief narratives of deaths reported in OBD-1033 and OBD-06S1.

Table 82. Brief Narratives of Deaths in Double-blind Trial and Open-label Trial

Trial	Narrative	Probable Cause of Death	Time Interval of Lubiprostone Dose
OBD-1033	Subject 3014015: 53 year-old female with insomnia, fibromyalgia, headache, depression, and OIC. Medications included Vicodin, Norco, Soma, Effexor, Valium, and zolpidem. The subject was found dead 2 days after she received last dose of lubiprostone. The cause of death based on autopsy report was multiple drug toxicity.	Multiple drug toxicity	2 days after last dose
OBD-06S1	Subject 1069031: 45 year-old female with asthma, COPD, depression, fibromyalgia, osteoarthritis, anxiety, borderline personality disorder, back pain, erosive duodenitis, tobacco use, and OIC who was taking Dilaudid, fentanyl, morphine, oxycodone, hydrocodone with acetaminophen, Advair, albuterol, ipratropium, Zoloft, and Xanax. The patient was hospitalized with shortness of breath believed to be due to an unresolved case of pneumonia, at which time the study drug was discontinued. She was subsequently found to have severe pulmonary embolism, an esophageal mass, and pleural effusion. On hospital day #3, she developed severe septic shock, respiratory failure, and acute renal failure and died 3 days later. Subject had been in the lubiprostone arm of OBD-0631.	Multi-organ system failure	6 days after last dose

Source: Reviewer's table, based on narratives from page 771 of CSR for OBD-1033, and page 721 of CSR for OBD-06S1.

Reviewer comments: *In this reviewer's assessment, the cause of these subjects' deaths does not appear to be related to the study drug.*

7.3.2 Nonfatal Serious Adverse Events

The Sponsor presented nonfatal serious adverse events (SAEs) for the three double-blind trials OBD-1033, OBD-0631, and OBD-0632, and for the open-label safety trial OBD-06S1. For the overall safety pool consisting of all 4 trials, there were 80 subjects (24 placebo and 56 lubiprostone) that reported at least 1 nonfatal SAE. A total of 114 nonfatal SAEs were reported by the 80 subjects. A summary of all patients with at least one nonfatal SAE in the three double-blind trials is provided below in [Table 83](#). Data for all subjects with at least one nonfatal SAE in the open-label trial are summarized in [Table 84](#). In both tables, subjects who were taking methadone or a congener of methadone are displayed with their subject ID underlined.

Table 83. Summary of All Nonfatal Serious Adverse Events for the Double-blind Trials Pool

Treatment Subject ID	Age (years)/ Gender	Time of AE (days)	Preferred Term/Verbatim Term	Relationship*	Action Taken
Lubiprostone					
0631-1019-007	40/M	32	Bipolar disorder / exacerbation of bipolar disorder	Unrelated	Drug discontinued permanently
0631-1023-003	47/F	89	Ilium fracture / left iliac fracture (due to motorcycle accident) Pelvic fracture / left hemipelvis fracture	Unrelated	No change
0631-1033-004 ^a	50/F	101	Back pain / increased pain (back)	Unrelated	No change
0631-1034-022	44/F	20	Hypertension / hypertension (history of hypertension on medications)	Unrelated	No change
0631-1038-013	54/M	22	Angina unstable / unstable angina Coronary artery disease / coronary artery disease progression; stenosis of the left anterior descending artery and right coronary artery	Unrelated	Drug withdrawn temporarily
0631-1043-006 ^a	42/F	111	Cellulitis / preseptal cellulitis	Unrelated	No change
0631-1050-009	37/F	68	Small intestinal obstruction / small bowel obstruction (no surgery required)	Unrelated	Drug withdrawn temporarily
0631-1054-002	29/F	1	Postpartum depression / postpartum depression	Unrelated	Drug withdrawn temporarily
0631-1063-008	49/M	60	Duodenal ulcer perforation / perforated duodenal ulcer	Unrelated	Drug discontinued permanently
0631-1072-010	38/F	3	Suicide attempt / attempted suicide (overdose of ramelteon and acetaminophen/oxycodone upon husband asking for divorce)	Unrelated	Drug withdrawn permanently
		9	Presyncope / near syncope (while moving boxes)		
0631-1072-018	51/M	22	Toxic encephalopathy / toxic encephalopathy due to substance abuse (urine toxicology positive for cocaine)	Unrelated	Drug withdrawn temporarily
0632-2015-010	58/M	25	Herpes zoster / exacerbation of herpes zoster	Unrelated	No change
0632-2018-040	58/F	77	Irritable bowel syndrome / irritable bowel syndrome (history of intestinal functional disorder with prior esophagogastric fundoplasty; symptoms responded initially to fundoplication of hiatal hernia, but had recurrent issues with delayed gastric emptying) Impaired gastric emptying / impaired gastric emptying	Unrelated	No change
0632-2026-009	56/M	46	Intestinal obstruction / bowel obstruction (history of hernia repair and orchiectomy; bowel obstruction treated medically)	Unrelated	Drug withdrawn temporarily
0632-2035-002	54/M	84	Pneumonia / pneumonia	Unrelated	No change
0632-2039-008	35/F	11	Cholecystitis / cholecystitis	Unrelated	Drug withdrawn temporarily
0632-2049-009	52/F	70	Multiple sclerosis relapse / exacerbation of multiple sclerosis	Unrelated	Drug discontinued permanently
0632-2072-001	55/F	7	Migraine / migraine headache	Unrelated	Drug discontinued permanently

Treatment Subject ID	Age (years)/ Gender	Time of AE (days)	Preferred Term/Verbatim Term	Relationship*	Action Taken
1033-3000-013	51/F	81	Back pain / back pain (history of back surgery) Abdominal pain / abdominal pain (history of intestinal ischemia and intestinal operation) Nausea / nausea Vomiting / vomiting	Unrelated	Drug discontinued permanently
<u>1033-3022-001^b</u>	43/M	99	Depression suicidal / Suicidal depression (history of suicide attempt)	Unrelated	No change
1033-3024-007	54/M	85	Ankle fracture / right and left bilateral ankle fracture	Unrelated	Drug withdrawn temporarily
1033-3044-007	61/F	68	Syncope / syncope (possibly due to carotid disease)	Unrelated	No change
1033-3097-006	52/F	8	Migraine / migraine	Unrelated	Drug discontinued permanently
1033-3098-003 ^c	47/F	87	Hepatic enzyme increase / elevated liver enzymes (no etiology identified, noted to be resolved on day 149)	Unrelated	No change
1033-3402-006	50/M	87	Nephrolithiasis / nephrolithiasis	Unrelated	No change
Placebo					
0631-1006-009	56/F	55	Gastroenteritis / gastroenteritis (nausea, vomiting, diarrhea, and chest pain, treated in emergency room)	Unrelated	Drug withdrawn temporarily
0631-1007-001	55/F	51	Myocardial infarction / myocardial infarction (history of type 2 diabetes)	Unrelated	Drug discontinued permanently
0631-1008-017	60/M	27	Pneumonia / pneumonia (history of emphysema and pneumonia)	Possibly related	No change
0631-1032-003	43/F	83	Bronchitis / acute bronchitis	Unrelated	No change
0631-1033-001	48/M	14	Bursitis / left olecranon bursitis	Unrelated	Drug discontinued permanently
		81	Pulmonary embolism / pulmonary embolism		
<u>0631-1034-007</u>	55/F	21	Gastroenteritis / gastroenteritis (requiring hospitalization for IV fluids)	Unrelated	No change
		64	Transient ischemic attack / transient ischemic attack (history of diabetes and on clopidogrel)		
0631-1043-007	36/M	33	Appendicitis / acute appendicitis	Unrelated	Drug withdrawn temporarily
0631-1050-021	63/F	85	Musculoskeletal pain / right shoulder pain (history of coronary artery disease)	Unrelated	No change
0631-1058-005	76/F	6	Chronic obstructive pulmonary disease / COPD exacerbation	Unrelated	Drug withdrawn temporarily
0632-2002-003	42/F	14	Abdominal pain upper / left upper quadrant abdominal pain (history of four laparoscopies; hospitalized due to bowel obstruction but treatment during hospitalization not provided)	Unrelated	Drug discontinued permanently
0632-2015-009	49/F	34	Tricuspid valve disease / tricuspid valve disease (symptoms of shortness of breath and edema; extent of tricuspid disease not discussed)	Unrelated	Drug discontinued permanently
0632-2032-001 ^a	57/M	122	COPD exacerbation	Unrelated	No change
0632-2080-011	66/F	17	Fecaloma / impacted stool (history of impacted stool)	Unrelated	Drug withdrawn temporarily

Treatment Subject ID	Age (years)/ Gender	Time of AE (days)	Preferred Term/Verbatim Term	Relationship*	Action Taken
0632-2081-001	49/M	14	Hypersensitivity / allergic reaction (itching, hives, extremity swelling with subsequent rash; was also on multiple other medications, including losartan)	Probably related	Drug discontinued permanently
<u>0632-2083-017</u>	53/M	33	Diverticulitis / diverticulitis	Unrelated	No change
0632-2093-013	44/F	16	Confusional state / confusion Chills / chills Malaise / malaise Pyrexia / fever (occurred 2 days following toe surgery)	Unrelated	Drug discontinued permanently
0632-2149-012	50/M	3	Angina pectoris / worsening cardiac chest pain (history of myocardial infarction)	Unrelated	No change
1033-3003-009	55/M	4	Coronary artery disease / coronary artery disease with balloon angioplasty (history of hypertension and baseline medications included aspirin and Plavix)	Unrelated	Drug withdrawn temporarily
1033-3036-007	47/F	19	Back pain / intractable back pain	Unrelated	Drug withdrawn temporarily
1033-3036-009	63/F	36	Syncope / syncope (etiology not specified, but had history of stroke and diabetes) Contusion / left hip contusion	Unrelated	No change
1033-3045-011	55/M	98	Aspartate aminotransferase (AST) increased / elevated AST (No report of event end date; had history of hepatitis A hepatic enzymes increased)	Possibly related	No change
1033-3066-007	59/F	36	Abdominal pain upper / epigastric pain (also had nausea, vomiting, and difficulty swallowing; no clear etiology provided) Chest pain / atypical chest pain	Unrelated	No change
1033-3081-002	49/F	41	Muscle spasms / muscle spasms Cardiac failure congestive / worsening of congestive heart failure Renal failure acute / acute renal insufficiency	Unrelated	Drug discontinued permanently
1033-3111-003	50/F	20	Fecaloma / fecal obstruction causing impaction (attributed to worsening of opioid-induced bowel dysfunction)	Possibly related	Drug discontinued permanently

Note 1: The Double-blind trials pool includes trials OBD-1033, OBD-0631, and OBD-0632.

Note 2: Subjects whose subject ID numbers are underlined were those taking a diphenylheptane opioid (e.g., methadone).

Note 3: Time to AE reflects number of days to AE after first dose of study medication in the double-blind trial.

* Relationship to study drug as assessed by the investigator.

^a Per the trial schedule, the final trial assessment was to occur at Visit 9, which was to take place no later than Day 101. The AEs for subjects 0631-1033-004, 0631-1043-006, and 0632-2032-001 occurred after the last day of study medication (Visit 8, Day 84 ±3), but before their final follow up visit (Visit 9), which occurred later than pre-specified. Visit 9 for 0631-1033-004 was on Day 133, for 0631-1043-006 was on Day 117, and for 0632-2032-001 was on Day 168.

^b Subject 1033-3022-001 was not on methadone at time of randomization, but subsequently was prescribed methadone by a provider while the trial was ongoing. The Sponsor reported that the subject did not realize methadone was a prohibited medication. The subject took 3 doses of methadone and then stopped because he said it made him nauseated.

^c The ALT trends for subject 1033-3098-003, who had SAE of hepatic enzyme increase, are presented in Table 95 of section 7.4.2. Source: Reviewer's table, from narratives pages 1143-1152 of CSR OBD-0631, pages 1145-1152 of CSR OBD-0632; pages 773-778 of CSR OBD-1033; and module 5.3.5.3, Table 2.7.2.2, Integrated Summary of Safety.

Table 84. Summary of All Nonfatal Serious Adverse Events for the Open-label Trial OBD-06S1

Treatment/ Subject ID	Age (years)/ Gender	Time to AE (days)	Preferred Term/Verbatim Term	Relationship*	Action Taken
Placebo-LBP					
<u>06S1-1006-003^a</u>	45/F	300	Papilloma viral infection / HPV (underwent hysterectomy with partial vaginectomy)	Unrelated	No change
06S1-1007-007	70/F	202	Dyspnea/ shortness of breath	Unrelated	No change
		218	Pulmonary embolism / pulmonary embolism (history of pulmonary embolism)		
06S1-1010-005	56/F	58	Pleural effusion / left pleural effusion	Unrelated	Drug discontinued permanently
		68	Jugular vein thrombosis / acute thrombosis of the right internal jugular vein		
06S1-1016-012	61/M	71	Lung neoplasm malignant / lung cancer	Unrelated	Drug discontinued permanently
06S1-1022-006	46/F	218	Lumbar spinal stenosis / lumbar stenosis with radiculopathy	Unrelated	No change
06S1-1032-003 ^b	44/F	77	Gastroenteritis / acute gastroenteritis (hematochezia with internal hemorrhoids on endoscopy)	Unrelated	Drug withdrawn temporarily
06S1-1069-024	59/M	31	Depression / exacerbation of depression	Unrelated	Drug discontinued permanently
<u>06S1-1095-005</u>	68/F	221	Asthma / asthma exacerbation	Unrelated	No change
			Chronic obstructive pulmonary disease / COPD exacerbation		
06S1-1126-004	50/F	135	Pain / acute intractable neck pain	Unrelated	No change
<u>06S1-2023-024</u>	59/M	46	Mental status changes / altered mental status (possibly due to hypoglycemia)	Unrelated	No change
06S1-2026-011	50/M	33	Anxiety / anxiety	Unrelated	No change
			Non-cardiac chest pain / chest pain, non-cardiac (history of angina pectoris)		
<u>06S1-2048-006</u>	55/F	181	Cholecystitis acute/ acute cholecystitis	Unrelated	No change
06S1-2080-012	48/F	162	Intervertebral disc protrusion / acute herniated cervical disc at C6-C7	Unrelated	Drug withdrawn temporarily
06S1-2103-002 ^a	48/M	293	Gastroenteritis / gastroenteritis	Unrelated	Drug discontinued permanently
06S1-2127-004	52/F	150	Coronary artery disease / severe native 3-vessel coronary artery disease progression (history of myocardial infarction)	Unrelated	No change
<u>06S1-2127-014</u>	51/M	135	Headache / chronic headache with recent worsening (following cervical epidural steroid injection)	Unrelated	No change
LBP-LBP					
06S1-1049-003	53/M	125	Pancytopenia / severe acute pancytopenia	Unrelated	Drug withdrawn temporarily
		198	Pneumonia / pneumonia		
			Pulmonary cavitation / cavitory pulmonary lesion		
		231	Nocardiosis / nocardia infection right posterior thigh		
			Abscess limb / multiple abscesses on thigh due to nocardia		

Treatment/ Subject ID	Age (years)/ Gender	Time to AE (days)	Preferred Term/Verbatim Term	Relationship*	Action Taken
06S1-1051-003	43/F	47	Pancreatitis / pancreatitis Cholelithiasis / cholelithiasis Cholecystitis / cholecystitis Abdominal abscess / intra-abdominal abscess	Unrelated	Drug discontinued permanently
06S1-1056-008	52/F	202	Coronary artery disease / worsening of coronary artery disease (history of coronary artery disease with prior stenting)	Unrelated	No change
06S1-1066-013	58/M	226	Myocardial infarction / minor heart attack (type 2 diabetes)	Unrelated	No change
06S1-1069-005	44/M	117	Appendicitis / appendicitis	Unrelated	No change
06S1-1069-013	54/F	22	Cellulitis / cellulitis right lower extremity	Unrelated	No change
<u>06S1-1069-036</u>	33/F	128	Back pain / low back pain	Unrelated	Drug discontinued permanently
		147	Cellulitis / bilateral cellulitis		
06S1-1073-002	67/M	65	Cognitive impairment / severe cognitive impairment (following hip replacement surgery)	Unrelated	Drug discontinued permanently
06S1-2010-003	43/M	90	Edema peripheral / bilateral lower leg edema (with antecedent cellulitis)	Unrelated	No change
06S1-2013-002	49/F	200	Costochondritis / costochondritis (possible pericarditis)	Unrelated	Drug withdrawn temporarily
06S1-2026-009 ^b	56/M	47	Atrial fibrillation / atrial fibrillation with rapid ventricular response	Unrelated	No change
06S1-2056-004	57/F	102	Chronic obstructive pulmonary disease / COPD exacerbation	Unrelated	Drug discontinued permanently
		112	Dizziness / dizziness		
<u>06S1-2059-013</u>	61/F	132	Spinal compression fracture / lumbar compression fracture Osteomyelitis / osteomyelitis of spine (due to methicillin-resistant <i>Staphylococcus aureus</i>)	Unrelated	No change
06S1-2059-014	34/F	115	Abdominal adhesions / intra-abdominal adhesions (underwent laparoscopic lysis of adhesion with repair of incisional hernia)	Unrelated	No change
		193	Meningitis aseptic / possible aseptic meningitis		
06S1-2083-002	43/F	193	Multiple fractures / multiple fractures Road traffic accident / motor vehicle accident attributed to increased use of zolpidem	Unrelated	Drug discontinued permanently
06S1-2127-006	60/F	208	Respiratory failure / acute respiratory distress syndrome with respiratory failure (no clear etiology presented)	Unrelated	Drug discontinued permanently
06S1-2138-004	61/F	103	Pneumonia / pneumonia	Unrelated	Drug withdrawn temporarily

Abbreviations: LBP, lubiprostone

Note 1: Subjects whose subject ID numbers are underlined were those taking a diphenylheptane opioid (e.g., methadone).

Note 2: Time to AE reflects number of days to AE after first dose of study medication in trial OBD-06S1.

* Relationship to study drug as assessed by the investigator.

^a Per the trial schedule, the final trial assessment was to occur at Visit 23, which was to take place no later than Day 269. The AEs for these subjects occurred after the last day they were supposed to have taken study medication (Visit 22, Day 252 ±3), and before their final follow up visit (Visit 23), which occurred later than pre-specified. Subject 06S1-1006-003's final visit was on Day 315, and 06S1-2103-002's final visit was on Day 307.

^b Denotes a subject in trial OBD-06S1 who also reported an SAE in one of the two double-blind trials, OBD-0631 or OBD-0632.

There were two such subjects.

Source: Reviewer's table, based on narratives on pages 723-726 of CSR OBD-06S1; and module 5.3.5.3, Table 2.7.2.2, Integrated Summary of Safety.

Reviewer comments: *This officer assessed all the non-fatal SAEs by CRFs, narratives and datasets provided by the Sponsor. As adjudicated by this reviewer, none of the non-fatal SAEs were attributed by the PI to administration of lubiprostone. For the following four subjects, all of whom received placebo, the PI indicated that their SAEs were possibly/probably related to study drug:*

- *Subject 0631-1008-017's SAE of pneumonia was determined to be possibly related to the study drug by the PI. This subject, however, was reported to have underlying lung disease (history of emphysema and pneumonia) and this reviewer cannot clearly relate the SAE to the study drug.*
- *Subject 0632-2081-001 experienced an allergic reaction 14 days following first dose of study drug, and the presenting symptoms could feasibly be related to the study drug, although an allergic response 2 weeks after first dose would be somewhat unusual.*
- *Subject 1033-3045-011 experienced a rise in AST 98 days following initiation of study drug (measured at the follow up visit), and this SAE was reported by the PI as possibly related to study drug. The subject's baseline AST at screening was 73 IU/L (with reference upper limit of normal of AST being 40 IU/L). AST trended as follows: 110 IU/L at Visit 4 (day 27), 115 IU/L at Visit 6 (day 55), 99 IU/L at the end-of-treatment visit (day 84), 124 IU/L at follow up visit (day 98), and 139 IU/L at an unscheduled additional visit (day 115). Of note, the subject reportedly had a history of hepatic enzyme elevation. The subject's baseline ALT was 50 IU/L and fluctuated between 59 IU/L and 74 IU/L at various time points during the trial. In this reviewer's assessment, given the baseline elevation in AST/ALT and fluctuation in AST/ALT during the trial while on study drug (placebo), it is not clear whether the rise in the subject's AST was related to study drug.*
- *Subject 1033-3111-003's fecaloma/fecal obstruction causing impaction was, as reported by the PI, possibly related to the study drug. The association made by the PI to the study drug, however, is unclear to this reviewer because the subject's SAE was attributed to worsening of underlying OBD.*

This reviewer does not note any SAEs that were clearly indicative of, or related to, opioid withdrawal. Further, there appear to be no trends or patterns in the SAEs of subjects on a diphenylheptane opioid (e.g., methadone) as compared with subjects not on an opioid from this class. Evaluation for opioid withdrawal is discussed at length in section [7.3.5 Submission Specific Primary Safety Concerns](#).

7.3.3 Dropouts and/or Discontinuations

[Table 85](#) provides disposition data for subjects in the double-blind trials pool and the open-label trial. A total of 377 subjects (28%) discontinued during the 12-week double-blind period for the following reasons:

- 54 subjects experienced AEs that led to discontinuation
- 51 subjects were lost to follow up
- 95 subjects were withdrawn at their request
- 88 subjects withdrew for other reasons, most frequently due to protocol violations

In the double-blind trials pool, more subjects in the placebo treatment arm (74%) completed the trials as compared with the lubiprostone treatment groups (70%). In the double-blind trials pool, patient choice was the most common reason for discontinuation in the placebo group (8%), while “other” was the most common reason for discontinuation in the lubiprostone group (7%).

A total of 152 subjects (35%) discontinued the open-label trial due to the following:

- 23 subjects experienced AEs that led to discontinuation
- 31 subjects were lost to follow up
- 47 subjects were withdrawn at their request
- 15 subjects withdrew due to lack of efficacy

Table 85. Subject Discontinuation in Pooled Double-blind Trials and Open-label Trial – Randomized Subjects

Variable	Double-blind Trials (OBD-1033, OBD-0631, OBD-0632)		Open-label Trial OBD-06S1	
	Placebo N=662 n (%)	LBP N=679 n (%)	Placebo-LBP N=225 n (%)	LBP-LBP N=214 n (%)
Subjects Randomized, n (%)	662 (100)	679 (100)	225 (100)	214 (100)
Safety Evaluable, n (%)	652 (98.5)	663 (97.6)	225 (100)	214 (100)
Completed Subjects, n (%)	491 (74.2)	473 (69.7)	143 (63.6)	143 (66.8)
Reasons for Discontinuation from Trial, n (%)				
Adverse Event	16 (2.4)	38 (5.6)	15 (6.7)	8 (3.7)
Lack of Efficacy	15 (2.3)	16 (2.4)	8 (3.6)	7 (3.3)
Discontinuation of Opioids	1 (0.2)	11 (1.6)	3 (1.3)	4 (1.9)
Patient Choice	54 (8.2)	41 (6.0)	26 (11.6)	21 (9.8)
Lost to F/U	21 (3.2)	30 (4.4)	13 (5.8)	18 (8.4)
Noncompliance	14 (2.1)	13 (1.9)	6 (2.7)	3 (1.4)
Investigator Decision	2 (0.3)	6 (0.8)	4 (1.8)	1 (0.5)
Sponsor Request	7 (1.1)	4 (0.6)	0 (0)	2 (0.9)
Other	41 (6.2)	47 (6.9)	7 (3.1)	6 (2.8)
Total	171 (25.8)	206 (30.3)	82 (36.4)	70 (32.7)

Abbreviations: LBP, lubiprostone

* There were actually 71 LBP-LBP subjects who discontinued from the trial. Subject 1018028 completed the end-of-treatment visit on 8/21/2009, but did not return for the follow up final visit. The site did not provide a reason for discontinuation for this subject in the electronic chart. As such, the subject is not included in the tabular summary of reasons for discontinuation.

Source: Reviewer’s Table modified from Table 2.7.4.1-3, page 15 and Table 2.7.4.1-5, page 18, Summary of Clinical Safety.

Reviewer comments: *It appears that in the double-blind trials pool, a higher percentage of patients discontinued the trials due to AEs in the lubiprostone treatment group (6%) than in the placebo group (2%). In the open-label trial, patient choice was the most common reason for discontinuation in both the placebo-lubiprostone (12%) and lubiprostone-lubiprostone (10%) groups.*

In the double-blind trials pool, nausea (3%) and diarrhea (1%) were the most common AEs that led to discontinuation from treatment in the lubiprostone group and were the only AEs that led to discontinuation from treatment in ≥1% of the subjects. All of the AEs that led to discontinuation from treatment in the double-blind trials in the placebo group

were reported in <1% of the subjects. The AEs that led to discontinuation from treatment in ≥1% of the subjects in either treatment group are shown in [Table 86](#).

Table 86. Adverse Events Leading to Discontinuation from Treatment in 1% or More of Lubiprostone Subjects – Double-blind Trials Pool (Safety Evaluable Subjects)

Preferred Term	Placebo (N=652) n (%)	Lubiprostone (N=663) n (%)
Nausea	0	17 (2.6)
Diarrhea	2 (0.3)	8 (1.2)

Note: The double-blind trials pool includes trials OBD-1033, OBD-0631, and OBD-0632.

Subjects who experienced the same event more than once were counted only once for that event.

Source: Reviewer's table, adapted from Sponsor's Table 2.7.4.2-20, page 67 of 167, Summary of Clinical Safety.

In the open-label trial, all the AEs that led to discontinuation from treatment were reported in <1% of subjects. Among these, constipation was the most common (0.7%), followed by diarrhea, nausea, vomiting, and dizziness, all with an incidence of 0.5%.

In the overall safety pool, nausea (2%) and diarrhea (1%) were the most commonly reported AEs that led to discontinuation from treatment in the lubiprostone group. All other AEs that led to discontinuation were reported in <1% of the lubiprostone subjects. The AEs that led to discontinuation from treatment in the overall safety pool in ≥1% of the lubiprostone subjects are summarized in [Table 87](#).

Table 87. Adverse Events Leading to Discontinuation from Treatment in 1% or More of Lubiprostone Subjects – Overall Safety Pool (Safety Evaluable Subjects)

Preferred Term	Placebo (N=652) n (%)	Lubiprostone (N=889) n (%)
Nausea	0	19 (2.1)
Diarrhea	2 (0.3)	10 (1.1)

Note: The overall safety pool includes trials OBD-1033, OBD-0631, OBD-0632, and OBD-06S1.

Subjects who experienced the same event more than once were counted only once for that event.

Source: Reviewer's table, adapted from Sponsor's Table 2.7.4.2-22, page 69 of 167, Summary of Clinical Safety.

Reviewer comments: *Because nausea and diarrhea are among the well-established adverse events associated with lubiprostone, it is not surprising that these AEs were the most common reasons for discontinuation from treatment among lubiprostone subjects.*

It was initially unclear to this reviewer how the Sponsor derived the information in the tables summarizing discontinuation due to AEs (as presented by the Sponsor in Tables 2.7.4.2-20 and 2.7.4.2-22 of the Summary of Clinical Safety). In an information request, this reviewer asked the Sponsor clarify how it had generated these AE tables. The Sponsor responded that the tables summarize subjects whose study drug was discontinued permanently during the trial (i.e., subjects for whom the variable AEACN=1, indicating that drug was discontinued permanently). This reviewer asked the Sponsor why the dataset variable AEDISCC, which was supposed to capture subjects who had discontinued due to an AE, was not used instead. The Sponsor clarified that some subjects who discontinued due to an AE had multiples AEs on different study days with different actions taken and, in some cases, had multiple AEs designated as

having led to discontinuation from treatment. In these cases, the Sponsor argued, it cannot be determined which AE was the main reason (if there was one) for treatment discontinuation. Thus, the Sponsor summarized all AEs from these subjects that were marked as action taken of “drug discontinued permanently.” This reviewer acknowledges that this approach, although imperfect, is the most conservative one because it captures all AEs that possibly contributed to treatment discontinuation.

7.3.4 Significant Adverse Events

AEs leading to discontinuation were discussed in section [7.3.3 Dropouts and/or Discontinuations](#). In order to facilitate logical presentation of safety data, tables listing severe cases of the most common AEs are presented in section [7.4.1 Common Adverse Events](#), immediately following the tables presenting the most common AEs.

7.3.5 Submission Specific Primary Safety Concerns

Opioid Withdrawal

The Sponsor indicated that there is no interference with the analgesic effect of diphenylheptane-type opioids or other classes of opioids with concomitant use of lubiprostone, and that the safety profile of patients taking these opioids is similar to the overall patient population with OIC. In this reviewer’s assessment, given that lubiprostone is not known to interact with mu-opioid receptors, lubiprostone would not be expected to elicit withdrawal symptoms.

To adjudicate the Sponsor’s reports, this reviewer performed additional analysis on the AEs dataset for the overall safety pool. The dataset was evaluated to isolate all subjects who reported any of the following AEs (by PT): (1) anxiety; (2) cold sweat; (3) hot flush; (4) hyperhidrosis; (5) piloerection; (6) tremor; (7) abdominal pain; (8) abdominal discomfort; (9) abdominal pain lower; (10) abdominal pain upper; (11) agitation; (12) blood pressure fluctuation; (13) blood pressure increased; (14) decreased appetite; (15) drug withdrawal syndrome; (16) flushing; (17) heart rate increased; (18) insomnia; (19) nausea; (20) rhinorrhea; (21) tachycardia; (22) vomiting; and (23) withdrawal syndrome.

The AE profile of subjects with various combinations of these AEs of interest was then individually reviewed by this medical officer. Subjects that, in this reviewer’s clinical judgment, had a constellation of AEs that could potentially represent opioid withdrawal, were then selected for further review. Narratives and CRFs for these nine subjects were requested from the Sponsor and reviewed by this medical officer. Brief narratives for these subjects are in [Appendix 7: Narratives of Subjects Selected for Review Based on Adverse Events Suggestive of Possible Opioid Withdrawal](#).

Reviewer comments: *Based on thorough review of the safety database, given the totality of the data and review of subject narratives, this medical officer finds no safety signal to suggest that lubiprostone is associated with opioid withdrawal.*

Opioid Use – Changes in Opioid Dose as Measured by MEDD

Opioid dose adjustment by month during the course of the four trials is discussed separately for each trial in the Appendices (Table 107 for OBD-1033, Table 117 for OBD-0631, Table 124 for OBD-0632, and Table 150 for OBD-06S1). Opioid dose adjustment by month for the double-blind trials pool is summarized in Table 88. The Sponsor reported no notable changes from baseline in mean MEDD at Month 1, 2, or 3.

Table 88. Change from Baseline in Opioid Dose by Month in Double-blind Trials Pool – OBD-1033, OBD-0631, and OBD-0632 (ITT Population)

Time Point	Change from Baseline in Opioid Dose (Observed Combined MEDD)	Placebo (N=649)	Lubiprostone (N=663)
Month 1	n	644	659
	Mean ± Standard Dev	-0.9 ± 18.61	-0.9 ± 29.08
	Median (Min, Max)	0 (-336, 83)	0 (-439, 309)
Month 2	n	573	574
	Mean ± Standard Dev	0.1 ± 26.46	0 ± 61.61
	Median (Min, Max)	0 (-490, 258)	0 (-845, 990)
Month 3	n	513	509
	Mean ± Standard Dev	-1.8 ± 48.78	-13.6 ± 256.31
	Median (Min, Max)	0 (-816, 244)	0 (-5432, 990)

Source: Reviewer's table, adapted from Table 1.1.7.5, module 5.3.5.3, pages 385 to 387 of 2585, Integrated Summary of Efficacy.

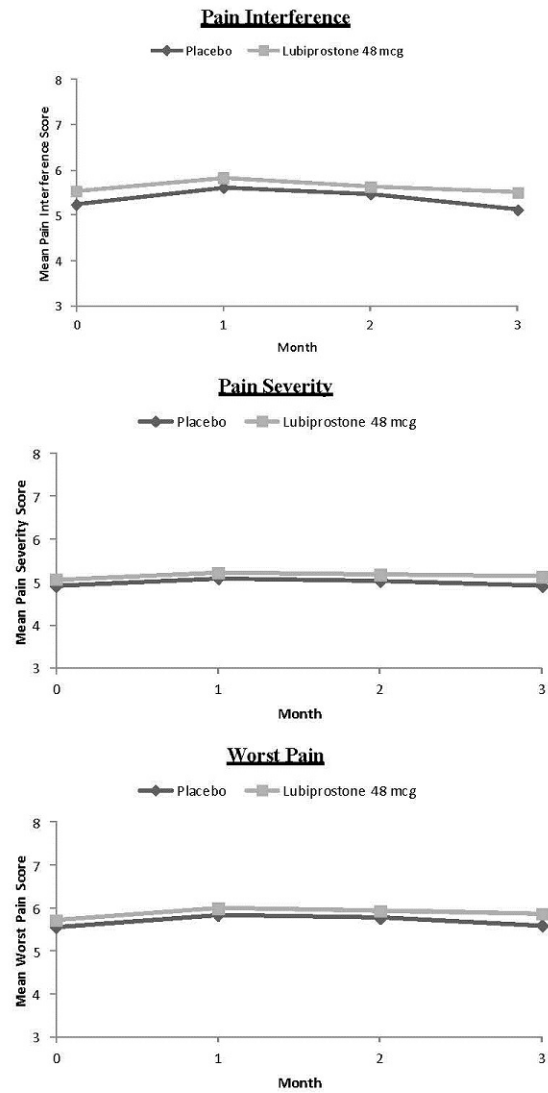
Reviewer comments: Although the MEDD was collected in the eDiary daily, the Sponsor only analyzed this change on a monthly basis, which is not frequent enough to detect potentially clinically important changes in opioid use at specified points in time. Thus, this officer cannot make definite conclusions about lubiprostone's effects on opioid use.

Opioid Analgesia – Pain Assessments

The Sponsor administered the Brief Pain Inventory-Short Form (BPI-SF) monthly during the four trials. The BPI-SF is a PRO measure that assesses the severity of pain and the impact of pain on daily functions. The BPI-SF comprises the two domains pain severity and pain interference. An additional score is given for “worst” pain, and “worst” pain is included in the pain severity domain. Subjects completed the BPI-SF, which was modified so that only multiple-choice questions about pain were answered, at baseline and at the end of each month. Descriptive statistics were used to evaluate the mean changes from baseline at monthly intervals for “worst pain” and for the two domains.

The Sponsor noted no differences in the mean changes from baseline in the pain interference, pain severity, or worst pain scores between the placebo and lubiprostone groups at the end of 1, 2, or 3 months of treatment or at the end of treatment (defined as the last non-missing post-baseline assessment) for the subjects in the 12-week double-blind trials. The Sponsor's findings for the pooled double-blind trials are summarized in Figure 1. The Sponsor noted similar findings for the open-label trial OBD-06S1 (see Figure 2).

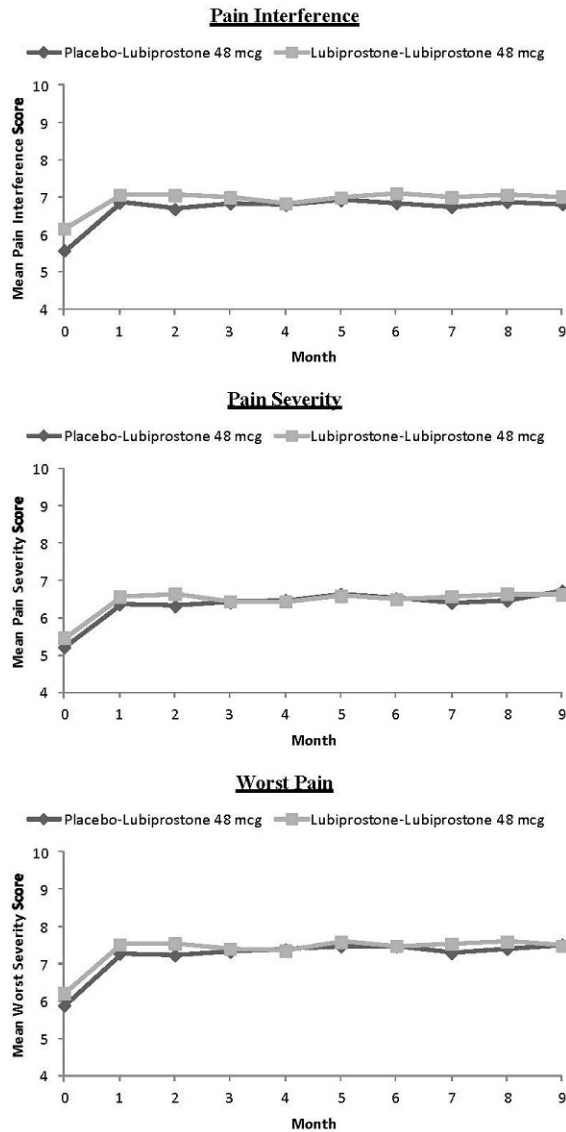
Figure 1. Brief Pain Inventory Pain Interference, Pain Severity, and Worst Pain Scores – Double-blind Trials Pool (Safety-Evaluable Subjects)



	Placebo N =	544	512	461	396
	Lubiprostone 48 mcg N =	550	497	444	370

Note: The double-blind studies pool includes studies OBD-1033, OBD-0631, and OBD-0632.
 Source: Sponsor's Figure 2.7.4.4-1, page 107 of 167, Clinical Summary of Safety.

Figure 2. Brief Pain Inventory Pain Interference, Pain Severity, and Worst Pain Scores – Open-label Trial (Safety-Evaluable Subjects)



Placebo-Lubiprostone 48 mcg N = 181 130 119 114 112 98 96 86 124 85
 Lubiprostone 48 mcg N = 169 146 142 123 119 114 103 98 113 87
 Source: Sponsor's Figure 2.7.4.4-2, page 109 of 167, Clinical Summary of Safety.

Regarding pain assessments, DAAAP noted that the BPI-SF appears to be an appropriate tool to assess pain in this chronic pain population as it incorporates the use of a Numeric Rating Scale from 0 to 10 and evaluates pain intensity (worst pain). DAAAP added, however, that the BPI-SF was administered on a monthly basis, which is not frequent enough to adequately assess changes in pain intensity that may occur on a daily basis. In addition, DAAAP indicated that because the assessments were performed only monthly, there is no way to correlate the daily changes in MEDD usage with the level of pain. Further, because it was considered a protocol violation only if the opioid dose adjustment lasted more than 7 days, there could have been episodes of increased MEDD usage just under 7 days, but still clinically relevant.

DAAAP also commented on the high number of missing BPI-SF assessments in the OIC trials. Specifically, in OBD-1033, by Month 3, there were BPI-SF assessments on 160 subjects compared with 199 at baseline, a drop off of nearly 20% in the lubiprostone arm. In OBD-0631, by Month 3, there were BPI-SF assessments on 113 subjects compared with 203 at baseline, a drop off of nearly 44% in the lubiprostone arm. In OBD-0632, by Month 3, there were BPI-SF assessments on 97 subjects compared with 148 at baseline, a drop off of nearly 34% in the lubiprostone arm. Further, in each trial, there were discrepancies between the observed value number of subjects and change from baseline number of subjects, without an explanation by the Sponsor for the difference.

The missing BPI-SF assessments may in turn have skewed the results, suggesting little change in baseline BPI-SF assessments for a select number of subjects, but findings may not be representative of the entire group actually included in the study. DAAAP noted that the Sponsor did not discuss the reasons for the missing BPI-SF assessments and discrepancies in observed number of subject scores versus change in baseline number of subject scores. Further, DAAAP commented that the Sponsor's figures showing monthly change from baseline in BPI-SF scores were difficult to interpret because the Sponsor did not indicate whether a positive change in mean pain score

reflected worsening or improving pain. Finally, the Sponsor did not analyze use of rescue non-opioid analgesics, which DAAAP noted could confound interpretation of MEDD usage by affecting the requirement for opioid analgesia.

Reviewer comments: *Although the BPI was developed for use in cancer patients, it has been validated in patients with chronic non-cancer pain.^{5,6} Given the evidence suggesting that diphenylheptane opioids affect the action of lubiprostone at CIC-2 channels, it is of interest to examine whether lubiprostone may impact the analgesic effects of this class (or other classes) of opioids. DAAAP noted that the Sponsor's submission did not analyze key data in a clinically meaningful or interpretable way due to the deficiencies in the controlled and uncontrolled trial designs discussed above.*

(b) (4)

Given what is known about lubiprostone's mechanism of action, this reviewer would not expect lubiprostone to interfere with the analgesic effects of opioids. In response to an Information Request by DAAAP, the Sponsor provided a listing of TEAEs potentially related to inadequate pain control. When AEs of interest (e.g., back pain, arthralgia) were examined, this listing showed that only 2 subjects out of 663 who received lubiprostone in the double-blind trials pool discontinued with AEs of worsening pain. These AEs were listed as AEs of worsening back pain in both subjects. Given the paucity of subjects discontinuing due to worsening pain, this reviewer does not find a safety signal with respect to lubiprostone's effect (if any) on opioid analgesia or use.

(b) (4)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In all clinical trials submitted as part of this sNDA, subjects were to voluntarily report any AEs in response to open-ended questioning (e.g., "How has your health been since the last visit?"). In the three double-blind trials, AEs were assessed upon randomization, at Week 1, and then every other week through follow up assessment at Week 14. In the open-label trial, AEs were assessed at Week 2, then every 3 weeks from Week 6 to Week 36, and a final time at the Week 38 follow up visit. In the Sponsor's presentation of common AEs, the most common AEs were those reported in $\geq 2\%$ of lubiprostone subjects in the overall safety pool and in a larger percentage of lubiprostone subjects than placebo subjects and/or the following events of interest: nausea, diarrhea, headache, vomiting, dyspnea, chest pain, abdominal pain, and peripheral edema.

⁵ Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the Brief Pain Inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain.* 2004;20(5):309-318.

⁶ Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the Brief Pain Inventory for chronic nonmalignant pain. *J Pain.* 2004;5(2):133-137.

Reviewer comments: *Based on the known safety profile of lubiprostone, in this reviewer's assessment, the events of interest the Sponsor reported along with common AEs (those reported in $\geq 2\%$ of lubiprostone subjects in the overall safety pool and in a larger percentage of lubiprostone subjects than placebo subjects) were appropriately selected. This reviewer independently analyzed the safety database to assess for AEs with incidence $\geq 1\%$ among lubiprostone subjects in the overall safety pool that were reported in a larger percentage of lubiprostone subjects than placebo subjects. These AEs included anxiety, blood cholesterol increased, pain in extremity, cough, white blood cell count increased, gastroesophageal reflux disease, influenza, muscle spasms, pyrexia, blood glucose increased, blood lactate dehydrogenase increased, dizziness, fatigue, migraine, pain, cellulitis, pneumonia, joint sprain, and wheezing. To prevent the AE tables from becoming unwieldy in length, this reviewer finds that a presentation of common AEs with incidence cutoff at 2% is reasonable, captures the established AE profile for lubiprostone in CIC and IBS-C trials, and does not omit important information.*

In the 12-week double-blind trials pool, there were a total of 433 TEAEs. In the open-label trial, there were a total of 416 TEAEs. [Table 89](#) summarizes the most common AEs by SOC and PT for the overall safety pool and [Table 90](#) presents the most common AEs for the double-blind trials and the open-label trial.

Table 89. Incidence of Most Common Adverse Events – Overall Safety Pool (Safety Evaluable Subjects)

System Organ Class Preferred Term¹	Placebo (N=652) n (%)	Lubiprostone (N=889) n (%)
Gastrointestinal Disorders		
Nausea	42 (6.4)	128 (14.4)
Diarrhea	25 (3.8)	105 (11.8)
Abdominal pain	30 (4.6)	62 (7.0)
Vomiting	26 (4.0)	47 (5.3)
Flatulence	20 (3.1)	35 (3.9)
Abdominal distension	14 (2.1)	30 (3.4)
Abdominal discomfort	7 (1.1)	26 (2.9)
General Disorders and Administration Site Conditions		
Edema peripheral	7 (1.1)	36 (4.0)
Chest pain	8 (1.2)	8 (0.9)
Infections and Infestations		
Upper respiratory tract infection	15 (2.3)	42 (4.7)
Urinary tract infection	13 (2.0)	31 (3.5)
Bronchitis	11 (1.7)	30 (3.4)
Sinusitis	11 (1.7)	26 (2.9)
Gastroenteritis viral	8 (1.2)	24 (2.7)
Nasopharyngitis	13 (2.0)	22 (2.5)
Investigations		
Blood triglycerides increased	9 (1.4)	29 (3.3)
Hepatic enzyme increased	16 (2.5)	23 (2.6)
Musculoskeletal and Connective Tissue Disorders		
Back pain	12 (1.8)	39 (4.4)
Arthralgia	12 (1.8)	26 (2.9)
Nervous System Disorders		
Headache	14 (2.1)	32 (3.6)
Psychiatric Disorders		
Depression	7 (1.1)	20 (2.2)
Insomnia	6 (0.9)	20 (2.2)
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	4 (0.6)	12 (1.3)
Skin and Subcutaneous Tissue Disorders		
Rash	5 (0.8)	19 (2.1)

Note 1: The overall safety pool includes trials OBD-1033, OBD-0631, OBD-0632, and OBD-06S1.

Note 2: Most common AEs were those reported in ≥2% of lubiprostone subjects and in a larger percentage of lubiprostone subjects than placebo subjects and/or the following events of interest: nausea, diarrhea, headache, vomiting, dyspnea, chest pain, abdominal pain, and peripheral edema.

¹Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOCs) and Preferred Terms are listed in descending order of frequency based on the lubiprostone group. Subjects who experienced the same event more than once were counted only once for that event.

Source: Reviewer's table, generated from adverse events dataset, module 5.3.5.3, Integrated Summary of Safety.

Table 90. Incidence of Most Common Adverse Events – Double-blind Trials Pool and Open-label Long-Term Trial (Safety Evaluable Subjects)

System Organ Class Preferred Term ¹	Double-blind Pool		Open-label Trial	
	Placebo (N=652) n (%)	LBP (N=663) n (%)	Placebo-LBP (N=225) n (%)	LBP-LBP (N=214) n (%)
Gastrointestinal Disorders				
Nausea	42 (6.4)	89 (13.4)	22 (9.8)	17 (7.9)
Diarrhea	25 (3.8)	63 (9.5)	23 (10.2)	19 (8.9)
Abdominal pain	30 (4.6)	43 (6.5)	9 (4.0)	10 (4.7)
Vomiting	26 (4.0)	26 (3.9)	10 (4.4)	11 (5.1)
Flatulence	20 (3.1)	28 (4.2)	4 (1.8)	3 (1.4)
Abdominal distension	14 (2.1)	27 (4.1)	2 (0.9)	1 (0.5)
Abdominal discomfort	7 (1.1)	11 (1.7)	7 (3.1)	8 (3.7)
General Disorders and Administration Site Conditions				
Edema peripheral	7 (1.1)	15 (2.3)	6 (2.7)	15 (7.0)
Chest pain	8 (1.2)	4 (0.6)	4 (1.8)	0 (0.0)
Infections and Infestations				
Upper respiratory tract infection	15 (2.3)	14 (2.1)	14 (6.2)	14 (6.5)
Urinary tract infection	13 (2.0)	16 (2.4)	10 (4.4)	5 (2.3)
Bronchitis	11 (1.7)	9 (1.4)	9 (4.0)	12 (5.6)
Sinusitis	11 (1.7)	6 (0.9)	10 (4.4)	10 (4.7)
Gastroenteritis viral	8 (1.2)	13 (2.0)	6 (2.7)	5 (2.3)
Nasopharyngitis	13 (2.0)	8 (1.2)	4 (1.8)	10 (4.7)
Investigations				
Blood triglycerides increased	9 (1.4)	10 (1.5)	9 (4.0)	10 (4.7)
Hepatic enzyme increased	16 (2.5)	13 (2.0)	4 (1.8)	6 (2.8)
Musculoskeletal and Connective Tissue Disorders				
Back pain	12 (1.8)	16 (2.4)	8 (3.6)	15 (7.0)
Arthralgia	12 (1.8)	13 (2.0)	6 (2.7)	7 (3.3)
Nervous System Disorders				
Headache	14 (2.1)	18 (2.7)	8 (3.6)	6 (2.8)
Psychiatric Disorders				
Depression	7 (1.1)	7 (1.1)	9 (4.0)	4 (1.9)
Insomnia	6 (0.9)	7 (1.1)	9 (4.0)	4 (1.9)
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea	4 (0.6)	6 (0.9)	4 (1.8)	2 (0.9)
Skin and Subcutaneous Tissue Disorders				
Rash	5 (0.8)	12 (1.8)	2 (0.9)	5 (2.3)

Abbreviations: LBP, lubiprostone

Note: The double-blind trials pool includes trials OBD-1033, OBD-0631, and OBD-0632.

¹SOCs and PTs are listed in descending order of frequency based on the lubiprostone group in the overall safety pool (Table 89).

Subjects who experienced the same event more than once were counted only once for that event.

Source: Reviewer's table, generated from adverse events dataset, module 5.3.5.3, Integrated Summary of Safety.

Reviewer comments: *In the overall safety pool, the most common AEs were in the gastrointestinal disorders SOC and included nausea, diarrhea, abdominal pain, flatulence, abdominal distension, abdominal discomfort, and vomiting, all of which occurred more frequently in lubiprostone subjects than subjects receiving placebo, and all of which are in the current label for lubiprostone. Peripheral edema and headache*

were also more common in lubiprostone subjects than placebo subjects. When the incidence of these AEs is examined in the double-blind trials pool, the same general findings for trends in AEs from the overall safety pool hold. Further, a separate analysis of AEs listed by the investigator as possibly, probably, or definitely related to treatment identified nausea, diarrhea, abdominal pain, flatulence, abdominal distension, vomiting, abdominal discomfort, peripheral edema, headache, and hepatic enzyme increased as AEs with incidence of $\geq 1\%$ in lubiprostone subjects in the overall safety pool that were reported in a larger percentage of lubiprostone subjects than placebo subjects. Nausea, diarrhea, abdominal pain, flatulence, abdominal distension, abdominal discomfort, and vomiting are all biologically plausible as adverse reactions due to lubiprostone. The mechanisms by which lubiprostone might cause peripheral edema or headache are less clear to this reviewer, but these AEs were also listed as adverse reactions in clinical trials of CIC (for subjects treated with lubiprostone at the same dose (24 mcg BID) as in the OIC clinical trials). Hepatic enzyme increased is further discussed below and in [Table 95](#) of section 7.4.2 [Laboratory Findings](#).

In the overall safety pool, upper respiratory tract infections, urinary tract infections, bronchitis, sinusitis, gastroenteritis viral, nasopharyngitis, back pain, arthralgia, depression, and insomnia were reported in a larger percentage of lubiprostone subjects than placebo subjects. It is noteworthy, however, that when these AEs are examined separately for the double-blind trials pool and the open-label long-term trial, the incidence of these AEs is comparable across treatment arms in the double-blind pool and higher in the open-label trial. All of these AEs have a fairly common background rate and this reviewer cannot propose an established mechanism by which lubiprostone might cause most of these AEs. With respect to gastroenteritis viral, because this is frequently a clinical diagnosis made without laboratory or other diagnostic testing, it is unclear to this reviewer how many of these cases of gastroenteritis may have represented a true viral infection and how many may have represented diarrhea related to study drug. Further, because it appears that these AEs were reported more frequently in the long-term trial than the double-blind trials, it is this reviewer's assessment that these AEs do not necessarily represent adverse reactions.

Less common previously reported AEs of chest pain and dyspnea (both in the current label) were also examined. In the overall safety pool, although dyspnea was more common in the treatment group (1.3%) than the placebo group (0.6%), the incidence of chest pain was comparable between the two treatment groups (0.9% in the lubiprostone arm and 1.2% in the placebo arm). The overall incidence of both these AEs was lower among lubiprostone subjects in the OIC trials than in subjects receiving lubiprostone 24 mcg BID in previous CIC trials.

The only AEs relating to laboratory findings that were more common in lubiprostone subjects than placebo subjects in the overall safety pool, as presented in [Table 89](#), were hepatic enzyme increased and elevated blood triglycerides. Of note, hepatic enzyme increased was actually more common in the placebo arm than the lubiprostone arm for the double-blind trials pool. Further, based on investigation by this reviewer, this medical officer does not attribute causality of hepatic enzyme increased to lubiprostone

(see [Table 95](#) of section [7.4.2 Laboratory Findings](#)). Blood triglyceride levels are difficult to interpret due to lack of dietary restrictions and non-fasting conditions during blood draws. Triglyceride elevations are further discussed in section [7.4.2 Laboratory Findings](#). Of note, the incidence of elevated blood triglycerides in the double-blind trials pool was comparable between the two treatment arms (1.5% in the lubiprostone arm and 1.4% in the placebo arm), while the incidence in the open-label long-term trial was >4%. In this reviewer's assessment, given the non-fasting conditions during blood draws, the more blood draws a subject had, the more likely an elevated blood triglyceride level would be detected at some point, and this might explain why the incidence of elevated blood triglycerides in the open-label trial was higher than in the double-blind trials pool.

Severe Adverse Events

Among safety evaluable subjects in the double-blind trials pool, 52 (8%) placebo subjects and 59 (9%) lubiprostone subjects experienced at least one severe AE. [Table 91](#) summarizes the incidence of severe cases of the most common AEs for the overall safety pool and [Table 92](#) presents the incidence of severe cases of the most common AEs for the double-blind trials pool and open-label trial.

Table 91. Incidence of Severe Cases of Most Common Adverse Events – Overall Safety Pool (Safety Evaluable Subjects)

System Organ Class Preferred Term¹	Placebo (N=652) n (%)	Lubiprostone (N=889) n (%)
Gastrointestinal Disorders		
Diarrhea	2 (0.3)	14 (1.6)
Abdominal pain	3 (0.5)	11 (1.2)
Nausea	7 (1.1)	9 (1.0)
Vomiting	4 (0.6)	5 (0.6)
Flatulence	1 (0.2)	3 (0.3)
Abdominal distension	4 (0.6)	1 (0.1)
Abdominal discomfort	0	0
General Disorders and Administration Site Conditions		
Edema peripheral	0	1 (0.1)
Chest pain	2 (0.3)	1 (0.1)
Infections and Infestations		
Upper respiratory tract infection	0	2 (0.2)
Urinary tract infection	0	1 (0.1)
Bronchitis	0	2 (0.2)
Sinusitis	0	0
Gastroenteritis viral	2 (0.3)	2 (0.2)
Nasopharyngitis	1 (0.2)	0
Investigations		
Blood triglycerides increased	0	1 (0.1)
Hepatic enzyme increased	0	2 (0.2)
Musculoskeletal and Connective Tissue Disorders		
Back pain	3 (0.5)	10 (1.1)
Arthralgia	0	2 (0.2)
Nervous System Disorders		
Headache	0	2 (0.2)
Psychiatric Disorders		
Depression	1 (0.2)	4 (0.4)
Insomnia	0	1 (0.1)
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	0	2 (0.2)
Skin and Subcutaneous Tissue Disorders		
Rash	1 (0.2)	0

Note: The overall safety pool includes trials OBD-1033, OBD-0631, OBD-0632, and OBD-06S1.

¹SOCs and PTs are listed in descending order of frequency based on the lubiprostone group in the overall safety pool (Table 89). Subjects who experienced the same event more than once were counted only once for that event.

Source: Reviewer's table, generated from adverse events dataset, module 5.3.5.3, Integrated Summary of Safety.

Table 92. Incidence of Severe Cases of Most Common Adverse Events – Double-blind Trials Pool and Open-label Trial (Safety Evaluable Subjects)

System Organ Class Preferred Term ¹	Double-blind Trials		Open-label Trial	
	Placebo (N=652) n (%)	LBP (N=663) n (%)	Placebo-LBP (N=225) n (%)	LBP-LBP (N=214) n (%)
Gastrointestinal Disorders				
Nausea	7 (1.1)	7 (1.1)	1 (0.4)	1 (0.5)
Diarrhea	2 (0.3)	12 (1.8)	2 (0.9)	0
Vomiting	4 (0.6)	2 (0.3)	2 (0.9)	1 (0.5)
Abdominal pain	5 (0.8)	6 (0.9)	4 (1.8)	1 (0.5)
Flatulence	1 (0.2)	2 (0.3)	1 (0.4)	0
Abdominal distension	4 (0.6)	0	0	1 (0.5)
Abdominal discomfort	0	0	0	0
General Disorders and Administration Site Conditions				
Edema peripheral	0	0	0	1 (0.5)
Chest pain	2 (0.3)	1 (0.2)	0	0
Infections and Infestations				
Upper respiratory tract infection	0	1 (0.2)	1 (0.4)	0
Urinary tract infection	0	0	0	0
Bronchitis	0	0	2 (0.9)	0
Sinusitis	0	0	0	0
Gastroenteritis viral	2 (0.3)	1 (0.2)	0	1 (0.5)
Nasopharyngitis	1 (0.2)	0	0	0
Investigations				
Blood triglycerides increased	0	0	1 (0.4)	0
Hepatic enzyme increased	0	0	1 (0.4)	1 (0.5)
Musculoskeletal and Connective Tissue Disorders				
Back pain	3 (0.5)	5 (0.8)	1 (0.4)	4 (1.9)
Arthralgia	0	2 (0.3)	0	0
Nervous System Disorders				
Headache	0	0	1 (0.4)	1 (0.5)
Psychiatric Disorders				
Depression	1 (0.2)	2 (0.3)	2 (0.9)	0
Insomnia	0	0	1 (0.4)	0
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea	0	0	2 (0.9)	0
Skin and Subcutaneous Tissue Disorders				
Rash	1 (0.2)	0	0	0

Abbreviations: LBP, lubiprostone. Note: The double-blind trials pool includes trials OBD-1033, OBD-0631, and OBD-0632.

¹SOCs and PTs are listed in descending order of frequency based on the lubiprostone group in the overall safety pool (Table 89).

Subjects who experienced the same event more than once were counted only once for that event.

Source: Reviewer's table, generated from adverse events dataset, module 5.3.5.3, Integrated Summary of Safety.

Reviewer comments: *In the overall safety and double-blind trials pool, severe cases of diarrhea and abdominal pain were more common in the lubiprostone arm than the placebo arm. These findings are in keeping with the established AE profile of lubiprostone.*

7.4.2 Laboratory Findings

In the three double-blind trials, laboratory tests were obtained at screening; at baseline; at the end of weeks 4, 8 and 12; and at the 2-week follow-up visit (Week 14). In OBD-06S1, laboratories were obtained at screening; at the end of weeks 6, 12, 18, 24, 30, and 36; and at the 2-week follow-up visit (Week 38). Laboratory reference ranges are summarized in [Table 152](#) of [Appendix 8: Laboratory Reference Ranges](#).

Hematology

Hematology parameters included: White blood cell (WBC) count, lymphocytes (%), neutrophils (%), monocytes (%), eosinophils (%), basophils (%), absolute lymphocytes, absolute neutrophils, absolute monocytes, absolute basophils, absolute eosinophils, hemoglobin, hematocrit, RBC count, platelet count, mean corpuscular volume, mean corpuscular hemoglobin concentration, and mean corpuscular hemoglobin. [Table 93](#) shows shifts in key values (hematocrit, hemoglobin, platelet count, and WBC count).

Table 93. Shift Table of Key Hematology Lab Values – Double-blind Pool and Open-label Trial

Serum Laboratory Parameter	Double-blind Trials Pool				Open-label Trial			
	Normal-to-Low		Normal-to-High		Normal-to-Low		Normal-to-High	
	Placebo (N=652) n/d (%)	LBP (N=663) n/d (%)	Placebo (N=652) n/d (%)	LBP (N=663) n/d (%)	Placebo-LBP (N=225) n/d (%)	LBP-LBP (N=214) n/d (%)	Placebo-LBP (N=225) n/d (%)	LBP-LBP (N=214) n/d (%)
Hemoglobin	30/503 (6.0)	34 (534 (6.4)	7/503 (1.4)	7/534 (1.3)	14/180 (7.8)	10/181 (5.5)	5/180 (2.8)	2/181 (1.1)
Hematocrit	35/501 (7.0)	26/522 (5.0)	21 /501 (4.2)	16/522 (3.1)	13/178 (7.3)	11/173 (6.4)	7/178 (3.9)	10/173 (5.8)
Platelet Count	4/553 (0.7)	5/574 (0.9)	6/553 (1.1)	10/574 (1.7)	5/201 (2.5)	2/192 (1.0)	4/201 (2.0)	8/192 (4.2)
WBC Count	25/522 (4.8)	25/528 (4.7)	20/522 (3.8)	18/528 (3.4)	8/195 (4.1)	5/176 (2.8)	16/195 (8.2)	12/176 (6.8)

Abbreviations: LBP, lubiprostone; WBC, white blood cell.

Note 1: Normal-to-low and normal-to high shifts are from baseline to last assessment (last non-missing post-baseline assessment).

Note 2: Percentages are calculated as n/d, where n is the number of subjects with the respective pattern, and d is the number of subjects with respective baseline category who are present at the particular visit.

Source: Reviewer's table created from Sponsor's Table 2.2.12.2.1, pages 2591-2319; Table 2.2.11.2.1 and Table 2.2.11.2.2, pages 2614-2637; module 5.3.5.3, Integrated Summary of Safety.

Reviewer comments: The shifts in clinically important hematology parameters discussed above are acceptable and demonstrate no safety signals. For the double-blind trials pool, shifts from normal to low or high were comparable between placebo and lubiprostone subjects. The findings from these trials are in line with the established safety profile of lubiprostone, which has not demonstrated clinically important potential effects on hematologic parameters.

Serum Chemistry

Biochemistry parameters included total cholesterol, triglycerides, glucose, total protein, albumin, alkaline phosphatase, aspartate aminotransaminase, alanine aminotransaminase, gamma-glutamyl transferase, iron, lactate dehydrogenase, total bilirubin, direct bilirubin, blood urea nitrogen, uric acid, creatinine, sodium, potassium, chloride, bicarbonate, calcium, phosphorus, and magnesium. [Table 94](#) summarizes shifts in electrolytes, liver tests, and other laboratory tests, with results presented for both the pooled double-blind trials and the open-label long-term trial.

Table 94. Shift Table of Serum Chemistry Lab Values – Double-blind Pool and Open-label Trial (Safety Evaluable Subjects)

Serum Laboratory Parameter	Double-blind Trials (OBD-0631, OBD-0632, OBD-1033)				Open-label Trial			
	Normal-to-Low		Normal-to-High		Normal-to-Low		Normal-to-High	
	Placebo (N=652) n/d (%)	LBP (N=663) n/d (%)	Placebo (N=652) n/d (%)	LBP (N=663) n/d (%)	Placebo-LBP (N=225) n/d (%)	LBP-LBP (N=214) n/d (%)	Placebo-LBP (N=225) n/d (%)	LBP-LBP (N=214) n/d (%)
Electrolytes								
Sodium	12/575 (2.1)	20/583 (3.4)	0	0	1/213 (0.5)	10/197 (5.1)	0	1/197 (0.5)
Potassium	18/579 (3.1)	20/588 (3.4)	6/579 (1.0)	2/588 (0.3)	10/213 (4.7)	3/200 (1.5)	2/213 (0.9)	2/200 (1.0)
Chloride	15/574 (2.6)	10/585 (1.7)	3/574 (0.5)	3/585 (0.5)	3/208 (1.4)	5/195 (2.6)	1/208 (0.5)	1/195 (0.5)
Bicarbonate	20/579 (3.5)	15/581 (2.6)	7/579 (1.2)	3/581 (0.5)	9/208 (4.3)	5/190 (2.6)	1/208 (0.5)	2/190 (1.1)
BUN	3/578 (0.5)	3/591 (0.5)	10/578 (1.7)	3/591 (0.5)	2/215 (0.9)	1/201 (0.5)	4/215 (1.9)	3/201 (1.5)
Creatinine	13/546 (2.4)	14/552 (2.5)	9/546 (1.6)	6/552 (1.1)	0	0	1/216 (0.5)	2/202 (1.0)
Glucose	7/374 (1.9)	5/383 (1.3)	118/374 (31.6)	129/383 (33.7)	2/129 (1.6)	3/133 (2.3)	37/129 (28.7)	50/133 (37.6)
Calcium	2/582 (0.3)	1/592 (0.2)	8/582 (1.4)	7/592 (1.2)	2/214 (0.9)	1/201 (0.5)	3/214 (1.4)	3/201 (1.5)
Magnesium	1/587 (0.2)	1/602 (0.2)	4/587 (0.7)	4/601 (0.7)	0	1/204 (0.5)	0	0
Phosphorus	14/536 (2.6)	7/560 (1.3)	46/536 (8.6)	30/560 (5.4)	2/197 (1.0)	5/194 (2.6)	12/197 (6.1)	10/194 (5.2)
Liver Tests								
AST	0	0	21/557 (3.8)	18/554 (3.2)	0	0	10/205 (4.9)	9/184 (4.9)
ALT	0	0	19/551 (3.4)	20/559 (3.6)	0	0	8/201 (4.0)	5/183 (2.7)
Alkaline Phosphatase	1/582 (0.2)	0	1/582 (0.2)	9/598 (1.5)	0	0	2/212 (0.9)	3/201 (1.5)
Bilirubin, Total	0	0	1/594 (0.2)	3/603 (0.5)	0	0	1/217 (0.5)	0
Bilirubin, Direct	0	0	16/566 (2.8)	13/578 (2.2)	0	0	3/201 (1.5)	4/191 (2.1)
Albumin	4/590 (0.7)	2/600 (0.3)	7/590 (1.2)	1/600 (0.2)	5.217 (2.3)	3/202 (1.5)	0	1/202 (0.5)
Total Protein	4/590 (0.7)	2/601 (0.3)	1/590 (0.2)	2/601 (0.3)	3/217 (1.4)	1/201 (0.5)	1/217 (0.5)	1/201 (0.5)
GGT	0	0	23/525 (4.4)	18/507 (3.6)	0	0	12/191 (6.3)	7/172 (4.1)
Other								
Total cholesterol	2/337 (0.6)	2/326 (0.6)	50/337 (14.8)	62/326 (19.0)	1/120 (0.8)	0	19/120 (15.8)	15/112 (13.4)
Triglycerides	0	0	80/311 (25.7)	71/304 (23.4)	0	0	24/105 (22.9)	23/98 (23.5)
Iron	18/546 (3.3)	23/561 (4.1)	16/546 (2.9)	17/561 (3.0)	17/194 (8.8)	11/194 (5.7)	7/194 (3.6)	4/194 (2.1)
LDH	1/575 (0.2)	1/584 (0.2)	24/575 (4.2)	15/584 (2.6)	0	0	10/207 (4.8)	2/192 (1.0)
Uric acid	0	0	21/557 (3.8)	14/563 (2.5)	1/206 (0.5)	0	5/206 (2.4)	9/187 (4.8)

Abbreviations: LBP, lubiprostone

Note: Normal-to-low and normal-to high shifts are from baseline value to last assessment (last non-missing post-baseline assessment).

Source: Reviewer's table created from Sponsor's Table Module 5.3.5.3, 2.2.12.2.1, pages 2591-2613 and Table 2.2.12.2.2, pages 2614-2637, Integrated Summary of Safety.

Reviewer comments: *The shifts in serum chemistry parameters discussed above are acceptable and demonstrate no safety signals. For the double-blind trials pool, shifts from normal to low or high were comparable between placebo and lubiprostone subjects. There does appear to be a large percentage of subjects whose serum glucose shifted from normal to high, but the results are balanced across both treatment arms in the double-blind trials pool. Serum cholesterol shifted from normal to high in a larger percentage of lubiprostone subjects (19%) than placebo subjects (15%), but interpretation is limited because there were no dietary restrictions on subjects during the trials and no requirements for fasting conditions during blood draws. The findings from these trials are in line with the established safety profile of lubiprostone, which has not previously shown clinically important potential effects on serum chemistry parameters.*

Hepatic Enzymes

For completeness, this reviewer analyzed the provided laboratory datasets and found no lubiprostone subjects in the double-blind trials or open-label trial who represented possible Hy's Law cases. More specifically, there were no lubiprostone subjects in the double-blind trials or open-label long-term trial who had 3-fold or greater elevations above the upper limit of normal (ULN) of AST or ALT *and* one or more elevations of total bilirubin to levels greater than twice the ULN.

Given the occurrence of one non-fatal SAE of hepatic enzyme increased in a lubiprostone subject (1033-3098-003), this reviewer examined the laboratory datasets for trends in ALT among subjects with elevations of ALT ≥ 3 times the ULN at any time point during the double-blind or open-label trials. ALT was chosen over other hepatic enzymes for further examination because ALT has become the leading biomarker for acute liver injury or inflammation.⁷ The cutoff of ALT ≥ 3 times ULN was selected based on the recommendations of the FDA Guidance on drug-induced liver injury.⁸

Review of the lab database revealed 18 unique subjects exposed to lubiprostone who had an ALT value ≥ 3 times the ULN at one or more laboratory evaluation time point. The Sponsor defined the ULN for ALT as 40 IU/L for females and 55 IU/L for males. As a more conservative threshold, this medical officer set 40 IU/L as the ULN for all subjects, regardless of gender. Of these 18 subjects, 5 were in OBD-1033, 7 were in OBD-0631 (of whom 5 subjects continued on to OBD-06S1), and 6 were in OBD-0632 (of whom 4 subjects continued on to OBD-06S1). This reviewer examined the trends in ALT over time for each of these subjects. Of the 18 subjects with ALT ≥ 120 IU/L at any time point in trials OBD-1033, OBD-0631, OBD-0632, or OBD-06S1, 5 subjects were further assessed based on a trend of rising ALT without clear resolution, or in the case of one subject, based on marked rise in ALT (into the 700+ IU/L range). The ALT trends for these five subjects are summarized in [Table 95](#).

⁷ Senior JR. Alanine aminotransferase: a clinical and regulatory tool for detecting liver injury-past, present, and future. *Clin Pharmacol Ther.* 2012;92(3):332-339.

⁸ FDA guidance for industry, 2009, Drug-induced Liver Injury – Premarketing Clinical Evaluation. Available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>.

Table 95. Trends in Serum ALT Level in Lubiprostone Subjects with ALT Greater than or Equal to 120 IU/L at Any Laboratory Time Point in Double-blind and Open-label Trials

Subject ID	Double-blind Phase						Open-label Phase							
	Screening	Visit 4	Visit 6	EOT	F/u	F/u*	Visit 10	Visit 12	Visit 14	Visit 16	Visit 18	Visit 20	EOT	F/u
1033-3087-007	23	15	16	28	150									
1033-3098-003	11	13	19	730	658	32								
0631-1072-018	90	240		208	186									
06S1-1069-022	84	75	42	99				103	114	120	166	159	188	185
06S1-1069-025	25	26	28	29			25	26	26	24	25	70	131	190

Abbreviations: ALT, alanine aminotransferase; EOT, end-of-treatment; F/u, follow-up.

Note 1: Serum ALT levels are in IU/L. Reference range for serum ALT is 0 IU/L to 40 IU/L.

Note 2: Double-blind timeline: Screening=Day -24 to -21, Visit 4=Day 28±3, Visit 6=Day 56±3, EOT=Day 84±3, F/u= Day 98±3.

Note 3: Open-label timeline: Visit 10=Day 1, Visit 12=Day 42±3, Visit 14=Day 84±3, Visit 16=Day 126±3, Visit 18=Day 168±3, Visit 20=Day 210±3, EOT=Day 252±3, F/u=Day 266±3.

*This F/u value was an unscheduled follow-up that occurred on Day 149, after the final follow-up visit scheduled in the double-blind phase (which occurred on Day 101).

Source: Reviewer's table, generated from ADAE labs dataset, module 5.3.5.3, Integrated Summary of Safety.

The increased ALT in subject 1033-3098-003 was part of an SAE (hepatic enzyme increased) and was previously discussed in section 7.3.2 [Nonfatal Serious Adverse Events](#). Although this subject's AST and alkaline phosphatase rose concurrently with the ALT (AST trend: 18 IU/L at Visit 6, 387 IU/L at end-of-treatment visit, 332 IU/L at follow up visit, 23 IU/L at unscheduled follow up visit; alkaline phosphatase trend: 72 IU/L at Visit 6, 205 IU/L at end-of-treatment visit, 281 IU/L at follow up visit, 97 IU/L at unscheduled follow up visit), total bilirubin did not exceed the upper limit of normal at any time point. Subject 0631-1072-018 had an SAE of toxic induced encephalopathy, and this subject was also discussed in section 7.3.2 [Nonfatal Serious Adverse Events](#). Subject 06S1-1069-022 had a baseline history of hepatitis C and had elevated ALT at screening. For the remaining two subjects, the Sponsor was asked to provide patient narratives and case report forms.

Reviewer comments: *This medical officer reviewed the additional requested data and has the following comments:*

- *Subject 1033-3087-007: 61-year-old male with diabetes whose GGT level was elevated to 299 IU/L (ULN is 65 IU/L) at screening visit and remained elevated at all laboratory time points. AST was normal at each time point, except for the follow up visit, when AST was 98 IU/L (ULN is 40 IU/L) and GGT had risen to 489 IU/L. Alkaline phosphatase and total bilirubin were within normal range at each time point. The subject completed the full 12 weeks of treatment. No clear reason for elevation of GGT at baseline and throughout the trial could be delineated, nor was there a clear explanation for the elevated AST/ALT at the follow up visit. In the setting of baseline and sustained GGT elevation, however, this reviewer does not attribute the elevated ALT to lubiprostone. The subject may have had underlying liver disease.*

- *Subject 06S1-1069-025: 61-year-old male with high cholesterol on simvastatin (begun ~1 year before starting trial) who completed the 12-week efficacy trial with normal ALT, AST, GGT, and alkaline phosphatase at each time point. During the open-label trial, AST rose concurrently with ALT (48 IU/L at Visit 20, 85 IU/L at end-of-treatment visit, and 109 IU/L at f/u visit) and GGT (96 IU/L at Visit 20, 165 IU/L at end-of-treatment visit, and 236 IU/L at f/u visit). The subject completed the open-label trial. Alkaline phosphatase and total bilirubin were within normal range at each time point. No clear reason for the rise in AST, ALT, and GGT exists, but based on the lack of expected temporal correlation between the rise in liver enzymes (first elevations occurred >10 months after first exposure to study drug) and possible alternative causes of liver enzyme elevation (e.g., statin), this reviewer cannot relate the abnormal liver enzymes to lubiprostone.*

Lastly, this reviewer examined the incidence of abnormal liver tests in the overall safety pool. The preferred terms “alanine aminotransferase increased,” “aspartate aminotransferase increased,” “blood alkaline phosphatase increased,” “blood bilirubin increased,” “gamma-glutamyl transferase increased,” “hepatic enzyme increased,” and “liver function test abnormal” were selected and incidences are summarized in [Table 96](#).

Table 96. Incidence of Adverse Events Relating to Liver Tests – Overall Safety Pool

Preferred Term	Placebo (N=652) n (%)	Lubiprostone (N=889) n (%)
Alanine aminotransferase increased	14 (2.1)	13 (1.5)
Aspartate aminotransferase increased	10 (1.5)	13 (1.5)
Blood alkaline phosphatase increased	2 (0.3)	6 (0.7)
Blood bilirubin increased	0	2 (0.2)
Gamma-glutamyl transferase increased	14 (2.1)	17 (1.9)
Hepatic enzyme increased	2 (0.3)	5 (0.6)
Liver function test abnormal	1 (0.2)	3 (0.3)

Note 1: The overall safety pool includes trials OBD-1033, OBD-0631, OBD-0632, and OBD-06S1.

Note 2: For this table, in order to separately list all AEs relating to liver tests, this reviewer did not recode “alanine aminotransferase increased” or “aspartate aminotransferase increased” as “hepatic enzyme increased.”

Source: Reviewer’s table generated from ADAE laboratory datasets, module 5.3.5.3, Integrated Summary of Safety.

Reviewer comments: *Although not all of the above AEs necessarily correlate with liver injury (e.g., blood alkaline phosphatase may be elevated due to bone disease), the incidence of these laboratory abnormalities typically is balanced across the treatment arms in the overall safety pool. Further, as mentioned previously, no lubiprostone subjects in the four OIC trials represented possible Hy’s Law cases. Given the totality of the data, this medical officer finds no safety signal for lubiprostone with respect to liver injury. This finding is concordant with previous reviews for the CIC and IBS-C indication and with postmarket information.*

Potassium

Because lubiprostone is an activator of intestinal chloride channels and is associated with AEs of diarrhea and vomiting, both of which can deplete serum potassium, this

reviewer further examined potassium trends across the two treatment arms. Review of the AE dataset for the overall safety pool demonstrated a slightly higher incidence among lubiprostone subjects than placebo subjects of “blood potassium decreased” (0.6% and 0.8%, respectively) and “hypokalemia” (0.2% and 0.3%, respectively). The Sponsor defined low potassium as a level <3.5 mmol/L, but specific focus by this clinical reviewer was placed on subjects whose serum potassium was <3.0 mmol/L at any laboratory evaluation time point. Symptoms of low potassium generally do not become manifest until the serum potassium is <3.0 mmol/L (severe hypokalemia), unless the serum potassium falls rapidly or the patient has a potentiating factor, such as a predisposition to arrhythmia due to the use of digitalis.⁹ Potassium supplementation should be given at serum levels <3.0 mmol/L because of the increased risk of arrhythmias below this level. From the four clinical trials submitted for this sNDA, there were six subjects whose potassium level was <3.0 mmol/L during at least one time point while exposed to lubiprostone. The potassium trends of these subjects are summarized in Table 97, with the potassium levels <3.0 mmol/L underlined.

Table 97. Trends in Serum Potassium Level in Subjects with Potassium Less than 3.0 mmol/L While Exposed to Lubiprostone in Double-blind and Open-label Trials

Subject ID	Double-blind Phase					Open-label Phase						
	Screening	Visit 4	Visit 6	EOT	F/u	Visit 12	Visit 14	Visit 16	Visit 18	Visit 20	EOT	F/u
1033-3039-003	4.4	4.3	<u>2.7</u>	3.6	4.6							
0631-1018-013 ^a	3.2	3.2	3.3	3.1		<u>2.9</u>	3.8	3.4	3.8	3.6	3.8	3.6
0631-1018-032	3.4	<u>2.9</u>	3.1	3.4	3.3							
0631-1033-003	3.3	<u>2.9</u>										
0632-2059-008	3.7	<u>2.9</u>	3.2	3.7								
0632-2098-019	3.7	3.0	3.7	3.2		<u>2.9</u>	3.4	3.7	3.4	3.4	3.7	3.9

Abbreviations: EOT, end-of-treatment; F/u, follow-up.

Note 1: Serum potassium levels are in mmol/L. Reference range for serum potassium is 3.5 mmol/L to 5 mmol/L.

Note 2: Double-blind timeline: Screening=Day -24 to -21, Visit 4=Day 28±3, Visit 6=Day 56±3, EOT=Day 84±3, F/u= Day 98±3.

Note 3: Open-label timeline: Visit 12=Day 42±3, Visit 14=Day 84±3, Visit 16=Day 126±3, Visit 18=Day 168±3, Visit 20=Day 210±3, EOT=Day 252±3, F/u=Day 266±3.

^aSubject was in the placebo arm during the double-blind phase.

Source: Reviewer’s table, generated from ADAE laboratory dataset, module 5.3.5.3, Integrated Summary of Safety.

All subjects demonstrated improvement of the low potassium from <3.0 mmol/L to the normal range (3.5 to 5 mmol/L) at a subsequent assessment with the exception of two subjects: (1) subject 0631-1018-032, but this subject had a low potassium at baseline screening (3.4 mmol/L); and (2) subject 0631-1033-003, but this subject also had a low potassium at baseline screening (3.3 mmol/L) and did not follow up for any more laboratory evaluations after Visit 4 (at which time potassium was 2.9 mmol/L). Of note, subject 1033-3039-003 also had an AE of vomiting and subject 0632-2098-019 had two separate AEs of gastroenteritis viral. Although these are AEs which might be expected to lower blood potassium, these AEs were not temporally correlated with the visit dates on which the low blood potassium was measured for either subject.

⁹ Paltiel O, Salakhov E, Ronen I, Berg D, Israeli A. Management of severe hypokalemia in hospitalized patients: a study of quality of care based on computerized databases. *Arch Intern Med.* 2001;161(8):1089-1095.

Reviewer comments: *The correction of the low potassium to within normal levels for four of the subjects, and return to the baseline low level in the case of a fifth subject, are reassuring to this medical officer. Furthermore, for comparison, there were nine subjects in the overall safety pool who had a potassium level <3.0 mmol/L during at least one laboratory visit beyond screening while on placebo, as compared with six subjects in the overall safety pool who had a potassium level <3.0 mmol/L during at least one laboratory visit beyond screening while on lubiprostone. The low potassium levels in lubiprostone-exposed subjects all occurred between Visit 4 and Visit 12 (for subjects who continued into the open-label trial), but the number of subjects with potassium values <3.0 mmol/L at any time point is too low to allow any definitive conclusions about a possible temporal relation between study drug and decrease in serum potassium.*

Triglycerides

Because blood triglyceride elevations were reported more often in lubiprostone subjects than placebo subjects, this reviewer further examined trends in triglyceride levels. In the double-blind trials, there were a total of 52 lubiprostone subjects and 48 placebo subjects with normal triglyceride levels (<150 mg/dL) at the screening visit who had a subsequent triglyceride level >200 mg/dL. None of the 52 lubiprostone subjects had triglyceride elevations at any time point that would meet criteria for severe hypertriglyceridemia (defined as triglyceride levels >500 mg/dL). In the open-label trial, there were 47 subjects with normal triglyceride levels (<150 mg/dL) at the screening visit who had a subsequent triglyceride level >200 mg/dL. One of these 47 subjects had a triglyceride elevation at one time point that would meet criteria for severe hypertriglyceridemia. The subject's triglyceride level was recorded as 1326 mg/dL at Visit 14, but this reviewer suspects this value was incorrectly recorded in the lab dataset because the level at the following visit (Visit 16) was 227 mg/dL and all of the other 6 documented triglyceride levels were in the range of 135 mg/dL to 227 mg/dL.

Reviewer comments: *Triglyceride levels are difficult to interpret due to lack of dietary restrictions and non-fasting conditions during blood draws. This reviewer notes that in prior NDA submissions of lubiprostone for CIC and IBS-C, triglyceride, blood glucose and total cholesterol levels shifted from normal to high in >5% of trial subjects. All of these parameters are affected by diet and fasting conditions at the time of blood draws.*

Urinalysis

Urinalysis parameters included: Specific gravity and urine pH.

Double-blind Trials Group

There was no shift from normal to low for **pH** in placebo or lubiprostone subjects and a shift from normal to high in 0.7% of placebo subjects vs. 0.5% of lubiprostone subjects.

There was a shift from normal to low for **specific gravity** in 4.4% of placebo subjects vs. 4.6% of lubiprostone subjects and a shift from normal to high in 20.4% of placebo subjects vs. 17.1% of lubiprostone subjects.

Open-label Trial Group

There was no shift from normal to low for **pH** in placebo-lubiprostone or lubiprostone-lubiprostone subjects and a shift from normal to high in 0.9% of placebo-lubiprostone subjects vs. 0% of lubiprostone-lubiprostone subjects.

There was a shift from normal to low for **specific gravity** in 7.7% of placebo-lubiprostone subjects vs. 5% of lubiprostone-lubiprostone subjects and a shift from normal to high in 18.9% of placebo-lubiprostone subjects vs. 18.0% of lubiprostone-lubiprostone subjects.

Reviewer comments: *The shifts in urinalysis parameters discussed above are acceptable and demonstrate no safety signals.*

7.4.3 Vital Signs

Double-blind Trials Group

In OBD-1033, OBD-0631, and OBD-0632, blood pressure and, heart rate, respiration rate, oral temperature, and weight were measured at screening; at baseline; at the end of weeks 4, 8, and 12; and at the 2-week post-treatment follow-up visit (Week 14). Vital sign data were not pooled for the three double-blind trials. Analysis of variance (ANOVA) was used to compare changes from baseline across treatment arms.

OBD-1033

Changes from baseline in vital signs were small between treatment groups. The difference in mean change from baseline in weight, with the placebo group losing weight (mean change, -0.57 kg) and the lubiprostone group gaining weight (mean change, 0.20 kg) was noted by the Sponsor as being “statistically significant.”

OBD-0631

The Sponsor noted a “statistically significant” difference across the groups in the mean change from baseline in heart rate at the Week 14 visit (-1.7 beats/minute for placebo vs. 1.0 beat/minute for lubiprostone). In the placebo group, mean respiration rate decreased slightly whereas it increased in the lubiprostone group. However, the mean respiration rate did not exceed 17 breaths per minute in either group at any of the measured time points.

OBD-0632

The Sponsor reported a “statistically significant” difference across the groups in the mean change from baseline in diastolic blood pressure at the last value time point (0.9 mmHg for placebo vs. -1.1 mmHg for lubiprostone). There were no other notable trends in vital signs data over time.

Reviewer comments: *None of the double-blind trials was a safety trial and was thus not powered nor designed to test safety-related hypotheses. As such, the term “statistically significant” should be avoided. Regarding findings in OBD-0631, this clinical reviewer cannot conclude that an increase in heart rate of 1 beat per minute (lubiprostone) is*

clinically significant. Of note, these changes in heart rate were noted at the final follow-up visit (2 weeks after last exposure to study drug), which would not clinically corroborate with concerns about vital sign changes relating to effects of study drug. Similarly, this medical officer does not find the differences across treatment groups in change from baseline diastolic blood pressure in OBD-0632 to be clinically relevant. Comparison of vital sign parameters in the double-blind trials pool demonstrated no clinically important effects on systolic or diastolic blood pressure, heart rate, or respiratory rate.

Open-label Trial Group

In OBD-06S1, the same vital signs were measured at screening; at the end of weeks 6, 12, 18, 24, 30, and 36; and at the 2-week post-treatment follow-up visit (Week 38). There was minimal difference observed between the two enrollment groups throughout the 36 weeks of treatment period for any vital signs measure with no consistent trends.

Reviewer comments: *The totality of findings in subjects enrolled in the double-blind and open-label trials does not raise concerns about adverse effects of lubiprostone on vital signs (BP, heart rate, respiration rate, temperature, and weight) in the adult population.*

7.4.4 Electrocardiograms (ECGs)

The Sponsor has previously performed phase 1 and phase 2 trials to evaluate the effects of lubiprostone on ECG parameters with the initial NDA approval. The Sponsor performed 12-lead ECGs in three of the four trials discussed in this review as follows:

In OBD-0631 and OBD-0632, ECG was obtained at screening, end of Week 12, and at 2-week post-treatment follow-up visit. In OBD-06S1, ECG was performed at screening and at the end of weeks 18 and 36. Shift tables of ECG results were presented by the Sponsor, along with ECG results for all enrolled subjects. ECG findings were categorized as:

- Normal
- Abnormal / not clinically significant (NCS)
- Abnormal / clinically significant

ECG findings for subjects with ECG shift from normal or abnormal / NCS to abnormal / clinically significant are summarized in [Table 98](#) for the double-blind trials pool and in [Table 99](#) for the open-label long-term trial.

Table 98. Subjects with ECG Shifts to Abnormal / Clinically Significant in Double-blind Trials Pool

Trial ID/ Subject ID	Treatment Arm	Description of ECG changes
OBD-0631		
1024004	Lubiprostone	ECG at screening abnormal but NCS: Incomplete RBBB and anterior fascicular block; ECG at Visit 8: Incomplete RBBB and LAFB, T wave abnormality ; No further ECGs performed and subject did not continue into trial OBD-06S1
1040011	Lubiprostone	ECG at screening normal; ECG at Visit 8: Anterior ischemia
1072006	Placebo	ECG at screening abnormal but NCS: Bradycardia; ECG at Visit 8: Changes since ECG of 3/7/2008 suggestive of acute ischemia ; ECG at Visit 10: abnormal but NCS; ECG done at Visit 16: normal
OBD-0632		
2011001	Lubiprostone	ECG at screening abnormal but NCS: Normal P axis, PR, rate & rhythm, leftward axis QRS axis -15 to -30, early transition, QRS positive in V2; ECG at Visit 8: NSR rate 83, QT interval long for rate QT_c >470 ms, nonspecific T abnormalities ; ECG at Visit 10: abnormal but NCS

Abbreviations: ECG, electrocardiogram; LAFB, left anterior fascicular block; NCS, not clinically significant; NSR, normal sinus rhythm; RBBB, right bundle branch block

Source: Reviewer's table, with data obtained from module 5.3.5.1, OBD-0631 CSR, listing 16.2.9, pages 1382-1456, and module 5.3.5.1 OBD-0632 CSR, listing 16.2.9, pages 1351-1427.

Reviewer Comments: *The Sponsor's report of a finding of "anterior ischemia" on the ECG of subject 1040011 at Visit 8 (end-of-treatment visit) prompted this reviewer to request additional information for this subject. Review of the CRF for subject 1040011 revealed that she was a 58-year-old Asian female with a history of hypertension taking hydrocodone/acetaminophen for chronic pain who was in the lubiprostone arm of OBD-0631 and whose ECG at Visit 8 (occurring on January 13, 2009) showed "anterior ischemia." Blood pressure and heart rate were unremarkable at the visit (BP 115/83, heart rate 77 bpm), cardiovascular exam was documented as normal, there was no mention of the subject having any complaints at that visit, and the subject had no documented laboratory testing of cardiac enzymes or follow up ECGs.*

At the follow up visit 2 weeks later (January 27, 2009), AEs of dyspnea beginning in December 2008 (reported as moderate severity, intermittent, and unrelated to study drug) and anterior wall ischemic changes beginning January 13, 2009 (reported as moderate severity, continuous, and unrelated to study drug) were documented. No further information was provided. Upon completion of OBD-0631, the subject did not continue into OBD-06S1. Based on the limited information provided, it is difficult to fully piece together the narrative. However, this medical officer cannot clearly correlate the subject's ECG findings with the study drug.

Table 99. Subjects with ECG Shifts to Abnormal / Clinically Significant in OBD-06S1

Subject ID	Treatment Arm	Description of ECG changes
1007009	Lubiprostone-Lubiprostone	ECG at screening and Visit 10 normal; ECG at Visit 22: Change from baseline decreased T-wave abnormalities
1074019	Lubiprostone-Lubiprostone	ECG at screening normal; ECG at Visit 10: S-T abnormality in patient with history of atrial flutter ablation procedure April 2008 ; ECG at Visit 16 and 22 reported as normal
2018019	Placebo-Lubiprostone	ECG at screening abnormal but NCS: Sinus bradycardia with occasional PACs, LAD, nonspecific S-T and T-wave abnormality; ECG at Visit 10: Marked sinus bradycardia, LAFB ; ECG at Visit 22 abnormal but NCS: Sinus bradycardia with occasional PACs. Nonspecific T-wave abnormality
2127004	Placebo-Lubiprostone	ECG at screening abnormal but NCS: Chronic changes consistent with previous cardiac history, including q wave in lead III, T-wave inversion in lead V2/V3; ECG at Visit 10: Normal; ECG at Visit 16: Subject was ended for the study due to the abnormal ECG ; ECG at Visit 22 abnormal but NCS: Right precordial repolarization disturbance, consider ischemia, large negative T in V2 with negative T in V3
2127010	Placebo-Lubiprostone	ECG at Visit 1, 10, and 16 normal; ECG at Visit 22: Mid and left precordial repolarization disturbance, consider ischemia or LV overload, large negative T in V4 with negative T in V3/V5 with small negative T in V6 ; No further ECGs performed
2130006	Placebo-Lubiprostone	ECG at Visit 1: normal; ECG at Visit 10 abnormal but NCS: atrial fibrillation; ECG at Visit 16 abnormal but NCS: sinus bradycardia; ECG at Visit 22: atrial fibrillation ; No further ECGs performed

Abbreviations: ECG, electrocardiogram; LAD, left axis deviation; LAFB, left anterior fascicular block; LV, left ventricular; NCS, not clinically significant; PAC, premature atrial contraction

Source: Reviewer's table, with data obtained from module 5.3.5.2, OBD-06S1 CSR, listing 16.2.9, pages 2382-2580.

Reviewer Comments: *Rigorous ECG data (e.g., criteria for determining potentially important values in ECG results or abnormal ECG intervals) were not provided by the Sponsor. This medical reviewer scrutinized the provided tables and datasets pertaining to ECG findings, with the intent of identifying potentially clinically significant ECG changes during the trial. Based on this evaluation, no clear cardiac safety signals emerge with lubiprostone at the 24 mcg BID dose. None of the subjects in the open-label trial (presented in [Table 99](#)) had ECG findings that, based on the assessment of this medical officer, correlated with an acute cardiovascular event. Further, this reviewer is reassured by the fact that only one of these subjects was reported by the Sponsor as having an SAE, and this subject (2127004) had underlying severe native 3-vessel coronary artery disease with history of myocardial infarction (see [Table 84](#)).*

Lubiprostone has already undergone a phase I study that evaluated cardiac safety in healthy volunteers (protocol SPI/0211SC-0411, report dated February 17, 2005). In that study, which used 24 mcg and 144 mcg doses of lubiprostone, the only notable findings were increases in heart rate compared with placebo (4 beats per minute at the 24 mcg dose and 11 beats per minute at the 144 mcg dose) and a QT_c interval change of +2 ms from baseline for lubiprostone at the 144 mcg dose. The Sponsor reported these findings were not clinically significant.

7.4.5 Special Safety Trials/Clinical Trials

No special safety trials or clinical trials were conducted.

7.4.6 Immunogenicity

Lubiprostone is not a protein. Immunogenicity trials were not performed.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Lubiprostone was administered at a fixed dose of 24 mcg BID during the three double-blind trials OBD-0631, OBD-0632, and OBD-1033. A dose reduction was permitted by the investigator if severe nausea, severe diarrhea, or another AE was reported by the subject to the site and was ongoing for 3 or more days. In these cases the investigator may have reduced study medication to once daily dosing.

In a previous trial of lubiprostone in CIC, among subjects receiving lubiprostone 24 mcg three times daily, nausea, diarrhea, headache, and abdominal pain were the most commonly reported AEs, all occurring with an incidence higher than subjects receiving lubiprostone 24 mcg BID.

7.5.2 Time Dependency for Adverse Events

The Sponsor performed an exploratory analysis of cumulative AE incidence rates, time to first AEs, and a Cox proportional hazard analysis for the occurrence of any AE and several specific AEs of interest, including nausea, diarrhea, abdominal pain, vomiting, headache, peripheral edema, dyspnea, and chest pain. A Cox regression model showed that the rate at which lubiprostone subjects experienced the first occurrence of an AE of any kind was increased relative to placebo subjects (hazard ratio=1.19). Based on the cumulative hazard rate, the likelihood of experiencing a first occurrence of an AE of any kind was greatest during the first week of treatment with lubiprostone or placebo.

With respect to specific AEs of interest, the rate at which lubiprostone subjects experienced nausea, diarrhea, abdominal pain, or peripheral edema was increased relative to placebo subjects, while the rate at which lubiprostone subjects experienced vomiting, headache, dyspnea, or chest pain was comparable to the rate at which placebo subjects experienced these AEs. Based on the cumulative hazard rate, the likelihood of experiencing a first episode of nausea, diarrhea, abdominal pain, vomiting, headache, or dyspnea was greatest during the first week of treatment, while the likelihood of experiencing a first episode of peripheral edema or chest pain was greatest during the second week of treatment.

According to the Cox regression analysis, among the AEs of interest, the only AE that was more likely to occur in females than males was peripheral edema (hazard ratio = 3.61). The rate at which subjects aged ≥ 65 years experienced nausea, diarrhea,

abdominal pain, vomiting, headache, peripheral edema, dyspnea, or chest pain was not increased relative subjects aged <65 years.

Reviewer comments: *Because time to AE analyses were exploratory and involved pooling of data across several trials, statistical significance of findings should not be claimed. Nonetheless, numerical trends are still potentially informative. The clinical significance of the higher rate of peripheral edema among females than males is unclear to this medical officer. This reviewer interprets these findings with some caution, particularly because the Cox regression analyses performed by the Sponsor to compare rates of various AEs between genders or age groups have not yielded consistent results across the three NDA submissions to-date for lubiprostone. For example, as part of the CIC and IBS-C NDAs, based on the same Cox regression analysis, the Sponsor reported higher rates of nausea in females than males, but rates of peripheral edema were not different between genders. In the present sNDA, the rate of nausea did not differ between males and females, but the rate of peripheral edema did. However, the overall incidence of peripheral edema was low and subjects may have developed peripheral edema for reasons other than study drug.*

Nausea is the most frequent AE associated with lubiprostone. In the four trials submitted as part of this sNDA, the Sponsor evaluated the impact of nausea on quality of life. The Functional Living Index-Emesis (FLIE) is a patient-reported emesis- and nausea-specific quality of life questionnaire that measures the effects of vomiting and nausea on daily life. The questionnaire comprises 18 items, 9 of which assess nausea and 9 of which assess vomiting. Each item is rated on a scale from 1 to 7 (1 = a great deal of impact on daily life to 7 = no impact on daily life), with a higher score corresponding to a higher quality of life.

The Sponsor administered a modified FLIE (containing only the nausea subscale) to subjects twice during the 14-day screening period assessing baseline status and weekly during the 12-week treatment period in the double-blind trials, and monthly during the 9-month treatment period in the open-label trial. Subjects were given up to 3 nights to record the data in their diary. The average nausea score was computed at monthly intervals for each of the trials. Results are presented in [Figure 5](#) and [Figure 6](#) of [Appendix 9: Functional Living Index-Emesis \(FLIE\) Nausea Scores](#). Overall, mean FLIE nausea scores did not worsen over the duration of the double-blind trials or open-label trial, and scores were comparable between treatment arms at each month interval in the 3-month double-blind trials and 9-month open-label trial.

Reviewer comments: *Although this medical officer is reassured by the similarity of modified FLIE scores between lubiprostone and placebo subjects for the duration of all four trials as a qualitative indicator that nausea due to lubiprostone does not worsen with time, the findings should be interpreted with caution. The FLIE is a validated PRO,*

but was developed in the setting of chemotherapy-induced nausea and vomiting and has only been validated for short-term use with a 5-day recall period.¹⁰

7.5.3 Drug-Demographic Interactions

In the following tables that present the most common AEs by demographic (age, gender, race, and baseline opioid class), the most common AEs are those that were reported in $\geq 2\%$ of lubiprostone subjects in the overall safety pool and in a larger percentage of lubiprostone subjects than placebo subjects and/or the following selected events: nausea, diarrhea, headache, vomiting, dyspnea, chest pain, abdominal pain, and peripheral edema. SOCs and PTs are listed in descending order of frequency based on the lubiprostone group in the overall safety pool (Table 89). Subjects who experienced the same event more than once were counted only once for that event. Brief comments from this reviewer are provided following each table.

Treatment-Emergent Adverse Events (TEAEs) by Age

The majority of subjects in trials OBD-0631, OBD-0632, and OBD-1033, and OBD-06S1 were <65 years old. Table 100 provides the most common AEs by age for the double-blind trials pool and open-label long-term trial.

Treatment-Emergent Adverse Events (TEAEs) by Gender

The majority of subjects in the four clinical trials were female. In the double-blind trials pool, 54% of male lubiprostone subjects experienced ≥ 1 TEAE, as compared with 59% of female lubiprostone subjects. In the open-label trial, 71% of males experienced ≥ 1 TEAE, as compared with 72% of females. Table 101 lists the most common AEs by gender for the double-blind trials pool and open-label trial.

Treatment-Emergent Adverse Events (TEAEs) by Race

The majority of subjects in the four clinical trials were white. Table 102 provides the most common AEs by race for the double-blind trials pool and open-label trial.

Treatment-Emergent Adverse Events (TEAEs) by Baseline Opioid Use

In the double-blind trials pool, the most common AE for subjects on lubiprostone, regardless of opioid subgroup, was nausea. In the double-blind trials pool, the incidence of diarrhea in lubiprostone subjects on diphenylheptane opioids (e.g., methadone) was 1%, as compared with 11% of lubiprostone subjects on non-diphenylheptane opioids. There was a higher incidence of peripheral edema in the lubiprostone subjects on diphenylheptane opioids (6%) as compared with lubiprostone subjects on non-diphenylheptane opioids (2%). The incidence of other AEs was generally comparable across opioid subgroups. Results are summarized in Table 103.

¹⁰ Martin AR, Pearson JD, Cai B, Elmer M, Horgan K, Lindley C. Assessing the impact of chemotherapy-induced nausea and vomiting on patients' daily lives: a modified version of the Functional Living Index-Emesis (FLIE) with 5-day recall. *Support Care Cancer*. 2003;11(8):522-527.

Table 100. Incidence of Most Common Adverse Events by Age – Double-blind Trials Pool and Open-label Long-Term Trial (Safety Evaluable Subjects)

System Organ Class Preferred Term ¹	Double-blind Trials Pool				Open-label Trial	
	<65 Years		≥65 Years		<65 Years	≥65 Years
	Placebo (N=583) n (%)	LBP (N=618) n (%)	Placebo (N=69) n (%)	LBP (N=45) n (%)	LBP (N=408) n (%)	LBP (N=31) n (%)
At Least One TEAE	308 (52.8)	357 (57.8)	34 (49.3)	24 (53.3)	291 (71.3)	23 (74.2)
Gastrointestinal Disorders						
Nausea	37 (6.3)	84 (13.6)	5 (7.2)	5 (11.1)	36 (8.8)	3 (9.7)
Diarrhea	24 (4.1)	60 (9.7)	1 (1.4)	3 (6.7)	37 (9.1)	5 (16.1)
Vomiting	26 (4.5)	25 (4.0)	0	1 (2.2)	21 (5.1)	0
Abdominal pain	25 (4.3)	41 (6.6)	5 (7.2)	2 (4.4)	19 (4.7)	0
Flatulence	19 (3.3)	26 (4.2)	1 (1.4)	2 (4.4)	6 (1.5)	1 (3.2)
Abdominal distension	13 (2.2)	26 (4.2)	1 (1.4)	1 (2.2)	3 (0.7)	0
Abdominal discomfort	7 (1.2)	9 (1.5)	0	2 (4.4)	14 (3.4)	1 (3.2)
General Disorders and Administration Site Conditions						
Edema peripheral	6 (1.0)	13 (2.1)	1 (1.4)	2 (4.4)	20 (4.9)	1 (3.2)
Chest pain	5 (0.9)	4 (0.6)	3 (4.3)	0	4 (1.0)	0
Infections and Infestations						
Upper respiratory tract infection	14 (2.4)	14 (2.3)	1 (1.4)	0	27 (6.6)	1 (3.2)
Urinary tract infection	11 (1.9)	15 (2.4)	2 (2.9)	1 (2.2)	12 (2.9)	3 (9.7)
Bronchitis	10 (1.7)	9 (1.5)	1 (1.4)	0	21 (5.1)	0
Sinusitis	11 (1.9)	6 (1.0)	0	0	19 (4.7)	1 (3.2)
Gastroenteritis viral	8 (1.4)	12 (1.9)	0	1 (2.2)	10 (2.5)	1 (3.2)
Nasopharyngitis	12 (2.1)	6 (1.0)	1 (1.4)	2 (4.4)	12 (2.9)	2 (6.5)
Investigations						
Blood triglycerides increased	9 (1.5)	8 (1.3)	0	2 (4.4)	19 (4.7)	0
Hepatic enzyme increased	14 (2.4)	11 (1.8)	2 (2.9)	2 (4.4)	10 (2.5)	0
Musculoskeletal and Connective Tissue Disorders						
Back pain	12 (2.1)	15 (2.4)	0	1 (2.2)	21 (5.1)	2 (6.5)
Arthralgia	9 (1.5)	12 (1.9)	3 (4.3)	1 (2.2)	10 (2.5)	3 (9.7)
Nervous System Disorders						
Headache	12 (2.1)	16 (2.6)	2 (2.9)	2 (4.4)	12 (2.9)	2 (6.5)
Psychiatric Disorders						
Depression	7 (1.2)	7 (1.1)	0	0	12 (2.9)	1 (3.2)
Insomnia	5 (0.9)	7 (1.1)	1 (1.4)	0	12 (2.9)	1 (3.2)
Respiratory, Thoracic, and Mediastinal Disorders						
Dyspnea	4 (0.7)	6 (1.0)	0	0	5 (1.2)	1 (3.2)
Skin and Subcutaneous Tissue Disorders						
Rash	5 (0.9)	11 (1.8)	0	1 (2.2)	6 (1.5)	1 (3.2)

Source: Reviewer's table, generated from adverse events dataset, module 5.3.5.3, Integrated Summary of Safety.

Reviewer comments: No single AE appears to increase with age in lubiprostone subjects but it is difficult to make conclusions regarding AE trends in the ≥65 year age group due to small numbers.

Table 101. Incidence of Most Common Adverse Events by Gender – Double-blind Trials Pool and Open-label Long-Term Trial (Safety Evaluable Subjects)

System Organ Class Preferred Term ¹	Double-blind Trials Pool				Open-label Trial	
	Male		Female		Male	Female
	Placebo (N=244) n (%)	LBP (N=247) n (%)	Placebo (N=408) n (%)	LBP (N=416) n (%)	LBP (N=176) n (%)	LBP (N=263) n (%)
At Least One TEAE	127 (52.0)	134 (54.3)	215(52.7)	247 (59.4)	124 (70.5)	190 (72.2)
Gastrointestinal Disorders						
Nausea	14 (5.7)	31 (12.6)	28 (6.9)	58 (13.9)	14 (8.0)	25 (9.5)
Diarrhea	8 (3.3)	24 (9.7)	17 (4.2)	39 (9.4)	14 (8.0)	28 (10.6)
Vomiting	7 (2.9)	11 (4.5)	19 (4.7)	15 (3.6)	11 (6.3)	10 (3.8)
Abdominal pain	10 (4.1)	15 (6.1)	20 (4.9)	28 (6.7)	10 (5.7)	9 (3.4)
Flatulence	3 (1.2)	14 (5.7)	17 (4.2)	14 (3.4)	2 (1.1)	5 (1.9)
Abdominal distension	6 (2.5)	7 (2.8)	8 (2.0)	20 (4.8)	2 (1.1)	1 (0.4)
Abdominal discomfort	5 (2.0)	3 (1.2)	2 (0.5)	8 (1.9)	5 (2.8)	10 (3.8)
General Disorders and Administration Site Conditions						
Edema peripheral	1 (0.4)	3 (1.2)	6 (1.5)	12 (2.9)	6 (3.4)	15 (5.7)
Chest pain	3 (1.2)	0	5 (1.2)	4 (1.0)	2 (1.1)	2 (0.8)
Infections and Infestations						
Upper respiratory tract infection	4 (1.6)	8 (3.2)	11 (2.7)	6 (1.4)	9 (5.1)	19 (7.2)
Urinary tract infection	0	1 (0.4)	13 (3.2)	15 (3.6)	0	15 (5.7)
Bronchitis	2 (0.8)	5 (2.0)	9 (2.2)	4 (1.0)	2 (1.1)	19 (7.2)
Sinusitis	1 (0.4)	0	10 (2.5)	6 (1.4)	3 (1.7)	17 (6.5)
Gastroenteritis viral	4 (1.6)	1 (0.4)	4 (1.0)	12 (2.9)	3 (1.7)	8 (3.0)
Nasopharyngitis	8 (3.3)	2 (0.8)	5 (1.2)	6 (1.4)	9 (5.1)	5 (1.9)
Investigations						
Blood triglycerides increased	6 (2.5)	8 (3.2)	3 (0.7)	2 (0.5)	10 (5.7)	9 (3.4)
Hepatic enzyme increased	6 (2.5)	7 (2.8)	10 (2.5)	6 (1.4)	2 (1.1)	8 (3.0)
Musculoskeletal and Connective Tissue Disorders						
Back pain	5 (2.0)	7 (2.8)	7 (1.7)	9 (2.2)	11 (6.3)	12 (4.6)
Arthralgia	5 (2.0)	5 (2.0)	7 (1.7)	8 (1.9)	6 (3.4)	7 (2.7)
Nervous System Disorders						
Headache	8 (3.3)	6 (2.4)	6 (1.5)	12 (2.9)	5 (2.8)	9 (3.4)
Psychiatric Disorders						
Depression	4 (1.6)	2 (0.8)	3 (0.7)	5 (1.2)	8 (4.5)	5 (1.9)
Insomnia	2 (0.8)	2 (0.8)	4 (1.0)	5 (1.2)	7 (4.0)	6 (2.3)
Respiratory, Thoracic, and Mediastinal Disorders						
Dyspnea	1 (0.4)	1 (0.4)	3 (0.7)	5 (1.2)	2 (1.1)	4 (1.5)
Skin and Subcutaneous Tissue Disorders						
Rash	2 (0.8)	3 (1.2)	3 (0.7)	9 (2.2)	4 (2.3)	3 (1.1)

Source: Reviewer's table, generated from adverse events dataset, module 5.3.5.3, Integrated Summary of Safety.

Reviewer comments: No AEs showed a clear gender trend in lubiprostone subjects compared with placebo subjects.

Table 102. Incidence of Most Common Adverse Events by Race – Double-blind Trials Pool and Open-label Trial (Safety Evaluable Subjects)

System Organ Class Preferred Term ¹	Double-blind Trials Pool				Open-label Trial	
	White		Non-White		White	Non-White
	Placebo (N=539) n (%)	LBP (N=545) n (%)	Placebo (N=113) n (%)	LBP (N=118) n (%)	LBP (N=367) n (%)	LBP (N=72) n (%)
At Least One TEAE	295 (54.7)	317 (58.2)	47 (41.6)	64 (54.2)	260 (70.8)	54 (75.0)
Gastrointestinal Disorders						
Nausea	39 (7.2)	76 (13.9)	3 (2.7)	13 (11.0)	36 (9.8)	3 (4.2)
Diarrhea	23 (4.3)	57 (10.5)	2 (1.8)	6 (5.1)	39 (10.6)	3 (4.2)
Vomiting	22 (4.1)	24 (4.4)	4 (3.5)	2 (1.7)	20 (5.4)	1 (1.4)
Abdominal pain	27 (5.0)	34 (6.2)	3 (2.7)	9 (7.6)	16 (4.4)	3 (4.2)
Flatulence	18 (3.3)	25 (4.6)	2 (1.8)	3 (2.5)	5 (1.4)	2 (2.8)
Abdominal distension	10 (1.9)	18 (3.3)	4 (3.5)	9 (7.6)	3 (0.8)	0
Abdominal discomfort	7 (1.3)	7 (1.3)	0	4 (3.4)	14 (3.8)	1 (1.4)
General Disorders and Administration Site Conditions						
Edema peripheral	6 (1.1)	11 (2.0)	1 (0.9)	4 (3.4)	17 (4.6)	4 (5.6)
Chest pain	5 (0.9)	3 (0.6)	3 (2.7)	1 (0.8)	4 (1.1)	0
Infections and Infestations						
Upper respiratory tract infection	14 (2.6)	12 (2.2)	1 (0.9)	2 (1.7)	22 (6.0)	6 (8.3)
Urinary tract infection	9 (1.7)	15 (2.8)	4 (3.5)	1 (0.8)	14 (3.8)	1 (1.4)
Bronchitis	10 (1.9)	5 (0.9)	1 (0.9)	4 (3.4)	14 (3.8)	7 (9.7)
Sinusitis	10 (1.9)	5 (0.9)	1 (0.9)	1 (0.8)	17 (4.6)	3 (4.2)
Gastroenteritis viral	8 (1.5)	12 (2.2)	0	1 (0.8)	10 (2.7)	1 (1.4)
Nasopharyngitis	11 (2.0)	7 (1.3)	2 (1.8)	1 (0.8)	11 (3.0)	3 (4.2)
Investigations						
Blood triglycerides increased	8 (1.5)	10 (1.8)	1 (0.9)	0	18 (4.9)	1 (1.4)
Hepatic enzyme increased	14 (2.6)	11 (2.0)	2 (1.8)	2 (1.7)	7 (1.9)	3 (4.2)
Musculoskeletal and Connective Tissue Disorders						
Back pain	11 (2.0)	12 (2.2)	1 (0.9)	4 (3.4)	15 (4.1)	8 (11.1)
Arthralgia	12 (2.2)	11 (2.0)	0	2 (1.7)	11 (3.0)	2 (2.8)
Nervous System Disorders						
Headache	14 (2.6)	17 (3.1)	0	1 (0.8)	10 (2.7)	4 (5.6)
Psychiatric Disorders						
Depression	7 (1.3)	4 (0.7)	0	3 (2.5)	11 (3.0)	2 (2.8)
Insomnia	6 (1.1)	5 (0.9)	0	2 (1.7)	11 (3.0)	2 (2.8)
Respiratory, Thoracic, and Mediastinal Disorders						
Dyspnea	2 (0.4)	5 (0.9)	2 (1.8)	1 (0.8)	5 (1.4)	1 (1.4)
Skin and Subcutaneous Tissue Disorders						
Rash	4 (0.7)	8 (1.5)	1 (0.9)	4 (3.4)	4 (1.1)	3 (4.2)

Source: Reviewer's table, generated from adverse events dataset, module 5.3.5.3, Integrated Summary of Safety.

Reviewer comments: *Although diarrhea appeared to be more common among white subjects receiving lubiprostone (11%) than non-white subjects receiving lubiprostone (5%) in the double-blind trials pool and the open-label trial (11% and 4%, respectively), it is difficult to make conclusions regarding AE trends in the non-white group due to small numbers.*

Table 103. Incidence of Most Common Adverse Events by Opioid Class (Diphenylheptane Versus Other Opioid Classes) – Double-blind Trials Pool and Open-label Trial (Safety Evaluable Subjects)

System Organ Class Preferred Term ¹	Double-blind Trials Pool				Open-label Trial	
	Diphenylheptane		Non-Diphenylheptane		Diphenylheptane	Non-Diphenylheptane
	Placebo (N=75) n (%)	LBP (N=89) n (%)	Placebo (N=577) n (%)	LBP (N=574) n (%)	LBP (N=89) n (%)	LBP (N=350) n (%)
At Least One TEAE	25 (33.3)	33 (37.1)	164 (28.4)	220 (38.3)	47 (52.8)	166 (47.4)
Gastrointestinal Disorders						
Nausea	7 (9.3)	13 (14.6)	35 (6.1)	76 (13.2)	7 (7.9)	32 (9.1)
Diarrhea	1 (1.3)	1 (1.1)	24 (4.2)	62 (10.8)	7 (7.9)	35 (10.0)
Vomiting	2 (2.7)	5 (5.6)	24 (4.2)	21 (3.7)	3 (3.4)	18 (5.1)
Abdominal pain	3 (4.0)	4 (4.5)	27 (4.7)	37 (6.4)	3 (3.4)	16 (4.6)
Flatulence	1 (1.3)	6 (6.7)	20 (3.5)	22 (3.8)	2 (2.2)	5 (1.4)
Abdominal distension	1 (1.3)	5 (5.6)	13 (2.3)	22 (3.8)	2 (2.2)	1 (0.3)
Abdominal discomfort	1 (1.3)	2 (2.2)	6 (1.0)	9 (1.6)	2 (2.2)	13 (3.7)
General Disorders and Administration Site Conditions						
Edema peripheral	1 (1.3)	5 (5.6)	6 (1.0)	10 (1.7)	5 (5.6)	16 (4.6)
Chest pain	2 (2.7)	1 (1.1)	6 (1.0)	3 (0.5)	0	4 (1.1)
Infections and Infestations						
Upper respiratory infection	1 (1.3)	3 (3.4)	14 (2.4)	11 (1.9)	8 (9.0)	20 (5.7)
Urinary tract infection	3 (4.0)	1 (1.1)	10 (1.7)	15 (2.6)	3 (3.4)	12 (3.4)
Bronchitis	1 (1.3)	0	10 (1.7)	9 (1.6)	4 (4.5)	17 (4.9)
Sinusitis	2 (2.7)	0	9 (1.6)	6 (1.0)	3 (3.4)	17 (4.9)
Gastroenteritis viral	3 (4.0)	3 (3.4)	5 (0.9)	10 (1.7)	3 (3.4)	8 (2.3)
Nasopharyngitis	0	2 (2.2)	13 (2.3)	6 (1.0)	5 (5.6)	9 (2.6)
Investigations						
Blood triglycerides increased	1 (1.3)	1 (1.1)	8 (1.4)	9 (1.6)	4 (4.5)	15 (4.3)
Hepatic enzyme increased	1 (1.3)	1 (1.1)	15 (2.6)	12 (2.1)	2 (2.2)	8 (2.3)
Musculoskeletal and Connective Tissue Disorders						
Back pain	2 (2.7)	2 (2.2)	10 (1.7)	14 (2.4)	4 (4.5)	19 (5.4)
Arthralgia	2 (2.7)	0	10 (1.7)	13 (2.3)	1 (1.1)	12 (3.4)
Nervous System Disorders						
Headache	2 (2.7)	2 (2.2)	12 (2.1)	16 (2.8)	5 (5.6)	9 (2.6)
Psychiatric Disorders						
Depression	0	1 (1.1)	7 (1.2)	6 (1.0)	2 (2.2)	11 (3.1)
Insomnia	1 (1.3)	1 (1.1)	5 (0.9)	6 (1.0)	1 (1.1)	12 (3.4)
Respiratory, Thoracic, and Mediastinal Disorders						
Dyspnea	0	1 (1.1)	4 (0.7)	5(0.9)	1 (1.1)	5 (1.4)
Skin and Subcutaneous Tissue Disorders						
Rash	0	2 (2.2)	5 (0.9)	10 (1.7)	3 (3.4)	4 (1.1)

Source: Reviewer's table, generated from adverse events dataset, module 5.3.5.3, Integrated Summary of Safety.

Reviewer comments: The Sponsor attributes the lower incidence of diarrhea among lubiprostone subjects on diphenylheptane opioids compared to placebo subjects on diphenylheptane opioids to the potential interference of this class of opioids with the

activation of CIC-2 channels by lubiprostone. Because the OIC trials submitted for this sNDA were not powered or designed to test this hypothesis, it is unclear if this difference in the incidence of diarrhea between the two treatment arms has a mechanistic explanation as proposed by the Sponsor.

Given the nonclinical findings suggesting an interaction between diphenylheptane opioids and lubiprostone, this reviewer focused on potential differences in incidence of AEs in subjects taking opioids in the diphenylheptane class versus those taking opioids from other classes (Table 103). The Sponsor did perform multiple other similar analyses comparing the incidence of common AEs by other opioid classes (e.g., phenanthrene class versus other opioid classes, phenylpiperidine class versus other opioid classes, etc.). Those results were reviewed by this medical officer, who noted no safety signals with respect to incidence of common AEs when lubiprostone was used in conjunction with one opioid class versus other classes.

7.5.4 Drug-Disease Interactions

Evaluation of these interactions was not planned or performed.

7.5.5 Drug-Drug Interactions

A nonclinical study of the effects of opioids in the diphenylheptane class (e.g., methadone) on the action of lubiprostone was performed as part of this sNDA and results of the study are discussed in section 4.4.2 [Pharmacodynamics](#).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity trials were not performed.

7.6.2 Human Reproduction and Pregnancy Data

Trials of lubiprostone in pregnant or lactating women were not conducted for this sNDA application. Pregnant women were excluded from all clinical trials of lubiprostone and any women who became pregnant during a trial were to be immediately discontinued from trial participation. No pregnancies were reported in any of the four clinical trials (OBD-1033, OBD-0631, OBD-0632, and OBD-06S1).

7.6.3 Pediatrics and Assessment of Effects on Growth

Pediatric Study Requirement under PREA

For this sNDA, the Sponsor submitted a request for a partial waiver in pediatric patients 0 to <6 months of age and a partial deferral for pediatric patients 6 months to 17 years of age for trials of lubiprostone in pediatric patients with OIC and chronic non-cancer pain. Because there is an inadequate number of pediatric patients who receive opioid

therapy for non-life limiting illnesses for more than 4 weeks,¹¹ DGIEP proposed a full waiver for pediatric patients in all age groups. The efficacy trials OBD-1033, OBD-0631, and OBD-0632 required that adult subjects take opioids for ≥ 30 days prior to screening and have stable doses of opioids for ≥ 30 days prior to the screening period to enroll. There are limited data and literature available in the use of opioids in the pediatric population for chronic non-malignant pain.¹² Previous efforts to conduct efficacy trials of chronically administered opioids (lasting >2 weeks) in pediatric patients have not been feasible.¹¹ In addition, trials addressing chronic pain in sickle cell disease are lacking.¹³ A PeRC PREA subcommittee meeting, held on February 13, 2013, agreed with DGIEP's request for a full waiver of lubiprostone in pediatric patients with OIC and chronic non-cancer pain.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no reported cases of overdose during the clinical trials of lubiprostone in subjects with OIC. Lubiprostone has been studied in humans at a dose of up to 144 mcg, which is three times the proposed dose of 48 mcg (24 mcg BID) for OIC. During the phase 1 study, which involved an administration of a single dose of lubiprostone 144 mcg, 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, three overdose cases (two confirmed reports and one possible) were noted. One of the overdose cases experienced four episodes each of vomiting and diarrhea. 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. The Sponsor reports that the pharmacologic profile of lubiprostone is not consistent with a drug that would have potential for drug addiction or dependence, a claim that is plausible given what is known about the mechanism of action of the drug.

The Sponsor did not evaluate withdrawal and rebound during the clinical program for lubiprostone in OIC. A previous randomized trial (protocol SPI/022SIB-0431, dated May 15, 2007) in subjects with IBS-C assessed for withdrawal and rebound and did not

¹¹ Berde CB, Walco GA, Krane EJ et al. Pediatric analgesic clinical trial designs, measures, and extrapolation: report of an FDA scientific workshop. *Pediatrics*. 2012;128(2): 354-364.

¹² Slater ME, De Lima J, Campbell K, Lane L, Collins J. Opioids for the management of severe chronic non-malignant pain in children: a retrospective 1-year practice survey in a children's hospital. *Pain Medicine*. 2010;11(2): 207-214.

¹³ Dunlop R, Bennett KCLB. Pain management for sickle cell disease in children and adults. The Cochrane Collaboration. 2009;1;1-27.

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003350.pub2/pdf>

demonstrate any obvious safety risks following immediate cessation or after 7 days of withdrawal from lubiprostone treatment.

7.7 Additional Submissions / Safety Issues

The Sponsor submitted a Periodic Safety Update Report (PSUR) covering the period from February 1, 2011 to January 31, 2012. The review of medically confirmed cases of AEs did not reveal any new safety concerns during this reporting period. The Sponsor reports that dyspnea, chest pain/chest discomfort, nausea, diarrhea, pregnancy and lactation, and ischemic colitis are the important events being monitored closely. Of these, dyspnea and chest pain/chest discomfort, nausea, diarrhea, and pregnancy and lactation are discussed in the current drug label.

Ischemic Colitis

Reports of ischemic colitis (IC) in the postmarket setting in patients on lubiprostone for CIC and IBS-C prompted this reviewer to examine the AE database of the OIC trials. As of the most recent PSUR, cumulatively (from February 31, 2006 to January 31, 2012), the Sponsor reported 12 cases of IC, noting one as non-medically confirmed, and considering 10 as serious. As part of this safety review, this officer screened the overall safety pool AE dataset for lubiprostone subjects reporting the following AEs (by PT): (1) abdominal discomfort; (2) abdominal pain; (3) abdominal pain upper; (4) abdominal pain lower; (5) abdominal tenderness; (6) body temperature increased; (7) pyrexia; (8) colitis; (9) hematochezia; (10) occult blood positive; (11) rectal hemorrhage; and (12) rectal ulcer. Subjects with any of the last five AEs (i.e., colitis, hematochezia, occult blood positive, rectal hemorrhage, or rectal ulcer), either alone or in combination with one or more of the other previously mentioned AEs, were selected. This process isolated five subjects with AEs warranting further investigation. The Sponsor was asked to provide case report forms and patient narratives for these subjects, which were reviewed by this medical officer. Relevant history for these five subjects is briefly summarized below:

- 1033-3402-006: AEs of abdominal pain and hematochezia; 50-year-old male with history of chronic gastritis taking pantoprazole and celecoxib who had 5 separate non-serious events of hematochezia (each spaced 1 to 4 days apart from the next), with the first event occurring ~2.5 months after initial dose of lubiprostone. None of the events required medical intervention or change in study drug. The subject completed the 12-week trial.
- 0632-2056-004: AE of hematochezia; 57-year-old female with history of heartburn and hematochezia taking clopidogrel who reported 2 episodes of mild, non-serious hematochezia, with the first event occurring ~9 days after first exposure to lubiprostone. Both events resolved spontaneously without sequelae. The subject completed the 12-week trial.
- 06S1-2018-006: AE of rectal hemorrhage; 22-year-old female taking celecoxib who reported mild, intermittent non-serious rectal bleeding over an 8-day period, with the first report occurring ~6 days after initial dose of lubiprostone. No changes were made to study drug and the event resolved spontaneously without

sequelae. The subject was withdrawn from the trial by the investigator due to non-compliance.

- 06S1-2056-005: AE of hematochezia; 60-year-old male with history of coronary artery disease taking aspirin who reported mild, intermittent non-serious hematochezia, with the event occurring ~6 months after initial dose of lubiprostone. No changes were made to study drug and the event resolved spontaneously without sequelae after 1 day. The subject completed the full 9 months of the trial.
- 06S1-2059-014: AE of hematochezia; 34-year-old female with gastroesophageal reflux disease and hemorrhoids taking medications including methylprednisolone who reported one instance of mild, non-serious hematochezia, with the event occurring ~4 months after initial dose of lubiprostone. No changes were made to study drug and the event resolved spontaneously without sequelae.

Reviewer comments: In this reviewer's assessment, none of the five subjects had a constellation of signs and symptoms suggestive of IC. Given the postmarket cases of IC, DGIEP consulted the Office of Safety and Epidemiology to review the FDA Adverse Event Reporting System (FAERS) database for cases of IC. Findings are discussed in section 8 [Postmarket Experience](#).

8 Postmarket Experience

Lubiprostone was approved on January 31, 2006 at 24 mcg BID for the treatment of CIC and has been marketed in the United States since April 15, 2006. Since its marketing in 2006, the Sponsor has supplied the agency postmarketing safety updates as part of the approval requirement. A total of 5830 adverse events were spontaneously reported by healthcare professionals to the Sponsor between February 1, 2006 and January 31, 2012. The majority of AEs reported between February 1, 2006 and January 31, 2012 were in the SOC of gastrointestinal disorders (34%). Other AEs by SOC reported by at least 5% of individuals were general disorders and administration site conditions (21%), nervous system disorders (12%), and respiratory, thoracic and mediastinal disorders (8%). [Table 104](#) summarizes the AEs by PT reported to the Sponsor since approval of lubiprostone until January 31, 2012. It is difficult to establish causality because causality ratings information was not available. By PT, AEs reported by at least 2% of individuals (**bolded in [Table 104](#)**) were nausea (9%), drug ineffective (8%), diarrhea (7%), dyspnea (5%), dizziness (4%), abdominal pain (3%), headache (3%), abdominal distension (3%), vomiting (2%), and drug tolerance (2%).

Table 104. Postmarketing Adverse Events from February 1, 2006 to January 31, 2012

Preferred Term	Number of Events ¹		
	Medically Confirmed (N=3221)	Non-Medically Confirmed (N=2609)	Total (N=5830) n (%)
Nausea	245	261	506 (8.7%)
Drug ineffective	178	267	445 (7.6%)
Diarrhea	208	195	403 (6.9%)
Dyspnea	201	59	260 (4.5%)
Dizziness	130	89	219 (3.8%)
Abdominal pain	134	65	199 (3.4%)
Headache	97	89	195 (3.3%)
Abdominal distension	50	95	145 (2.5%)
Vomiting	81	48	129 (2.2%)
Drug tolerance	88	37	125 (2.1%)
Chest discomfort	77	29	106 (1.8%)
Edema peripheral	68	25	93 (1.6%)
Flatulence	21	68	89 (1.5%)
Chest pain	51	16	67 (1.1%)
Palpitations	39	18	57 (1.0%)

¹Events that represent at least 1% of the total postmarketing AE reports.

Source: Reviewer's table, modified from Sponsor's Table 2.7.4.6-2, page 154 of 156, Summary of Clinical Safety.

Reviewer comments: *The AEs reported most commonly in the postmarket setting are generally consistent with the most commonly reported AEs in the OIC clinical trials and in previous clinical trials of lubiprostone in subjects with CIC and IBS-C.*

As of the most recent PSUR, cumulatively (from February 31, 2006 to January 31, 2012), the Sponsor reported 12 cases of ischemic colitis (IC). A review by the Office of Surveillance and Epidemiology/Division of Pharmacovigilance-1 (OSE/DPV1), conducted in September 2008, demonstrated six postmarketing cases of IC from initiation of marketing through August 12, 2008. Of the six cases, five patients had a serious outcome of hospitalization. Four of the six patients were female, all six patients were on lubiprostone for chronic constipation, and mean age was 62 years. Two of the patients were concomitantly on estrogen, a medication that has been associated with IC. Four patients had underlying conditions that might have predisposed them to development of IC, including hypertension, dehydration, and congestive heart failure.

During the current review cycle, OSE/DPV1 searched the AERS database for the period from August 13, 2008 to January 2, 2013 and identified six new cases of ischemic colitis. Of the six cases, five patients had a serious outcome of hospitalization. Four of the six patients were female, five of the six patients were on lubiprostone for chronic constipation, and mean age was 54 years. None of the patients was on concomitant medications with potential to cause ischemic colitis.

Reviewer comments: *Although several patients in these case series had underlying medical history or were taking concomitant medications that could have contributed to the development of IC, a causal role of lubiprostone cannot be ruled. This reviewer is somewhat reassured that there have been no reports of colectomy or death in these 12 patients. Given the totality of the data from the reports by OSE/DPV-1 since lubiprostone's first approval in January 2006, this reviewer recommends updating the labeling to include IC in the Adverse Reactions Postmarketing Experience section.*

Cumulatively between February 1, 2006 and January 31, 2012, the Sponsor has received 11 medically confirmed cases of death, which include 19 events: 8 events in clinical trials and 11 events from postmarketing sources. Of the 19 events, 4 events were received during the reporting period for the most recent PSUR covering February 1, 2011 to January 31, 2012. Of the remaining 15 events, 7 were received from clinical trials and were all considered by the investigator and the company to be unrelated to lubiprostone. Of the eight remaining events, four were considered by the reporting healthcare professional to be unrelated to lubiprostone; the causality to lubiprostone was not reported in the remaining four cases. [Table 105](#) lists the primary fatal events.

Table 105. Primary Fatal Events from February 1, 2006 to January 31, 2012 in Postmarket Setting

System Organ Class	Preferred Term
Cardiac Disorders (n=2)	Cardiac arrest
	Cardiac failure congestive
General Disorders and Administration Site Conditions (n=3)	Chest discomfort
	Death (2)
Injury, Poisoning and Procedural Complications (n=1)	Toxicity to various agents
Neoplasms Benign, Malignant, and Unspecified (n=1)	Colon cancer metastatic
Renal and Urinary Disorders (n=1)	Renal failure
Respiratory, Thoracic, and Mediastinal Disorders (n=3)	Pleural effusion
	Pneumonia aspiration (2)

Source: Reviewer's table modified from Sponsor's Table, page 157 of 167, Summary of Clinical Safety.

9 Appendices

Appendix 1: Benefit-Risk Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Opioid-induced constipation (OIC) is a common condition that affects up to 90% of patients taking opioids for chronic non-cancer pain.¹⁴ - OIC is a serious, albeit not life-threatening, condition that does not improve with continued opioid therapy, negatively affects quality of life, and may lead to patients reducing or terminating treatment with opioids.^{15,16,17}	OIC does not cause mortality but can cause morbidity, such as pseudo-obstruction and fecal incontinence, and may reduce the value of effective pain relief in adult patients using opioids for chronic non-cancer pain. ¹⁵
Unmet Medical Need	- There are currently no FDA-approved therapies for this indication. - There are no standard guidelines for treatment of OIC, and non-pharmacological therapies (e.g., exercise, increased intake of dietary fiber and fluids) are generally insufficient.¹⁵ - Over-the-counter (OTC) laxatives are widely used “off-label,” but their effectiveness in this population may be inadequate.¹⁸	There may be a need for alternative options for treatment of OIC in the chronic non-cancer adult patient population, especially if the drug has demonstrated efficacy in the target population.
Clinical Benefit	- OBD-1033 was a randomized, double-blind, 12-week trial comparing lubiprostone 24 mcg BID with placebo in 439 adults with chronic, non-cancer pain and OIC who were not taking diphenylheptane opioids (e.g., methadone). - The primary endpoint was overall spontaneous bowel movement (SBM) response, defined as ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥ 3 SBMs per week for at least 9 of the 12 treatment weeks. - Lubiprostone demonstrated a statistically significant and clinically meaningful treatment difference (8%) versus placebo. - To assess durability of effect, an exploratory analysis used a modified overall SBM response definition. In this modified definition, patients were considered overall responders if they had ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥ 3 SBMs per week for at least 9 of the 12 treatment weeks <i>and</i> for at least 3 of the last 4 weeks. Lubiprostone showed a clinically meaningful treatment difference (7%) versus placebo. - OBD-0631 was a randomized, double-blind, 12-week trial comparing lubiprostone 24 mcg BID with placebo in 438 adults with OIC and chronic, non-cancer pain. - The primary endpoint was mean change from baseline in SBM frequency at Week 8 in subjects without dose reduction. - Lubiprostone demonstrated a statistically significant treatment difference (0.8) versus placebo. - In an exploratory analysis using the overall SBM response endpoint, lubiprostone demonstrated a	Lubiprostone 24 mcg BID is effective in treatment of OIC in adults with chronic non-cancer pain and demonstrated durability of effect over 12 weeks. The effectiveness of lubiprostone in patients with OIC taking diphenylheptane opioids (e.g., methadone) has not been established. Because patients in the phase 3 trials (OBD-1033 and OBD-0631) were required to discontinue all their laxatives and use only the permitted rescue laxative medication throughout the screening, treatment, and follow-up periods of the trials, it is unclear whether lubiprostone provided enough subjective relief of OIC symptoms among subjects in the clinical trials to reliably reduce use of rescue laxatives.

¹⁴ Panchal SJ, Muller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. *Int J Clin Pract.* 2007;61(7):1181-1187.

¹⁵ Kurz A, Sessler DI. Opioid-induced bowel dysfunction: pathophysiology and potential new therapies. *Drugs.* 2003;63:649-671.

¹⁶ Bell TJ, Panchal SJ, Miaskowski C, et al. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1). *Pain Med.* 2009;10(1):35-42.

¹⁷ Tuteja AK, Biskupiak J, Stoddard GJ, Lipman AG. Opioid-induced bowel disorders and narcotic bowel syndrome in patients with chronic non-cancer pain. *Neurogastroenterol Motil.* 2010;22:424-431.

¹⁸ Pappagallo M. Incidence, prevalence, and management of opioid bowel dysfunction. *Am J Surg.* 2001;12:11S-8S.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	clinically meaningful treatment difference (10%) versus placebo. • OBD-0632 was a trial identical in design to OBD-0631 (435 adults). The trial failed on the primary endpoint (mean change from baseline in SBM frequency at Week 8). A subsequent nonclinical study by the Sponsor demonstrated that diphenylheptane opioids (e.g., methadone) may interfere with the mechanism of action of lubiprostone.	
Risk	• The main safety risks of lubiprostone are already labeled and include nausea, diarrhea, abdominal pain, flatulence, abdominal distension, vomiting, peripheral edema, dyspnea, and chest pain. The incidence of these adverse events (AEs) was lower than or comparable to the incidence of the same AEs in clinical trials of lubiprostone 24 mcg BID for chronic idiopathic constipation (CIC). • Gastrointestinal (GI) AEs were more frequent with lubiprostone (27%) than placebo (15%). • There were no data suggestive of opioid withdrawal with lubiprostone. • Although there were no cases of ischemic colitis among lubiprostone-treated patients in the clinical trials, lubiprostone has been associated with ischemic colitis in the postmarket setting.	The overall safety profile of lubiprostone is acceptable for a laxative and comparable with the safety profile established for other approved indications (CIC and IBS-C). GI AEs were more frequent with lubiprostone compared to placebo, but were manageable. Ischemic colitis should be added to the Postmarketing Experience section of the label.
Risk Management	• No novel safety concerns were present requiring additional risk management. • The effectiveness of lubiprostone in patients with OIC taking diphenylheptane opioids (e.g., methadone) has not been established.	No risk evaluation and mitigation strategies are required. There are no recommendations for postmarket requirements or commitments.
Benefit-Risk Summary and Assessment		
Over the last two decades, the use of opioids for management of chronic non-cancer pain has risen sharply in the United States,¹⁹ and OIC is an increasingly common condition that affects a substantial proportion of patients taking opioids for chronic non-cancer pain. Although it does not cause mortality, OIC can be a serious condition that does not improve with continued opioid therapy, negatively affects quality of life, and frequently leads to patients reducing or terminating treatment with opioids. There are currently no FDA-approved therapies for this indication and the effectiveness of existing pharmacological (OTC laxatives) and non-pharmacological therapies has been questioned.		
The efficacy of lubiprostone is demonstrated by two randomized, double-blind 12-week trials (OBD-1033 and OBD-0631) comparing lubiprostone 24 mcg BID with placebo in a total of 877 adult patients with OIC and chronic non-cancer pain. Both trials demonstrated a clinically meaningful treatment effect favoring lubiprostone (8% in OBD-1033 and 10% in OBD-0631). One of the two trials (OBD-0631) enrolled subjects using diphenylheptane opioids (e.g., methadone). A third trial (OBD-0632) that also enrolled subjects using diphenylheptane opioids (e.g., methadone) and was identical in design to OBD-0631 failed to show a statistically significant treatment difference between lubiprostone and placebo. A subsequent nonclinical study demonstrated that diphenylheptane opioids (e.g., methadone) may interfere, in a concentration-dependent manner, with the action of lubiprostone.		
Most of the primary safety risks of lubiprostone are gastrointestinal (nausea, diarrhea, abdominal pain, flatulence, abdominal distension, vomiting) and are related to its pharmacological activity. GI AEs were more frequent with lubiprostone (27%) compared to placebo (15%) but were manageable. Less well-understood, but also labeled, safety risks include dyspnea, chest pain, and peripheral edema. The rates of all these AEs in the OIC clinical trials were lower than or comparable to the incidence of the same AEs in clinical trials of lubiprostone 24 mcg BID for CIC. Additional review did not suggest opioid withdrawal with lubiprostone, and there were no cases of ischemic colitis among lubiprostone-treated patients in the OIC clinical trials. No risk management tools are necessary at this time.		
Lubiprostone represents an alternative option for treatment of OIC in the chronic non-cancer adult patient population. Lubiprostone 24 mcg BID is superior to placebo in treating OIC in this population and the benefit of lubiprostone in treating OIC outweighs the risk of its use in an appropriate patient population. The effectiveness of lubiprostone in patients with OIC taking diphenylheptane opioids (e.g., methadone) has not been established.		

¹⁹ Camilleri M. Opioid-induced constipation: challenges and therapeutic opportunities. *Am J Gastroenterol.* 2011;106:835-842.

Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033

Title

A Multicenter, Randomized, Placebo-Controlled, Double-blinded Trial of the Efficacy and Safety of Lubiprostone in Subjects with Opioid-induced Bowel Dysfunction

Objectives

“To assess the efficacy and safety of oral lubiprostone at 48 mcg/day (24 mcg BID), as compared to placebo, when administered orally for 12 weeks to subjects with opioid-induced bowel dysfunction (OBD)”

Trial Design

Randomized, placebo-controlled, double-blind, parallel-group phase 3 trial

Duration

The trial started on December 7, 2010 and ended on November 16, 2011. The trial consisted of a screening visit 3 weeks prior to first dose of medication, a double-blind period of 12 weeks, and a follow up visit at Week 14.

Key Inclusion Criteria

1. Male or non-pregnant female ≥ 18 years of age.
2. History of being treated consistently for chronic, non-cancer-related pain with any oral, transdermal, intravenous, or subcutaneous opioid (full agonist) *other than methadone* for at least 30 days prior to screening, and continued opioid therapy throughout the trial.
3. Presence of OBD, defined as having an average of < 3 spontaneous bowel movements (SBMs) per week during the screening period (with “spontaneous” defined as bowel movements occurring without the use of laxatives/stool softeners) and at least one of the following for at least 25% of SBMs during each week of the screening period (as reported in the daily diary):
 - Hard or very hard stools
 - Sensation of incomplete evacuation
 - Moderate to very severe straining associated with SBMs
4. In those with history of chronic constipation (≥ 90 days), condition of constipation must have been exacerbated by the initiation of opioid treatment.
5. If taking concomitant medication (prescribed or over-the-counter) that affects gastrointestinal motility (other than opioid therapy), must have discontinued use from the Screening Visit through the completion of the trial; these medications included: anticholinergics, anti-spasmodics, cholinesterase inhibitors, anti-diarrhea agents, anti-constipation agents, prokinetic agents, laxative agents (including homeopathic remedies), tricyclic antidepressants and any medications at the discretion of the investigator known to relieve or cause constipation, bloating, or constipation-related symptoms.
6. If had confirmed diagnosis of clinical depression and had been treated with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine

reuptake inhibitors (SNRIs), or monoamine oxidase (MAO) inhibitors, treatment must have been at a stable dose for at least 30 days prior to the Screening Visit and not likely to change during the trial.

7. Willing to discontinue use of laxative and stool softeners from the Screening Visit through the completion of the trial (use of approved rescue laxatives was allowed under certain protocol-specified circumstances).
8. If taking a fiber supplement, must have been at a stable dose and schedule for ≥ 30 days prior to the Screening Visit and not likely to change during trial.
9. Willing and able to fill out eDiary and could comply with daily data collection.
10. Daily diary at least 70% compliant for the screening period.
11. Capable of making an informed decision, and had read, understood, and signed the approved Informed Consent Form.

Key Exclusion Criteria

1. Receiving opioid therapy for cancer-related pain, abdominal pain, scleroderma, and/or for the management of drug addiction.
2. Receiving methadone, methadone HCl, or a congener of methadone either alone or as part of opioid regimen.
3. Current evidence of, or had been treated for, cancer within the past 5 years (with the exception of localized basal cell or squamous cell skin cancer, or *in situ* cancer that had been resected).
4. Had adjusted (increased or decreased by $\pm 30\%$) dosage (in morphine equivalent daily dose [MEDD]) of opioid treatment, had changed opioid agents, or had changed route of opioid administration within 30 days of screening, or was likely to discontinue or adjust dosage by $\pm 30\%$ over the course of the trial.
5. Known or suspected anatomic or organic disorders of the large or small bowel; e.g. associated with a mechanical bowel obstruction (e.g., tumor, hernia, obstructive polyps), or pseudo-obstruction or associated with large or small bowel disorder such as ulcerative colitis or Crohn's disease.
6. History of constipation that, according to the investigator's clinical judgment, was not the result of or not exacerbated by opioid use, or was suffering from known or suspected secondary cause of constipation, including but not limited to: dietary disorders (e.g., malnutrition), neurologic disorders (e.g., spinal cord disorders), other congenital disorder, or endocrine disorders (e.g., diabetes).
7. Impaired renal function identified at the Screening Visit (i.e., serum creatinine concentration > 1.8 mg/dL).
8. History of unexplained, clinically significant weight loss defined as $> 5\%$ weight loss within 90 days prior to Screening Visit.
9. History of gastrointestinal or abdominal surgical procedure within 90 days prior to the Screening Visit or had a bowel resection at any time.
10. Non-ambulatory.
11. Inability to eat or drink, take oral medications, or to hold down oral medications due to vomiting.
12. Female of childbearing potential who was unable or unwilling to use a protocol-specified method of birth control.

13. Female of childbearing potential who had positive screening pregnancy test, was currently pregnant/nursing, or planned to become pregnant/nurse during the trial.
14. History of clinically significant cardiovascular disease (according to the investigator's clinical judgment).
15. History of clinically significant, unexplained liver or lung disease, neurologic or psychiatric disorders (excluding depression), or any other systemic disease. If explained, the subject may have been enrolled, if in the investigator's opinion, the condition would not interfere with safety or efficacy assessments, or result in an increased risk of participation to the subject.
16. History of alcohol or drug abuse within 180 days prior to Screening Visit.
17. Demonstrated a potential for non-compliance with the trial protocol (i.e., dosing schedule, visit schedule, diary completion, or trial procedures).
18. Participated in another study with an investigational drug, device, or procedure within the 30 days preceding the Screening Visit.
19. Had received Amitiza®, lubiprostone, SPI-0211 or RU-0211 at any time prior to participation in this trial.

Treatments

Screening period: Eligible subjects participated in a 3-week screening period where no study drug was administered. Within the screening period, the baseline period began with the signing of the informed consent at Visit 1 (screening visit) and ended with the first dose of study drug. Prohibited concomitant medications were stopped at the screening visit. For efficacy analyses, the baseline period was 14 days prior to the first dose of study drug and was used to determine disease status and other demographic factors at baseline. For example, constipation status at baseline was defined based on the average of diary entries for the 14 days prior to administration of the first drug dose.

Treatment period: This period began with the first dose of study medication, which, for most subjects, was the day of Visit 2 (randomization visit). This period ended upon completion of Visit 8 (end of treatment visit) or upon administration of the last dose. Eligible subjects were randomly assigned to blinded doses of lubiprostone (24 mcg) twice daily or matching placebo in a 1:1 ratio. The first bottle of study medication was dispensed at the study site, with first dose taken at home on Day 0. Each bottle of study medication contained a supply of capsules for 28 days plus a 6-day overage (68 capsules total) in the event that any capsules were lost, accidentally destroyed, or there was a delay in the completion of the scheduled clinic visit.

Subjects were instructed to take one capsule in the morning and one in the evening with meals, and at least 8 ounces of fluid. Each treatment day consisted of two doses of study medication, one capsule per dose. If a dose was missed, the subject should have taken the missing dose as soon as possible, but not "doubled up" doses (i.e., take two doses at one meal). All doses were to be taken at least 5 hours apart. If taken late, the subject should have recorded the actual time the dose was taken in the eDiary. If the dose was missed entirely, the subject should have indicated the omission in the eDiary.

The schedule of visits for the trial is summarized in [Table 106](#).

Table 106. Schedule of Visits – Trial OBD-1033

Study Stage	Screening	Randomization	Study Treatment and Evaluation (Day 0 to 84)						Follow-up
			1	4	6	8	10	12	
Study Week	-3	0	1	4	6	8	10	12	14
Study Day	-21 (- 3)	0	7 (± 3)	28 (± 3)	42 (± 3)	56 (± 3)	70 (± 3)	84 (± 3)	98 (± 3)
Visit Number	1	2	3	4	5	6	7	8	9
Visit Type	Screening	Randomization	Telephone Assessment	Clinic Examination	Telephone Assessment	Clinic Examination	Telephone Assessment	Clinic Examination	Follow-up Clinic Examination
Assessment									
Informed Consent	X								
Demographics	X								
Medical History	X	X							
Vital Signs ¹	X	X		X		X		X	X
Physical Examination	X			X ²		X ²		X	X ²
Blood Chemistry, Hematology, Urinalysis	X			X		X		X	X
Pregnancy Test ³	X	X		X		X		X	X
Concomitant Medications	X ⁴	X	X	X	X	X	X	X	X
Adverse Events ⁵		X	X	X	X	X	X	X	X
Study Med Distribution		X		X		X			
Study Treatment ⁶		X	X	X	X	X	X	X	
Study Medication Collection				X		X		X	
Electronic Diary	X ⁷	X	X	X	X	X	X	X	X
EQ-5D™ Health Questionnaire		X						X	
PAC-QOL® Questionnaire		X		X		X		X	

¹ Height is captured at the Screening Visit only. Weight is captured at the Screening and Follow-up Visits;

² Abbreviated physical examinations will be performed at designated visits;

³ A serum pregnancy test will be performed at the Screening Visit. Urine pregnancy tests will be performed at all other study visits;

⁴ Will include history of medications used within 30 days of the Screening Visit as well as full history of all constipation treatment administered since onset of OBD;

⁵ AEs occurring prior to the first dose will be recorded as medical history. All AEs reported after the first administration of study medication will be recorded on the AE eCRF;

⁶ First treatment administration is to be self-administered by the subject on Study Day 0 (the day of the Randomization Visit). If the subject has used any rescue laxative within 24 hours of the Randomization Visit (Visit 2), the subject will be instructed to start study medication on the second day after the Randomization Visit. The day of first dose will be considered Study Day 0 and all subsequent visits will be scheduled based on the first treatment day;

⁷ Electronic diaries are to be distributed to subjects at the Screening Visit.

Source: Sponsor's table, module 5.3.5.1.4 Clinical Protocol SMR/0211OBD-1033, page 16 of 66.

Trial Conduct

Screening: Days -24 to -21

- Aimed to determine subject's eligibility for participation in the trial
- Medical history, inclusion/exclusion criteria reviewed
- Sign informed consent
- Physical examination and laboratory tests, including urine pregnancy test
- Review of concomitant medications used within past 30 days
- Electronic diary (eDiary) dispensed with instructions for use and should have been completed each day starting with the evening of the screening visit
- Review of contraception with female subjects who were sexually active
- Gather baseline data

Initiation of double-blind period: Day 0

- Completion of paper copies of PAC-QOL and EQ-5D questionnaires
- Review of any changes to medical history to confirm continued trial eligibility
- Review of eDiary for compliance and further confirmation of eligibility criteria
- Vital signs recorded, urine pregnancy test obtained
- Concomitant medications since screening visit reviewed and subjects instructed not to use prescription or OTC laxatives unless prescribed by the investigator
- Randomization to one of two treatment groups, study medication dispensed and first dose to be taken starting the evening of the randomization visit
- If a subject had used rescue laxative within 24 hours prior to this visit, the subject was to start study medication on the second day after the randomization visit. In either case, the Sponsor considered the day of first dose as study Day 0 and all subsequent visits were scheduled based on the first treatment day

Double-blind period: Days 0 to 84

- On study days 7, 42 and 70 (± 3 days), a telephone assessment was performed by site personnel to evaluate subject's compliance with study medication and eDiary and to identify any AEs or changes in concomitant medications
- On study days 28, 56 (± 3 days), a clinic visit occurred, during which the following evaluations were performed:
 - Completion of PAC-QOL questionnaire
 - AEs or changes in concomitant medications
 - Subject's overall condition, physical examination
 - Blood and urine samples for laboratory analyses
 - eDiary review
 - Previously dispensed bottle of study medication collected, new bottle of study medication dispensed, and compliance reviewed
- Day 84 (± 3 days), an end-of-treatment clinic visit occurred, during which the following evaluations were performed:
 - Completion of PAC-QOL and EQ-5D questionnaire
 - AEs or changes in concomitant medications

- Subject's overall condition, physical examination
- Blood and urine samples for laboratory analyses, ECG
- eDiary review
- Previously dispensed bottle of study medication collected and compliance reviewed

Final follow-up assessment: Day 98 (+3 days)

A follow-up clinic visit occurred (or before for subjects who discontinued treatment prematurely) to:

- Review any ongoing or new onset of AEs or changes in concomitant medications
- Assess the subject's condition, physical examination
- Blood and urine samples for laboratory analyses
- eDiary collected

A weekly nausea assessment (using the Functional Living Index Emesis [FLIE] questionnaire) was administered via the eDiary. The pain assessment (using the Brief Pain Inventory Short Form [BPI-SF]) was administered monthly on the eDiary. For the opioid dose assessments, all medications including name, dosage parameters, and dose adjustments were captured for all opioid treatment administered to the subject during their participation in the trial.

Removal of Subjects from Therapy or Assessment

Subject participation may have been terminated prior to completion of the clinical trial for AEs, lack of efficacy, permanent discontinuation of chronic opioid therapy or discontinuation of administration of chronic opioid therapy for >48 hours, subject choice, lost to follow-up, noncompliance, investigator's decision, Sponsor's request, or any other reason upon agreement between the investigator and the Sponsor.

Subjects who withdrew or terminated early from the trial were to complete the final visit of the treatment period (Visit 8) and the follow-up visit (Visit 9) per protocol. When a subject withdrew prior to completing the trial, the reason for withdrawal was to be documented in the electronic CRF and in the source document. Study medication assigned to the withdrawn subject was not assigned to another subject. Subjects who withdrew were not replaced. If a subject discontinued chronic opioid therapy, they withdrew from the trial and completed the final visit of the treatment period (Visit 8) and the follow-up visit (Visit 9).

Reduction in Study Medication

A dose reduction may have been initiated by the investigator if severe nausea, severe diarrhea, or another AE was reported by the subject to the site and was ongoing for ≥3 days. In these cases the investigator, in consultation with the subject and/or medical monitor, may have reduced study medication to QD dosing. Once a dose reduction occurred, the subject could resume the BID regimen at the investigator's discretion. Investigators assessed the need for reduction of the study medication at each visit.

Prior and Concurrent Therapy

Methadone, methadone HCl, and congeners of methadone, taken alone or in conjunction with other opioids, was considered exclusionary, and subjects who were administering these treatments were not considered for trial enrollment.

The use of a daily fiber supplement (e.g., Metamucil, PerDiem) was permitted as long as the usage schedule and dose was stable for at least 30 days prior to the screening visit. The schedule of usage and dose of the daily fiber supplement should not have changed during the course of the trial. Any fiber supplement used should have been documented as a concomitant medication.

All medications (prescription, OTC, herbal, and/or supplemental; including contraceptives) taken at the start of the trial or during the trial were to be documented on the concomitant medication CRF page. If any medication was started, stopped, or modified, this was documented on the CRF as well. For any concomitant therapy given as a treatment for a new condition or a worsening of an existing condition, the condition was to be documented on the AE CRF page.

Use of the following treatments was not permitted:

- Anticholinergics (excluding ipratropium bromide and other inhaled and nasal-spray forms of ipratropium)
- Opioid antagonists
- Antispasmodics
- Cholinesterase inhibitors
- Antidiarrheal medications
- Anticonstipation medications including bowel stimulants (e.g., senna or bisacodyl), laxative agents (e.g., MiraLax, ExLax, Colonix, lactulose), suppositories and phosphate enemas (except as use for rescue laxative at investigator discretion), and stool softeners
- Antiemetics (selective, those known to alter gastric motility)
- Prokinetic agents
- Tricyclic antidepressants
- Any medications at the discretion of the investigator known to relieve or cause constipation or constipation symptoms

Rescue Laxatives

Subjects were allowed to use rescue laxatives during the trial; however, the use of rescue laxatives was not allowed within 24 hours prior to the first dose of the study drug or during the first 72 hours following treatment initiation.

In the event that no BM occurred within a 3-day period, the use of rescue laxatives was permitted at the discretion of the investigator as described below:

- Rescue laxative 1: the investigator may have instructed the subject to administer the clinically recommended dose (10 mg) of bisacodyl (Dulcolax) suppository.

- Rescue laxative 2: if the first rescue laxative failed to induce a BM, the investigator instructed the subject to administer a repeat dose of bisacodyl suppository or administer a saline enema.

If both rescue laxatives failed, the investigator may have prescribed another medication for immediate short-term use, including a medication from the excluded medication list other than MiraLax, Relistor, and Resolor. If the use of rescue therapy was necessary, it was recorded on the rescue laxative eCRF page and in the eDiary by the subject.

Compliance

Designated trial personnel were to maintain a log of all study medications dispensed and returned. Study medication supplies for each subject were to be inventoried and accounted for throughout the trial. Study medication administration was to be documented in the source documentation, including dispensation information and capsule counts and on the study medication CRF. Study medication dosing was also to be recorded by the subject in the eDiary. Assessments of the actual exposure to study medication were to be based on the medication usage recorded in the daily diary. If the number of capsules taken per the diary was greater than the number of capsules in the bottle-return counts or the percentage of diary entries during the treatment period was <70% (total diary entries divided by the number of days), then bottle return counts were used to calculate exposure. If bottle counts were not available in the above instances, then diary data were used for exposure.

Outcome Measures

Efficacy

Subjects were to have recorded daily using an eDiary system starting on the evening of the screening visit and continuing until Day 84 or early termination and follow-up. The diary prompted the subject to provide information each evening prior to bedtime about the constipation events during the preceding day. The subject entry window was since the prior night's entry, if available, or for the entire previous day, if a diary entry was not completed the prior night. Information from the subject diary was automatically downloaded each night to a secure database and available for review by the site as needed. The site also had the ability to transmit an electronic back-up of the subject diary to the secure database at the study visits. The site provided the subject with initial training regarding the diary use during the screening visit (Visit 1). The site was to review the subject diary information at the time of the baseline visit, to verify that at least 70% of the daily entries were completed by the subject or guardian in order to be considered eligible for the trial.

Primary Efficacy Endpoint

The primary endpoint was the overall SBM response rate in ITT subjects. This information was determined based on subject responses to the daily eDiary questions.

Proportion of subjects who were overall responders is a binary endpoint. A responder was defined as a subject who had ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥ 3 SBMs per week

for at least 9 of the 12 treatment weeks. For a bowel movement to count as an SBM, the BM could not have occurred within 24 hours after use of a rescue laxative.

Secondary Efficacy Endpoints

Secondary efficacy endpoints for this trial included:

- Change from baseline in SBM frequency at Weeks 8, 12, and overall
- Percentage of subjects with a first postdose SBM within 24 hours
- Percentage of subjects with a first postdose SBM within 48 hours
- Weekly responder rates (weekly SBM response defined as ≥ 1 SBM increase over baseline weekly SBM rate and a ≥ 3 SBM in a given week)
- Health-related quality of life (PAC-QOL and EQ-5D)
- Overall mean change from baseline in the following
 - Straining associated with SBMs
 - Stool consistency of SBMs
 - Constipation severity
 - Abdominal bloating
 - Abdominal discomfort
- Overall treatment effectiveness

Exploratory Efficacy Endpoints:

- Change from baseline in SBM frequency at each week for Weeks 1–7 and 9–11
- Change from baseline in SBM frequency at Months 1, 2, and 3
- Overall mean change from baseline in bowel habit regularity
- Frequency of SBMs and BMs
- Frequency of complete SBMs and BMs
- Monthly assessment of treatment effectiveness
- Median time to first SBM
- Proportion of subjects with first SBM at 4, 8, and 12 hours

Statistical Analysis

Five datasets were used for analyses: safety, intent-to-treat, modified intent-to-treat, per-protocol, and completer population. The definition of these datasets was as follows:

- Safety-evaluable population: All randomized subjects who took at least one dose of study medication were in the safety population and included in safety analysis.
- Intent-to-treat (ITT) population: All randomized subjects who took at least one dose of study medication and had at least one treatment-period diary entry were used for efficacy, demographic and baseline characteristics data analysis. Subjects in the ITT population were grouped with the treatment group to which they were randomized, regardless of which treatment they actually received.
- Modified intent-to-treat (mITT) population: Routine monitoring and subsequent audit of data collected at Sites # 3019 and 3119 led the Sponsor to question the suitability of the data. As a result, a mITT population was used that excluded data from Sites # 3019 and 3119. See section [3.2 Compliance with Good Clinical Practices](#) for additional discussion.

- Per-protocol population: ITT subjects who were randomized and met the detailed inclusion and exclusion criteria. The determination of the per-protocol population was made during the blinded, “frozen” data review.
- Completer population: Subjects who completed the treatment regimen through Week 12; this population was used for supportive analyses.

Subjects in the ITT, mITT, per-protocol, and completer populations were grouped by their randomly assigned treatment; one of the two treatment groups. Subjects in the safety-evaluable population were grouped by the treatment they actually received. All inferential analyses of efficacy were based on the principle of two-tailed tests at a significance level of $\alpha=0.05$.

Sponsor’s Plan for Handling of Missing Data

Imputation of missing SBM data was dependent upon the amount of data observed. A week was considered a 168-hour interval. If at least 85 hours was observed during a week then the missing data within that week were imputed with the average SBM data for that week. If at least 25, but less than 85 hours were observed during a week, and at least 85 hours were observed during the prior week, then data were imputed from the prior week to provide a total of 85 hours of data. If the number of hours in a week was less than 25, then that week was considered missing.

The LOCF technique was used to impute missing values for weeks with no data. For a given subject, the most recent non-missing treatment period data point was carried forward to subsequent weeks where data were missing. Supportive analyses of the secondary endpoints were also conducted by not performing any missing value imputation. The Sponsor considered subjects with fewer than 9 weeks of weekly SBM rates as nonresponders rather than missing.

Primary and Secondary Analyses

The primary analysis was the overall SBM response rate in ITT subjects. Subjects were required to demonstrate ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data was available, and were additionally required to demonstrate ≥ 3 SBMs per week for at least 9 of the 12 treatment weeks to be defined as treatment responders. Baseline was defined as the weekly average SBM frequency from the diary entries during the last 2 weeks of the screening period. The number of hours was the number of hours observed in the eDiary during the week (168-hour interval) that the subject was actively enrolled in the trial and taking study medication. Weeks were calculated as 168-hour intervals starting with the exact time of the first intake of study medication. If the number of hours observed was less than 85, then the Sponsor considered the data insufficient and the rate missing for that week. The Sponsor did not use LOCF in the primary analysis.

For secondary analysis, no hierarchy of evaluation was pre-specified (i.e., no secondary efficacy endpoints were pre-specified as key secondary endpoints, from which results of analysis would then be used to determine a stepwise hierarchy for evaluation of other secondary endpoints).

For the secondary efficacy endpoints of change from baseline in SBM frequency at weeks 8, 12, and overall, analysis was performed via a stratified analysis of covariance (ANCOVA) using the Week 8 and Week 12 values as the dependent variable, controlling for pooled site. Paired t-tests were used to determine significant changes from baseline within treatment groups.

For SBM frequency at Week 8, ITT subjects were used in this analysis provided they did not have a dose reduction prior to Week 8. For SBM frequency at Week 12 and overall, all ITT subjects, inclusive of those whose dose was reduced, were analyzed. The overall endpoint was defined as the average weekly SBM frequency rate while on study medication. The assumption of normality was examined with a Shapiro-Wilk test. A supportive analysis was performed using ITT subjects with at least 85 hours of data each week for all 8 weeks and no dose reductions prior to Week 8. Hommel's stagewise rejective method was used to determine if Week 8, Week 12, and overall time points were statistically significant.

For SBMs within 24 and 48 hours of first dose, the proportion of subjects in each treatment group with their first SBM reported within 24 hours of first dose administration was obtained from the Kaplan-Meier life table estimates and Cox proportional hazards regression model. The Sponsor compared treatment groups using the likelihood-ratio chi-square test. If the Sponsor's p-value for 24 hours was ≤ 0.05 , then the Sponsor also compared groups at 48 hours. Significance level was set at 0.05 for both comparisons.

For weekly responder rates, weekly SBM response was defined as at least one SBM increase over baseline weekly SBM rate and a minimum of three SBMs in a given week. The weekly rates were analyzed using CMH tests stratified by pooled site. A generalized estimating equations (GEE) model was used to compare treatment arms over all 12 weeks with factors for treatment and, if possible, clinical site. No adjustment for multiple comparisons was made.

Health-Related Quality of Life was measured using the PAC-QOL scale and the EQ-5D. The PAC-QOL has four subscales (dissatisfaction, physical discomfort, psychosocial discomfort, and worries and concerns) and a total score. PAC-QOL was assessed at baseline, Month 1, Month 2, and Month 3. A 1-point improvement from baseline was considered clinically meaningful in subjects with constipation. Response was assessed for each domain and total score. Summary evaluations of response for every domain and total score at each month were provided by treatment arm. For each subscale and for the total score, the change from baseline at each visit was analyzed using either a stratified ANCOVA or van Elteren test using factors for the treatment, pooled site, and baseline value as a covariate. A GEE model was used to compare treatment groups for each domain and total score across the 12-week period. Hommel's stagewise rejective method was used to adjust for multiple comparisons of the five PAC-QOL endpoints.

The EQ-5D is a measure of health status designed to provide a measure of health for clinical and economic appraisal. The questionnaire consists of two components, the EQ-

5D descriptive system and the EQ visual analogue scale (EQ-VAS), the former of which comprises five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), with each dimension having three levels. The EQ-VAS records the respondent's self-rated health on a vertical, visual analogue scale, from "best imaginable health state" to "worst imaginable health state." For the EQ-5D descriptive score and EQ-VAS scores, the change from baseline at each visit was analyzed using either a stratified ANCOVA or van Elteren test using factors for treatment, pooled site, and baseline value as a covariate. A GEE model was used to compare treatment groups for each score across the 12-week trial period. Hommel's stagewise rejective method was used to adjust for multiple comparisons of the two EQ-5D endpoints.

For mean change from baseline analyses, mean change from baseline was generated based on subject reported data as to the degree of straining associated with SBMs; stool consistency of SBMs; constipation severity; abdominal bloating; and abdominal discomfort. Subjects were asked to rate these parameters in the daily diary. Assessments were separated into weeks (168-hour period) and months (4-week period) using the first day of study treatment dosing. The assessments made on the evening of the day when first dose was taken served as Day 1. Baseline values were determined using the average of all values collected during the 2 weeks prior to randomization.

Improvement from baseline within each treatment group was assessed by pairwise t-tests or Wilcoxon signed-rank tests, depending on whether the corresponding between-group comparison for the given endpoint was analyzed using a parametric or nonparametric method. Stratified ANCOVA included the baseline value (the covariate). If the model assumptions did not hold, then the van Elteren test was used. For straining, stool consistency, abdominal bloating, and abdominal discomfort endpoints, Hommel's stagewise rejective method was used to adjust for multiple comparisons.

For overall treatment effectiveness, a change from baseline analysis was not performed because this measurement did not apply at baseline. Stratified ANOVA was used unless model assumptions did not hold, in which case the van Elteren test was used.

Exploratory Analyses

Analysis of change from baseline in SBM frequency at each week for Weeks 1–7 and 9–11 was included as an exploratory analysis. In addition, change from baseline in SBM frequency was analyzed at Months 1, 2, and 3. Month 1 was Weeks 1–4; Month 2 was Weeks 5–8; and Month 3 was Weeks 9–12. The SBM frequency rate per week was computed. LOCF was employed to impute data for missing weeks. The analyses of the months followed the same paradigm as the analysis of weeks.

Analyses of the frequency of SBMs and BMs and of complete SBMs and BMs at Weeks 1–12 and Months 1–3 were performed using stratified ANOVA models. If the above analyses indicated that a parametric model was not appropriate, then the van Elteren test was used. BM frequency was calculated similarly to SBM, except it included all BMs regardless of the timing of use of rescue laxatives. Analyses were also completed with missing data imputed using LOCF.

To assess median time to first SBM and SBMs within 4, 8, and 12 hours of first dose of study medication, the first SBM (documented in the subject's daily diary) was used. Time was computed from the time of first dose to the time of first SBM, in hours. Subjects who did not have an SBM were censored at the last time of diary collection. The time to SBM was displayed graphically by treatment group using Kaplan-Meier estimates. Median time and quartiles were determined for each treatment group. The treatment groups were compared using the stratified Cox proportional hazards regression model. The treatment groups were compared at 4, 8, and 12 hours using the likelihood-ratio chi-square test. No stratification was used.

Treatment effectiveness was analyzed weekly for Weeks 1–12, and monthly for Months 1–3. A change from baseline analysis was not performed because this measurement was not collected (and did not apply) at baseline. Stratified ANOVA was used. If the model assumptions did not hold, then the van Elteren test was employed. Analyses were also completed with missing data imputed using LOCF.

A bowel habit question was derived and applied in this trial as an exploratory endpoint. The question was administered weekly and asked the following:

“During the past week, have you experienced irregularities in your bowel habits?”

1 = very regular 2 3 4 5 6 7 = severe irregularity

Changes from baseline in bowel habit irregularities were analyzed overall, weekly at Weeks 1–12 and monthly for Months 1–3. These analyses were also performed with missing data imputed using LOCF.

Protocol Amendments

There were two protocol amendments to the original protocol dated August 20, 2010.

Amendment #1 occurred on October 19, 2010 and included the following changes:

- Updated the exclusion criteria to include any subjects receiving methadone congeners
- Explicitly noted that analyses will be stratified by baseline SBM frequency (in addition to clinical site)

Amendment #2 occurred on June 13, 2011 and included the following changes:

- Completed statistical methods clarifications and expanded explanations
- Updated section on risks and benefits
- Clarified inclusion criterion #11 that pertained to informed consent
- Indicated that analyses will not be stratified by baseline SBM frequency
- Clarified inclusion of clinical site as a stratification factor in analyses by indicating that sites with less than 3 subjects per treatment group will be pooled

Results

Disposition of Subjects

A total of 447 subjects enrolled at 105 sites in the United States and Europe, of whom 226 were randomized to receive placebo and 221 to receive lubiprostone 24 mcg BID. A total of 353 (79%) subjects completed the trial. A total of 94 subjects (21%) discontinued during the trial. A total of 17 subjects (4%) experienced AEs that led to discontinuation from the trial. Thirteen of these subjects (6%) were in the lubiprostone group and four subjects (2%) were in the placebo group. Further details are in section [6.1.3](#)

[Subject Disposition](#) and section [7.3.3 Dropouts and/or Discontinuations](#).

Protocol Deviations and Violations

ITT subjects who were determined to be protocol violators were excluded from the per-protocol analyses. Criteria used to determine protocol violations included:

- Subjects not meeting inclusion criteria numbers 1, 2, 3, 4, 5, 6, and/or 7
- Subjects not meeting exclusion criteria numbers 1, 2, 5, 6, 9, 10, 11, 16, 17, 18 and/or 19
- Those who received the wrong treatment or incorrect dose based on the randomization code
- Subjects who demonstrated inconsistent use of potentially confounding concomitant medications during the trial
- Dose of fiber supplement was not stable from Day -21 through Day 60
- Change from baseline MEDD of $\pm 30\%$ between 7 days before screening visit and end of treatment, with duration of adjusted dose lasting >7 consecutive days
- Less than 65% dosing compliance (with exception for subjects who reduced dose due to AE), or $>120\%$ dosing compliance
- Diary completion rate was $<50\%$ for eligibility determination

Of the 439 ITT subjects, a total of 83 subjects (41 subjects in the placebo arm and 42 in the lubiprostone arm) were excluded from the per-protocol population for a variety of reasons. Details are provided in [Table 9](#) in section 6.1.3.

Demographics and Other Baseline Characteristics

Overall, 63% of subjects were female, and the mean age of subjects was 52 years. Bowel function at baseline was not notably different between the treatment groups. Mean SBM frequency was 1.3 SBMs/week and mean constipation severity was 2.4 (moderate). See [Table 2](#), [Table 4](#) and [Table 5](#) in section 6.1.2 for further details.

Rescue Laxative Use

See section [6.1.10 Additional Efficacy Issues/Analyses](#).

Opioid Medication Use

Opioid classes and subclasses used were summarized in [Table 6](#) in section 6.1.2. As shown in [Table 3](#), median duration of opioid use at baseline was 33.6 months in the placebo arm and 27.7 months in the lubiprostone arm. [Table 107](#) shows changes in MEDD at Month 1, Month 2, or Month 3 for both treatment groups.

Table 107. Change from Baseline in Opioid Dose by Month in OBD-1033 (ITT Population)

Time Point	Change from Baseline in Opioid Dose (Observed Combined MEDD)	Placebo (N=220)	Lubiprostone (N=219)
Month 1	n	220	219
	Mean ± Standard Deviation	0.1 ± 5.13	0.8 ± 10.62
	Median (Min, Max)	0 (-50, 39)	0 (-61, 90)
Month 2	n	204	196
	Mean ± Standard Deviation	0.6 ± 4.47	0.7 ± 10.39
	Median (Min, Max)	0 (-11, 37)	0 (-65, 120)
Month 3	n	188	179
	Mean ± Standard Deviation	0 ± 10.43	2.2 ± 16.49
	Median (Min, Max)	0 (-96, 48)	0 (-58, 159)

Source: Reviewer's table, adapted from Sponsor's Table 1.1.7.5, pages 379 to 384 of 2585, Integrated Summary of Efficacy.

Reviewer comments: *Although the Sponsor notes that there were no notable differences between treatment groups in change from baseline MEDD at any month, this reviewer notes that monthly analysis of MEDD changes is inadequate. A monthly average does not provide an adequate picture of changes in opioid use over the course of the trial, as daily or weekly changes may be lost when all values are averaged over the month. Thus, rigorous conclusions regarding the effects of lubiprostone on opioid use cannot be made. See section 7.3.5 [Submission Specific Primary Safety Concerns](#).*

Treatment Compliance

Mean compliance with the double-blind drug was 91% in the lubiprostone group and 88% in the placebo group. At least 70% compliance was demonstrated by 95% of subjects in the lubiprostone group and 94% of subjects in placebo group. There were no notable differences between treatment groups in compliance measures.

Analysis of Efficacy

Of the 447 subjects randomized in trial OBD-1033, 8 subjects (6 placebo subjects and 2 lubiprostone subjects) were excluded from the safety evaluable and ITT population due to not taking any doses of study medication.

Primary Efficacy Analyses

Primary efficacy analyses are in section [6.1.4 Analysis of Primary Endpoint\(s\)](#).

Secondary Efficacy Analyses

Secondary efficacy analyses are presented in section [6.1.5 Analysis of Secondary Endpoints\(s\)](#). Results of additional secondary efficacy analyses are included below.

Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction – mITT, Completer, and Per-Protocol Populations

The mean change from baseline in SBM frequency at Week 8 in subjects without dose reduction (the primary efficacy endpoint in trials OBD-0631 and OBD-0632) was analyzed as a secondary efficacy endpoint in trial OBD-1033. Results for the ITT population were presented previously in [Table 18](#). Results for the mITT, completer, and per-protocol populations are presented in [Table 108](#), [Table 109](#) and [Table 110](#). Because analysis of this endpoint in these populations was supportive, the Sponsor's p-values in the tables are for informational purposes only.

Table 108. Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-1033 (mITT Population)

Variable ¹	Placebo (N=213)	Lubiprostone (N=211)	P-Value ²
Baseline Observed Value			
n	210	199	
Mean ± Standard Deviation	1.4 ± 0.81	1.3 ± 0.8	
Median (Minimum, Maximum)	1.5 (0, 4)	1.0 (0, 5)	
Week 8 Observed Value			
n	175	161	
Mean ± Standard Deviation	4.0 ± 3.12	4.2 ± 3.16	
Median (Minimum, Maximum)	4.0 (0, 20)	3.7 (0, 14)	
Change from Baseline at Week 8			
n	175	161	0.079
Mean ± Standard Deviation	2.5 ± 3.06	2.9 ± 3.19	
Median (Minimum, Maximum)	2.0 (-3, 20)	2.3 (-3, 13)	

¹Weekly SBM (BM) frequency rate: (168 x number of SBMs (BMs)/number of hours observed)

²Sponsor's p-value is based on the treatment effect from a van Elteren test stratified by pooled site.

Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups. Additionally, Shapiro-Wilk p-value testing for normality was performed by the Sponsor and p-value was <0.001. A small p-value (<0.05) indicates non-normality.

Source: Reviewer's table, modified from Sponsor's Table 14.2.3.5, page 153 of 785, CSR of OBD-1033.

Table 109. Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-1033 (Completer Population)

Variable ¹	Placebo (N=184)	Lubiprostone (N=169)	P-Value ²
Baseline Observed Value			
n	182	161	
Mean ± Standard Deviation	1.5 ± 0.77	1.3 ± 0.78	
Median (Minimum, Maximum)	1.5 (0, 4)	1.0 (0, 3)	
Week 8 Observed Value			
n	175	155	
Mean ± Standard Deviation	4.0 ± 3.13	4.2 ± 3.13	
Median (Minimum, Maximum)	4.0 (0, 20)	4.0 (0, 14)	
Change from Baseline at Week 8			
n	175	155	
Mean ± Standard Deviation	2.5 ± 3.07	2.9 ± 3.16	0.113
Median (Minimum, Maximum)	2.0 (-3, 20)	2.5 (-3, 13)	

¹Weekly SBM (BM) frequency rate: (168 x number of SBMs (BMs)/number of hours observed)

²Sponsor's p-value is based on the treatment effect from a van Elteren test stratified by pooled site.

Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups. Additionally, Shapiro-Wilk p-value testing for normality was performed by the Sponsor and p-value was <0.001. A small p-value (<0.05) indicates non-normality.

Source: Reviewer's table, modified from Sponsor's Table 2.7.3.3-19, page 54 of 119, Summary of Clinical Efficacy.

Table 110. Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction in OBD-1033 (Per-Protocol Population)

Variable ¹	Placebo (N=179)	Lubiprostone (N=177)	P-Value ²
Baseline Observed Value			
n	177	169	
Mean ± Standard Deviation	1.3 ± 0.74	1.2 ± 0.76	
Median (Minimum, Maximum)	1.5 (0, 3)	1.0 (0, 3)	
Week 8 Observed Value			
N	153	143	
Mean ± Standard Deviation	3.9 ± 3.15	4.3 ± 3.17	
Median (Minimum, Maximum)	3.1 (0, 20)	4.0 (0, 14)	
Change from Baseline at Week 8			
n	153	143	
Mean ± Standard Deviation	2.5 ± 3.08	3.0 ± 3.19	0.056
Median (Minimum, Maximum)	2.0 (-2, 20)	2.5 (-3, 13)	

¹Weekly SBM (BM) frequency rate: (168 x number of SBMs (BMs)/number of hours observed)

²Sponsor's p-value is based on the treatment effect from a van Elteren test stratified by pooled site.

Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups. Additionally, Shapiro-Wilk p-value testing for normality was performed by the Sponsor and p-value was <0.001. A small p-value (<0.05) indicates non-normality.

Source: Reviewer's table, modified from Sponsor's Table 2.7.3.3-20, page 55 of 119, Summary of Clinical Efficacy.

The change from baseline in SBM frequency at Week 8 favored the lubiprostone and placebo groups in the mITT population (2.9 versus 2.5), completer population (2.9 versus 2.5) and per-protocol population (3.0 versus 2.5) in a fashion similar to the analysis in the ITT population.

Health-Related Quality of Life: PAC-QOL Subscale Scores

Health-related quality of life measures were analyzed for the ITT population. Changes in PAC-QOL total score (a pre-specified secondary endpoint) were discussed in [Table 23](#) of section 6.1.5. In addition to the total score, the PAC-QOL comprises four subscales

(dissatisfaction, physical discomfort, psychosocial discomfort, and worries and concerns), each scored on a 5-point Likert scale (from 0 to 4). A lower score indicates better quality of life and according to the Sponsor, a 1-point improvement from baseline is considered to be clinically meaningful in subjects with constipation. The Sponsor analyzed changes from baseline in these subscales at Month 1, 2, and 3, and results are summarized in [Table 111](#).

Table 111. Change from Baseline in PAC-QOL Subscale Scores by Month for OBD-1033 (ITT)

Change from Baseline in Subscale Score by Month	Placebo (N=220)	Lubiprostone (N=219)
Dissatisfaction		
Month 1, n	207	210
Mean ± Standard Deviation, Median	-0.80 ± 1.118, -0.60	-1.01 ± 1.195, -0.80
Month 2, n	194	191
Mean ± Standard Deviation, Median	-1.00 ± 1.178, -0.80	-1.14 ± 1.337, -1.00
Month 3, n	150	132
Mean ± Standard Deviation, Median	-1.08 ± 1.346, -0.60	-1.22 ± 1.415, -1.00
Physical Discomfort		
Month 1, n	207	210
Mean ± Standard Deviation, Median	-0.65 ± 0.847, -0.50	-0.78 ± 0.946, -0.75
Month 2, n	194	191
Mean ± Standard Deviation, Median	-0.89 ± 0.995, -0.75	-0.95 ± 1.047, -1.00
Month 3, n	150	132
Mean ± Standard Deviation, Median	-1.05 ± 0.997, -1.00	-0.97 ± 1.108, -0.88
Psychosocial Discomfort		
Month 1, n	207	210
Mean ± Standard Deviation, Median	-0.41 ± 0.911, -0.25	-0.56 ± 0.897, -0.38
Month 2, n	194	191
Mean ± Standard Deviation, Median	-0.61 ± 0.909, -0.38	-0.70 ± 0.955, -0.50
Month 3, n	150	132
Mean ± Standard Deviation, Median	-0.67 ± 0.923, -0.50	-0.72 ± 0.956, -0.63
Worries and Concerns		
Month 1, n	207	210
Mean ± Standard Deviation, Median	-0.55 ± 0.877, -0.45	-0.68 ± 0.941, -0.45
Month 2, n	194	191
Mean ± Standard Deviation, Median	-0.71 ± 0.977, -0.55	-0.83 ± 1.012, -0.73
Month 3, n	150	132
Mean ± Standard Deviation, Median	-0.80 ± 1.018, -0.68	-0.87 ± 1.074, -0.73

Source: Reviewer's table, adapted from Sponsor's Table 14.2.16, pages 211 to 222 of 785, CSR for OBD-1033.

Reviewer comments: As with changes from baseline in the PAC-QOL total score by month, changes from baseline in scores for the four PAC-QOL subscales were not notably different between treatment groups at any of the observed time points.

Exploratory Efficacy Analyses

Weekly and Monthly Assessment of Overall Treatment Effectiveness

Treatment effectiveness (a PRO) was assessed using scores ranging from 0 for not at all effective to a score of 4 for extremely effective, using both LOCF analysis and non-LOCF analysis. For completeness, the non-LOCF results by week and month, respectively, are summarized in [Table 112](#) and [Table 113](#). An assessment of the results was discussed previously in section [6.1.6 Other Endpoints](#).

Table 112. Treatment Effectiveness by Week in OBD-1033 (ITT Population)

Time Point	Treatment Effectiveness by Week ¹	Placebo (N=220)	Lubiprostone (N=219)
Week 1	n	206	198
	Mean ± Standard Deviation, Median	1.3 ± 1.09, 1.0	1.6 ± 1.19, 1.0
Week 2	n	202	192
	Mean ± Standard Deviation, Median	1.5 ± 1.10, 1.0	1.6 ± 1.15, 2.0
Week 3	n	194	187
	Mean ± Standard Deviation, Median	1.5 ± 1.18, 1.5	1.7 ± 1.19, 2.0
Week 4	n	196	185
	Mean ± Standard Deviation, Median	1.6 ± 1.23, 2.0	1.9 ± 1.24, 2.0
Week 5	n	193	187
	Mean ± Standard Deviation, Median	1.6 ± 1.14, 2.0	1.8 ± 1.27, 2.0
Week 6	n	186	185
	Mean ± Standard Deviation, Median	1.7 ± 1.17, 2.0	1.8 ± 1.25, 2.0
Week 7	n	178	178
	Mean ± Standard Deviation, Median	1.7 ± 1.17, 2.0	1.8 ± 1.19, 2.0
Week 8	n	178	178
	Mean ± Standard Deviation, Median	1.8 ± 1.24, 2.0	2.0 ± 1.28, 2.0
Week 9	n	177	168
	Mean ± Standard Deviation, Median	1.8 ± 1.24, 2.0	2.0 ± 1.26, 2.0
Week 10	n	181	165
	Mean ± Standard Deviation, Median	1.8 ± 1.24, 2.0	2.0 ± 1.25, 2.0
Week 11	n	179	160
	Mean ± Standard Deviation, Median	1.8 ± 1.27, 2.0	2.0 ± 1.23, 2.0
Week 12	n	176	153
	Mean ± Standard Deviation, Median	1.8 ± 1.32, 2.0	1.9 ± 1.29, 2.0

¹Treatment effectiveness: 0 = Not at all, 1 = A little bit, 2 = Moderately, 3 = Quite a bit, 4 = Extremely

Source: Reviewer's table, adapted from Table 1.3.22.2, module 5.3.5.3, pages 2305-2308, Integrated Summary of Efficacy.

Table 113. Treatment Effectiveness by Month in OBD-1033 (ITT Population)

Time Point	Treatment Effectiveness by Week ¹	Placebo (N=220)	Lubiprostone (N=219)
Month 1	n	216	209
	Mean ± Standard Deviation, Median	1.5 ± 0.96, 1.5	1.7 ± 1.04, 1.7
Month 2	n	200	195
	Mean ± Standard Deviation, Median	1.7 ± 1.11, 1.7	1.8 ± 1.14, 2.0
Month 3	n	190	180
	Mean ± Standard Deviation, Median	1.8 ± 1.21, 1.9	1.9 ± 1.19, 2.0

¹Treatment effectiveness: 0 = Not at all, 1 = A little bit, 2 = Moderately, 3 = Quite a bit, 4 = Extremely

Source: Reviewer's table, adapted from Table 1.3.23.2, module 5.3.5.3, page 2330 of 2585, Integrated Summary of Efficacy.

Subgroup Analyses

Opioid Class and Subclass

Results of subgroup analyses of the primary efficacy endpoint (overall SBM response) by opioid class and phenanthrene opioid subclass were previously presented in [Table 57](#) and [Table 58](#), respectively. As an additional post hoc analysis, the Sponsor evaluated the primary efficacy endpoint for OBD-0631 (the mean change from baseline at Week 8 in subjects without dose reduction) by opioid class/subclass for trial OBD-1033. Results are presented in [Table 114](#) and [Table 115](#).

Table 114. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Opioid Class in OBD-1033 (ITT Population)

Change from Baseline at Week 8	Placebo (N=220)	Lubiprostone (N=219)
Phenylpiperidines		
n	12	14
Mean ± SD	2.6 ± 2.90	2.2 ± 3.05
Median	1.7	1.9
Phenanthrenes		
n	180	161
Mean ± SD	2.5 ± 3.03	2.9 ± 3.23
Median	2.0	2.3

Source: Reviewer's table, modified from Sponsor's Response to 74-Day Letter, Table 5, page 11 and Table 7, page 15.

Table 115. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Phenanthrene Opioid Subclass in OBD-1033 (ITT Population)

Change from Baseline at Week 8	Placebo (N=220)	Lubiprostone (N=219)
Hydrocodones		
n	115	97
Mean ± SD	2.7 ± 3.28	3.2 ± 3.31
Median	2.5	2.5
Morphines		
n	28	26
Mean ± SD	2.2 ± 2.65	2.4 ± 3.14
Median	1.5	1.5
Oxycodones		
n	49	52
Mean ± SD	2.4 ± 2.41	3.0 ± 3.36
Median	1.8	2.1

Source: Reviewer's table, modified from Response to 74-Day Letter, Table 11, page 21; Table 13, page 23; and Table 15, page 25.

Reviewer comments: *As with the findings for OBD-1033 using the overall SBM response endpoint (see [Table 57](#)) and the findings for OBD-0631 using the mean change from baseline in SBM frequency at Week 8 endpoint (see [Table 60](#)), the number of subjects taking a phenylpiperidine opioid was probably too small to draw any meaningful conclusions. Similarly, as with the findings for OBD-1033 (see [Table 58](#)), the treatment difference between arms was negligible for the morphine subclass, but among the opioid subclasses, the morphine subclass also had the smallest sample size. Further, although the mean treatment difference between arms favoring lubiprostone was minimal for the oxycodone subclass in OBD-0631 (see [Table 61](#)), this finding was not corroborated by the oxycodone subclass analysis in OBD-1033, which shows a more substantial mean change from baseline in SBM frequency at Week 8 in the lubiprostone group than the placebo group (3.0 versus 2.4).*

Safety Monitoring and Adverse Events

Safety

Safety was evaluated by AE reporting, vital signs, physical examination, and laboratory evaluations. AEs were assessed from the start of the trial through the final follow-up visit. Verbatim AEs were coded into standardized system organ classes and preferred

terms using MedDRA. The safety window for determining whether or not an AE was treatment emergent was defined as the span of time between the first dose of study drug and the last dose of study drug plus 7 days. The Sponsor considered an AE treatment emergent if it occurred within the safety window.

Safety Analyses

The safety analyses included all randomized subjects who took at least one dose of study medication and were performed based on observed data. A total of 439 subjects took at least one dose of study drug and were included in safety evaluations: 219 subjects in the lubiprostone group and 220 subjects in the placebo group.

Adverse Events

Of the 439 subjects in the safety population, 228 (52%) experienced at least one treatment-emergent AE. At least one AE was reported by 120 subjects (55%) in the lubiprostone group and 108 subjects (49%) in the placebo group. Among the safety population, 59 (27%) subjects in the lubiprostone group experienced an AE in the gastrointestinal disorders SOC; whereas 41 (19%) of the placebo group experienced an AE in the gastrointestinal disorders SOC. At total of 94 subjects (21%) had AEs that the Sponsor reported as treatment related, 62 (28%) in the lubiprostone group, and 32 (15%) in the placebo group.

Serious Adverse Events

A total of 14 subjects (3%) experienced at least one SAE; 7 subjects (3%) were in the lubiprostone group and 7 subjects (3%) were in the placebo group. The most frequent SAEs, at the SOC level, were gastrointestinal disorders; injury, poisoning and procedural complications; musculoskeletal and connective tissue disorders; and nervous system disorders in three subjects (1%) each. Of the three subjects in the gastrointestinal disorders SOC who experienced SAEs, one subject in the lubiprostone group had abdominal pain, nausea, and vomiting; in the placebo group, one subject had upper abdominal pain and one subject had a fecaloma. Detailed listings of subjects with SAEs are provided in [Table 83](#) of section 7.3.2.

Deaths

One subject died in trial OBD-1033, from causes that could not be clearly linked to the study drug. The subject's death narrative is presented in section [7.3.1 Deaths](#).

Reviewer's Summary of Trial OBD-1033

For the primary endpoint of overall SBM response in the ITT population, there were 27% (59 of 219 subjects) in the lubiprostone group compared with 19% (41 of 220 subjects) in the placebo group. The results of the primary endpoint demonstrated statistically significant improvement (8%, $p=0.035$) compared to placebo.

Inferential analyses were not statistically valid with respect to most secondary efficacy endpoints due to a lack of pre-specified hierarchies and incomplete or absent adjustments for multiplicity. When descriptive statistics alone are considered for the ITT population, the results of the secondary endpoints of mean change from baseline in

SBM frequency at Week 8 in subjects without dose reduction, mean change from baseline in SBM frequency at Week 12, and overall change from baseline in SBM frequency also supported the findings of the primary endpoint.

AEs were discussed earlier in this Appendix and there was one death in the trial, which, in this medical officer's assessment, is not related to the study medication.

Appendix 3: Discussion of Individual Trials: Trial SMR/0211 OBD-0631

Title

"A Multicenter, Randomized, Placebo-controlled, Double-blinded Study of the Efficacy and Safety of Lubiprostone in Subjects with Opioid-induced Bowel Dysfunction"

Objectives

"To assess the efficacy and safety of oral lubiprostone at 48 mcg/day (24 mcg BID), as compared to placebo, when administered orally for 12 weeks to subjects with OBD"

Trial Design

Randomized, placebo-controlled, double-blind, parallel-group phase 3 trial

Duration

The trial started on August 3, 2007 and ended on March 6, 2009. The trial consisted of a screening visit 3 weeks prior to first dose of medication, a double blind period of 12 weeks, and a follow up visit at Week 14. Once subjects completed treatment, they had the option to enroll in a long-term, open-label, safety extension trial (OBD-06S1) for an additional 9 months.

Key Inclusion Criteria

Key inclusion criteria were identical to those for trial OBD-1033, with the notable exception that subjects with a history of being treated consistently for chronic, non-cancer related pain with any oral, transdermal, intravenous, or subcutaneous opioid (full agonist), *including methadone or a congener of methadone*, for at least 30 days prior to screening, and continued opioid therapy throughout the trial, were eligible. The numbering of inclusion criteria was identical to trial OBD-1033 (see [Appendix 2: Discussion of Individual Trials: Trial SMR/0211 OBD-1033](#)).

Key Exclusion Criteria

Key exclusion criteria were identical to those for trial OBD-1033, with the exception that use of methadone or a congener of methadone either alone or as part of opioid regimen was *not* an exclusion criterion. This key difference in exclusion criteria between trials OBD-1033 and OBD-0631 accounts for the slightly different numbering of exclusion criteria between the two trials. Complete exclusion criteria for OBD-0631 were:

1. Receiving opioid therapy for cancer-related pain, abdominal pain, scleroderma, and/or for the management of drug addiction.

2. Current evidence of, or had been treated for, cancer within the past 5 years (with the exception of localized basal cell skin cancer, squamous cell skin cancer, or *in situ* cancer that had been resected).
3. Had adjusted (increased or decreased by $\pm 30\%$) dosage (in morphine equivalent daily dose [MEDD]) of opioid treatment, had changed opioid agents, or had changed route of opioid administration within 30 days of screening, or was likely to discontinue or adjust dosage by $\pm 30\%$ over the course of the trial.
4. Known or suspected anatomic or organic disorders of the large or small bowel; e.g. associated with a mechanical bowel obstruction (e.g., tumor, hernia, obstructive polyps), or pseudo-obstruction or associated with large or small bowel disorder such as ulcerative colitis or Crohn's disease.
5. History of constipation that, according to investigator's clinical judgment, was not result of or not exacerbated by opioid use, or was suffering from known or suspected secondary cause of constipation, including but not limited to: dietary disorders (e.g., malnutrition), neurologic disorders (e.g., spinal cord disorders), other congenital disorder, or endocrine disorders (e.g., diabetes).
6. Impaired renal function at Screening Visit (i.e., serum creatinine >1.8 mg/dL).
7. History of unexplained, clinically significant weight loss defined as $>5\%$ weight loss within 90 days prior to Screening Visit.
8. History of gastrointestinal or abdominal surgical procedure within 90 days prior to the Screening Visit or had a bowel resection at any time.
9. Non-ambulatory.
10. Inability to eat or drink, take oral medications, or to hold down oral medications due to vomiting.
11. Female of childbearing potential who was unable or unwilling to use a protocol-specified method of birth control.
12. Female of childbearing potential who had a positive screening pregnancy test, was currently pregnant or nursing, or planned to become pregnant or nurse during the clinical trial.
13. History of clinically significant cardiovascular disease (according to the investigator's clinical judgment).
14. History of clinically significant, unexplained liver or lung disease, neurologic or psychiatric disorders (excluding depression), or any other systemic disease. If explained, the subject may have been enrolled, if in the investigator's opinion, the condition would not interfere with safety or efficacy assessments, or result in an increased risk of participation to the subject.
15. History of alcohol or drug abuse within 180 days prior to Screening Visit.
16. Demonstrated a potential for non-compliance with the trial protocol (i.e., dosing schedule, visit schedule, diary completion, or trial procedures).
17. Participated in another study with an investigational drug, device, or procedure within the 30 days preceding the Screening Visit.
18. Had received Amitiza®, at any time prior to participation in this trial.

Treatments

Treatment screening period and treatment period were essentially identical to the design of trial OBD-1033. The schedule of visits is summarized in [Table 116](#).

Table 116. Schedule of Visits – Trials OBD-0631 and OBD-0632

Study Stage	Screening	Randomization	Study Treatment and Evaluation (Day 0 to 84)						Follow-up
			1	4	6	8	10	12	
Study Week	-3	0	1	4	6	8	10	12	14
Study Day	-21 (- 3)	0	7 (± 3)	28 (± 3)	42 (± 3)	56 (± 3)	70 (± 3)	84 (± 3)	98 (± 3)
Visit Number	1	2	3	4	5	6	7	8	9
Visit Type	Screening	Randomization	Telephone Assessment	Clinic Examination	Telephone Assessment	Clinic Examination	Telephone Assessment	Clinic Examination	Follow-up Clinic Examination
Assessment									
Informed Consent	X								
Demographics	X								
Medical History	X	X							
Vital Signs ¹	X	X		X		X		X	X
Physical Examination	X			X ²		X ²		X	X ²
Blood Chemistry, Hematology, Urinalysis	X			X		X		X	X
Electrocardiogram	X							X	X
Pregnancy Test ³	X	X		X		X		X	X
Concomitant Medications	X ⁴	X	X	X	X	X	X	X	X
Adverse Events ⁵		X	X	X	X	X	X	X	X
Study Medication Distribution		X		X		X			
Study Treatment ⁶			X	X	X	X	X	X	
Study Medication Collection				X		X		X	
Electronic Diary	X ⁷	X	X	X	X	X	X	X	X

¹ Height is captured at the Screening Visit only. Weight is captured at the Screening and Follow-up Visits;

² Abbreviated physical examinations will be performed at designated visits;

³ A serum pregnancy test will be performed at the Screening Visit. Urine pregnancy tests will be performed at all other study visits;

⁴ Will include history of medications used within 30 days of the Screening Visit as well as full history of all constipation treatment administered since onset of OBD;

⁵ AEs occurring prior to the first dose will be recorded as medical history. All AEs reported after the first administration of study medication will be recorded on the AE eCRF;

⁶ First treatment administration is to be self-administered by the subject on Study Day 0 (the day of the Randomization Visit). If the subject has used any rescue laxative within 24 hours of the Randomization Visit (Visit 2), the subject will be instructed to start study medication on the second day after the Randomization Visit. The day of first dose will be considered Study Day 0 and all subsequent visits will be scheduled based on the first treatment day;

⁷ Electronic diaries are to be distributed to subjects at the Screening Visit.

Source: Sponsor's Table, module 5.3.5.1.4 Clinical Protocol SMR/0211OBD-0631, page 13 of 60.

Trial Conduct

Trial conduct was identical to trial OBD-1033, with the following differences:

- The PAC-QOL and EQ-5D questionnaires were not used in trial OBD-0631.
- For subjects who were eligible and who chose to participate in the 9-month open label trial OBD-06S1, the visit on Day 84 was the last visit prior to entry into the open-label trial. The final assessments that would otherwise be performed at the final follow-up assessment visit on Day 98 would instead be conducted at the last visit of the open-label extension trial.

Removal of Subjects from Therapy or Assessment

The approach to removal of subjects from therapy or assessment was identical to that used in trial OBD-1033.

Reduction in Trial Medication

As in trial OBD-1033, a dose reduction may have been initiated by the investigator if severe nausea, severe diarrhea, or another AE was reported by the subject to the site and was ongoing for 3 or more days. In these cases the investigator, in consultation with the subject and/or medical monitor, may have reduced study medication to once daily (QD) dosing. In OBD-0631, however, once a dose reduction occurred, the dose remained reduced for the remainder of the trial. In contrast, in OBD-1033, the subject could resume the BID regimen at the investigator's discretion.

Prior and Concurrent Therapy

The protocol for prior and concurrent therapy was identical to that for OBD-1033, with the exception that the CSR for OBD-0631 does not explicitly state that use of ipratropium bromide (an anticholinergic) was allowed during the trial.

Rescue Laxatives

Subjects were allowed to use rescue laxatives during the trial; however, the use of rescue laxatives was not allowed within 24 hours prior to the first dose of the study drug or during the first week of treatment (as compared with OBD-1033, which permitted rescue laxative use beyond 72 hours following treatment initiation).

The protocol for use of rescue laxatives in OBD-0631 was identical to OBD-1033, with the exception that in OBD-0631, if both rescue laxatives failed, the investigator was permitted to prescribe another medication other than MiraLax or Zelnorm (OBD-1033 permitted another rescue laxative other than MiraLax, Relistor, or Resolor).

Compliance

The approach to assessment of compliance in trial OBD-0631 was identical to that used in trial OBD-1033.

Outcome Measures

Efficacy

Primary Efficacy Endpoint

The primary efficacy endpoint was the change in frequency of SBMs from baseline at Week 8 for subjects without dose reductions. This information was determined based on subject responses to the daily eDiary questions.

Secondary Efficacy Endpoints

Secondary efficacy endpoints for this trial included:

- Change from baseline in SBM frequency at Week 12 and overall
- Percentage of subjects with a first postdose SBM within 24 hours and 48 hours
- Overall responder rates
- Overall mean change from baseline in the following bowel function parameters:
 - Straining associated with SBMs
 - Stool consistency of SBMs
 - Constipation severity
 - Abdominal bloating
 - Abdominal discomfort
- Overall treatment effectiveness

Exploratory Efficacy Endpoints:

- Change from baseline in SBM frequency at each week for Weeks 1–11
- Change from baseline in SBM frequency at Months 1, 2, and 3
- Frequency of SBMs and BMs
- Frequency of complete SBMs and BMs
- Weekly and monthly assessment of treatment effectiveness
- Median time to first SBM
- Proportion of subjects with their first SBM at 4, 8, and 12 hours
- Overall mean change from baseline in bowel habit regularity
- Weekly and monthly change from baseline in bowel function parameters (straining, stool consistency, constipation severity, abdominal bloating, abdominal discomfort, and bowel habit regularity)

Statistical Analysis

Four datasets were to have been used for analyses: safety, ITT, per-protocol, and completer population. The definition of these datasets was identical to those for trial OBD-1033. There was no modified ITT (mITT) population in trial OBD-0631. All inferential analyses of efficacy were based on the principle of two-tailed tests at a significance level of $\alpha=0.05$.

Sponsor's Plan for Handling of Missing Data

This plan was identical to that employed for trial OBD-1033 with respect to secondary and exploratory analyses, but not so with respect to analysis of the primary efficacy endpoint. For the primary analysis, as with trial OBD-1033, for a bowel movement to count as an SBM, the BM could not have occurred within 24 hours after use of a rescue laxative. Unlike OBD-1033, however, in which the rate for subjects with <85 hours of

weekly data was considered missing for that week, in OBD-0631, if ≥ 25 but < 85 hours were observed during a week and ≥ 85 hours were observed during the prior week, then the Sponsor imputed data from the prior week to provide a total of 85 hours of data. If subjects had < 25 hours of observed data in a week, then the Sponsor considered the data insufficient and the rate missing for that week.

Primary and Secondary Analyses

The primary analysis for this trial was the change in SBM frequency from baseline at Week 8 for ITT subjects without dose reduction. The Sponsor considered subjects with no reported SBMs during the screening period to have 0 SBMs at baseline and evaluable. Weekly SBM frequency rates were calculated as: $(168 \times \text{Number of SBMs}) / (\text{Number of hours observed})$.

The number of hours was the number of hours observed in the eDiary during the week that the subject was actively enrolled in the trial and taking study medication. Weeks were calculated as 168-hour intervals starting with the exact time of the first intake of study medication. ANCOVA was used to analyze this data with baseline rate being a covariate for the Week 8 SBM rate. ITT subjects were used in this analysis provided they did not have a dose reduction prior to Week 8. The assumption of normality was examined with a Shapiro-Wilk test. The effect of clinical site was examined to determine if it should be included as a stratification factor. If the normality assumption did not hold then the Wilcoxon signed-rank test or the van Elteren test (stratified extension of the Wilcoxon) was performed to determine if significant changes from baseline occurred. Baseline was defined as the average of the diary entries from the 2 weeks prior to the administration of the first dose.

For secondary analysis, the secondary efficacy endpoints of change from baseline in SBM frequency at Week 12 and overall were analyzed in the same manner as described for the primary efficacy endpoint for all ITT subjects, inclusive of those whose dose was reduced. The overall endpoint was defined as the average weekly SBM frequency while on study medication. Inferential analysis was only to be performed if the analysis of the primary endpoint yielded a p-value < 0.05 , but there was no specified hierarchy of evaluation for these secondary endpoints. Hommel's stagewise rejective method was used to determine if either or both Week 12 and overall time points were statistically significant.

For SBMs within 24 and 48 hours of first dose, the analysis was identical to that used in OBD-1033. For overall responder rates (an endpoint intended, according to the Sponsor, to assess treatment response and to account for trial drop out and rescue laxative use), a trichotomous responder definition was employed. A non-responder was defined as any subject with an SBM frequency rate of less than 3 for a given week, any subject who dropped out during or prior to the given week due to lack of efficacy, or any subject who used rescue laxative during or within 24 hours prior to the given week. If the subject dropped out for a reason other than lack of efficacy, did not use rescue laxative, and had fewer than 85 hours within the given week, then that subject's responder status was missing. Otherwise, the subject was considered a responder. A

responder with an SBM frequency rate ≥ 3 but < 4 was considered a moderate responder. A subject with an SBM frequency rate of ≥ 4 was considered a full responder. Overall responder was defined as achieving at least moderate response for at least 50% of the weeks on trial, provided the subject was on trial for at least 8 weeks. The Cochran-Mantel-Haenszel test was used to compare overall response rates with clinical site as a stratification factor.

For mean change from baseline analyses, mean change from baseline was generated based on subject reported data as to the degree of straining associated with SBMs; stool consistency of SBMs; constipation severity; abdominal bloating; abdominal discomfort; and bowel habit irregularity. Approach to analysis was the same as in trial OBD-1033.

Exploratory Analyses

Approach to analysis was the same as in trial OBD-1033.

Protocol Amendments

There were three protocol amendments to the original protocol dated April 25, 2007.

Amendment #1 occurred on May 7, 2007 and included the following changes:

- Clarified the dose justification and trial treatment duration
- Clarified tests that comprise the safety evaluations

Amendment #2 occurred on August 30, 2007 and included the following changes:

- Updated statistical section of the protocol including sample size, endpoint analysis, and methodology
- Clarified dose reduction plan
- Clarified early termination criteria

Amendment #3 occurred on June 9, 2008 and included the following changes:

- Updated excluded medication list (allowing subjects taking antihistamines concurrently to be in trial)
- Clarified dose reduction plan
- Clarified wording of eDiary questions

Results

Disposition of Subjects

A total of 443 subjects enrolled at 80 centers in the USA and Canada, of whom 220 were randomized to receive placebo and 223 to receive lubiprostone 24 mcg BID. A total of 306 (69%) subjects completed the trial. A total of 137 subjects (31%) discontinued during the trial. Sixteen subjects (7%) in the lubiprostone group and seven subjects (3%) in the placebo group discontinued the trial due to AEs. Further details are provided in section [6.1.3 Subject Disposition](#) and section [7.3.3 Dropouts and/or Discontinuations](#).

Protocol Deviations and Violations

The Sponsor excluded ITT subjects who were determined to be protocol violators from the per-protocol analyses. The criteria utilized to determine protocol violations were identical to those used in trial OBD-1033, with one modification: in trial OBD-1033, subjects not meeting exclusion criteria numbers 1, 2, 5, 6, 9, 10, 11, 16, 17, 18, and/or 19 were considered to be in violation of protocol, whereas in trial OBD-0631, subject not meeting exclusion criteria 1, 4, 5, 8, 9, 10, 15, 16, 17, and/or 18 were considered to be in violation of protocol. The differences in numbering of exclusion criteria were due to the exclusion of subjects using methadone or congener of methadone in OBD-1033.

Of the 438 ITT subjects, a total of 129 subjects (61 subjects in the placebo arm and 68 in the lubiprostone arm) were excluded from the per-protocol population for a variety of reasons. Details of protocol violations are provided in [Table 9](#) in section 6.1.3.

Demographics and Other Baseline Characteristics

Overall, 64% of subjects were female and the mean age of subjects was 50 years. Bowel function at baseline was not notably different between the treatment groups. Mean SBM frequency was 1.4 SBMs/week and mean constipation severity was 2.3 (moderate). See [Table 2](#), [Table 4](#) and [Table 5](#) in section 6.1.2 for further details.

Rescue Laxative Use

See section [6.1.10 Additional Efficacy Issues/Analyses](#).

Opioid Medication Use

Opioid classes and subclasses used were summarized in [Table 6](#) in section 6.1.2. For the ITT population, a total of 36 subjects (17%) in the placebo group and 45 subjects (20%) in the lubiprostone group were on methadone or a congener of methadone. As shown in [Table 3](#), median duration of opioid use at baseline was 33.2 months in the placebo arm and 35.8 months in the lubiprostone arm. [Table 117](#) shows changes in MEDD at Month 1, Month 2, or Month 3 for both treatment groups.

Table 117. Change from Baseline in Opioid Dose by Month in OBD-0631 (ITT Population)

Time Point	Change from Baseline in Opioid Dose (Observed Combined MEDD)	Placebo (N=217)	Lubiprostone (N=221)
Month 1	n	216	220
	Mean ± Standard Deviation	-0.9 ± 25.56	-1.5 ± 39.89
	Median (Min, Max)	0 (-336, 83)	0 (-419, 309)
Month 2	n	188	180
	Mean ± Standard Deviation	0.5 ± 44.95	-0.7 ± 100.72
	Median (Min, Max)	0 (-490, 258)	0 (-845, 990)
Month 3	n	162	161
	Mean ± Standard Deviation	-4.6 ± 84.42	-0.4 ± 86.4
	Median (Min, Max)	0 (-816, 244)	0 (-270, 990)

Source: Reviewer's table, adapted from Sponsor's Table 1.1.7.5, pages 379 to 384 of 2585, Integrated Summary of Efficacy.

Reviewer comments: *Although the Sponsor notes that there were no notable differences between treatment groups in change from baseline MEDD at any month, this reviewer notes that monthly analysis of MEDD changes is inadequate. See discussion in section [7.3.5 Submission Specific Primary Safety Concerns](#).*

Treatment Compliance

At least 70% compliance was demonstrated by 90% of subjects in the lubiprostone group and 94% of subjects in placebo group. There were no notable differences between treatment groups in compliance measures.

Analysis of Efficacy

Of the 443 subjects randomized in trial OBD-0631, five subjects were excluded from the efficacy analysis (ITT population). Four of these subjects were excluded due to not receiving treatment (three assigned to placebo and one to lubiprostone). One subject in the lubiprostone group was randomized, but no post-baseline data were reported.

Primary Efficacy Analyses

Primary efficacy analyses are presented in section [6.1.4](#) [Analysis of Primary Endpoint\(s\)](#).

Secondary Efficacy Analyses

Secondary efficacy analyses are presented in section [6.1.5](#) [Analysis of Secondary Endpoints\(s\)](#).

Exploratory Efficacy Analyses

Weekly and Monthly Assessment of Overall Treatment Effectiveness

Treatment effectiveness (a PRO) was assessed using scores ranging from 0 for not at all effective to a score of 4 for extremely effective, using both LOCF analysis and non-LOCF analysis. For completeness, the non-LOCF results by week and month, respectively, are summarized in [Table 118](#) and [Table 119](#). An assessment of the results was discussed previously in section [6.1.6](#) [Other Endpoints](#).

Table 118. Treatment Effectiveness by Week in OBD-0631 (ITT Population)

Time Point	Treatment Effectiveness by Week ¹	Placebo (N=217)	Lubiprostone (N=221)
Week 1	n	202	198
	Mean ± Standard Deviation, Median	1.2 ± 1.09, 1.0	1.5 ± 1.17, 1.0
Week 2	n	192	191
	Mean ± Standard Deviation, Median	1.3 ± 1.17, 1.0	1.7 ± 1.20, 2.0
Week 3	n	190	190
	Mean ± Standard Deviation, Median	1.3 ± 1.17, 1.0	1.6 ± 1.14, 2.0
Week 4	n	185	182
	Mean ± Standard Deviation, Median	1.3 ± 1.13, 1.0	1.8 ± 1.27, 2.0
Week 5	n	174	173
	Mean ± Standard Deviation, Median	1.4 ± 1.12, 1.0	1.8 ± 1.16, 2.0
Week 6	n	169	168
	Mean ± Standard Deviation, Median	1.4 ± 1.16, 1.0	1.8 ± 1.20, 2.0
Week 7	n	165	167
	Mean ± Standard Deviation, Median	1.4 ± 1.10, 1.0	1.8 ± 1.18, 2.0
Week 8	n	165	166
	Mean ± Standard Deviation, Median	1.4 ± 1.13, 1.0	1.8 ± 1.23, 2.0
Week 9	n	157	162
	Mean ± Standard Deviation, Median	1.4 ± 1.23, 1.0	1.8 ± 1.22, 2.0
Week 10	n	163	155
	Mean ± Standard Deviation, Median	1.4 ± 1.19, 1.0	1.8 ± 1.28, 2.0
Week 11	n	153	150
	Mean ± Standard Deviation, Median	1.4 ± 1.21, 1.0	1.8 ± 1.25, 2.0
Week 12	n	107	104
	Mean ± Standard Deviation, Median	1.5 ± 1.27, 1.0	1.8 ± 1.34, 2.0

¹Treatment effectiveness: 0 = Not at all effective, 1 = A little bit effective, 2 = Moderately effective, 3 = Quite a bit effective, 4 = Extremely effective

Source: Reviewer's table, adapted from Table 1.3.22.2, module 5.3.5.3, pages 2305 to 2308, Integrated Summary of Efficacy.

Table 119. Treatment Effectiveness by Month in OBD-0631 (ITT Population)

Time Point	Treatment Effectiveness by Month ¹	Placebo (N=217)	Lubiprostone (N=221)
Month 1	n	205	210
	Mean ± Standard Deviation, Median	1.3 ± 1.02, 1.3	1.6 ± 1.05, 1.8
Month 2	n	182	179
	Mean ± Standard Deviation, Median	1.3 ± 1.01, 1.3	1.8 ± 1.09, 2.0
Month 3	n	165	162
	Mean ± Standard Deviation, Median	1.4 ± 1.15, 1.3	1.8 ± 1.19, 2.0

¹Treatment effectiveness: 0 = Not at all effective, 1 = A little bit effective, 2 = Moderately effective, 3 = Quite a bit effective, 4 = Extremely effective

Source: Reviewer's table, adapted from Sponsor's Table 1.3.23.2, module 5.3.5.3, page 2330, Integrated Summary of Efficacy.

Subgroup Analyses

Opioid Class and Subclass

Results of subgroup analyses of the primary efficacy endpoint (overall SBM response) by opioid class and phenanthrene opioid subclass were previously presented in [Table 60](#) and [Table 61](#), respectively. As additional exploratory analyses, the Sponsor evaluated the primary efficacy endpoint for OBD-1033 (overall SBM response) by opioid class/subclass for trial OBD-0631. Results are presented in [Table 120](#) and [Table 121](#).

Table 120. Analysis of Overall SBM Response by Opioid Class in OBD-0631 (ITT Population)

Overall SBM Response ¹	Placebo (N=217)	Lubiprostone (N=221)
Phenylpiperidines		
n	17	24
Responder, n (%)	3 (17.6)	3 (12.5)
Phenanthrenes		
n	179	174
Responder, n (%)	28 (15.6)	44 (25.3)
Diphenylheptanes		
n	35	43
Responder, n (%)	2 (5.7)	9 (20.9)

¹Overall SBM response defined as ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥ 3 SBMs per week for at least 9 of the 12 treatment weeks.

Source: Reviewer's table, modified from Response to 74-Day Letter, Table 4, page 10; Table 6, page 14; and Table 8, page 17.

Table 121. Overall SBM Response by Phenanthrene Opioid Subclass in OBD-0631 (ITT Population)

Overall SBM Response ¹	Placebo (N=217)	Lubiprostone (N=221)
Hydrocodones		
n	81	97
Responder, n (%)	20 (24.7)	28 (28.9)
Morphines		
n	59	53
Responder, n (%)	8 (13.6)	11 (20.8)
Oxycodones		
n	70	72
Responder, n (%)	9 (12.9)	14 (19.4)

¹Overall SBM response defined as ≥ 1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥ 3 SBMs per week for at least 9 of the 12 treatment weeks.

Source: Reviewer's table, modified from Response to 74-Day Letter, Table 10, page 20; Table 12, page 22; and Table 14, page 24.

Reviewer comments: *The number of subjects taking a phenylpiperidine opioid was probably too small to draw any meaningful conclusions. The treatment effect favoring lubiprostone subjects by phenanthrene class was 9.7%. Notably, analysis of the overall SBM response by diphenylheptane class favored the lubiprostone subjects over the placebo subjects by a sizeable margin (20.9% versus 5.7% responders). Although firm conclusions are limited by the small sample size and the post hoc nature of these analyses, the findings are still unexpected given the nonclinical study in which the Sponsor demonstrated an inhibitory action by methadone on lubiprostone. The treatment difference favored lubiprostone for each of the phenanthrene subclasses, and although firm conclusions are limited for reasons mentioned previously, overall SBM response does not appear to be influenced by the phenanthrene class or subclasses.*

Safety Monitoring and Adverse Events

Safety

Safety evaluation was identical to the approaches employed in OBD-1033. The safety window for determining whether or not an AE was treatment emergent was defined as the span of time between the first dose of study drug and the last dose of study drug plus 7 days. If subjects enrolled in the extension trial (OBD-06S1), then the safety window ended on the date of first dose for the extension trial or last dose in the double-

blind trial plus 7 days, whichever came first. An AE was considered treatment emergent if it occurred within the safety window.

Safety Analyses

The safety analyses included all randomized subjects who took at least one dose of study medication and were performed based on observed data. A total of 439 subjects took at least one dose of study drug and were included in safety evaluations: 221 subjects in the lubiprostone group and 218 subjects in the placebo group.

Adverse Events

Of the 439 subjects in the safety population, 259 (59%) experienced at least one TEAE. At least one AE was reported by 142 subjects (64%) in the lubiprostone group and 117 subjects (54%) in the placebo group. Among the safety population, 80 (36%) subjects in the lubiprostone group experienced an AE in the gastrointestinal disorders SOC; whereas 42 (19%) of the placebo group experienced an AE in the gastrointestinal disorders SOC. A total of 129 subjects (29%) had AEs that the Sponsor considered treatment related, 80 (36%) in the lubiprostone group, and 49 (23%) in the placebo group.

Serious Adverse Events

A total of 20 subjects (5%) experienced at least one SAE; 11 subjects (2%) were in the lubiprostone group and 9 subjects (2%) were in the placebo group. The most frequent SAEs, at the SOC level, were infections and infestations, experienced by two subjects (1%) in the lubiprostone group and four subjects (2%) in the placebo group. Of the subjects in the infections and infestations SOC who experienced SAEs, one subject in the lubiprostone group had gastroenteritis and one had cellulitis; in the placebo group, one subject had gastroenteritis, one had pneumonia, one had bronchitis, and one subject had appendicitis. Detailed listings of subjects with SAEs are provided in [Table 83](#) of section 7.3.2.

Deaths

No subjects died in trial OBD-0631.

Reviewer's Summary of Trial OBD-0631

For the primary endpoint of change from baseline in SBM frequency at Week 8 in subjects without dose reduction in the ITT population, the mean change was 3.2 in the lubiprostone group compared with 2.4 in the placebo group. The results of the primary endpoint demonstrated statistically significant improvement (0.8, $p=0.019$) compared to placebo.

Inferential analyses were not statistically valid with respect to most secondary efficacy endpoints due to a lack of pre-specified hierarchies and incomplete or absent adjustments for multiplicity. When descriptive statistics alone are considered for the ITT population, the results of the secondary endpoints of mean change from baseline in SBM frequency at Week 12, overall change from baseline in SBM frequency, and overall responder rates also supported the findings of the primary endpoint.

AEs were discussed earlier in this Appendix and there were no deaths in the trial.

Appendix 4: Discussion of Individual Trials: Trial SMR/0211 OBD-0632

Title

“A Multicenter, Randomized, Placebo-controlled, Double-blinded Study of the Efficacy and Safety of Lubiprostone in Subjects with Opioid-induced Bowel Dysfunction”

The trial started on August 6, 2007 and ended on March 6, 2009. The objectives, trial design, inclusion/exclusion criteria, trial protocol, protocol amendments, and outcome measures were identical to trial OBD-0631 (see [Appendix 3: Discussion of Individual Trials: Trial SMR/0211 OBD-0631](#)). For schedule of visits, see [Table 116](#).

Results

Disposition of Subjects

A total of 451 subjects enrolled at 88 centers in the USA and Canada, of whom 216 were randomized to receive placebo and 235 to receive lubiprostone 24 mcg BID. A total of 305 (68%) subjects completed the trial. A total of 146 subjects (32%) discontinued during the trial. Nine subjects (4%) in the lubiprostone group and five subjects (2%) in the placebo group discontinued due to AEs. Further details are in section [6.1.3 Subject Disposition](#) and [7.3.3 Dropouts and/or Discontinuations](#).

Protocol Deviations and Violations

ITT subjects who were determined to be protocol violators were excluded from the per-protocol analyses. The criteria utilized to determine protocol violations were identical to those used in trial OBD-0631. Of the 435 ITT subjects, a total of 138 subjects (65 subjects in the placebo arm and 73 in the lubiprostone arm) were excluded from the per-protocol population for a variety of reasons. See [Table 9](#) in section 6.1.3.

Demographics and Other Baseline Characteristics

Overall, 61% of subjects were female and the mean age of subjects was 49 years. Bowel function at baseline was not notably different between the treatment groups. Mean SBM frequency was 1.6 SBMs/week and mean constipation severity was 2.3 (moderate). See [Table 2](#), [Table 4](#) and [Table 5](#) in section 6.1.2 for further details.

Rescue Laxative Use

As summarized in [Table 122](#), there were no notable differences between treatment groups in overall rescue laxative use at baseline, overall, or at Months 1, 2, or 3. At baseline, 63% of lubiprostone subjects used rescue laxatives as compared with 51% overall at the end of the trial (decline of 12%). As presented in [Table 123](#), overall, the mean percent of days of rescue laxative use was 8% for placebo and 7% for lubiprostone. Differences between treatment groups at Month 1, Month 2, and Month 3 were also small, with the placebo group having a higher mean percent of days of rescue laxative use for each month than the lubiprostone group.

Table 122. Monthly Summary of Subjects with Rescue Laxative Use - OBD-0632 (Safety-Evaluable)

Time Point	Placebo (N=213)	Lubiprostone (N=224)
Baseline, n	212	224
Rescue med used, n (%)	132 (62.3)	142 (63.4)
Month 1, n	212	223
Rescue med used, n (%)	99 (46.7)	93 (41.7)
Month 2, n	186	202
Rescue med used, n (%)	71 (38.2)	61 (30.2)
Month 3, n	170	174
Rescue med used, n (%)	52 (30.6)	50 (28.7)
Overall, n	213	222
Rescue med used, n (%)	116 (54.5)	113 (50.9)

Source: Reviewer's table, from Sponsor's data, module 5.3.5.3, Table 1.1.10, pages 415-416, Integrated Summary of Efficacy.

Table 123. Percent Days of Rescue Laxative Use by Month - OBD-0632 (Safety-Evaluable)

Time Point	Percent of Days of Rescue Laxative Use	Placebo (N=213)	Lubiprostone (N=224)
Overall	n	116	113
	Mean ± Standard Deviation	7.7 ± 14.49	6.7 ± 15.80
	Median (Min, Max)	1.3 (0.0, 93.8)	1.2 (0.0, 100.0)
Month 1	n	99	93
	Mean ± Standard Deviation	8.3 ± 15.12	6.6 ± 15.43
	Median (Min, Max)	0.0 (0.0, 96.4)	0.0 (0.0, 100.0)
Month 2	n	71	61
	Mean ± Standard Deviation	6.9 ± 13.56	5.0 ± 12.88
	Median (Min, Max)	0.0 (0.0, 84.0)	0.0 (0.0, 100.0)
Month 3	n	52	50
	Mean ± Standard Deviation	5.2 ± 11.15	4.7 ± 11.28
	Median (Min, Max)	0.0 (0.0, 81.5)	0.0 (0.0, 92.9)

Source: Reviewer's table, adapted from Sponsor's Table 14.3.16, page 456 to 457 of 1157, CSR of OBD-0632.

Opioid Medication Use

Opioid classes and subclasses used were summarized in [Table 6](#) in section 6.1.2. For the ITT population, a total of 41 subjects (19%) in the placebo group and 44 subjects (20%) in the lubiprostone group were on methadone or a congener of methadone. As shown in [Table 3](#), median duration of opioid use at baseline was 35.3 months in the placebo arm and 37.7 months in the lubiprostone arm. As shown in [Table 124](#), there were no notable differences between treatment groups in changes in MEDD at Month 1, Month 2. For Month 3, the lubiprostone group appears on average to have had a larger reduction in MEDD than the placebo group, but the mean change in the lubiprostone group (-42.8) might be a reflection of outlier values. Indeed, median change in MEDD dose was 0 for both treatment groups at Month 3.

Table 124. Change from Baseline in Opioid Dose by Month in OBD-0632 (ITT Population)

Time Point	Change from Baseline in Opioid Dose (Observed Combined MEDD)	Placebo (N=212)	Lubiprostone (N=223)
Month 1	n	208	220
	Mean ± Standard Deviation	-2.0 ± 19.15	-2.0 ± 30.2
	Median (Min, Max)	0 (-202, 15)	0 (-439, 59)
Month 2	n	181	198
	Mean ± Standard Deviation	-0.9 ± 10.08	-0.2 ± 41.41
	Median (Min, Max)	0 (-1168, 18.2)	0 (-439, 326)
Month 3	n	163	169
	Mean ± Standard Deviation	-1.1 ± 17.36	-42.8 ± 435.85
	Median (Min, Max)	0 (-144, 54)	0 (-5432, 480)

Source: Reviewer's table, adapted from Sponsor's Table 1.1.7.5, pages 379 to 384 of 2585, Integrated Summary of Efficacy.

Reviewer comments: *In this reviewer's opinion, monthly analysis of MEDD changes is inadequate. A monthly average does not provide an adequate picture of changes in opioid use over the course of the trial, as daily or weekly changes may be lost when all values are averaged over the month. Thus, rigorous conclusions regarding the effects of lubiprostone on opioid use cannot be made. See discussion in section 7.3.5*
Submission Specific Primary Safety Concerns.

Treatment Compliance

At least 70% compliance was demonstrated by 89% of subjects in the lubiprostone group and 92% of subjects in placebo group. There were no notable differences between treatment groups in compliance measures.

Analysis of Efficacy

Of the 451 subjects randomized in trial OBD-0632, 16 subjects were excluded from the efficacy analysis due to never being dosed or having no post-baseline data. Fourteen of the 451 randomized subjects did not receive treatment (3 assigned to placebo and 11 to lubiprostone). Two subjects in the lubiprostone group were randomized, but no post-baseline data were reported.

Primary Efficacy Analyses

Primary efficacy analyses are presented in section 6.1.4 [Analysis of Primary Endpoint\(s\)](#). The trial failed to demonstrate statistically significant differences between placebo and lubiprostone in the primary efficacy endpoint (mean change from baseline in SBM frequency at Week 8 in subjects without dose reduction) in the ITT population (see [Table 15](#)). Analysis of this endpoint in the completer and per-protocol populations was summarized previously in [Table 16](#) and [Table 17](#), respectively.

Secondary Efficacy Analyses

Because the primary endpoint was not significant ($p > 0.05$) in OBD-0632, inferential analyses were not statistically valid on any of the secondary efficacy analyses. Therefore, the Sponsor's p-values presented below are for informational purposes only.

Mean Change from Baseline in SBM Frequency at Week 12

The difference between treatment groups in change from baseline SBM frequency at Week 12 was evaluated as a secondary endpoint in OBD-0632. Analysis was

performed both with LOCF and without LOCF. The non-LOCF results are presented in [Table 125](#) for the ITT, completer, and per-protocol populations of OBD-0632. In the ITT, completer, and per-protocol population, there was a numerical trend in favor of placebo subjects. Results were similar when LOCF analysis was carried out.

Table 125. Summary of Change from Baseline in SBM Frequency at Week 12 in OBD-0632 (ITT, Completer, and Per-Protocol Populations)

Change from Baseline in SBM Frequency ¹ at Week 12	Placebo	Lubiprostone	P-Value ²
ITT	(N=212)	(N=223)	0.761
n	148	152	
Mean ± Standard Deviation	2.7 ± 3.59	2.6 ± 3.42	
Median (Minimum, Maximum)	2.0 (-4.7, 25.0)	1.9 (-2.3, 23.2)	
Completer	(N=153)	(N=152)	0.756
n	143	141	
Mean ± Standard Deviation	2.8 ± 3.64	2.6 ± 3.48	
Median (Minimum, Maximum)	2.0 (-4.7, 25.0)	1.9 (-2.3, 23.2)	
Per-Protocol	(N=147)	(N=150)	0.346
n	110	119	
Mean ± Standard Deviation	2.7 ± 3.14	2.6 ± 3.15	
Median (Minimum, Maximum)	2.0 (-1.5, 12.5)	1.9 (-2.3, 18.5)	

¹Weekly SBM (BM) frequency rate: (168 x number of SBMs (BMs)/number of hours observed)

²Sponsor's p-value was initially based on the treatment effect from a van Elteren test stratified by pooled site and then adjusted using Hommel's stagewise rejective method for Week 8, Week 12, and overall. **P-values are for informational purposes only.** Source: Reviewer's table, adapted from Tables 14.2.2.1.2, 14.2.2.2.2, 14.2.2.3.2, pages 131-135 of 1157, CSR of OBD-0632.

Overall Change from Baseline in SBM Frequency

[Table 126](#) shows results for the ITT, completer, and per-protocol populations in overall difference between treatment groups in change from baseline SBM frequency.

Table 126. Summary of Overall Change from Baseline in SBM Frequency in OBD-0632 (ITT, Completer, and Per-Protocol Populations)

Overall Change from Baseline in SBM Frequency ¹	Placebo	Lubiprostone	P-Value ²
ITT	(N=212)	(N=223)	0.673
n	209	217	
Mean ± Standard Deviation	2.3 ± 2.57	2.6 ± 2.73	
Median (Minimum, Maximum)	1.7 (-5.6, 16.3)	2.2 (-6.8, 14.5)	
Completer	(N=154)	(N=152)	0.930
n	153	152	
Mean ± Standard Deviation	2.3 ± 2.31	2.6 ± 2.57	
Median (Minimum, Maximum)	1.8 (-5.6, 9.2)	2.3 (-1.3, 14.5)	
Per-Protocol	(N=147)	(N=150)	0.343
n	147	148	
Mean ± Standard Deviation	2.3 ± 2.31	2.8 ± 2.69	
Median (Minimum, Maximum)	1.5 (-1.7, 9.2)	2.5 (-1.3, 14.5)	

¹Weekly SBM (BM) frequency rate: (168 x number of SBMs (BMs)/number of hours observed)

²Sponsor's p-value was initially based on the treatment effect from a van Elteren test stratified by pooled site and then adjusted using Hommel's stagewise rejective method for Week 8, Week 12, and overall. **P-values are for informational purposes only.** Source: Reviewer's table, from Sponsor's Tables 14.2.3.1, 14.2.3.2, and 14.2.3.3, pages 137 to 139 of 1159, CSR of OBD-0632.

In the ITT, completer, and per-protocol population, there was a numerical trend in favor of lubiprostone subjects, although the difference between the lubiprostone and placebo was small in each case.

SBMs within 24 and 48 Hours after First Dose of Study Medication

The Sponsor evaluated SBMs within 24 and 48 hours after first dose of study medication as secondary endpoints. These results are presented in [Table 127](#).

Table 127. Summary of SBMs within 24 and 48 Hours of First Study Medication Dose in OBD-0632 (ITT, Completer, and Per-Protocol Populations)

Time to First SBM	Number at Risk (% with SBM) ¹		P-Value ²
	Placebo	Lubiprostone	
ITT	(N=212)	(N=223)	
24 Hours	148 (30.2)	149 (33.2)	0.502
48 Hours	94 (55.7)	87 (61.0)	
Completer	(N=153)	(N=152)	
24 Hours	109 (28.8)	98 (35.5)	0.205
48 Hours	68 (55.6)	57 (60.5)	
Per-Protocol	(N=147)	(N=150)	
24 Hours	104 (29.3)	103 (31.3)	0.696
48 Hours	68 (53.7)	57 (62.0)	

Note: Proportions determined using Kaplan-Meier estimates in a time-to-event analysis. Subjects with no SBMs or with first SBM during the first 24 hours of the rescue laxative phase are censored; if no SBM, time to first SBM set to trial duration.

¹Number at risk (i.e., not yet achieving first SBM and not censored) prior to specified time and Kaplan-Meier estimate for percent already experiencing first SBM prior to specified time.

²Treatment groups were compared using a likelihood-ratio chi-square test. **Sponsor's p-values for informational purposes only.** Source: Reviewer's table, adapted from Tables 14.2.4.1, 14.2.4.2, and 14.2.4.3, pages 140 to 142 of 1157, CSR of OBD-0632.

In the ITT, completer, and per-protocol populations, although larger percentages of lubiprostone subjects experienced a first SBM either within 24 hours or within 48 hours after taking the first dose of study medication dose than placebo subjects, the magnitude of differences between the treatment groups was marginal.

Overall Responder Rates

Overall responder rates were a secondary endpoint in OBD-0632. The Sponsor performed analysis with and without LOCF and results without LOCF are in [Table 128](#).

Table 128. Overall Responder Rates in OBD-0632 (ITT, Completer, and Per-Protocol Populations)

Overall Responder ¹ Rates	Placebo	Lubiprostone	P-Value ²
ITT	(N=212)	(N=223)	
Responder	97 (45.8%)	105 (47.1%)	0.894
Completer	(N=154)	(N=152)	
Responder	88 (57.5%)	93 (61.2%)	0.630
Per-Protocol	(N=147)	(N=150)	
Responder	73 (49.7%)	77 (51.3%)	0.856

¹An overall responder achieves at least moderate response for ≥50% of the weeks on study, and is on study for at least 8 weeks.

²Sponsor's p-values are from Cochran-Mantel-Haenszel test stratified by site. **P-values are for informational purposes only.** Source: Reviewer's table, adapted from Sponsor's Tables 14.2.5.1.2, 14.2.5.2.2, and 14.2.5.3.2, pages 144-148, CSR of OBD-0632.

Overall responder rates in the ITT, completer and per-protocol lubiprostone subjects were numerically higher than overall responder rates in placebo subjects, but the

magnitude of the differences between treatment groups was negligible. The Sponsor's analysis of the overall response rate endpoint in the ITT, completer, and per-protocol populations with LOCF, though not presented, produced similar results.

Overall Mean Change from Baseline in Bowel Function Parameters

As a secondary endpoint, the Sponsor assessed overall changes from baseline in the following bowel function parameters: (1) straining; (2) stool consistency of SBMs; (3) constipation severity; (4) abdominal bloating; (5) abdominal discomfort; and (6) bowel habit regularity. Results for the ITT population of OBD-0632 are presented in [Table 129](#).

Table 129. Overall Change from Baseline in Bowel Parameters – OBD-0632 (ITT Population)

Overall Change from Baseline in:	Statistic	Placebo (N=212)	Lubiprostone (N=223)	P-Value ⁴
Straining ¹	n	181	187	0.019
	Mean ± SD	-0.5 ± 0.89	-0.5 ± 0.96	
	Median	-0.5	-0.8	
Stool consistency of SBMs ²	n	181	187	0.124
	Mean ± SD	-0.4 ± 0.81	-0.6 ± 0.84	
	Median	-0.5	-0.7	
Constipation severity ¹	n	212	223	0.246
	Mean ± SD	-0.5 ± 0.72	-0.6 ± 0.79	
	Median	-0.4	-0.5	
Abdominal bloating ¹	n	212	223	0.157
	Mean ± SD	-0.4 ± 0.64	-0.5 ± 0.70	
	Median	-0.3	-0.3	
Abdominal discomfort ¹	n	212	223	0.020
	Mean ± SD	-0.4 ± 0.64	-0.5 ± 0.69	
	Median	-0.3	-0.4	
Bowel habit regularity ³	n	208	218	0.157
	Mean ± SD	-0.6 ± 1.57	-0.8 ± 1.57	
	Median	-0.4	-0.7	

Abbreviations: SD, standard deviation

¹Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe

²Scale: 0 = very loose, 1 = loose, 2 = normal, 3 = hard, 4 = very hard (little balls)

³Scale: 1 (very regular) to 7 (very irregular)

⁴Sponsor's p-value is based on the treatment effect from a van Elteren test stratified by pooled site.

Note: Within-group p-values (test of change from baseline), based on the Wilcoxon signed-rank test, were also performed by the Sponsor and p-value was <0.001 for both placebo and lubiprostone groups. **P-values are for informational purposes only.**

Source: Sponsor's Table 2.7.3.3-33, page 79 of 119, Summary of Clinical Efficacy.

The differences in change between treatment groups in all of the bowel function parameters were marginal. The Sponsor also performed analyses of change from baseline in bowel function parameters for the completer, and per-protocol populations, with results similar to the results for the ITT population.

Overall Treatment Effectiveness

Overall treatment effectiveness was assessed using scores ranging from 0 for not at all effective to a score of 4 for extremely effective (PRO). Results are in [Table 130](#).

Table 130. Summary of Overall Treatment Effectiveness in OBD-0632 (ITT, Completer, and Per-Protocol Populations)

Overall Treatment Effectiveness ¹	Placebo (N=212)	Lubiprostone (N=223)	P-Value ²
ITT			
n	201	213	0.160
Mean ± Standard Deviation	1.4 ± 1.04	1.5 ± 1.07	
Median (Minimum, Maximum)	1.3 (0.0, 4.0)	1.5 (0.0, 4.0)	
Completer	(N=153)	(N=152)	
n	152	152	0.071
Mean ± Standard Deviation	1.4 ± 1.06	1.6 ± 1.04	
Median (Minimum, Maximum)	1.2 (0.0, 3.8)	1.6 (0.0, 3.9)	
Per-Protocol	(N=147)	(N=150)	
n	144	148	0.135
Mean ± Standard Deviation	1.4 ± 1.06	1.6 ± 1.10	
Median (Minimum, Maximum)	1.2 (0.0, 4.0)	1.7 (0.0, 4.0)	

¹Overall treatment effectiveness: 0 = Not at all effective, 1 = A little bit effective, 2 = Moderately effective, 3 = Quite a bit effective, 4 = Extremely effective

²Sponsor's p-values are from Wilcoxon rank-sum test. **P-values are for informational purposes only.**

Source: Reviewer's table, adapted from Tables 14.2.11.1, 14.2.11.2, and 14.2.11.3, pages 164 to 166 of 1157, CSR of OBD-0632.

Overall treatment effectiveness scores in the ITT, completer and per-protocol lubiprostone subjects were numerically higher than overall treatment effectiveness scores in placebo subjects, but the differences were small.

Exploratory Efficacy Analyses

Median Time to First SBM and SBMs within 4, 8, and 12 Hours of First Drug Dose

As an exploratory endpoint, the Sponsor analyzed median time to first SBM and proportion of subjects in each treatment group with their first SBM at 4, 8, and 12 hours. These results are presented in [Table 131](#).

Table 131. Time to First SBM and Proportion of Subjects with First SBM within 4, 8, and 12 Hours of First Dose of Study Drug in OBD-0632 (ITT Population)

Time to First SBM	Number at Risk (% with SBMs) ¹		P-Value ²
	Placebo (N=212)	Lubiprostone (N=223)	
0 Hours	212 (0)	222 (0)	
4 Hours	191 (9.9)	186 (16.6)	0.039
8 Hours	178 (16.0)	175 (21.5)	0.143
12 Hours	169 (20.3)	171 (23.3)	0.443
Median (95% Confidence Interval)	38.6 (30.0, 49.0)	35.1 (29.1, 46.2)	0.591

Note: Proportions and median times estimated using Kaplan-Meier estimates in a time-to-event analysis. Subjects with no SBMs or with first SBM during the first 24 hour rescue laxative phase were censored; if no SBM, time to first SBM set to trial duration.

¹Number at risk (i.e., not yet achieving first SBM and not censored) prior to specified time and Kaplan-Meier estimate for percent already experiencing first SBM prior to specified time.

²Proportions were compared using a likelihood-ratio chi-square test. Median times were compared using the Cox proportional hazards regression model. **Sponsor's p-values are for informational purposes only.**

Source: Reviewer's table, adapted from Table 1.3.7.1, module 5.3.5.3, page 1203 of 2585, Integrated Summary of Efficacy.

A greater percentage of lubiprostone subjects than placebo subjects had their first SBM within 4 hours (17% versus 10%), 8 hours (22% versus 16%), and 12 hours (23% versus 20%) of the first dose of study drug. The median time to first SBM was about 4 hours less for lubiprostone subjects than placebo subjects (35 hours versus 39 hours).

Subgroup Analyses

The subgroup analyses of the primary endpoint by gender, age, and race were presented by the Sponsor with limited descriptive statistics (e.g., no standard deviations or minimum/maximum values). Given the failure of OBD-0632 on the primary endpoint, results are presented below for completeness, but are of limited interpretability.

Gender

As shown in [Table 132](#), change from baseline in SBM frequency at Week 8 was lower among female lubiprostone subjects than male lubiprostone subjects (2.5 versus 2.9).

Table 132. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Gender in OBD-0632 (ITT Population)

Change from Baseline at Week 8	Female		Male	
	Placebo (N=106)	Lubiprostone (N=104)	Placebo (N=69)	Lubiprostone (N=64)
Mean	2.7	2.5	2.1	2.9
Median	2.0	2.0	1.5	1.7

Source: Reviewer's table, modified from Sponsor's Response to 74-Day Letter, Table 17, page 28.

Reviewer comments: *Subgroup analysis by gender suggests a greater response to lubiprostone among male subjects than female subjects. However, interpretation of these results is limited given the post hoc nature of these subgroup analyses and given the failed nature of trial OBD-0632.*

Age

As presented in [Table 133](#), the mean change from baseline in SBM frequency at Week 8 was higher in lubiprostone subjects aged ≥ 50 years to < 65 years than in those aged < 50 years (2.7 versus 2.4) and in lubiprostone subjects aged ≥ 65 years than in those aged ≥ 50 years to < 65 years (4.9 versus 2.7).

Table 133. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Age in OBD-0632 (ITT Population)

Change from Baseline at Week 8	< 50 Years		≥ 50 to < 65 Years		≥ 65 Years	
	Placebo (N=86)	Lubiprostone (N=89)	Placebo (N=77)	Lubiprostone (N=69)	Placebo (N=12)	Lubiprostone (N=10)
Mean	2.0	2.4	2.7	2.7	3.8	4.9
Median	13	1.8	2.0	2.0	3.1	4.8

Source: Reviewer's table, modified from Sponsor's Response to 74-Day Letter, Table 19, page 32.

Reviewer comments: *The number of subjects who were 65 years of age and older was probably too small to draw any meaningful conclusions.*

Race

As presented in [Table 134](#), the change from baseline in SBM frequency at Week 8 was similar between white lubiprostone subjects and black lubiprostone subjects (2.7 versus 2.5). The treatment difference in the change from baseline in SBM frequency at Week 8 between the white lubiprostone and placebo subjects (0.4) slightly favored lubiprostone while the treatment difference between the black lubiprostone and placebo subjects (-0.3) slightly favored the placebo subjects.

Table 134. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Race in OBD-0632 (ITT Population)

Change from Baseline at Week 8	White		Black		Asian		Other	
	Placebo (N=155)	LBP (N=143)	Placebo (N=13)	LBP (N=16)	Placebo (N=1)	LBP (N=1)	Placebo (N=6)	LBP (N=8)
Mean	2.3	2.7	2.8	2.5	2.5	4.9	4.3	1.8
Median	1.5	2.0	3.0	2.1	2.5	4.9	3.8	0.3

Abbreviations: LBP, lubiprostone

Source: Reviewer's table, modified from Sponsor's Response to 74-Day Letter, Table 21, page 37.

Reviewer comments: *There were too few black/African-American subjects to adequately assess differences in that population.*

Opioid Class and Subclass, Duration of Opioid Use

Subgroup analyses by opioid class, opioid subclass, and baseline opioid use duration are presented separately in this reviewer's summary of trial OBD-0632 (at the end of this Appendix) as part of a larger discussion that compares OBD-0632 with OBD-0631 and examines possible reasons for the failure of OBD-0632.

Safety Monitoring and Adverse Events

Safety

The safety evaluation protocol in OBD-0632 was identical to the protocol in OBD-0631.

Safety Analyses

The safety analyses included all randomized subjects who took at least one dose of study medication and were performed based on observed data. A total of 437 subjects took at least one dose of study drug and were included in safety evaluations: 223 subjects in the lubiprostone group and 214 subjects in the placebo group.

Adverse Events

Of the 437 subjects in the safety population, 233 (53%) experienced at least one treatment-emergent AE. At least one AE was reported by 118 subjects (53%) in the lubiprostone group and 115 subjects (54%) in the placebo group. Among the safety population, 61 (27%) subjects in the lubiprostone group experienced an AE in the gastrointestinal disorders SOC; whereas 49 (23%) of the placebo group experienced an AE in the gastrointestinal disorders SOC. At total of 113 subjects (26%) had AEs that the Sponsor considered treatment related, 62 (28%) in the lubiprostone group, and 51 (24%) in the placebo group.

Serious Adverse Events

A total of 15 subjects (3%) experienced at least one SAE; 7 subjects (3%) were in the lubiprostone group and 8 subjects (4%) were in the placebo group. The Sponsor considered only one SAE as probably related to study drug and it was for a subject in the placebo group. The most frequent SAEs, at the SOC level, were gastrointestinal disorders, experienced by two subjects (1%) in the lubiprostone group and two subjects (1%) in the placebo group. Of the subjects in the gastrointestinal disorders SOC who had SAEs, one subject in the lubiprostone group had intestinal obstruction and one had

irritable bowel syndrome; in the placebo group, one subject had a fecaloma and one had upper abdominal pain. SAEs were summarized in [Table 83](#) of section 7.3.2.

Deaths

No subjects died in trial OBD-0632.

Reviewer’s Summary of Trial OBD-0632

OBD-0632, which enrolled subjects on chronic opioids inclusive of methadone, was a failed trial. For the primary endpoint of mean change from baseline at Week 8 in ITT subjects without dose reduction, there was not a statistically significant difference between lubiprostone and placebo subjects (2.6 versus 2.4, $p=0.842$). The trial also failed on all major secondary efficacy endpoints. On the other hand, OBD-0631, a trial of identical design that also included subjects on chronic methadone, demonstrated a statistically significant difference favoring the lubiprostone group over the placebo group on the same primary endpoint in the ITT population (3.2 versus 2.4, $p=0.019$).

A nonclinical study conducted by the Sponsor showed that methadone inhibits the chloride currents activated by lubiprostone in a concentration-dependent manner (see section [4.4.2 Pharmacodynamics](#)). Given the findings of this nonclinical study, the Sponsor proposed several possible reasons why OBD-0632 was a failed trial. Three potential explanations set forth by the Sponsor are discussed below.

The Sponsor’s first explanation was based on the assertion that there was a higher percentage of methadone-treated subjects in OBD-0632 than OBD-0631. This reviewer adjudicated the percentage of subjects treated with methadone or a congener of methadone in OBD-0631 and OBD-0632. Results are in [Table 135](#).

Table 135. Summary of Subjects Using a Diphenylheptane at Baseline in OBD-0631 and OBD-0632

Subjects on Methadone or Methadone Congener by Trial Population	OBD-0631		OBD-0632	
	Placebo	Lubiprostone	Placebo	Lubiprostone
ITT¹	N=217	N=221	N=212	N=223
Yes, n (%)	36 (16.6%)	45 (20.4%)	41 (19.3%)	44 (19.7%)
Efficacy Evaluable²	N=169	N=164	N=175	N=168
Yes, n (%)	26 (15.4%)	31 (18.9%)	35 (20.0%)	35 (20.8%)

¹ITT: All randomized subjects who received at least one dose of study medication and had at least one treatment-period diary entry

²Efficacy evaluable: Subjects who continued trial to Week 8, had no dose reduction, and no LOCF of weekly SBM frequency data.

Source: Reviewer’s table, generated from Sponsor’s efficacy datasets.

Reviewer comments: *The percentage of subjects on a diphenylheptane opioid is only slightly higher in the ITT population of OBD-0632 than OBD-0631. Further, the distribution of subjects on methadone is balanced across treatment arms for both the ITT and efficacy evaluable populations in OBD-0632. In this reviewer’s assessment, even if there were a significant treatment interaction with methadone, the slightly higher percentage of diphenylheptane opioid subjects in OBD-0632 than OBD-0631 would not adequately explain the failure of trial OBD-0632 on efficacy endpoints.*

The Sponsor’s second explanation was based on the higher baseline MEDD of subjects in OBD-0632 than OBD-0631, in particular that subjects on diphenylheptane opioids in

OBD-0632 had a higher mean MEDD than subjects on diphenylheptane opioids in OBD-0631. As presented in [Table 136](#), subjects on methadone in OBD-0632 did have a higher average MEDD than subjects on methadone in OBD-0631.

Table 136. Baseline MEDD of Subjects by Opioid Class in OBD-0631 and OBD-0632 (ITT)

Baseline MEDD	OBD-0631				OBD-0632			
	Placebo (N=217)		Lubiprostone (N=221)		Placebo (N=212)		Lubiprostone (N=223)	
	Methadone	Non-Methadone	Methadone	Non-Methadone	Methadone	Non-Methadone	Methadone	Non-Methadone
n	36	180	45	175	41	167	44	176
Mean ± SD	706.8 ± 830.69	159.5 ± 254.75	772.4 ± 826.36	160.4 ± 181.1	729.9 ± 572.26	233.8 ± 344.69	992.0 ± 1484.51	217.8 ± 336.21
Median	427.5	90	450	100	517.5	131	480	118.5
Min, Max	30, 3656	4.5, 2772	22.5, 4000	7.5, 1050	23, 2290	4.5, 2736	54, 7605	4, 3269

Source: Reviewer's table, derived from ADOPCALC and ADOP datasets in Module 5.1.25 for trials OBD-0631 and OBD-0632.

The Sponsor reasoned that because methadone inhibited chloride channels in a dose-dependent manner in the nonclinical study and because subjects on methadone in OBD-0632 had a higher average MEDD than subjects on methadone in OBD-0631, methadone-treated subjects in OBD-0632 had a greater impact on reduction of lubiprostone efficacy in that trial than methadone-treated subjects in OBD-0631. In support of this argument, the Sponsor performed an exploratory (not pre-specified) analysis of the overall SBM response endpoint and the mean change from baseline in SBM frequency at Week 8 endpoint by MEDD group (either <200 mg or ≥200 mg) for both OBD-0631 and OBD-0632. Results using the overall SBM response endpoint are in [Table 137](#) and results using the mean change endpoint are in [Table 138](#).

Table 137. Overall SBM Response by Baseline MEDD in OBD-0631 and OBD-0632 (ITT Population)

Overall SBM Response by Baseline MEDD ¹	OBD-0631		OBD-0632	
	Placebo (N=217)	Lubiprostone (N=221)	Placebo (N=212)	Lubiprostone (N=223)
MEDD <200 mg				
n	141	130	119	118
Responder, n (%)	27 (19.1)	36 (27.7)	20 (16.8)	25 (21.2)
MEDD ≥200 mg				
n	75	90	90	103
Responder, n (%)	4 (5.3)	18 (20)	8 (8.9)	11 (10.7)

¹Overall SBM response defined as ≥1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available and ≥3 SBMs per week for at least 9 of the 12 treatment weeks.

Source: Reviewer's table, modified from Sponsor's Response to 74-Day Letter, Table 32, page 54.

Table 138. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Baseline MEDD in OBD-0631 and OBD-0632 (ITT Population)

Change From Baseline at Week 8 by Baseline MEDD	OBD-0631		OBD-0632	
	Placebo (N=217)	Lubiprostone (N=221)	Placebo (N=212)	Lubiprostone (N=223)
MEDD <200 mg				
n	114	101	101	88
Mean	2.4	3.6	2.7	3.3
Median	1.4	3.0	2.3	2.6
MEDD ≥200 mg				
n	54	63	74	80
Mean	2.4	2.5	2	1.9
Median	1.4	2.3	1	1.3

Source: Reviewer's table, modified from Sponsor's Response to 74-Day Letter, Table 33, page 55.

Reviewer comments: Based on this reviewer's analysis of the datasets for OBD-0631 and OBD-0632, the baseline median MEDD for ITT subjects on a diphenylheptane opioid ranged from 427.5 mg to 517.5 mg. In this reviewer's assessment, the Sponsor's selection of 200 mg as the cutoff value for MEDD subgroup analyses is too low because it excludes the majority of subjects on a diphenylheptane opioid in the efficacy evaluable population of both OBD-0631 and OBD-0632. Nonetheless, in both trials, the overall SBM response rate is higher in the lubiprostone arm both for the MEDD <200 and the MEDD ≥200 subgroups (see [Table 137](#)). The magnitude of the treatment difference favoring the lubiprostone group in OBD-0632 is smaller in the higher MEDD subgroup (1.8%) than the lower MEDD subgroup (4.4%), but this pattern is not as clearly duplicated in the results for OBD-0631, where the treatment effect is larger in the higher MEDD subgroup (14.7%) than the lower MEDD subgroup (8.6%).

Results by MEDD subgroup are also inconsistent between OBD-0631 and OBD-0632 when the mean change from baseline at Week 8 is evaluated (see [Table 138](#)). The lack of a consistent relationship between the MEDD and primary endpoint makes this reviewer unable to agree with the Sponsor that the failure of trial OBD-0632 was due to the higher overall MEDD and the higher MEDD in the subgroup of diphenylheptane subjects in OBD-0632 as compared with OBD-0631. The Sponsor asserts that in well-controlled studies of lubiprostone, patients receiving higher dosages of diphenylheptane opioids (e.g., methadone) failed to demonstrate a significant response to lubiprostone. Based on incongruent results between OBD-0631 and OBD-0632 (see [Table 137](#) and [Table 138](#)), however, this reviewer does not concur with the Sponsor's assertion.

In conjunction with Dr. Cooner, the statistical reviewer for this sNDA, graphical analyses of the MEDD versus the primary endpoint (mean change from baseline in SBM frequency at Week 8) were performed from the efficacy datasets for both OBD-0631 and OBD-0632. These analyses failed to demonstrate a clear or consistent correlation between the MEDD and the primary endpoint. Further, although in OBD-0632, lubiprostone subjects taking a diphenylheptane opioid did worse with respect to the primary endpoint than lubiprostone subjects not taking a diphenylheptane opioid, this pattern did not clearly hold for the same analysis of OBD-0631. Sub-analyses that excluded outliers with high baseline MEDDs (i.e., subjects with average baseline MEDD >1000 mg) in both trials did not appreciably affect the aforementioned conclusions.

The Sponsor's third explanation involved an assertion that there was a higher number of patients who did not demonstrate the requisite number of weekly SBMs at baseline (i.e., <3 SBMs per week) in OBD-0632 than OBD-0631. Trial inclusion criterion #3 had defined subjects with OIC as those with an average of <3 SBMs per week during the screening period and ≥1 of the following for at least 25% of SBMs during each week of the screening period: (1) hard or very hard stools; (2) sensation of incomplete evacuation; and/or (3) moderate to very severe straining associated with SBMs. The Sponsor noted that the number of patients randomized to treatment in OBD-0632 despite having ≥3 SBMs per week at baseline was nearly twice as high (23 subjects) as in OBD-0631 (12 subjects). The Sponsor argued that this imbalance between the two trials negatively influenced the possibility for lubiprostone to demonstrate normalization of SBM frequency in OBD-0632 as compared with OBD-0631.

This medical officer independently reviewed the list of protocol violations pertaining to inclusion criterion #3 for subjects in both trials. Because there were several subjects who violated more than one of the OIC definition criteria, this reviewer analyzed data of subjects with baseline SBM frequency ≥3, but also more broadly analyzed data of subjects who violated any component of inclusion criterion #3. Results are in [Table 139](#).

Table 139. Subjects in Violation of Inclusion Criteria for OIC in OBD-0631 and OBD-0632

Subjects Not Meeting Inclusion Criteria for OIC by Patient Population	OBD-0631		OBD-0632	
	Placebo	Lubiprostone	Placebo	Lubiprostone
Randomized				
n	220	223	216	235
Baseline SBM Frequency ≥3	5 (2.3)	9 (4.0)	12 (5.6)	18 (7.7)
Not meeting OIC Criteria, ¹ n (%)	12 (5.5)	17 (7.6)	19 (8.8)	31 (13.2)
ITT				
n	217	221	212	223
Baseline SBM Frequency ≥3	4 (1.8)	7 (3.2)	11 (5.2)	12 (5.8)
Not meeting OIC criteria ¹ , n (%)	12 (5.5)	17 (7.7)	18 (8.3)	25 (11.2)

¹Study inclusion criterion #3 had defined subjects with OIC as subjects with an average of <3 SBMs per week during the screening period and ≥1 of the following for at least 25% of SBMs during each week of the screening period: (1) hard or very hard stools; (2) sensation of incomplete evacuation; and/or (3) moderate to very severe straining associated with SBMs.

Source: Reviewer's table, generated from tables listing protocol violations in OBD-0631 and OBD-0632 provided in response to IR4.

Reviewer comments: Although the percentage of subjects violating baseline Sponsor-defined OIC criteria is higher among lubiprostone subjects than placebo subjects in the randomized population of OBD-0632 (13.2% versus 8.8%), it bears noting that the Sponsor did not perform the primary analysis on the randomized population, but rather on the pre-specified ITT population. In the Sponsor's pre-specified ITT population, the percentage of subjects violating baseline OIC criteria is more balanced across the treatment arms (11.2% versus 8.3%). Further, as in OBD-0632, the percentage of subjects violating baseline OIC criteria in OBD-0631 is consistently higher in the lubiprostone group than the placebo group (7.6% versus 5.5% in the randomized population and 7.7% versus 5.5% in the ITT population). These marginal differences between OBD-0632 and OBD-0631 with respect to protocol violations do not adequately explain the failure of OBD-0632 on the primary endpoint.

Additional Considerations

In further examining potential reasons for the failure of OBD-0632, this reviewer compared OBD-0631 and OBD-0632 with respect to several factors at baseline, including demographic characteristics, use of rescue laxatives, duration of opioid use, medical conditions for which subjects were on opioids, and opioid class and subclass. With respect to distribution of gender, race, age, and age group, subjects in OBD-0631 and OBD-0632 were generally comparable across treatment arms (see [Table 2](#)).

Rescue Laxatives

Use of rescue laxatives for each trial was summarized in [Table 5](#) and was comparable across treatment arms for both OBD-0631 and OBD-0632. Post hoc, the Sponsor examined the relationship between baseline percentage of days of rescue laxative use and the primary endpoint. [Table 140](#) presents results using the overall SBM response endpoint and [Table 141](#) presents results using the mean change endpoint.

Table 140. Overall SBM Response by Baseline Percentage of Days of Rescue Laxative Use in OBD-0631 and OBD-0632 (ITT Population)

Overall SBM Response by Baseline Percentage of Days of Rescue Laxative Use	OBD-0631		OBD-0632	
	Placebo (N=217)	Lubiprostone (N=221)	Placebo (N=212)	Lubiprostone (N=223)
0 to ≤5%				
n	109	128	112	114
Responder, n (%)	20 (18.3)	34 (26.6)	13 (11.6)	13 (11.4)
>5 to ≤20%				
n	88	72	82	86
Responder, n (%)	9 (10.2)	14 (19.4)	12 (14.6)	18 (20.9)
≥20%				
n	20	21	18	23
Responder, n (%)	3 (15)	6 (28.6)	3 (16.7)	5 (21.7)

Source: Reviewer's table, modified from Sponsor's Response to 74-Day Letter, Table 46, page 83.

Table 141. Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Baseline Percent Days of Rescue Laxative Use – OBD-0631 and OBD-0632 (ITT)

Summary of Change from Baseline at Week 8 by Baseline Percentage of Days of Rescue Laxative Use	OBD-0631		OBD-0632	
	Placebo (N=217)	Lubiprostone (N=221)	Placebo (N=212)	Lubiprostone (N=223)
0 to ≤5%				
n	90	100	95	89
Mean	2.3	3.3	2.6	1.9
Median	1.4	2.8	2.1	1.4
>5 to ≤20%				
n	65	51	68	64
Mean	2.5	2.8	2.3	3.6
Median	1.4	2.4	1.5	3.1
≥20%				
n	14	13	12	15
Mean	2.3	3.4	2.4	3.2
Median	1.0	3.0	2.2	2.5

Source: Reviewer's table, modified from Sponsor's Response to 74-Day Letter, Table 47, page 84.

Reviewer comments: *This reviewer would expect that subjects with less use of rescue laxatives at baseline might have a greater response to lubiprostone than subjects who used rescue laxatives more frequently (and were thus possibly more dependent on such*

medications to produce BMs). This theoretical expectation is corroborated by the findings in OBD-0631 for subjects using rescue laxatives at baseline $\leq 5\%$, where overall SBM response was higher in the lubiprostone arm than placebo arm (26.6% versus 18.3%), and mean change from baseline in SBM frequency at Week 8 was higher in the lubiprostone arm than placebo arm (3.3 versus 2.3). Of note, this trend did not hold in OBD-0632 for subjects using rescue laxatives at baseline $\leq 5\%$, where overall SBM response was lower in the lubiprostone arm than placebo arm (11.4% versus 11.6%), and mean change from baseline in SBM frequency at Week 8 was lower in the lubiprostone arm than placebo arm (1.4 versus 2.1).

Conversely, one might argue that subjects with the least use of rescue laxatives at baseline were those with better bowel regularity and thus less need for rescue laxatives. Regardless, one would expect to see the same response pattern for the two treatment arms in both trials, but this pattern did not hold for subjects with the least use of rescue laxatives at baseline. With respect to subjects using rescue laxatives >5 to $\leq 20\%$ of the time at baseline, both trials showed findings favoring lubiprostone subjects in terms of both overall SBM response and mean change from baseline in SBM frequency at Week 8. Treatment difference favoring lubiprostone was larger in OBD-0631 than OBD-0632 with regard to the overall SBM response endpoint (9.2% versus 6.3%), but larger in OBD-0632 than OBD-0631 with regard to the mean change from baseline in SBM frequency endpoint (1.3 versus 0.3). Sample size for the subgroup using rescue laxatives $\geq 20\%$ of the time at baseline was too small to permit meaningful conclusions.

Duration of Opioid Use

Post hoc, the Sponsor examined the relationship between baseline duration of opioid use and the primary endpoint. Results using the overall SBM response endpoint are presented in [Table 142](#) and results using the mean change endpoint are in [Table 143](#).

Table 142. Overall SBM Response by Opioid Use Duration at Baseline in OBD-0631 and OBD-0632 (ITT Population)

Overall SBM Response by Opioid Use Duration at Baseline	OBD-0631		OBD-0632	
	Placebo (N=217)	Lubiprostone (N=221)	Placebo (N=212)	Lubiprostone (N=223)
<3 Months				
n	3	5	11	4
Responder, n (%)	1 (33.3)	0 (0)	0 (0)	0 (0)
≥ 3 Months and <6 Months				
n	17	21	25	20
Responder, n (%)	3 (17.6)	4 (19)	5 (20)	4 (20)
≥ 6 Months and <12 Months				
n	24	26	16	25
Responder, n (%)	3 (12.5)	6 (23.1)	4 (25)	4 (16)
≥ 12 Months and <60 Months				
n	101	97	99	98
Responder, n (%)	16 (15.8)	22 (22.7)	10 (10.1)	15 (15.3)
≥ 60 Months				
n	72	71	60	74
Responder, n (%)	9 (12.5)	22 (31)	9 (15)	13 (17.6)

Source: Reviewer's table, modified from Response to 74-Day Letter, Table I1.2.2.1.1, page 739, and Table I2.2.2.1.1, page 757.

Table 143. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Opioid Use Duration at Baseline in OBD-0631 and OBD-0632 (ITT Population)

Change from Baseline at Week 8 by Opioid Use Duration at Baseline	OBD-0631		OBD-0632	
	Placebo (N=169)	Lubiprostone (N=164)	Placebo (N=175)	Lubiprostone (N=168)
<3 Months				
n	2	3	9	3
Mean ± Standard Deviation	1.5 ± 0.89	-0.6 ± 1.62	1.5 ± 1.99	3.2 ± 2.88
Median (Min, Max)	1.5 (1, 2)	-0.5 (-2, 1)	1.0 (-1, 6)	3.3 (0, 6)
≥3 Months and <6 Months				
n	10	16	17	11
Mean ± Standard Deviation	2.6 ± 3.36	3.6 ± 2.97	2.8 ± 2.15	2.6 ± 2.64
Median (Min, Max)	1.9 (-2, 10)	2.9 (1, 11)	2.7 (-1, 7)	3.2 (-2, 7)
≥6 Months and <12 Months				
n	19	21	11	22
Mean ± Standard Deviation	2.2 ± 2.58	3.6 ± 2.83	3.9 ± 5.18	2.7 ± 2.92
Median (Min, Max)	1.0 (-2, 8)	3.5 (-2, 9)	2.5 (-4, 15)	2.3 (-2, 11)
≥12 Months and <60 Months				
n	85	72	92	80
Mean ± Standard Deviation	2.3 ± 3.17	2.5 ± 2.70	2.2 ± 2.95	2.5 ± 3.37
Median (Min, Max)	1.4 (-3, 16)	2.0 (-2, 10)	1.5 (-4, 13)	1.5 (-2, 16)
≥60 Months				
n	53	52	46	52
Mean ± Standard Deviation	2.6 ± 3.66	4.0 ± 4.19	2.6 ± 3.58	2.9 ± 3.45
Median (Min, Max)	1.5 (-2, 15)	3.5 (-1, 21)	1.8 (-2, 21)	2.0 (-3, 12)

Source: Reviewer's table, from Response to 74-Day Letter, Table I1.2.2.1.1, pages 742-746; and Table I2.2.2.1.1, pages 760-764.

Reviewer comments: The number of subjects in each subgroup was similar in both OBD-0631 and OBD-0632 and the distribution of subjects in each subgroup was balanced across treatment arms for each trial. The number of subjects in the subgroup with baseline opioid use duration <3 months, ≥3 months and <6 months, and ≥6 months and <12 months was probably too small to draw any meaningful conclusions. In the subgroup with baseline opioid use duration ≥12 months and <60 months (largest subgroup), the mean change from baseline in SBM frequency at Week 8 was only marginally higher in the lubiprostone arm than the placebo arm for both OBD-0631 (2.5 versus 2.3) and OBD-0632 (2.5 versus 2.2).

For this same subgroup, analysis of the overall SBM response endpoint more strongly favored the lubiprostone arm than the placebo arm in OBD-0631 (22.7% versus 15.8%) as compared with OBD-0632 (15.3% versus 10.1%). In the subgroup with baseline opioid use duration ≥60 months, analysis of both the mean change from baseline in SBM frequency at Week 8 and overall SBM response endpoints more strongly favored the lubiprostone arm in OBD-0631 than OBD-0632. Overall, this reviewer does not find that there were any notable differences in duration of opioid use at baseline among subjects in OBD-0632 as compared with OBD-0631 that would explain the failure of OBD-0632 to win on the primary endpoint.

Principal Medical Conditions for Which Subjects Were on Opioids

In reviewing OBD-0631 and OBD-0632, this medical officer sought to compare the two trials with regard to possible differences between trials in the distribution of principal underlying medical conditions for which subjects were receiving chronic opioid therapy. The Sponsor had not performed a pre-specified analysis of this demographic

characteristic at baseline and DGIEP requested this analysis. In response, the Sponsor noted that the trials had not directly captured medical conditions associated with opioid use. As such, there was no clear delineation of a primary pain condition for which subjects were on chronic opioids. Table 144 reflects the Sponsor’s identification of potential conditions that may have been associated with opioid use. Overall, back pain was the most common condition potentially associated with opioid use in OBD-0631 and OBD-0632. Incidence of back pain was comparable across the two treatment arms.

Table 144. Medical Diagnoses Potentially Associated with Opioid Use in OBD-0631 and OBD-0632 (ITT Population)

Medical Diagnosis	OBD-0631		OBD-0632	
	Placebo (N=217)	Lubiprostone (N=221)	Placebo (N=212)	Lubiprostone (N=223)
Arthralgia	27 (12.4)	28 (12.7)	26 (12.3)	23 (10.3)
Arthritis	23 (10.6)	40 (18.1)	32 (15.1)	34 (15.2)
Back pain	96 (44.2)	115 (52)	91 (42.9)	103 (46.2)
Fibromyalgia	35 (16.2)	27 (12.2)	22 (10.4)	32 (14.3)
Intervertebral Disc Degeneration, etc... ¹	69 (31.8)	81 (36.7)	70 (33)	91 (40.8)
Muscle Spasms	38 (17.5)	34 (15.4)	30 (14.2)	28 (12.6)
Musculoskeletal Pain	8 (3.7)	13 (5.9)	9 (4.2)	7 (3.1)
Neck Pain	24 (11.1)	25 (11.3)	20 (9.4)	21 (9.4)
Osteoarthritis	49 (22.6)	68 (30.8)	60 (28.3)	61 (27.4)
Spinal Column Stenosis, etc... ²	51 (23.5)	57 (25.8)	58 (27.4)	52 (23.3)

¹Includes intervertebral disc degeneration / intervertebral disc disorder / intervertebral disc protrusion.

²Includes spinal column stenosis / spinal cord injury / spinal fusion surgery / spinal osteoarthritis.

Source: Reviewer’s table, modified from Response to 74-Day Letter, Table I1.1.1.2.1, page 794 and Table I2.1.1.2.1, page 851.

Reviewer comments: *There are no substantial differences between the two trials with respect to the most common baseline diagnoses for which subjects may have been taking chronic opioids. Thus, it is unlikely that there were considerable differences between the patient populations with respect to underlying medical conditions in OBD-0632 as compared with OBD-0631. Stronger conclusions cannot be meaningfully drawn from the data provided, however, given the failure of the original study protocols to clearly document the principal diagnosis for which subjects were on opioid therapy.*

The Sponsor provided post hoc exploratory analyses of overall SBM response and mean change from baseline in SBM frequency at Week 8 by active medical condition. In this medical officer’s assessment, these analyses are of little value because the conditions evaluated do not necessarily represent the principal reason for which subjects were on chronic opioids. Further, the sample sizes of each subgroup in the analyses were generally too small to permit meaningful interpretation. Overall, it is this medical officer’s conclusion that differences in underlying medical conditions among subjects in OBD-0632 as compared with OBD-0631 are likely minimal and would not explain the failure of OBD-0632 to win on the primary endpoint.

Opioid Class and Subclass

As shown in Table 145, for the phenanthrene class (largest opioid subgroup), the mean change from baseline in SBM frequency at Week 8 was higher in the lubiprostone group than in the placebo group in both trials (3.3 versus 2.5 in OBD-0631 and 3 versus 2.5 in OBD-0632) and comparable between the two trials. Efficacy results between the two

trials were more discordant for the phenylpiperidine and diphenylheptane classes, though the small sample sizes may be a factor in the discordance. Of particular interest are the findings for the diphenylheptane class. Given the nonclinical study suggesting that diphenylheptane opioids interfere with lubiprostone's action, it would not be expected for the treatment effect to favor the lubiprostone group. However, the results for the two trials were discordant. Specifically, the mean treatment effect (0.9) favored lubiprostone in OBD-0631, but favored placebo in OBD-0632 (-0.9).

Table 145. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Opioid Class in OBD-0631 and OBD-0632 (ITT Population)

Change from Baseline at Week 8	OBD-0631		OBD-0632	
	Placebo (N=217)	Lubiprostone (N=221)	Placebo (N=212)	Lubiprostone (N=223)
Phenylpiperidines				
n	13	14	28	22
Mean ± SD	2.5 ± 3.04	2.5 ± 1.81	1.7 ± 2.63	4.2 ± 4.89
Median	1.4	2.9	0.7	3.3
Phenanthrenes				
n	141	133	132	129
Mean ± SD	2.5 ± 3.38	3.3 ± 3.48	2.5 ± 2.76	3 ± 3.34
Median	1.4	2.8	2.0	2.5
Diphenylheptanes				
n	25	29	35	35
Mean ± SD	1.6 ± 2.25	2.5 ± 2.75	2.4 ± 4.63	1.5 ± 2.82
Median	0.9	2.4	1.0	1.0

Source: Reviewer's table, modified from Response to 74-Day Letter, Table 5, page 11; Table 7, page 15; and Table 9, page 18.

As additional exploratory analyses, the Sponsor evaluated the primary endpoint for OBD-1033 (overall SBM response) by opioid class/subclass for OBD-0631 and OBD-0632. Results are in [Table 146](#). The pattern of findings is similar to that for the analysis of the mean change from baseline in SBM frequency at Week 8.

Table 146. Overall SBM Response by Opioid Class in OBD-0631 and OBD-0632 (ITT Population)

Overall SBM Response	OBD-0631		OBD-0632	
	Placebo (N=217)	Lubiprostone (N=221)	Placebo (N=212)	Lubiprostone (N=223)
Phenylpiperidines				
n	17	24	33	29
Responder, n (%)	3 (17.6)	3 (12.5)	1 (3)	9 (31)
Phenanthrenes				
n	179	174	162	174
Responder, n (%)	28 (15.6)	44 (25.3)	22 (13.6)	34 (19.5)
Diphenylheptanes				
n	35	43	41	44
Responder, n (%)	2 (5.7)	9 (20.9)	5 (12.2)	1 (2.3)

Source: Reviewer's table, modified from Response to 74-Day Letter, Table 4, page 10 and Table 6, page 14, and Table 8, page 17.

As presented in [Table 147](#), results of analysis of change from baseline in SBM frequency at Week 8 by phenanthrene subclass yielded similar results for OBD-0631 and OBD-0632. The treatment effect favoring lubiprostone was largest in the hydrocodone subclass in both trials, and the treatment effect actually slightly favored placebo subjects in the morphine subclass for both trials. Analysis of the same

subclasses using the overall SBM response endpoint is summarized in [Table 148](#). Given the small sample sizes and the fact that many subjects were on multiple opioids, however, meaningful conclusions are difficult to make. What is apparent is the general consistency of results with respect to phenanthrene subclasses across the two trials.

Table 147. Summary of Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Phenanthrene Subclass in OBD-0631 and OBD-0632 (ITT Population)

Change from Baseline at Week 8	OBD-0631		OBD-0632	
	Placebo (N=217)	Lubiprostone (N=221)	Placebo (N=212)	Lubiprostone (N=223)
Hydrocodones				
n	64	73	71	57
Mean ± SD	2.9 ± 3.65	3.6 ± 3.85	2.8 ± 3.04	3.9 ± 3.89
Median	2.0	3.0	2.3	3.4
Morphines				
n	47	45	44	46
Mean ± SD	2.5 ± 3.72	2.4 ± 2.65	2.4 ± 2.91	2.1 ± 2.49
Median	1.0	2.0	1.6	1.5
Oxycodones				
n	56	56	53	55
Mean ± SD	2.5 ± 3.58	2.6 ± 2.65	2.2 ± 2.28	2.4 ± 3.34
Median	1.7	2.2	2.0	2.4

Source: Reviewer's table, modified from Response to 74-Day Letter, Table 11, page 21; Table 13, page 23; and Table 15, page 25.

Table 148. Overall SBM Response by Phenanthrene Subclass in OBD-0631 and OBD-0632 (ITT)

Overall SBM Response	OBD-0631		OBD-0632	
	Placebo (N=217)	Lubiprostone (N=221)	Placebo (N=212)	Lubiprostone (N=223)
Hydrocodones				
n	81	97	85	79
Responder, n (%)	20 (24.7)	28 (28.9)	12 (14.1)	18 (22.8)
Morphines				
n	59	53	49	58
Responder, n (%)	8 (13.6)	11 (20.8)	7 (14.3)	7 (12.1)
Oxycodones				
n	70	72	69	69
Responder, n (%)	9 (12.9)	14 (19.4)	4 (5.8)	14 (20.3)

Source: Reviewer's table, modified from Response to 74-Day Letter, Table 10, page 20; Table 12, page 22; and Table 14, page 24.

Reviewer comments: *Although the number of subjects taking a diphenylheptane opioid in OBD-0631 was probably too small to allow for rigorous conclusions, it is noteworthy that despite a nonclinical study demonstrating a negative treatment interaction between methadone and lubiprostone, the treatment effect in this class still favored the lubiprostone group. As discussed previously, examination of the relationship between MEDD and efficacy response did not demonstrate a consistent trend, so this reviewer cannot conclude that OBD-0632 failed on the primary endpoint because of the slightly higher percentage of subjects using diphenylheptane opioids and the higher MEDD for those subjects as compared with OBD-0631.*

The failure of OBD-0632 was likely related to multiple factors interacting in a complex manner. For instance, the timing of methadone administration in relation to lubiprostone administration may have affected efficacy. As demonstrated in the nonclinical study, chloride channel currents were more extensively inhibited when methadone was added

before lubiprostone. Given the relatively small number of subjects on diphenylheptane opioids in both trials and the multitude of other factors that may have contributed to the efficacy response, a clear reason for the failure of OBD-0632 cannot be delineated.

Nonclinical data demonstrated that at oral doses as low as 2.5 mg, methadone yielded high enough local (GI) concentrations to interact with the activity of lubiprostone at the CIC-2 channel. Further, the extent of inhibition of chloride currents by methadone was concentration-dependent. Doses of methadone used for management of chronic pain often exceed 2.5 mg (starting doses are generally 2.5 to 10 mg every 8 to 12 hours). In conclusion, given the nonclinical findings and the failure of a clinical trial that enrolled subjects using methadone for chronic pain, it is this medical officer's assessment that the effectiveness of lubiprostone in the treatment of OIC in patients taking diphenylheptane opioids (e.g., methadone) has not been established.

Appendix 5: Discussion of Individual Trials: Trial SMR/0211 OBD-06S1

Title

“A Multicenter, Open-labeled Study of the Long-term Safety and Efficacy of Lubiprostone in Subjects with Opioid-induced Bowel Dysfunction”

Objectives

“To assess the long-term safety and efficacy of oral lubiprostone at 48 mcg/day (24 mcg BID), when administered orally as needed for 36 weeks to patients with OIC”

Trial Design

Open-labeled, multicenter, safety and efficacy phase 3 trial

Duration

The trial duration was approximately 38 weeks from the beginning of the screening period through follow-up. All patients participating in this trial had completed treatment in one of two 12-week treatment trials (OBD-0631 or OBD-0632).

Key Inclusion Criteria

1. Completed 12 weeks of blinded treatment in the OBD-0631 or OBD-0632 trial.
2. Continued to be treated consistently for chronic, noncancer-related pain with any full agonist opiate and continued opiate therapy for the duration of the trial.
3. According to the principal investigator's clinical judgment, the subject did not have any condition in their medical history or a concurrent condition that would be contraindicated for prolonged use of lubiprostone (Amitiza®).
4. Willing to continue to abstain from use of disallowed medications as defined per protocol.
5. Willing and able to fill out his/her own eDiary and could comply with daily data collection.
6. Subject had read, understood, and signed the informed consent form.

Key Exclusion Criteria

1. Newly diagnosed impaired renal function identified at the screening visit (i.e., serum creatinine concentration >1.8 mg/dL).
2. According to investigator's clinical judgment, the patient had a concurrent, clinically significant, unexplained disease, including endocrine, cardiovascular, liver, or lung disease, neurologic or psychiatric disorders (excluding depression), or any other systemic disease. If explained, the patient may be enrolled, if in the investigator's opinion, the condition would not interfere with safety or efficacy assessments, or result in an increased risk of participation to the patient.
3. Subject had experienced an unexplained and/or clinically significant weight loss defined as >5% within 90 days prior to Screening Visit.
4. Female patient of childbearing potential who was unable or unwilling to use a protocol specified method of birth control, had a positive screening pregnancy test, was pregnant or nursing, or planned to become pregnant or nurse during the clinical trial.
5. Patient demonstrates a potential for non-compliance with trial protocol (i.e., dosing schedule, visit schedule, diary completion, or trial procedures).
6. Patient planned to participate in another trial with an investigational drug or device during the course of the extension trial.

Treatments

Screening period: This occurred in conjunction with the last visit of the 12-week treatment trial (OBD-0631 or OBD-0632).

Treatment period: Eligible subjects received a 3-month supply (3 bottles each containing a 28-day supply plus 6-day overage) of open-label study medication, 24 mcg lubiprostone, at the screening visit. Subjects were instructed to take one capsule in the morning and one in the evening with meals, and at least 8 ounces of fluid, as needed. Each treatment consisted of one capsule per dose. A maximum of two doses could be taken per day. If two doses of study medication were administered in 1 day, the doses were to be taken at least 5 hours apart.

The design of the trial allowed subjects to administer study medication based on their perceived need for relief from their OBD symptoms. It also provided for treatment adjustment at the discretion of the investigator and allowed for periodic use of rescue laxative, also at the discretion of the investigator. The subject was instructed on the signs and symptoms that may have necessitated a dose reduction. The subject was to record any change in study medication administration in the eDiary. The treatment period began on the day the first dose of study medication was administered (Day 1) and ended upon administration of the last dose.

The schedule of visits is summarized in [Table 149](#).

Table 149. Schedule of Visits – Trial OBD-06S1

Study Week(s)	0	2	6	9	12	15	18	21	24	27	30	33	36	38
Study Day(s)	1	14 (± 3)	42 (± 3)	63 (± 3)	84 (± 3)	105 (± 3)	126 (± 3)	147 (± 3)	168 (± 3)	189 (± 3)	210 (± 3)	231 (± 3)	252 (± 3)	266 (± 3)
Visit Number	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Visit Type	Screen- ing ¹	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	End-of- Treatment Clinic Exam	Follow-up Clinic Exam
Assessment														
Informed Consent	X													
Demographics	X													
Medical History	X													
Vital Signs	X		X		X		X		X		X		X	X
Physical Examination ²	X		X		X		X		X		X		X	X
Blood Chemistry, Hematology, Urinalysis	X		X		X		X		X		X		X	X
Pregnancy Test ³	X		X		X		X		X		X		X	X
ECG ⁴	X						X						X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Study Medication Distribution			X		X		X		X		X			
Study Treatment ⁵	X		X	X	X	X	X	X	X	X	X	X	X	
Study Medication Collection			X		X		X		X		X		X	
Electronic Diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X

¹The End-of-Treatment Visit in trial OBD-0631 or OBD-0632 will serve as the Screening Visit unless there is a scheduling conflict and an additional Screening Visit will need to be scheduled separately.

²Weight is captured at the Screening and Follow-up Visits. Complete comprehensive physical examinations should be performed at the Screening and Follow-up Visits. An abbreviated physical examination is to be performed at all other visits.

³Urine pregnancy tests will be performed at all study visits.

⁴All 12-lead ECGs are to be done while the patient is resting.

⁵First treatment administration is to be self-administered by the patient on Study Day 1 (the day of the Screening Visit).

Source: Sponsor's Table, module 5.3.5.2.4 Clinical Protocol SMR/0211OBD-06S1, page 12 of 45.

Trial Conduct

Screening: Day 1

- Medical history, inclusion/exclusion criteria reviewed
- Physical examination and laboratory tests, including urine pregnancy, ECG
- Review of concomitant medications used since end of 12-week treatment trial
- Ongoing AEs followed up
- Continued use of the eDiary dispensed to the subject in the preceding blinded trial; diary should have been completed each day, starting with screening visit
- Review of contraception with female subjects who were sexually active
- New supply of study medication dispensed, with first to begin the same day

Treatment period: Day 1 to 252

- On study days 14, 63, 105, 147, 189, and 231 (± 3 days), a telephone assessment was performed by site personnel to evaluate the compliance of the subject with the study medication and eDiary and to identify any AEs or changes in concomitant medications.
- On study days 42, 84, 126, 168, and 210 (± 3 days), a clinic visit occurred, during which the following evaluations were performed:
 - Subject's overall condition, abbreviated physical examination
 - ECG on Day 126 visit
 - Blood and urine samples for laboratory analyses
 - eDiary review
 - Previously dispensed bottle of study medication collected, new bottle of study medication dispensed, and compliance reviewed
- Day 252 (± 3 days), an end-of-treatment clinic visit occurred, during which the following evaluations were performed:
 - AEs or changes in concomitant medications
 - Subject's overall condition, complete physical examination
 - Blood and urine samples for laboratory analyses, ECG
 - eDiary review
 - Previously dispensed bottle of study medication collected and compliance reviewed

Final follow-up assessment: Day 266 (± 3 days)

A follow-up clinic visit occurred (or before for subjects who discontinued treatment prematurely) to:

- Review any ongoing or new onset of AEs or changes in concomitant medications
- Assess the subject's condition, physical examination
- Blood and urine samples for laboratory analyses
- eDiary collected

A monthly nausea assessment (using the FLIE questionnaire) was administered via the eDiary. The pain assessment (using the BPI-SF) was also administered monthly on the eDiary. For the opioid dose assessments, all medications including name, dosage

parameters, and dose adjustments were captured for all opioid treatment administered to the subject during their participation in the trial.

Removal of Subjects from Therapy or Assessment

Subject participation may have been terminated prior to completion of the clinical trial for AEs, lack of efficacy, permanent discontinuation of chronic opioid therapy or discontinuation of administration of chronic opioid therapy for >48 hours, subject choice, lost to follow-up, noncompliance, investigator's decision, Sponsor's request, or any other reason upon agreement between the investigator and the Sponsor.

Subjects who withdrew or terminated early from the trial were to complete the final visit of the treatment period (Visit 22, Day 252) and the follow-up visit (Visit 23, Day 266) per protocol. When a subject withdrew prior to completing the trial, the reason for withdrawal was to be documented in the electronic CRF and in the source document. Study medication assigned to the withdrawn subject was not assigned to another subject. Subjects who withdrew were not replaced. If a subject discontinued chronic opioid therapy, they were to withdraw from the trial and complete the final visit of the treatment period (Visit 22) and the follow-up visit (Visit 23).

Prior and Concurrent Therapy

The protocol followed for prior and concurrent therapy was identical to that followed in the double-blind trials OBD-0631 and OBD-0632.

Rescue Laxatives

The protocol followed for rescue laxatives was identical to that employed in the double-blind trials OBD-0631 and OBD-0632, except that the restriction of no rescue laxative use within 24 hours of the first dose of study medication or during the first week of treatment did not apply.

Compliance

Designated trial personnel maintained a log of study medications dispensed and returned. Study medication supplies for each subject were inventoried and accounted for throughout the trial. Study medication administration was documented in the source documentation, including dispensation information and capsule counts and on the CRF. Study medication dosing was also recorded by the subject in the eDiary.

Outcome Measures

Efficacy

Trial OBD-06S1 was not primarily an efficacy trial, but the Sponsor examined the following efficacy variables:

- Change from baseline in monthly SBM and BM frequency
- Frequency of SBMs and BMs monthly
- Monthly responder rates
- Mean change from baseline monthly in:
 - Straining associated with SBMs
 - Stool consistency of SBMs

- Constipation severity
- Abdominal bloating
- Abdominal discomfort
- Regularity of bowel habit
- Frequency of complete SBMs and BMs monthly
- Treatment effectiveness

Statistical Analysis

All tests of change from baseline were two-tailed at a significance level of $\alpha=0.05$. There were no multiplicity adjustments. Two datasets were used for analyses: safety and ITT. The definition of these datasets is as follows:

- Safety-evaluable population: All enrolled subjects who took at least one dose of study medication
- ITT population: All enrolled subjects who took at least one dose of study medication and had at least one treatment-period diary entry

Sponsor's Plan for Handling of Missing Data

With a week considered a 168-hour interval, if ≥ 85 hours was observed during a week then the missing data within that week were imputed with the average SBM data for that week. Monthly data were imputed based on the amount of data observed. If there were no data within a month then that month was considered missing and no imputation was performed. If there was ≥ 1 week of data in a month, but < 4 weeks, then LOCF was used as follows:

- If weeks 2, 3, or 4 were missing in a month then the last observed value in that month was carried forward to complete the data within that month.
- If week 1 was missing within a month but data for weeks 2, 3, or 4 were available then data from the month prior were carried forward, if available. In this case, the data from either week 3 or 4 of the prior month were carried forward if available. If week 3 and 4 of the prior month were missing then no data were imputed.

Protocol Amendments

There was one protocol amendment to the original protocol dated October 3, 2007.

Amendment #1 occurred on June 9, 2008 and included the following changes:

- Changed sample size from 380 subjects to 420 subjects
- Removed antihistamines from the list of excluded medications
- Revised wording of daily rescue laxative question

Results

Disposition of Subjects

A total of 443 subjects were enrolled in the trial, 439 subjects were treated, and 286 subjects (65%) completed the trial at 137 sites in the United States and Canada. A total of 153 subjects (35%) discontinued during the trial. A total of 23 subjects (5%)

experienced AEs that led to discontinuation; 15 subjects (7%) were in the placebo/lubiprostone group and 8 subjects (4%) were in the lubiprostone/lubiprostone group. [Table 85](#) in section [7.3.3 Dropouts and/or Discontinuations](#) provides further details of subject disposition.

Protocol Deviations and Violations

Protocol violations included subjects who entered the trial even though they did not strictly meet inclusion/exclusion criteria, subjects who deviated from the conduct of the trial after the start of study drug, and subjects who did not participate in study assessments as required by the protocol. Subjects with protocol violations were not excluded from the efficacy analysis, as only the ITT and safety populations were used for analysis and tabulations.

Demographics and Other Baseline Characteristics

Baseline demographics are detailed in [Table 80](#) and baseline constipation status is summarized in [Table 81](#). Overall, 60% of subjects were female, and the mean age of subjects was 50 years. Mean baseline SBM frequency rate was 1.4 SBMs/week, and mean baseline constipation severity was 2.4 (moderate).

Rescue Laxative Use

The percentage of subjects using rescue medication at each of 9 study months is as follows: (1) 33%; (2) 26%; (3) 26%; (4) 18%; (5) 19%; (6) 18%; (7) 18%; (8) 16%; and (9) 19%. Overall, there was a trend toward decrease in rescue laxative use throughout the first 4 months of the trial, which was then sustained through the end of the trial.

Opioid Medication Use

As shown in [Table 150](#), there was an overall trend of increase in mean MEDD during the 9 months of the trial in the both the placebo-lubiprostone and lubiprostone-lubiprostone groups. There were outliers in most months and these extreme values may have affected the mean MEDD change from baseline. In considering median changes from baseline MEDD by month, it is notable that the median change in both groups is zero at each month.

Table 150. Change from Baseline in Opioid Dose by Month in OBD-06S1

Time Point	Change from Baseline in Opioid Dose (Observed Combined MEDD)	Placebo-LBP (N=225)	LBP-LBP (N=214)
Month 1	n	224	214
	Mean ± Standard Deviation	11.5 ± 76.58	-1.1 ± 95.34
	Median (Min, Max)	0 (-26, 693)	0 (-1142, 575)
Month 2	n	218	214
	Mean ± Standard Deviation	15.5 ± 121.41	4.2 ± 145.98
	Median (Min, Max)	0 (-431, 1035)	0 (-1326, 1468)
Month 3	n	208	214
	Mean ± Standard Deviation	13.5 ± 108.46	5.2 ± 167.12
	Median (Min, Max)	0 (-431, 840)	0 (-1333, 1465)
Month 4	n	200	213
	Mean ± Standard Deviation	17.0 ± 108.32	2.6 ± 206.90
	Median (Min, Max)	0 (-360, 840)	0 (-1543, 1463)
Month 5	n	184	211
	Mean ± Standard Deviation	16.9 ± 117.33	23.9 ± 168.94
	Median (Min, Max)	0 (-423, 840)	0 (-1077, 1496)
Month 6	n	171	204
	Mean ± Standard Deviation	25.7 ± 119.83	33.7 ± 274.42
	Median (Min, Max)	0 (-360, 840)	0 (-1961, 1915)
Month 7	n	208	214
	Mean ± Standard Deviation	24.1 ± 119.30	49.1 ± 251.61
	Median (Min, Max)	0 (-360, 840)	0 (-1223, 1915)
Month 8	n	154	182
	Mean ± Standard Deviation	38.0 ± 201.66	48.4 ± 266.17
	Median (Min, Max)	0 (-360, 2018)	0 (-885, 1915)
Month 9	n	149	176
	Mean ± Standard Deviation	43.7 ± 319.13	57.0 ± 270.55
	Median (Min, Max)	0 (-360, 3584)	0 (-885, 1915)

Abbreviations: LBP, lubiprostone

Source: Reviewer's table, adapted from Sponsor's Table 1.1.7.6, pages 394 to 402 of 2585, Integrated Summary of Efficacy.

Reviewer comments: *In this reviewer's opinion, monthly analysis of MEDD changes is inadequate. A monthly average does not provide an adequate picture of changes in opioid use over the course of the trial, as daily or weekly changes may be lost when all values are averaged over the month. Interpretation of results is further limited by the uncontrolled nature of trial OBD-06S1. Thus, rigorous conclusions regarding the effects of lubiprostone on opioid use cannot be made. See discussion in section 7.3.5*

Submission Specific Primary Safety Concerns.

Treatment Compliance

The Sponsor did not measure treatment compliance in this trial.

Analysis of Efficacy

Change from Baseline in Monthly Frequency of SBMs

The mean change from baseline in the frequency of SBMs generally demonstrated an increase in weekly SBM frequency of 3.5 to 4.3 SBMs per week in the subjects in the placebo-lubiprostone group and in the subjects in the lubiprostone-lubiprostone group throughout the 9 months of the trial. Results are presented in [Table 151](#).

Table 151. Change from Baseline in SBM Frequency by Month in OBD-06S1 (ITT Population)

Time Point	Change from Baseline in SBM Frequency by Month ¹	All Intent-to-Treat Subjects	
		Placebo-LBP (N=225)	LBP-LBP (N=214)
Month 1	n	164	169
	Mean ± Standard Deviation	3.6 ± 2.84	3.5 ± 2.68
	Median (Min, Max)	3.0 (-2, 19)	3.1 (-1, 18)
Month 2	n	151	149
	Mean ± Standard Deviation	3.6 ± 2.98	3.6 ± 2.63
	Median (Min, Max)	3.2 (-3, 19)	3.4 (-2, 17)
Month 3	n	142	138
	Mean ± Standard Deviation	4.0 ± 3.13	3.6 ± 2.60
	Median (Min, Max)	3.3 (-1, 18)	3.4 (-1, 15)
Month 4	n	129	121
	Mean ± Standard Deviation	4.1 ± 2.83	3.8 ± 2.83
	Median (Min, Max)	3.8 (-1, 17)	3.6 (-1, 18)
Month 5	n	113	111
	Mean ± Standard Deviation	4.2 ± 3.44	3.7 ± 2.52
	Median (Min, Max)	3.6 (-1, 19)	3.5 (-1, 14)
Month 6	n	108	114
	Mean ± Standard Deviation	4.0 ± 3.19	3.6 ± 2.39
	Median (Min, Max)	3.5 (-1, 20)	3.3 (-1, 15)
Month 7	n	103	102
	Mean ± Standard Deviation	4.3 ± 3.38	3.6 ± 3.01
	Median (Min, Max)	3.6 (0, 24)	3.4 (-1, 19)
Month 8	n	91	89
	Mean ± Standard Deviation	4.0 ± 2.93	4.1 ± 3.00
	Median (Min, Max)	3.4 (-1, 13)	3.8 (-1, 19)
Month 9	n	84	82
	Mean ± Standard Deviation	4.0 ± 3.00	3.6 ± 2.31
	Median (Min, Max)	3.5 (-1, 15)	3.5 (-1, 10)

Abbreviations: LBP, lubiprostone

Source: Reviewer's table, adapted from Sponsor's Table 2.7.3.5-1, page 108 of 119, Summary of Clinical Efficacy.

Reviewer comments: The durability of the increase in SBM frequency from baseline to Month 9 suggests preserved efficacy of lubiprostone over time. Nonetheless, because the medication was used as needed during the 9-month open-label period, clear association between the study drug and increased SBM frequency is difficult to make.

Safety Monitoring and Adverse Events

Safety

Safety was evaluated by AE reporting, vital signs, physical examination, and laboratory evaluations. AEs were assessed from the start of the trial through the final follow-up visit. Verbatim AEs were coded into standardized SOCs and PTs using MedDRA.

Safety Analyses

The safety analyses included all enrolled subjects who took at least one dose of study medication and were performed based on observed data. A total of 439 subjects took at least one dose of study drug and were included in safety evaluations.

Adverse Events

Of the 439 subjects in the safety population, 314 (72%) had at least one TEAE. Among the safety population, 137 (31%) subjects had an AE in the infections and infestations

SOC, followed by the gastrointestinal disorders SOC, reported by 121 (28%) subjects. A total of 108 subjects (25%) had AEs that the Sponsor reported as treatment related.

Serious Adverse Events

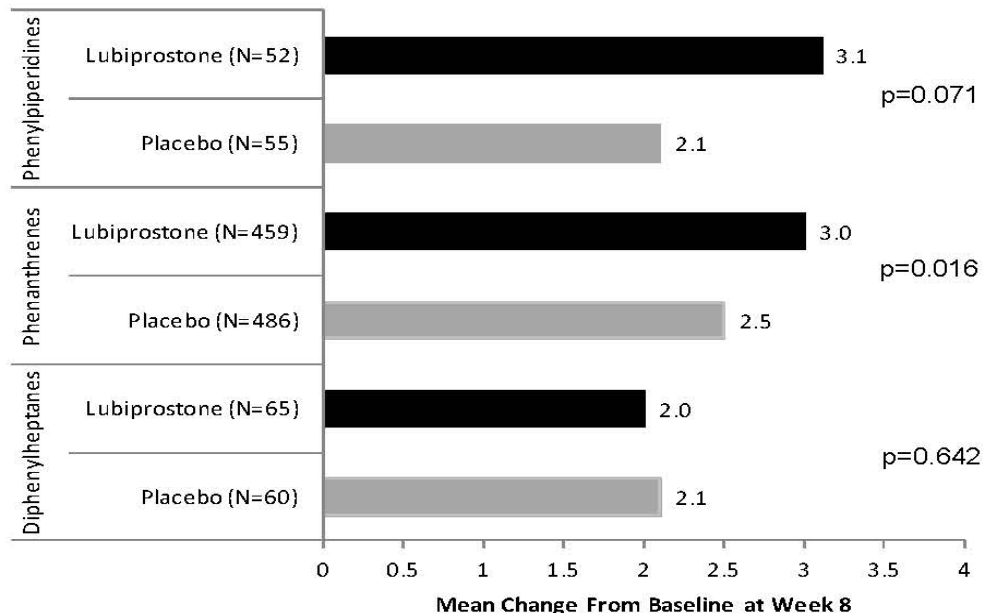
A total of 33 subjects (8%) had at least one nonfatal SAE, none of which the Sponsor considered as related to study medication. [Table 84](#) of section 7.3.2 summarized SAEs.

Deaths

One subject died in trial OBD-06S1, from causes that could not be clearly linked to the study drug. The subject's death narrative is in section [7.3.1 Deaths](#).

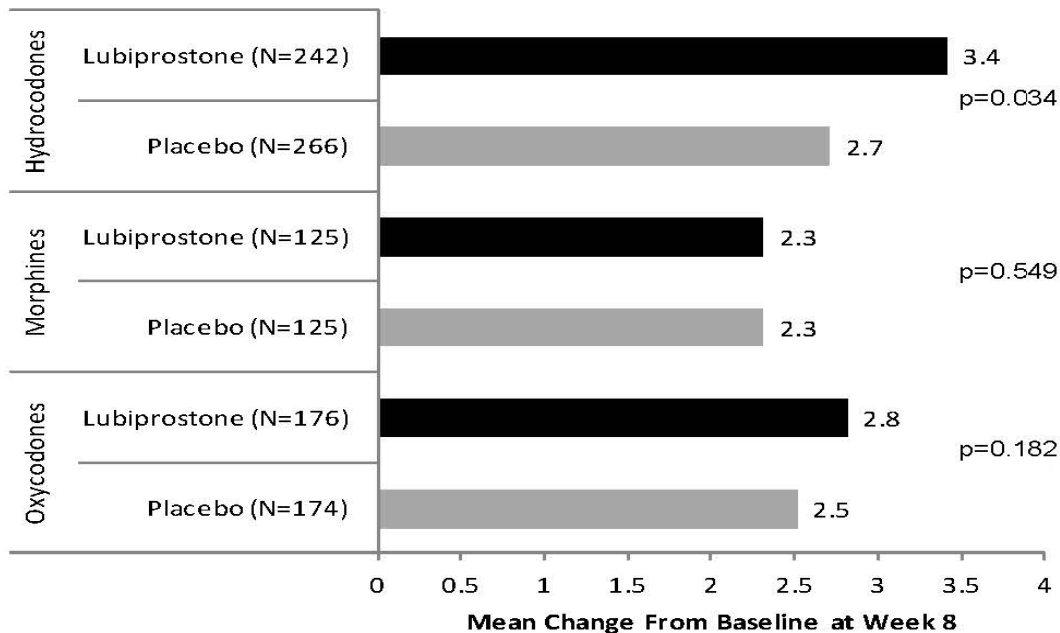
Appendix 6: Pooled Efficacy Data by Opioid Class and Subclass (OBD-1033, OBD-0631, and OBD-0632)

Figure 3. Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Opioid Class – Trials OBD-1033, OBD-0631, OBD-0632 (ITT Population)



Source: Sponsor's Figure 2.7.3.3.-11, page 104 of 119, Summary of Clinical Efficacy.
 Cross-reference: section [6.1.7 Subpopulations](#).

Figure 4. Change from Baseline in SBM Frequency at Week 8 in Subjects without Dose Reduction by Phenanthrene Subclass – Trials OBD-1033, OBD-0631, OBD-0632 (ITT Population)



Source: Sponsor's Figure 2.7.3.3.-12, page 105 of 119, Summary of Clinical Efficacy.
 Cross-reference: section 6.1.7 Subpopulations.

Appendix 7: Narratives of Subjects Selected for Review Based on Adverse Events Suggestive of Possible Opioid Withdrawal

- 1033-3044-002: AEs of hyperhidrosis, tachycardia, and nausea on the same day; 47-year-old female with history of gastric bypass surgery and OIC on hydrocodone 1 tab BID beginning ~9 years before trial (no dose changes during trial) who, on the day of first lubiprostone dose, reported mild worsening of pre-existing nausea, mild, intermittent dyspnea, and single events of hyperhidrosis and tachycardia, both of moderate severity. All AEs were considered possibly related to lubiprostone by the investigator, did not require medical intervention or change in study drug, and resolved without sequelae (hyperhidrosis and tachycardia had resolved by the next day). The subject completed the 12-week trial and had no other reported AEs.

Reviewer comments: *This reviewer cannot assert with reasonable confidence that the constellation of signs and symptoms represented opioid withdrawal, particularly in the absence of hemodynamic measurements (i.e., blood pressure, heart rate) at the time of the AEs. Alternative possibilities for some of the subject's AEs exist. Dyspnea is a labeled adverse reaction associated with lubiprostone, typically occurring shortly after drug initiation. Further, the patient continued study drug with no further reported AEs and had no reported adverse cardiovascular (CV) outcomes.*

- 1033-3081-004: AE of abdominal pain and flushing on the same day; 40-year-old female on hydrocodone 10 mg QID beginning ~1 year before trial (no dose changes during trial), who on the day after first lubiprostone dose, reported intermittent moderate vertigo and 30 minutes later, reported intermittent abdominal pain and facial flushing, both of moderate severity. All AEs were considered probably related to lubiprostone, did not require medical intervention or change in study drug, and resolved without sequelae by the following day. Vital signs obtained the day after all AEs had resolved were unremarkable (blood pressure 118/72 mmHg, hear rate 72). The subject chose to discontinue from the trial 3 days after randomization. The subject had no other reported AEs.

Reviewer comments: *This reviewer cannot assert with reasonable confidence that the constellation of signs and symptoms represented opioid withdrawal. Further, although the patient discontinued the trial, she had no further reported AEs or adverse CV outcomes.*

- 0631-1028-002: AE of abdominal pain, nausea, diarrhea, and headache on the same day; 63-year-old female on Percocet 5 mg QID beginning ~1.3 years before trial (no dose changes during trial), who on the day of first lubiprostone dose, reported intermittent diarrhea (severe), abdominal cramps (moderate), headache (moderate), and nausea (moderate). All AEs were considered probably related to lubiprostone, did not require medical intervention or change in study drug, and resolved without sequelae 3 days later. No vital signs were obtained at time of reported AEs. The subject chose to discontinue study drug 3 days after randomization. Subject was assessed at end-of-treatment visit and follow-up visit (~45 days after randomization) and had no other reported AEs.

Reviewer comments: *This reviewer cannot assert with reasonable confidence that the constellation of signs and symptoms represented opioid withdrawal, particularly in the absence of hemodynamic measurements at the time of the AEs. Further, although the patient discontinued the trial, she had no further reported AEs or adverse CV outcomes.*

- 0631-1028-045: AE of drug withdrawal syndrome; 47-year-old male on Actiq 1200 mcg TID and oxycodone 30 mg QD since 2006 and morphine 60 mg TID since 6/2008 who began lubiprostone on 9/28/2007. On 11/23/2008, all opioids were discontinued (for unclear reasons) and subject was switched to Lortab 20 mg Q6H. The next day, drug withdrawal syndrome (verbatim term: narcotic withdrawal) was reported. The AE was moderate, non-serious, assessed as unrelated to study drug, and resolved without sequelae within 1 day. No vital signs were obtained at time of reported AEs. The subject completed the 12-week trial and had three other AEs (flatulence, worsening hyperlipidemia, and elevated liver function tests), none of which were temporally or clinically related (in this reviewer's assessment) to the AE of drug withdrawal syndrome.

Reviewer comments: *This subject's opioid withdrawal was quite clearly related to modifications in his opioid regimen rather than study drug.*

- 0632-2080-013: AEs of agitation, flushing, nausea, and tremor on the same day; 58-year-old male on Avinza 120 mg BID until 7/16/2008 who was switched to Opana ER 40 mg BID from 7/16/2008 until 7/24/2008, and switched back to Avinza 120 mg BID on 7/24/2008. The subject began lubiprostone on 7/17/2008 and on that day, reported intermittent nausea, shakiness, flushing, and agitation, all moderate in intensity and all assessed as unrelated to study drug. No vital signs were obtained at time of reported AEs. All AEs resolved without sequelae on 7/27/2008. The subject completed the 12-week trial and enrolled in the open-label long-term trial. No other AEs other than "tastelessness" were reported.

Reviewer comments: *The constellation of this subject's signs and symptoms likely represent opioid withdrawal, but the subject's opioid withdrawal was quite clearly related to concurrent modifications in his opioid regimen.*

- 06S1-1010-007: AE of drug withdrawal syndrome; 54-year-old female on methadone 20 mg BID who had completed 12 weeks of treatment with lubiprostone in trial OBD-0631 (first exposure 3/7/2008). On 8/25/2008, the subject's methadone was discontinued and the following day, drug withdrawal syndrome (verbatim term: narcotic withdrawal syndrome) was reported. The AE was moderate, non-serious, assessed as unrelated to study drug, and resolved without sequelae 5 days later. No vital signs were obtained at time of AEs.

Reviewer comments: *This subject's opioid withdrawal was temporally quite clearly related to modifications in her opioid regimen rather than study drug.*

- 06S1-2014-003: AE of nausea, vomiting, blood pressure fluctuation, irregular heart rate, and tremor; 64-year-old female with history of hypertension, and OIC on Duragesic 125 mcg Q72H and Fentora 600 mcg Q4H PRN, who had completed 12-weeks of placebo in trial OBD-0632. Three days after first lubiprostone dose, she reported nausea, vomiting, blood pressure fluctuation, erratic pulse, and tremor (all mild). All AEs were considered possibly related to lubiprostone, did not require medical intervention or change in study drug, and resolved without sequelae by day 5. No vital signs were obtained at time of AEs. The subject chose to discontinue from trial 28 days after randomization. During the double-blind phase (while taking placebo), the subject had AEs of eructation, flatulence, nasopharyngitis, and electrocardiogram abnormal (~3 weeks prior to first dose of lubiprostone, no additional details provided).

Reviewer comments: *This reviewer cannot assert with reasonable confidence that the constellation of signs and symptoms represented opioid withdrawal, particularly in the absence of hemodynamic measurements at the time of the AEs. Given the high dose of PRN opioids the subject was using (Fentora), it is possible that erratic use of the Fentora may have contributed to her AEs on day*

3. Further, although the patient discontinued the trial, she had no reported adverse CV outcomes.

- 06S1-2044-003: AE of withdrawal syndrome; 52-year-old female on oxycodone 10 mg Q6H who had completed 12 weeks of treatment with lubiprostone in trial OBD-0632 (first exposure 3/4/2008). On 5/23/2008, the subject's oxycodone was discontinued and 4 days later, withdrawal syndrome (verbatim term: narcotic withdrawal) was reported. The AE was non-serious, assessed as unrelated to study drug, and resolved without sequelae on 6/6/2008, when an opioid was resumed. No vital signs were obtained at time of reported AEs. The subject chose to discontinue study drug on 6/6/2008. No other AEs were reported.

Reviewer comments: *This subject's opioid withdrawal was temporally related to modifications in her opioid regimen.*

- 06S1-2048-006: AEs of nausea, hyperhidrosis, and abdominal pain upper on the same day; 55-year-old female on methadone 5 mg Q6H beginning ~3.5 years before trial (no dose changes during trial), who approximately 3 months after first lubiprostone dose, reported mild, intermittent nausea, sweating, and stomach cramps. All AEs were considered possibly related to lubiprostone, did not require medical intervention or change in study drug, and resolved without sequelae. No vital signs were obtained at time of reported AEs. The subject completed the trial and had no other reported AEs.

Reviewer comments: *This reviewer cannot assert with reasonable confidence that the constellation of signs and symptoms represented opioid withdrawal. The absence of symptoms until ~3 months after first dose of study drug makes it less likely that AEs were related to study drug. Further, the patient had no other reported AEs or adverse CV outcomes.*

Cross-reference: section [7.3.5](#) [Submission Specific Primary Safety Concerns](#).

Appendix 8: Laboratory Reference Ranges

Table 152. Laboratory Reference Ranges

Complete Blood Count	Lower Limit of Normal	Upper Limit of Normal	Units
Hematocrit ¹	35 (female), 37 (male)	47 (female), 51 (male)	%
Hemoglobin ²	11.7 (female), 12.6 (male)	16.1 (female), 17.4 (male)	g/dL
Platelet count	150	400	10 ⁹ /L
White Blood Cell count	4.5	13 (<21 yrs), 11 (≥21 yrs)	10 ⁹ /L
Electrolytes			
Sodium	135	148	mEq/L
Potassium	3.5	5.5	mEq/L
Chloride	96	109	mEq/L
Bicarbonate	20	32	mEq/L
BUN	5	26	mg/dL
Creatinine	0.5	1.5	mg/dL
Glucose	65	99	mg/dL
Calcium	8.5	10.6	mg/dL
Magnesium	1.6	2.6	mg/dL
Phosphorus ³	2.5	4.5	mg/dL
Liver Function Tests			
AST	0	40	IU/L
ALT	0	40 (female), 55 (male)	IU/L
Alkaline Phosphatase ⁴	25	300	IU/L
Bilirubin, Total	0.1	1.2	mg/dL
Bilirubin, Direct	0	0.4	mg/dL
Albumin ⁵	3.5	5.5	g/dL
Total Protein	6	8.5	g/dL
Gamma Glutamyl Transferase	0	60 (female), 65 (male)	IU/L
Other			
Total cholesterol ⁶	100	199	mg/dL
Triglycerides	0	149	mg/dL
Iron	35 (female), 40 (male)	155	µg/dL
Lactate Dehydrogenase	100	250	IU/L
Uric Acid	1.5 (female), 2.2 (male)	6.7 (female), 8.7 (male)	mg/dL
Urinalysis			
pH	5	7.5	pH
Specific Gravity	1.005	1.030	SGU
Urobilinogen	0	1.9	EU/dL

Abbreviations: IU, international unit; SGU, specific gravity unit; EU, Ehrlich unit.

¹Hematocrit: Females – 18 to 45 yrs, range 35 to 45%; >45 yrs, range 35 to 47%. Males – 18 to 45 yrs, range 39 to 49%; 45 to 65 yrs, range 39 to 50%; >65 yrs, range 37 to 51%.

²Hemoglobin: Females – 18 to 45 yrs, range 11.7 to 15.5 g/dL; 45 to 65 yrs, range 11.7 to 16 g/dL; >65 yrs, range 11.7 to 16.1 g/dL. Males – 18 to 45 yrs, range 13.2 to 17.3 g/dL; 45 to 65 yrs, range 13.1 to 17.2 g/dL; >65 yrs, range 12.6 to 17.4 g/dL.

³Phosphorus: Females – 9 to 19 yrs, range 2.5 to 5.3 mg/dL; >19 yrs, range 2.5 to 4.5 mg/dL. Males – 9 to 19 yrs, range 2.5 to 5.6 mg/dL; >19 yrs, range 2.5 to 4.5 mg/dL.

⁴Alkaline phosphatase: Females – 14 to 20 yrs, range 45 to 300 IU/L; 20 to 60 yrs, range 25 to 150 IU/L; >60 yrs, range 25 to 165 IU/dL. Males – 14 to 20 yrs, range 60 to 400 IU/L; 20 to 60 yrs, range 25 to 150 IU/L; >60 yrs, range 25 to 160 IU/dL.

⁵Albumin: 2 to 59 yrs, range 3.5 to 5.5 g/dL; 59 to 69 yrs, range 3.6 to 4.8 g/dL; 69 to 79 yrs, range 3.5 to 4.8 g/dL, 79 to 89 yrs, range 3.5 to 4.7 g/dL.

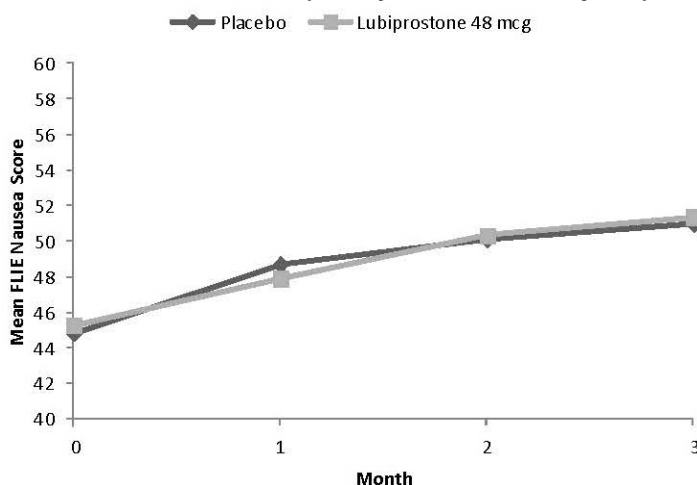
⁶Cholesterol: <19 yrs, range 100 to 169 mg/dL; >19 yrs, range 100 to 199 mg/dL.

Source: Sponsor's Tables entitled "Protocol Reference Range Definitions," Response to 74-Day Letter, pages 681 to 734.

Cross-reference: section 7.4.2 Laboratory Findings.

Appendix 9: Functional Living Index-Emesis (FLIE) Nausea Scores

Figure 5. FLIE Scores – Double-blind Trials Pool (Safety Evaluable Subjects)

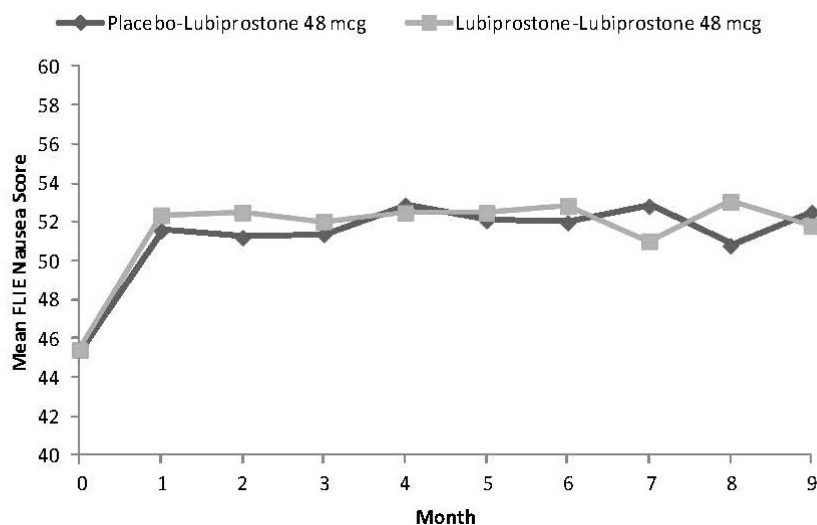


Placebo N =	651	646	570	525
Lubiprostone 48 mcg N =	663	650	576	514

Note: The double-blind studies pool includes studies OBD-1033, OBD-0631, and OBD-0632.
 Source: Sponsor’s Figure 2.7.4.4-3, page 110 of 167, Summary of Clinical Safety.

Cross-reference: section [7.5.2 Time Dependency for Adverse Events](#).

Figure 6. FLIE Scores – Open-label Trial OBD-06S1 (Safety Evaluable Subjects)



Placebo N =	225	205	195	181	167	154	147	141	132	127
Lubiprostone 48 mcg N =	214	201	196	180	171	162	147	141	140	126

Source: Sponsor’s Figure 2.7.4.4-4, page 111 of 167, Summary of Clinical Safety.

Cross-reference: section [7.5.2 Time Dependency for Adverse Events](#).

Appendix 10: Daily Electronic Diary

1. Date and time of dose administration.

- Did you take your morning dose of study medication today? Y/N
- Did you take your evening dose of study medication today? Y/N

- c. If “Yes” to either/both, the following information will be collected:
Morning Dose – xx:xx AM
Evening Dose – xx:xx PM

2. Date and time of any rescue medications used.

- a. Did you take a medication, aside from your study medication, to help you have a BM in the past 24 hours (since yesterday’s bedtime report)? Y/N
- b. If “Yes”.....How many medications of each type did you use?
 - i. Suppository – xx (number)
 - ii. Enema – xx (number)
 - iii. Other – xx (number)
- c. Did you take a medication to help you have a BM since your office visit today? Y/N
- d. For each rescue medication used, the following information will be collected: For the [first, second, etc.] medication used, indicate the date and time of administration.
 - i. Suppository Date DD-MM-YYYY, xx:xx AM/PM
 - ii. Enema Date DD-MM-YYYY, xx:xx AM/PM
 - iii. Other Date DD-MM-YYYY, xx:xx AM/PM

3. Date and time of any adjustment of opioid medication.

- a. Did you or your doctor change your opioid medication dose today? Y/N
- b. For each change in opioid medication used, the following information will be collected:
 - i. Are you still taking your opioid medication? Y/N
 - ii. Did the name or type of your opioid medication change? Y/N
 - iii. Did the way you take your opioid medication change? Y/N
 - iv. Did the number of times per day that you take your opioid medication change? Y/N

4. The date and time of BMs (if any).

- a. How many BMs did you have in the past 24 hours (since yesterday’s bedtime report)?
XXX
- b. For each BM, the following series of questions will be asked:
 - i. What time did the [first, second, etc.] BM occur?
Date DD-MM-YYYY, xx:xx AM/PM
 - ii. Did your bowels feel completely empty after the BM? Y/N
 - iii. How would you rate the consistency of this BM?
 - 0 = very loose
 - 1 = loose
 - 2 = normal
 - 3 = hard
 - 4 = very hard (little balls)
 - iv. How would you rate the straining associated with this BM?
 - 0 = none
 - 1 = mild
 - 2 = moderate
 - 3 = severe
 - 4 = very severe

5. Evaluation of abdominal symptoms (bloating and discomfort) and constipation severity, using the following 5-point scale for each:

- a. How would you rate your abdominal discomfort/pain today?

- b. How would you rate your abdominal bloating today?
- c. How would you rate your constipation today?
 - 0 = absent
 - 1 = mild
 - 2 = moderate
 - 3 = severe
 - 4 = very severe

9.1 Literature Review/References

The Sponsor's literature search provided for this review was appropriate. The following references were used for this review:

Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1). *Pain Med.* 2009;10(1):35-42.

Berde CB, Walco GA, Krane EJ et al. Pediatric analgesic clinical trial designs, measures, and extrapolation: report of an FDA scientific workshop. *Pediatrics.* 2012;128(2); 354-364.

Camilleri M. Opioid-induced constipation: challenges and therapeutic opportunities. *Am J Gastroenterol.* 2011;106:835-842.

Dubois D, Gilet H, Viala-Danten M, Tack J. Psychometric performance and clinical meaningfulness of the Patient Assessment of Constipation-Quality of Life questionnaire in prucalopride (RESOLOR) trials for chronic constipation. *Neurogastroenterol Motil.* 2010;22(2):e54-63.

Dunlop R, Bennett KCLB. Pain management for sickle cell disease in children and adults. The Cochrane Collaboration. 2009;1;1-27.

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003350.pub2/pdf>

FDA guidance for industry, 2006, Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075059.pdf>

FDA guidance for industry, 2009, Drug-induced Liver Injury – Premarketing Clinical Evaluation. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>.

FDA guidance for industry, 2009, Patient-Reported Outcome Measures – Use in Medical Product Development to Support Labeling Claims. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>.

Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the Brief Pain Inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain*. 2004;20(5):309-318.

Kurz A, Sessler DI. Opioid-induced bowel dysfunction: pathophysiology and potential new therapies. *Drugs*. 2003;63:649-671.

Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. *N Engl J Med*. 2012;367(14):1355-1360.

Marquis P, De La Loge C, Dubois D, McDermott A, Chassany O. Development of the Patient Assessment of Constipation Quality of Life Questionnaire. *Scand J Gastroenterol*. 2005;40:540-551.

Martin AR, Pearson JD, Cai B, Elmer M, Horgan K, Lindley C. Assessing the impact of chemotherapy-induced nausea and vomiting on patients' daily lives: a modified version of the Functional Living Index-Emesis (FLIE) with 5-day recall. *Support Care Cancer*. 2003;11(8):522-527.

Paltiel O, Salakhov E, Ronen I, Berg D, Israeli A. Management of severe hypokalemia in hospitalized patients: a study of quality of care based on computerized databases. *Arch Intern Med*. 2001;161(8):1089-1095.

Panchal SJ, Muller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. *Int J Clin Pract*. 2007;61(7):1181-1187.

Pappagallo M. Incidence, prevalence, and management of opioid bowel dysfunction. *Am J Surg*. 2001;12:11S-8S.

Senior JR. Alanine aminotransferase: a clinical and regulatory tool for detecting liver injury-past, present, and future. *Clin Pharmacol Ther*. 2012;92(3):332-339.

Slater ME, De Lima J, Campbell K, Lane L, Collins J. Opioids for the management of severe chronic non-malignant pain in children: a retrospective 1-year practice survey in a children's hospital. *Pain Medicine*. 2010;11(2); 207-214.

Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the Brief Pain Inventory for chronic nonmalignant pain. *J Pain*. 2004;5(2):133-137.

Tuteja AK, Biskupiak J, Stoddard GJ, Lipman AG. Opioid-induced bowel disorders and narcotic bowel syndrome in patients with chronic non-cancer pain. *Neurogastroenterol Motil*. 2010;22:424-431.

9.2 Labeling Recommendations

Discussions regarding labeling recommendations are ongoing at the time of this review. The statistical review of this sNDA is also currently pending. As such, the analysis results (e.g., p-values, ITT population as defined by the Sponsor versus ITT population consisting of all randomized patients) presented in this review may differ somewhat from the analysis results presented by the statistical review team. For final labeling agreements, see the approved product label for Amitiza®.

Regarding the proposed indication of OIC, the following changes are being recommended to the following labeling sections: 1 indications and usage, 6 adverse reactions, 8 use in specific populations, and 14 clinical trials. The Sponsor's proposed labeling language is provided with edits recommended by this medical officer presented in the following manner: (1) strikethrough denotes the Sponsor-proposed labeling language that this medical officer recommends removing; and (2) underlined red text represents language that this medical officer recommends adding. Comments explaining rationale for edits/additions are also provided.

1 INDICATIONS AND USAGE 1.2 Opioid-induced Constipation

Amitiza is indicated for the treatment of opioid-induced constipation (OIC) ^{(b) (4)}
 n adults with chronic, non-cancer pain.

Reviewer comments:  ^{(b) (4)}

 ^{(b) (4)}

6 ADVERSE REACTIONS 6.1 Clinical Studies Experience



Reviewer comments:



Because this section is intended to discuss the most common adverse reactions, this reviewer recommends deletion of the strikethrough text above (i.e., text that is redundant with text in the CIC Adverse Reactions section) and addition of the underlined red text.



[Redacted] (b) (4)

[Redacted] (b) (4)

Reviewer comments: *The clinical trials that form the basis for these labeling claims regarding (b) (4) were not designed to test specified hypotheses (b) (4)*

Apparent findings that emerge from an assessment of dozens of potential endpoints (adverse events) of interest cannot be described with statistical certainty using conventional significance levels. In light of the fact that these findings were the result of exploratory analyses, this medical officer recommends removing the strikethrough text because these claims in the label are not justified. Underlined red text reflects pertinent information that is congruent with the presentation format for (b) (4)

[Redacted] (b) (4)

Reviewer comments: *This claim regarding (b) (4) runs counter to the (b) (4)*

[Redacted]

[Redacted] (b) (4)

Reviewer comments: [Redacted] (b) (4)

[Redacted]

the above labeling claim is not adequately supported by the submitted data.

(b) (4)

Reviewer comments: *Because the open-label trial was not adequate and well-controlled and does not contribute any new safety information, this medical officer recommends removing description of this trial from Section 6 of the label.*

8 USE IN SPECIFIC POPULATIONS

8.5 Geriatrics

(b) (4)

Reviewer comments: *The above edits reflect recommendations to keep labeling language consistent with that for the CIC and IBS-C indications in the current label.*

14 CLINICAL TRIALS

14.2 Opioid-induced Constipation

(b) (4)

Reviewer comments: *Because OBD-0632 was a failed clinical trial,* (b) (4)

”

(b) (4)

(b) (4)

(b) (4)

Reviewer comments: *Because the three efficacy trials did not use the same primary endpoint and one of the three efficacy trials (OBD-0632) was a failed trial, this officer recommends that results of the three trials, including key baseline demographic data, be presented separately for each trial. In this officer's opinion, the strikethrough text above does not provide useful information to the prescribing healthcare provider and should be deleted. Lastly, this officer notes that although the SAP of OBD-1033 specified that no rescue laxatives could be using during the first 72 hours following treatment initiation, the SAP of OBD-0631 and OBD-0632 stated that no rescue laxative should be used during the first week of treatment. This officer recommends that the underlined sentence above be modified to reflect these differences between the SAPs of the three trials.*

(b) (4)

Reviewer comments: *This officer recommends deletion of the strikethrough text because analyses relating to the (b) (4). Following a review of subgroup analyses for OBD-1033 (section 6.1.7 [Subpopulations](#)) this*

officer recommends addition of the above statements in underlined red text regarding efficacy differences in subgroups by gender, race, and age group.

(b) (4)

A large rectangular area of the document is completely redacted with a solid grey fill. The redaction covers the majority of the page's content.

(b) (4)

A second large rectangular area of the document is completely redacted with a solid grey fill, similar to the first block.A third large rectangular area of the document is completely redacted with a solid grey fill, covering the bottom portion of the page's content.

Reviewer comments: According to the 2006 FDA Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products,²⁰ analyses of data combined from multiple efficacy studies can be useful for estimating the treatment effect, but should be included only when they are scientifically appropriate and better characterize the treatment effect. [REDACTED] (b) (4)

[REDACTED] Instead, this medical officer recommends describing the key results of each trial separately (underlined red text).

[REDACTED] (b) (4)

[REDACTED] (b) (4)

Reviewer comments: In this medical officer's assessment, [REDACTED] (b) (4)

[REDACTED] Therefore, this officer recommends the strikethrough text above be removed from labeling.

²⁰ FDA guidance for industry, 2006, Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075059.pdf>

(b) (4)



Reviewer comments: *According to the 2006 FDA Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products, studies that are not adequate and well-controlled studies within the meaning of 21 CFR 314.126 should not be included in the Clinical Studies section of labeling. In this medical officer's assessment, in chronic, subjective, non-life-threatening diseases (e.g., OIC), data from open-label studies are not adequate and well-controlled. Therefore, this officer recommends removal of the strikethrough text above from labeling.*

9.3 Advisory Committee Meeting

No advisory committee (AC) meeting was held.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FARROKH SOHRABI
04/03/2013

ROBERT FIORENTINO
04/04/2013



Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Response to Consultation Request

TO: Farrokh Sohrabi, MD., Medical Officer
Division of Gastroenterology and Inborn Errors Products (DGIEP)

FROM: Elizabeth Kilgore, MD., Medical Officer
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

THROUGH: Ellen Fields, MD., MPH, Team Leader, DAAAP

THROUGH: Sharon Hertz, MD., Deputy Director, DAAAP

THROUGH: Bob Rappaport, MD., Director, DAAAP

SUBJECT: NDA 21908/S011; IND 77771

DRUG NAME: Lubiprostone

TRADENAME: AMITIZA

SPONSOR: Sucampo

CONSULT DATE: 11/30/12 (DARRTS)

REVIEW DATE: 3/18/13

DGIEP Consult Request:

“This consult encompasses our request for review of assessment of pain severity and impact of pain on daily functions as part of the sNDA submission for Amitiza for the proposed indication of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain. In each of three double-blind efficacy studies and one long-term open-label safety study, the Sponsor administered the Brief Pain Inventory-Short Form (BPI-SF) to subjects on a monthly basis. The Sponsor reported no significant differences in the mean changes from baseline in the pain interference, pain severity, or worst pain scores between the placebo and Amitiza groups at the end of

each study month or end of treatment. (b) (4)

[REDACTED]

[REDACTED] (b) (4)

With regard to the BPI-SF, the Division requests:

- 1) ascertainment of whether effects of Amitiza on pain control were assessed adequately by the BPI-SF instrument and
- 2) [REDACTED] (b) (4)

Background: According to the Applicant's submission, "Lubiprostone is a locally acting CIC-2 [chronic idiopathic constipation] chloride channel activator and member of a group of compounds known as prostones that enhances a chloride-rich intestinal fluid secretion without altering electrolyte concentrations in the serum. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine thereby increasing the passage of stool and alleviating symptoms associated with constipation." Lubiprostone, Tradename AMITIZA, is approved in the US, Switzerland and Japan for the treatment of chronic idiopathic constipation (CIC) in adult men and women and for the treatment of irritable bowel syndrome with constipation (IBS-C) in women aged 18 years and older, at doses of 48mcg/day, taken as 24mcg twice a day (BID) and 16mcg/day taken as 8mcg BID. The Applicant maintains that "As a local activator of chloride and fluid secretion with no effect on opioid-induced central analgesia, lubiprostone's mechanism of action would suggest, in conjunction with results of pharmacology studies of lubiprostone in morphine-treated mice and transit studies in humans, the potential benefit of lubiprostone treatment in patients with OBD [opioid induced bowel dysfunction]."

This sNDA was originally submitted on 7/20/12 for AMITIZIA (lubiprostone) capsules 24mcg as a Prior Approval Supplement to NDA 21-908 (AMITIZIA) for a new indication of "the treatment of opioid-induced constipation (OIC) [REDACTED] (b) (4)

[REDACTED] in adults with chronic, non-cancer pain". The Applicant stated that the clinical efficacy of oral lubiprostone in the treatment of OIC was demonstrated via three well-controlled studies OBD-0631, OBD-0632, OBD-1033 and an open-label extension study OBD-06S1 conducted under IND 77,771.

On 11/16/12 the Sponsor submitted a major amendment to the application resulting in an extension of the PDUFA goal date by 3 months to 4/20/13.

Materials Reviewed:

- Protocols OBD-1033, OBD-0631, OBD-0632, and OBD-06S1
- Brief Pain Inventory-Short Form (BPI-SF) assessments, Morphine Equivalent Daily Dose (MEDD) and other relevant findings for above studies

- NDA 21908/S011 Summary of Clinical Safety (Pages 106 -109); other relevant sections
- NDA 21908/S011 Integrated Summary of Safety relevant sections
- Applicant's responses to DAAAP Information Requests sent via email 2/7/2013 and 2/15/13

Review Organization:

- I) Overview of Applicant's Key Efficacy and Safety Studies
- II) Discussion of Brief Pain Inventory-Short Form (BPI-SF)
- III) Review of Individual Protocols with Applicant's Relevant Findings
 - BPI-SF Findings
 - Morphine Equivalent Daily Dose (MEDD) Findings
 - Reviewer's Comments
- IV) Applicant's Pooled Analysis Findings
- V) DAAAP Discussion
- VI) DAAAP's Response to DGIEP Questions

I) Overview of Applicant's Key Efficacy and Safety Studies

The Applicant plans to rely on three placebo-controlled studies (OBD-0631, 0632 and 1033) and one open-label long term extension study (OBD-06S1) to support findings of efficacy and safety, which are the subject of this review and are summarized below:

- Studies OBD-0631 and 0632 are identical in design (double-blind, placebo-controlled), enrolled patients with opioid-induced bowel dysfunction (OBD) taking any opioids for chronic noncancer pain for at least one month, and received either oral lubiprostone 48mcg/day [24mcg twice daily (BID)] or placebo administered orally for 12 weeks.
- Study 1033 is essentially the same design as Studies 00631 and 0632 except that it enrolled patients taking any opioids except methadone for chronic noncancer pain as, according to the Applicant, diphenylheptanes such as methadone and propoxyphene are known confounders of lubiprostone's treatment response due to the potential for competition with CIC-2 channels.
- Study OBD-06S1 was a 36-week, open-label extension study for patients who completed the 12-week double-blind treatment period with lubiprostone or placebo in Study 0631 or 0632 and who required continued treatment with opioids.

A general overview of the Applicant's clinical program and patient exposure is shown in Table 1, followed by more detailed descriptions of the individual studies.

Table 1. Scope of Clinical Program for Lubiprostone in Opioid-Induced Bowel Dysfunction (Safety Evaluable Population)

Study Design	Treatment Duration	Study Number	Placebo	Lubiprostone 48 mcg	Total
Adequate and well-controlled	12 weeks	OBD-1033	220	219	439
		OBD-0631	218	221	439
		OBD-0632	214	223	437
		Total	652	663	1315
Open-label extension ¹	36 weeks	OBD-06S1	~~220~~	439 ²	439

¹ Subjects who completed the 12-week double-blind treatment period in either Study OBD-0631 or Study OBD-0632 were eligible to enter the extension study if they required continued treatment with opioids for chronic noncancer-related pain.

² These subjects represent a subset of the subjects who were previously treated with placebo or lubiprostone in Study OBD-0631 or Study OBD-0632.

Cross-reference: Section 5.3.5.3, ISS, Table 2.1.3.1, Table 2.1.3.2

(Applicant’s table, SCS, p. 10)

II) Discussion of Brief Pain Inventory-Short Form (BPI-SF)

This consultative review focuses on the findings of the Brief Pain Inventory-Short Form (BPI-SF) and the Morphine Equivalent Daily Dose (MEDD) change in opioid use to address DGIEP’s questions for DAAAP input.

The BPI-SF is a patient-reported outcome measure that assesses the severity of pain and the impact of pain on daily functions. The BPI-SF comprises two domains: pain severity and pain interference. “Worst” pain is included in the pain severity domain. The Applicant modified the BPI-SF so that only the multiple-choice questions about pain were answered at baseline and at the end of each treatment month. In the protocols, subjects had up to 3 nights to record their answers in the electronic diary, if after the third day the questions were not answered, the questionnaire would be missed. Because the Applicant’s protocols did not include a copy of the BPI-SF used in the studies or the exact modification they made to the assessment tool, a DAAAP Information Request (IR) was sent to the Applicant on 2/7/13 as follows:

The protocols for the controlled (OBD-0631, 0632 and 1033) and uncontrolled (OBD-06S1) studies state that the Brief Pain Inventory-SF (BPI-SF) used in the studies was modified. Clarify where in the protocols a copy of the modified BPI-SF can be found and how the modifications differ from the standard BPI-SF. If a copy of the BPI-SF is not in the protocols, provide a copy with explanations for how scoring was performed on the assessment tool.

Applicant’s response to DAAAP IR (Key Points Summary)

- Copies of the BPI-SF Questionnaire (see Appendix A of review) and User Guide were included in the response.
- Questions 2 and 7 of the nine questions on the BPI-SF are qualitative and do not affect the scoring of the questionnaire so were omitted. As per the BPI User Guide (attached in Applicant’s response), calculation of scores for pain interference, pain severity, and worst pain do not require input from these questions.
- The programming of these scores is consistent with the scoring methodology described in the User Guide. It should be noted that, in cases where a patient responded “no” to

question #1 regarding whether he/she had experienced pain that day, subsequent multiple choice questions asking patient to describe pain were not queried within the eDiary, and therefore assessed as a “0” rating for the purposes of score calculation.

III) Review of Individual Protocols with Applicant’s Relevant Findings

A) Studies OBD-0631 and 0632

Title: A Multicenter, Randomized, Placebo-controlled, Double-Blinded Study of the Efficacy and Safety of Lubiprostone in Subjects with Opioid-Induced Bowel Dysfunction

Objectives: To assess the efficacy and safety of oral Lubiprostone 48mcg/day [24mcg twice daily (BID)], as compared to placebo, when administered orally for 12 weeks to subjects with OBD

Design: Phase 3, 12-week, multicenter (US and Canada), randomized, placebo-controlled, double-blinded

Population: Patients who were receiving consistent treatment with opioids for chronic, noncancer related pain.

Study Overview: Total of 9 visits (6 in clinic and 3 telephone assessments) with Screening, Baseline/Randomization, In clinic visits on Days 28, 56, 84 (end of treatment) and 98 (end of study). Telephone assessments on Days 7, 42 and 70.

Key Inclusion Criteria:

1. ≥ 18 years of age
2. Treated consistently for chronic, non-cancer-related pain with any oral, transdermal, intravenous, or subcutaneous opioid (full agonist) for at least 30 days prior to screening, and continue opioid therapy throughout the study
3. Diagnosed with OBD; OBD defined as an average of <3 SBMs/week and at least 1 of the following for at least 25% of SBMs during each week of the screening period:
 - Hard or very hard stools;
 - Sensation of incomplete evacuation; and/or
 - Moderate to very severe straining associated with SBMs
4. Willing to continue opioid therapy and discontinue the use of laxatives, stool softeners, and other concomitant medications affecting GI motility throughout the study

Key Exclusion Criteria:

1. Use of opioids for the treatment of cancer-related pain
2. Adjusted (increased or decreased by $\pm 30\%$) the dosage of opioid treatment, changed opioid agents, or changed route of opioid administration within 30 days of screening, or was likely to discontinue or adjust dosage by $\pm 30\%$ over the course of the study
3. Mechanical bowel obstructions
4. Bowel disorders and constipation not arising from opioid use

Primary Efficacy Endpoint: Change in frequency of SBMs from baseline at Week 8, for subjects who had no dose reduction

Secondary Efficacy Endpoints:

- Change from baseline in SBM frequency at Week 12 and overall;
- Percentage of subjects with a first postdose SBM within 24 hours;
- Percentage of subjects with a first postdose SBM within 48 hours;
- Overall responder rates;
- Overall mean change from baseline in the following
 - Straining associated with SBMs
 - Stool consistency of SBMs
 - Constipation severity
 - Abdominal bloating
 - Abdominal discomfort
 - Bowel habit regularity
- Overall treatment effectiveness

Relevant Safety Evaluations:

- Pain Assessments (Brief Pain Inventory-SF) assessed monthly via eDiary
- Opioid Dose Assessments (monthly) - opioids were translated to equivalents and the mean equivalent was computed per subject over the month

Statistical Methods:

- Descriptive statistics were provided to evaluate the mean changes from baseline at Weeks 4, 8, and 12 for worst pain and the 2 domains. ANOVA was used to compare the changes from baseline across treatment groups for worst pain. Within-group comparisons were made using paired t-tests.
- Change in pain severity and pain interference at Months 1, 2 and 3 were graphically displayed using the cumulative distribution.

DAAAP Comment: In studies of analgesics, the most meaningful endpoint and that typically used as a primary endpoint in studies is either worst pain or average pain. Pain interference and pain severity (made up of four subquestions) are not used to assess analgesia per se, as they are comprised of multiple domains in addition to pain. Therefore, this review will focus on the results regarding “worst pain.”

Applicant’s Findings Study 0631

1. BPI-SF:

- The BPI-SF, collected at baseline and monthly at Weeks 4, 8, and 12, consisted of the domains of pain severity and pain interference. “Worst pain” was included in the pain severity domain.
- According to the Applicant, the lubiprostone group achieved statistically significant improvements in the BPI-SF responses at Month 2 compared to placebo for pain interference and compared to placebo, the subjects treated with lubiprostone experienced a statistically significant change from baseline responses to the BPI-SF for pain interference at Month 2 ($p=0.0114$) based on treatment effect. The placebo group only had significant changes from baseline for pain interference at Month 1 ($p=0.002$) and Month 2 ($p=0.003$), pain severity at Month 1 ($p=0.014$) and Month 2 ($p=0.028$), and worst pain at Months 1, 2, and 3 ($p=0.004$, 0.008 , and 0.038 , respectively). The findings for

Worst Pain are summarized in Table 2 below, as taken from the Applicant's Table 14.3.14 depicting the change from BL for the BPI for safety evaluable subjects, with cross reference to the Applicant's Figures 14.3.1.1 and 14.3.1.2, shown below as Figures 1 and 2, respectively following the table.

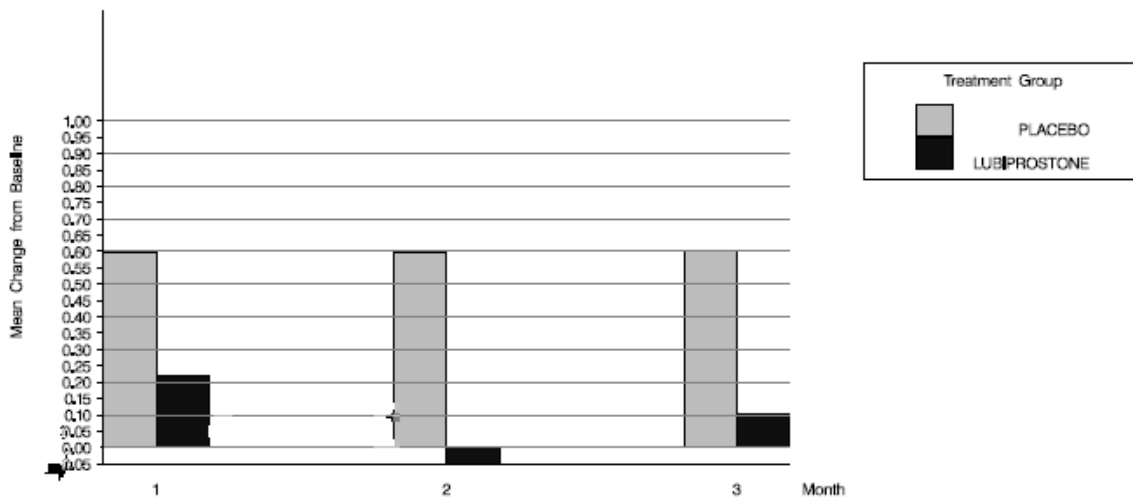
Table 2. Summary of Change from Baseline Brief Pain Inventory, Safety Evaluable Subjects (Worst Pain) Study 0631

Domain	Timepoint	Variable Statistic	Treatment Group		p-Value ¹
			Placebo (N=218)	Lubiprostone (N=221)	
WORST PAIN	Baseline Period	Observed Value			
		N	202	203	
		Mean	5.0	5.7	
		SD	3.36	3.02	
		Median	6.0	7.0	
		Min	0.0	0.0	
		Max	10.0	10.0	
WORST PAIN	Month 1	Observed Value			
		N	175	167	
		Mean	5.7	5.9	
		SD	3.12	3.13	
		Median	7.0	7.0	
		Min	0.0	0.0	
		Max	10.0	10.0	
		Change from Baseline			
	N	171	164	0.2542	
	Mean	0.8	0.4		
	SD	3.50	3.08		
	Median	0.0	0.0		
	Min	-8.0	-9.0		
	Max	10.0	10.0		
p-Value ²	0.004*	0.137			
Month 2	Observed Value				
	N	154	143		
	Mean	5.6	5.8		
	SD	3.22	3.17		
	Median	7.0	7.0		
	Min	0.0	0.0		
	Max	10.0	10.0		

WORST PAIN	Month 2	Change from Baseline			
		N	150	142	0.0667
		Mean	0.8	0.0	
		SD	3.60	3.22	
		Median	0.0	0.0	
		Min	-8.0	-9.0	
		Max	10.0	8.0	
		p-Value ²	0.008*	0.855	
	Month 3	Observed Value			
		N	118	113	
		Mean	5.6	5.8	
		SD	3.34	3.25	
		Median	7.0	7.0	
		Min	0.0	0.0	
		Max	10.0	10.0	
		Change from Baseline			
		N	112	110	0.2496
		Mean	0.7	0.2	
		SD	3.69	3.41	
		Median	0.0	0.0	
		Min	-8.0	-9.0	
		Max	10.0	10.0	
		p-Value ²	0.038*	0.577	

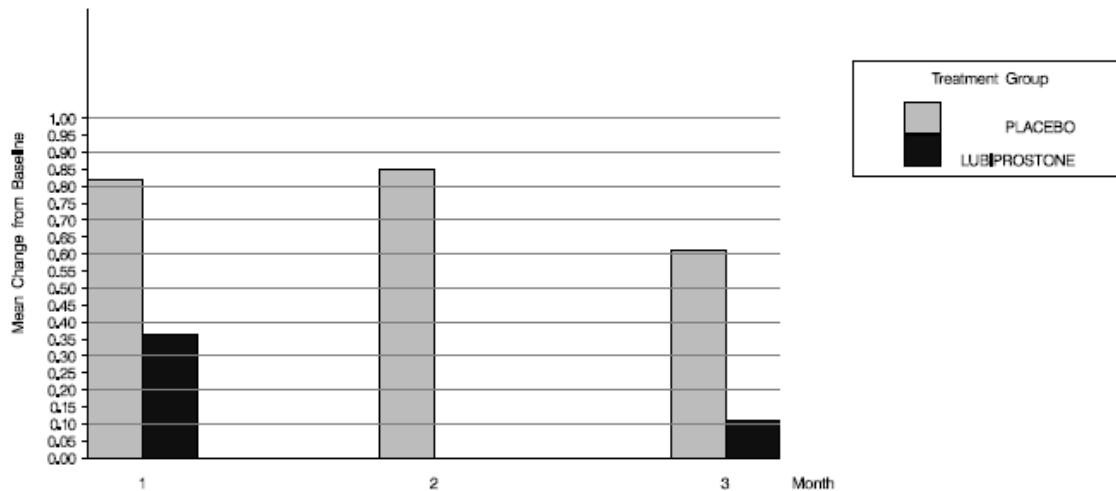
(Source: Applicant's Table 14.3.14, CSR 0631, edited by reviewer to show Worst Pain only, p. 449-451)

Figure 1. Monthly Change from Baseline in BPI Pain Severity by Treatment Arm, Safety Evaluable Subjects (Study 0631)



(Source: Applicant's Figure 14.3.1.1, Study 0631 Final CSR, p. 165)

Figure 2. Monthly Change from Baseline in BPI Pain Intensity by Treatment Arm, Safety Evaluable Subjects (Study 0631)



(Source: Applicant’s Figure 14.3.1.2 , Study 0631 Final CSR, p. 166)

Applicant’s Findings MEDD:

- Protocol violation of opioid dose adjustment of $\pm 30\%$ from baseline morphine equivalent daily dose (MEDD) occurred in 6.5% placebo and 7.7% lubiprostone.
- Per Applicant, there were no statistically significant differences between treatment groups in changes in MEDD from baseline at Month 1, 2, or 3. The mean MEDD of Darvocet was higher in the lubiprostone group compared to placebo (Sponsor notes that Darvocet is a congener of methadone).

Reviewer’s Comments (Study 0631):

1. Missing BPI-SF Assessments: There was loss of subjects with available BPI-SF data over time. By Month 3, there were BPI-SF assessments on only 113 subjects compared to the 203 at baseline, a drop off of approximately 44% in the lubiprostone treatment arm. Additionally, the Applicant did not provide an explanation for why there is a discrepancy between the Observed Number and the Change from Baseline number of subjects. Without this information, the Applicant’s findings cannot be fully evaluated. These findings are summarized in Table 3, below.

Table 3. Change in Number of Patients Over Time Resulting in Missing BPI-SF Scores by Timeperiod (Treatment Duration)

Timeperiod	Placebo (N=218)	Lubiprostone (N=221)	Lubiprostone
	Observed N		Change from BL (N)
Baseline	202	203	N/A
Month 1	175	167	164
Month 2	154	143	142
Month 3	118	113	110

(Source: Table, reviewer)

2. Figures 1 and 2: These figures attempt to show the monthly mean change in worst pain over the course of the study, comparing the lubiprostone group with the placebo group. It is unclear whether the mean change in pain score in the positive direction on the Y-axis is an improvement or a worsening in pain. In addition, since pain scores were collected very infrequently (monthly), it is difficult to assess the true changes in pain in the study groups over the course of the study.
3. MEDD: According to the protocol, opioid doses were collected daily in the e-diary for each study subject, however the MEDD data was presented as a monthly value for analysis. This makes it impossible to interpret the relationship of the MEDD to the pain scores, since each variable may vary over the course of the month, i.e., the pain score may increase resulting in an increase in opioid usage, leading to a decrease in pain and a decrease in opioid usage. These potential changes cannot be analyzed from the information the Applicant has provided, and therefore the potential effect of lubiprostone on analgesia cannot be assessed.
4. Although opioid adjustment $\pm 30\%$ for >7 days was considered a protocol violation and those patients were excluded from efficacy analysis, it was not clear from the submission how many of those patients experienced opioid increase <7 days.
5. The Applicant reports p-values for the analyses of MEDD and pain scores, however since the analyses of these endpoints did not control for Type I error, the results are merely descriptive and the p-values are not meaningful.

Applicant's Findings Study 0632

- *BPI-SF*
 - Per Applicant, there was no statistically significant change from baseline responses to the BPI-SF for pain interference based on treatment effect from an ANOVA model. The placebo group only demonstrated significance within treatment in changes from baseline for pain interference at Month 1 ($p=0.022$) and worst pain at Month 1 ($p=0.019$ for placebo and 0.034 for lubiprostone) and at Month 2 ($p=0.029$ for placebo and 0.031 for lubiprostone) and there was no statistical difference between the treatments of placebo and lubiprostone for any of the months for pain interference, pain severity, and worst pain.
 - The Applicant's findings for Worst Pain are summarized in Table 4 below, as taken from the Applicant's Table 14.3.14 depicting the change from BL for the BPI for safety evaluable subjects, with cross reference to the Applicant's Figures 14.3.1.1 and 14.3.1.2, shown below as Figures 3 and 4, respectively following the table.

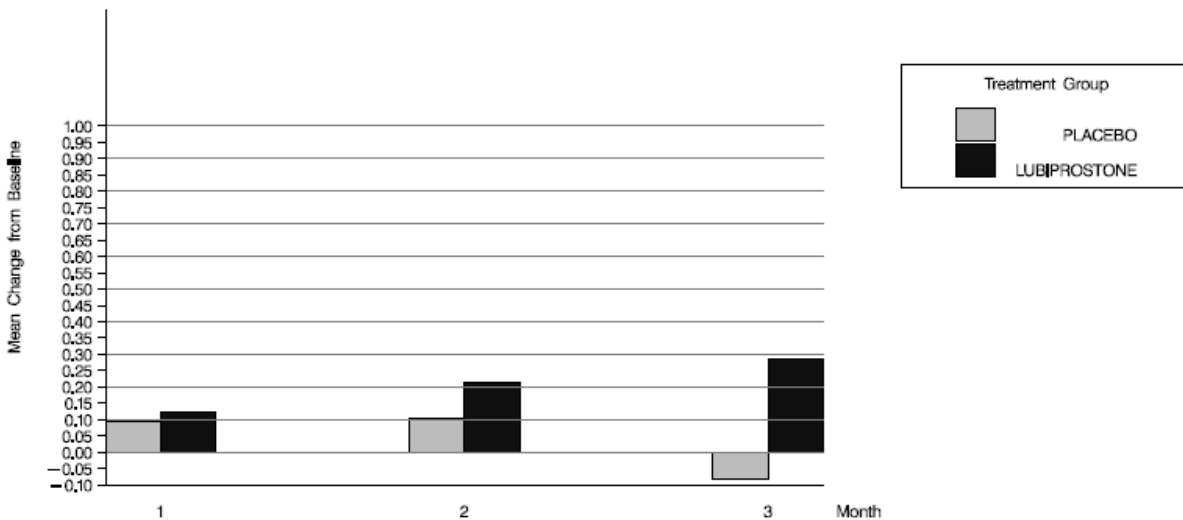
Table 4. Summary of Change from Baseline Brief Pain Inventory Safety Evaluable Subjects, Study 0632

Domain	Timepoint	Variable Statistic	Treatment Group		p-Value ¹
			Placebo (N=214)	Lubiprostone (N=223)	
WORST PAIN	Baseline Period	Observed Value			
		N	142	148	
		Mean	7.1	6.9	
		SD	1.33	1.39	
		Median	7.0	7.0	
		Min	1.0	3.0	
		Max	10.0	10.0	
WORST PAIN	Month 1	Observed Value			
		N	140	145	
		Mean	7.2	7.1	
		SD	1.54	1.33	
		Median	7.0	7.0	
		Min	2.0	3.0	
		Max	10.0	10.0	
		Change from Baseline			
		N	111	114	0.6667
		Mean	0.3	0.3	
		SD	1.47	1.27	
		Median	0.0	0.0	
		Min	-5.0	-3.0	
		Max	4.0	4.0	
	p-Value ²	0.019*	0.034*		
	Month 2	Observed Value			
		N	133	126	
		Mean	7.2	7.0	
		SD	1.42	1.37	
		Median	7.0	7.0	
		Max	10.0	10.0	

WORST PAIN	Month 2	Change from Baseline			
		N	104	97	0.9264
		Mean	0.3	0.3	
		SD	1.46	1.35	
		Median	0.0	0.0	
		Min	-3.0	-5.0	
		Max	5.0	4.0	
		p-Value ²	0.029*	0.031*	
	Month 3	Observed Value			
		N	95	97	
		Mean	7.1	7.2	
		SD	1.63	1.48	
		Median	7.0	7.0	
		Min	3.0	2.0	
		Max	10.0	10.0	
		Change from Baseline			
		N	67	69	0.4563
		Mean	0.1	0.3	
		SD	1.38	1.51	
		Median	0.0	0.0	
		Min	-4.0	-6.0	
		Max	3.0	4.0	
		p-Value ²	0.539	0.114	

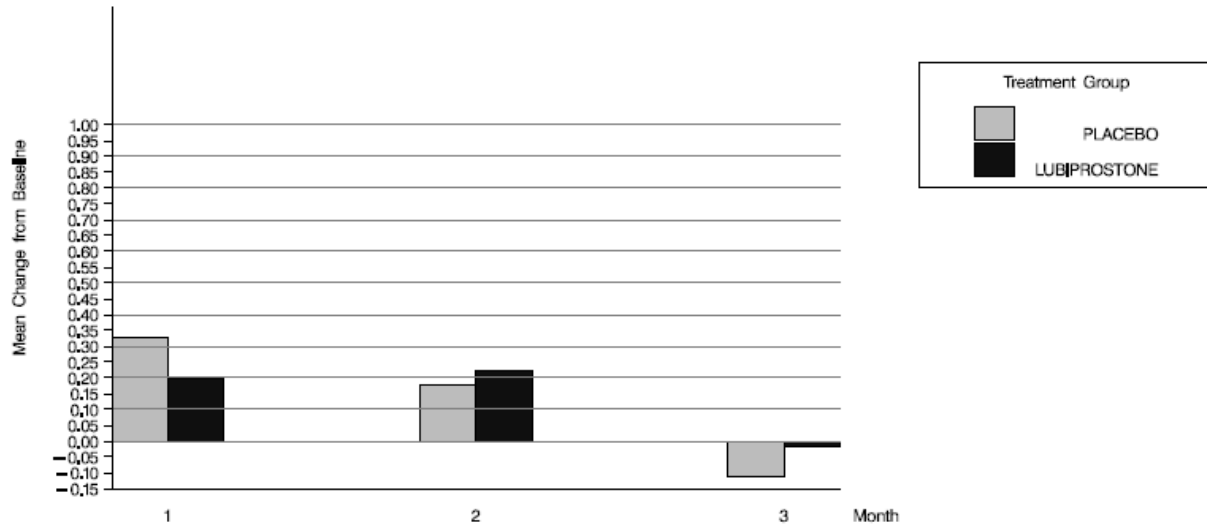
(Source: Applicant's Table 14.3.14, CSR 0632, edited by reviewer to show Worst Pain only, p. 450-452)

Figure 3. Monthly Change from Baseline in BPI Pain Severity by Treatment Arm, Safety Evaluable Subjects, Study 0632



(Source: Applicant's Figure 14.3.1.1, Final CSR 0632, p. 169)

Figure 4. Monthly Change from Baseline in BPI Pain Intensity by Treatment Arm, Safety Evaluable Subjects, Study 0632



(Source: Applicant’s Figure 14.3.1.2, Final CSR 0632, p. 170)

- Applicant’s MEDD Findings:
 - According to the Applicant, nearly 20% of subjects in this trial used methadone, with an average MEDD of approximately 1000.
 - Protocol violations for opioid dose adjustment of $\pm 30\%$ from baseline MEDD included 10 patients (4.7%) for placebo and 10 patients (4.5%) for lubiprostone.
 - The most commonly used opioid medication was oxycodone (placebo 13.7% vs lubiprostone 9.9%).
 - There were no statistically significant differences between treatment groups in changes in MEDD from baseline in Months 1, 2 or 3.

Reviewer’s Comments (Study 0632):

1. Missing BPI-SF Assessments: By Month 3, there were BPI-SF assessments on only 97 subjects compared to the 148 at baseline, a drop off of approximately 34% in the lubiprostone treatment arm. The Applicant did not provide an explanation for why there is a discrepancy between the Observed Number and the Change from Baseline number of subjects. These findings are summarized in the table below.

Table 5 . Change in Number of Patients Over Time Resulting in Missing BPI-SF Scores by Timeperiod (Treatment Duration)

Timeperiod	Placebo (N=214)	Lubiprostone (N=223)	Lubiprostone
	Observed N		Change from BL (N)
Baseline	142	148	N/A
Month 1	140	145	114
Month 2	133	126	97
Month 3	95	97	69

(Source: reviewer)

2. See Comments 2-5 for Study 0631 as they apply to this study as well.

B) Study SMR/0211OBD-1033 (Study 1033)

Title: A Multicenter, Randomized, Placebo-controlled, Double-blinded Study of the Efficacy and Safety of Lubiprostone in Subjects with Opioid-Induced Bowel Dysfunction

Objective: To assess the efficacy and safety of oral lubiprostone at 48mcg/day (24mcg twice daily [BID]), as compared to placebo, when administered orally for 12 weeks in subjects with opioid-induced bowel dysfunction (OBD)

Design: Phase 3, multicenter (US and Europe), double-blinded, randomized, placebo-controlled 12-week study

Duration: 18 weeks total; 84 days treatment

Population: Patients who were receiving consistent treatment with non-diphenylheptane class of opioids for chronic, noncancer related pain. A total of 439 subjects were randomized and received at least one dose of study drug; 219 received lubiprostone and 220 received placebo.

Key Inclusion:

1. 18 years of age or older with chronic, non-cancer-related pain being prescribed opioids
2. Chronic use of opioids other than methadone or congeners of methadone
3. Current diagnosis of opioid bowel dysfunction (using criteria as described in protocols 0631 and 0632)

Key Exclusion:

1. Receiving methadone, methadone HCL, or a congener of methadone either alone or as part of opioid regimen
2. Had adjusted (increased or decreased by $\pm 30\%$) dosage (in morphine equivalent daily dose [MEDD]) of opioid treatment, had changed opioid agents, or had changed route of opioid administration within 30 days of screening, or was likely to discontinue or adjust dosage by $\pm 30\%$ over the course of the study

Applicant's Findings Study 1033

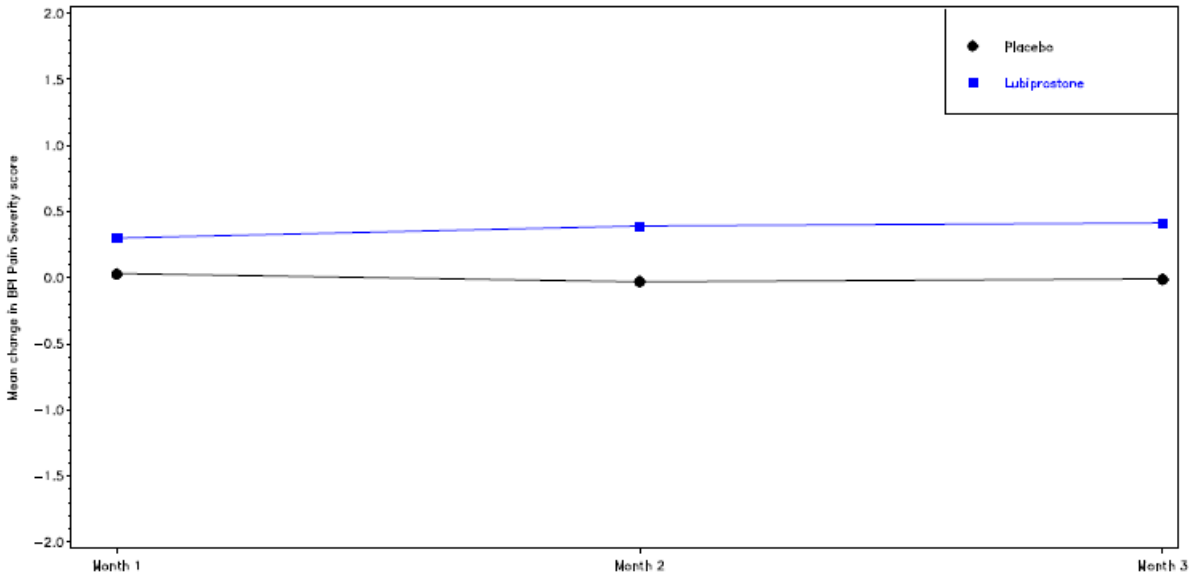
- BPI-SF
 - The baseline BPI scores for pain interference and pain severity were similar between the treatment arms.
 - According to the Applicant, changes in the BPI domains of pain interference, pain severity, and worst pain were not significantly different from baseline values for either treatment group at Months 1-3 and at end of treatment.
 - The Applicant's findings for Worst Pain are summarized in Table 6 below, as taken from the Applicant's Table 14.3.13 depicting the change from BL for the BPI for safety evaluable subjects, with cross reference to the Applicant's Figures 14.4.1.1 and 14.4.1.2, shown below as Figures 5 and 6, respectively following the table.

Table 6. Summary of Change from Baseline Brief Pain Inventory Safety Evaluable Subjects, Study 1033

Domain	Timepoint	Variable/ Statistic	Placebo (N=220)	Lubiprostone (N=219)	p-Value [1]	
Worst Pain	Baseline Period	Observed Value				
		N	200	199		
		Mean	5.04	4.85		
		SD	3.291	3.248		
		Median	6.00	6.00		
		Min Max	0.0 10.0	0.0 10.0		
	Month 1	Observed Value				
		N	197	185		
		Mean	5.01	5.17		
		SD	3.284	3.196		
		Median	6.00	6.00		
		Min Max	0.0 10.0	0.0 10.0		
	Change from Baseline	Observed Value				
		N	182	171	0.210	
		Mean	-0.01	0.43		
		SD	3.141	3.498		
		Median	0.00	0.00		
		Min Max	-9.0 9.0	-9.0 9.0		
p-Value [2]	0.962	0.108				
Worst Pain	Month 2	Observed Value				
		N	174	175		
		Mean	4.82	5.23		
		SD	3.499	3.136		
		Median	6.00	6.00		
		Min Max	0.0 10.0	0.0 10.0		
	Change from Baseline	Observed Value				
		N	160	164	0.132	
		Mean	-0.12	0.50		
		SD	3.598	3.765		
		Median	0.00	0.00		
		Min Max	-9.0 8.0	-9.0 9.0		
	p-Value [2]	0.677	0.091			
	Worst Pain	Month 3	Observed Value			
			N	183	160	
			Mean	4.79	5.08	
			SD	3.511	3.261	
			Median	6.00	6.00	
Min Max			0.0 10.0	0.0 10.0		
Change from Baseline		Observed Value				
		N	169	148	0.131	
		Mean	-0.14	0.50		
		SD	3.478	4.062		
		Median	0.00	0.00		
		Min Max	-9.0 9.0	-10.0 10.0		
p-Value [2]		0.596	0.136			
Worst Pain		End of Treatment [3]	Observed Value			
			N	219	219	
			Mean	4.79	5.26	
			SD	3.550	3.305	
			Median	6.00	6.00	
	Min Max		0.0 10.0	0.0 10.0		
	Change from Baseline	Observed Value				
		N	200	199	0.110	
		Mean	-0.15	0.45		
		SD	3.495	3.937		
		Median	0.00	0.00		
		Min Max	-9.0 9.0	-8.0 10.0		
	p-Value [2]	0.558	0.107			

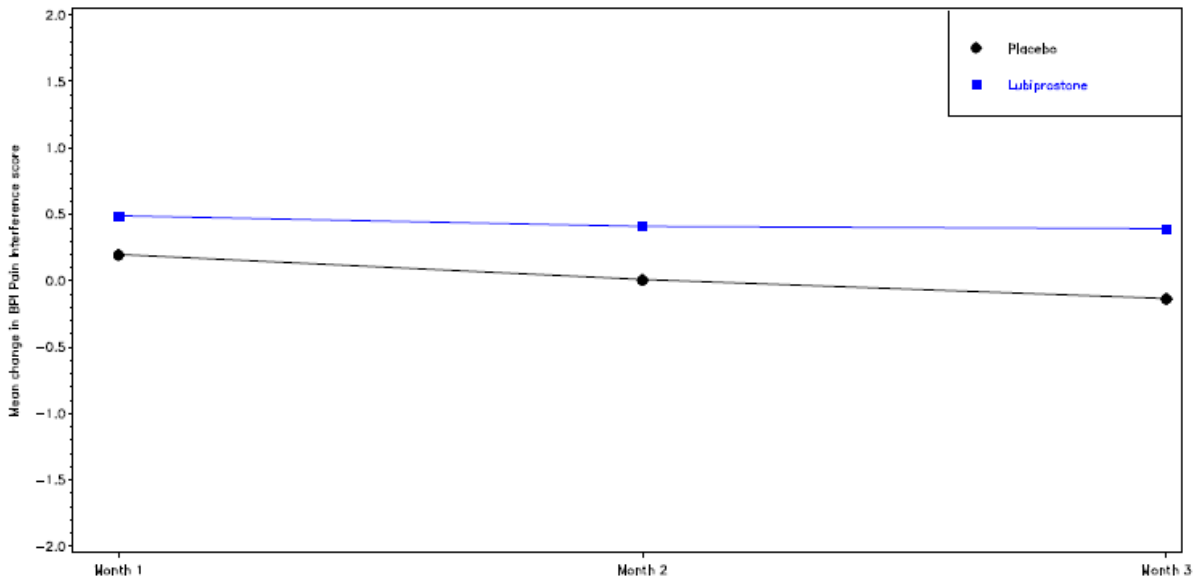
(Source: Applicant's Table 14.3.13, Final CSR 1033, modified to show Worst Pain only, p. 475-478); Lower scores (closer to 0) indicate less pain interference or severity

Figure 5. Monthly Change from Baseline in BPI Pain Severity by Treatment Arm, Safety Evaluable Subjects, Study 1033



(Source: Applicant's Figure 14.4.1.1, Final CSR 0133, p. 765)

Figure 6. Monthly Change from Baseline in BPI Pain Interference by Treatment Arm, Safety Evaluable Subjects, Study 1033



(Source: Applicant's Figure 14.4.1.2, Final CSR 1033, p. 766)

- Applicant’s MEDD Findings
 - The most commonly used opioid was oxycodone (17.8%) overall. There were no statistically significant differences between treatment groups in changes in MEDD from baseline at Month 1, 2 or 3. The Sponsor reported that 42 (18.6%) placebo and 52 (23.5%) lubiprostone discontinued the study. Fourteen subjects were excluded because opioid dose was adjusted $\pm 30\%$ from baseline dose.

Reviewer’s Comments Study 1033

1. Missing BPI-SF Assessments: By Month 3, there were BPI-SF assessments on 160 subjects compared to the 199 at baseline, a drop off of approximately 20% in the lubiprostone treatment arm. The Applicant did not provide an explanation for why there is a discrepancy between the Observed Number and the Change from Baseline number of subjects. These findings are summarized in the Table 7 below.

Table 7 . Change in Number of Patients Over Time Resulting in Missing BPI-SF Scores by Timeperiod (Treatment Duration), Study 1033

Timeperiod	Placebo (N=220)	Lubiprostone (N=219)	Lubiprostone
	Observed N		Change from BL (N)
Baseline	200	199	N/A
Month 1	197	185	171
Month 2	174	174	164
Month 3	183	160	148
End of Treatment	219	219	199

(Source: reviewer)

2. See comments 2-5 for controlled studies 0631 and 0632.

C) Study OBD-06S1

Title: A Multicenter, Open-labeled Study of the Long-term Safety and Efficacy of Lubiprostone in Patients with Opioid-induced Bowel Dysfunction

Objective: To assess the long-term safety and efficacy of oral Lubiprostone at 48mcg/day (24mcg twice daily [BID]), when administered orally as needed for 36 weeks in patients with OBD

Duration of Treatment: 252 days; up to 266 days from screening and follow up

Study Overview: The study consisted of 14 visits (starting with Visit 10 from roll-over from study 0631 or 0632 for a total of 23 visits). The end-of-treatment visit from study 0632 or 0632 served as the Screening Visit for the study.

Methods: Subjects were to take 24mcg of Lubiprostone prn. The maximum daily dose was 48mcg (24mcg BID).

Key Inclusion:

1. Completed 12 weeks of blinded treatment in Study 0631 or 0632
2. Continue to be treated consistently for chronic, non-cancer-related pain with any full agonist opiate and continue opiate therapy for the duration of the study

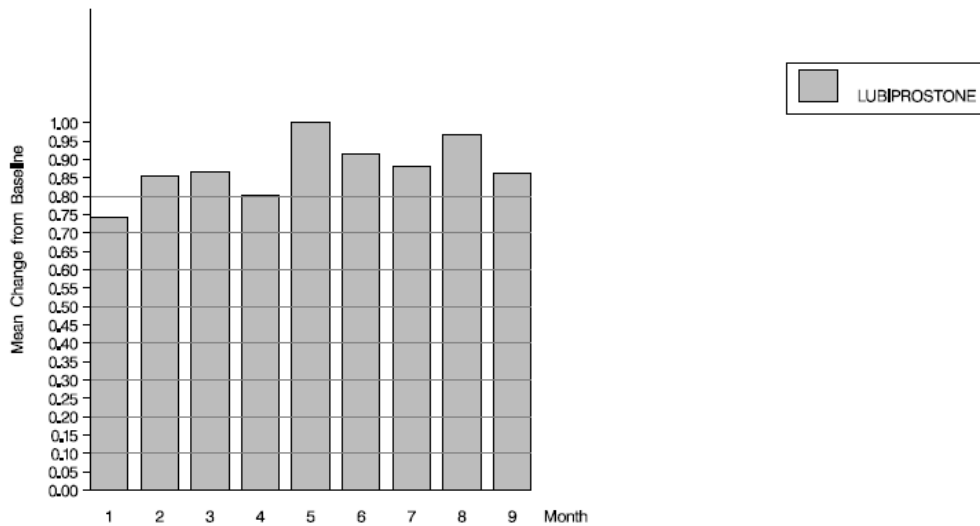
Relevant Evaluations:

- Brief Pain Inventory
- MEDD

Applicant’s Findings Study 06S1:

- BPI-SF:
 - The mean score at baseline was 5.3 with SD of 2.43.
 - The submission included a Table (14.3.14) which depicted changes from baseline in the BPI-SF domains of Pain Interference, Pain Severity and Worst Pain for each month 1-9 which, according to the Applicant, were not significant changes.
 - Per Applicant, there was improvement in BPI pain severity scores greatest at Months 5 and 8, although no clear trends in improvement were observed as shown in Figure 7 below.

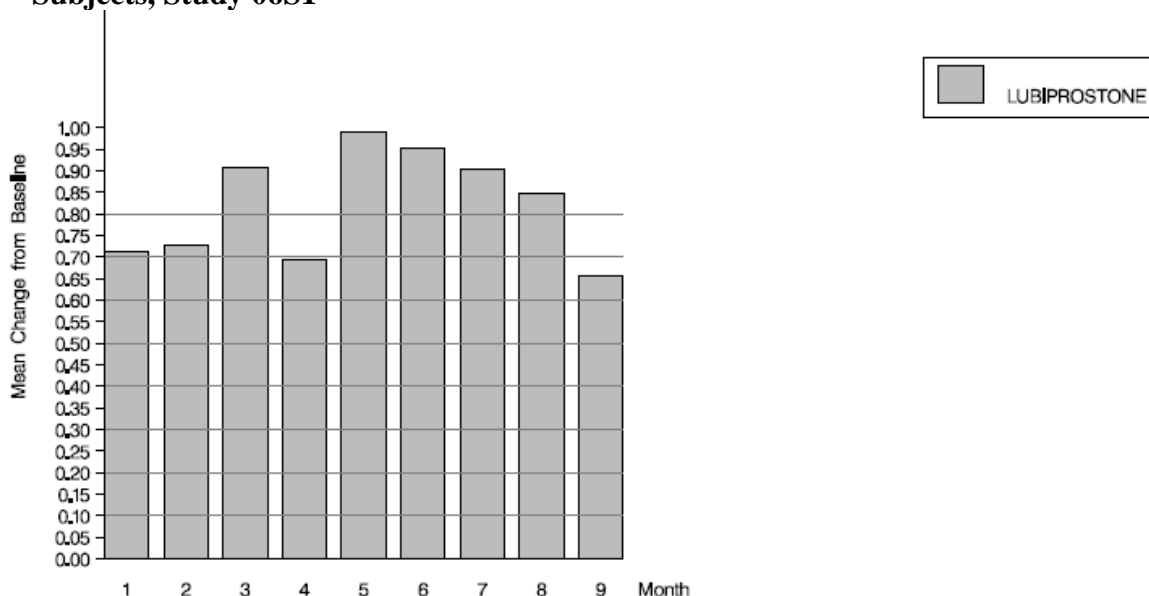
Figure 7. Monthly Change from Baseline in BPI Pain Severity, Safety Evaluable Subjects, Study 06S1



(Source: Applicant’s Figure 14.3.1, Final CSR 06S1, p. 170)

- Improvement in pain intensity (severity) scores peaked at Month 5 and then declined for the remainder of the study as shown in Figure 8 below,

Figure 8. Monthly Change from Baseline in BPI Pain Intensity, Safety Evaluable Subjects, Study 06S1



(Source: Applicant's Figure 14.3.2, Final CSR 06S1, p. 188)

- MEDD:
 - The most commonly used opioid was methadone (16.9%), followed by oxycodone (16.2%). At Months 6, 7 and 8 there was a significant increase in MEDD from baseline ($p=0.013$, 0.031 and 0.035 , respectively).

Reviewer's Comments Study 06S1

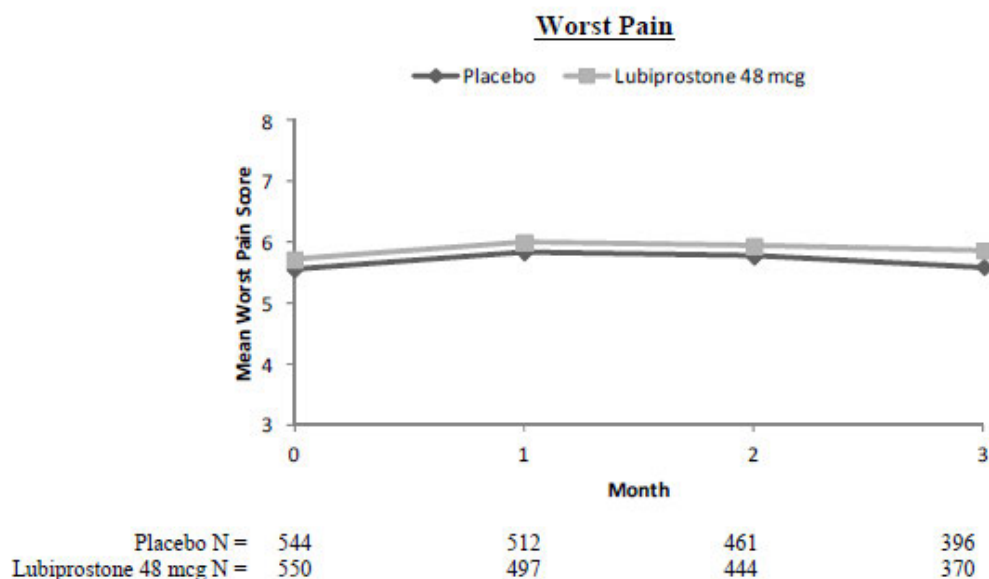
1. The missing BPI-SF data were similar to the controlled studies with the number at Baseline for Worst Pain being 350 (total $N=439$ lubiprostone) and by Month 9 the observed value $N=192$. There were discrepancies between the observed value N and change from Baseline N , as seen in the controlled studies again without an explanation for the difference.
2. Months 6, 7 and 8 showed increase in MEDD from baseline which suggests that an effect on analgesic efficacy was possible. However, the significance of this finding in an uncontrolled study is not clear.

Applicant's Pooled Findings: For the purposes of this consultative review, pooled findings provide little informative data to address the specific questions posed by DGIEP but highlights are summarized here for completeness.

Pooled Controlled Studies Results

- BPI-SF: In the controlled studies (0631, 0632 and 1033) overall, per the Applicant, no statistically significant differences in the mean changes from baseline in the pain interference, pain severity, or worst pain scores were observed between the placebo and lubiprostone groups at the end of 1, 2, or 3 months of treatment or at the end of treatment (defined as the last non-missing postbaseline assessment) for the subjects in the 12 week double-blind studies (1033, 0631 and 0632) as shown in Figure 9 below for Worst Pain Scores.

Figure 9. Brief Pain Inventory Pain Worst Pain Scores Well-Controlled Studies Pool (Safety Evaluable Subjects)



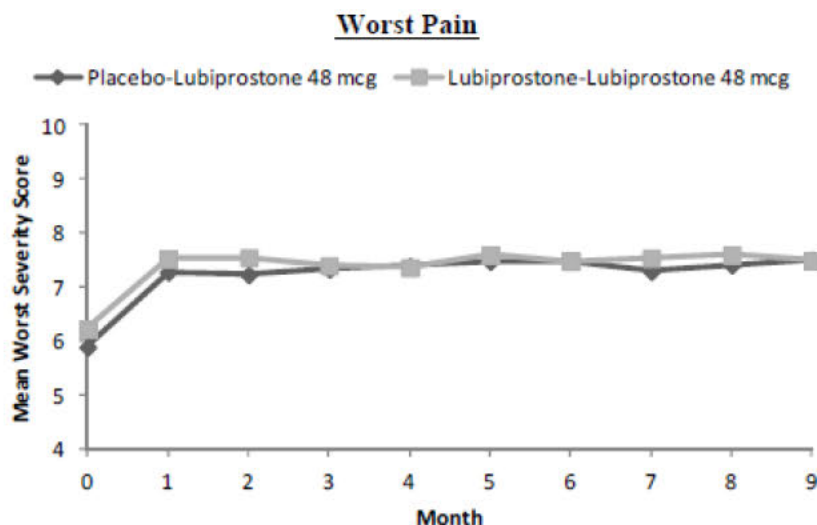
(Source: Applicant's figure, SCS, p. 107)

- MEDD
 - Per the Applicant, mean changes from baseline in the opioid dose (based on combined MEDD) at the end of Weeks 2, 4 and 8 of treatment were compared between the placebo and lubiprostone groups using the van Elteren test stratified by study. No statistically significant differences were observed between the placebo and lubiprostone groups in the mean changes from BL in the opioid dose at the end of Weeks 2, 4 or 8 of treatment.

Long-term Study Results (Per Applicant)

- The baseline BPI-SF scores were similar between the treatment arms.
- Per Applicant, the mean changes from baseline in the pain interference, pain severity, and worst pain scores were not statistically significant at the end of 1, 2, 3, 4, 5, 6, 7, 8 or 9 months of treatment or at the end of treatment (defined as the last non-missing post-baseline assessment) for the subjects who received treatment with lubiprostone. The worst pain scores are shown below in Figure 10.

Figure 10. Brief Pain Inventory Worst Pain Scores-Long Term Safety Study (Safety Evaluable Subjects)



Placebo-Lubiprostone 48 mcg N =	181	130	119	114	112	98	96	86	124	85
Lubiprostone 48 mcg N =	169	146	142	123	119	114	103	98	113	87

(Source: Applicant's figure, SCS, p. 109)

- MEDD:
 - Per Applicant, the mean change from BL in the opioid dose (based on combined MEDD) during the Long-Term safety study was compared between the placebo-lubiprostone and lubiprostone-lubiprostone groups at the end of each month of treatment. The subjects used a variety of opioid analgesics. No statistically significant differences were observed between the placebo-lubiprostone and lubiprostone-lubiprostone groups in the mean change from baseline in the opioid dose at the end of Months 1 through 9 of treatment.

AEs of Interest

(b) (4)

- In the pooled clinical studies, AEs of interest included back pain, arthralgia and headache. In the well-controlled studies, back pain occurred in 1.8% placebo compared to 2.4% study drug. Arthralgia occurred in 1.8% placebo compared to 2.0% study drug. In the open label study, the incidence of back pain was 2.9 times higher with lubiprostone during OL treatment than with double blind treatment. The Sponsor maintains that this is likely a reflection of longer follow up. However, in this reviewer's opinion, consideration must be given that this could have represented lack of efficacy with pain medication resulting in increased or uncontrolled pain (i.e back pain, arthralgia) or a negative effect of the study drug on analgesic efficacy.

- Clinical IR: Because of the Applicant’s findings noted above regarding the incidence of back pain and arthralgia, the following clinical IR was sent to the Applicant on 2/15/13: Provide the reasons for drop out by treatment group (placebo or lubiprostone) and time (Baseline, Months 1, 2 or 3) for the subjects for whom there are no BPI-SF assessments for the three controlled studies 1033, 0631 and 0632. Specifically, identify all subjects who dropped out due to inadequate pain control or AEs potentially related to inadequate pain control (i.e worsening pain).
- The Applicant’s response to the IR included a Listing of Treatment Emergent AEs Potentially Related to Inadequate Pain Control – Safety Population (Well-controlled Studies) which showed that in the controlled studies, there were 29 subjects out of a total 663 subjects who received lubiprostone and experienced AEs which could have been potentially related to worsening pain. When excluding the AEs of abdominal pain, increased gas pain and hemorrhoids, there were 24 subjects listed. Of those, only two patients discontinued with AEs of worsening pain, listed as AEs of worsening back pain in both with the reasons for discontinuation due to AE of dyspepsia in one patient and withdrawal due to “Discontinuation of Chronic Opioid Therapy” in the other.

DAAAP Discussion:

There were limitations in the study designs (both controlled studies and uncontrolled study), discussed below, which would affect the Applicant’s results and potentially confound their findings as they relate to the effect of analgesic efficacy and safety of lubiprostone in patients with chronic, noncancer pain and OIC as follows:

- **Pain Assessments**
 - *Tool:* The BPI-SF appears to be an appropriate tool to assess pain in this chronic pain population as it incorporates the use of a Numeric Rating Scale from 0-10 (see Appendix A) and evaluates pain intensity (worst pain). The Applicant’s scoring of the BPI-SF in the protocols appears consistent with the recommendations in the BPI-SF User Guide.
 - *Frequency of Assessments:* The BPI-SF was administered on a monthly basis only, which is not frequent enough to adequately assess changes in pain intensity that occur on a day to day basis. In addition, because the assessments were performed only monthly, there is no way to correlate the daily changes in MEDD usage with the level of pain. Further, since it was considered a protocol violation only if the opioid dose adjustment lasted >7 days, there could have been several episodes of increased MEDD usage just under 7 days, but still clinically relevant.
 - *Missing BPI-SF Assessments:*
 - The missing BPI-SF Assessments may have skewed the results, suggesting little change in baseline BPI-SF assessments for a select number of subjects but findings may not be representative of the entire group actually included in the study.
 - The reasons for the missing BPI-SF Assessments and discrepancies in observed number of subject scores vs. change in baseline number of subject scores was not discussed in the submission.

- **Opioid use**
 - *MEDD*: The use of the change of MEDD is acceptable to determine opioid use change over time. However, although the MEDD was collected in the eDiary daily, the Applicant only analyzed this change on a monthly basis, which is not frequent enough to detect clinically important changes in opioid use at prespecified points in time.
- **Presentation of the Data**
 - The Applicant's Figures pertaining to BPI-SF were uninterpretable. The Applicant failed to indicate whether a positive change in mean pain score was worsening or improving pain.
- **Use of Non-opioid Rescue Analgesics**
 - Use of Rescue Analgesic Medication (non-opioid) was not analyzed. The use of non-opioid analgesics (at other than stable dosing) during the trial could affect the requirement for opioid analgesia, and therefore confound the interpretation of MEDD usage.

DAAAP's Response to DGIEP questions: (DGIEP question in italics; DAAAP response in bold font)

I) DGIEP Question 1) ascertainment of whether effects of Amitiza on pain control were assessed adequately by the BPI-SF instrument

DAAAP Response Question 1: No, the effects of Amitiza on analgesia were not assessed adequately during the Phase 3 clinical trials due to the following:

- **Collecting pain scores on a monthly basis is much too infrequent to adequately assess change in pain. In order to analyze the data, it would be useful to have at least weekly pain assessments.**
- **Although opioid dosages were collected daily in the eDiaries, the data was presented as monthly MEDD. It is not possible to assess opioid usage as it relates to pain assessments using such infrequent intervals. Opioid usage may vary day to day based on changes in the patient's pain, and these changes may relate to the effect of lubiprostone on the analgesic efficacy of the opioids. Therefore, the MEDD must be analyzed by the Applicant at more frequent intervals, at least weekly, in order to provide meaningful results that can be interpreted in regards to MEDD and analgesia.**
- **Patients whose pain was not adequately controlled may have used additional non-opioid analgesic rescue which may confound the interpretation of MEDD usage. This was not analyzed by the Sponsor.**

(b) (4)

Appendix A: Brief Pain Inventory Short Form

 1903	Date: / / (month) (day) (year)	Study Name: _____ Protocol #: _____ PI: _____ Revision: 07/01/05
Subject's Initials: _____		
Study Subject #:		

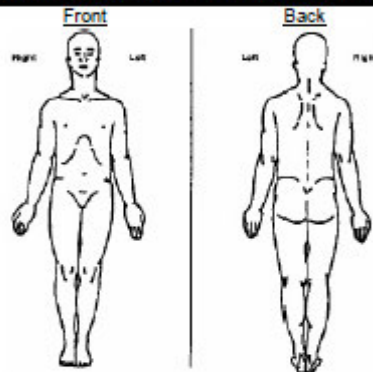
PLEASE USE BLACK INK PEN

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

Yes No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its **worst** in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its **least** in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the **average**.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have **right now**.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine

Applicant's Brief Pain Inventory Short Form (BPI-SF) -- Modified

Brief Pain Inventory

Date questionnaire started Time questionnaire started

Date questionnaire stored Time questionnaire stored Status

1. Throughout our lives, most of us have had minor aches and pain that don't disrupt our daily activities. Have you experienced significant pain today?
2. Please rate your pain by marking the one number that best describes your pain at its worst in the last 24 hours.
3. Please rate your pain by marking the one number that best describes your pain at its least in the last 24 hours.
4. Please rate your pain by marking the one number that best describes your pain on the average.
5. Please rate your pain by marking the one number that tells how much pain you have right now.
6. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the one percentage that shows how much relief you have received.
7. Mark the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General activity	
B. Mood	
C. Walking ability	
D. Normal work (includes both work outside the home and housework)	
E. Relations with other people	
F. Sleep	
G. Enjoyment of life	

(Source: Applicant's submission, CRF)

Appendix C

Applicant's Table. Morphine Equivalent Daily Dose (MEDD) Conversion Table

Table 2.7.3.6-3: Morphine Equivalent Daily Dose (MEDD) Conversion Table

Instructions: Select the MEDD Factor corresponding to the medication and route of administration. Use the MEDD Conversion Worksheet to calculate the total MEDD for each subject at baseline and upon change in medication (type, dose, frequency, etc.). Units should be converted to mg prior to calculation, except for Fentanyl Duragesic Patch.

MEDICATION (Full Agonist)	ROUTE	MEDD FACTOR
Codeine	PO	0.15
Fentanyl citrate	IV	300
Fentanyl citrate	IM	300
Fentanyl 200 mcg	PO	30
Fentanyl 800 mcg	PO	37.5
Fentanyl	transmucosal	30
Fentanyl	buccal	30
Hydrocodone	PO	1
Hydromorphone	IV	20
Hydromorphone	IM	20
Hydromorphone	PO	4
Meperidine	PO	0.1
Meperidine	IV	0.4
Meperidine	IM	0.4
Morphine	PO	1
Morphine	IV	3
Morphine	IM	3
Oxycodone	PO	1.5
Oxymorphone	PO	3

For **Fentanyl Duragesic Patch ONLY**, select the transdermal dose and use the corresponding MEDD.

Fentanyl Transdermal system (Duragesic) (mcg/hr)	MEDD
25	97
50	179.5
75	269.5
100	359.5
125	449.5
150	539.5
175	629.5
200	719.5
225	809.5

NOTE: For partial doses, i.e., resulting from subjects cutting patches, divide the MEDD for dosage of the patch accordingly.

Partial Agonist: Use of the following partial agonist opioids as standalone treatment for non-cancer related pain does not meet the requirements of protocol Inclusion Criteria #2. However, they are allowed if they are taken concomitantly with a full agonist opioid, from the list to the left.

MEDICATION (Partial Agonist)	ROUTE	MEDD FACTOR
Butorphanol	IV	15
Butorphanol	IM	15
Butorphanol	NAS	15
Tramadol	PO	0.3

If you have questions on calculations or need assistance calculating a MEDD factor for an opioid not listed above, please contact the Kendle Medical Monitor.

Excluded Medications:

- Excluded opioids: Methadone, Methadone HCl, Propoxyphene (Darvocet, Darvon).
- Excluded opioid antagonists: Buprenorphine (Subutex, Temgesic, Suboxone), any combination drug with Naloxone (Narcan, Nalone, Narcanti), Naltrexone (Revia, Vivitrol, Depade), Nalmefene (Revex), Methylnaltrexone, Alvimopan (Entereg), Pentazocine (Talwin NX, Talacen).

(Source: Applicant's Table, Summary of Clinical Efficacy, p. 116)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELIZABETH M KILGORE
03/18/2013

ELLEN W FIELDS
03/18/2013

SHARON H HERTZ
03/18/2013

BOB A RAPPAPORT
03/18/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 and #3: OBD-631 and OBD-632 Indication: OIC				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			Protocol SPI/0211SC-0411 done as part of original NDA 2/2005; No new studies
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Partial waiver for 0 to <6 months; Deferral for 6 months to 17 yrs
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			Indicated on front page of all study report bodies

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Farrokh Sohrabi	8-30-2012
Reviewing Medical Officer	Date
Robert Fiorentino	8-30-2012
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

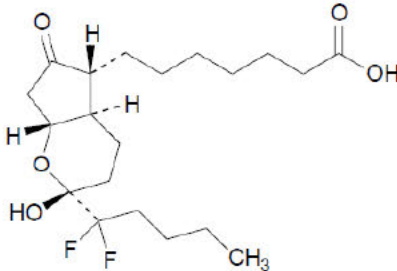
FARROKH SOHRABI
08/30/2012

ROBERT FIORENTINO
08/30/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021908/S-011

CHEMISTRY REVIEW(S)

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
	ONDQA Div II, Branch VI and HFD-180 (DGP)	NDA 21-908/ S-011
3. NAME AND ADDRESS OF APPLICANT		4. COMMUNICATION, DATE
Applicant name: Sucampo Pharma Americas, Inc. Address: 4520 East-West Highway, Suite 300, Bethesda, MD 20814		Efficacy Letter date: July 20, 2012 Stamp date: July 20, 2012 Received by reviewer: September 13, 2012 PDUFA due date: November 18, 2012
5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
Amitiza®	Lubiprostone	
8. SUPPLEMENT PROVIDES FOR:		
Sucampo Pharma Americas, Inc. submitted this application to seek approval of lubiprostone 24 µg administered twice daily for a new indication: the treatment of opioid-induced constipation (OIC) ^{(b) (4)} [REDACTED] [REDACTED] in adults with chronic, non-cancer pain.		
9. PHARMACOLOGICAL CATEGORY:	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Intended for use in the treatment of opioid induced constipation, idiopathic constipation, and irritable bowel syndrome with constipation	Rx only	
12. DOSAGE FORM	13. POTENCY	
Capsules	Two strengths: 24 µg and 8 µg per capsule	
14. CHEMICAL NAME AND STRUCTURE		
USAN: Lubiprostone Chemical name: (-)-7-[(2R,4aR,5R,7aR)-2-(1,1-difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[b]pyran-5-yl]heptanoic acid Empirical formula: C ₂₀ H ₃₂ F ₂ O ₅ MW 390.46		
		
15. COMMENTS		
The products are currently FDA approved drug products as 8 µg and 24 µg capsules. No changes of formulation, dosage form, manufacturing, and packaging processes are proposed in this supplement.		

Only the 24 µg capsule would be used for the currently proposed indication. The proposed new indication will result in an increase of drug consumption. Consequently, the applicant is required to prepare an environment assessment. Based on their calculation, Sucampo Pharma claims categorical exclusion from preparing an environmental assessment on the basis of 21 CFR 25.31(b): the estimated concentration of drug substance at the point of entry into the aquatic environment will not exceed 1 part per billion. Hence, the claim for categorical exclusion is acceptable and the supplement is recommended for approval.

16. CONCLUSION AND RECOMMENDATION

AP

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Yong Wang	See appended electronic signature sheet	September 26, 2012
DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE		

CR

Chemistry Review Notes

Sucampo Pharma Americas, Inc. submitted this Clinical Efficacy supplement to seek approval of lubiprostone 24 µg administered twice daily for a new indication: the treatment of opioid-induced constipation (OIC) [REDACTED] (b) (4) [REDACTED] in adults with chronic, non-cancer pain.

Clinical studies to support this submission were conducted under IND 77771. Priority review of this supplement has been requested by the applicant.

Comments: The products are currently FDA approved drug products as 8 µg and 24 µg capsules. Only the 24 µg capsule would be used for the currently proposed indication. No changes of formulation, dosage form, and manufacturing process are proposed in this supplement. The applicant submitted an environment assessment due to an increase of drug consumption. Sucampo Pharma claims categorical exclusion from preparing an environmental assessment on the basis of 21 CFR 25.31(b): the estimated concentration of drug substance at the point of entry into the aquatic environment will not exceed 1 part per billion.

Evidence Supporting Qualification for Categorical Exclusion

The estimated concentration of lubiprostone at the point of entry into the aquatic environment is calculated using the method suggested by COER in its "Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications" (FDA, July 1998).

The expected introduction concentration (EIC) for the aquatic environment, assuming all drug substance produced is used, is evenly distributed throughout the US per day, and there are no metabolism or depletion mechanisms, should be calculated as follows:

EIC-Aquatic (ppb) = A×B×C×D where,

A= kg/year produced for direct use (as active moiety)

B=1/liters per day entering POTWs*

C=year/365 days

D=10⁹ µg/kg (conversion factor)

*1.214x10¹¹ liters per day entering publicly-owned treatment works (POTWs)

Source: 1996 Needs Survey, Report to Congress.

Using this calculation method, the 1ppb upper limit specified for the categorical exclusion computes to a yearly production of 44,311 kg/year. The estimated production of the active moiety, lubiprostone, is significantly less than 44,311 kg/year.

Production of a 250 kg batch of lubiprostone soft capsule requires 60 grams of lubiprostone. In order to exceed the 44,311 kg/year requirement for production of lubiprostone, more than 738,517 batches of lubiprostone soft capsule would need to be produced. This is well beyond production and sales capabilities. The additional indications of Opioid Induced Constipation and

Irritable Bowel Syndrome with constipation that have been sought since the original approval for Chronic Idiopathic Constipation do not significantly affect this calculation.

Comments: The products are currently FDA approved drug products as 8 µg and 24 µg capsules. No changes of formulation, dosage form, manufacturing, and packaging processes are proposed in this supplement. Only the 24 µg capsule would be used for the currently proposed indication. The proposed new indication will result in an increase of drug consumption. Consequently, the applicant is required to prepare an environment assessment. Based on its calculation, Sucampo Pharma claims categorical exclusion from preparing an environmental assessment on the basis of 21 CFR 25.31(b): the estimated concentration of drug substance at the point of entry into the aquatic environment will not exceed 1 part per billion. Hence, the claim for categorical exclusion is acceptable and the supplement is recommended for approval.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YONG WANG
09/28/2012

THOMAS F OLIVER
10/01/2012

MEMORANDUM

To: NDA 21-908
Amitiza (lubiprostone) Capsules
SUCAMPO Pharmaceuticals

From: Marie Kowblansky, Ph.D., CMC Lead, Branch IV, ONDQA

Through: Tom Oliver, Ph.D., Branch Chief, Branch VI, ONDQA

Date: September 7, 2012

Subject: Filing Review for Clinical Efficacy Supplement (**S-011**)

The current submission, dated July 20, 2012, is a Clinical Efficacy Supplement to NDA 21-908 [Amitiza (lubiprostone) Capsules], seeking approval for expanding the indication for this product to include treatment of opioid-induced constipation.

The product is currently approved as 8 µg and 24 µg capsules. The approved 24 µg capsules would be used for the currently proposed indication, with no CMC modifications to the approved product or manufacturing process.

The applicant claims categorical exclusion from preparing an environmental assessment on the basis of 21 CFR 25.31(b): the estimated concentration of drug substance at the point of entry into the aquatic environment will not exceed 1 part per billion

Clinical studies to support this submission were conducted under IND 77771.

Priority review of this supplement has been requested by the applicant and is currently under consideration by FDA.

Conclusion: The applicant has included sufficient information to make this application fileable from a CMC perspective

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARIE KOWBLANSKY
09/07/2012

THOMAS F OLIVER
09/07/2012

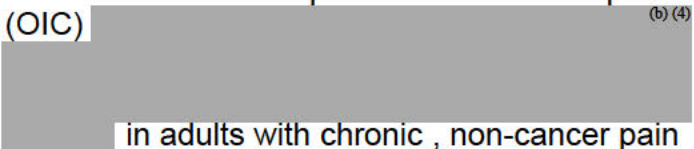
**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021908/S-011

PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 21-908
Supporting document/s: 0112
Applicant's letter date: July 20, 2012
CDER stamp date: July 20, 2012 (electronic submission)
Product: Amitiza (lubiprostone) Capsules
Indication: The treatment of opioid-induced constipation (OIC) (b) (4)

in adults with chronic , non-cancer pain
Applicant: Sucampo Pharmaceuticals, Inc.
Review Division: Division of Gastroenterology and Inborn Errors products (DGIEP)
Reviewer: Sushanta Chakder, Ph.D.
Supervisor/Team Leader: Sushanta Chakder, Ph.D.
Division Director: Donna Griebel, M.D.
Project Manager: Maureen Dewey, MPH

Disclaimer

Except as specifically identified, all data and information discussed below are necessary for approval of NDA 21-908, and are owned by Sucampo Pharmaceuticals, Inc. or are data for which Sucampo Pharmaceuticals, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 21-908 that Sucampo Pharmaceuticals, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Sucampo Pharmaceuticals, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-908.

TABLE OF CONTENTS

EXECUTIVE SUMMARY	3
1.1 RECOMMENDATIONS	3
1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS	5
2 DRUG INFORMATION	7
3 STUDIES SUBMITTED.....	8
4 PHARMACOLOGY	8
4.3 SAFETY PHARMACOLOGY	13
5 PHARMACOKINETICS/ADME/TOXICOKINETICS	21
6 GENERAL TOXICOLOGY.....	21
7 GENETIC TOXICOLOGY	21
8 CARCINOGENICITY	21
9 REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY	22
10 SPECIAL TOXICOLOGY STUDIES.....	22
11 INTEGRATED SUMMARY AND SAFETY EVALUATION.....	22
12 APPENDIX/ATTACHMENTS: NONE	23

Executive Summary

1.1 Recommendations

1.1.1 Approvability

From a nonclinical standpoint, the NDA Supplement is recommended for approval.

1.1.2 Additional Non Clinical Recommendations

None

Labeling

8.1 Pregnancy

Sponsor's version:



(b) (4)



Comments: The proposed text is acceptable, and no changes are recommended in this section.

8.3 Nursing Mothers

(b) (4)



Comments: This section is acceptable as proposed, and no changes are recommended.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Sponsor's version:

Carcinogenesis

(b) (4)





Comments: The proposed text for this section is acceptable, and no changes are recommended. In the last sentence of the 'Impairment of Fertility' section –  should be changed to - **The 1000 mcg/kg/day dose in rats is approximately 169 times the highest recommended human dose of 48 mcg/day, based on body surface area.**

1.2 Brief Discussion of Nonclinical Findings:

Amitiza (lubiprostone) Capsules are approved for the treatment of chronic idiopathic constipation in adults, and treatment of irritable bowel syndrome with constipation in women ≥ 18 years old. In the current NDA supplement, the applicant is seeking an expansion of the indication for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain. Nonclinical studies of lubiprostone were reviewed in earlier submissions where the safety of lubiprostone has been established. In the current submission, the following three pharmacology studies were submitted-

- Effects of combination of RU-0211 and oxycodone on oxycodone-induced constipation in mice;
- A study of the gastrointestinal effects of SPI-0211 on opioid-induced constipation in male CD-1 mice;
- Methadone but not morphine Inhibits lubiprostone-stimulated Cl^- currents in T84 intestinal cells and recombinant human ClC-2 , but not CFTR Cl^- currents.

In addition, a published study showing a reversal by lubiprostone of the morphine-induced inhibition of the human intestinal mucosal fluid secretion was submitted (Sun et al, 2011 Dig Dis Sci, 56: 330-338).

In male mice, oral administration of oxycodone (5 mg/kg) caused a significant reduction of the intestinal transit, measured by the propulsion of a graphite marker. Lubiprostone (RU-0211), at doses of 0.1, 1, 10 and 100 µg/kg, caused a dose dependent reversal of the oxycodone-induced decrease in propulsion of the graphite marker (significant only at 100 µg/kg). In another study, the effect of lubiprostone on morphine and/or methadone (a diphenylheptane opioid)-induced constipation (measured by the intestinal length travelled by a charcoal meal) was investigated in male mice. Intraperitoneal doses of 5 mg/kg morphine or 10 mg/kg methadone caused a decrease in the intestinal transit of the charcoal meal. Lubiprostone, at a dose of 100 µg/kg, caused a partial (60.7%), but significant reversal of the effect of morphine on the intestinal charcoal meal transit. There was also a partial reversal (not significant) of the methadone (22.7%) or methadone plus morphine (28.4%)-induced reduction of the intestinal transit of the charcoal meal by 100 µg/kg lubiprostone. The findings suggest that lubiprostone may be more effective on morphine induced constipation than methadone-induced constipation.

To examine the differences between the effects of lubiprostone on morphine and methadone-induced inhibition of GI transit, the effects of these two opioids on lubiprostone-stimulated Cl⁻ currents were examined in T84 intestinal cells. Morphine, 5 µM, had no effect on lubiprostone (250 nM)-induced short circuit current, while methadone (5 µM) caused an inhibition (88%) of the lubiprostone-stimulated short circuit current. Naloxone (10 µM) had no effect on methadone-induced inhibition of lubiprostone-stimulated short circuit current. Methadone also inhibited the lubiprostone-stimulated Cl⁻ currents in HEK293 cells in a concentration-dependent manner, while morphine (5 µM) had no effect on this current. Other opioid agonists, such as oxycodone, oxymorphone and hydromorphone (at 5 µM) had no effects on lubiprostone-stimulated Cl⁻ currents in T84 cells. In addition to methadone, fentanyl and loperamide also caused an inhibition of the lubiprostone-stimulated Cl⁻ currents in T84 cells.

Lubiprostone caused a reversal of short circuit current (a marker for chloride secretion) in isolated segments of human jejunum, and this effect of lubiprostone was not blocked by tetrodotoxin, a blocker of enteric nerves, suggesting that the effect of lubiprostone is not mediated via enteric neurons, and it acts directly by activating intestinal chloride channels.

Thus, lubiprostone appears to be less effective in reversing the constipating effect of methadone than that of morphine in mice. In *in vitro* electrophysiology studies using T84 and HEK-29 cells, methadone was shown to cause an inhibition of lubiprostone-induced Cl⁻ currents, while morphine had no effect on this current. In addition to methadone, fentanyl and loperamide also caused an inhibition of the lubiprostone-stimulated Cl⁻ currents in T84 cells. Thus, there is a possibility that methadone and other diphenylheptane opioids may reduce the effectiveness of lubiprostone.

2 Drug Information

2.1 Drug: Amitiza (lubiprostone) Capsules

2.1.1 CAS Registry Number: 136790-76-6, 333963-40-9

2.1.2 Generic Name: Lubiprostone

2.1.3 Code Name: RU-0211/SPI-0211

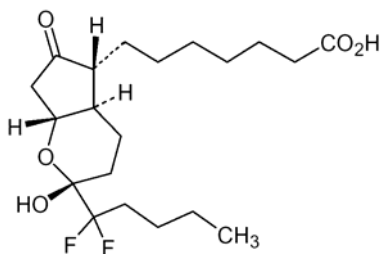
2.1.4 Chemical Name

(-)-7-[(2R, 4aR, 5R, 7aR)-2-(1, 1-difluoropentyl)-2-hydroxy-6-oxaoctahydrocyclopenta[b]pyran-5-yl] heptanoic acid.

2.1.5 Molecular Formula/Molecular Weight

$C_{20}H_{32}F_2O_5/390.46$

2.1.6 Structure



2.1.7 Pharmacologic class: Prostaglandin analog/chloride channel activator

2.2 Relevant IND/s, NDA/s, and DMF/s

IND 59,623, Sucampo Pharmaceuticals Inc.

IND 60,540, Sucampo Pharmaceuticals Inc.

2.3 Clinical Formulation:

2.3.1 Drug Formulation

Each soft gelatin capsule contains 8 or 24 µg lubiprostone. Lubiprostone is dissolved in medium chain fatty acid triglyceride (MCT) before encapsulation.

2.3.2 Comments on Novel Excipients

N/A

2.3.3 Comments on Impurities/Degradants of Concern

None

2.4 Proposed Clinical Population and Dosing Regimen

Patients with chronic idiopathic constipation (24 µg twice daily), opioid-induced constipation (24 µg twice daily), and irritable bowel syndrome with constipation (8 µg twice daily).

2.5 Regulatory Background

3 Studies Submitted

The following three pharmacology studies were submitted-

- a. Effects of combination of RU-0211 and oxycodone on oxycodone-induced constipation in mice;
- b. A study of the gastrointestinal effects of SPI-0211 on opioid-induced constipation in male CD-1 mice;
- c. Methadone but not morphine Inhibits lubiprostone-stimulated Cl⁻ currents in T84 intestinal cells and recombinant human CIC-2, but not CFTR Cl⁻ currents.

In addition, a published study showing a reversal by lubiprostone of the morphine-induced inhibition of the human intestinal mucosal fluid secretion was submitted (Sun et al, 2011 Dig Dis Sci, 56: 330-338).

3.3 Previous Reviews Referenced

Previous nonclinical reviews of the following submissions are referenced:

IND 59,623, Sucampo Pharmaceuticals, Inc.
IND 60,540, Sucampo Pharmaceuticals, Inc.
NDA 21-908, Sucampo Pharmaceuticals, Inc.

4 Pharmacology

Effects of Combination of RU-0211 and Oxycodone on Oxycodone-induced Constipation in Mice (Study No. 050627)

Methods: The study was conducted in male Crlj: CD1 (ICR) mice (b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

Results: Following oral administration of oxycodone and RU-0211 to male mice, the positive animal ratios were 6.7, 0, 13.3, 6.7 and 26.7% for groups treated with 5 mg/kg oxycodone plus 0, 0.1, 1, 10 and 100 µg/kg RU-0211, respectively. The positive animal ratio for the normal group, receiving the vehicle only, was 93.3%. In the control group,

treated with 5 mg/kg oxycodone alone, the graphite marker propulsion rate was $62.3 \pm 5.6\%$, and the graphite marker was detected in the cecum of 1 of 15 animals (6.7%). The graphite marker propulsion ratios were 62.3, 67.5, 71.0, 76.0 and 80.5% for 0, 0.1, 1, 10 and 100 $\mu\text{g}/\text{kg}$ RU-0211 groups, respectively. Thus, RU-0211 caused a dose-dependent increase in the propulsion of the graphite marker in mice treated with oral oxycodone. The positive animal ratios and the graphite marker propulsion rate for different groups are summarized in the sponsor's Table below.

Table 2. Effects of Combination of RU-0211 and Oxycodone on Oxycodone-induced Constipation in Mice -Full Test-

Test Group	Dosage of test article $\mu\text{g}/\text{kg}$	Dosage of oxycodone mg/kg	Positive animal ratio, % (Number of positive animals)	The graphite marker propulsion rate Mean $\pm$ S.E.
Normal	—	0	93.3 (14/15)	99.8 $\pm$ 0.2
Control	—	5	6.7 (1/15) ##	62.3 $\pm$ 5.6 ##
RU-0211	0.1	5	0.0 (0/15)	67.5 $\pm$ 4.8
	1	5	13.3 (2/15)	71.0 $\pm$ 5.0
	10	5	6.7 (1/15)	76.0 $\pm$ 4.6
	100	5	26.7 (4/15)	80.5 $\pm$ 5.5 *

N=15.

$$\text{Propulsion rate} = \frac{\text{Moving distance of graphite marker}}{\text{Distance from the stomach to the cecum}} \times 100$$

* ($p < 0.05$): Significantly different from the control value.

($p < 0.01$): Significantly different from the normal value.

Thus, oxycodone (5 mg/kg) caused a significant decrease in the intestinal propulsion rate of the graphite marker in male mice, and RU-0211 improved the oxycodone-induced impaired intestinal transit in a dose-dependent manner. The effect of RU-0211 was statistically significant only at the 100 $\mu\text{g}/\text{kg}$ dose.

Study Title: A Study of the Gastrointestinal Effects of SPI-0211 on Opioid-induced Constipation in Male CD-1 Mice (Study No. 8222-133)

Methods: The study was conducted to assess the effects of SPI-0211 (lubiprostone) on opioid-induced constipation in male CD-1 mice. SPI-0211 was orally administered to groups of male mice at 0 (vehicle, 0.01% polysorbate 80 in physiological saline), 10 or 100 $\mu\text{g}/\text{kg}$. Immediately after administration of SPI-0211 or the vehicle, the mice were intraperitoneally administered morphine (5 mg/kg) and/or methadone (10 mg/kg). Fifteen minutes following administration of morphine and/or methadone, the mice were administered a charcoal meal orally. Twenty minutes after administration of the charcoal meal, the animals were euthanized, the intestines removed, and the total

length (pylorus to appendix) and the total distance travelled by the charcoal meal were measured.

Results: Administration of the combination of the vehicle and 5 mg/kg morphine and/or 10 mg/kg methadone produced significant decreases in charcoal meal transit relative to the vehicle control group.

The combination of 100 µg/kg SPI-0211 and 5 mg/kg/ morphine caused a significant increase (60.7%) in the charcoal meal transit relative to the vehicle plus 5 mg/kg morphine. The administration of 100 µg/kg SPI-0211 had a small but statistically insignificant effect (22.7%) on the reduced charcoal meal transit caused by 10 mg/kg methadone.

SPI-0211, at a dose of 100 µg/kg, also caused a small but insignificant effect (28.4%) on the reduced charcoal meal transit caused by 5 mg/kg morphine plus 10 mg/kg methadone.

Thus, SPI-0211 appears to be more effective on morphine-induced constipating effects in mice than that caused by methadone.

The effects of different agents on charcoal meal transit in the rat intestine are summarized in the Table below.

Table 1
Effects of Orally Administered SPI-0211 on Intraperitoneal Morphine or Methadone-Induced Constipation in Male CD-1 Mice, Study 8222-133

Compound ^a ($\mu\text{g}/\text{kg}$ and mg/kg)	Distance Traveled ^b (% Intestinal Length)	Standard Error
Vehicle (0 $\mu\text{g}/\text{kg}$ SPI-0211) ^c	52.2	3.6
0 $\mu\text{g}/\text{kg}$ SPI-0211 + 5 mg/kg morphine	20.1*	1.3
10 $\mu\text{g}/\text{kg}$ SPI-0211 + 5 mg/kg morphine	23.2*	1.7
100 $\mu\text{g}/\text{kg}$ SPI-0211 + 5 mg/kg morphine	32.3* [†]	2.2
Vehicle (0 $\mu\text{g}/\text{kg}$ SPI-0211) ^c	58.6	2.6
0 $\mu\text{g}/\text{kg}$ SPI-0211 + 10 mg/kg methadone	19.4*	1.5
10 $\mu\text{g}/\text{kg}$ SPI-0211 + 10 mg/kg methadone	19.9*	0.7
100 $\mu\text{g}/\text{kg}$ SPI-0211 + 10 mg/kg methadone	23.8*	1.5
Vehicle (0 $\mu\text{g}/\text{kg}$ SPI-0211) ^c	58.0	2.9
0 $\mu\text{g}/\text{kg}$ SPI-0211 + 5 mg/kg morphine + 10 mg/kg methadone	17.6*	1.3
10 $\mu\text{g}/\text{kg}$ SPI-0211 + 5 mg/kg morphine + 10 mg/kg methadone	16.7*	1.7
100 $\mu\text{g}/\text{kg}$ SPI-0211 + 5 mg/kg morphine + 10 mg/kg methadone	22.6*	1.7

* Significantly different from vehicle control value ($p \leq 0.05$).

[†] Significantly different from vehicle/morphine control value ($p \leq 0.05$).

^a $n = 10$ mice/treatment group.

^b Values represent [(distance (cm) of charcoal meal movement/total length of intestine (cm)) x 100].

^c Vehicle = 0.01% polysorbate 80 and 0.5% ethanol in physiological saline.

Study Title: Methadone but not Morphine Inhibits Lubiprostone-Stimulated Cl⁻ Currents in T84 Intestinal Cells and Recombinant Human CIC-2, but not CFTR Cl⁻ Currents (Study Report No. NSR0211-12-003-01)

The study was conducted at the [REDACTED] (b) (4)

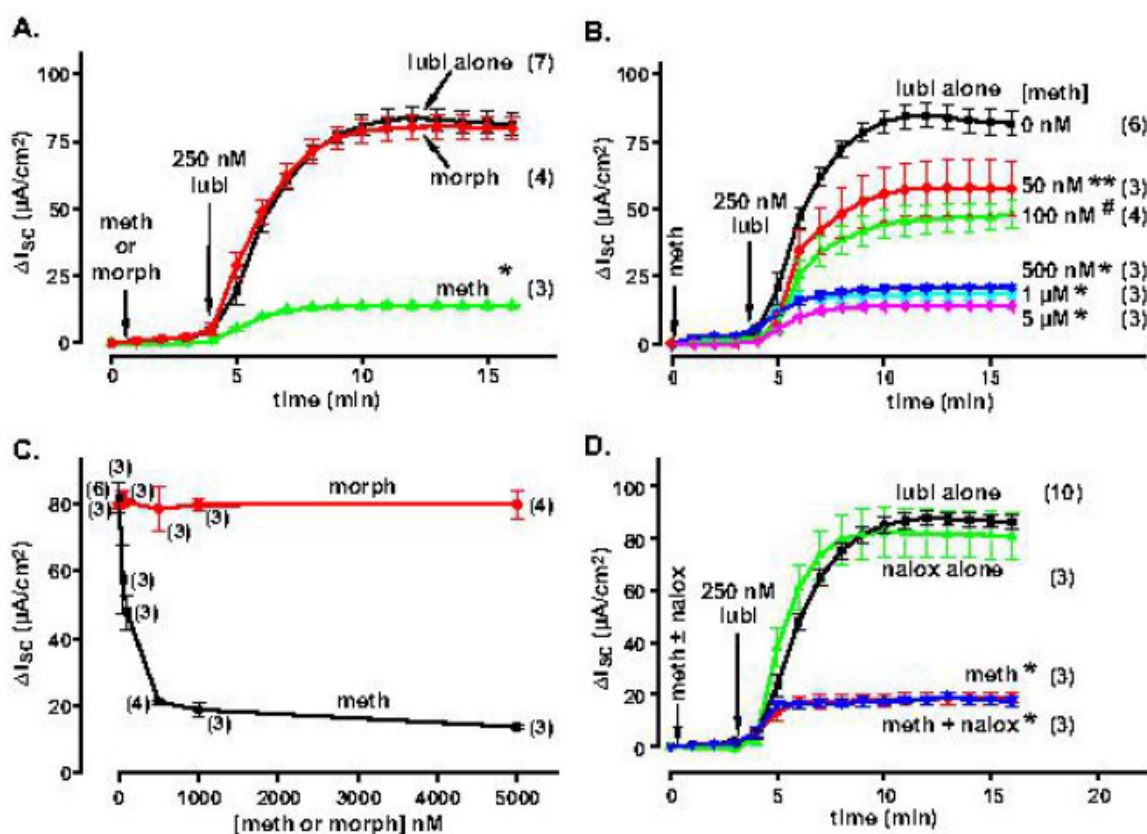
Methods: [REDACTED] (b) (4)

Results:

Effects of varying concentrations of methadone and morphine on lubiprostone-stimulated Cl⁻ currents in T84 cells and effect of naloxone.

Morphine (5 μ M) had no effect on 250 nM lubiprostone-stimulated short circuit current (I_{sc}). However, 5 μ M methadone caused approximately 88% inhibition of the lubiprostone-stimulated I_{sc} . Methadone caused a concentration-dependent inhibition of lubiprostone-stimulated I_{sc} with the half maximal inhibition of I_{sc} at about 100 nM. The effect of opioid receptor antagonist, naloxone on the methadone inhibition of Cl⁻ currents in T84 cells was also examined. Naloxone (10 μ M) alone had no effect on Cl⁻ currents, while methadone caused an inhibition of lubiprostone-stimulated I_{sc} . In addition, naloxone had no effect on methadone-induced inhibition of lubiprostone-stimulated I_{sc} .

The effects of methadone and morphine on lubiprostone-stimulated I_{sc} across T84 cells and the effect of naloxone on the I_{sc} are shown in the Sponsor's Figures below.



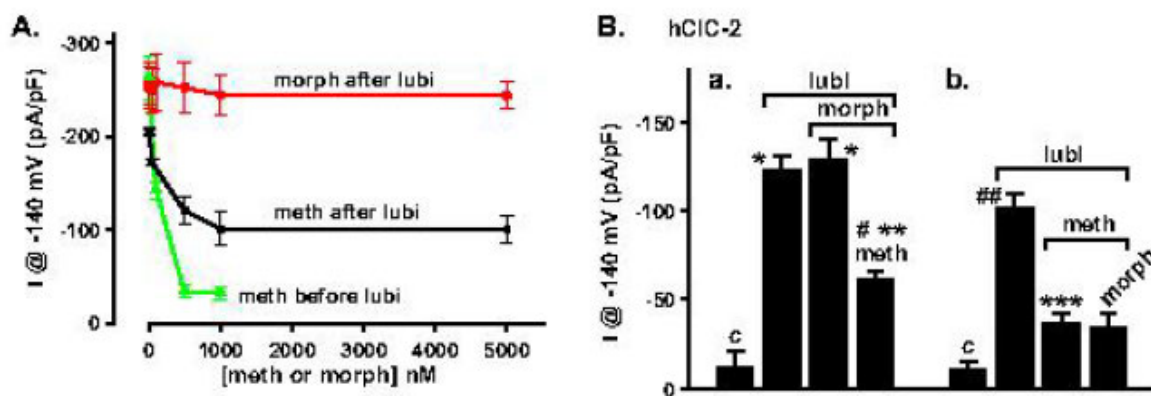
Effect of varying concentrations of methadone and morphine on lubiprostone-stimulated hClC-2 Cl⁻ currents in HEK293 cells.

The effects of different concentrations of methadone and morphine on lubiprostone (100 nM)-stimulated ClC chloride currents were investigated in HEK293 cells. Morphine, at concentrations up to 5 μM , had no effect on the lubiprostone-stimulated chloride currents. Methadone, added before or after 100 nM lubiprostone inhibited the current in a concentration-dependent manner with an IC_{50} of 109.3 ± 8.5 nM and 117.3 ± 32.4 nM, respectively. When methadone was added before lubiprostone, there was a greater inhibition (approximately 90% at 1 μM) observed as compared to when methadone was added after lubiprostone (approximately 60% at 1 μM)

Effect of methadone and morphine together on lubiprostone-stimulated hClC-2 Cl⁻ currents in HEK293 cells.

Chloride currents in hClC transfected cells were measured without lubiprostone (control), cells treated with 100 nM lubiprostone and with either 1 μM methadone, followed by 100 nM morphine, or the reverse, 100 nM morphine followed by 1 μM methadone. Lubiprostone caused a stimulation of chloride currents, and morphine (100 nM) had no effect on the currents; however, subsequent addition of 1 μM methadone caused an inhibition of lubiprostone-stimulated Cl⁻ currents. Methadone (1 μM) alone

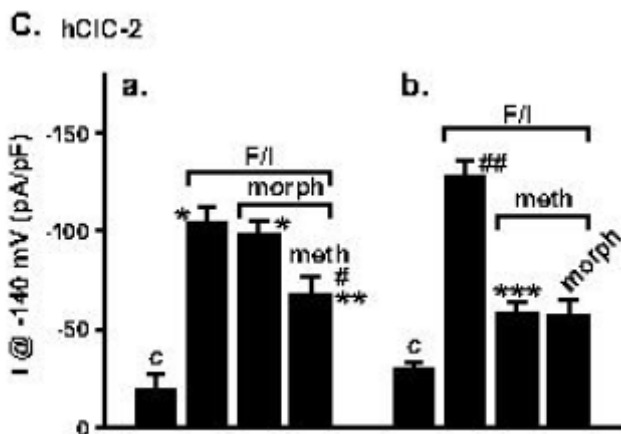
inhibited lubiprostone-stimulated chloride currents, and subsequent addition of 100 nM morphine had no additional inhibitory effect on the Cl⁻ currents. The effects of morphine and methadone on lubiprostone-stimulated hCIC Cl⁻ currents are shown in the Figures below.



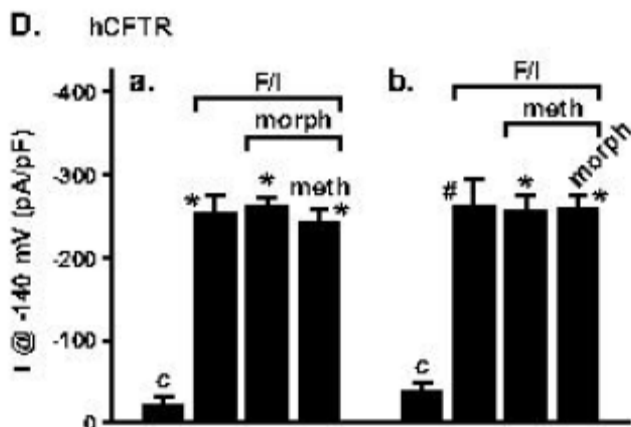
Effect of methadone and morphine on forskolin/IBMX-stimulated hCIC-2 and hCFTR Cl⁻ currents in HEK293 cells.

The effects of morphine (100 nM) and methadone (1 μ M) on Cl⁻ currents activated by 5 μ M forskolin/20 μ M IBMX (that raises the levels of intracellular cAMP and is an alternate means of activation of human ClC-2) were studied *in vitro*.

Forskolin/IBMX-activated hCIC chloride currents were not affected by morphine. However, methadone inhibited the currents regardless of whether methadone was added before or after morphine.

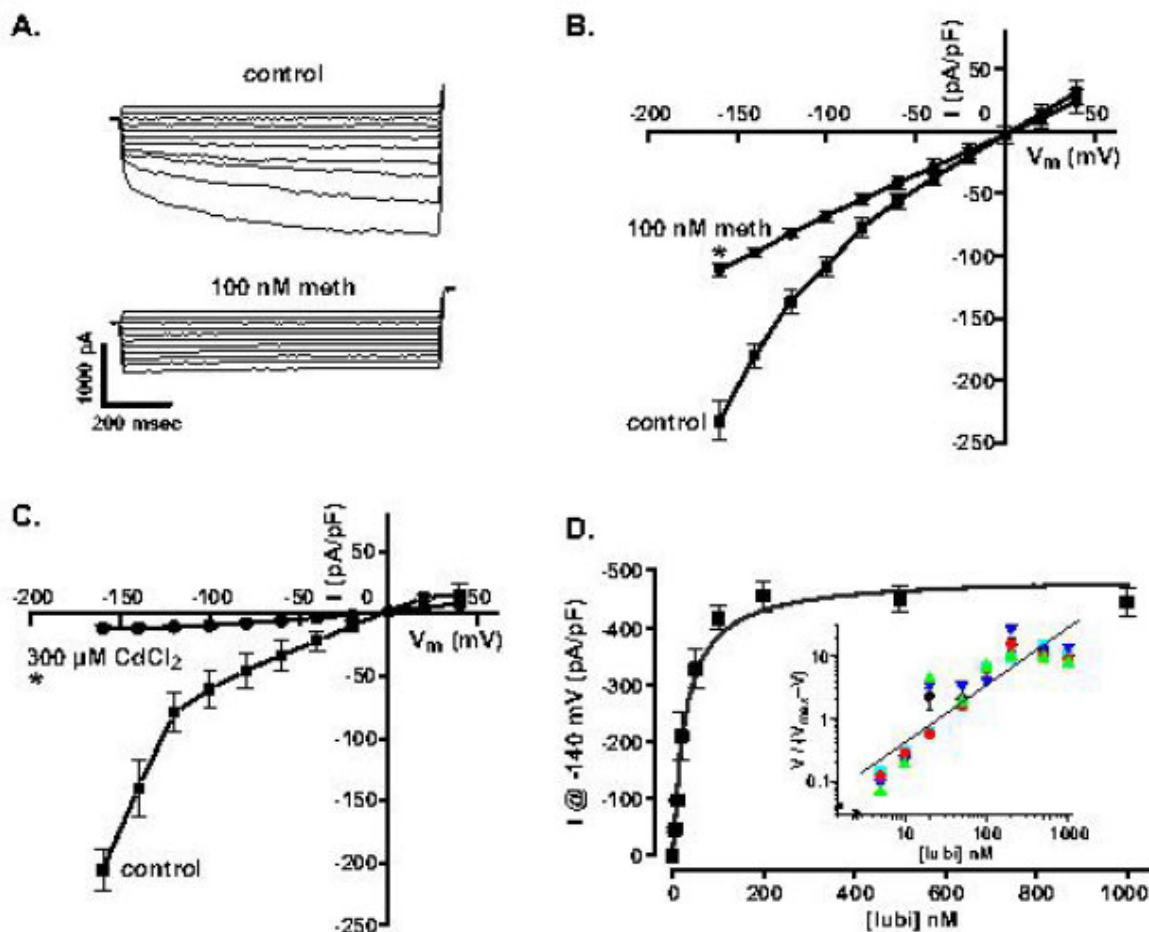


Morphine (100 nM) and methadone (1 μ M) had no inhibitory effect on forskolin/IBMX-stimulated hCFTR Cl⁻ currents in HEK293 cells, as shown in the Figure below.



Effect of methadone and CdCl₂ on time-dependent, voltage-activated hClC-2 Cl⁻ currents expressed in HEK293EBNA cells.

The effects of methadone and CdCl₂ on time-dependent, voltage-activated hClC-2 Cl⁻ currents were examined in HEK293EBNA cells, stably transfected with recombinant hClC-2 in pCEP4. The time-dependent and voltage activated Cl⁻ currents in HEK293EBNA cells were inhibited by 100 nM methadone. The currents were also inhibited by 300 μM CdCl₂. Methadone caused about 50% inhibition of the currents, while CdCl₂ caused an abolition of the chloride currents in HEK293EBNA cells. The effects of methadone and CdCl₂ on hClC chloride currents are shown in the Figures below.



- A and B show representative current recordings for hCIC-transfected cells before and after addition of 100 nM methadone. B and C show I-V curves for effects of 100 nM methadone and 300 μ M CdCl₂.

Effect of lubiprostone and methadone on Cl⁻ currents in hCIC-2 and mock-transfected HEK293EBNA cells.

Lubiprostone (20 nM) increased the chloride currents in hCIC-transfected HEK293EBNA cells, and subsequent addition of 1 μ M methadone decreased these currents. Both control (without lubiprostone) and lubiprostone-stimulated Cl⁻ currents in hCIC-2-transfected HEK293EBNA cells showed inward rectification, while mock-transfected cells had linear I/V curves, exhibiting very small currents.

The effects of varying concentrations of methadone and morphine on the Cl⁻ currents in HEK293EBNA cells were also examined in the absence or presence of 100 nM lubiprostone. Lubiprostone significantly increased the Cl⁻ currents and Morphine, at concentrations up to 5 μ g/mL, had no effect on the chloride currents. Methadone, added either before or after lubiprostone, inhibited the chloride current with IC₅₀ values of 130.7 $\pm$ 25.4 and 102.7 $\pm$ 12.2 nM, respectively. Similar to the inhibition of the chloride currents in HEK293 cells, the inhibition by methadone was greater when methadone was added before as compared to that observed after lubiprostone addition.

Forskolin/IBMX (5 μ M/20 μ M) caused significant stimulation of the chloride currents in HEK293EBNA cells, and methadone (1 μ M) significantly inhibited this response to the control level.

Effects of other opioids on lubiprostone-stimulated Cl⁻ currents in T84 cells and hClC-2 Cl⁻ currents in HEK293EBNA expressing hClC-2.

When the effects of other opioids from four opioid classes, such as phenanthrenes, benzomorphones, phenylpiperidines and phenylheptanes were examined, only diphenylheptanes were found to interfere with the lubiprostone activation of ClC-2 currents at relevant concentrations. Oxycodone, oxymorphone and hydromorphone had no inhibitory effects at a concentration of 5 μ M. Fentanyl and loperamide caused an inhibition of the current with an IC₅₀ of 3 μ M, while methadone exhibited an IC₅₀ of 0.075 μ M. Thus, methadone was the most potent among all the opioids tested in inhibiting the lubiprostone-stimulated chloride currents in HEK293EBNA cells.

In summary, the study was conducted to determine whether methadone inhibits Cl⁻ transport by epithelial cells. Lubiprostone-stimulated Cl⁻ currents, measured by short circuit currents (I_{sc}) in T84 cells, were inhibited by methadone. The hClC Cl⁻ currents in HEK293 cells were inhibited by methadone, but not by morphine. Naloxone alone, or with methadone, had no inhibitory effect. Morphine, at a concentration of 5 μ M, had no effect on I_{sc}. The inhibition of hClC Cl⁻ currents was lower when lubiprostone was added before methadone as compared to that observed when lubiprostone was added after methadone, suggesting that lubiprostone does not bind to channels previously bound to methadone.

In addition, the sponsor submitted the following published study in this submission.

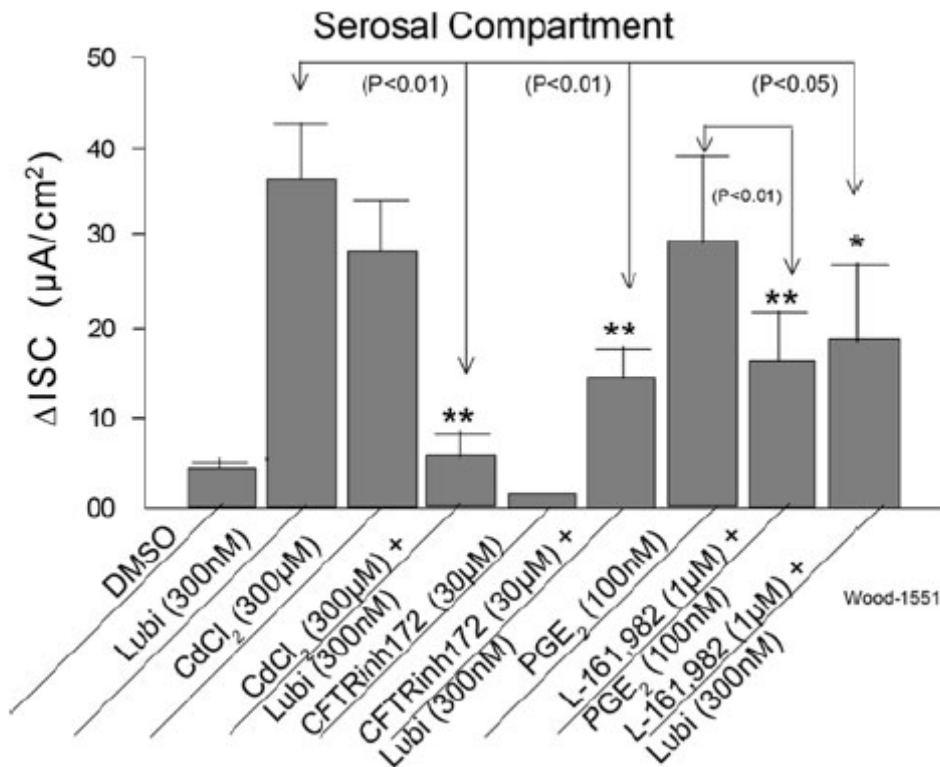
Lubiprostone Reverses the Inhibitory Action of Morphine on Mucosal Secretion in Human Small Intestine- Xiahong Sun, Xiyu Wang, Guo-Du Wang, Yun Xia, Sumei Liu, Meihua Qu, Bradley J. Needleman, Dean J. Mikami, W. Scott Melvin, Laura M. Bohn, Ryuji Ueno, Jackie D. Wood. *Dig Dis Sci.*, 2011; 56: 330-338.

In this study, the effect of lubiprostone on morphine-induced suppression of mucosal fluid secretion was examined in isolated human intestinal segments. Fresh segments of jejunum discarded during Roux-En-Y gastric bypass surgeries were used in the study. Flat-sheet jejunal muscle preparations were mounted between halves of the Ussing chambers and the tissues were bathed on both sides with circulating Krebs's solution, maintained at 37°C. Changes in short-circuit current (Δ I_{sc}) were measured in Ussing flux chambers as a marker for chloride secretion in the presence of different agents, such as, morphine, prostaglandin receptor antagonists, chloride channel blockers and lubiprostone.

Treatment with morphine caused a suppression of the basal I_{sc}. Lubiprostone caused a reversal of the morphine suppression of basal I_{sc}. Lubiprostone, applied to the mucosal side of muscle stripped jejunum, evoked an increase in I_{sc} in a concentration-dependent manner. Blockade of nerves in the enteric nervous system (ENS) by 1 μ M

tetrodotoxin (TTX) had no effect on stimulation of Isc by lubiprostone (30 nM) suggesting that enteric neurons are not involved with this effect. Removal of chloride or treatment with bumetanide or 5-nitro-2-(2-(phenylpropylamino) benzoic acid (NPPB) suppressed or abolished the lubiprostone response. Antagonism of CFTR channels or prostaglandin EP₄ receptors partially suppressed the lubiprostone stimulation of Isc. Antagonism of E₁ and EP₁₋₃ receptors had no effect on lubiprostone-stimulated Isc. Thus, lubiprostone causes an increase in intestinal chloride secretion by directly opening the mucosal chloride channels, bypassing the antisecretory effect of morphine via the enteric nervous system.

The effects of different agents on the short circuit currents are shown in the Figures below.



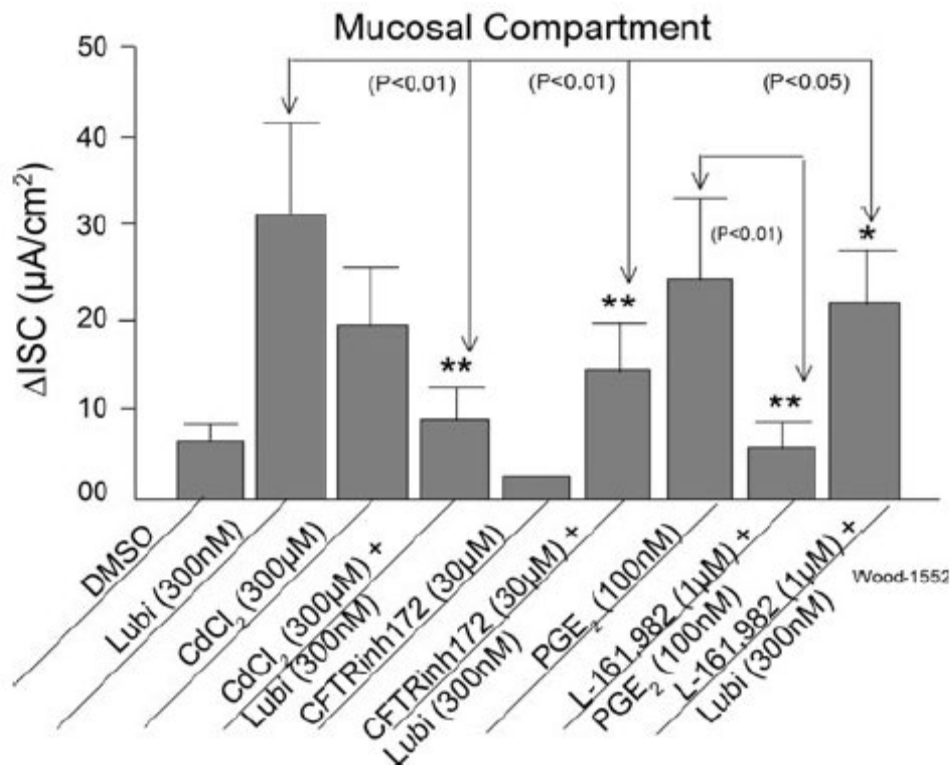


Fig. 5 Effects of cadmium (CdCl₂), CFTR(inh)-172, and L-161-982 on lubiprostone-evoked ΔI_{sc} in human small intestine. CdCl₂, which suppressed K⁺ conductance, depolarized the enterocytes and thereby reduced the driving force on intracellular Cl⁻, suppressed lubiprostone-evoked ΔI_{sc} . Suppression of CFTR channel conductance by CFTR(inh)-172 reduced responses to lubiprostone. Prostaglandin PGE₂ mimicked the action of lubiprostone. The EP₄ receptor antagonist, L-161,982, suppressed the responses to PGE₂ and the lubiprostone-evoked responses. The effects were generally the same for applications in the serosal and mucosal compartments of the Ussing chambers. Values are expressed as means $\pm$ SE (**P* < 0.05; ***P* < 0.01). *N* = 4 patients, 6 preparations

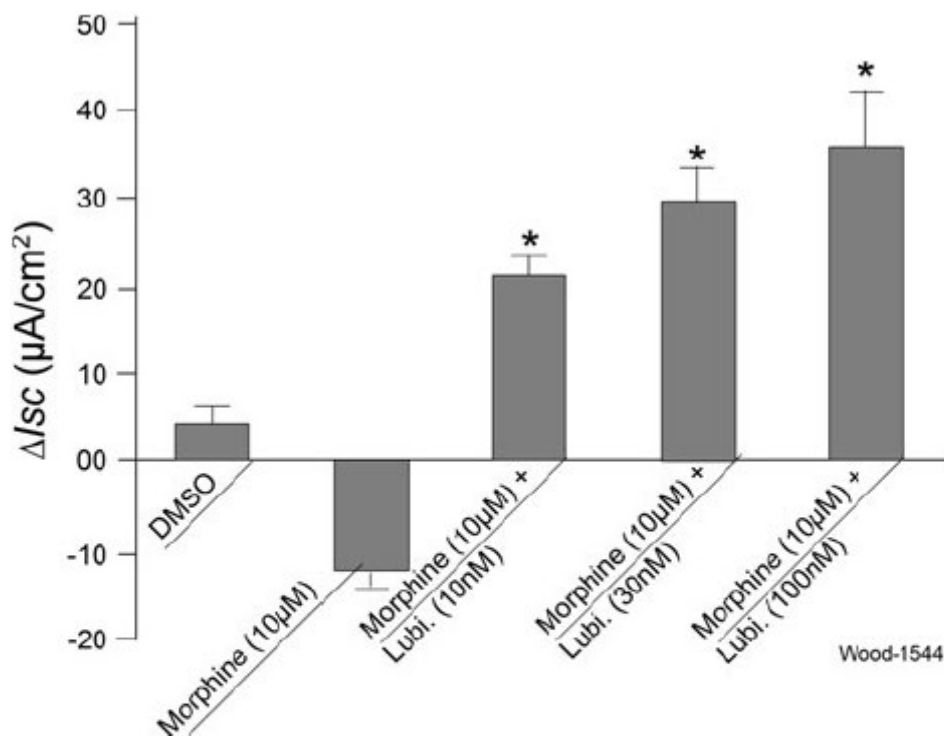


Fig. 6 Lubiprostone reversed morphine-induced suppression of *Isc* in human jejunum. Morphine alone suppressed basal *Isc*. Lubiprostone (10, 30 or 100 nM), applied on the same side 5 min later, reversed morphine-induced suppression in a concentration-dependent manner. Values are expressed as means $\pm$ SE (* $P < 0.01$). $N = 7$ patients, 12 preparations

5 Pharmacokinetics/ADME/Toxicokinetics

N/A

6 General Toxicology

N/A

7 Genetic Toxicology

N/A

8 Carcinogenicity

N/A

9 Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies were submitted in this submission.

10 Special Toxicology Studies

N/A

11 Integrated Summary and Safety Evaluation

Amitiza (lubiprostone) Capsules are currently approved for the treatment of chronic idiopathic constipation in adults, and treatment of irritable bowel syndrome with constipation in women ≥ 18 years old. In the current NDA supplement, the applicant is seeking an expansion of the indication for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain. In the current submission, the following three pharmacology studies were submitted-

a. Effects of combination of RU-0211 and oxycodone on oxycodone-induced constipation in mice; b. A study of the gastrointestinal effects of SPI-0211 on opioid-induced constipation in male CD-1 mice; c. Methadone but not morphine Inhibits lubiprostone-stimulated Cl^- currents in T84 intestinal cells and recombinant human CIC-2, but not CFTR Cl^- currents.

In addition, a published study showing a reversal by lubiprostone of the morphine-induced inhibition of the human intestinal mucosal fluid secretion was submitted (Sun et al, 2011 Dig Dis Sci, 56: 330-338).

In male mice, lubiprostone caused a dose dependent reversal of the oxycodone-induced decrease in propulsion of a graphite marker (significant at 100 $\mu\text{g}/\text{kg}$). Lubiprostone had no significant effect on methadone (a diphenylheptane opioid)-induced constipation in male mice, while lubiprostone, at a dose of 100 $\mu\text{g}/\text{kg}$, caused a significant reversal of the effect of morphine on the intestinal charcoal meal transit. Lubiprostone (100 $\mu\text{g}/\text{kg}$) caused a partial reversal (not significant) of the methadone or methadone plus morphine-induced reduction of the intestinal transit of the charcoal meal. The findings suggest that lubiprostone may be more effective on morphine induced constipation than methadone-induced constipation.

In T84 cells expressing hCIC chloride channels, morphine (5 μM) had no effect on lubiprostone (250 nM)-induced short circuit current, while methadone (5 μM) caused an inhibition (88%) of the lubiprostone-stimulated short circuit current. Methadone also inhibited lubiprostone-stimulated Cl^- currents in HEK293 cells in a concentration-dependent manner, while morphine (5 μM) had no effect on this current. Other opioid agonists, such as oxycodone, oxymorphone and hydromorphone (at 5 μM) had no effects on lubiprostone-stimulated Cl^- currents in T84 cells. In addition to methadone,

fentanyl and loperamide also caused an inhibition of the lubiprostone-stimulated Cl⁻ currents in T84 cells.

Lubiprostone caused a reversal of the short circuit current (a marker for chloride secretion) in isolated segments of human jejunum, and this effect of lubiprostone was not blocked by tetrodotoxin, a blocker of enteric nerves, suggesting that the effect of lubiprostone is not mediated via enteric neurons, and it acts directly by activating intestinal chloride channels.

Thus, lubiprostone appears to be less effective in reversing the constipating effect of methadone than that of morphine in mice. In *in vitro* electrophysiology studies using T84 and HEK-29 cells, methadone was shown to cause an inhibition of lubiprostone-induced Cl⁻ currents, while morphine had no effect on this current. In addition to methadone, fentanyl and loperamide also caused an inhibition of the lubiprostone-stimulated Cl⁻ currents in T84 cells. Thus, there is a possibility that methadone and other diphenylheptane opioids may reduce the effectiveness of lubiprostone.

The nonclinical safety of lubiprostone has been established in previous *in vitro* and *in vivo* studies reviewed under earlier submissions. The pharmacology studies submitted in the current submission suggest that lubiprostone might be effective in improving altered gastrointestinal transit caused by certain opioids. From a nonclinical perspective, the supplemental NDA application is approvable.

12 Appendix/Attachments: None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSHANTA K CHAKDER
03/18/2013

MEMORANDUM

FROM: Baichun Yang, Ph.D., DABT, Pharmacologist, Division of Cardiovascular and Renal Products (DCRP)

THROUGH: Thomas Papoian, Ph.D., DABT, Supervisory Pharmacologist, DCRP
Norman Stockbridge, M.D., Ph.D., Director, DCRP

TO: Maureen D Dewey, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Sushanta Chakder, Ph.D., DGIEP

SUBJECT: Consult for NDA021908, SD885 (eCTD sequence number 0109) – DGIEP requested that we evaluate the cardiovascular (CV) effects of lubiprostone in juvenile rats and provide comments.

DATE: Oct 11, 2012

BACKGROUND:

Amitiza (lubiprostone) Capsules are approved for the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation. The sponsor submitted a 13-week oral toxicity study with lubiprostone in juvenile albino rats prior to the initiation of clinical trials in pediatric patients. We are requested to evaluate the cardiovascular (CV) effects of lubiprostone in this juvenile rat study, and provide feedback whether there is any significant CV risk in pediatric subjects treated with the drug and if any additional precautions/ monitoring would be required while conducting studies in pediatric patients.

RELEVANT SUBMISSION: Lubiprostone: A 13-Week Oral (Gavage) Toxicity Study in Juvenile Albino Rats (Testing Facility Study No. 670665)

Lubiprostone is a prostaglandin analog. It is a specific activator of CIC-2 chloride channels. In the 13-week oral toxicity study in juvenile Sprague Dawley rats albino rats (# 670665), with a 6-week recovery period, the pups (14 days old) were treated with lubiprostone at doses 0, 5, 50, and 500 µg/kg/day (Dose volume 1 ml/kg; n=10 rats/group/sex). For the CV safety pharmacology assessments, 3 rats/sex/group were implanted on dosing Day 7 (without disruption in the dosing regimen). On dosing Days 14 and 88, the blood pressure of 3 implanted animals/sex/group was recorded and all derived parameters (heart rate, and systolic, diastolic, mean and pulse pressures) were recorded, as 1-minute means, from the completion of dosing (within 3 minutes) to approximately 22 hours after dosing. No measurements were performed at the end of the recovery period.

Dr. Sushanta Chakder of DGIEP reviewed this study (# 670665). The summary of Dr. Sushanta Chakder' review is quoted here in italic.

In the 13-week repeated dose oral (gavage) toxicity study of lubiprostone in juvenile Sprague Dawley rats, with a 6-week recovery period, the pups (14 days old) were treated with 0.005, 0.05 and 0.5 mg/kg/day doses. There were deaths of one male and one female pup at 0.5 mg/kg/day during the study period. Treatment-related clinical signs, including salivation, wet fur and red staining of fur in the muzzle were observed at 0.05 and 0.005 mg/kg/day doses. Signs of dehydration and staining of the fur/skin in the urogenital/tail/sacral area were observed at 0.5 mg/kg/day. There was a trend for delayed physical development (decreased crown-to-rump length, compared to controls) in male pups at 0.05 and 0.5 mg/kg/day doses. Decreased hemoglobin and hematocrit, total protein, albumin and globulin levels were observed in males and females at 0.5 mg/kg/day. Decreased urine volume and increased urine specific gravity were observed in males and females in Weeks 6 and 13 at 0.05 and 0.5 mg/kg/day. No changes in the biochemical markers of bone resorption and bone formation were observed in any group. Whole body densitometric analysis (DXA scan) showed lower bone mineral concentration and bone mineral density for the high dose males (not statistically significant), compared with the control. DXA evaluation of the lumbar spine showed trends for lower bone densitometry parameters for males treated with the high dose of lubiprostone, as compared to controls. Higher trends for BMC, area and BMD were also observed for this group during the recovery period. Peripheral quantitative computed tomography (pQCT) determinations showed significantly lower values for total and trabecular bone mineral density for females at 0.5 mg/kg/day. At the tibia diaphysis of 0.5 mg/kg males, a slight but statistically significantly lower value (5%) for cortical thickness was noted. This was consistent with the trends for smaller bone diameter (lower values for total slice area and periosteal circumference). At the end of the recovery period, the bone densitometry or bone geometry parameters were similar to those observed during the treatment period. The heart rates of the 0.5 mg/kg male and female pups were significantly higher than controls on Days 28 and 102 post partum throughout the monitoring period (22 hr). The heart rates of the 0.05 mg/kg group were also higher than control during this period. Mean systolic, diastolic and mean arterial blood pressures for the high dose group were higher than controls, generally, from 30 minutes to 1.0 hr following dosing. There was also a trend for higher blood pressures for 0.05 mg/kg males and females during this period. ECG recordings were not conducted in this study. The NOAEL was 0.005 mg/kg/day in this study, and the target organs were the bones, stomach and the cardiovascular system.

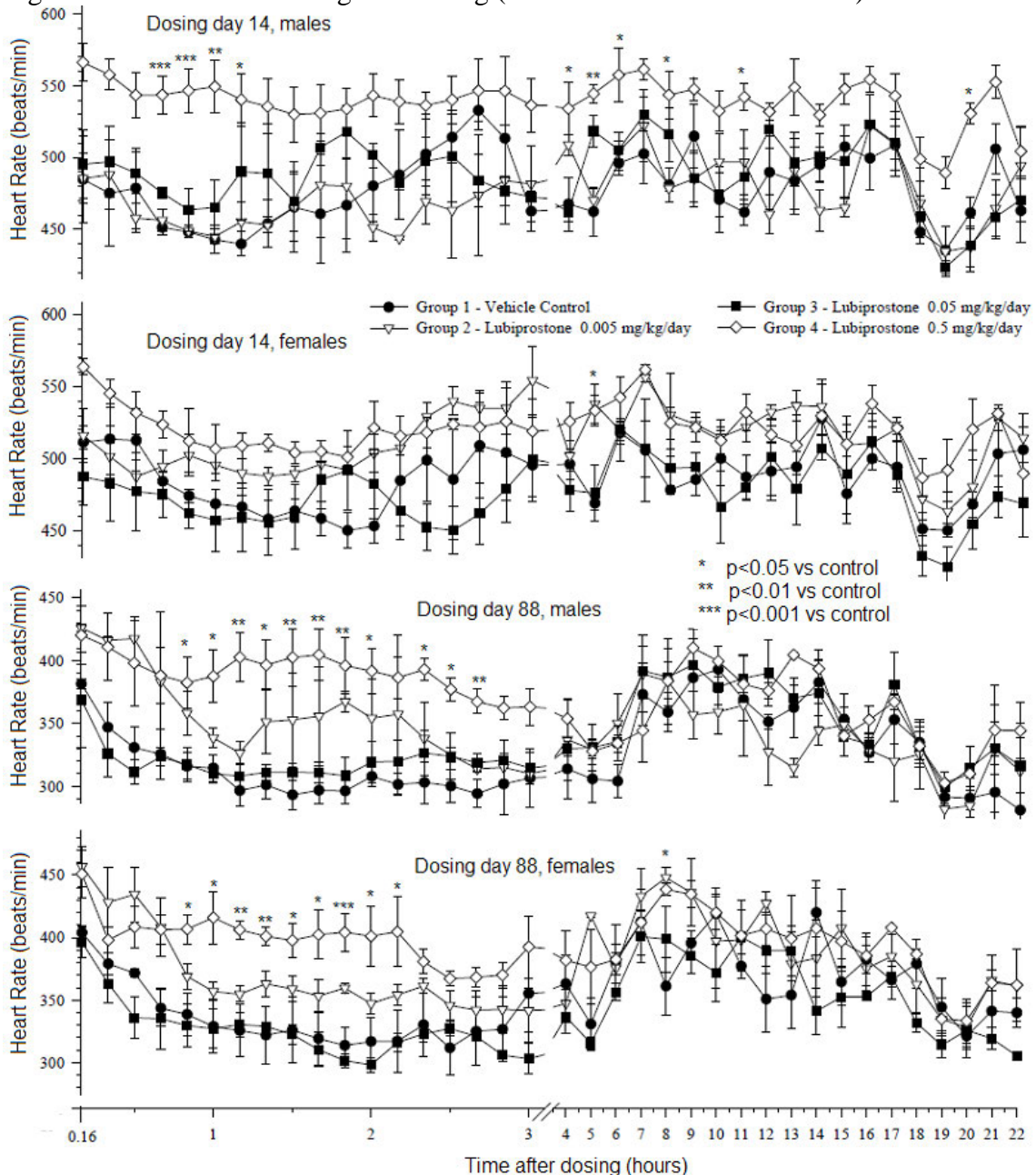
EVALUATION:

The animal number at each dose level in the CV safety pharmacology study is only 3/group/sex. Data generated from the limited sample size may confound the interpretation. There were no data collected at the pre-dose point. The comparison can only be made between concurrent control and treated animals.

Compared with concurrent control values, heart rate was markedly higher in both male and female rats at lubiprostone dose 500 µg/kg/day on both dosing days 14 and 88 (Figure 1). The maximum differences were noted at 1 hour post dose (19%) on dosing day 14 and 2 hours post dose (33%) on dosing day 88, which were at or following T_{max}.

Although the heart rate from immediately following dosing to T_{max} may be affected by dosing-associated stress, the marked differences in heart rate between control and treated animals at and following T_{max} can be attributed to lubiprostone. This difference should not be considered as biologically insignificant. The lack of dose-response relationship regarding heart rate at lower dose levels could be attributed to low exposure or limited sample size. There were also higher blood pressures in treated animals than controls. Since the higher blood pressures were transient and mild, they may be secondary to the elevated heart rate, and are of limited biological significance. There were deaths of one male and one female pup at 500 µg/kg/day during the study period. LOAEL for CV effect was 50 µg/kg/day.

Figure 1. Heart rate following oral dosing (modified from the submission)



Lubiprostone is a prostaglandin E1 analog, was shown to have high affinities for prostaglandin E receptors 2 and 3, and was ~50% as potent as prostaglandin E1 regarding smooth muscle contraction (1). In anesthetized dogs, oral lubiprostone up to 1000 µg/kg had no effect on heart rate and ECG parameters (1). Although there is no information regarding receptor binding and ion channel activity of lubiprostone, lubiprostone, as a prostanoid, may have effects on vascular and other smooth muscle, and juveniles may be more sensitive to lubiprostone. Therefore, the elevated heart rate in lubiprostone-treated juvenile rats indicates a potential CV risk in pediatric subjects treated with lubiprostone.

The lubiprostone dose for adults is 24 µg, BID, or ~0.8 µg/kg/day. Considering a dose of 50 µg/kg/day to be LOAEL in juvenile rats, the NOAEL is likely to be 1/10 of LOAEL or 5 µg/kg/day. The human equivalent dose at NOAEL will be 0.8 µg/kg/day. Applying a safety factor of 10 for variation in humans, a starting dose of 0.08 µg/kg/day, or 1/10 of the adult dose, should be reasonably safe for the proposed pediatric study.

RECOMMENDATION:

The clinical trials with lubiprostone in pediatric patients should start with a dose-escalation study. We recommend the starting dose in pediatric patients to be 1/10 of the adult dose, or 0.08 µg/kg/day. Heart rate and blood pressure should be monitored during the study.

To help further understand the risk for pediatric patients, screening assays for receptor binding and ion channel activities should be performed with lubiprostone.

References

(1) Sushanta Chakder. 2005. Pharmacology review for NDA021908.
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021908s000_Amitiza_PHARMR.pdf, Assessed on Oct 11, 2012

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BAICHUN YANG

10/11/2012

The related submission should be SD885 (eCTD sequence number 0109).

THOMAS PAPOIAN

10/12/2012

NORMAN L STOCKBRIDGE

10/12/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 21-908

**Applicant: Sucampo
Pharmaceuticals, Inc.**

Stamp Date: 07/20/2012

**Drug Name: Amitiza
(lubiprostone) Capsules**

**NDA/BLA Type: Prior Approval
Supplement (Seq. 0112)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		For nonclinical studies, the applicant referred to studies previously submitted to the agency.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			N/A

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _YES

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant. N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Sushanta K. Chakder, Ph.D.	8/23/12
Reviewing Pharmacologist	Date
Sushanta K. Chakder, Ph.D.	8/23/12
Team Leader/Supervisor	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSHANTA K CHAKDER
08/23/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021908/S-011

STATISTICAL REVIEW(S)



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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #: 21-908

Supplement #: 011

Drug Name: Amitiza[®] Lubiprostone capsule (24 mcg) twice daily

Indication(s): Opioid-Induced Constipation (OIC)

Applicant: Sucampo Pharma Americas, Inc.

Date(s): Stamp Date: 7/20/2012
PDUFA Date: 4/19/2013 (extended by 3 months):

Review Priority: Priority

Biometrics Division: Division of Biometrics 3

Statistical Reviewer: Freda W. Cooner, Ph.D.

Concurring Reviewers: Mike Welch, Ph.D.

Medical Division: Division of Gastroenterology and Inborn Error Products (DGIEP)

Clinical Team: Farrokh Sohrabi, M.D., Medical Reviewer
Robert Fiorentino, M.D., Team Leader

Project Manager: Maureen Dewey

Keywords:
Clinical studies, NDA review

Table of Contents

1	EXECUTIVE SUMMARY	3
2	INTRODUCTION	3
2.1	OVERVIEW.....	3
2.2	DATA SOURCES	5
3	STATISTICAL EVALUATION	5
3.1	DATA AND ANALYSIS QUALITY	5
3.2	EVALUATION OF EFFICACY	6
3.2.1	<i>Study Design and Endpoints</i>	7
3.2.2	<i>Statistical Methodologies</i>	9
3.2.3	<i>Patient Disposition, Demographic and Baseline Characteristics</i>	11
3.2.4	<i>Results and Conclusions</i>	13
3.3	OVERVIEW OF SAFETY.....	15
4	FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	16
4.1	GENDER, RACE, AGE, AND GEOGRAPHIC REGION	16
4.2	OTHER SPECIAL/SUBGROUP POPULATIONS	20
5	SUMMARY AND CONCLUSIONS	21
5.1	STATISTICAL ISSUES	21
5.2	COLLECTIVE EVIDENCE	21
5.3	CONCLUSIONS AND RECOMMENDATIONS	22
5.4	LABELING RECOMMENDATIONS	22

1 EXECUTIVE SUMMARY

Lubiprostone 24 mcg BID, under the trade name Amitiza[®], was approved in the US since January 2006 for the treatment of chronic idiopathic constipation (CIC). This application consisted of three 12-week studies (OBD-1033, OBD-0631, and OBD-0632) and a 36-week open-label safety extension study (OBD-06S1), to support the indication of oral lubiprostone in the treatment of opioid induced constipation (OIC), which is similar to CIC. A statistically significant difference, favoring lubiprostone over placebo, was observed for the primary efficacy endpoint (change from baseline in the frequency of spontaneous bowel movements [SBMs] at Week 8) in Study OBD-0631 but significance was not shown in Study OBD-0632. A subsequent investigation suggested that methadone likely inhibits the treatment effect of lubiprostone. Hence, Study OBD-1033 was subsequently conducted in subjects receiving non-methadone opioid therapy and the primary endpoint was changed to an overall SBM response evaluation over the entire 12-week study period upon discussion and agreement with the FDA. Study OBD-1033 showed a statistically significant difference in this endpoint in favor of lubiprostone using the sponsor's method specified in the final protocol. However, the significance was only marginal. Statistical significance could be observed in the post hoc analyses for Study OBD-0631 in the efficacy endpoint of overall SBM response, although these findings should be considered exploratory. Statistical significance was not observed for Study OBD-1033 for the secondary efficacy endpoint of change from baseline in the SBM frequency at Week 8. Study OBD-0632 did not show statistical significance in either of these efficacy endpoints. The statistical evidence of the treatment efficacy in lubiprostone, presented by the three 12-week clinical trials, is not strong; however, it is sufficient to conclude that lubiprostone demonstrated benefit in improving weekly SBM frequency for OIC patients.

2 INTRODUCTION

2.1 Overview

Lubiprostone is a member of a group of structurally- and pharmacologically-related compounds known as prostones. By increasing intestinal fluid secretion, lubiprostone potentially enhances motility in the intestine, thereby facilitating the passage of stool.

Opioids, widely used in the management of acute and chronic pain, inhibit gastrointestinal motility by binding to opioid receptors. Consequently, patients can experience opioid induced constipation (OIC), which is associated with a range of additional signs and symptoms. Studies indicate that tolerance develops to the analgesic effects of opioids, and opioid adverse effects. However, tolerance rarely develops for constipation.

The clinical development program for lubiprostone began in 1999 with the conduct of the initial phase 1 safety, tolerance, pharmacodynamic (PD), and pharmacokinetic (PK) study in healthy normal volunteers. It was followed by subsequent studies to support a NDA to the FDA for chronic idiopathic constipation (CIC). To date, lubiprostone (24 mcg capsules administered

twice daily [BID]) has been evaluated in approximately 3,500 subjects in clinical studies. The characteristics of OIC are similar to CIC. Lubiprostone 24 mcg BID, under the trade name Amitiza[®], was approved in the United States in January 2006, for the treatment of CIC in the adult population. In addition, lubiprostone 8 mcg BID was approved in April 2008 to treat irritable bowel syndrome with constipation (IBS-C) in adult women. Lubiprostone was recently approved (marketing authorization granted in November, 2009), and is marketed in Switzerland for the treatment of CIC as well.

In November, 2003, a complementary development program aiming at the CIC indication was started in Japan with the conduction of a single-dose phase 1 safety and PK study in healthy Japanese subjects. The Japanese program comprised a total of five clinical trials and was completed in August, 2010. Lubiprostone is now approved for marketing in Japan. A marketing application for CIC is currently under review in the United Kingdom.

Opioid induced constipation (OIC), [REDACTED] (b) (4)

[REDACTED] Following several rounds of communication with the FDA, the sponsor is currently seeking approval of lubiprostone for a new indication: the treatment of OIC (b) (4)

[REDACTED] in adults with chronic, non-cancer pain.

The clinical efficacy of oral lubiprostone in the treatment of OIC was supported by three adequate and well-controlled 12-week studies (OBD-1033, OBD-0631, and OBD-0632) and a 36-week open-label safety extension study (OBD-06S1). The three pivotal studies used similar study designs, i.e. randomized, double-blind, placebo-controlled, multicenter (OBD-1033: U.S. and Europe; OBD-0631 and OBD-0632: U.S. and Canada), 12-week studies. The development program initially comprised two phase 3 studies (OBD-0631 and OBD-0632) and one safety extension study (OBD-06S1). A statistically significant difference, favoring lubiprostone over placebo, was observed for the primary efficacy endpoint (change from baseline in the frequency of spontaneous bowel movements [SBMs] at Week 8) in Study OBD-0631 but was not observed in Study OBD-0632. A subsequent laboratory investigation suggested that methadone likely inhibits the treatment effect of lubiprostone. Hence, Study OBD-1033 was subsequently conducted in subjects receiving non-methadone opioid therapy and the primary endpoint was changed to an overall SBM response evaluation over the entire 12-week study period upon discussion and agreement with the FDA. The three phase 3 studies and one long-term safety extension study are summarized in the following table.

Type of Study	Study Identifier	Study Objective	Study Design & Type of Control	Test Product; Dosage Regimen; Route of Administration	Subjects Enrolled (Treated)	Patient Population	Duration of Treatment
Efficacy & Safety	SPI/0211OBD-0631	Efficacy & Safety	Double-blind, Randomized, Multicenter, Placebo-controlled	Capsule; Placebo BID, 24 mcg BID; Multiple-Dose, Oral	443 (439)	Patients with opioid-induced bowel disorder	12 Weeks
Efficacy & Safety	SPI/0211OBD-0632	Efficacy & Safety	Double-blind, Randomized, Multicenter, Placebo-controlled	Capsule; Placebo BID, 24 mcg BID; Multiple-Dose, Oral	451 (437)	Patients with opioid-induced bowel disorder	12 Weeks
Efficacy & Safety	SMR/0211OBD-1033	Efficacy & Safety	Double-blind, Randomized, Multicenter, Placebo-controlled	Capsule; Placebo BID, 24 mcg BID; Multiple-Dose, Oral	447 (439)	Patients with opioid-induced bowel disorder	12 Weeks
Long-term Extension	SPI/0211OBD-06S1	Long-term Safety & Efficacy	Open-label, Multicenter, Extension	Capsule; 24 mcg BID; Multiple-Dose, Oral	443 (439)	Patients with opioid-induced bowel disorder	36 Weeks

Source: Reviewer's Table

2.2 Data Sources

The tabulation data in the CDISC-SDTM format and the analysis datasets in legacy format, as well as the study reports for this submission have been submitted in electronic Common Technical Document (eCTD) format to the EDR at: <\\Cdsesub1\evsprod\NDA021908\0112>.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Study OBD-1033 started on December 7, 2010 and ended on November 16, 2011. The original protocol, dated August 20, 2010, was amended twice: one on October 19, 2010, the other on June 13, 2011. The first amendment, which was prior to the study initiation, included some administrative changes; updated the exclusion criteria to include any subjects receiving methadone congeners; and noted that the randomization and analyses would be stratified by baseline weekly SBM frequency. The second amendment, which was around the same time as the first version of the statistical analysis plan (SAP; dated June 10, 2011), updated primary and

secondary analyses section to include statistical methods details. Those include removing the stratification on baseline SBM frequency from all the applicable analyses. After the study ended, the SAP was amended on December 6, 2011, to include some minor changes. Additional changes made in the clinical study reports included an additional site pooling strategy and some additional exploratory analyses.

Study OBD-0631 started on August 3, 2007, Study OBD-0632 started three days later on August 6, 2007, and both ended on March 6, 2009. Although these two studies were conducted concurrently, the original protocols and the first amendments were issued on different dates: Study OBD-0631 had the original protocol dated April 25, 2007 and the first amendment on May 7, 2007; while Study OBD-0632 had the original protocol dated May 7, 2007 and the first amendment on May 15, 2007. However, the two protocols were identical and amended three times. The first amendment prior to the studies' initiation was purely administrative. The second amendment, both dated August 30, 2007, shortly after the studies' initiation, included updates in the statistical section, such as secondary endpoints. The third amendment, both dated June 9, 2008, increased the studies sample size from 380 to 420. The SAPs for these two studies were also identical and both amended twice with some minor changes; however, the dates of the documents were noticeably different. For Study OBD-0631, the original SAP was dated January 28, 2008, the first amendment was dated March 25, 2008, and the second amendment on December 16, 2008; while for Study OBD-632, the original SAP was dated June 6, 2008, first amendment on December 16, 2008, and second amendment on April 14, 2009 (after the study ended). The clinical study reports made some additional changes in the safety tables and added some exploratory analyses.

The supporting documentation for this application was not adequate. For example, only the final versions (posterior to the amendments) of the protocols were provided with listed changes from earlier versions. Moreover, the explanation in the define files for the variables in the datasets were insufficient to be stand-alone without reference to other documents. The protocols were not consistent with the statistical analysis plans (SAPs); in addition, there were also a few inconsistencies within each of these documents. The datasets provided were in either SDTM (tabulation datasets) or a sponsor-defined format (analysis datasets), which was similar to the ADaM format. Although the data formats were acceptable, the datasets for Studies OBD-0631 and OBD-0632 were similar but were significantly different than those for Study OBD-1033. Following the filing decision, a 74-day letter was issued on October 15, 2012, requesting additional datasets and supportive analyses with the program files. The response from the sponsor was received on November 16, 2012. The newly submitted datasets were not sorted and still lacked some necessary variables. Few programs were submitted in non-executable pdf format. Multiple Information Requests (IRs) were sent during the review process regarding various sensitivity analyses, and the sponsor's responses are deemed acceptable. Although difficult, it was possible to conduct all the statistical analyses needed with the datasets provided.

3.2 Evaluation of Efficacy

A clinical development program for lubiprostone in the treatment of OIC began in 2007. The development program initially comprised two phase 3 studies (Studies OBD-0631 and OBD-0632). These two studies employed the primary efficacy endpoint of change from baseline in the

frequency of SBMs at week 8, although the studies were designed for 12-week of treatment. The sponsor observed a statistically significant difference in this endpoint favoring lubiprostone over placebo in Study OBD-0631 only, but not in Study OBD-0632,

Per the recommendation of the FDA, the sponsor conducted an additional phase 3 study (OBD-1033). Based on the sponsor's clinical findings and laboratory investigation, this study was conducted in non-methadone-treated subjects with OIC. Moreover, this study used the primary efficacy endpoint of overall SBM responder over 12-week treatment period, which was recommended by the FDA and modified by the sponsor.

3.2.1 Study Design and Endpoints

Three phase 3, multicenter, randomized, double-blind, placebo-controlled studies of the efficacy and safety of lubiprostone for the treatment of OIC were conducted in adult subjects aged 18 years and older who had chronic non-cancer-related pain that was treated consistently with an oral, transdermal, intravenous, or subcutaneous opioid for at least 30 days before the screening evaluation and that would require continued treatment with the opioid throughout study period. In all three studies, the diagnosis of OIC required that subjects have an average of three or fewer SBMs per week during the screening period and at least one of the following three OIC-associated signs and symptoms for at least 25% of the SBMs during each week of the screening period: hard or very hard stools, sensation of incomplete evacuation, and/or moderate to very severe straining associated with the SBMs. A BM had to occur without the use of laxatives or stool softeners within the prior 24-hour period to be a SBM. Subjects who had a history of chronic constipation (at least 90 days) were required to have experienced an exacerbation in their constipation after initiation of opioid therapy in order to qualify for study entry.

Subjects who were receiving treatment with opioids for cancer-related pain, abdominal pain, scleroderma, or the management of drug addiction, were specifically excluded from the study. Other exclusion criteria included known or suspected anatomic or organic disorders of the large or small bowel associated with a mechanical bowel obstruction or pseudo-obstruction, or with a large or small bowel disorder such as ulcerative colitis or Crohn's disease, constipation attributable to causes other than opioid use, and/or significant comorbid disease.

Each of the phase 3 studies consisted of a 3-week screening period followed by a randomization visit (Visit 2; Week 0), a 12-week double-blind treatment period with interim telephone assessments (Visits 3, 5, and 7; Weeks 1, 6, and 10), clinic examinations (Visits 4, 6, and 8; Weeks 4, 8, and 12), and a follow-up visit (Visit 9; Week 14) at 2-week post-treatment. Total study duration, including a 3-week screening period, a 12-week double-blind treatment, and a 2-week follow-up period, was approximately 18 weeks. Subjects completed treatment in Studies OBD-0631 and OBD-0632 had the option to enroll in a long-term, safety extension study (Study OBD-06S1) for an additional nine months. The subjects who entered Study OBD-06S1 were not required to complete the 2-week post-treatment follow-up period before entering the study.

Subjects who were initially determined to meet the study inclusion and exclusion criteria underwent a 3-week screening/washout period during which they were required to discontinue use of any medications that are known to have an effect on gastric motility. In addition to the

aforementioned exclusion criteria, which applied to all three of the phase 3 studies, Study OBD-1033 also excluded enrollment of subjects who were receiving treatment with methadone, methadone hydrochloride, or a congener of methadone either alone or as part of an opioid regimen. Other than this criterion, the inclusion and exclusion criteria were essentially identical across the three phase 3 studies.

Subjects were provided with a hand-held electronic diary (eDiary), which queried the subjects about the status of their constipation and current therapy, and were required to use the eDiary to report the occurrence of SBMs each evening during the screening period. Information from the eDiary was automatically transmitted nightly to a secure study database where it was available for review by study personnel as needed. Subjects who were more than 70% compliant with their screening diary entries and who qualified as having OIC as per entries that were made during the 2-week period immediately before their Randomization Visit were randomized in a 1:1 ratio via an interactive voice response system (IVRS) or interactive web response system (IWRS) to one of the two treatment groups:

- Lubiprostone 24 mcg BID (total daily dose of 48 mcg)
- Matching placebo BID

Subjects in both treatment groups were to receive double-blind treatment with study medication for 12 weeks. Subjects were to continue to receive treatment with their opioid analgesic during the double-blind treatment period; subjects who discontinued the use of their opioid analgesic during the double-blind treatment period were to be immediately withdrawn from the study.

Subjects were to take one capsule of study medication in the morning and one capsule of study medication in the evening with meals and with at least eight ounces of fluid. Doses were to be taken at least five hours apart. Missed doses were to be made up as soon as possible, but the subjects were instructed not to take both doses at the same time. The dose of study medication could be reduced to one capsule daily (total daily dose of lubiprostone, 24 mcg) if the subject experienced severe diarrhea, severe nausea, or other adverse events (AEs) for three or more days. Once a dose reduction occurred, the dose was to remain at the reduced dose for the remainder of the study in Studies OBD-0631 and OBD-0632. Subjects in Study OBD-1033 could resume administration of the BID dose regimen at the investigator's discretion.

Use of a rescue medication was allowed if no BM occurred within a 3-day period. Subjects were first to attempt to induce a BM by using the clinically recommended dose of a bisacodyl suppository. If this was unsuccessful, an enema was to be administered. If neither was successful, the investigator could prescribe another medication for immediate short-term use.

Subjects were to complete the eDiary each evening during the treatment period. The diary could be completed for the preceding day if the prior night's assessment had not been completed. As in screening period, the diary data were automatically transmitted nightly to a secure study database where it was available for review by study personnel.

Subjects were contacted by telephone at the end of treatment Weeks 1, 6, and 10 to review compliance with the study medication and the eDiary completion. Clinic visits were scheduled at the end of treatment Weeks 4, 8, and 12. A follow-up visit was conducted at two weeks post-

treatment, except the subjects in Studies OBD-0631 and OBD-0632 who entered the open-label extension study (OBD-06S1).

In Study OBD-1033, the protocol-specified primary efficacy endpoint was overall SBM response, which was defined as at least a moderate response (at least one SBM improvement per week over baseline weekly SBM frequency) for all treatment weeks with available data in addition to a full response (at least three SBMs per week) for at least nine of the 12 treatment weeks. Note that the FDA recommended overall SBM response definition was at least three SBMs per week and an increase from baseline of at least one SBM per week in that week for at least nine out of the 12 treatment weeks. In Studies OBD-0631 and OBD-0632, the protocol-specified primary efficacy endpoint was the change from baseline in the weekly frequency of SBMs at Week 8 for subjects without dose reductions. However, assessing primary endpoint in a subgroup based on the patient's response after randomization is not a valid procedure, and all randomized subjects should be included in the primary analysis. The endpoint of overall SBM response rate, which was primary for Study OBD-1033, was not pre-specified in the protocol for Studies OBD-0631 and OBD-0632;

Secondary efficacy endpoints of all three phase 3 studies were largely the same, except for the following differences:

- Studies OBD-0631 and OBD-0632 included a secondary endpoint of overall responder rate that was defined as a subject with at least moderate response for at least 50% of the weeks on the study, where weekly SBM response was classified as:
 - Full response: SBM frequency at least four for that week;
 - Moderate response: SBM frequency at least three but less than four for that week;
 - Non-response: SBM frequency less than three for that week, dropped out during or before the given week due to lack of efficacy, or used rescue medication during or within 24 hours prior to the given week;
- The endpoint of change from baseline in weekly SBM frequency at Week 8 was secondary for Study OBD-1033, but primary for Studies OBD-631 and OBD-0632;
- Study OBD-1033 also added two secondary endpoints of weekly SBM responder rate that described above, and health-related quality of life.

Other secondary efficacy endpoints listed in the protocol included change from baseline in weekly SBM frequency at Week 12 and overall; percentage of subjects with first post-dose SBM within 24 hours and 48 hours after first dose; overall mean change from baseline in: straining associated with SBMs, stool consistency of SBMs, constipation severity, abdominal bloating, abdominal discomfort, and bowel habit regularity; and overall treatment effectiveness assessed in the patient diary. The protocols did not specify any multiplicity adjustment approach for the whole set of secondary efficacy endpoints.

3.2.2 Statistical Methodologies

The pre-specified primary efficacy endpoint in Study OBD-1033 was the overall SBM response rate. Responders, was determined based on subjects' daily record of BMs. Spontaneous BM was defined as any BM that did not occur within 24 hours after rescue medication use. The sample size for this study was estimated using the anticipated average response rate of 17% for

the placebo group and 33% for the lubiprostone group. A sample size of 336 evaluable subjects (168 subjects per group) would provide at least 95% study power under a two-sided alpha of 0.05. Assuming 20% dropout rate by Week 9, the study planned to enroll 420 subjects.

The pre-specified primary efficacy endpoint in Studies OBD-0631 and OBD-0632 was the change in frequency of SBMs from baseline to Week 8 on the sponsor-specified ITT population who did not have a dose reduction prior to Week 8. The sample size for these two studies was estimated using t-test and based on the anticipated treatment effect of 1.5 with standard deviation of 3.5. A sample size of 260 evaluable subjects (130 subjects per group) would provide at least 93% study power under a two-sided alpha of 0.05. Assuming 30% dropout rate by Week 8 and an additional 8% of subjects with dose reduction by Week 8, each study planned to enroll 420 subjects. Note that originally the planned study size was 380 subjects. The sponsor did not provide proper documentation on the sample size increase. However, based on this reviewer's calculation, it appears that the original sample size calculation did not take the 8% dose reduction subjects into account.

The sponsor defined the intent-to-treat (ITT) population for the primary analysis for all three studies. Their definition was based on all randomized subjects who took at least one dose of double-blinded study medication and had at least one treatment-period diary entry. Moreover, as mentioned earlier, for Studies OBD-0631 and OBD-0632, the sponsor only included those ITT subjects without dose reduction prior to Week 8 for the primary analysis. A true ITT population should include all randomized subjects. Analyses use both populations (all randomized subjects and sponsor-defined ITT population) were conducted based on the treatment as randomization. In the amended SAP for Study OBD-1033, the sponsor identified the data from Sites 3019 and 3119 as questionable after their routine monitoring and auditing, and subsequently conducted sensitivity analyses with the data from these two sites excluded.

In addition, the sponsor defined per-protocol (PP) population as ITT subjects without major protocol violations (identified after the study ended, allegedly during the blinded data review); and completer population as subjects who completed the treatment regimen through Week 12. Supportive analyses on these two populations were conducted.

This sponsor used a unique hourly-based calculation for weekly SBM frequency rates for all three phase 3 studies. In particular, weekly SBM frequency rates were calculated as 168 multiplied by the number of SBMs and divided by the number of hours observed in that week. The number of hours observed in a certain week, where the subject was actively enrolled in the study and taking study medication, was calculated programmatically based on the diary entry windows for each day and each week. Weeks were calculated as 168-hour intervals starting with the exact time of the first intake of study medication. The sponsor responded to the FDA's IR on the details of weekly number of hours observed calculation and the algorithm seems acceptable. Sensitivity analyses using a daily-based calculation of weekly SBM frequency rates were also conducted. Baseline was defined as the weekly average SBM frequency from the diary entries during the last two weeks preceding the randomization.

For Study OBD-1033, if the number of hours observed was less than 85 (roughly three and a half days), then the data would be considered insufficient and the SBM rate would be missing for that

week. The subjects would be considered non-responder for the weeks with missing SBM rate. Subjects with fewer than nine weeks of weekly SBM rates were automatically considered overall non-responders. Subjects were required to demonstrate at least moderate response (at least one SBM improvement over baseline SBM frequency) for all treatment weeks with available data, and a full response (at least three SBMs per week) for at least nine of the 12 treatment weeks to be defined as treatment responders. The overall SBM response rates were compared between treatment groups by a Cochran-Mantel-Haenszel (CMH) test stratified by pooled site.

For Studies OBD-0631 and OBD-0632, for the primary efficacy endpoint of change from baseline in weekly SBM frequency rate at Week 8 was analyzed by an analysis of covariance (ANCOVA) model using baseline SBM rate as a covariate. This endpoint was also identified as a secondary endpoint for Study OBD-1033, and the treatment effect was estimated from a similar ANCOVA model but stratified by pooled site. The sponsor also specified, for all three studies, that the normality of the data was examined by a Shapiro-Wilk test. If statistically significant, which was declared true by the sponsor for all three studies, a Wilcoxon signed-rank test (for Studies OBD-0631 and OBD-0632 only) or the van Elteren test stratified by pooled sites, would be employed. This reviewer did not agree with the sponsor's judgment on the data normality. Moreover, ANCOVA model is fairly reliable in general. Hence, ANCOVA model will be assessed for the primary analysis in this review.

The sponsor did not specify a multiplicity adjustment strategy for the whole list of secondary efficacy endpoints in any of these three studies. However, for the endpoints that were assessed at different time point, such as change from baseline in SBM frequency at Weeks 8, 12, and overall, the sponsor stated that Hommel's stage-wise method was used to adjust multiplicity.

(b) (4)

For all three studies, the last-observation-carried-forward (LOCF) rule was implemented on the missing data for the secondary endpoints and as a sensitivity analysis for the primary efficacy endpoint. The sponsor specified that to implement LOCF rule, if at least 25 but less than 85 hours were observed during a week and at least 85 hours were observed during the prior week, then data were imputed from the prior week to provide a total of 85 hours of data. If the number of hours in a week was less than 25, then that week would be considered missing. For the primary analysis on the primary efficacy endpoint in Study OBD-1033, the subject was treated as a non-responder for any weeks with missing SBM rate, and was counted in the overall responder definition.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 1341 subjects with OIC were randomized into the three phase 3 studies: 662 subjects were randomized to receive placebo and 679 subjects were randomized to receive lubiprostone. Comparable percentages of subjects in the placebo and the lubiprostone groups (74.2% and 69.7%, respectively) completed the 12-week studies. The study population in three pivotal studies combined was approximately two-thirds female and one-third male, primarily white (82.6%). Subjects ranged in age from 19 to 86 years with mean of 50.4 years. Approximately

97% of the subjects were enrolled in US and Canada. The patient disposition and baseline characteristics were comparable across treatment groups and studies.

For Study OBD-1033, a total of 447 subjects were enrolled randomized at 105 sites (91 in the US and 14 in European Union). Among these 447 subjects, 226 were randomized to receive placebo and 221 to receive lubiprostone 24 mcg BID. Eight of the 447 randomized subjects did not receive treatment (six in the placebo and two in the lubiprostone group). So a total of 439 subjects were included in the sponsor-defined ITT population. Out of these 439 subjects, 15 (3 in the placebo and 12 in the lubiprostone group) had dose-reduction before Week 8.

A total of 353 (79.0%) subjects completed Study OBD-1033 and 94 (21.0%) discontinued. Reasons for discontinuation were mostly due to subject choice (6.0%), AEs (3.4%), lack of efficacy (2.5%) or other reasons (3.1%). Most of the discontinuation rates were comparable between treatment groups, except that eleven subjects (5.0%) in the lubiprostone group and four subjects (1.8%) in the placebo group discontinued the study due to AEs.

Study OBD-1033 consisted of 63.3% females. The age range was 20 to 82 years with median age of 52 years across groups. The subjects were predominantly white (81.7%) and mostly in the US (92.1%) with four (0.9%) subjects in Belgium, seven (1.6%) subjects in Germany, five (1.1%) subjects in United Kingdom, four (0.9%) subjects in Poland, and 15 (3.4%) subjects in Czech Republic. A majority of subjects at baseline (97.5%) reported less than three SBMs per week, with median frequency of 1.5 SBMs per week. Overall, 99.3% of subjects received opioid medications classified as analgesics. The most commonly used opioid medications were oxycodone (18.2% in the placebo and 17.4% in the lubiprostone group), hydrocodone (18.2% in the placebo and 17.4% in the lubiprostone group) and hydrocodone with acetaminophen (15.9% in the placebo and 12.8% in the lubiprostone group). Most of the baseline characteristics were comparable between treatment groups.

For Study OBD-0631, a total of 443 subjects were enrolled and randomized at 80 sites (77 in the US and 3 in Canada). Among these 443 subjects, 220 were randomized to receive placebo and 223 to receive lubiprostone 24 mcg BID. Four of the 443 randomized subjects did not receive treatment (three in the placebo and one in the lubiprostone group). One subject in the lubiprostone group was randomized, but no post-baseline data were reported. These subjects were excluded from the sponsor-defined ITT population. Out of the 443 subjects, 9 (all in the lubiprostone group) had dose-reduction before Week 8.

A total of 306 (69.1%) subjects completed Study OBD-0631 and 137 (30.9%) discontinued. Reasons for discontinuation were mostly due to subject choice (6.1%), AEs (5.2%), lost to follow-up (4.3%) or other reasons (7.7%). Overall, the discontinuation rates were comparable between treatment groups.

Study OBD-0631 consisted of 63.7% females. The age range was 19 to 77 years with median age of 49 years across groups. The subjects were predominantly white (78.6%) and mostly in the US (99.1%) with four (0.9%) subjects in Canada. A majority of subjects at baseline (96.7%) reported less than three SBMs per week, with median frequency of 1.5 SBMs per week. Overall, more than 87% of subjects received opioid medications classified as analgesics. The most

commonly used opioid medications were oxycodone (18.4% in the placebo and 15.8% in the lubiprostone group), hydrocodone with acetaminophen (10.1% in the placebo and 18.1% in the lubiprostone group) and oxycontin (10.6% in the placebo and 12.7% in the lubiprostone group). Most of the baseline characteristics were comparable between treatment groups.

For Study OBD-0632, a total of 451 subjects were enrolled and randomized at 88 sites (84 in the US and 4 in Canada). Among these 451 subjects, 216 were randomized to receive placebo and 235 to receive lubiprostone 24 mcg BID. Fourteen of the 451 subjects did not receive treatment (three in the placebo and 11 in the lubiprostone group). One subject in each group was randomized, but no post-baseline data were reported. All these subjects were excluded from the sponsor-defined ITT population. Out of these 437 sponsor-defined ITT subjects, 8 (one in the placebo and seven in the lubiprostone group) had dose-reduction before Week 8.

A total of 305 (67.6%) subjects completed Study OBD-0632 and 146 (32.4%) discontinued. Reasons for discontinuation was mostly due to subject choice (9.1%), AEs (3.1%), lost to follow-up (5.5%) or other reasons (10.0%). Overall, the discontinuation rates were fairly comparable between treatment groups.

Study OBD-0632 consisted of 60.1% females. The age range was 21 to 89 years with median age of 50 years across groups. The subjects were predominantly white (86.7%) and mostly in the US (98.0%) with nine (2.0%) subjects in Canada. A majority of subjects at baseline (93.3%) reported less than three SBMs per week, with median frequency of 1.5 SBMs per week. Overall, more than 85% of subjects received opioid medications classified as analgesics. The most commonly used opioid medications were oxycodone (13.7% in the placebo and 9.9% in the lubiprostone group), hydrocodone with acetaminophen (11.8% in the placebo and 5.8% in the lubiprostone group) and oxycontin (10.8% in the placebo and 13.9% in the lubiprostone group). Most of the baseline characteristics were comparable between treatment groups.

3.2.4 Results and Conclusions

The pre-specified primary efficacy endpoint for Study OBD-1033 was the overall SBM response rate over 12-week treatment period; while the pre-specified primary efficacy endpoint for Studies OBD-0631 and OBD-0632 was the change from baseline in SBM frequency at Week 8. The population the sponsor used for the primary analyses for all three studies was a sponsor-defined ITT population. Especially for Studies OBD-0631 and OBD-0632, only the sponsor-defined ITT subjects without dose-reduction prior to Week 8 were included for the primary analysis. It is important to recognize that basing analysis on a post-randomization event does not preserve the randomization, and since the event is treatment related, the subgrouping is further invalidated. The sponsor's ITT analysis should have been based on all randomized subjects regardless of which efficacy endpoint was assessed. The study results for both efficacy endpoints in the true ITT population, all randomized subjects, are presented for all three studies for comparison. However, the results from the post-hoc analyses on the non-pre-specified efficacy endpoints (overall 12-week SBM response rate for Studies OBD-0631 and OBD-632, and change from baseline in SBM frequency at Week 8 for Study OBD-1033) should be viewed with caution.

For the efficacy endpoint of overall SBM response rate, the results are presented below. Note that only Study OBD-1033 pre-specified this endpoint as primary (shaded column). For this study, the results showed a statistically significant difference favoring lubiprostone over placebo using a significance level of 5% based on a CMH test stratified by pooled site. The lubiprostone group also showed benefit over placebo group on this efficacy endpoint for Study OBD-0631, but not for Study OBD-0632.

Table 3.1 Analysis of Overall SBM Response (All Randomized Subjects)

Study	OBD-1033		OBD-0631		OBD-0632	
	Placebo	Lubiprostone	Placebo	Lubiprostone	Placebo	Lubiprostone
N	226	221	220	223	216	235
Responder, n (%)	41 (18.1%)	59 (26.7%)	32 (14.5%)	54 (24.2%)	28 (13.0%)	36 (15.3%)
Non-responder, n (%)	185 (81.9%)	162 (73.3%)	188 (85.5%)	169 (75.8%)	188 (87.0%)	199 (84.7%)
Difference, %		8.6%		9.7%		2.3%
95% CI^a, %		(0.9%, 16.3%)		(2.4%, 17.0%)		(-4.1%, 8.8%)
P-value^b		0.030		0.004		0.479

Source: Reviewer's Table

^a: CI = Confidence Interval; CI based on normal approximation

^b: Based on a CMH test stratified by pooled site

During the review cycle, the FDA's inspection has found that the data from Site 3019 and 3119 in Study OBD-1033 was unacceptable, which was in agreement with the sponsor's assessment. Moreover, data from Site 1069 in Study OBD-0631 could not be verified because the records had been inadvertently shredded. Please refer to the review from Office of Scientific Investigation (OSI) for more information. Excluding the data from the 11 subjects randomized at Site 3019 and the 6 subjects randomized at Site 3119 did not cause notable difference in the treatment effect estimates or alter the conclusion for Study OBD-1033. Excluding the data from the 25 subjects randomized at Site 1069 did not cause notable difference in the treatment effect estimates or alter the conclusion for Study OBD-0631. Note that based on a CMH test stratified by baseline SBM frequency, which was the stratification variable used for randomization in Study OBD-1033, the p-values were generally larger and was 0.045 when the data from the two aforementioned sites were excluded. Hence, the significance of Study OBD-1033 should only be considered marginal. The results on this efficacy endpoint were largely consistent among the sensitivity analyses using other populations, such as the sponsor-defined ITT population, and Completers population, for all three studies. However, the p-value using the PP population for Study OBD-1033 was greater than 5% with the treatment difference of 9.2%. Given that the primary analysis was only marginally statistically significant and the smaller number of subjects in the PP population, it was not surprising that the statistical significance could not hold for this population even with a larger estimated treatment difference. Other missing data handling strategies and daily (vs. hourly) based weekly SBM frequency were also investigated, and the results were fairly consistent with those from the primary analyses.

For the efficacy endpoint of change of from baseline in SBM frequency at Week 8, the results are presented below. Note that this was the primary efficacy endpoint for Studies OBD-0631 and OBD-0632 only (shaded columns). It can be observed that lubiprostone demonstrated a statistically significant benefit over placebo in Study OBD-0631, while the same level of benefit

was not observed for the other two studies. Unfortunately, Study OBD-0631 did not show sufficiently strong evidence of efficacy as would be required for a single large clinical trial; the lack of a strong effect is not unexpected, as the study was not designed or powered accordingly.

Table 3.2 Analysis of Change from Baseline in SBM Frequency at Week 8 (All Randomized Subjects)

Study	OBD-1033		OBD-0631		OBD-0632	
	Placebo	Lubiprostone	Placebo	Lubiprostone	Placebo	Lubiprostone
N	226	221	220	223	216	235
Baseline						
n	217	212	216	218	209	217
Mean (SD)^a	1.42 (0.81)	1.25 (0.77)	1.46 (0.96)	1.42 (1.09)	1.59 (1.30)	1.56 (1.30)
Week 8						
n	179	173	169	171	176	174
Mean (SD)	4.06 (3.14)	4.43 (3.54)	3.81 (3.24)	4.56 (3.69)	3.97 (3.28)	4.17 (3.26)
Change from Baseline at Week 8						
n	179	173	169	171	176	174
Mean (SD)	2.58 (3.08)	3.14 (3.54)	2.39 (3.25)	3.17 (3.33)	2.46 (3.21)	2.71 (3.27)
Difference (SE)^b	0.56 (0.35)		0.78 (0.36)		0.25 (0.35)	
95% CI^c	(-0.13, 1.26)		(0.08, 1.48)		(-0.43, 0.93)	
P-value^d	0.163		0.024		0.497	

Source: Reviewer's Table

^a: SD = Standard Deviation

^b: SE = Standard Error

^c: CI = Confidence Interval

^d: Based on ANCOVA model with baseline value as covariate and stratified by pooled site

The results on this efficacy endpoint were largely consistent among the sensitivity analyses using other populations, such as the sponsor-defined ITT population, and Completers population, for all three studies. However, the p-value based on the PP population analysis for Study OBD-0631 was greater than 5% with the treatment difference of 0.5 in change from baseline weekly SBM response rate. Similar to the analysis for the PP efficacy endpoint of overall SBM response, this observation was not surprising. The results were fairly consistent among the other sensitivity analyses, including baseline-observation-carried-forward (BOCF) and last-observation-carried forward (LOCF) for treating missing data.

For the secondary efficacy endpoints specified in the protocols, most of them showed numerical improvement in the lubiprostone group comparing to the placebo group in each of the three studies. Some of them had p-values under 5% in Studies OBD-1033 and OBD-631, but not in Study OBD-632. (b) (4)

3.3 Overview of Safety

The safety evaluation for the lubiprostone program in OIC was based on a total of four phase 3 clinical trials: three pivotal studies and one long-term extension study conducted in Northern America and Europe. The clinical trial data were supported by cumulative post-marketing data

from February 1, 2006 through January 31, 2012, primarily from the use of the drug for the treatment of CIC and IBS-C.

Reportedly, clinical studies for lubiprostone indicate that a majority of AEs occurring secondary to treatment with lubiprostone are gastrointestinal (GI) in nature. Nausea was the most commonly reported AE in the lubiprostone group (13.9%), followed by diarrhea (11.4%), abdominal pain (5.3%), and vomiting (5.3%). Nausea (6.4%), vomiting (4.0%), diarrhea (3.8%), and abdominal pain (1.5%) were also among the most commonly reported AEs in the placebo group. One death was reported in the lubiprostone group during the 12-week double-blind periods; and one death in the open-label lubiprostone group in the long-term extension study. Neither was attributed to the study drug. More lubiprostone-treated subjects (4.4%) than placebo-treated subjects (0.9%) discontinued from the studies because of GI-related AEs.

Lubiprostone has been marketed in the US since April 15, 2006, and in Switzerland since February 23, 2012. A total of 5830 AEs were spontaneously reported between February 1, 2006 and January 31, 2012. Of these, 3221 AEs were medically confirmed and 2609 were not. Events in GI were the most commonly reported, and nausea (8.7%), drug ineffective (7.6%), and diarrhea (6.9%) were the most frequently reported AEs.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The sponsor conducted subgroup analyses on selected efficacy endpoints by age, gender, race and type of opioid used to treat the non-cancer-related pain. This review focuses on the two primary efficacy endpoints employed in the three phase 3 studies.

4.1 Gender, Race, Age, and Geographic Region

The overall SBM response rates and the mean change from baseline in SBM frequency at Week 8 were fairly comparable among the subpopulations for all three studies. It can be observed that males responded to lubiprostone better than females; however, the study was not powered for either of the subgroups comparisons, and the analysis was only exploratory. So the difference between the two subgroups should be interpreted carefully. Some of the relatively small sample size groups, such as non-white subjects and subjects from outside of the US, also showed notably different responses than the counterpart. Also note that the efficacy endpoint being evaluated was not pre-specified as the primary efficacy endpoint for Studies OBD-0631 and OBD-0632. The results are presented in the tables below. All p-values are for exploratory purposes only.

Table 4.1 Analysis of Overall SBM Response by Gender, Race, Age and Geographic Region (All Randomized Subjects)

Study	OBD-1033		OBD-0631		OBD-0632	
	Placebo	Lubiprostone	Placebo	Lubiprostone	Placebo	Lubiprostone
Gender						
Female						
N	144	139	145	137	126	145
Responder, n (%)	26 (18.1%)	32 (23.0%)	23 (15.9%)	33 (24.1%)	18 (14.3%)	19 (13.1%)
Non-responder, n (%)	118 (81.9%)	107 (77.0%)	122 (84.1%)	104 (75.9%)	108 (85.7%)	126 (86.9%)
Difference, %	4.9%		8.2%		-1.2%	
95% CI ^a , %	(-4.4%, 14.4%)		(-1.1%, 17.5%)		(-9.4%, 7.0%)	
P-value ^b	0.301		0.084		0.777	
Male						
N	82	82	75	86	90	90
Responder, n (%)	15 (18.3%)	27 (32.9%)	9 (12.0%)	21 (24.4%)	10 (11.1%)	17 (18.9%)
Non-responder, n (%)	67 (81.7%)	55 (67.1%)	66 (88.0%)	65 (75.6%)	80 (88.9%)	73 (81.1%)
Difference, %	14.6%		12.4%		7.8%	
95% CI ^a , %	(1.5%, 27.8%)		(0.7%, 24.1%)		(-2.6%, 18.1%)	
P-value ^b	0.032		0.044		0.144	
Race						
White						
N	181	184	176	172	189	202
Responder, n (%)	31 (17.1%)	43 (23.4%)	22 (12.5%)	39 (22.7%)	22 (11.6%)	33 (16.3%)
Non-responder, n (%)	150 (82.9%)	141 (76.6%)	154 (87.5%)	133 (77.3%)	167 (88.4%)	169 (83.7%)
Difference, %	6.3%		10.2%		4.7%	
95% CI ^a , %	(-2.0%, 14.5%)		(2.2%, 18.1%)		(-2.2%, 11.5%)	
P-value ^b	0.138		0.013		0.182	
Non-White						
N	45	37	44	51	27	33
Responder, n (%)	10 (22.2%)	16 (43.2%)	10 (22.7%)	15 (29.4%)	6 (22.2%)	3 (9.1%)
Non-responder, n (%)	35 (77.8%)	21 (56.8%)	34 (77.3%)	36 (70.6%)	21 (77.8%)	30 (90.9%)
Difference, %	21.0%		6.7%		-13.1%	
95% CI ^a , %	(1.0%, 41.1%)		(-10.9%, 24.3%)		(-31.6%, 5.4%)	
P-value ^b	0.042		0.461		0.156	
Age						
< 65 years						
N	193	207	197	204	201	222
Responder, n (%)	33 (17.1%)	57 (27.5%)	29 (14.7%)	51 (25.0%)	23 (11.4%)	30 (13.5%)
Non-responder, n (%)	160 (82.9%)	150 (72.5%)	168 (85.3%)	153 (75.0%)	178 (88.6%)	192 (86.5%)
Difference, %	10.4%		10.3%		2.1%	
95% CI ^a , %	(2.4%, 18.5%)		(2.5%, 18.0%)		(-4.2%, 8.4%)	
P-value ^b	0.012		0.010		0.521	

Table 4.1 Analysis of Overall SBM Response by Gender, Race, Age and Geographic Region (All Randomized Subjects)

Study	OBD-1033		OBD-0631		OBD-0632	
	Placebo	Lubiprostone	Placebo	Lubiprostone	Placebo	Lubiprostone
≥ 65 years						
N	33	14	23	19	15	13
Responder, n (%)	8 (24.2%)	2 (14.3%)	3 (13.0%)	3 (15.8%)	5 (33.3%)	6 (46.2%)
Non-responder, n (%)	25 (75.8%)	12 (85.7%)	20 (87.0%)	16 (84.2%)	10 (66.7%)	7 (53.8%)
Difference, %	-9.9%		2.8%		12.9%	
95% CI ^a , %	(-33.4%, 13.5%)		(-18.7%, 24.2%)		(-23.3%, 48.9%)	
P-value ^b	0.446		0.800		0.489	
Geographic Region						
US						
N	208	204	219	220	211	231
Responder, n (%)	41 (19.7%)	57 (27.9%)	32 (14.6%)	53 (24.1%)	28 (13.3%)	36 (15.6%)
Non-responder, n (%)	167 (80.3%)	147 (72.1%)	187 (85.4%)	167 (75.9%)	183 (86.7%)	195 (84.4%)
Difference, %	8.2%		9.5%		2.3%	
95% CI ^a , %	(0.04%, 16.4%)		(2.1%, 16.8%)		(-4.2%, 8.9%)	
P-value ^b	0.050		0.012		0.490	
Non-US						
N	18	17	1	3	5	4
Responder, n (%)	0 (0.0%)	2 (11.8%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)
Non-responder, n (%)	18 (100.0%)	15 (88.2%)	1 (100.0%)	2 (66.7%)	5 (100.0%)	4 (100.0%)
Difference, %	11.8 %		33.3%		0.0%	
95% CI ^a , %	(-3.6%, 27.1%)		(-20.0%, 86.7%)		(-46.4%, 51.9%)	
P-value ^b	0.134		0.505		0.739	

Source: Reviewer's Table

^a: CI = Confidence Interval; CI based on normal approximation

^b: Based on a chi-square test

Table 4.2 Analysis of Change from Baseline in SBM Frequency at Week 8 by Gender, Race, Age and Geographic Region (All Randomized Subjects)

Study	OBD-1033		OBD-0631		OBD-0632	
	Placebo	Lubiprostone	Placebo	Lubiprostone	Placebo	Lubiprostone
Gender						
Female						
N	144	139	145	137	126	145
Change from Baseline at Week 8 n	106	110	112	103	106	107
Mean (SD) ^a	2.61 (3.07)	2.99 (3.46)	2.58 (3.35)	3.52 (3.28)	2.68 (3.69)	2.48 (3.02)
Difference (SE) ^b	0.38 (0.45)		0.94 (0.45)		-0.20 (0.46)	
95% CI ^c	(-0.50, 1.26)		(0.05, 1.83)		(-1.11, 0.71)	
P-value ^d	0.433		0.044		0.495	
Male						
N	82	82	75	86	90	90
Change from Baseline at Week 8 n	73	63	57	68	70	67

Table 4.2 Analysis of Change from Baseline in SBM Frequency at Week 8 by Gender, Race, Age and Geographic Region (All Randomized Subjects)

Study	OBD-1033		OBD-0631		OBD-0632	
	Placebo	Lubiprostone	Placebo	Lubiprostone	Placebo	Lubiprostone
Mean (SD ^a)	2.53 (3.10)	3.40 (3.68)	2.03 (3.04)	2.65 (3.37)	2.14 (2.30)	3.08 (3.62)
Difference (SE ^b)	0.88 (0.58)		0.62 (0.58)		0.94 (0.52)	
95% CI ^c	(-0.27, 2.03)		(-0.53, 1.77)		(-0.08, 1.96)	
P-value ^d	0.175		0.263		0.048	
Race						
White						
N	181	184	176	172	189	202
Change from Baseline at Week 8						
n	144	144	135	130	156	149
Mean (SD ^a)	2.69 (3.19)	2.97 (3.55)	2.32 (3.24)	3.03 (3.06)	2.36 (3.29)	2.76 (3.19)
Difference (SE ^b)	0.28 (0.40)		0.70 (0.39)		0.41 (0.37)	
95% CI ^c	(-0.50, 1.06)		(-0.06, 1.46)		(-0.32, 1.14)	
P-value ^d	0.626		0.062		0.259	
Non-White						
N	45	37	44	51	27	33
Change from Baseline at Week 8						
n	35	29	34	41	20	25
Mean (SD ^a)	2.12 (2.55)	3.99 (3.41)	2.67 (3.32)	3.64 (4.08)	3.26 (2.49)	2.37 (3.73)
Difference (SE ^b)	1.87 (0.74)		0.97 (0.87)		-0.89 (0.97)	
95% CI ^c	(0.38, 3.36)		(-0.77, 2.71)		(-2.85, 1.07)	
P-value ^d	0.015		0.205		0.235	
Age						
< 65 years						
N	193	207	197	204	201	222
Change from Baseline at Week 8						
n	150	162	154	160	164	164
Mean (SD ^a)	2.54 (3.06)	3.20 (3.61)	2.35 (3.27)	3.14 (3.40)	2.36 (3.26)	2.57 (3.25)
Difference (SE ^b)	0.66 (0.38)		0.79 (0.38)		0.21 (0.36)	
95% CI ^c	(-0.09, 1.41)		(0.05, 1.53)		(-0.50, 0.92)	
P-value ^d	0.128		0.029		0.580	
≥ 65 years						
N	33	14	23	19	15	13
Change from Baseline at Week 8						
n	29	11	15	11	12	10
Mean (SD ^a)	2.78 (3.20)	2.27 (2.13)	2.87 (3.00)	3.67 (2.14)	3.82 (2.12)	4.93 (2.96)
Difference (SE ^b)	-0.51 (1.05)		0.80 (1.06)		1.12 (1.08)	
95% CI ^c	(-2.63, 1.61)		(-1.39, 2.99)		(-1.15, 3.38)	
P-value ^d	0.551		0.531		0.057	
Geographic Region						
US						
N	208	204	219	220	211	231
Change from Baseline at Week 8						
n	164	158	168	168	172	171
Mean (SD ^a)	2.63 (3.12)	3.28 (3.63)	2.39 (3.26)	3.17 (3.36)	2.47 (3.24)	2.71 (3.30)
Difference (SE ^b)	0.64 (0.38)		0.78 (0.36)		0.24 (0.35)	
95% CI ^c	(-0.10, 1.38)		(0.07, 1.49)		(-0.46, 0.93)	
P-value ^d	0.123		0.026		0.557	

Table 4.2 Analysis of Change from Baseline in SBM Frequency at Week 8 by Gender, Race, Age and Geographic Region (All Randomized Subjects)

Study	OBD-1033		OBD-0631		OBD-0632	
	Placebo	Lubiprostone	Placebo	Lubiprostone	Placebo	Lubiprostone
Non-US						
N	18	17	1	3	5	4
Change from Baseline at Week 8						
n	15	15	1	3	4	3
Mean (SD)^a	1.93 (2.52)	1.67 (1.93)	2.50 (--)	3.30 (0.98)	2.08 (2.05)	2.76 (0.66)
Difference (SE)^b	-0.26 (0.82)		0.80 (1.13)		0.68 (1.26)	
95% CI^c	(-1.94, 1.41)		(-4.05, 5.65)		(-2.54, 3.91)	
P-value^d	0.671		0.489		0.153	

Source: Reviewer's Table

^a: SD = Standard Deviation

^b: SE = Standard Error

^c: CI = Confidence Interval

^d: Based on ANCOVA model with baseline value as covariate and stratified by pooled site

4.2 Other Special/Subgroup Populations

Other subgroups conducted by the sponsor were mostly based on the opioids taken at the baseline, especially for Studies OBD-0631 and OBD-0632. The subgroups of methadone or non-methadone users were of particular interest because the sponsor suspected that methadone likely inhibited the primary mechanism of action for lubiprostone. Consequently, the sponsor argued that the failure of Study OBD-0632 could be contributed to its relatively larger proportion of subjects taking methadone than Study OBD-0631. However, as discussed earlier, the baseline characteristics across the studies were rather comparable, including the methadone users. The results for this subgroup for Studies OBD-0631 and OBD-0632 are presented in the tables below. Although the non-clinical evidence may back up sponsor's stipulation, there was no consistent clinical treatment effect trend for these two subgroups between the two studies although methadone users did show a noticeable reversal of the treatment effect.

Table 4.3 Analysis of Overall SBM Response by Methadone Usage at Baseline (All Randomized Subjects)

Study	OBD-0631		OBD-0632	
	Placebo	Lubiprostone	Placebo	Lubiprostone
Methadone				
N	29	40	35	39
Responder, n (%)	0 (0.0%)	8 (20.0%)	2 (5.7%)	0 (0.0%)
Non-responder, n (%)	29 (100.0%)	32 (80.0%)	33 (94.3%)	39 (100.0%)
Difference, %	20.0%		-5.7%	
95% CI^a, %	(7.6%, 32.4%)		(-13.4%, 2.0%)	
P-value^b	0.010		0.130	
Non-Methadone				
N	191	183	181	196
Responder, n (%)	32 (16.8%)	46 (25.1%)	26 (14.4%)	36 (18.4%)
Non-responder, n (%)	159 (83.2%)	137 (74.9%)	155 (85.6%)	160 (81.6%)
Difference, %	8.3%		4.0%	
95% CI^a, %	(0.2%, 16.6%)		(-3.4%, 11.5%)	
P-value^b	0.046		0.295	

Source: Reviewer's Table

^a: CI = Confidence Interval; CI based on normal approximation

^b: Based on a chi-square test

Table 4.4 Analysis of Change from Baseline in SBM Frequency at Week 8 by Methadone Usage at Baseline (All Randomized Subjects)

Study	OBD-0631		OBD-0632	
	Placebo	Lubiprostone	Placebo	Lubiprostone
Methadone				
N	29	40	35	39
Change from Baseline at Week 8				
n	19	27	28	29
Mean (SD ^a)	1.19 (1.53)	2.29 (2.71)	2.44 (4.73)	1.41 (2.89)
Difference (SE ^b)		1.10 (0.69)		-1.03 (1.04)
95% CI ^c		(-0.29, 2.48)		(-3.11, 1.04)
P-value ^d		0.250		0.399
Non-Methadone				
N	191	183	181	196
Change from Baseline at Week 8				
n	150	144	148	145
Mean (SD ^a)	2.55 (3.37)	3.34 (3.42)	2.46 (2.86)	2.97 (3.29)
Difference (SE ^b)		0.79 (0.40)		0.50 (0.36)
95% CI ^c		(0.01, 1.57)		(-0.20, 1.21)
P-value ^d		0.042		0.159

Source: Reviewer's Table

^a: SD = Standard Deviation

^b: SE = Standard Error

^c: CI = Confidence Interval

^d: Based on ANCOVA model with baseline value as covariate and stratified by pooled site

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The sponsor defined ITT population was not a true ITT population, which should include all randomized subjects. Especially for Studies OBD-0631 and OBD-0632, the primary analyses were conducted on a selective subgroup of the study subjects who experienced no dose-reduction. A subgroup based on treatment response is a biased assessment and not valid. Moreover, the sponsor did not propose an adequate multiplicity adjustment strategy to control the family-wise significance level for the secondary efficacy endpoints, (b) (4)

Finally, due to the fact that different primary efficacy endpoints were pre-specified, analyses of the overall SBM response rate over 12-week treatment period for Studies OBF-0631 and OBD-0632, and the analyses of the change from baseline in SBM frequency at Week 8, were post hoc.

5.2 Collective Evidence

This application contains three pivotal studies (OBD-1033, OBD-0631, and OBD-0632) in order to support the OIC indication of lubiprostone. Two of those (Studies OBD-0631 and OBD-

0632) were conducted concurrently; however, markedly different results were observed between these two studies. Only Study OBD-0631 reached statistical significance on the primary efficacy endpoint (change from baseline in SBM frequency at Week 8), and the sponsor conducted a third study (OBD-1033). The new study was conducted in a different patient population and specified a different primary efficacy endpoint (overall SBM response rate over 12-week treatment period). The results from the new study were only marginally significant. Moreover, neither of the Studies OBD-0631 or OBD-1033 was designed as a single large clinical trial to show a strong evidence of treatment efficacy. The inconsistency in results among these pivotal studies makes it difficult to compare and interpret the study findings.

Pre-specified sensitivity analyses and post-hoc exploratory analyses for all three pivotal studies support a benefit of lubiprostone over placebo in improving weekly SBM frequency. However, statistical significance was only shown for Study OBD-0631 and was marginal for Study OBD-1033.

5.3 Conclusions and Recommendations

The sponsor is seeking the treatment of OIC indication with three adequate and well-controlled 12-week studies (OBD-1033, OBD-0631, and OBD-0632) and a 36-week open-label safety extension study (OBD-06S1). The three pivotal studies used similar study designs; however, did not show consistent results. Study OBD-0632 failed to show statistical significance in either of the primary efficacy endpoints used in the clinical program. Neither of the Studies OBD-1033 or OBD-0631 showed sufficiently strong evidence of treatment efficacy as a single large clinical trial as they were not designed as such. Study OBD-0631 consistently showed a strong treatment benefit of lubiprostone over placebo (both on the pre-specified primary endpoint of change from baseline in SBM frequency and on the post-hoc efficacy endpoint of overall SBM response rate), while the treatment difference in Study OBD-1033 was only marginally significant on the pre-specified primary endpoint of overall SBM response rate. Based on the necessary sensitivity and post-hoc analyses, the findings were supportive of the conclusion that lubiprostone showed benefit in the treatment of OIC by improving weekly SBM frequency.

5.4 Labeling Recommendations

(b) (4)



(b) (4)



[Redacted] (b) (4)

[Redacted] (b) (4)

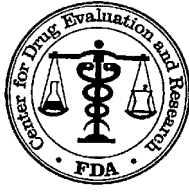
Such information in the labeling would be misleading and is not recommended.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FREDA COONER
04/12/2013

MICHAEL E WELCH
04/15/2013
Concur with review.



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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-908/127
Drug Name: Amitiza (lubiprostone)
Applicant: Sucampo Pharma Americas, INC.
Date(s): Submission: 5/29/2009
Consult request: 10/18/2012
Review Priority Standard
Biometrics Division: Division of Biometrics 7
Statistical Reviewer: Bradley McEvoy, MS, DrPH
Concurring Reviewers: LaRee Tracy, MA, PhD, Team Leader

Medical Division: Division of Gastroenterology and Inborn Error Products
Clinical Team: Medical Reviewer: Farrokh Sohrabi, MD
Medical Team Lead: Robert Fiorentino, MD
Project Manager: Maureen Dewey

Keywords: Vital signs, change from baseline, pediatric study, non-randomized design

Table of Contents

1	EXECUTIVE SUMMARY	3
2	INTRODUCTION.....	4
2.1	Overview	4
2.2	Data Sources	4
3	STATISTICAL EVALUATION.....	5
3.1	Data and Analysis Quality	5
3.2	Evaluation of Efficacy	5
3.3	Evaluation of Safety	5
3.3.1	Design and Endpoints	5
3.3.2	Statistical Methodologies.....	7
3.3.3	Patient Disposition, Demographics & Baseline Characteristics	7
3.3.4	Results and Conclusion.....	8
4	FINDINGS IN SPECIAL /SUBGROUP POPULATIONS	10
5	SUMMARY AND CONCLUSIONS.....	10
5.1	Statistical Issues.....	10
5.2	Collective Evidence.....	10
5.3	Conclusions and Recommendations	11
6	Appendix: Supplemental Results	12

List of Tables

Table 1.	Schedule of Evaluations.....	6
Table 2.	Safety population by age and weight groups	7
Table 3.	Patient disposition.....	8
Table 4.	Demographic and baseline characteristics	8
Table 5.	Baseline vital signs levels	9
Table 6.	Mean change from baseline in vital sign by follow-up visit and dose-levels	9
Table 7.	Number of observations per vital sign endpoint by study visit.....	9
Table 8.	Mean change from baseline in other vital sign parameters by follow-up visit and dose-levels....	12

1 EXECUTIVE SUMMARY

The Division of Gastroenterology and Inborn Error Products (DGIEP) consulted the Division of Biometrics VII requesting a statistical safety review of vital sign data from a previously completed pediatric study for Amitiza (lubiprostone). The sponsor, Sucampo Pharma Americas, INC., is seeking to expand lubiprostone's indication to include "treatment of opioid induced constipation (b) (4) in adults with chronic, non-cancer pain." During the review of the supplement, the need to review the pediatric study arose from i) review of a pediatric clinical study report was incomplete with respect to the findings and description of vital signs data, and ii) signals of changes in hemodynamic parameters were observed in a 13-week toxicity study of lubiprostone administered to juvenile rats.

The pediatric clinical study was a four-week, multi-center, non-randomized, open-label study to evaluate the safety and efficacy of lubiprostone for the treatment of chronic constipation in pediatric patients; a follow-up visit was scheduled at week six. Patients that satisfied the study inclusion criteria were assigned to, depending on their weight and age at baseline, one of following dose-regimens: 12 mcg QD, 12 mcg BID, or 24 mcg BID. As a consequence of the non-random dosing assignment, it is not possible to compare findings across dose levels since the dosing is confounded by age and weight, which is a significant limitation of this study.

This study was not a safety study and was therefore neither powered nor designed to test safety-related hypotheses. Therefore, results from analyses should be considered exploratory only.

In total, 124 of the 127 patients enrolled in the study received lubiprostone and were included in the safety analysis population. At baseline, the safety population included 27 patients in the 12 mcg QD group, 65 in the 12 mcg BID group, and 32 in the 24 mcg BID group.

Fewer patients in the 24 mcg BID group completed the study (72%) compared to patients in the 12 mcg QD group (93%) and the BID group (94%). The 24 mcg BID group had 10 patients discontinue the study, with most of discontinuations due to an adverse event (5 patients) followed by patient choice (3 patients).

Mean heart rates tended to be larger from baseline at each follow-up visit in each dose group. The largest increases, about four (4) additional beats per minute, were observed in the 12 mcg BID group at week 1 and at the final visit (week 4).

Both mean systolic and diastolic blood pressures tended to be lower from baseline at each follow-up visit in each dose group. For systolic blood pressure, potential signals were observed in the 12 mcg BID at week 1, and at the follow-up visit (week 6) in the 24 mcg BID group. For diastolic blood pressure, a potential signal was observed in the 12 mcg QD group at week 1.

In conclusion, there appears to be a potential signal of increased heart rate from baseline in the 12 mcg BID group, and potential signals of decreased blood pressure (both systolic or diastolic) in each dose group. However, due to the non-randomized study design and small sample size, unadjusted comparisons across treatments groups are difficult to interpret. To fully assess if

lubiprostone is associated with clinically relevant changes in hemodynamic parameters, a sufficiently powered, randomized, controlled trial would be recommended.

2 INTRODUCTION

2.1 Overview

Sucampo Pharma Americas, INC. submitted an efficacy supplement to expand the indication for Amitiza (lubiprostone) to include “Treatment of opioid induced constipation [REDACTED] (b) (4) [REDACTED] in adults with chronic, non-cancer pain.” Lubiprostone is currently indicated for the treatment of chronic idiopathic constipation in adults, and treatment of irritable bowel syndrome with constipation in women $\geq$ 18 years old.

During the review of the supplement, the need arose for a targeted statistical safety review of vital sign data from a previously completed pediatric clinical study (protocol no. SPI/0211SC-0641, study report date: 5/22/2009). More specifically, the impetus for this review came, in part, from hemodynamic signals observed in a 13-week toxicity study of lubiprostone in juvenile rats, submitted May 22, 2012 (Seq no. 0109). In the pharmacology/toxicology review by Dr. Chakder (DGIEP; review date: 07/27/2012) it was noted:

- “The heart rates of the 0.5 mg/kg male and female pups were significantly higher than controls on Days 28 and 102 post partum throughout the monitoring period (22 hr). The heart rates of the 0.05 mg/kg group were also higher than control during this period.”
- “Mean systolic, diastolic and mean arterial blood pressures for the high dose group were higher than controls, generally, from 30 minutes to 1.0 hr following dosing. There was also a trend for higher blood pressures for 0.05 mg/kg males and females during this period.”

An additional review of the juvenile rat toxicity study performed by Dr. Yang (DCRP; review date: 10/12/2012) had similar findings.

The sponsor’s clinical study report for the pediatric study noted that there were several statistically significant changes from baseline and concluded that the changes were small and not clinically significant. However, the study report is lacking in detail regarding which vital signs were statistically significant and in an explanation for why these changes were not considered clinically significant.

Given the hemodynamic findings from the juvenile rat study, DGIEP consulted the Division of Biometrics VII (DB7) to review the vital sign data from the pediatric study, particularly systolic and diastolic blood pressure and heart rate. This review is a statistical evaluation of vital sign data from the pediatric study (protocol no. SPI/0211SC-0641).

2.2 Data Sources

The demographics and vital sign analysis datasets for the pediatric study is available in the Electronic Document Room at: \\Cdsesub1\evsprod\NDA021908\0127.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The statistical reviewer was able to replicate the baseline and follow-up vital sign summary statistics provided in Table 14.3.3 of the sponsor's report, which was the only source of results pertaining to vital sign data.

3.2 Evaluation of Efficacy

This review does not include an assessment of efficacy.

3.3 Evaluation of Safety

3.3.1 Design and Endpoints

Trial Design

Study SPI/0211SC-0641 is a four-week, non-randomized, multi-center, open-label study to evaluate the safety and efficacy of lubiprostone for the treatment of chronic constipation in pediatric patients.

Patients that satisfied the study inclusion criteria were assigned one of three doses of lubiprostone depending on age and weight as follows:

- Adolescents (12-17 years of age)
 - 12 mcg BID (up to 24 patients)
 - At least 36 kg body weight – 24 mcg BID
- Children (6-11 years of age)
 - At least 36 kg body weight – 24 mcg BID
 - At least 24 kg, but less than 36 kg body weight – 12 mcg BID
 - At least 12 kg, but less than 24 kg body weight – 12 mcg QD
- Young children (< 6 years of age and able to swallow capsules)
 - At least 12 kg body weight – 12 mcg QD.

In protocol amendment 4 (November 08, 2007), adolescents and children at least 36 kg had their lubiprostone dose adjusted to 24 mcg BID; prior to this amendment, adolescents and children at least 24 kg were to receive lubiprostone 12 mcg BID. The first dose of lubiprostone was to be administered at the physician's office. Subsequent doses were to be given with breakfast and/or dinner; the QD doses were to be taken at dinner.

Reviewer comments: A major limitation of the study is its non-randomized design, thus making comparisons across dose levels complicated as dose is confounded by the patient's age and weight. The absence of a non-lubiprostone group is another design limitation that makes the interpretation of study results difficult. Due to these limitations the statistical reviewer will not compare findings across doses levels.

In total, there were 6 visits completed over 8 weeks. The schedule of study vital sign evaluation and other study features are displayed in Table 1.

Table 1. Schedule of Evaluations

Visit	1 Screening	2 Baseline	3 Interim	4 Interim	5 Final	6 follow-up
Study day	Week -2 (day -16 to -14)	Day 1	Week 1 (day 8 + 2)	Week 2 (day 15 + 2)	Week 4 (day 29 + 2)	Week 6 (day 43 + 2)
Location	Office	Office	Office	Phone	Office	Office
informed consent/assent	×					
medical history	×	×				
inclusion/exclusion criteria	×	×				
vital signs	×	×	×		×	×
administration of first dose		×				
Study medication collection					×	

Source: adapted from page 10 of the clinical protocol, version 5.0.

Patients 17 years of age or less that signed the consent (or legal guardian if the patient was too young) were included in the study if they had a history of constipation, as defined by the Rome III diagnostic criteria for childhood functional constipation, weighed at least 12 kg and capable of swallowing capsules. Other inclusion criteria included concomitant medication use for gastrointestinal motility and ADHD, willing and able to use a rescue medication, willing and able to fill out a study diary, achieved certain compliance and SBM benchmarks which were to be captured in the diary during the baseline period (between screening and visit 1).

Patients were excluded from the study if they had constipation that was attributable to dietary, physical, anatomic, neurological, endocrine/metabolic, or organic disorders, or was secondary to medication use. Additionally, patient reporting episodes of fecal incontinence not associated with stool retention, or those with untreated episodes of fecal impactions or impactions requiring digital manipulations for removal, were not eligible.

Reviewer Comment: Changes in vital signs levels shortly after receiving lubiprostone, as seen in the juvenile rat study within the first day (See Section 2.1), can not be assessed using data from the pediatric clinical study since the first follow-up visit was one week after the first dose.

Vital sign endpoints

Vital signs data investigated in this review are systolic and diastolic blood pressure (mmHg) and heart rate (beats per minute). Two other two vital sign parameters that were collected in the study but are not discussed in this review are respiratory rate (breaths per minute) and body temperature (°C); for completeness, results for these two endpoints are presented in Appendix.

Analysis of vital signs is performed on the safety analysis set, defined as all patients that received at least one dose of lubiprostone.

Sample size determination

The sample size was based on the primary efficacy endpoint of sudden bowel movement (SBM) frequency at week 1. As stated in the statistical analysis plan, with the planned sample size of 120 patients, the study has 90% power to detect an average change of 1.5 SBMs at baseline (assuming a standard deviation of 5), with a type-I error rate of 5%.

Reviewer comment: Because the study was designed to test around hypothesis for SBMs and not vital signs, we consider the results from the analysis of the vital signs endpoints exploratory.

3.3.2 Statistical Methodologies

One sample t-tests will be used at each post-baseline visit (i.e., week 1, follow-up and final) and dose level to identify vital signs that significantly changed from baseline. For each analysis the mean change and 95% confidence intervals (CIs) will be presented. The CIs will not be adjusted for multiple comparisons.

3.3.3 Patient Disposition, Demographics & Baseline Characteristics

Patient Disposition

In total, 124 of the 127 patients enrolled in the study received lubiprostone, and were thus included in the safety analysis population. The three patients that enrolled in the study and were not included in the safety population refused study medication (subject ids: 11-020, 17-026, and 17-028). The safety population included 27 patients in the 12 mcg QD group, 65 in the 12 mcg BID group, and 32 in the 24 mcg BID group. The breakdown of patients by age and weight group is displayed in Table 2.

Patient 35-005 was assigned an incorrect dose of lubiprostone; this patient should have received 12 mcg QD according to his baseline weight (22.5 kg), but instead received lubiprostone 12 mcg BID.

Table 2. Safety population by age and weight groups

Age & Weight Group	12 mcg QD N=27	12 mcg BID N=65	24 mcg BID N=32
Adolescents (N=)	0	22	26
24-36 kg	-	3	-
> 36 kg	-	19	26
Children (N=)	12	43	6
12-24 kg	12	1	-
24-36 kg	-	27	-
> 36 kg	-	15	6
Young Children (N=)	15	0	0
12-24 kg	13	-	-
24-36 kg	2	-	-

Table 3 displays the disposition of study patients. Fewer patients completed the study in the 24 mcg BID group (72%) compared to the 12 mcg QD group (93%) and the BID group (94%). The 24 mcg BID group also had the greatest number of patients that discontinued the study (10);

most of these patients discontinued due to an adverse event (5 patients) followed by patient choice (3 patients), non-compliance (1 patient) and other (1 patient).

Table 3. Patient disposition

	12 mcg QD	12 mcg BID	24 mcg BID
Number enrolled	29	65	33
Enrolled but did not receive lubiprostone	2	0	1
Safety population	27	65	32
Completed treatment†	25	62	23
Completed study‡	25	61	23
Discontinued study	4	4	10
<i>Adverse event</i>	0	3	5
<i>Lack of efficacy</i>	0	0	0
<i>Patient choice</i>	2	0	3
<i>Lost to follow-up</i>	0	0	0
<i>Non-compliance</i>	2	0	1
<i>Sponsor request</i>	0	1	0
<i>Other</i>	0	0	1

† Treatment completer: a patient who completes all visits through visit 5

‡ Study completer: a patient who complete all visits through visit 6

Demographics and Baseline Characteristics

Patient demographics are displayed in Table 4. Both the 12 mcg QD and BID group had slightly more males (56% and 63% respectively), while the 24 mcg BID had considerably fewer males (28%). Almost all children in the 12 mcg QD group were White, and about 80% in the other two groups. By design the age and weight composition of the dose groups differed; note that two patients with missing weight (ids 06-023 and 20-005) both were included in the ≥ 36 kg weight group. As expected, due to no randomization, demographic and baseline characteristics vary across dose groups.

Table 4. Demographic and baseline characteristics

Demographic & Baseline Characteristics	12 mcg QD	12 mcg BID	24 mcg BID
	N=27 n (%)	N=65 n (%)	N=32 n (%)
<i>Sex</i>			
Male	15 (56)	41 (63)	9 (28)
<i>Age (years)</i>			
mean (sd)	5.5 (1.7)	10.3 (2.8)	13.9 (3.0)
min/max	3/9	6/17	6/17
<i>Weight (kg)</i>			
mean (sd)	19.9 (2.8)	43.4 (17.9)	60.0 (16.9)
min/max	14/25	22/102	36/99
missing	0	1	1
<i>Race</i>			
White	26 (96)	51 (78)	26 (81)
Black or African American	1 (4)	9 (14)	5 (16)
Asian	0 (0)	1 (2)	0 (0)
Missing	0 (0)	4 (6)	1 (3)

3.3.4 Results and Conclusion

Average baseline vital sign levels for the three dose level are displayed in Table 5.

Table 5. Baseline vital signs levels

Endpoint	12 mcg QD mean (sd)	12 mcg BID mean (sd)	24 mcg BID mean (sd)
BP: Diastolic	63.0 (7.4)	64.1 (8.5)	66.6 (8.0)
BP: Systolic	101.7 (10.1)	107.9 (8.4)	113.0 (8.5)
Heart rate	92.7 (15.7)	83.7 (16.1)	80.1 (9.1)

Table 6 displays the mean change from baseline in blood pressure and heart rate by follow-up visit and dose-level. Table 7 lists the number of patients with a vital sign measurement by visit.

Table 6. Mean change from baseline in vital sign by follow-up visit and dose-levels

Endpoint	Visit	12 mcg QD mean chg (95% CI)	12 mcg BID mean chg (95% CI)	24 mcg BID mean chg (95% CI)
BP: Diastolic	Week 1	-3.42 (-6.47, -0.37)	-0.63 (-2.54, 1.28)	-2.18 (-5.52, 1.16)
	Final	-1.26 (-4.88, 2.36)	-0.49 (-2.70, 1.71)	-0.62 (-3.49, 2.26)
	Follow-up	-2.50 (-5.40, 0.40)	0.05 (-2.20, 2.30)	-0.71 (-3.43, 2.01)
BP: Systolic	Week 1	-1.04 (-6.65, 4.57)	-2.37 (-4.53, -0.21)	-0.32 (-3.65, 3.01)
	Final	0.04 (-4.26, 4.34)	-0.16 (-2.72, 2.40)	-2.27 (-5.90, 1.37)
	Follow-up	-1.92 (-7.05, 3.21)	-0.82 (-3.43, 1.79)	-7.29 (-12.82, -1.77)
Heart rate	Week 1	1.23 (-3.77, 6.23)	4.08 (0.39, 7.77)	1.89 (-2.89, 6.68)
	Final	-0.81 (-6.93, 5.30)	4.37 (0.67, 8.06)	2.15 (-2.80, 7.11)
	Follow-up	1.00 (-5.43, 7.43)	2.44 (-0.94, 5.81)	2.67 (-2.18, 7.51)

BP-blood pressure

Table 7. Number of observations per vital sign endpoint by study visit

Visit	12 mcg QD	12 mcg BID	24 mcg BID
Baseline	27	65	32
Week 1	26	62	28
Final	27	63	26
Follow-up	26	62	24

Blood Pressure: Diastolic

For each dose group the mean diastolic blood pressure tended to be lower at post-baseline visit compared to baseline. The greatest decrease from baseline was in the 12 mcg QD group at week 1. We defer to the clinical reviewers to judge the whether these changes, which were not elevated from baseline, are clinically significant.

Blood Pressure: Systolic

For each dose group the mean systolic blood pressure tended to be smaller at each post-baseline visit compared to the baseline level; this finding was consistent across the three dose levels. We defer to the clinical reviewers to judge the whether these changes, which were not elevated from baseline, are clinically significant.

Heart Rate

For each dose group there was an increase in the mean heart rate from baseline; this finding was consistent across the three dose levels. The greatest increase from baseline was in the 12 mcg BID group, with an additional four (4) beats per minute at week 1 and at the final visit.

4 FINDINGS IN SPECIAL /SUBGROUP POPULATIONS

Subgroup analyses were not performed due to challenges interpreting results due to non-randomized study design and small number of subjects within each dose group.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The major weakness of this pediatric clinical study is that treatment was not randomly assigned. Since the dosing regimens were confounded by age and weight, it is not appropriate to compare the safety of the different dosing regimens from this study. The small sample size prevents any meaningful adjusted analyses controlling for confounding variables. An additional limitation is the lack of a non-Amitiza control group.

Fewer patients in the 24 mcg BID group completed the study (72%) compared to the 12 mcg QD group (93%) and to the BID group (94%). The 24 mcg BID group had 10 patients discontinue the study, with most of discontinuations due to an adverse event (5 patients) followed by patient choice (3 patients).

The pediatric clinical study was neither designed nor powered to test changes in specific vital signs levels. Therefore, results from analyses presented in this review should not be considered confirmatory. In addition, given the large number of comparisons performed without any adjustments for multiplicity, the 95% confidence interval that exclude the null value should not be taken as confirmatory evidence of statistical significance.

Changes in vital signs levels shortly after receiving lubiprostone, as seen in the juvenile rat study within the first day (See Section 2.1), can not be assessed using data from the pediatric clinical study since the first follow-up visit was one week after the first dose.

5.2 Collective Evidence

In total, 124 of the 127 patients enrolled in the study received lubiprostone and were included in the safety analysis population. At baseline the 12 mcg QD group included 27 patients, 65 in the 12 mcg BID group, and 32 in the 24 mcg BID group.

Both systolic and diastolic blood pressure tended to be lower from baseline at each follow-up visit for each dose group. For systolic blood pressure, statistically significant decreases were observed in the 12 mcg BID at week 1, and at the follow-up visit in the 24 mcg BID group. For diastolic blood pressure, the greatest change from baseline occurred in the 12 mcg QD group, with the decrease at week 1 being statistically significantly.

Heart rates tended to be increased from baseline at each follow-up visit, with the largest increases, about four (4) additional beats per minute, in the 12 mcg BID group at week 1 and the final visit; both these increases were statistically significant.

5.3 Conclusions and Recommendations

DGIEP consulted DB7 to review vital sign data from a previously completed non-randomized pediatric clinical study since i) review of a pediatric clinical study report was incomplete with respect to the findings and description of vital signs data, and ii) signals of changes in hemodynamic parameters were observed in a 13-week toxicity study of lubiprostone administered to juvenile rats. The reviewer was able to replicate the sponsor's limited results provided in the pediatric clinical study report. There appears to be a signal of increased heart rate from baseline at week 1 and at the final follow-up visit in the 12 mcg BID group. In addition, the review found possible signals for decreased diastolic blood pressure at week 1 in the 12 mcg QD group and decreased systolic blood pressure at week 1 in the 12 mcg BID group and at the follow-up visit in the 24 mcg BID group. However, due to the non-randomized study design and small sample size, these unadjusted comparisons across treatments groups are difficult to interpret and conclusions of statistical significance are inappropriate. To fully assess if lubiprostone is associated with clinically relevant changes in hemodynamic parameters, a sufficiently powered, randomized, controlled trial would be recommended.

6 Appendix: Supplemental Results

Table 8. Mean change from baseline in other vital sign parameters by follow-up visit and dose-levels

Endpoint	Visit	12 mcg QD	12 mcg BID	24 mcg BID
		mean chg (95% CI)	mean chg (95% CI)	mean chg (95% CI)
Respiratory rate	Week 1	0.48 (-0.81, 1.77)	-0.06 (-0.66, 0.53)	-0.74 (-2.59, 1.11)
	Final	0.65 (-1.04, 2.34)	-0.10 (-0.92, 0.73)	-0.28 (-1.56, 1.00)
	Follow-up	1.80 (0.16, 3.44)	-0.67 (-1.66, 0.31)	-0.30 (-1.29, 0.68)
Body temperature (°C)	Week 1	0.15 (-0.06, 0.37)	0.04 (-0.06, 0.15)	0.10 (-0.07, 0.26)
	Final	0.17 (0.00, 0.35)	0.10 (-0.00, 0.21)	0.09 (-0.05, 0.22)
	Follow-up	0.13 (-0.08, 0.34)	0.05 (-0.06, 0.17)	0.08 (-0.09, 0.25)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRADLEY W MCEVOY
01/11/2013

LAREE A TRACY
01/11/2013
I concur with this review.

STATISTICS FILING REVIEW

NDA Number: 21908/011
SDN: 901

Applicant: Sucampo
Pharma Americas, Inc.

Stamp Date: July 20, 2012

Drug Name: Amitiza®
Lubiprostone capsule (24 mcg)
twice daily

NDA Type: 505(b)(1) NDA
Supplement SE1

Indication: Opioid-Induced
Constipation (OIC) ^{(b) (4)}

On **initial** overview of the Supplemental NDA application for RTF:

	Content Parameter for RTF	Yes	No	NA	Comments
1	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

THE STATISTICAL SECTION OF THE APPLICATION IS FILEABLE

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	Not present
Appropriate references for novel statistical methodology (if present) are included.			X	Not present
Safety data organized to permit analyses across clinical trials in the NDA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING REVIEW

Background

Sucampo Pharmaceuticals submits this efficacy supplement to NDA 21-908 (Amitiza[®]) seeking approval of lubiprostone 24 mcg administered twice daily for a new indication: the treatment of opioid-induced constipation (OIC) [REDACTED] (b) (4) in adults with chronic, non-cancer pain. The sponsor requests a Priority Review of this supplement based on its opinion of a significant unmet medical need.

The content of this efficacy supplement was discussed with the FDA at the Type B pre-sNDA meeting held on March 7, 2012. During the meeting, the FDA reminded the sponsor of its recommended primary and secondary efficacy endpoints with the missing data handling details. The sponsor agreed to conduct several sensitivity and/or subgroup analyses on both the original and new endpoints.

Opioids, widely used in the management of acute and chronic pain, inhibit gastrointestinal motility by binding to opioid receptors. Consequently, patients can experience OIC, which is associated with a range of additional signs and symptoms, e.g., hard stool consistency, abdominal discomfort such as cramping, spasm and bloating, and eventually other symptoms such as gastroesophageal reflux. Lubiprostone is a member of a group of structurally- and pharmacologically-related compounds known as prostones. By increasing intestinal fluid secretion, lubiprostone enhances motility in the intestine, thereby facilitating the passage of stool.

The characteristics of OIC are similar to chronic idiopathic constipation (CIC). To date, lubiprostone (24 mcg capsules administered twice daily [BID]) has been evaluated in approximately 3,500 subjects in clinical trials. Lubiprostone was approved in the U.S. in January 2006 for the treatment of CIC in the adult population based on three well-controlled clinical studies. In addition, lubiprostone 8 mcg BID was approved in April 2008 to treat irritable bowel syndrome with constipation (IBS-C) in adult women.

The tabulation data in the CDISC-SDTM format and the analysis datasets in legacy format, as well as the study reports for this submission have been submitted in electronic Common Technical Document (eCTD) format to the EDR at: <\\Cdsub1\evsprod\NDA021908\0112>.

Overview of studies

The clinical development program for lubiprostone began in 1999 with the conduct of the initial phase 1 safety, tolerance, pharmacodynamic, and pharmacokinetic study in healthy volunteers. It was followed by subsequent studies to support a NDA to the FDA for CIC indication. That application was approved in the U.S. on January 31, 2006, and lubiprostone has been marketed under the name AMITIZA[®] since then. The marketing authorization in Switzerland for the treatment of CIC was granted November 2009. Lubiprostone for CIC indication was also recently approved for marketing in Japan, but the marketing has not been initiated. The Japanese program comprised of a total of five clinical trials and was completed in August 2010. A marketing application for CIC is currently under review in the U.K.

The clinical efficacy of oral lubiprostone in the treatment of OIC was supported by three adequate and well-controlled 12-week studies (OBD-1033, OBD-0631, and OBD-0632) and a 36-week open-label safety extension study (OBD-06S1). The three pivotal studies used similar study designs, i.e. randomized, double-blind, placebo-controlled, multicenter (OBD-1033: U.S. and

STATISTICS FILING REVIEW

Europe; OBD-0631 and OBD-0632: U.S. and Canada), 12-week studies. The development program initially comprised two phase 3 studies (OBD-0631 and OBD-0632) and one safety extension study (OBD-06S1). A statistically significant difference, favoring lubiprostone over placebo, was observed for the primary efficacy endpoint (change from baseline in the frequency of spontaneous bowel movements [SBMs] at Week 8) in Study OBD-0631 but failed in Study OBD-0632. A subsequent laboratory investigation suggested that methadone likely inhibited the treatment effect of lubiprostone. Hence, Study OBD-1033 was subsequently conducted in subjects receiving non-methadone opioid therapy and the primary endpoint was changed to an overall SBM response evaluation over the entire 12-week study period upon discussion and agreement with the FDA.

The three phase 3 studies and one long-term safety extension study are summarized in the table on the next page.

Issues for 74-day letter

1. In addition to the subgroup analyses you have conducted on the pooled datasets, please provide subgroup analyses for each pivotal study individually for the following subpopulations: age, gender, race, and type of opioid used to treat the noncancer-related pain. Please also conduct a subgroup analysis by geographic region (US vs. non-US) for each study individually and studies combined. Please further identify the non-white race group (e.g., Black, Asian) used in your race subgroup analyses.
2. Please provide your well-commented and organized software programming code that was written for each primary analysis dataset and efficacy table created for each pivotal study. In addition, please provide the programming code used to analyze the primary variables in the integrated study of efficacy.

STATISTICS FILING REVIEW

Type of Study	Study Identifier	Study Objective	Study Design & Type of Control	Test Product; Dosage Regimen; Route of Administration	Subjects Enrolled (Treated)	Patient Population	Duration of Treatment
Efficacy & Safety	SPI/0211OBD-0631	Efficacy & Safety	Double-blind, Randomized, Multicenter, Placebo-controlled	Capsule; Placebo BID, 24 mcg BID; Multiple-Dose, Oral	443 (439)	Patients with opioid-induced bowel disorder	12 Weeks
Efficacy & Safety	SPI/0211OBD-0632	Efficacy & Safety	Double-blind, Randomized, Multicenter, Placebo-controlled	Capsule; Placebo BID, 24 mcg BID; Multiple-Dose, Oral	451 (437)	Patients with opioid-induced bowel disorder	12 Weeks
Efficacy & Safety	SMR/0211OBD-1033	Efficacy & Safety	Double-blind, Randomized, Multicenter, Placebo-controlled	Capsule; Placebo BID, 24 mcg BID; Multiple-Dose, Oral	447 (439)	Patients with opioid-induced bowel disorder	12 Weeks
Long-term Extension	SPI/0211OBD-06S1	Long-term Safety & Efficacy	Open-label, Multicenter, Extension	Capsule; 24 mcg BID; Multiple-Dose, Oral	443 (439)	Patients with opioid-induced bowel disorder	36 Weeks

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FREDA COONER
09/17/2012

MICHAEL E WELCH
09/17/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021908/S-011

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 21908/ S 011	Submission Date(s): 07/20/2012
Brand Name	Amitiza
Generic Name	Lubiprostone
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Sue Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology III
OND Division	DGIEP
Sponsor	Sucampo Pharma
Submission Type	Efficacy Supplement; Priority with extension
Formulation; Strength(s)	Soft gelatin capsules; 8 mcg, 24 mcg
Indication	Opioid-Induced-Constipation, OIC in adults

Final Recommendation: NDA 21908/Supplement 011 is acceptable from a Clinical Pharmacology perspective.

Regulatory Background: Lubiprostone 24 mcg BID, under the trade name Amitiza® was approved in the United States in January, 2006 for the treatment of adults with chronic idiopathic constipation (CIC). In addition, lubiprostone 8 mcg BID was approved in April 2008 to treat irritable bowel syndrome with constipation (IBS-C) in adult women.

Introduction to the NDA supplement: Through this efficacy supplement to NDA 21908, Sucampo Pharma Americas, Inc. is seeking approval of lubiprostone 24 mcg, administered twice daily, for the treatment of opioid-induced constipation (OIC (b) (4)

in adults with chronic, non-cancer pain.

Presumed mechanism of action in OIC: Lubiprostone is a locally acting prostone drug that acts by stimulating the chloride channels (ClC2) expressed on the apical surface of the intestinal epithelium. Through its action, it increases the intestinal fluid secretions thus facilitating transit of feces through the colon. Opioid-induced Constipation, OIC is primarily mediated by opioids binding to peripheral, gastrointestinal opioid receptors, leading to interference with normal tone and contractility of the bowel wall, resulting in delayed transit time of the fecal contents. The constipating effects of opioids may also be attributed to the reduction in secretion and increased reabsorption of water and electrolytes in the gut. Lubiprostone, via activation of apical ClC-2 channels in intestinal epithelial cells, is expected to bypass the antisecretory action of morphine that results from suppression of excitability of secretomotor neurons. Results from pharmacology

studies of lubiprostone in morphine-treated mice and transit studies in humans, suggests there is a potential benefit of lubiprostone treatment for subjects with OIC.

Clinical Pharmacology contents of the NDA supplement: There are no new Clinical Pharmacology studies in human subjects in this efficacy supplement. Sponsor has conducted phase 3 and long term safety studies in support of the new indication (see table of clinical trials below) that are under review by the clinical reviewers for this application. Please see clinical review by Dr. Farrokh Sohrabi and Rob Fiorentino for further information in this regard.

An in vitro pharmacology study that evaluated the interaction potential of methadone and lubiprostone has been submitted to the non-clinical sections of this NDA supplement and has been reviewed from a Clinical Pharmacology perspective. In addition, the proposed revisions to Amitiza labeling including those pertaining to the new mechanistic drug-drug interaction information with methadone have been reviewed from a Clinical Pharmacology perspective and recommendations proposed. This brief review will capture essentials of these two components. Detailed review of the in vitro study will be provided in the appendix to this review.

Doses evaluated in phase 3 for OIC: There were no dose-ranging or phase 2 trials in support of the new indication. A dose of 24 mcg BID has been evaluated in phase 3 trials of OIC, chosen based on its efficacy and approval in CIC patients.

Tabular listing of all clinical studies in SE11:

Type of Study	Study Identifier	Location of Study Report	Study Objective	Study Design & Type of Control	Test Product; Dosage Regimen; Route of Administration	Subjects Enrolled (Treated)	Patient Population	Duration of Treatment	Study Status
Efficacy & Safety	SPI/0211OBD-0631	5.3.5.1.1	Efficacy & Safety	Double-blind, Randomized, Multicenter, Placebo-controlled	Capsule; Placebo BID, 24 mcg BID; Multiple-Dose, Oral	443 (439)	Patients with opioid-induced bowel disorder	12 Weeks	Completed
Efficacy & Safety	SPI/0211OBD-0632	5.3.5.1.2	Efficacy & Safety	Double-blind, Randomized, Multicenter, Placebo-controlled	Capsule; Placebo BID, 24 mcg BID; Multiple-Dose, Oral	451 (437)	Patients with opioid-induced bowel disorder	12 Weeks	Completed
Efficacy & Safety	SMR/0211OBD-1033	5.3.5.1.3	Efficacy & Safety	Double-blind, Randomized, Multicenter, Placebo-controlled	Capsule; Placebo BID, 24 mcg BID; Multiple-Dose, Oral	447 (439)	Patients with opioid-induced bowel disorder	12 Weeks	Completed
Long-term Extension	SPI/0211OBD-06S1	5.3.5.2.1	Long-term Safety & Efficacy	Open-label, Multicenter, Extension	Capsule; 24 mcg BID; Multiple-Dose, Oral	443 (439)	Patients with opioid-induced bowel disorder	36 Weeks	Completed

Formulation: The formulation is that of drug dissolved in medium chain fatty acid triglyceride (medium-chain triglycerides, MCT) and filled into a soft gelatin capsule. The clinical phase III studies on the drug were conducted using 24 µg RU-0211 (lubiprostone) capsules. The 24 µg capsule has been approved by the FDA (NDA #21-908) for the treatment of chronic idiopathic constipation (CIC). Sponsor notes in the clinical overview of the NDA that “All Phase 3 clinical trials were conducted with the same dosage form, soft gelatin oral capsules, which is also the same dosage form that is intended for marketing”.

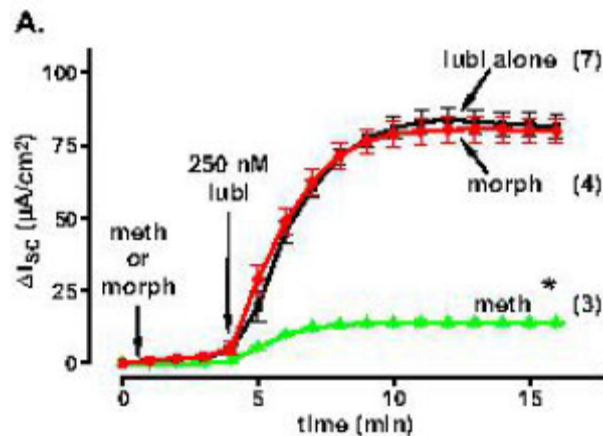
Summary of Important Clinical Pharmacology and Biopharmaceutics Findings:

Review of the in vitro mechanistic study NSR0211-12-003-01: Methadone but not Morphine Inhibits Lubiprostone-Stimulated Cl⁻ Currents in T84 Intestinal Cells and Recombinant Human ClC-2, but not CFTR Cl⁻ Currents

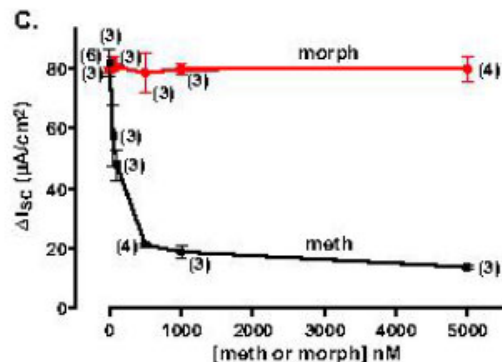
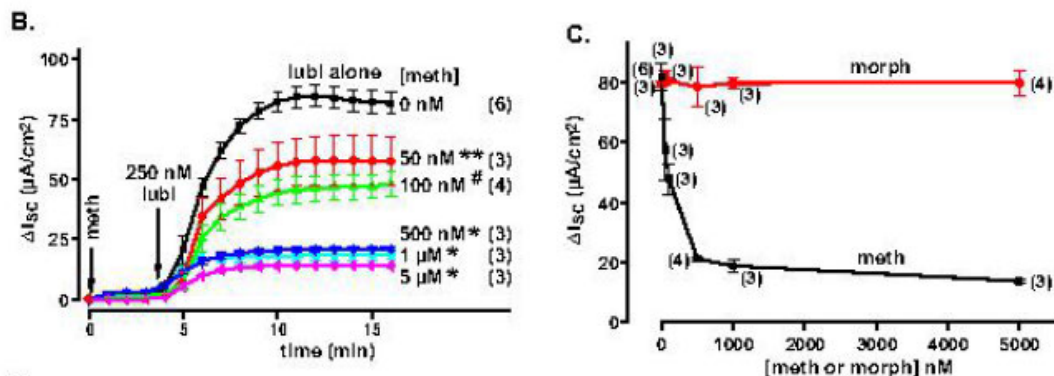
Lubiprostone-stimulated Cl⁻ currents were measured by short circuit current (I_{sc}) across T84 cells, and by whole cell patch clamp of recombinant human ClC-2 (hClC-2) in stably transfected HEK293 cells in the presence and absence of methadone and morphine.

Results are summarized:

- The effect of methadone and morphine on lubiprostone-stimulated I_{sc} in T84 cells was determined. Prior addition of 5 μM morphine had no effect on 250 nM lubiprostone-stimulated I_{sc}, but prior addition of 5 μM methadone caused major (approximately 88%) inhibition of lubiprostone-stimulated I_{sc} (Fig. 1A):



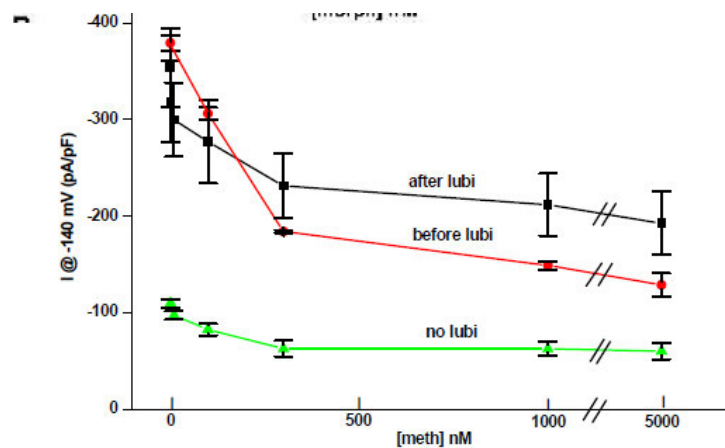
- The effect of varying concentrations of methadone on lubiprostone-stimulated I_{sc} was evaluated next and is shown in Fig. 1B. Pre-incubation with methadone demonstrated a concentration-dependent reduction in the I_{sc} currents induced by lubiprostone treatment, with an IC₅₀ (half-maximal inhibition of the I_{sc}) of about 100 nM. Morphine had no effect at any concentration tested. The concentration-response curves for methadone and morphine are summarized in Fig. 1c:



- The effect of the non-specific opioid receptor antagonist, naloxone on the methadone inhibition of Cl⁻ currents (I_{sc}) in T84 cells was examined. In this

experiment, 250 nM lubiprostone stimulated I_{sc} across T84 cells. Prior addition of 10 μ M naloxone alone had no effect, while prior addition of 1 μ M methadone was inhibitory. Addition of 10 μ M naloxone had no effect on methadone inhibition of lubiprostone-stimulated I_{sc} .

- Methadone also inhibited the Cl^- currents activated by forskolin/IBMX and these currents were not affected by morphine, but inhibited by methadone, whether added after or before morphine. Thus methadone appears to inhibit hCIC-2, regardless of the method of activation.
- In HEK293 cell line (cell line developed to express CIC2 channels), morphine at any concentration up to 5 μ M had no effect on Cl^- currents induced by lubiprostone. In contrast, methadone added before or after 100 nM lubiprostone inhibited hCIC-2 Cl^- currents in a concentration dependent manner with concentrations resulting in half-maximal inhibition of 109.3 ± 8.5 nM (3) and 117.3 ± 32.4 nM (3) respectively, values not significantly different from each other. However, when methadone was added before lubiprostone, greater inhibition (approximately 90% at 1 μ M) was observed compared to when methadone was added after lubiprostone (approximately 60% at 1 μ M).
- Similar findings with regard to dose-dependent inhibition of lubiprostone mediated stimulated of Cl^- currents (and lack thereof by morphine) were also replicated using studies on Cl^- currents in hCIC2 overexpressing cell line HEK293EBNA.



Study Conclusions: Results of these *in vitro* investigations suggest that *in vitro*, methadone inhibits the CIC2 chloride channel currents induced by lubiprostone in a concentration-dependent manner. Data *in vitro* suggest a possibility that co-administration with methadone or methadone-type opioids (diphenylheptane class) may reduce the effect of lubiprostone in improving intestinal secretions and transit.

Reviewer comments: *In vitro* data suggests that the efficacy of lubiprostone could be lower in presence of methadone-type opioids (diphenylheptanes). Depending on the strength of clinical evidence from the submitted OIC clinical trials (methadone users vs. non-users), the *in vitro* data may support labeling language under 'limitations of use'. If clinical efficacy was not perceived to be compromised due to concomitant

methadone usage in the clinical trial data, then appropriate language could be included in the precautions and/or drug-drug interactions sections of the label. We defer the final language to the clinical review team of this NDA.

The clinical relevance and rationale for the drug concentrations evaluated in these in vitro investigations is not fully understood but is addressed here briefly:

The observed IC50 (half-maximal inhibition of lubiprostone-activated ClC2 currents by methadone) is ~ 100 nM; concentrations of methadone up to 5 µM were evaluated in vitro and produced significant (concentration-dependent) inhibition of lubiprostone-induced Cl- channel currents, with 90 % inhibition noted at 5 µM concentration of methadone in the T84 cell line.

Per Dolophine label (oral methadone), the dose for management of pain is individualized but generally the usual starting dose in opioid non-tolerant patients is 2.5 to 10 mg every 8 to 12 hours, slowly titrated to effect. Peak (Cmax) concentrations of methadone following a 10 mg oral dose are noted to be ~124 ng/mL (~ 358 nM) and steady-state concentrations at this dose were ~ 65 ng/mL (~ 187 nM). Thus the IC50 values for methadone noted in the various in vitro cell lines appear within the concentrations achievable following clinically relevant dose of methadone.

Whether this interaction with methadone that was noted in vitro, actually translates into reduced efficacy of lubiprostone in the clinical setting could only be determined by evaluation of the available clinical evidence in this regard.

Labeling Review: Revisions have been proposed by the sponsor to the approved Amitiza labeling to include the new OIC information. Sections 7.0 (drug-drug interactions), section 8.0 (specific populations), and section 12.0 (Clinical pharmacology) have been reviewed and recommendations have been proposed from a Clinical Pharmacology perspective. The content from section 7.0 and revisions proposed are shown below. The hepatic impairment (HI) language has been reviewed and revised in the highlights and sections 2.0, 8.0 and 12.0 of the labeling as needed to ensure consistency and clarity of dose adjustment language across the labeling.

Revisions to the Drug Interactions section 7.0 are shown below in light of the new *in vitro* evidence of methadone interaction (underline indicates new/revised content):





Appendices

1.1 Individual Study Review

Study Report Number: NSR0211-12-003-01: Methadone but not Morphine Inhibits Lubiprostone-Stimulated Cl⁻ Currents in T84 Intestinal Cells and Recombinant Human ClC-2, but not CFTR Cl⁻ Currents

Proposed study Rationale: The reported finding of differential effects of methadone and morphine in the clinical trial in OIC was difficult to relate to mu receptors, since both agents bind to mu receptors with similar affinity (EC₅₀): 5.6 nM for methadone and 2.0 nM for morphine tested with the cloned human mu receptor. Thus, investigators hypothesized that methadone might interfere with lubiprostone action by a mechanism independent of binding to mu receptors. Direct action on ion channels or a process required for expression of ion channel function might be responsible for inhibition by methadone. Methadone, but not morphine, is known to inhibit L-type calcium channels, various potassium channels and hERG. Direct inhibition of hERG might underlie cardiotoxicity seen with methadone treatment. Thus, there was a basis for examination of whether methadone affected the function of either recombinant hClC-2 or hCFTR. Both of these ion channels have been suggested to be involved in lubiprostone stimulation of T84 cell Isc.

Introduction: Present study investigated whether methadone and/or morphine inhibited lubiprostone-stimulated Cl⁻ currents in T84 cells using short circuit current (Isc). Studies were also carried out in HEK293 cells stably transfected with either rhClC-2 or rhCFTR.

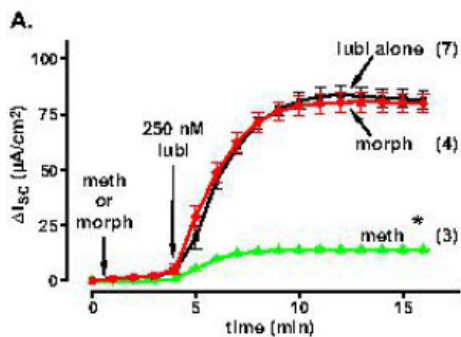
Cell culture: T84 cells (short-circuit currents Isc in this cell line are presumed to be due to ClC2 due to prior experiments in ClC2 knock-out T84 cell lines) were grown in DMEM/Ham's F-12 medium with 6% heat-inactivated FBS, 15 mM HEPES, 14.3 mM NaHCO₃, 100 U/ml penicillin, and 100 µg/ml streptomycin sulfate and then grown to confluence on 1.13 cm² Snapwell permeable supports. Human ClC-2-transfected and human CFTR-transfected HEK293 cells were grown in MEM supplemented with 5% heat-inactivated horse serum, 0.1 mM nonessential amino acids, 2 mM L-glutamine, 1 mM sodium pyruvate, 100 U/ml penicillin, 100 µg/ml streptomycin sulfate and 300 µg/ml G418 and 100 µg/ml hygromycin respectively.

In order to examine time-dependent, voltage-activated hClC-2 Cl⁻ currents in the absence of the activator lubiprostone, a stable cell line greatly overexpressing hClC-2 was made using HEK293EBNA cells. These cells have been transformed to constitutively express the Epstein Barr Virus nuclear antigen 1 (EBNA-1). This allows for high copy episomal replication of oriP containing plasmids such as pCEP4. Recombinant human ClC-2 was subcloned into the pCEP4 vector, and transfected into HEK293EBNA cells using Lipofectamine (Invitrogen). HEK293EBNA cells were grown in DMEM containing 10% FCS and 0.25 mg/ml G418.

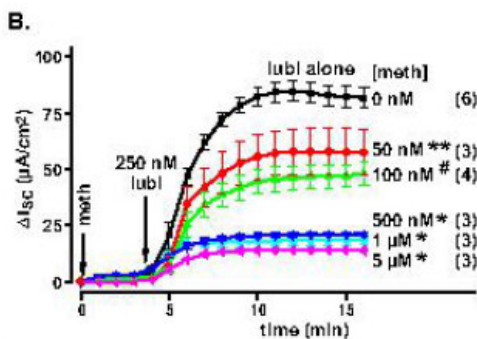
Methods: Short-circuit current measurements: The EasyMount Ussing chamber system (8 chambers) with VCCMC8 8-channel current-voltage (I-V) clamps from Physiologic Instruments (San Diego, CA), was used for I_{sc} measurements across confluent T84 cell monolayers. The clamps were connected to Acquire & Analyse software (Physiologic Instruments) for automatic data collection from all eight of the Ussing chambers. Ag/AgCl reference electrodes were used for measuring transepithelial voltage and passing current.

Effect of varying concentrations of methadone and morphine on lubiprostone-stimulated Cl⁻ currents in T84 cells and effect of naloxone.

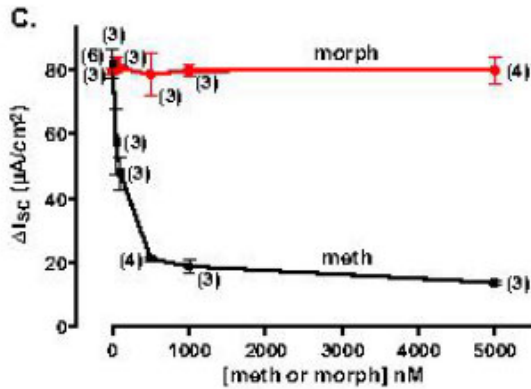
The effect of methadone and morphine on lubiprostone-stimulated I_{sc} in T84 cells was determined. Prior addition of 5 μM morphine had no effect on 250 nM lubiprostone-stimulated I_{sc}, but prior addition of 5 μM methadone caused major (approximately 88%) inhibition of lubiprostone-stimulated I_{sc} (**Fig. 1A**).



The effect of varying concentrations of methadone on lubiprostone-stimulated I_{sc} is shown in **Fig. 1B**.

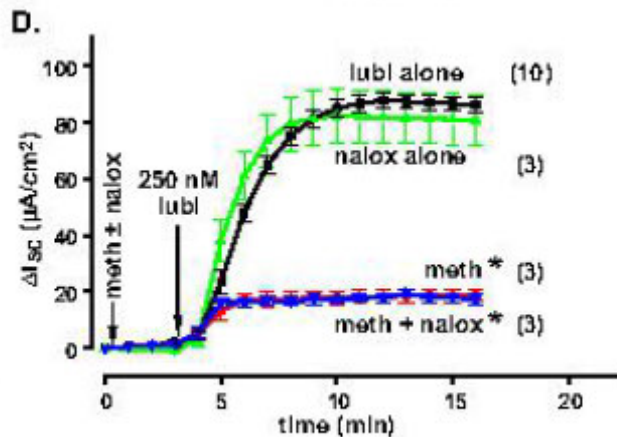


The methadone and morphine concentration response curves are shown in **Fig. 1C**.



Morphine had no effect at any concentration tested. However, methadone inhibited the lubiprostone-stimulated Isc in a concentration dependent manner with half maximal inhibition of Isc of about 100 nM.

The effect of the non-specific opioid receptor antagonist, naloxone on the methadone inhibition of Cl⁻ currents (Isc) in T84 cells was examined. As shown in Fig. 1D, 250 nM lubiprostone stimulated Isc across T84 cells. Prior addition of 10 μM naloxone alone had no effect, while prior addition of 1 μM methadone was inhibitory. Addition of 10 μM naloxone had no effect on methadone inhibition of lubiprostone-stimulated Isc.



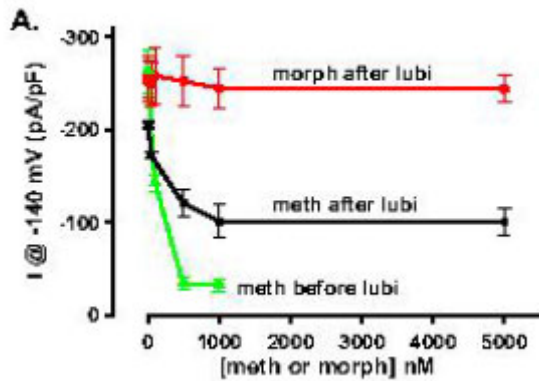
Effect of methadone and morphine together on lubiprostone-stimulated hClC-2 Cl⁻ currents in HEK293 cells.

Morphine at any concentration up to 5 μM had no effect on lubiprostone induced Cl⁻ channel currents in this cell line.

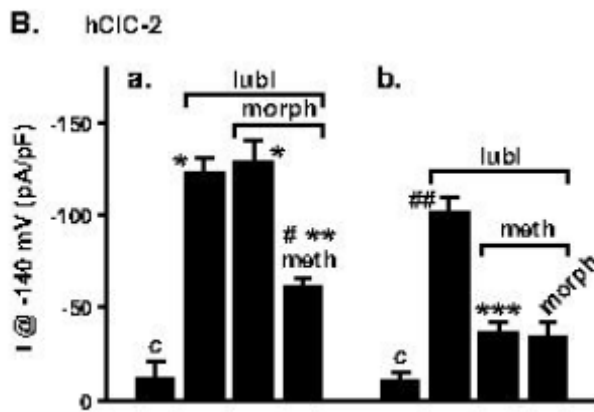
In contrast, methadone added before or after 100 nM lubiprostone inhibited hClC-2 Cl⁻ currents in a concentration dependent manner with concentrations resulting in half-maximal inhibition of 109.3 ± 8.5 nM (3) and 117.3 ± 32.4 nM (3) respectively, values not significantly different from each other.

However, when methadone was added before lubiprostone, greater inhibition (approximately 90% at 1 μ M) was observed compared to when methadone was added after lubiprostone (approximately 60% at 1 μ M).

Figure 2A: Effect of varying concentrations of methadone added before or after lubiprostone and morphine added after 100 nM lubiprostone. Similar IC₅₀ values were obtained when methadone was added before or after lubi (109 nM vs. 117 nM); however, the extent of inhibition was greater when methadone was added before lubi (90 % versus 60 % when methadone was added after lubiprostone).



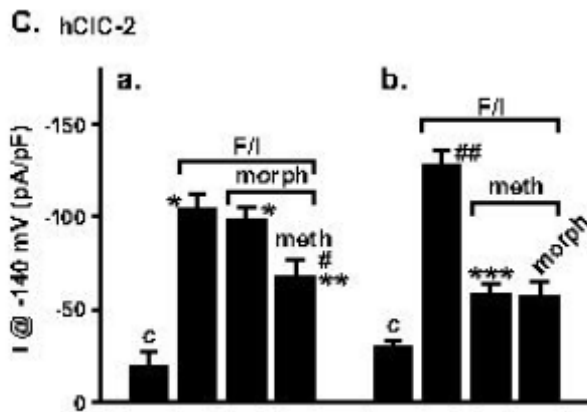
Patients may receive methadone and morphine together. Therefore the effect of methadone and morphine, together and separately, on lubiprostone-stimulated hClC-2 Cl⁻ currents was next determined. Cl⁻ currents in hClC-2 transfected HEK293 cells were measured in cells without lubiprostone (control), cells treated with 100 nM lubiprostone (DMSO 0.1% final), and with either 1 μ M methadone followed by 100 nM morphine or the reverse 100 nM morphine followed by 1 μ M methadone. As shown in Fig. 2B, 100 nM lubiprostone stimulated hClC-2 Cl⁻ currents and 100 nM morphine had no effect on the currents. Subsequent addition of 1 μ M methadone inhibited lubiprostone-stimulated Cl⁻ currents. Also shown in Fig. 2B, addition of 1 μ M methadone inhibited lubiprostone-stimulated Cl⁻ currents. Subsequent addition of 100 nM morphine had no effect.



Effect of methadone and morphine on forskolin/IBMX-stimulated hClC-2 Cl⁻ currents

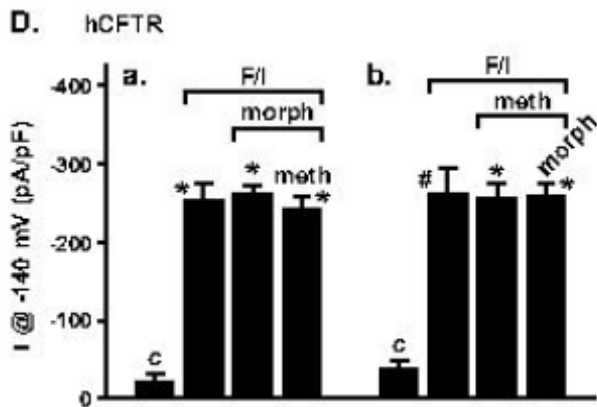
in HEK293 cells:

The effects of 100 nM morphine and 1 μ M methadone were also studied on hCIC-2 Cl⁻ currents activated by 5 μ M forskolin/20 μ M IBMX to raise levels of intracellular cAMP, an alternative means of activation of human CIC-2. As shown in Fig. 2C, forskolin/IBMX activated hCIC-2 Cl⁻ currents and these currents were not affected by morphine, but inhibited by methadone, whether added after or before morphine. Thus methadone appears to inhibit hCIC-2, regardless of the method of activation, whether by lubiprostone or forskolin/IBMX. Thus methadone, but not morphine, whether added together or separately, inhibited both lubiprostone- and forskolin/IBMX-stimulated Cl⁻ currents in hCIC-2 transfected HEK293 cells. Methadone thus apparently inhibits the hCIC-2 Cl⁻ channel by a mechanism independent of lubiprostone, per se.



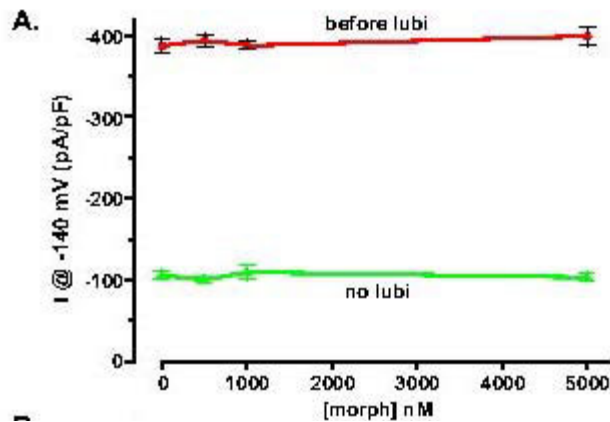
Effect of methadone and morphine on forskolin/IBMX-stimulated hCFTR Cl⁻ currents.

The effects of 100 nM morphine and 1 μ M methadone were studied on Cl⁻ currents in HEK293 cells expressing recombinant hCFTR after activation by 5 μ M forskolin/20 μ M IBMX. As shown in Fig. 2D, human CFTR Cl⁻ channel activity activated by forskolin/IBMX was not inhibited by methadone or morphine.

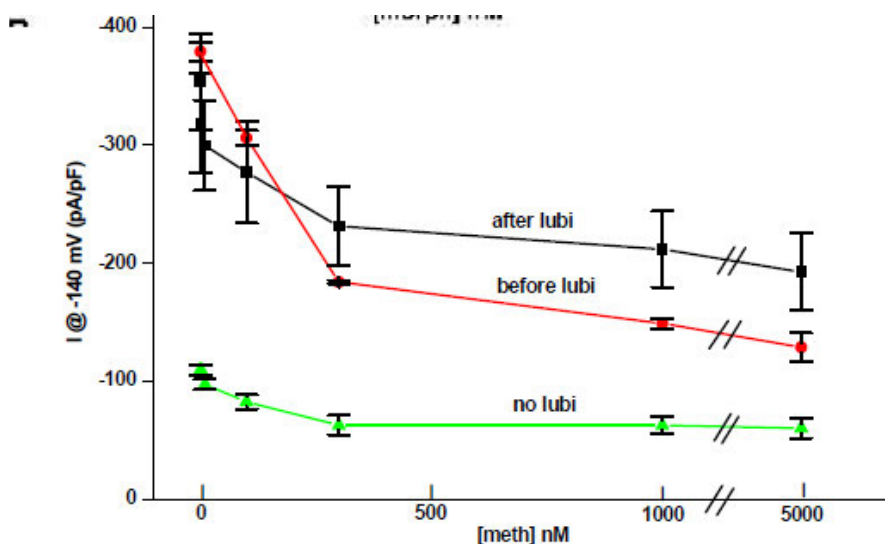


Effect of varying concentrations of methadone and morphine on time-dependent, voltage-activated hCIC-2 Cl⁻ currents without (control) and with 100 nM lubiprostone.

Cl⁻ currents in HEK293EBNA cells stably expressing hClC-2 without lubiprostone (control), and with 100 nM lubiprostone were treated with varying concentrations of either morphine sulfate (Fig. 5A) or methadone hydrochloride (Fig. 5B) added either before or after lubiprostone. As shown in Fig. 5A lubiprostone significantly increased the Cl⁻ current, and morphine up to 5 μM had no effect on hClC-2 Cl⁻ currents without (control) or with lubiprostone.



In contrast, methadone inhibited time-dependent, voltage-activated hClC-2 Cl⁻ currents in the absence of lubiprostone with a concentration giving half-maximal inhibition of 103.0 ± 21.5 nM. Adding methadone before lubiprostone and after lubiprostone inhibited hClC-2 Cl⁻ currents with concentrations giving half-maximal inhibition of 130.7 ± 25.4 nM and 102.7 ± 12.2 nM respectively. These values were not significantly different from each other or the value without lubiprostone. However as measured with hClC-2 in HEK293 cells (Fig. 2A), adding methadone before lubiprostone resulted in greater inhibition of the lubiprostone-stimulated currents.



Sponsor notes that as shown in Table 1, a survey of other commonly used opioids showed lack of Isc inhibition by oxycodone, oxymorphone and hydromorphone at 5 μM ; and fentanyl and loperamide exhibited half maximal inhibition at approximately 3 μM . Norpropoxyphene, the major metabolite of propoxyphene (no longer used in treatment in the US or Europe), is a diphenylheptane like methadone with a half maximal inhibition at approximately 0.075 μM as measured by whole cell patch clamp.

	Half Maximal Inhibition	No Effect Level	Class	Method
Fentanyl	3 μM	-	Phenylpiperidine	Isc
Loperamide	3 μM	-	Benzomorphan	Isc
Oxycodone	-	5 μM	Phenanthrene	Isc
Oxymorphone	-	5 μM	Phenanthrene	Isc
Hydromorphone	-	5 μM	Phenanthrene	Isc
Morphine	-	5 μM	Phenanthrene	Isc Patch Clamp
Methadone	0.1 μM	-	Diphenylheptane	Isc Patch Clamp
Norpropoxyphene	0.075 μM	-	Diphenylheptane	Patch Clamp

Study suggests that methadone may inhibit effect of lubiprostone on opioid-dependent constipation by inhibiting the ClC-2 chloride channel currents induced by lubiprostone.

Investigators suggest possible interaction between methadone and hClC-2 (or a closely related process required for expression of hClC-2 dependent Cl⁻ currents). Per authors, further studies will be required to determine if hClC-2 interacts directly with methadone.

1.2 Cover Sheet and OCP Filing Memo

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
NDA Number	21908/S 011	Brand Name	Amitiza	
OCP Division (I, II, III, IV, V)	DCPIII	Generic Name	Lubiprostone	
Medical Division	DGIEP	Drug Class	Chloride Channel 2, CIC2 Activator	
OCP Reviewer	Sandhya Apparaju	Indication(s)	Opioid Induced Constipation	
OCP Team Leader	Sue Chih Lee	Dosage Form	Soft Gel Capsules	
Pharmacometrics Reviewer	N/A	Dosing Regimen	24 mcg BID	
Date of Submission	07/20/2012	Route of Administration	Oral	
Estimated Due Date of OCP Review	03/12/2013	Sponsor	Sucampo	
Medical Division Due Date	03/27/2013	Priority Classification	Priority	
PDUFA Due Date	April 20, 2013 (Priority with 3-month extension)			
Clinical Pharmacology and Biopharmaceutics Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X	4		Phase 3 and long-term safety trials
HPK Summary	X			No new PK studies
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				No new PK studies and assays; refer to original approval of Amitiza
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				

In-vitro:	X				In vitro study suggestive of interaction between methadone and lubiprostone; methadone may inhibit activation of CIC2 channels by lubiprostone
Subpopulation studies -					
ethnicity:					
gender:					
pediatrics:					
geriatrics:					
renal impairment:					
hepatic impairment:					
PD -					
Phase 2:					
Phase 3:					
PK/PD -					
Phase 1 and/or 2, proof of concept:					
Phase 3 clinical trial:					
Population Analyses -					
Data rich:					
Data sparse:					
II. Biopharmaceutics					
Absolute bioavailability					
Relative bioavailability -					
solution as reference:					
alternate formulation as reference:					
Bioequivalence studies -					
traditional design; single / multi dose:					
replicate design; single / multi dose:					
Food-drug interaction studies					
Bio-waiver request based on BCS					
BCS class					
Dissolution study to evaluate alcohol induced dose-dumping					
III. Other CPB Studies					
Genotype/phenotype studies					
Chronopharmacokinetics					
Pediatric development plan					
Literature References					
Total Number of Studies	X	4	1		Lubiprostone-methadone DDI- in vitro pharmacology study

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Clinical and TBM Formulations are same
2	Has the applicant provided metabolism and drug-drug interaction information?	X			In vitro study suggestive of PD interaction between methadone and lubiprostone at CIC2 channels; likely to reduce

					efficacy of lubiprostone in patients using methadone;
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	Formulation previously approved
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?	X			Dose approved for CIC was investigated for OIC
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			X	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			X	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?			X	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		X		One dose of lubiprostone (same as that approved for CIC) was evaluated in phase3 trials
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	Systemic exposure of lubiprostone is not relevant as action is local in GIT
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might			X	

	affect the pharmacokinetic or pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

 Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Sandhya Apparaju

 Reviewing Clinical Pharmacologist Date

Sue Chih Lee

 Team Leader/Supervisor Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDHYA K APPARAJU
03/06/2013

SUE CHIH H LEE
03/06/2013

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA 21908 Supplement 011**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21908/S 011	Brand Name	Amitiza
OCP Division (I, II, III, IV, V)	DCPIII	Generic Name	Lubiprostone
Medical Division	DGIEP	Drug Class	Chloride Channel 2, CIC2 Activator
OCP Reviewer	Sandhya Apparaju	Indication(s)	Opioid Induced Constipation
OCP Team Leader	Sue Chih Lee	Dosage Form	Soft Gel Capsules
Pharmacometrics Reviewer	N/A	Dosing Regimen	24 mcg BID
Date of Submission	07/20/2012	Route of Administration	Oral
Estimated Due Date of OCP Review	11/20/2012	Sponsor	Sucampo
Medical Division Due Date		Priority Classification	Priority
PDUFA Due Date	January 18, 2013		

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X	4		Phase 3 and long-term safety trials
HPK Summary	X			No new PK studies
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				No new PK studies and assays; refer to original approval of Amitiza
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 21908 Supplement 011

In-vitro:	X			In vitro study suggestive of interaction between methadone and lubiprostone; methadone may inhibit activation of CIC2 channels by lubiprostone
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4		One methadone DDI-relevant pharmacology study (in vitro) also provided

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Clinical and TBM Formulations are same
2	Has the applicant provided metabolism and drug-drug interaction information?	X			In vitro study suggestive of PD interaction between methadone and lubiprostone at CIC2 channels; likely to reduce efficacy of lubiprostone in patients using

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA 21908 Supplement 011**

					methadone;
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	Formulation previously approved
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?	X			Dose approved for CIC was investigated for OIC
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			X	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			X	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?			X	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		X		One dose of lubiprostone (same as that approved for CIC) was evaluated in phase3 trials
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	Systemic exposure of lubiprostone is not relevant as action is local in GIT
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the			X	

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA 21908 Supplement 011**

	pharmacokinetics and exposure-response in the clinical pharmacology section of the label?				
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

___ Yes ___

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Sandhya Apparaju

Reviewing Clinical Pharmacologist

Date

Sue Chih Lee

Team Leader/Supervisor

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDHYA K APPARAJU
08/28/2012

SUE CHIH H LEE
08/29/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021908/S-011

OTHER REVIEW(S)

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: No Format Deficiencies

Product Title	AMITIZA (lubiprostone) capsules, for oral use
Applicant	Sucampo Pharmaceuticals, Inc.
Application/Supplement Number	NDA 21908, supplement 011
Type of Application	Clinical Efficacy
Indication(s)	• Treatment of chronic idiopathic constipation in adults • Treatment of opioid-induced constipation in adults with chronic, non-cancer pain • Treatment of irritable bowel syndrome with constipation in women $\geq$ 18 years old
Established Pharmacologic Class ¹	chloride channel activator
Office/Division	ODE III/DGIEP
Division Project Manager	Maureen Dewey
Date FDA Received Application	July 20, 2012
Goal Date	April 19, 2013
Date PI Received by SEALD	April 15, 2013
SEALD Review Date	April 15, 2013
SEALD Labeling Reviewer	Jeanne M. Delasko
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, final agreed-upon prescribing information (PI) for critical format elements reveals **NO outstanding labeling format issues** and the SEALD Director has **NO OBJECTION** to the approval of this PI at this time.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

G

uide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item (**deficiency**).
- **YES:** The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A (not applicable):** This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*

Selected Requirements of Prescribing Information

• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

N/A

12. All text must be **bolded**.

Comment:

N/A

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

Selected Requirements of Prescribing Information

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- YES** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- YES** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- YES** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Selected Requirements of Prescribing Information

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Selected Requirements of Prescribing Information

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)

Selected Requirements of Prescribing Information

12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- N/A** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) in italics followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

Comment:

- YES** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Selected Requirements of Prescribing Information

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- N/A** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEANNE M DELASKO
04/15/2013

ANN M TRENTACOSTI
04/16/2013
Signing for Laurie Burke

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: March 29, 2013

To: Maureen Dewey, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 021908
OPDP Comments for draft PI for Amitiza (lubiprostone) Capsules

OPDP has reviewed the proposed draft PI for Amitiza (lubiprostone) Capsules. We have reviewed the draft PI version 49, last modified on March 25, 2013 and agree with those changes and have no additional comments at this time.

Thank you for the opportunity to comment on the proposed PI.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

21 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MEETA N PATEL
03/29/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

TEAM LEADER CLINICAL INSPECTION SUMMARY

DATE: March 27, 2013

TO: Maureen Dewey, Regulatory Project Manager
Farrokh Sohrabi, M.D.

FROM: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Ann Meeker O'Connell
Acting Division Director
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 021-908/S-011

APPLICANT: Sucampo Pharma Americas, L.L.C.

DRUG: Amitiza[®] (Lubiprostone) Capsules

NME: No

THERAPEUTIC CLASSIFICATION: Priority review

INDICATIONS: Treatment of opioid-induced constipation [REDACTED] (b) (4)
[REDACTED] in adults with chronic non-cancer pain

CONSULTATION REQUEST DATE: September 11, 2012
INSPECTION SUMMARY GOAL DATE: December 21, 2012
DIVISION ACTION GOAL DATE: April 18, 2013 Extended from January
PDUFA DATE: April 18, 2013

EXECUTIVE SUMMARY:

In Dr. Malek's review of the NDA 021908/S-011, he outlines deficiencies in the conduct of the SMR/0211OBD-1033 and SPI/0211OBD-0631 trials identified in the inspections conducted by FDA and concludes that:

“Since 50% of the sites were found to be un-reliable and inadequately monitored, I recommend that the Sponsor should be asked to perform a third party audit on a reasonable percentage of sites and respond directly to OND. We can evaluate the audit report and make a decision whether we will consider another cycle of inspections or accept the report.”

However, based on my review, the data from these two pivotal trials can be considered reliable, and third-party audits are unlikely to reveal additional deficiencies that would materially impact application review. While the sponsor inspection uncovered deficiencies in the conduct and monitoring of the trials, the sponsor inspection also established that, for each trial, when the sponsor detected these deficiencies, the sponsor took steps to mitigate the deficiencies. Additionally, the sponsor has already undertaken extensive re-monitoring for the SMR/0211OBD-0631 trial. These actions ultimately render the data reliable for both trials. In my review below, I discuss the specific aspects of the sponsor inspection, not noted in Dr. Malek's review, supporting the conclusion that the data from the studies are reliable. I also review the inspections of clinical investigator sites and the impact of deficiencies noted during inspection. Finally, my review takes into account the randomized, double-blind, superiority design of these trials; the fact that the primary endpoint data were captured through direct patient entry into an eDiary; and the fact that this is a supplemental application for a product with a known safety profile. Each of these affords assurance that the data from these trials can be used for the respective indication of opioid induced constipation.

I. BACKGROUND:

The sponsor submitted a supplemental NDA 021908/S011 for the indication of treatment of opioid-induced constipation [REDACTED] (b) (4) in adults with chronic non-cancer pain. The product has been approved since 2006 for the treatment of chronic idiopathic constipation (CIC).

The review division requested inspection of two protocols:

1. Protocol SMR/0211OBD-1033 entitled “A Multicenter, Randomized, Placebo-controlled, Double-blinded Study of the Efficacy and Safety of Lubiprostone in Subjects with Opioid-Induced Bowel Dysfunction” was conducted from December 7, 2010 to November 16, 2011 and enrolled 447 subjects at a total of 105 investigative sites.
2. Protocol SPI/0211OBD-0631 entitled “A Multicenter, Randomized, Placebo-controlled, Double-blinded Study of the Efficacy and Safety of Lubiprostone in Patients with Opioid-induced Bowel Dysfunction” was conducted from August 3, 2007 to March 6, 2009, and

followed by an open label extension study period from Dec 2007 to September 2009. A total of 439 subjects received study drug at 80 investigative sites.

The following sites were chosen by the review division for inspection for Protocol SPI/0211OBD-0631:

- Site 1069 (Sandoval): Large number of subjects with disproportionately high responder status (~20%)
- Site 1018 (Leslie): Site with largest number of subjects

The following sites were chosen by the review division for inspection for Protocol SMR/0211OBD-1033:

- Site 3098 (Wolfson): Highest % of lubiprostone responders (32%) for a site with ≥ 10 subjects
- Site 3019 (Chilombo): Highest % of placebo non-responders (60%) for site with ≥ 10 subjects. The Sponsor informed FDA that a representative from the monitoring team of the CRO vendor expressed concerns regarding source documentation at Site 3019 while the trial was ongoing.

A sponsor inspection was not originally planned for this supplemental NDA review. However, in the course of inspections of the clinical sites, the following issues arose that warranted a sponsor inspection:

1. During the inspection of the Leslie site, FDA learned that remonitoring of the trial SMR/0211OBD-0631 had occurred after the study was closed, the database had been locked, and the study analyzed. A sponsor inspection was issued to determine the adequacy of monitoring during the trial and the adequacy of the remonitoring procedures, database lock and unlock and preservation of the blind for this study.
2. During the inspection of the clinical sites for both studies, it was determined that the primary efficacy endpoint submitted to the NDA (line listings) for both studies could not be verified at the clinical sites because a calculation was required to convert the raw eDiary data on the CDs at the clinical sites into the value that was submitted to the NDA.
3. When results of the inspection of the Chilombo and Dao sites became known, it became apparent that monitoring procedures and clinical trial conduct for both studies should be inspected and evaluated.

II. RESULTS (by Site):

Note that the table below, unlike Dr. Malek's review, indicates that all results are preliminary because they have not been formally reviewed and signed off in DARRTS.

Name of clinical investigator (CI) or Sponsor	Protocol #/ # of Subjects/ Site #	Inspection Date	Final Classification
Eric Wolfson, M.D. 6803 W. Tropicana, Las Vegas, NV89106	SMR/0211OBD-1033/ 19 Subjects/ Site 3098	November 26 to 29, 2012	Pending (Preliminary classification NAI)
Karamo Chilombo, M.D. 1530 E. South Street Long Beach, CA 90805	SMR/0211OBD-1033 10 Subjects/ Site 3019	October 30 to January 10, 2013	Pending (Preliminary classification OAI)
Nelson Sandoval, M.D. 5390 E. Erickson Drive Tucson, AZ 85712	SMR/0211OBD-0631 25 Subjects/ Site 1069	January 17 and 18, 2013	Pending (Preliminary classification VAI) ^a
Harvey Leslie, M.D. 3009 Rainbow Drive Decatur, GA 30034	SMR/0211OBD-0631 26 Subjects/ Site 1018	November 19 to 20 and November 26 to 29, 2012	Pending (Preliminary classification NAI) ^b
Sucampo Pharmaceuticals, Inc. 4520 East-West Highway Bethesda, MD 20814	SMR/0211OBD-1033 and SMR/0211OBD-0631	February 21 to 28, 2013	Pending (Preliminary classification VAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field. For each of these pending classifications, the EIR has been received from the field, but complete review of EIR is pending.

a. Dr. Dao participated in only the remonitoring, and was not responsible for the conduct of the study. While he signed a Form FDA 1572, he does not appear to meet the criteria to be a clinical investigator under FDA's regulations and is accordingly not responsible for record-keeping. The pending classification is VAI, but OSI considers that the data are not reliable in any case.

b. The field classification is NAI and the reclassification has not been discussed. Dr. Malik and I may not agree on a classification, but the data are considered reliable in any case.

I agree with Dr. Malek's findings concerning the Wolfson, Chilombo, and Dao sites, and those will not be discussed in this review, with the exception of the actions taken by the sponsor for the Chilombo site. My review of the Sponsor inspection and the Leslie clinical investigator site inspection, including additional information noted in the EIRs concerning these inspections, are discussed below.

1. **Harvey Leslie, M.D.**
Decatur, GA 30034

Note: Observations noted for this inspection are based on communications with the FDA investigator and preliminary review of the EIR. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

Additional observations/commentary: During the inspection of this site, OSI was made aware by the FDA field investigator of the existence of a re-monitoring program that occurred with Study SMR/0211OBD-0631 approximately two years after study closure. Concerning the remonitoring, according to the EIR and discussions with the FDA field investigator, [REDACTED]^{(b) (6)} signed a 1572 and conducted the remonitoring after the closure of the study. In the EIR, the FDA field investigator provides a narrative and evidence that a subject with an abnormal EKG was enrolled in the study. There is a note to file dated January 2009 concerning the abnormalities that were detected while the trial was ongoing and the subject was considered eligible. At the remonitoring, [REDACTED]^{(b) (6)} was requested to evaluate the EKG and determine eligibility. He initially changed the listing from eligible to ineligible and then back again. Evidence of any changing of data by [REDACTED]^{(b) (6)} was evident from the audit trails in the eCRF as observed by the FDA filed investigator.

Assessment of data integrity: Any changes made to the eCRF pages when the study was re-monitored were captured in the audit trails in the eCRF. The data generated at this site can be used in support of the NDA.

2. **Sucampo Pharmaceuticals, Inc.**
Bethesda, MD

Note: Observations noted for this inspection are based on communications with the FDA investigators and a preliminary review of the EIR. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

- a. **What was inspected:** The FDA investigators reviewed sponsor conduct related to the two clinical trials noted above. The inspection reviewed the oversight of the monitoring of the conduct and analysis of the trials noted above as well as expansion of monitoring into as well as the extension study 0631-s1 and 0632. Special attention was given to the computerized systems used to support the clinical trials.
- b. **General observations/commentary:** A Form FDA 483 was issued for failure to ensure proper monitoring while Study SMR/0211OBD-0631 was ongoing and for failing to report to the IRB a hold on enrollment for Site 1018. The field classification for the inspection is “voluntary action indicated” and the data is considered reliable.

The following are Dr. Malek's concerns (in italics) followed by my response to his concerns:

1. The CRO monitoring at the time of the study such as missing data, discrepant data, and unreported adverse events could not be resolved at study completion.

Team Leader Review:

As noted in the EIR, after the study, the sponsor worked to resolve the discrepancies concerning the safety data. The integrity of the efficacy data was not a concern because this patient reported outcome was collected via direct data capture. The nature of the discrepancies (adverse events [AEs], concomitant medications, abnormal physical findings that did not result in adverse events) and the eventual resolution provide evidence that the data are reliable. Additionally, the sponsor identified the issues and undertook a number of actions, including terminating their CRO, conducting audits, and instituting a remonitoring program to ensure the integrity of the data. The sponsor's actions are described in detail below.

According to the EIR and exhibits, Sucampo became aware of data discrepancies during the conduct of an extension study of Protocol 0631 (Extension Study 06S1) and also of Protocol 0632. Sucampo worked with (b) (4) the CRO responsible for monitoring at that time, to issue queries to resolve the discrepancies. Between September and November, 2009 six investigator site audits for Protocol 0631 were performed. The sites were chosen by enrollment levels, site staff turnover, and (b) (4) monitor turnover at the site during the study. The following sites were audited:

- Leslie: top enroller, had been on hold for screening earlier in the trial
- (b) (6)-Sandoval-Dao: second highest enroller
- Miller: third highest enroller
- Arif: third highest enroller
- St. James: first to enroll, encountered initial bugs in the eDiary, EDC and IVR systems
- Hazan: high staff turnover, problems in relationship with PI and monitor, long delay between enrollment and EDC entry.

Most discrepancies were resolved. The unresolved issues were further addressed with "notes to file" (NTF). An analysis of the category of the discrepancies and when they were detected (Study 0631 or 0632) was conducted. For Study 0631 the category of the 101 items of discrepant data was the following:

• Adverse events	15
• Concomitant medications	46
• ECG	2
• Medical History	14
• Opioid Medications	24

In November 2009, after the audits, Sucampo was concerned because of the large number of notes to file (101 NTF noted above) after the audits were conducted. The notes to file related to medical history or adverse events which were not recorded for the subjects during the time in Study 0631, but were subsequently reported in the Extension Study 06S1.

Because of the large numbers of NTFs, an audit of (b) (4) was conducted January and Feb 2010. The contract with (b) (4) was terminated and, on January 2011, a master services agreement between Sucampo and (b) (4) was executed that included remonitoring of the study.

Remonitoring

Remonitoring of clinical sites was primarily focused on capturing any unreported AEs. The efficacy data was considered reliable because it had been captured by patient direct entry into an eDiary and was sent directly to a CRO, (b) (4). The results of the audits conducted in 2009 were supplied to (b) (4) and a monitoring plan was established. Remonitoring of the data by (b) (4) was initiated in February 2011. The sponsor was concerned that data captured as abnormal during a physical examination, such as high blood pressure or as a laboratory value, were not appropriately captured per the protocol. Section 10.1.1 of the protocol defines adverse event as: An AE is any untoward event occurring to a patient during a clinical study, whether or not considered related to the study medication. This includes events not seen at baseline or which have worsened even if present at baseline.

From discussions with the FDA field investigator who conducted the sponsor investigation, there was confusion on the part of the sponsor and monitor as to whether to categorize abnormal findings noted on physical examination eCRF as being either an adverse event because it had not been recorded on the medical history and was newly noted or not to categorize it as an AE because it was documented in the medical history.

In the case of sites for which the CI of record was no longer available, assignment of a replacement CI was requested for the purposes of overseeing and signing-off on any changes to EDC data resulting from source document review and reconciliation. In total, five sites from Study 0631 required replacement of CI of record. Note that three of these five sites had been audited in 2009 shortly after the close of the trial.

- Leslie: top enroller, had been on hold for screening earlier in the trial
- (b) (6)-Sandoval-Dao: second highest enroller
- St. James: first to enroll, encountered initial bugs in the eDiary, EDC and IVR systems

According to information submitted to the NDA, the resultant remonitoring of the entire trial disclosed additional AEs in only three subjects, and these subjects had been randomized to active product.

Team Leader comment: Although there were numerous issues with monitoring while the study was ongoing, the sponsor identified inadequate monitoring during the extension study so that the sponsor could work with the original CRO in an effort to resolve the issues. As described above, the discrepancies do not appear to involve significant adverse events, but rather an attempt to characterize an abnormal physical finding or reconcile a concomitant medication record. Many of the issues were resolved through efforts to identify and rectify discrepancies. In addition, the sponsor identified high risk sites and conducted audits of these sites. It should be noted that FDA just

received notification that the Hazan site identified by this sponsor was terminated by another sponsor. The sponsor also acted appropriately by auditing the CRO, replacing the CRO, and conducting additional remonitoring.

2. *Site 1018 (Leslie site) was put on hold on 3/5/08 and it was never reported to the IRB, during the re-monitoring for study 0631, the sites were able to add data to the EDC.;*
3. *The monitoring for protocol 1033 was done less frequently than what was agreed upon.*
4. *The manually calculated SBM for some subjects were found identical to line listing data submitted to FDA.*

Team Leader Review:

Dr. Malek and I agree that Item 2 does not raise issues concerning data integrity at Site 1018. Item 3 cites minor violations in that, for four instances, the duration between monitoring visits was a maximum of 3 weeks outside the acceptable window. Item 4 notes that the efficacy data submitted to the NDA was able to be verified.

5. *CFR 212.53(a) states that “A sponsor shall select only investigators qualified by training and experience as appropriate experts to investigate the drug” It is noted that Dr. Chilombo had less than one year of research experience and Dr. Moreno was arrested for practicing without proper certification.*

Team Leader Review:

The sponsor and monitors identified issues with these sites while the study was ongoing. Both the Chilombo site and Moreno site were administered by [REDACTED] (b) (6), a clinical research associate. Dr. Chilombo’s site enrolled ten subjects and Dr. Moreno’s site enrolled five subjects. Although an independent third party audit could not find evidence of falsification at either site, the sponsor chose to submit a modified intent to treat (mITT) analysis of the data to FDA excluding the Chilombo and Moreno sites. The Clinical Study report Section 9.6 “Data Quality Assurance” states: Routine monitoring and subsequent audit of data collected at Sites 3019. As a result, the modified intent-to-treat population excluded data from Sites 3019 and 3119. (Note that the original CSR referred to Dr. Chilombo’s site as “3109”. This error was corrected in subsequent communications to the NDA.)

Team Leader comment: Note that the clinical study was conducted over the course of slightly over a year and that there is a short time frame during which the sponsor can detect issues and bring the CI into compliance. To Sucampo’s credit, the sponsor requested a third party audit and the auditor could not detect fraud in the two day inspection. The FDA field investigator that inspected the Chilombo site was alerted to problems because she had suspicions concerning [REDACTED] (b) (6) from a previous inspection. Her inspection and investigation for this NDA included review of the records over a two week period, affidavits from subjects and relatives, and investigations such as lack of existence of subject addresses on Google maps.

6. *At sites 1069 and 1018, there were 3 PIs for each site, one after the other. This caused improper supervision and less concentration on the different aspects of the study, in my opinion.*

Team Leader Review:

Although the observation concerning the number of PIs is correct, this finding, in and of itself, does not raise questions concerning data integrity.

7. *The re-monitoring of the study and changing some data, 2 years after closure of the study is alarming.*

Team Leader Review: refer to Item 1 above

As noted in response to Item 1 above, the remonitoring occurred for only the safety aspects, not the efficacy data and there was a plan for the remonitoring. Audit trails exist to document the changes in data. Although remonitoring so late after closure of a trial is unusual, this is not necessarily alarming. The changes to the data were evident in the audit trails in the eCRF.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Inspections of four clinical sites and the sponsor were conducted for this application. As noted in the Executive Summary above, based on my review, the data from these two pivotal trials can be considered reliable, and third-party audits are unlikely to reveal additional deficiencies that would materially impact application review. The data from the Wolfson site for Protocol SMR/0211OBD-1033 and from the Leslie site (Site 1018) for Protocol SMR/0211OBD-0631 are considered reliable. The source documents for Site 1069 (Sandoval-Dao) for Protocol SMR/0211OBD-0631 were destroyed; data cannot be verified, and are thus considered unreliable. As noted in Dr. Malek's review, the data from the Chilombo site (Site 3019) for Protocol SMR/0211OBD-1033 is considered unreliable based on the FDA inspection that indicates serious issues concerning non-compliance. These findings concerning the Chilombo and Dao sites were discussed with the review division in a series of e-mails and meetings while the review was ongoing.

Inspection of the sponsor observed deficiencies concerning monitoring as noted above and in Dr. Malek's review. However, the sponsor inspection also provided evidence that the sponsor took actions so that the data is considered reliable for both studies. For Protocol SMR/0211OBD-0631 the sponsor worked to mitigate issues with poor monitoring. For Protocol SMR/0211OBD-1033, there was an issue with falsification that was suspected by the sponsor but was not detected with a third party audit. Nevertheless, the sponsor, based on suspicions, provided the information concerning questionable data integrity to FDA and conducted an analysis in which data from the Chilombo and Moreno sites were removed.

For both studies, the efficacy data was captured with direct patient reporting and there were no questions concerning this data. Randomized double blind controlled study designs afford additional assurance that the efficacy data generated by the studies can be used for the support of this indication. It is interesting to note that the Chilombo site, the most violative, had the highest placebo response. Concerning the safety issues, the sponsor identified issues late in the trial for SMR/0211OBD-0631 and, during the extension trial and after the closure of the trials, worked with the auditors and the new CRO responsible for monitoring to correct the discrepancies.

An addendum to this CIS will be issued if conclusions change when the classifications for the inspections have been finalized.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Ann Meeker O'Connell
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN LEIBENHAUT
03/27/2013

WINIFRED M MEEKER - O'CONNELL
03/27/2013

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: March 27, 2013

TO: Maureen Dewey, Project Manager
Farrokh Sohrabi, Medical Officer

FROM: Khairy Malek, M.D., Ph.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 021-908/SD-011

APPLICANT: Sucampo Pharma, LLC

DRUG: Amitiza (lupiprostone)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: (b) (4)

CONSULTATION REQUEST DATE: September 6, 2012

DIVISION ACTION GOAL DATE: March 27, 2013

PDUFA DATE: April 18, 2013

I. BACKGROUND:

Constipation severity over 6-12 month periods. Data gathered from gastrointestinal transit tests in healthy volunteers treated with lubiprostone showed significant acceleration of small bowel and colon transit. Lubiprostone is approved for the treatment of chronic idiopathic constipation (CIC) in the adult population. CIC is generally associated with infrequent or difficult passage of stool, abdominal pain or discomfort, abdominal bloating, straining, and hard or lumpy stools. Long-term studies of lubiprostone showed improvements in abdominal bloating, abdominal discomfort, and Lubiprostone in doses of 24 mg BID was found to be safe and generally well tolerated in patients with CIC in clinical studies. The most commonly reported adverse events were nausea, diarrhea, headache, abdominal pain, abdominal distention, and flatulence.

Opioids are widely used in the management of acute and chronic pain and are known to inhibit gastrointestinal motility. One of the most common side effects reported in the use of opioids is opioid-induced bowel dysfunction (OBD). OBD is characterized by dry hard stools, straining during evacuation, nausea, vomiting and sometimes gastric retention. Studies have shown that long-term opioid use results in greater bowel dysfunction. Reducing this common and debilitating side effect is considered of great importance to the patient's quality of life.

The protocols inspected include:

1. Protocol SPI/0211OBD-0631: "A Multicenter, Randomized, Placebo-controlled, Double-blinded Study of the Efficacy and Safety of Lubiprostone in Patients with Opioid-induced Bowel Dysfunction."-Phase 3
2. Protocol SMR/0211OBD-1033: "A Multicenter, Randomized, Placebo-controlled, Double-blinded Study of the Efficacy and Safety of Lubiprostone in Subjects with Opioid-Induced Bowel Dysfunction."-Phase 3

II. RESULTS (by Site):

Name of CI & Location Site #	Protocol # and # of Subjects	Inspection Date	Final Classification
Eric Wolfson, D.O. Las Vegas, NV Site # 3098	SMR/021IOBD- 1033 19 Subjects	11/26-11/29, 2012	NAI
Karmo Chilombo, M.D. South St., Long Beach, CA Site # 3019	SMR/021IOBD- 1033 10 Subjects	10/30/12- 1/10/2013	OAI
Nelson Sandoval, M.D. (b) (6) Michael Dao, M.D. Site # 1069	SMR/021IOBD- 0631 25 Subjects	1/17-1/18, 2012	OAI
Harvey Leslie, M.D. (b) (6) Decatur, GA-Site 1018	SMR/021IOBD- 0631 28 Subjects	11/19-29, 2012	VAI
Sucampo Pharma Bethesda, MD	SMR/021IOBD- 0631 SMR/021IOBD- 1033	2/21-28/2013	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Eric Wolfson, D.O.-Site 3098
6803 W. Tropicana Ave., Suite 100, Las Vegas, NV 89106

a. What was inspected: 19 Subjects were randomized at this site. The field investigator reviewed the records of all subjects including: consent forms, medical records, source documents and case report forms. Source documents and CRFs were audited against data listings provided to the FDA and were found consistent. There was no under-reporting of adverse events. Efficacy data was transmitted electronically via the electronic diaries. The CI and study coordinator had access via username and password and they could make corrections to CRFs. Protocol deviations were all reported and entered in the CRFs as well as concomitant medications, adverse events, and opioids.

b. General observations/commentary: The field investigator did not report any

violations of federal regulations at this site

- c. **Assessment of data integrity:** The data collected from this site can be used in support of the NDA supplement.

2. **Karamo Chilombo, M .D.**

7301 State Street, Huntington Park, CA 90255

- a. **What was inspected:** Twelve subjects were screened at this site, 11 were randomized and 9 completed the study as one subject was in-eligible and one was lost to follow-up. The field investigator reviewed the records of all subjects including randomization, protocol deviations, adverse events, consent forms. A review of eCRF data for primary endpoint data showed that the bowel movement frequency was reported differently in the eCRFs than in the source documents.. The original eDiaries were not available for review and efficacy could not be confirmed. Drug accountability records were correct.
- b. **General observations/commentary:** Review of the EIR showed many deficiencies: lack of supervision by the CI; electronic diaries were not available and so efficacy parameters could not be confirmed; numerous protocol violations; the PI failed to maintain the study records.
- c. **Assessment of data integrity:** The data generated at this site are un-reliable, unacceptable and cannot be used in support of the NDA supplement.

3. **Nelson Sandoval,** [REDACTED] ^{(b) (6)} **& Michael Dao**
5390 E. Erickson Dr. , Tucson, AZ 85712

- a. **What was inspected:** Three PIs participated at this site. Dr. Dao was not a CI for the study, but was responsible for supervising the re-monitoring. At this site 25 subjects were supposedly enrolled.
- b. **General observations/commentary:** The field investigator did not find any records at the site and was told that the records were inadvertently shredded while in storage. The FDA could not verify the data.
- c. **Assessment of data integrity:** Data from this site could not be verified and unacceptable.

4. **Drs. Devon Briggs, Harvey Leslie,** [REDACTED] ^{(b) (6)} **:**
3009 Rainbow Drive, Suite 146, Decatur, GA 30034

- a. **What was inspected:** Dr. Briggs served as the first PI from November 2007 to August 2008; Dr. Leslie became PI in August 2008 until the end of the study in April 2009 and refused to stay after that. [REDACTED] ^{(b) (6)} signed the 1572 in 2011 and he was not a CI for the study but only supervised the re-monitoring visit in 2011. At this site 26 subjects

were randomized. One was randomized in error and was early terminated. Twenty four subjects completed the study. The field investigator reviewed all the records.

- b. General Observations/Commentary:** The first monitoring visit was done on 12/13/07. The second monitoring visit was done on 2/19/08. After the second monitoring visit, (b) (4) sent an e-mail to Sucampo reporting multiple CRF issues, in-eligible subjects randomized, multiple issues with source documents versus EDC and the PI was unavailable for 3 monitoring visits. The site was put on enrollment hold on 3/5/08. On the next monitoring visit on 3/25/08, the monitor found other deficiencies which included inconsistencies with the PI signature, sub-investigators with no US medical license although listed on the 1572v as MD, other staff members performing physical exams and review lab results and Inclusion criteria were corrected without source data being added. An audit was made on 4/29/08 and the PI and the monitor were changed. The site was allowed to enroll subjects in mid-August 2008. The re-monitoring of the site was done on June 6-10, 2011.
- c. Assessment of data integrity:** There are many violations reported, but the data can be used in support of the NDA Supplement

5. Inspection of the Sponsor Sucampo Pharmaceuticals:

- a. What was Inspected:** This inspection was performed by the field investigator and an Operation Research Analyst from OSI. The team reviewed the Sponsor/CRO agreement monitoring and re-monitoring reports (re-monitoring was done by (b) (4) in 2011). According to the field investigator, the only data which could be changed or updated is missing or discrepant data with clear supporting source documents in the file. The FDA team reviewed data from the sites inspected.
- b. General Observations/Commentary:** The FDA reported the following: 1. The CRO monitoring at the time of the study such as missing data, discrepant data, and unreported adverse events could not be resolved at study completion; Site 1018 (Leslie site) was put on hold on 3/5/08 and it was never reported to the IRB, during the re-monitoring for study 0631, the sites were able to add data to the EDC.; The monitoring for protocol 1033 was done less frequently than what was agreed upon. The manually calculated SBM for some subjects were found identical to line listing data submitted to FDA. The inspection was classified as VAI.
- Other Observations:
1. CFR 212.53(a) states that “A sponsor shall select **only** investigators qualified by training and experience as appropriate experts to investigate the drug” It is noted that Dr. Chilombo had less than one year of research experience and Dr. Moreno was arrested for practicing without proper certification.
 2. At sites 1069 and 1018, there were 3 PIs for each site, one after the other.. This caused improper supervision and less concentration on the different aspects of the study, in my opinion

3. The re-monitoring of the study and changing some data, 2 years after closure of the study is alarming.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from sites 3098 (Wolfson) and site 1018 (Dr. Leslie) are acceptable, while the data from site 3019 (Dr. Chilombo) and site 1069 (Dr. Dao) are unacceptable and cannot be used.

Since 50% of the sites were found to be un-reliable and inadequately monitored, I recommend that the Sponsor should be asked to perform a third party audit on a reasonable percentage of sites and respond directly to OND.

We can evaluate the audit report and make a decision and make a decision whether we will consider another cycle of inspections or accept the report.

{See appended electronic signature page}

Khairy Malek, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KHAIRY W MALEK
03/26/2013

SUSAN LEIBENHAUT
03/27/2013

Please see the team leader CIS review entered into DARRTS today and signed off by the Division Director for a different conclusion than this review.



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date: March 7, 2013

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Hari Cheryl Sachs, MD, Team Leader
Pediatric and Maternal Health Staff, Office of New Drugs

Lynne Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

NDA: 21908/S011 (Efficacy Supplement – New Indication)

Applicant: Sucampo Pharmaceuticals, Inc.

Drug: Amitiza (lubiprostone) Capsules

Indication: Treatment of opioid-induced constipation in adults with chronic, non-cancer pain

Consult Request:

On August 17, 2012, the Division of Gastroenterology and Inborn Errors of Metabolism Products (DGIEP) requested Pediatric and Maternal Health (PMHS) Pediatric Review Committee (PeRC) paperwork assistance for the new Efficacy Supplement for Amitiza (lubiprostone) Capsules for the treatment of opioid-induced constipation in adults with chronic, non-cancer pain.

INTRODUCTION

On July 20, 2012, Sucampo Pharmaceuticals, Inc. submitted an Efficacy Supplement (21908/S011) for Amitiza (lubiprostone) Capsules for the treatment of opioid-induced constipation in adults with chronic, non-cancer pain. The Pediatric Research Equity Act (PREA) was triggered because of this new indication and the applicant submitted their required Pediatric Plan with the Supplemental Application.

The Division of Gastroenterology and Inborn Errors of Metabolism Products (DGIEP) requested Pediatric and Maternal Health (PMHS) with Pediatric Review Committee (PeRC) preparation assistance.

BACKGROUND

Lubiprostone is a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. Lubiprostone acts by specifically activating ClC-2, which is a normal constituent of the apical membrane of the human intestine, in a protein kinase A-independent fashion.¹

Amitiza Regulatory History

- January 31, 2006: initial U.S. Approval for the treatment of chronic idiopathic constipation in the adult population.
- April 29, 2008: Approved for treatment of Irritable Bowel Syndrome with constipation in women 18 years and older.

The Applicant has outstanding, overdue PREA requirements for these two indications. A deferral/extension request was submitted on January 4, 2012, which will be discussed at a future Pediatric Review Committee (PeRC) meeting. The applicant has also requested a meeting to discuss these outstanding pediatric study requirements. These PREA requirements will be discussed and handled separately from the Efficacy Supplement under review.

The Applicant requested a deferral of PREA required studies in pediatric patients ages 6 months to 17 years of age and a waiver request in pediatric patients 0 to 6 months of age, both for the indication of opioid-induced constipation.

DISCUSSION

PMHS assisted with the PeRC preparation for the February 13, 2013 PeRC meeting at which PREA requirements for this Amitiza Supplemental Application were discussed. PeRC, PMHS, and DGIEP did not concur with the applicant's deferral request in pediatric patients ages 6 months to 17 years of age and instead recommended a full waiver of pediatric studies for opioid-induced constipation because studies would be impossible of highly impracticable. There is a lack of consensus on the use of opioids for treatment of chronic non-cancer pain in pediatric patients. Multiple published references have noted that conducting safety and efficacy trials in pediatric patients with opioid-induced constipation remains a challenge. Studies of pediatric patients with pain due to cancer or advanced medical illness are also challenging to conduct due to the difficulties

¹ See Amitiza approved labeling, November 26, 2012

of studying children in a palliative care environment. Thus, PMHS and DGIEP both agree that a waiver for studies in all pediatric age groups should be granted because studies would be impossible or highly impracticable.

CONCLUSION

PMHS assisted DGIEP with PeRC preparation for Amitiza for the indication of opioid-induced constipation with the treatment of chronic non-cancer pain. PeRC granted a full waiver of pediatric studies for this indication because studies would be impossible or highly impracticable. The outstanding, overdue PREA requirements for chronic idiopathic constipation and irritable bowel syndrome with constipation will be discussed and handled separately from this Supplemental Application.

Pediatric Use labeling was revised to reflect the appropriate regulatory statement under 21 CFR 201.57(c)(9)(iv) when safety and effectiveness have not been established:

 (b) (6)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEANINE A BEST
03/07/2013

HARI C SACHS
03/08/2013

LYNNE P YAO
03/08/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: December 13, 2012

Reviewer: Denise V. Baugh, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, PharmD, M.S.
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, R.Ph.
Division of Medication Error Prevention and Analysis

Drug Name: Amitiza (Lubiprostone) Capsules

Strength(s): 8 mcg, and 24 mcg

Application Type/Number: NDA 021908

Submission Number: S-011

Applicant: Sucampo Pharmaceuticals, LLC

OSE RCM #: 2012-2523

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1	Introduction.....	1
1.1	Regulatory History	1
1.2	Product Information	1
2	Methods and Materials Reviewed.....	1
2.1	Selection of Medication Error Cases.....	2
2.2	Labels and Labeling	2
2.3	Previously Completed Reviews	2
3	Medication Error Risk Assessment.....	3
3.1	Medication Error Cases.....	3
3.2	Integrated Summary of Medication Error Risk Assessment	4
4	Conclusions.....	4
5	Recommendations.....	5
	Appendices.....	6
	Appendix A. Database Descriptions.....	6

1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Amitiza (Lubiprostone) for NDA 021908. The Applicant submitted an efficacy supplement (S-011) which proposes the addition of an indication for treatment of opioid-induced constipation and associated signs and symptoms in adults with chronic, non-cancer pain.

1.1 REGULATORY HISTORY

Amitiza (Lubiprostone) was approved January 31, 2006 under NDA 021908 and was originally marketed as a 24 mcg capsule for the treatment of chronic idiopathic constipation in adults. In 2007, the indication was expanded to include irritable bowel syndrome with constipation in adults and an 8 mcg strength was added for this indication.

1.2 PRODUCT INFORMATION

The following product information is provided in the October 26, 2012 labeling submission.

- Active Ingredient: Lubiprostone
- Indication of Use: *current* – treatment of chronic idiopathic constipation in adults and treatment of irritable bowel syndrome with constipation in women 18 years of age and older; *proposed* - treatment of opioid induced constipation [REDACTED] (b) (4) [REDACTED] in adults with chronic, non-cancer pain
- Route of Administration: oral
- Dosage Form: capsules
- Strength: 8 mcg and 24 mcg
- Dose and Frequency: *current*: chronic idiopathic constipation – 24 mcg orally twice daily; irritable bowel syndrome with constipation – 8 mcg orally twice daily; *proposed*: treatment of opioid induced constipation [REDACTED] (b) (4) [REDACTED] in adults with chronic, non-cancer pain – 24 mcg orally twice daily
- How Supplied: 60 count bottles (8 mcg and 24 mcg); 100 count bottles (24 mcg)
- Storage: 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
- Container and Closure System: 60 count white HDPE bottle with child resistant container

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Amitiza medication error reports. We also reviewed the Amitiza labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 1.

Table 1: FAERS Search Strategy	
Date	November 20, 2012 (no time limitations)
Drug Names	Active Ingredient - Lubiprostone
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database searches identified thirty-three cases, respectively. Each case was reviewed for relevancy and duplication. After individual review, twenty-one cases were not included in the final analysis for the following reasons:

- Adverse event unrelated to a medication error
- Product complaints

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following label and labeling submitted in the Annual Report dated March 30, 2012:

- Container Labels submitted with the Annual Report dated March 30, 2012 (Appendix B)
- Professional Sample Carton Labeling (Appendix B)
- Professional Sample Blistercard (Appendix B)
- Insert Labeling submitted October 26, 2012 (no image)

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed label and labeling (OSE Review # 2007-1634 dated November 14, 2007) and we looked at the review to ensure all of our recommendations were implemented or considered.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

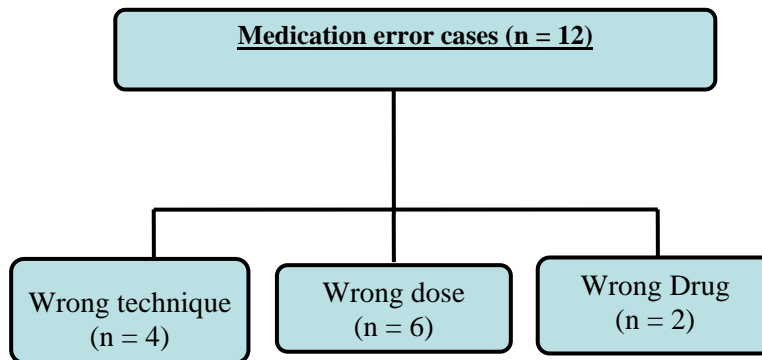
3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the Amitiza product design as well as the associated label and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, twelve Amitiza medication error cases remained for our detailed analysis. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter². Figure 1 provides a stratification of the number of cases included in the review by type of error. Appendix C provides listings of all case numbers for the cases summarized in this review.

Figure 1: Amitiza Medication Errors (n = 12) categorized by type of error



3.1.1 Wrong Technique (n = 4)

There were four wrong technique errors in which the patient punctured (n = 1) or chewed (n = 2) the capsule and in one case, the patient was given the product via a naso-gastric tube (n = 1). One of the reporters stated the capsule was punctured to remove a partial dose in an attempt to decrease the adverse effects. Another patient was instructed by their prescriber to chew the capsule after having difficulty swallowing it whole. This patient experienced mouth numbness and pieces of the shell became lodged in his windpipe making it difficult to breathe. He also found the product to be ineffective. Reasons for manipulating the capsule were not given in the other 2 cases. However, the outcome for both cases was difficulty breathing (described as dyspnea and shortness of breath).

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

3.1.2 Wrong Dose (n = 6)

The majority of the wrong dose cases (n = 5) were the result of the patient's confusion or forgetfulness and all of them exceeded the recommended dose and resulted in a labeled adverse event such as diarrhea, nausea, vomiting, or difficulty breathing. These events were severe enough in three of the cases that an action/intervention was necessary (e.g., hospitalization, use of inhaler or contacting the physician's office).

3.1.3 Wrong Drug (n = 2)

In the first accidental overdose case, the patient mistook Amitiza for a preparation to be ingested prior to their colonoscopy. The patient experienced headaches and diarrhea and was subsequently admitted to the hospital with a diagnosis of metabolic alkalosis. The second case describes a patient who awakened from his sleep and grabbed a bottle that he believed was his evening medications. Instead, he consumed 40 to 45 (Amitiza) 8 mcg capsules necessitating hospitalization for nausea, vomiting, and diarrhea.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

We do not anticipate that the addition of this new indication to the insert labeling will cause confusion since it does not require a new strength or a different regimen from that which has been used previously. Specifically, the dose, frequency of administration, duration of use and administration instructions ("with food and water") for this new indication is the same as that for patients with chronic idiopathic constipation.

However, four of the twelve medication error cases involved wrong technique and two of the cases resulted in distressing outcomes (e.g., difficulty breathing, shortness of breath). We note that the statement "The capsule should be swallowed whole and should not be broken apart or chewed" appears in the Patient Counseling Information subsection (17) under the Full Prescribing Information heading in the insert labeling, but this statement does not appear in the dosage and administration section or on the container label or sample carton labeling. Although the physician may instruct the patient in the proper administration of this product, the statement should be repeated in other locations to reinforce this issue to the user. See Section 5 for our recommendations.

4 CONCLUSIONS

DMEPA concludes that the proposed container label and sample labeling can be improved to increase the readability and prominence of important information to promote the safe use of the product and to clarify information.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA supplement:

A. Comments to the Division

Consider adding the following statement to the Dosage and Administration Subsection under the Highlights of Prescribing Information and the Full Prescribing Information Headings: “Capsules should be swallowed whole and should not be broken apart or chewed”. Addition of this statement will maintain consistency with its appearance in the Patient Counseling Information Subsection (17) of the insert labeling.

B. Comments to the Applicant

1. All Container Labels and Professional Sample Labeling

- a. Revise the presentation of the proprietary name, from all lower case “amitiza” to title case “Amitiza” to improve its readability and to further distinguish it from the active ingredient.
- b. Add the following statement to all container labels and sample labeling (e.g., blister card and sample tray): “Swallow Whole – Do NOT Break Apart or Chew”. Addition of this statement may reinforce this message, which is found in the Patient Counseling Information Subsection (17) of the insert labeling and may help minimize the occurrence of wrong technique errors.

2. All Container Labels (24 mcg [60 count and 100 count] and 8 mcg [60 count])

- a. Relocate the statement “Marketed by: Sucampo” to the side panel to accommodate recommendation B(1)(b)
- b. Consider deleting the statement (b) (4) from the side panel to minimize clutter and allow room for recommendation B(2)(a).

3. Professional Sample Blister Card

- a. Add the statement “Each capsule contains XX mcg” to clearly state the amount contained in each capsule and to minimize accidental overdoses.

4. Professional Carton Labeling and Sample Tray (24 mcg)

- a. Although the established name (active ingredient and dosage form) is at least half the size of the proprietary name, it lacks prominence due to either thin font size or lack of color contrast. Improve the prominence of the established name taking into consideration the typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

If you have further questions or need clarifications, please contact Phong (Pete) Do, OSE Project Manager at 301-796-4795.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Appendix C: Case numbers discussed in this review

Case #	Medication Error Type	FDA Recd Date	Narrative
6129489	Wrong technique	8/31/2006	Case Description: A 30-year-old female patient received oral lubiprostone (Amitiza) 24mcg for constipation in Aug2006, taking one capsule twice daily. While on Amitiza therapy, the patient experienced flushing, diarrhea, vertigo, and tachycardia. She also felt "horrible" and experienced heaviness in her chest. Feeling that the dosage was "too much for her, the patient punctured the capsules and took only half of the contents, which then failed to relieve her constipation.
6894056	Wrong Technique	1/21/2009	A female patient received oral lubiprostone (Amitiza) capsule (dosage indication, frequency and treatment dates were not reported). She took Amitiza by chewing the capsule and experienced wheezing and difficulty breathing. Amitiza therapy status and treatment for the events were not reported..
7964818	Wrong technique	5/4/2011	Case Description: A 51-year old male patient commenced treatment with oral Amitiza (lubiprostone), 24 mcg twice a day for chronic idiopathic constipation in 2008. After lubiprostone therapy started, the patient was unable to swallow an intact capsule which would become stuck in his esophagus. The patient described that is felt like the capsule was moving up and down his esophagus. The patient tried coating the capsules with a food oil to facilitate swallowing but this did not resolve the issue. The physician subsequently instructed the patient to bite down and chew the capsules gently to extrude the oily product and then spit out the shell pieces. After the patient bit into the capsules his mouth became numb. At unspecified times when the patient attempted to expectorate the capsule shell pieces of the shell would become lodged in his windpipe, became stuck in his throat which made it difficult to breathe. No treatment was reported.
8417906	Wrong technique	2/7/2012	A 59 year-old male patient commenced treatment with oral Amitiza (lubiprostone) 8 mcg once daily (in the evening) on 23JAN2012. The patient's wife reported that her husband was administered lubiprostone via his nasogastric (NG) tube, crushed with water. There was no administration of his liquid food supplement at that time. The patient experienced stomach distension and shortness of breath following the dose of lubiprostone. The time frame between the dose and the onset of the event was not reported. The patient's wife was unsure if the lubiprostone dose was related to the event, stating her husband had a history of stomach bloating and difficulty breathing when he was constipated. However, at the time of dosing, he was not constipated. No drug treatment for the events was reported. The events recovered. Therapy with lubiprostone was continued. No further information was reported.

6244406	Wrong dose (overdose)	2/8/2007	Case Description: A female patient aged 40 to 45 years old was prescribed lubiprostone (Amitiza) 24 mcg twice a day for constipation and irritable bowel syndrome. Subsequently, she experienced severe dehydration and diarrhea. She subsequently went to the emergency room. Relevant test results and treatment for the adverse events were not reported. On the first day of therapy, the patient took two capsules simultaneously. Within six hours, she experienced severe diarrhea and was taken to the emergency room. She was diagnosed with dehydration and treated with unspecified intravenous fluids. The events resolved and the patient was discharged from the emergency room on the same day. The Amitiza was discontinued after the initial use of the product.
6897762	Wrong dose (overdose)	1/21/2009	A female patient received oral lubiprostone (Amitiza) capsule twice daily (start date, indication and treatment dates were not reported). On an unspecified date, the patient left the physician's office by 14:00 and she went home and took one Amitiza capsule and then took another Amitiza capsule at bedtime. When she woke up the next morning, she experienced a headache and she took another Amitiza capsule by 09:00. Therefore, between 14:00 on the first day of when she took Amitiza and 09:00 on the second day when she took Amitiza, the patient had taken three Amitiza capsules. As a result, on this second day, she notified her physician's office she had experienced the "worse headache in her life", which was described as a severe headache. On that same day, she was taken to the local hospital via ambulance. Subsequently, she was admitted for three days. On an unspecified date, during her hospital stay a spinal tap was performed. Results for the spinal tap were not reported. Treatment for the events was not reported. Amitiza therapy was discontinued after only three capsules. It was not reported if the severe headache remained ongoing.
6960222	Wrong dose (overdose)	3/27/2009	My mother has been having chronic constipation with no relief over a few months. No over-the-counter medicines have been working. She was prescribed 2 tablets of Amitiza -24 mcg-. Mom was still in discomfort. She went to the ER. The GI specialist was called and he told the ER doctor to increase the dosage initially 2 more pills, but I asked the nurse to have the doctor to confirm the new dosage in writing. She returned with instructions to take 3 pills daily. I see nothing in your information to indicate a higher dosage could be used. Medication Error
6961076	Wrong dose (overdose)	3/27/2009	A 67-year-old female patient received oral lubiprostone (Amitiza) 24 mcg twice daily for the treatment of constipation. Sometime after she initiated Amitiza, she stated that one capsule did not work, therefore, on many occasions she took two tablets at a time. Subsequently, soon after she took Amitiza she experienced diarrhea. She also felt that her nausea and vomiting was controlled for several hours after she took her Amitiza, but it would come right back. As per the family, vomiting was usually more in the morning. It was not clear whether her nausea or vomiting was happening as a manifestation of acute renal failure or nausea or vomiting actually caused acute renal failure because of diminished oral intake. The Amitiza had caused significant nausea and vomiting. In 2008, she lost approximately ten pounds in the last three weeks and also was anorexic. She had generalized weakness. No

			difficulty in urination or frequency of urination.
7461905	Wrong dose (overdose)	6/30/2010	An approximately 37-year-old female patient commenced treatment with oral (Amitiza) lubiprostone 24 mcg samples twice daily, on 16JUN2010. On 16JUN2010, the patient took two lubiprostone 24 mcg capsules at the same time. Shortly after taking both capsules, she experienced dyspnea. The patient self treated herself with an unknown inhaler and the dyspnea resolved within four hours. Lubiprostone continued for one single dose of 48 mcg throughout the event. It was unknown if therapy with lubiprostone continued. The reporting RN did not provide the causality assessment of the event of dyspnea to lubiprostone.
8404102	Wrong dose (overdose)	2/1/2012	Case Description: A 70 year-old male patient commenced treatment with oral Amitiza (lubiprostone) 8 mcg twice daily for chronic constipation. The patient stated that he takes so many tablets for pain that he became confused and believed he took a second lubiprostone capsule by accident on, approximately 1 hour after his regular morning dose. The patient experienced gas, cramping, and diarrhea following this dose. Approximately 45 minutes to 1 hour later, the patient experienced shortness of breath, pressure in his throat, upper chest, head, and eyes and also felt woozy. He did not receive treatment for the events. The event outcomes were reported as unresolved.
6831132	Accidental Overdose	11/25/2008	The patient was instructed to receive an unspecified preparation (4 units every 15 minutes) for a colonoscopy. However, the patient mistook the Amitiza for the preparation and he overdosed on Amitiza and took 30 Amitiza capsules over 30 minutes instead. The patient began to experience headaches and diarrhea. Treatment for the events was not reported. Subsequently, the patient was admitted to the emergency room (ER) and was diagnosed with "metabolic alkalosis", which was not confirmed. Treatment consisted of electrolytes. On 05NOV2008, the patient recovered from taking an overdose of 30 Amitiza capsules. Amitiza therapy status and outcome of the rest of the events were not reported. It was unknown if the patient was admitted to the hospital. At the time of this report, the patient was not in the hospital.
7239164	Accidental overdose	12/22/2009	A male patient initiated oral lubiprostone (Amitiza) 8 mcg (frequency, therapy dates and indication were not provided). The patient fell asleep while watching television. Prior to midnight he awoke and realized that he had not taken his evening medications which he combined into one bottle. He grabbed a bottle and consumed 40-45 Amitiza 8 mcg capsules in error. He was taken by emergency workers to the hospital on 07DEC2009. He experienced nausea, vomiting and diarrhea for 6-8 hours. He was treated with charcoal and "anti-nausea shots." The events resolved and the patient was discharged. He was diagnosed with dehydration due to fluid loss and hypotension. His blood pressure was 126/98 that dropped to "63" when standing. The same day he also experienced "shiny black stools" and a "raw feeling throat

		making it hard to swallow." He believes that his oxygen therapy caused the raw feeling throat. He underwent a stool test that was negative for blood but positive for charcoal. The events resolved and the patient was discharged on 15DEC2009. On 15DEC2009, the patient also noticed a 15-20 pound weight loss. The patient's weight was 320 pounds on 07DEC2009 and on 15DEC2009 the patient's weight was 305-310 pounds. At the time of report, the weight loss had not resolved. Amitiza therapy continued.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

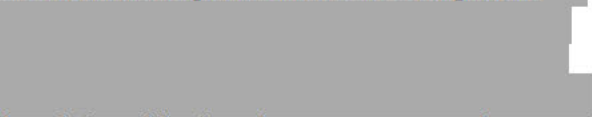
/s/

DENISE V BAUGH
12/13/2012

ZACHARY A OLESZCZUK on behalf of LUBNA A MERCHANT
12/14/2012

SCOTT M DALLAS
12/14/2012

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	AT 2012-102
APPLICATION NUMBER	IND 77771 NDA 21908/S011
LETTER DATE/SUBMISSION NUMBER	July 20, 2012
PDUFA GOAL DATE	January 18, 2013
DATE OF CONSULT REQUEST	August 23, 2012
REVIEW DIVISION	Division of Gastroenterology and Inborn Errors Products
MEDICAL REVIEWER	Farrokh Sohrabi
REVIEW DIVISION PM	Maureen Dewey
SEALD REVIEWER(S)	Ann Marie Trentacosti
REVIEW COMPLETION DATE	November 5, 2012
ESTABLISHED NAME	Lubiprostone
TRADE NAME	Amitiza
APPLICANT	Sucampo
ENDPOINT(S) CONCEPT(S)	Signs and Symptoms of Opioid Induced Constipation
MEASURE(S)	Electronic Diary
CLINICAL OUTCOME ASSESSMENT TYPE	Patient Reported Outcome
INDICATION	Treatment of opioid-induced constipation ^{(b) (4)}  in adults with chronic, non-cancer pain.

A. EXECUTIVE SUMMARY

This Study Endpoints and Labeling Development (SEALD) review is provided as a response to a request for consultation by the Division of Gastroenterology and Inborn Errors Products (DGIEP) regarding NDA 21908/S011 and the proposed indication of Amitiza for the treatment of opioid-induced constipation (OIC) [REDACTED] (b) (4)

[REDACTED] (b) (6)

[REDACTED] (b) (6)

Although statistically significant improvements relative to placebo in several OIC symptoms were observed in the Amitiza treated subjects in all three pivotal trials, it is unclear if these changes are clinically meaningful, because an a priori method of interpreting a treatment benefit (e.g., a responder definition) was not provided. The analyses of the OIC symptom data is also confounded by the fact that there was no adjustment for multiplicity in secondary endpoint statistical analyses which can inflate the probability of a Type I error.

A statistically significant change was not observed in all symptoms measured in the pivotal trials. Since a conceptual framework (relationship between items and the concepts they measure) was not proposed, it is unclear if this lack of statistical significance for individual items translates into a lack of efficacy for an overall domain (e.g., bowel movement symptoms). [REDACTED] (b) (6)

[REDACTED]

B. STUDY ENDPOINT REVIEW

[REDACTED] (b) (6)

1.2 Endpoint Model

The applicant did not submit an endpoint model.

2 CONCEPTUAL FRAMEWORK

The applicant did not provide a conceptual framework for their instrument.

3 CLINICAL OUTCOME ASSESSMENT MEASURE(S)

A patient-reported electronic daily diary that was administered at screening and throughout the Amitiza treatment phase included items which queried patients (b) (6)

(b) (6)

(b) (6)

(b) (6)

- (b) (6)
- (b) (6)
- (b) (6)

4 CONTENT VALIDITY

(b) (6)

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

(b) (6)

6 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

Studies OBD-0631 and OBD-0632 were conducted in North America (United States and Canada), whereas Study OBD-1033 was conducted in the United States and Europe.

Comments: Although Study OBD-1033 enrolled subjects from the European Union, the nationality of the European subjects was not identified. Therefore, it is unclear if the instrument required linguistic and cultural adaptation.

7 PROTOCOL AND ANALYSIS PLAN

The clinical efficacy of oral lubiprostone in the treatment of OIC was demonstrated through the conduct of 3 adequate and well-controlled studies OBD-1033, OBD-0631, and OBD-0632, and a 36-week open-label safety extension study OBD-06S1. Studies OBD-1033, OBD-0631 and OBD-0632 were carried out using similar study designs and these trials are considered the pivotal studies for this submission.

Enrollment Criteria:

In all 3 studies, the diagnosis of OIC required that subjects have an average of 3 or fewer SBMs per week during the last 2 weeks of the screening period and at least one of the following three OIC-associated symptoms for at least 25% of the SBMs during each week of the screening period: hard or very hard stools, sensation of incomplete evacuation, and/or moderate to very severe straining associated with the SBMs. “Spontaneous” was defined as bowel movements that occurred without the use of laxatives or stool softeners within the prior 24-hour period. Subjects who had a history of chronic constipation (≥ 90 days) were required to have experienced an exacerbation in their constipation after initiation of opioid therapy in order to qualify for study entry. Study OBD-1033 also excluded enrollment of subjects who were receiving treatment with methadone, methadone hydrochloride, or a congener of methadone either alone or as part of an opioid regimen.

Study Procedures:

Subjects who successfully completed the screening evaluations were randomized in a 1:1 ratio via an interactive voice response system (IVRS) or interactive web response system (IWRS) at the Randomization Visit to either the lubiprostone-treatment group, or the placebo treatment group. Subjects must have been compliant with screening diary entries ($>70\%$) and must have qualified as having OIC as per entries made during the two weeks immediately prior to their Randomization Visit. Subjects in both treatment groups were to receive double blind treatment with study medication for 12 weeks. Subjects were to continue to receive treatment with their opioid analgesic during the double-blind treatment period. Subjects were to take 1 capsule of study medication in the morning and 1 capsule of study medication in the evening with meals and with at least 8 ounces of fluid. Doses were to be taken at least 5 hours apart. Missed doses were to be made up as soon as possible, but the subjects were not to take both doses at the same time. The dose of study medication could be reduced to 1 capsule daily (total daily dose of lubiprostone, 24 mcg) if the subject experienced severe diarrhea, severe nausea, or another troublesome adverse event for 3 or more days. The subject was then to receive the reduced dose of study medication. Once a dose reduction occurred, the subject could resume administration of the twice daily dose regimen per Investigator discretion.

As part of the daily diary, subjects were asked to rate their stool consistency for any bowel movements that may have occurred during that day, straining associated with bowel movements, constipation severity, abdominal bloating, abdominal discomfort, and bowel habit regularity. Subjects were to complete the eDiary each evening during the treatment period. The diary was configured so that it could be completed each evening with the responses based on that day's activities or for the preceding day if the prior night's assessment had not been completed. Assessments will be separated into weeks (168-hour period) and months (4-week period) using the first day of study treatment dosing. The assessments made on the evening of the day when first dose was taken will serve as Day 1. Baseline values were determined using the average of all values collected during the 2-weeks (336 hours) prior to randomization.

Comments: As noted in the clinical protocols, the electronic diary was configured so that it could be completed each evening with the responses of that day's activities or for the preceding day, if the night's assessment had not been completed. Allowing patients to recall and record their symptoms 48 hours later could jeopardized the validity of the data.

Endpoints

A summary of the primary and secondary efficacy endpoints is described in Table 1.

Table 1. Protocol-Specific Primary and Secondary Efficacy Endpoints

Classification	Endpoint	Study Number		
		OBD-1033	OBD-0631	OBD-0632
Primary	Overall SBM response rate ^{1,2}	X	--	--
	Change from baseline in SBM ¹ frequency at Week 8 for subjects with no dose reductions	--	X	X
Secondary	Change from baseline in SBM frequency at:			
	Week 8	X	--	--
	Week 12	X	X	X
	Overall	X	X	X
	Percentage of subjects with first postdose SBM ¹ within 24 hours after first dose	X	X	X
	Percentage of subjects with first postdose SBM ¹ within 48 hours after first dose	X	X	X
	Weekly responder rates ³	X	--	--
	Overall responder rates ^{3,4}	--	X	X
	Health-related quality of life	X	--	--
	Overall mean change from baseline in:			
	Straining associated with SBMs ¹	X	X	X
	Stool consistency of SBMs ¹	X	X	X
	Constipation severity	X	X	X
	Abdominal bloating	X	X	X
	Abdominal discomfort	X	X	X
	Bowel habit regularity	X	X	X
Overall treatment effectiveness	X	X	X	

¹ A spontaneous bowel movement (SBM) was defined as any bowel movement that did not occur within 24 hours after use of a rescue medication.

² To be classified as an overall responder, subjects were required to demonstrate at least a moderate response (≥ 1 SBM improvement over baseline SBM frequency) for all treatment weeks for which observed data were available and to demonstrate a full response (≥ 3 SBMs per week) for at least 9 of the 12 treatment weeks.

³ Subjects were classified as full responders, moderate responders, or non-responders based on weekly SBM frequencies. A full responder was defined as a subject whose SBM frequency was ≥ 4 for the week; and a moderate responder had a SBM frequency of ≥ 3 but < 4 . A non-responder had < 3 SBM frequencies for the week, dropped out during or before the given week due to lack of efficacy, or used rescue medication during or within 24 hours prior to the given week.

⁴ An overall responder was in the study for at least 8 weeks and achieved at least moderate response for at least 50% of the weeks on the study.

There was only one primary endpoint which was the gatekeeper and there was no adjustment for multiplicity. Inferential analyses for secondary endpoints related to the primary endpoint were only performed if the primary endpoint was significant.

Comments: The analyses of the OIC symptom data is confounded by the fact that there was no adjustment for multiplicity in secondary endpoint statistical analyses which can inflate the probability of a Type I error.

Study Results

A statistically significant difference, favoring lubiprostone over placebo, was observed for the primary efficacy endpoint (change from baseline in the frequency of spontaneous bowel movements (SBMs) at Week 8) in one of the two Phase 3 studies (OBD-0631), whereas the second study (OBD-0632) failed to meet the threshold for statistical significance despite showing results in favor of lubiprostone. A subsequent laboratory investigation provided evidence that methadone likely inhibited the ability of lubiprostone to activate ClC-2 chloride channels, the primary mechanism of action for the drug, by negatively influencing both basal and stimulated ClC-2 currents at concentrations relevant to opioid therapy. Study OBD-1033 was subsequently conducted in subjects receiving non-methadone opioid therapy and the primary endpoint was changed to an overall SBM response evaluation over the entire 12-week study period upon discussion and agreement with the FDA.

Statistical findings concerning the secondary endpoints of individual symptoms of OIC in all 3 trials is described as follows:

- Study OBD-0631
Statistically significant improvements in **straining** associated with SBMs ($p \leq 0.001$), **stool consistency** ($p \leq 0.001$), **severity of constipation** ($p = 0.002$), and **abdominal discomfort** ($p = 0.024$) were observed with lubiprostone.
- Study OBD-0632
Statistically significant improvements, relative to placebo, were observed in the mean overall change from baseline in **straining** ($p = 0.039$) and **abdominal discomfort** ($p = 0.041$).
- Study OBD-1033
Statistically significant improvements in **straining** ($p = 0.002$), **stool consistency** ($p \leq 0.001$), and **constipation severity** ($p = 0.007$) were observed in the lubiprostone-treated subjects relative to the placebo-treated subjects. Mean changes from baseline between treatment groups in abdominal bloating and abdominal discomfort for the completer and per-protocol populations were not statistically significant.

Comments: For the two clinical trials in which a statistically significant improvement in the primary endpoint (Study OBD-0631: mean change from baseline in the frequency of SBMs at Week 8 in the subjects without dose reductions; and Study OBD-1033: overall SBM response rate) was observed in patients treated with lubiprostone compared with patients treated with placebo, a statistical improvement was also seen in straining, stool consistency, and constipation severity; but not in the other symptom endpoints (e.g., abdominal bloating or abdominal discomfort). The clinical protocols did not prespecify which secondary endpoints would show a statistical significance. In addition, information has not been provided concerning the interpretation of results (e.g., clinically meaningful change in score or responder). Therefore, the applicant has not justified how a statistical improvement equates

Ann Marie Trentacosti
NDA 21908/S011
Amitiza (Lubiprostone)

with a clinically significant improvement or that that a statistically significant improvement in a few but not all measured symptoms represents a clinically meaningful change in the overall condition for the patient.

D. APPENDICES

Daily Electronic Diary

1. Date and time of dose administration.
 - a. Did you take your morning dose of study medication today? Y/N
 - b. Did you take your evening dose of study medication today? Y/N
 - c. If “Yes” to either/both, the following information will be collected:
 - Morning Dose – xx:xx AM
 - Evening Dose – xx:xx PM

2. Date and time of any rescue medications used.
 - a. Did you take a medication, aside from your study medication, to help you have a BM in the past 24 hours (since yesterday’s bedtime report)? Y/N
If “Yes”.....How many medications of each type did you use?
 - Suppository – xx (number)
 - Enema – xx (number)
 - Other – xx (number)

 - b. Did you take a medication to help you have a BM since your office visit today? Y/N

 - c. For each rescue medication used, the following information will be collected:
For the [first, second, etc.] medication used, indicate the date and time of administration.
 - i. Suppository Date DD-MM-YYYY, xx:xx AM/PM
 - ii. Enema Date DD-MM-YYYY, xx:xx AM/PM
 - iii. Other Date DD-MM-YYYY, xx:xx AM/PM

3. Date and time of any adjustment of opioid medication.
 - a. Did you or your doctor change your opioid medication dose today? Y/N

 - b. For each change in opioid medication used, the following information will be collected:
 - i. Are you still taking your opioid medication? Y/N
 - ii. Did the name or type of your opioid medication change? Y/N
 - iii. Did the way you take your opioid medication change? Y/N
 - iv. Did the number of times per day that you take your opioid medication change? Y/N

4. The date and time of BMs (if any).
 - a. How many BMs did you have in the past 24 hours (since yesterday’s bedtime report)?
XXX

 - b. For each BM, the following series of questions will be asked:
 - i. What time did the [first, second, etc.] BM occur?
Date DD-MM-YYYY, xx:xx AM/PM

ii. Did your bowels feel completely empty after the BM? Y/N

iii. How would you rate the consistency of this BM?

0 = very loose

1 = loose

2 = normal

3 = hard

4 = very hard (little balls)

iv. How would you rate the straining associated with this BM?

0 = none

1 = mild

2 = moderate

3 = severe

4 = very severe

5. Evaluation of abdominal symptoms (bloating and discomfort) and constipation severity, using the following 5-point scale for each:

a. How would you rate your abdominal discomfort/pain today?

b. How would you rate your abdominal bloating today?

c. How would you rate your constipation today?

0 = absent

1 = mild

2 = moderate

3 = severe

4 = very severe

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN M TRENTACOSTI
11/05/2012

LAURIE B BURKE
11/06/2012

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Application: NDA 21908/S011

Application Type: Efficacy Supplement

Name of Drug: Amitiza (lubiprostone) Capsules

Applicant: Sucampo Pharmaceuticals LLC

Submission Date: 07/20/2012

Receipt Date: 07/20/2012

1.0 Regulatory History and Applicant's Main Proposals

PROPOSED INDICATION:

Treatment of opioid-induced constipation [REDACTED] (b) (4) in adults with chronic, non-cancer pain

BACKGROUND: Amitiza was approved on January 31, 2006, for the use in the treatment of chronic idiopathic constipation (CIC) in adults and was subsequently approved on April 29, 2008, as a treatment for IBS with constipation (IBS-C) in adult women employing a lower strength formulation (8 mcg). On July 20, 2012, the sponsor submitted a prior approval efficacy supplement for the proposed indication. On August 10, 2012, the sponsor submitted an amendment to the application to include request for waiver / deferral of pediatric studies and a pediatric plan.

Amitiza is currently approved for chronic idiopathic constipation and IBS-C. This supplement proposes to add the following indication:

"Treatment of opioid-induced constipation [REDACTED] (b) (4) in adults with chronic, non-cancer pain"

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and

Selected Requirements of Prescribing Information (SRPI)

resubmit the PI in Word format by October 24, 2012. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- NO** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

Selected Requirements of Prescribing Information (SRPI)

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

- YES** 10. Product title in HL must be **bolded**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

- N/A** 12. All text must be **bolded**.

Comment:

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- YES** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- YES** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- YES** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- YES** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES

Selected Requirements of Prescribing Information (SRPI)

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Selected Requirements of Prescribing Information (SRPI)

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading **“FULL PRESCRIBING INFORMATION: CONTENTS”** must be followed by an asterisk and the following statement must appear at the end of TOC: **“*Sections or subsections omitted from the Full Prescribing Information are not listed.”**

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: **“FULL PRESCRIBING INFORMATION”**.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS

Selected Requirements of Prescribing Information (SRPI)

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- YES** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

Selected Requirements of Prescribing Information (SRPI)

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- N/A** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
10/01/2012

RICHARD W ISHIHARA
10/03/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 21908 BLA#	NDA Supplement #:S-011 BLA Supplement #	Efficacy Supplement Type SE-01
Proprietary Name: Amitiza Established/Proper Name: lubiprostone Dosage Form: Capsules Strengths: 8 mcg, 24 mcg		
Applicant: Sucampo Pharmaceuticals LLC. Agent for Applicant (if applicable):		
Date of Application: July 20, 2012 Date of Receipt: July 20, 2012 Date clock started after UN:		
PDUFA Goal Date: January 18, 2013		Action Goal Date (if different):
Filing Date: September 18, 2012		Date of Filing Meeting: 8/23/2012
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication: Treatment of opioid-induced constipation (OIC) (b) (4) in adults with chronic, non-cancer pain.		
Type of Original NDA: AND (if applicable)	☐ 505(b)(1) ☐ 505(b)(2)	
Type of NDA Supplement:	☒ 505(b)(1) ☐ 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	☐ Standard ☒ Priority	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 77,771				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	☒			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	☒			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	☒			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒			

<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required																			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: ☒ Not in arrears ☐ In arrears																			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?																				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].																				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>																				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If yes, please list below: <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm		☒																		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		☒		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?				
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).	☒			
Index: Does the submission contain an accurate comprehensive index?	☒			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	☒			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?				
If yes, were all of them submitted on time?				
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?				
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	☒			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	☒			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	☒			

<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	☒			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	☒			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☒			
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>				

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	☒			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☒			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	☒			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		☒		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>			☒	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>			☒	
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	☐	Medication Guide (MedGuide)			
	☐	Carton labels			
	☐	Immediate container labels			
	☐	Diluent			
	☐	Other (specify)			
	YES	NO	NA	Comment	
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	☒				
Is the PI submitted in PLR format? ⁴	☒				
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>					
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒				
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)					
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?					
OTC Labeling	☒	Not Applicable			
Check all types of labeling submitted.	☐	Outer carton label			
	☐	Immediate container label			
	☐	Blister card			
	☐	Blister backing label			
	☐	Consumer Information Leaflet (CIL)			
	☐	Physician sample			
	☐	Consumer sample			
	☐	Other (specify)			
	YES	NO	NA	Comment	
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>					
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>					
If representative labeling is submitted, are all represented SKUs defined?					

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent: OSI (8/17/12) PMHS (8/17/2012) SEALD</i>	☒			
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		☒		2/3/2011 Advice Letter sent on Phase 3 protocol
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): March 6, 2012	☒			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		☒		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 23, 2012

BLA/NDA/Supp #: NDA 21908/S011

PROPRIETARY NAME: Amitiza

ESTABLISHED/PROPER NAME: lubiprostone

DOSAGE FORM/STRENGTH: Capsules (24 mcg, 8 mcg)

APPLICANT: Sucampo Pharmaceuticals LLC.

PROPOSED INDICATION:

Treatment of opioid-induced constipation [REDACTED] ^{(b) (4)} in adults with chronic, non-cancer pain

BACKGROUND: Amitiza was approved on January 31, 2006, for the use in the treatment of chronic idiopathic constipation (CIC) in adults and was subsequently approved on April 29, 2008, as a treatment for IBS with constipation (IBS-C) in adult women employing a lower strength formulation (8 mcg). On July 20, 2012, the sponsor submitted a prior approval efficacy supplement for the proposed indication. On August 10, 2012, the sponsor submitted an amendment to the application to include request for waiver / deferral of pediatric studies and a pediatric plan.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Maureen Dewey	y
	CPMS/TL:	Richard Ishihara	n
Cross-Discipline Team Leader (CDTL)	Rob Fiorentino		y
Clinical	Reviewer:	Farrokh Sohrabi	y
	TL:	Rob Fiorentino	y

Clinical Pharmacology	Reviewer:	Sandhya Apparaju	y
	TL:	Sue Chih Lee	n
Biostatistics	Reviewer:	Freda Cooner	y
	TL:	Mike Welch	y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sushanta Chakder	y
	TL:	Sushanta Chakder	y
Product Quality (CMC)	Reviewer:	Yong Wu	n
	TL:	Marie Kowblansky	y
Facility Review/Inspection	Reviewer:	Khairy Malek	y
	TL:	Susan Leibenhaut	n
Other reviewers			
Other attendees	Joyce Korvick (DDS), Denise Pica-Branco (PMHS), Nitin Patel (OSE), Matthew Scherer (RPM), Maria Walsh (ODE 3 ADRA)		

FILING MEETING DISCUSSION:

GENERAL 505(b)(2) filing issues? If yes, list issues:	☒ Not Applicable ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO
Electronic Submission comments List comments:	☐ Not Applicable
CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Clinical study site(s) inspections(s) needed? If no, explain:	☒ YES ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA , include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIostatistics	☐ Not Applicable

Comments:	☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments: Environmental assessment requested and subsequently received from the sponsor on 8/24/2012	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology (for sterile products)</u> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	☒ Not Applicable ☐ YES ☐ NO

<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? Comments: Not needed for Efficacy Supplement per CMC Reviewer.	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> Comments:	☐ Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: TBD Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): ~ October 26, 2012 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u>

	☐ Standard Review ☒ Priority Review
ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
09/12/2012

RICHARD W ISHIHARA
09/13/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021908/S-011

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21908

SUPPL # 011

HFD # 180

Trade Name Amitiza

Generic Name Lubiprostone

Applicant Name Sucampo Pharmaceuticals Americas, LLC

Approval Date, If Known: Original Approval 1/31/2006
Supplemental Approval 4/19/2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21908

Amitiza

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Protocol SMR/0211OBD-1033 entitled "A Multicenter, Randomized, Placebo-controlled, Double-blinded Study of the Efficacy and Safety of Lubiprostone in Subjects with Opioid-induced Bowel Dysfunction"; conducted from December 7, 2010 to November 16, 2011.

Protocol SPI/0211OBD-0631 entitled "A Multicenter, Randomized, Placebo-controlled, Double-blinded Study of the Efficacy and Safety of Lubiprostone in Patients with Opioid-induced Bowel Dysfunction"; conducted from August 3, 2007 to March 6, 2009.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, **investigations must be "new" to support exclusivity**. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

N/A

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Protocol SMR/0211OBD-1033 entitled "A Multicenter, Randomized, Placebo-controlled, Double-blinded Study of the Efficacy and Safety of Lubiprostone in Subjects with Opioid-induced Bowel Dysfunction"; conducted from December 7, 2010 to November 16, 2011.

Protocol SPI/0211OBD-0631 entitled "A Multicenter, Randomized, Placebo-controlled, Double-blinded Study of the Efficacy and Safety of Lubiprostone in Patients with Opioid-induced Bowel Dysfunction"; conducted from August 3, 2007 to March 6, 2009.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!

Farrokh Sohrabi, M.D.

Title: Medical Officer

Date: April 17, 2013

Maureen Dewey, M.P.H.

Title: Regulatory Project Manager

Date: April 17, 2013

Name of Office/Division Director signing form:

Joyce Korvick, M.D., M.P.H.

Title: Deputy Director for Safety

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
04/19/2013

JOYCE A KORVICK
04/19/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 21908 BLA #	NDA Supplement # 011 BLA Supplement #	If NDA, Efficacy Supplement Type: SE1
Proprietary Name: AMITIZA Established/Proper Name: Lubiprostone Dosage Form: Capsules (8 mcg, 25 mcg)		Applicant: Sucampo Pharma Americas, LLC Agent for Applicant (if applicable):
RPM: Maureen Dewey		Division: DGIEP
<u>NDA and NDA Efficacy Supplements:</u> NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)		<u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ This application does not rely upon a listed drug. ☐ This application relies on literature. ☐ This application relies on a final OTC monograph. ☐ This application relies on (explain) <u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u> <u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u> ☐ No changes ☐ Updated Date of check: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.
❖ Actions		
• Proposed action • User Fee Goal Date is <u>4/19/2013</u>		☒ AP ☐ TA ☐ CR
• Previous actions (<i>specify type and date for each action taken</i>)		☒ None

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics ³	
Review priority: ☐ Standard ☒ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rx-to-OTC full switch ☐ Rolling Review ☐ Rx-to-OTC partial switch ☐ Orphan drug designation ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC ☐ Submitted in response to a Pediatric Written Request BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies REMS: ☐ MedGuide ☐ Communication Plan ☐ ETASU ☐ MedGuide w/o REMS ☒ REMS not required Comments:	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☐ No
❖ Public communications (<i>approvals only</i>)	
Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
Press Office notified of action (by OEP)	☒ Yes ☐ No
Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i>	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i>	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). <i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i> <i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i>	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	4/19/2013
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	AP April 19, 2013
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	4/19/2013
• Original applicant-proposed labeling	7/20/2012
• Example of class labeling, if applicable	

⁴ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. • Original applicant-proposed labeling • Example of class labeling, if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	04/19/2013
❖ Proprietary Name • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.	n/a
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☒ RPM 10/03/2012 ☒ DMEPA 12/14/2012 ☐ DMPP/PLT (DRISK) ☒ ODPD (DDMAC) 3/29/2013 ☒ SEALD ☐ CSS ☐ Other review
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	RPM Filing Review 10/18/2012
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	☐ Not a (b)(2) ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC <u>2/13/2013</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	☐ Verified, statement is acceptable N/A Efficacy Supplement

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	08/07/2012 09/14/2012 Priority Design Ltr 09/14/2012 IR 10/02/2012 Filing Issues 10/05/2012 10/15/2012 11/9/2012 11/27/2012 Extension 11/29/2012 12/07/2012 01/18/2013 02/04/2013 02/07/2013 02/15/2013 03/7/2013 (Labeling) 03/15/2013 03/27/2013 03/28/2013 04/09/2013 04/17/2013(Labeling) 04/13/2013(Labeling) 04/17/2013(Labeling) 04/18/2013(Labeling) 04/19/2013(Labeling)
❖ Internal memoranda, telecons, etc.	11/19/2012 Tcon 04/04/2013 Tcon
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	☐ No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☐ N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☐ No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	☐ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	3/7/2012 PreEfficacy Suppl Mtg
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☐ None
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None 04/19/2013
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 04/19/2013
PMR/PMC Development Templates (<i>indicate total number</i>)	☒ None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	04/19/2013

⁶ Filing reviews should be filed with the discipline reviews.

Clinical review(s) <i>(indicate date for each review)</i>	4/4/2013; 08/30/2012
Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	☐ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	See page 21 of Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	☐ None SEALD Endpoints: 11/06/2012 PMHS: 03/08/2013 DAAAP 03/18/2013
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	☒ Not applicable
❖ Risk Management - REMS Documents and Supporting Statement <i>(indicate date(s) of submission(s))</i> - REMS Memo(s) and letter(s) <i>(indicate date(s))</i> - Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i>	☒ None
❖ OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i>	☐ None requested (2) 3/27/2013 No letters sent to investigators
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	☐ None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	☐ None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	☐ None
Statistical Review(s) <i>(indicate date for each review)</i>	☐ None 04/15/2013; 09/17/2012
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	☐ None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	☐ None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	☐ None 3/06/2013; 08/29/2012
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	☐ None

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	☐ None
• Supervisory Review(s) (<i>indicate date for each review</i>)	☐ None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	☐ None 3/18/2013; 08/23/2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☐ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☐ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	☐ None
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	☐ None
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	☐ None 10/01/2012; 09/07/2012
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>) ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)	☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	10/01/2012 (page 4 of CMC Review)
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: ☐ Acceptable ☐ Withhold recommendation ☒ Not applicable
☐ BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: ☐ Acceptable ☐ Withhold recommendation

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

❖ NDAs: Methods Validation (*check box only, do not include documents*)

- Completed
- Requested
- Not yet requested
- Not needed (per review)

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
04/19/2013

From: [Carey, Jeffrey](#)
To: [Dewey, Maureen](#)
Subject: RE: NDA 21908/S011
Date: Friday, April 19, 2013 2:05:13 PM

Hi Maureen,

Receipt confirmed. Thanks again.

Best regards,

Jeff

From: Dewey, Maureen [mailto:Maureen.Dewey@fda.hhs.gov]
Sent: Friday, April 19, 2013 1:56 PM
To: Carey, Jeffrey
Cc: Dewey, Maureen
Subject: NDA 21908/S011

Dear Mr. Carey,

Attached please find a courtesy copy of a formal correspondence regarding your supplemental new application for NDA 21908 Amitiza (lubiprostone) Capsules.

Kindly confirm receipt.

Regards,

Maureen Dewey, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Center for Drug Research and Evaluation
FDA
Office: (301) 796-0845
Fax: (301) 796-9904

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
04/19/2013

From: [Dewey, Maureen](#)
To: [Dewey, Maureen](#)
Subject: FW: Carton and Container Mock-Up
Date: Friday, April 19, 2013 10:08:25 AM

From: Baugh, Denise
Sent: Friday, April 19, 2013 9:44 AM
To: Dewey, Maureen
Cc: Merchant, Lubna; Korvick, Joyce A
Subject: RE: Carton and Container Mock-Up

Maureen,

DMEPA acknowledges that the Applicant is unwilling to consider the recommendations to revise the presentation of the proprietary name on the container label and carton labeling from all upper case to title case letters and to revise the "Each capsule contains XX mg" statement on the blister labels such that the information is not destroyed with the removal of a capsule from the blister. We therefore find the revised labels as submitted acceptable. However, if we retrieve medication error cases post marketing due to labeling, we may recommend additional regulatory action at that time.

Denise

Denise Baugh, PharmD, BCPS
Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Surveillance and Epidemiology
Bldg 22, Room 4428
(301)796-2266

"Together Everyone Achieves More"

From: Dewey, Maureen
Sent: Friday, April 19, 2013 9:25 AM
To: Baugh, Denise
Cc: Merchant, Lubna; Korvick, Joyce A
Subject: RE: Carton and Container Mock-Up

Denise,

The applicant is not amenable to changing the suggestion 1) and 2) at this point in time.

Maureen

From: Baugh, Denise
Sent: Thursday, April 18, 2013 4:24 PM
To: Dewey, Maureen
Cc: Merchant, Lubna
Subject: FW: Carton and Container Mock-Up
Importance: High

Hi, Maureen!

I have two recommendations remaining:

1) The Applicant presents their name as "AMITIZA" on all the labels/labeling and we would like it to be presented as 'Amitiza' (only the first letter is in upper case). This presentation improves readability of the name.

2) For the professional samples (marked as 8 mcg Print Mat and 24 mcg Print Mat on the attachments above), the statement "Each capsule contains XX mg" should be located where the removal of one capsule will not destroy any portion of the statement (e.g., the whole statement remains intact) and where a healthcare professional can read it should the patient be unable to speak for themselves (helps the HCP identify the product in an emergency).

I will be in the office ~ 8 am (or earlier) tomorrow morning if you need me to clarify any of this.

Denise

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
04/19/2013

DENISE V BAUGH
04/19/2013

From: [Carey, Jeffrey](#)
To: [Dewey, Maureen](#)
Subject: RE: NDA 21908 Amitiza Final Agreed Label
Date: Friday, April 19, 2013 10:19:03 AM
Attachments: [Amitiza FINAL Label w OIC April 19 2013.docx](#)
[Amitiza FINAL Label w OIC April 19 2013.pdf](#)

Hi Maureen,

Sucampo accepts the attached label revision which is identical to what you provided in the email below. We are providing this to our contractor Octagon to submit formally to the NDA as soon as possible. They expect they can make it before the gateway closes this afternoon. Thanks for all your expert assistance with this supplement. We greatly appreciate it.

Regards,

Jeff

From: Dewey, Maureen [mailto:Maureen.Dewey@fda.hhs.gov]
Sent: Friday, April 19, 2013 9:42 AM
To: Carey, Jeffrey
Cc: Dewey, Maureen
Subject: NDA 21908 Amitiza Final Agreed Label

Dear Mr. Carey,

We reviewed and accepted the label you sent yesterday, April 18, 2013.

Attached is the clean copy in word and pdf. Please submit the attached label formally to the NDA today as well and send an identical copy via email to me by 11:00 am today.

If you have questions, please feel free to contact me, at (301) 796-0845.

Regards,

Maureen Dewey, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Center for Drug Research and Evaluation
FDA
Office: (301) 796-0845
Fax: (301) 796-9904

From: Carey, Jeffrey [<mailto:jcarey@sucampo.com>]
Sent: Thursday, April 18, 2013 2:49 PM
To: Dewey, Maureen
Subject: RE: NDA 21908 Amitiza: Label
Importance: High

Hi Maureen,

Attached is the label from this morning with the requested responses. Please let me know if you need anything else. Thanks.

Regards,

Jeff

19 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
04/19/2013

From: [Dewey, Maureen](#)
To: [Carey, Jeffrey](#)
Cc: [Dewey, Maureen](#)
Subject: NDA 21908 Amitiza Final Agreed Label
Date: Friday, April 19, 2013 9:42:05 AM
Attachments: [FINAL to sponsor April 19 2013.pdf](#)
[FINAL to sponsor April 19 2013.docx](#)

Dear Mr. Carey,

We reviewed and accepted the label you sent yesterday, April 18, 2013.

Attached is the clean copy in word and pdf. Please submit the attached label formally to the NDA today as well and send an identical copy via email to me by 11:00 am today.

If you have questions, please feel free to contact me, at (301) 796-0845.

Regards,

Maureen Dewey, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Center for Drug Research and Evaluation
FDA
Office: (301) 796-0845
Fax: (301) 796-9904

From: Carey, Jeffrey [mailto:jcarey@sucampo.com]
Sent: Thursday, April 18, 2013 2:49 PM
To: Dewey, Maureen
Subject: RE: NDA 21908 Amitiza: Label
Importance: High

Hi Maureen,

Attached is the label from this morning with the requested responses. Please let me know if you need anything else. Thanks.

Regards,

Jeff

19 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
04/19/2013

Dewey, Maureen

From: Dewey, Maureen
Sent: Thursday, April 18, 2013 11:40 AM
To: Carey, Jeffrey (jcarey@sucampo.com)
Cc: Dewey, Maureen
Subject: NDA 21908 Amitiza: Label
Attachments: FDA Final back to sponsor April 18.pdf; FDA clean to sponsor April 18.docx

Dear Mr. Carey,

Please refer to your Supplemental New Drug Application (sNDA) dated July 20, 2012, received July 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amitiza (lubiprostone) Capsules (8 mcg, 24 mcg).

We have reviewed the label you submitted on April 17, 2013.

We are providing comments on the labeling in the attached two documents:

1. Please address the requests in the comment bubbles and review the track changes in the pdf document.
2. Please use the attached clean word document to submit your final label to us.

We would appreciate a prompt response by COB today, Thursday, April 18, 2013.

If you have questions, please feel free to contact me, at (301) 796-0845.

Regards,

Maureen Dewey, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Center for Drug Research and Evaluation
FDA
Office: (301) 796-0845
Fax: (301) 796-9904

19 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
04/18/2013

From: [Dewey, Maureen](#)
To: [Carey, Jeffrey \(jcarey@sucampo.com\)](mailto:jcarey@sucampo.com)
Cc: [Dewey, Maureen](#)
Subject: NDA 21908 Amitiza: Label
Date: Tuesday, April 16, 2013 4:55:20 PM
Attachments: [To Sponsor tracked changes April 16 2013.pdf](#)
[To Sponsor clean April 16 2013.docx](#)

Dear Mr. Carey,

Please refer to your Supplemental New Drug Application (sNDA) dated July 20, 2012, received July 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amitiza (lubiprostone) Capsules (8 mcg, 24 mcg).

We have reviewed the label you submitted on April 15, 2013.

We are providing comments on the labeling in the attached two documents:

1. Please address the requests in the comment bubbles and review the track changes in the pdf document.
2. Please use the attached clean word document to make the requested edits using "track changes".

We would appreciate a prompt response by COB Wednesday, April 17, 2013.

If you have questions, please feel free to contact me, at (301) 796-0845.

Regards,

Maureen Dewey, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Center for Drug Research and Evaluation
FDA
Office: (301) 796-0845
Fax: (301) 796-9904

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
04/17/2013

TELECON MEETING MINUTES

Meeting Date and Time: April 4, 2013 11:00 AM
Application Number: 21908/S011
Product Name: Amitiza (lubiprostone)
Indication: CIC, IBS-C proposed: OIC
Applicant Name: Sucampo
Meeting Chair: Joyce Korvick, M.D., M.P.H.
Meeting Recorder: Maureen Dewey, M.P.H.

FDA ATTENDEES

Joyce Korvick, M.D., M.P.H., Deputy Director for Safety
Robert Fiorentino, M.D., M.P.H., Medical Team Leader
Farrokh Sohrabi, M.D., Medical Officer
Sushanta Chakder, Ph.D., Supervisory Pharmacologist
Freda Cooner, Ph.D., Statistical Reviewer
Maureen Dewey, Regulatory Project Manager

APPLICANT ATTENDEES

Sucampo

Taryn Joswick, BS, Vice President of Clinical Development
Peter Lichtlen, M.D., Ph.D., Senior Medical Officer & VP European Operations
Gayle Dolecek, Ph.D., M.P.H., Executive Advisor, R&D
Glenn Noronha, Ph.D., Vice President of R&D
Stan Miele, President, Sucampo Pharma Americas
Greg Deener, Sr. Vice President Marketing
Yijun Sun, Ph.D., Senior Director, Biostatistics
Shadreck Mareya, Ph.D., Director of Clinical Program Management
Safiya Serrano-Creese, Regulatory Affairs Specialist
Sepideh Habibi, M.D., Director of Drug Safety
Jeffrey Carey, Senior Director of Regulatory Affairs

Takeda Global R&D Center, Inc.

Nanci Knipfer, Ph.D., RAC, Associate Director, Regulatory Affairs Strategy
Karen Lasch, M.D., Medical Director-GI, Medical Affairs, US Region
Justin Scopel, M.D., MBA, Associate Medical Director-GI

1.0 BACKGROUND

The Division received the applicant's supplemental NDA 21908/S011 on July 20, 2012. This supplement proposes the addition of the following indication: "treatment of opioid-induced constipation (OIC) in adults with chronic, non-cancer pain." The Division provided the sponsor revisions to the prescribing information on March 28, 2013. The purpose of the teleconference was to discuss and agree on specific sections of the label.

Prior to the teleconference the sponsor was sent the following revisions to Section 14.2:



2.0 DISCUSSION

- I. Section 5.1 Nausea:
The Division explained that the sponsor's proposed language describing nausea is too vague and that this section should be data-driven. The sponsor requested to propose new language and the Division agreed to review.

- II. Section 6.1 Clinical Studies Experience.
 - a. The Division rejected the sponsor's proposed sentence to [REDACTED] (b) (4).
However, the Division agreed to review the sponsor's revisions by adding clarifying language to exposure statement in Section 6.
 - b. 6.1 Opioid-induced Constipation.
The Division provided the rationale for deleting the statement [REDACTED] (b) (4).
 - c. Sponsor to update the OIC subsection excluding sites 3019/3119.

- III. Section 14: Clinical Studies Section.
 - a. The Division requested the sponsor to revise the sentence regarding rebound effect/randomized withdrawal trial results under sections 14.1 and 14.3.
 - b. Sponsor to update Section 14.2 to include [REDACTED] (b) (6)" for Study 1, however, excluding sites 3019/3119.
 - c. The Division explained the rationale for including Study 3 and that effectiveness has not been established in patients taking methadone. The sponsor agreed to include response rate data for Study 2 and Study 3 to reflect "all randomized subjects". [REDACTED] (b) (4).
[REDACTED] After further discussion, the

Division agreed to review the sponsor's revised wording, however requested the sponsor provide [REDACTED] (b) (4)

- d. The sponsor requested an explanation for the removal of text describing [REDACTED] (b) (4). The Division explained that the statement is not informative to prescribers, particularly for a chronic condition such as OIC.

[REDACTED] (b) (4)

2.0 ACTION ITEMS

1. Sponsor to propose new language for nausea statement in Section 5.1
2. Sponsor to add clarifying language to exposure statement in Section 6.
3. Sponsor to propose statement regarding BPI and MEDD level assessment during well-controlled clinical studies of Amitiza in OIC.
4. Sponsor to revise OIC subsection of Section 6.1 to remove all data from subjects enrolled at sites 3019 and 3119.
5. Sponsor to revise paragraphs regarding randomized withdrawal trial results under sections 14.1 and 14.3.
6. Sponsor to update Section 14.2:
 - a. Insert demographics and baseline bowel frequency data for Study 3 in 1st paragraph.
 - b. Update numbers presented for Study 1 results to reflect [REDACTED] (b) (6) population excluding data from Sites 3019 and 3119.
 - c. Remove [REDACTED] (b) (4) from presentation of results for each of the studies.
 - d. Update Study 2 and Study 3 response rate data to reflect [REDACTED] (b) (6).
 - e. Sponsor to propose additional statement of mean and median baseline MEDD values for those patients taking diphenylheptanes.

3.0 POST-MEETING ACTION ITEM

RPM notified sponsor through email correspondence to updated Section 1.2 Limitations of Use:

Section 1 INDICATIONS AND USAGE
1.2 Opioid-induced Constipation

Limitations of Use:

Effectiveness of Amitiza in the treatment of opioid-induced constipation in patients taking diphenylheptane opioids (e.g., methadone) has not been established.

This statement must match the statement in the Highlights section.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
04/15/2013

From: [Dewey, Maureen](#)
To: [Carey, Jeffrey](#)
Cc: [Dewey, Maureen](#)
Subject: SNDA 21908 Amitiza: Information Request
Date: Tuesday, April 09, 2013 11:46:55 AM

Dear Mr. Carey,

Please refer to your Supplemental New Drug Application (sNDA) dated July 20, 2012, received July 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amitiza (lubiprostone) Capsules (8 mcg, 24 mcg).

We also refer to your submissions dated August 8, August 24, August 30, September 12, September 25, October 22, October 26, November 16, December 11, 14, 17, 18, 20, 26, 2012, January 11, 17, February 11, 20 and March 1, 21 and March 27, 2013.

We are reviewing your application and have the following request for clarification:

1. Please provide descriptive statistics (mean $\pm$ standard deviation, median, minimum, maximum), treatment difference, 95% confidence intervals (exact), and p-values for analysis of the primary endpoint (mean change from baseline in SBM frequency at week 8 in subjects without dose reduction) in the population of all randomized subjects of trial OBD-0631, excluding subjects from site #1069. The analysis should stratify by site, as done in the original analysis.
2. Please revise labeling section 6.1 and section 14.2 to reflect removal of subjects from site #1069 (OBD-0631).
3. Please revise labeling section 5 to reflect removal of subjects from site #1069 (OBD-0631), site #3019 (OBD-1033), and site #3119 (OBD-1033).

If you have questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845. Kindly confirm receipt.

Regards,

Maureen Dewey, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Center for Drug Research and Evaluation
FDA
Office: (301) 796-0845

Fax: (301) 796-9904

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
04/09/2013

From: [Dewey, Maureen](#)
To: [Carey, Jeffrey \(jcarey@sucampo.com\)](mailto:jcarey@sucampo.com)
Cc: [Dewey, Maureen](#)
Subject: NDA 21908 Amitiza: Information Request & Label
Date: Thursday, March 28, 2013 4:54:16 PM
Attachments: [Track Changes to Sponsor March 28.pdf](#)
[Clean Label to Sponsor March 28.docx](#)

Dear Mr. Carey,

Please refer to your Supplemental New Drug Application (sNDA) dated July 20, 2012, received July 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amitiza (lubiprostone) Capsules (8 mcg, 24 mcg).

We are reviewing your application and have the following request for clarification:

Please provide event rates (% n/N), treatment difference, 95% confidence intervals (exact), and p-values for analyses of the primary endpoint (overall SBM response) in the following populations of trial OBD-1033:

- 1) The mITT population (as defined by Sucampo). Include two analyses, one that stratifies by baseline SBM frequency and one that does not. (However, both analyses should stratify by site, as done in the original analyses).
- 2) All randomized subjects, excluding subjects from site #3019 and site #3119. Include two analyses, one that stratifies by baseline SBM frequency and one that does not. (However, both analyses should stratify by site, as done in the original analyses).

We request a prompt written response by Tuesday, April 2, 2013 in order to continue our evaluation of your supplemental application.

Additionally, we are providing comments on the labeling in the attached two documents:

1. Please address the requests in the comment bubbles and review the track changes in the pdf document.
2. Please use the attached clean word document to make the requested edits using "track changes".

If you have questions, please feel free to contact me, at (301) 796-0845.

Regards,

Maureen Dewey, MPH
Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products
Center for Drug Research and Evaluation
FDA
Office: (301) 796-0845
Fax: (301) 796-9904

19 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
03/28/2013

From: [Dewey, Maureen](#)
To: [Carey, Jeffrey \(jcarey@sucampo.com\)](mailto:jcarey@sucampo.com)
Cc: [Dewey, Maureen](#)
Subject: SNDA 21908 Amitiza: Information Request
Date: Wednesday, March 27, 2013 10:50:22 AM

Dear Mr. Carey,

Please refer to your Supplemental New Drug Application (sNDA) dated July 20, 2012, received July 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amitiza (lubiprostone) Capsules (8 mcg, 24 mcg).

We also refer to your submissions dated August 8, August 24, August 30, September 12, September 25, October 22, October 26, November 16, December 11, 14, 17, 18, 20, 26, 2012, January 11, 17, February 11, 20 and March 1 and March 21, 2013.

We are reviewing your application and have the following request for clarification:

In reference to Study OBD-1033, you revised the primary analyses to include the baseline SBM frequency as a stratification in protocol amendment #001; however, you removed this stratification from the primary analyses in amendment #002.

1. Provide the results on the primary analyses stratified by baseline SBM frequency using both your ITT population and the population including all randomized subjects.
2. Provide the programs used to conduct the primary analyses.

We request a prompt written response by March 29, 2013 in order to continue our evaluation of your supplemental application.

Additionally, we have the following comments on your carton and container labeling:

- 1. All Container Labels and Professional Sample Labeling**
 - a. Revise the presentation of the proprietary name, from all lower case "amitiza" to title case "Amitiza" to improve its readability and to further distinguish it from the active ingredient.
 - b. Add the following statement to all container labels and sample labeling (e.g., blister card and sample tray): "Swallow Whole – Do NOT Break Apart or Chew". Addition of this statement may reinforce this message, which is found in the Patient Counseling Information Subsection (17) of the insert labeling and may help minimize the occurrence of wrong technique errors.
- 2. All Container Labels (24 mcg [60 count and 100 count] and 8 mcg [60**

count])

- a. Relocate the statement “Marketed by: Sucampo” to the side panel to accommodate recommendation (1)(b)
 - b. Consider deleting the statement (b) (4) from the side panel to minimize clutter and allow room for recommendation (2)(a).
- 3. Professional Sample Blister Card**
- a. Add the statement “Each capsule contains XX mcg” to clearly state the amount contained in each capsule and to minimize accidental overdoses.
- 4. Professional Carton Labeling and Sample Tray (24 mcg)**
- a. Although the established name (active ingredient and dosage form) is at least half the size of the proprietary name, it lacks prominence due to either thin font size or lack of color contrast. Improve the prominence of the established name taking into consideration the typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

If you have questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Regards,

Maureen Dewey, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Center for Drug Research and Evaluation
FDA
Office: (301) 796-0845
Fax: (301) 796-9904

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
03/27/2013



NDA 21908/S-011

INFORMATION REQUEST

Sucampo Pharma Americas, LLC.
Attention: Jeffrey Carey
Senior Director, Regulatory Affairs
4520 East-West Highway, Suite 300
Bethesda, MD 20814

Dear Mr. Carey:

Please refer to your Supplemental New Drug Application (sNDA) dated July 20, 2012, received July 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amitiza (lubiprostone) Capsules (8 mcg, 24 mcg).

We also refer to your submissions dated August 8, August 24, August 30, September 12, September 25, October 22, October 26, November 16, December 11, 14, 17, 18, 20, 26, 2012, January 11, 17, February 20 and March 1, 2013.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental application.

We refer to Table 2.7.3.3-37, Table 2.7.3.3-42, and Table 2.7.3.3-47. It appears you used N=220 as the denominator for the placebo group and N=219 as the denominator for the lubiprostone group. This is also apparent in Table 1.2.1.1 of the Integrated Summary of Efficacy.

We request that you re-calculate percentages using the denominator for each subgroup as listed in Table 2.7.3.3-37, Table 2.7.3.3-42, and Table 2.7.3.3-47.

If you have questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

R. Wes Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
03/14/2013

RICHARD W ISHIHARA
03/15/2013



NDA21908/ S-011

LABELING PMR/PMC DISCUSSION COMMENTS

Sucampo Pharma Americas, LLC.
Attention: Jeffrey Carey
Senior Director, Regulatory Affairs
4520 East-West Highway, Suite 300
Bethesda, MD 20814

Dear Mr. Carey:

Please refer to your Supplemental New Drug Application (sNDA) dated July 20, 2012, received July 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amitiza (lubiprostone) Capsules (8 mcg, 24 mcg).

We also refer to our November 27, 2012, letter in which we notified you of our target date of March 29, 2013 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

On January 11, 2013, we received your January 11, 2013 proposed labeling submission to this application, and have proposed revisions which are included as an enclosure. These revisions have been reviewed and cleared to the level of Deputy Director for Safety.

If you have any questions, call me, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey, M.P.H.
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE: Prescribing Information



22 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
03/07/2013

From: [Dewey, Maureen](#)
To: [Carey, Jeffrey \(jcarey@sucampo.com\)](mailto:jcarey@sucampo.com)
Cc: [Dewey, Maureen](#)
Subject: NDA 21908/S011 Information Request
Date: Friday, February 15, 2013 12:06:33 PM

Dear Jeff,

Please refer to your Supplemental New Drug Application (sNDA) dated July 20, 2012, received July 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amitiza (lubiprostone) Capsules (8 mcg, 24 mcg).

We are reviewing your application and have the following request for clarification:

In reference to the Division's Information Request dated February 4, 2013 and your email response, dated February 7, 2013, the Division has the following questions:

Sucampo presented 3 tables (Tables 2.7.4.2-20, 2.7.4.2-21, and 2.7.4.2-22) in the Summary of Clinical Safety (pages 67-69) labeled: "Adverse Events Leading to Discontinuation from Studies in 0.5% or More of Lubiprostone-Treated Subjects."

You indicated that these tables summarize those AEs with AEACN=1 (i.e., AEACNC = 'DRUG DISCONTINUED PERMANENTLY'). It appears that your approach selects all subjects for whom drug was discontinued permanently. However, this does not mean the drug was discontinued due to an AE. In some subjects, for example, the drug may have been permanently discontinued due to lack of efficacy or due to patient choice (e.g., there are subjects whose AEACNC = 'DRUG DISCONTINUED PERMANENTLY' whose disposition status (DSDECOD) says "lack of efficacy" or "patient choice" instead of "adverse event").

As such, Tables 2.7.4.2-20, 2.7.4.2-21, and 2.7.4.2-22 do not necessarily represent *solely* adverse events leading to discontinuation, but rather represent subjects whose drug was discontinued permanently for any reason, including a reason relating to an adverse event.

Please provide the following:

1. Clarify whether AEDISCC = 'YES' reflects a subject who discontinued from the *study* due to an AE or from *treatment* due to an AE (but continued in the study).
2. Correct Tables 2.7.4.2-20, 2.7.4.2-21, and 2.7.4.2-22, so that these tables summarize AEs leading to discontinuation *from treatment* in 0.5% or more of lubiprostone-treated subjects.

In reference to the Division's Information Request dated February 7, 2013, your response was acceptable.

Additionally, please provide the following:

1. Provide the reasons for drop out by treatment group (placebo or lubiprostone) and time (Baseline, Months 1, 2 or 3) for the subjects for whom there are no BPI-SF assessments for the three controlled studies 1033, 0631 and 0632.
 - a) Specifically, identify all subjects who dropped out due to inadequate pain control or AEs potentially related to inadequate pain control (i.e. worsening pain).

Please submit your responses formally to the NDA. A response by February 24, 2013 is kindly requested.

Regards,

Maureen Dewey, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Center for Drug Research and Evaluation
FDA
Office: (301) 796-0845
Fax: (301) 796-9904

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
02/15/2013

From: [Dewey, Maureen](#)
To: [Carey, Jeffrey](#)
Cc: [Dewey, Maureen](#)
Subject: NDA 21909/S011 Amitiza Request for Information
Date: Thursday, February 07, 2013 9:39:14 AM

Dear Mr. Carey:

Please refer to your Supplemental New Drug Application (sNDA) dated July 20, 2012, received July 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amitiza (lubiprostone) Capsules (8 mcg, 24 mcg).

We are reviewing your application and have the following request for clarification:

1. The protocols for the controlled (OBD-0631, 0632 and 1033) and uncontrolled (OBD-06S1) studies state that the Brief Pain Inventory-SF (BPI-SF) used in the studies was modified. Clarify where in the protocols a copy of the modified BPI-SF can be found and how the modifications differ from the standard BPI-SF. If a copy of the BPI-SF is not in the protocols, provide a copy with explanations for how scoring was performed on the assessment tool.
2. In response to the Agency's Information Request dated January 18, 2013, you sent an email correspondence dated January 28, 2013. In your response to Question #1, you state that the patient was able to enter data for the pervious calendar day if no nightly entry was provided the night before. However, you did not specify how the "observed hours" was calculated for the previous day in this situation. Please explain and provide the program used for the denominator calculation in weekly SBM frequency to facilitate our review.

Please respond to this inquiry no later than February 12, 2013.

Regards,

Maureen Dewey, M.P.H.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/FDA
(301) 796-0845 (office)
(301) 796-9905 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
02/07/2013

From: [Dewey, Maureen](#)
To: [Carey, Jeffrey \(jcarey@sucampo.com\)](mailto:jcarey@sucampo.com)
Cc: [Dewey, Maureen](#)
Subject: NDA 21909/S011 Amitiza Request for Clarification
Date: Monday, February 04, 2013 6:06:34 PM

Dear Mr. Carey:

Please refer to your Supplemental New Drug Application (sNDA) dated July 20, 2012, received July 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amitiza (lubiprostone) Capsules (8 mcg, 24 mcg).

We are reviewing your application and have the following request for clarification:

Provide the criteria used to generate the discontinuation tables on pages 67-69 of the Summary of Clinical Safety (Table 2.7.4.2-20, 2.7.4.2-21, and 2.7.4.2-22).

Specifically, the clinical reviewer used the following algorithm:

All safety-evaluable subjects in the adverse events dataset whose adverse events were treatment-emergent (as designated by "SAFETY" = 1 and "TRTMEMEG" = 1) for who the variable "AEDISCC" = YES were included in the pool of subjects who discontinued from the study due to adverse events. In so doing, the reviewer's discontinuation tables differ somewhat from the sponsor's in terms of incidence of various adverse events.

- Did Sucampo use any additional or other criteria to determine the subjects who discontinued studies due to adverse events?

Please respond to this inquiry no later than February 11, 2013.

Regards,

Maureen Dewey, M.P.H.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/FDA

(301) 796-0845 (office)
(301) 796-9905 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
02/04/2013



NDA 21908/S-011

INFORMATION REQUEST

Sucampo Pharma Americas, LLC.
Attention: Jeffrey Carey
Senior Director, Regulatory Affairs
4520 East-West Highway, Suite 300
Bethesda, MD 20814

Dear Mr. Carey:

Please refer to your Supplemental New Drug Application (sNDA) dated July 20, 2012, received July 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amitiza (lubiprostone) Capsules (8 mcg, 24 mcg).

We also refer to your submissions dated August 8, August 24, August 30, September 12, September 25, October 22, October 26, November 16, December 11, 14, 17, 18, 20, 26, 2012, January 11, 2013 and January 17, 2013.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental application.

For trials SPI/0211 OBD-631 and SMR/0211 OBD-1033, we have the following requests:

1. Provide both a narrative description and diagram of the flow of data from the electronic patient diary to the calculation for the primary endpoint, the spontaneous bowel movement (SBM) frequency rate. This should include a description of the data capture by the contract research organization (CRO), eTrials, and a description of the entity responsible for calculation and analysis of the primary endpoint. Specifically, state whether a CRO performed the data manipulations and analysis or whether this was performed by you, the sponsor. If performed by a CRO, provide the name of CRO. State the method for determining the number of hours that was used to calculate the derived primary endpoint for each subject.
2. State whether the systems described above for data capture and analysis were 21 CFR Part 11 compliant, and if not, what aspects were not compliant (audit trails, limited access, etc.).
3. Provide a both a narrative description and diagram of the flow of data from the electronic patient diary to the clinical investigator at the end of the trial in order for the clinical investigators (CI) to meet the responsibilities of 21 CFR 312.62(b) and (c). Clarify whether the data was provided to the CI directly from the CRO (eTrials). If the data were not

provided directly from eTrials, state the entity responsible for providing the data to the CIs and state the methods provided to ensure data integrity.

4. The following request pertains only to trial SPI/0211OBD-0631:
 - a. Clarify how it was determined which sites were to be remonitored, how many sites in this study were remonitored, and who was responsible for this determination.
 - b. Provide a timeline for the end of study monitoring visits and remonitoring visits by (b) (4) for this study. Specifically include how many sites were still active in the clinical trial and how many sites had closed out the study at the time of the remonitoring.
 - c. Clarify whether there were procedures for remonitoring for sites that had closed or for which the CI of record was not available. If there were, provide the procedures as part of your response.
 - d. Provide a timeline and narrative concerning the locking and unlocking of the database for this study. Include clarification on whether the data was unblinded at any point prior to the final lock and analysis.
 - e. Describe the findings on remonitoring that lead to adjustments to the exposure window due to imputations of first/last dose.

If you have questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

R. Wes Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD W ISHIHARA
01/18/2013

REQUEST FOR CONSULTATION

TO (Division/Office):

Mail: OSE

Safety Evaluator

Division of Pharmacovigilance 1

Office of Pharmacovigilance and Epidemiology

Office of Surveillance and Epidemiology

FROM: Maureen Dewey

Division of Gastroenterology & Inborn Errors Products

WO 22, Room 5159

(301) 796-0845

DATE
12/20/2012

IND NO.
77771

NDA NO.
21908/S011

TYPE OF DOCUMENT
Efficacy Supplement

DATE OF DOCUMENT
07/20/2012

NAME OF DRUG
Amitiza (lubiprostone)

PRIORITY CONSIDERATION
Priority

CLASSIFICATION OF DRUG
Cathartics and laxatives

DESIRED COMPLETION DATE
February 13, 2013

NAME OF FIRM: **Sucampo**

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE--NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☒ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	☐ OTHER (SPECIFY BELOW):
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILITY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Sucampo submitted a new efficacy supplement to expand the indication for Amitiza. Amitiza is currently approved for chronic idiopathic constipation and IBS-C. This supplement proposes to add the following indication: "*Treatment of opioid-induced constipation* (b) (4) *in adults with chronic, non-cancer pain*"

Last review of lubiprostone in the postmarketing setting by DPV1, completed September 5, 2008, demonstrated six cases of ischemic colitis (IC). At that time, DPV1 recommended that the lubiprostone labeling be updated to include IC in the Postmarketing Adverse Events section. The Division requests that DPV1 perform an updated review and provide updated recommendations on labeling changes with respect to IC in the postmarketing setting.

Original Submission located in the eDr: <\\CDSESUB1\EVSPROD\NDA021908\0112>

Gateway Location: <\\chdc9681\cderesub\inbound\ectd\ci1342793395601.882550@llnap12 te>

Eroom for Application

http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0_2f7b9

COMMENTS/SPECIAL INSTRUCTIONS:

SIGNATURE OF REQUESTER
Maureen Dewey

METHOD OF DELIVERY (Check one)
 MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
12/27/2012

MEMORANDUM OF TELECONFERENCE MEETING MINUTES

Deleted: ¶
¶

MEETING DATE: November 19, 2012
TIME: 12:30 p.m.
APPLICATION: 21908/S011
DRUG NAME: Amitiza (lubiprostone)
TYPE OF MEETING: Telecon
MEETING CHAIR: Robert Fiorentino, M.D., M.P.H.
MEETING RECORDER: Maureen Dewey

FDA ATTENDEES:

Division of Gastroenterology and Inborn Errors Products
Donna Griebel, M.D., Director
Andrew Mulberg, M.D., Deputy Director
Joyce Korvick, M.D., M.P.H., Deputy Director for Safety
Robert Fiorentino, M.D., MPH, Medical Team Leader
Farrokh Sohrabi, M.D., Medical Officer
Sushanta Chakder, Ph.D., Team Leader
Maureen Dewey, M.P.H., Senior Regulatory Health Project Manager
Matthew Scherer, Senior Regulatory Health Project Manager

Office of Clinical Pharmacology

Sandhya Apparaju, Ph.D., Clinical Pharmacology Reviewer

Pediatric and Maternal Health Staff

Jeanine A. Best, M.D., Medical Officer

Division of Biometrics III

Mike Welch, Ph.D, Statistical Team Leader
Freda Cooner, Ph.D., Statistics Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Sucampo Pharmaceuticals

Gayle Dolecek, P.D., M.P.H.

Taryn Joswick, B.S.

Shadreck Mareya, Ph.D.

(b) (6)

Safiya Serrano-Creese, M.S.

(b) (6)

Glenn Noronha, M.D.

(b) (6)

Jeff Carey, B.S.

Yijun Sun, Ph.D.

Peter Lichtlen, M.D. Ph.D.

Nanci Knipfer, PhD, RAC, Takeda
Karen Lasch, M.D., Takeda

(b) (4)

MEETING OBJECTIVES:

To discuss the ongoing review of pending efficacy supplement S011 expanding the indication of Opioid-Induced Constipation.

BACKGROUND

On July 20, 2012, the sponsor submitted an efficacy supplement to NDA 21908. This supplement proposes to add the following indication: "Treatment of opioid-induced constipation (b) (4) in adults with chronic, non-cancer pain".

On October 25, 2012 the Division held a mid-cycle meeting to present key review findings. The purpose of this teleconference was to share the findings with the sponsor. A tentative agenda with discussion points was sent to the sponsor in advance.

DISCUSSION

1. Supportive evidence of efficacy for results from primary analysis of overall SBM response endpoint in trial OBD-1033 will be needed.

Additional Discussion:

Sucampo noted that the analyses requested under an information request had very recently been provided to the Division.

2. Further evaluation of potential differences in response to lubiprostone depending on opioid class/subclass is needed. The Agency has requested analysis of the primary efficacy endpoints by opioid class/subclass for each individual trial.

Additional Discussion:

The Agency inquired whether or not there is actually a clinically significant interaction of lubiprostone with methadone or whether it is more relevant that the morphine equivalent daily dose (MEDD) in the methadone-treated subgroup of study 632 was higher than the methadone-treated subgroup of study 631. Sucampo responded that it appeared that there is a dose competition for the CLC target channel. The sponsor noted that when the diphenylheptane-taking patients who were on ≥ 200 mg MEDD subjects are removed from the analysis of study 632, and substituted with those patients taking non-diphenylheptans of ≥ 200 mg MEDD, 632 would have achieved statistical significance for the primary endpoint.

3. (b) (4)

Additional Discussion:

Sucampo acknowledged the Agency's concerns.

4. Mechanism of action of lubiprostone – There has been a recent publication¹ that suggests lubiprostone may activate the cystic fibrosis transmembrane conductance regulator (CFTR). Other publications have suggested that lubiprostone either increases membrane CFTR or requires CFTR for activation of intestinal chloride secretion.^{2,3} The Agency would like to obtain the Sponsor's thoughts about these findings.

Additional Discussion:

A subject matter expert on behalf of Sucampo provided an explanation contesting the above referenced findings. The sponsor agreed to provide the rationale in writing at a later date.

5. Pediatrics – Although the Agency may waive pediatric studies for the OIC indication, the following issues warrant further discussion with regard to the Sponsor's outstanding PREA requirements for the CIC and IBS-C indications:
 - o Potential cardiovascular risk in pediatric patients treated with lubiprostone (based on findings of 13-week oral (gavage) toxicity study in juvenile albino rats)
 - o Changes in bone mineralization (based on two non-clinical studies) – Bone growth assessments may need to be included in pediatric development plan

Additional Discussion:

The sponsor agreed to submit a separate meeting request to discuss the outstanding PREA PMRs.



The sponsor denied knowledge of any off-label use of lubiprostone in children to date. When asked what the average age of children studied was in the pediatric study previously conducted, the sponsor provided an approximate age range of 3- 17 years , average age between 7-8 years and median of 10 years of age.

¹ Norimatsu Y, Moran AR, Macdonald KD. Lubiprostone activates CFTR, but not CIC-2, via the prostaglandin receptor (EP(4)). *Biochem Biophys Res Commun.* 2012;426(3):374-379.

² Ao M, Venkatasubramanian J, Boonkaewwan C, et al. Lubiprostone activates Cl- secretion via cAMP signaling and increases membrane CFTR in the human colon carcinoma cell line, T84. *Dig Dis Sci.* 2011; 56(2):339-351.

³ Bijvelds MJ, Bot AG, Escher JC, De Jonge HR. Activation of intestinal Cl- secretion by lubiprostone requires the cystic fibrosis transmembrane conductance regulator. *Gastroenterology.* 2009;137(3):976-985.

Additional Discussion:

The Division inquired about Amitiza's effect on increasing the number of SBMs per day or increasing the number of days per week in which subjects are having at least one SBM. The sponsor referred the Division to Module 5.3.5.3, Table 1.4.22 and Summary of Clinical Efficacy, Table 2.7.3.3-1). The Division agreed to re-review this data.

The teleconference concluded with a summary of action items:

- 1. Sponsor to provide evidence of efficacy for results from primary analysis of overall SBM response endpoint in trial OBD-1033*
- 2. Sponsor to submit meeting request for pediatric PMRs.*
- 3. Division to review Module 5.3.5.3 Integrated Summary of Efficacy, Table 1.4.22 and Summary of Clinical Efficacy, Table 2.7.3.3-1.*
- 4. Sponsor to submit rationale for lubiprostone mechanism of action to the NDA*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY

12/11/2012

Do not send to sponsor, these are internal meeting minutes



NDA 21908/S-011

INFORMATION REQUEST

Sucampo Pharma Americas, LLC.
Attention: Jeffrey Carey
Senior Director, Regulatory Affairs
4520 East-West Highway, Suite 300
Bethesda, MD 20814

Dear Mr. Carey:

Please refer to your Supplemental New Drug Application (sNDA) dated July 20, 2012, received July 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amitiza (lubiprostone) Capsules (8 mcg, 24 mcg).

We also refer to your submissions dated August 8, August 24, August 30, September 12, September 25, October 22, October 26, and November 16, 2012.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental application.

- 1) Perform a sensitivity analysis of overall spontaneous bowel movement (SBM) response (primary efficacy endpoint of OBD-1033) in all subjects without dose reduction for trials OBD-1033, OBD-631, and OBD-632.
- 2) For the overall SBM responders in the intent-to-treat (ITT) population of OBD-1033 and OBD-631 (both placebo and lubiprostone arms), provide the proportion of SBMs in those responders that were complete SBMs.
- 3) In the statistical analysis plan (SAP) for the efficacy studies, a note was made that "subjects not meeting eligibility criteria at the time of the Screening Visit will be considered screen failures." Provide the number of subjects that were actually screened for each of the three efficacy studies and in tabular format. Additionally, provide the reasons for the screening failure for each of the three studies (OBD-1033, OBD-631, and OBD-632).
- 4) We remind you of the requirement to submit a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). Provide an update in your response to the items above on when the safety update will be submitted.

If you have questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

R. Wes Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
12/06/2012

RICHARD W ISHIHARA
12/07/2012

REQUEST FOR CONSULTATION

TO (Office/Division):
Parinda Jani / Sara Stradley
 Chief, Project Management Staff
 Division of Anesthesia, Analgesia, and Addiction
 Products ODE II
 Main Telephone: 301-796-2280
 Fax: 301-796-9723
 White Oak Building 22, Rm. 3179
 10903 New Hampshire Ave.
 Silver Spring, MD 20993

FROM (Name, Office/Division, and Phone Number of Requestor):
Maureen Dewey, M.P.H.
 Sr. Regulatory Project Manager
 DGIEP/ODE III
 Telephone (301) 796-0845

DATE 11/29/2012	IND NO. 77771	NDA NO. 21908	TYPE OF DOCUMENT Efficacy Supplement	DATE OF DOCUMENT 7/20/2012
NAME OF DRUG Amitiza (lubiprostone)		PRIORITY CONSIDERATION priority	CLASSIFICATION OF DRUG Cathartics and Laxatives	DESIRED COMPLETION DATE 2/1/2013

NAME OF FIRM: **Sucampo**

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL ☐ PROGRESS REPORT ☐ NEW CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ MANUFACTURING CHANGE / ADDITION ☐ MEETING PLANNED BY	☐ PRE-NDA MEETING ☐ END-OF-PHASE 2a MEETING ☐ END-OF-PHASE 2 MEETING ☐ RESUBMISSION ☒ SAFETY / EFFICACY ☐ PAPER NDA ☐ CONTROL SUPPLEMENT	☐ RESPONSE TO DEFICIENCY LETTER ☐ FINAL PRINTED LABELING ☐ LABELING REVISION ☐ ORIGINAL NEW CORRESPONDENCE ☐ FORMULATIVE REVIEW ☒ OTHER (SPECIFY BELOW):

II. BIOMETRICS

☐ PRIORITY P NDA REVIEW ☐ END-OF-PHASE 2 MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION ☐ BIOAVAILABILITY STUDIES ☐ PHASE 4 STUDIES	☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL - BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

This consult encompasses our request for review of assessment of pain severity and impact of pain on daily functions as part of the sNDA submission for Amitiza for the proposed indication of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain. In each of three double-blind efficacy studies and one long-term open-label safety study, the Sponsor administered the Brief Pain Inventory-Short Form (BPI-SF) to subjects on a monthly basis. The Sponsor reported no significant differences in the mean changes from baseline in the pain

interference, pain severity, or worst pain scores between the placebo and Amitiza groups at the end of each study month or end of treatment. (b) (4)

(b) (4)

With regard to the BPI-SF, the Division requests:

(b) (4)

Materials to review:

BPI-SF assessments and findings for studies OBD-1033, OBD-0631, OBD-0632, and OBD-06S1.

EDR Location: \\CDSESUB1\EVSPROD\NDA021908\0112

The findings are summarized in the Summary of Clinical Safety, Pages 106 through 109 and detailed in the Integrated Summary of Safety Module 5.3.5.3, Table 2.2.14.1, 2.2.14.2, 2.2.15.1 and Table 2.2.15.2.

Eroom for Application including proposed label

http://erom.fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0_2f7aa

SIGNATURE OF REQUESTOR

Farrokh Sohrabi, M.D., Medical Officer

Division of Gastroenterology and Inborn Errors Products

Center for Drug Evaluation & Research

METHOD OF DELIVERY (Check one)

DFS

EMAIL

MAIL

HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
11/30/2012

Dewey, Maureen

From: Dewey, Maureen
Sent: Thursday, November 29, 2012 4:55 PM
To: Carey, Jeffrey
Cc: Dewey, Maureen
Subject: NDA 21908/S011 Clarification

Dear Jeff,

In reference to NDA 21908/S011 and the Information Request dated November 9, 2012, the Division has the following clarification:

Efficacy:

5) We note that you used an hourly based assessment for SBM frequency calculation rather than a daily based assessment. Please recalculate weekly responder/non-responder rates using a daily based calculation. Present two analyses, one where all multiple daily bowel movements (BMs) count towards the weekly average and another which multiple BMs per day only contribute one BM towards the weekly average.

Clarification:

Please recalculate weekly responder/non-responder rates using a daily-based calculation.

The Division has reviewed the materials that Sucampo referenced during the teleconference held on November 19, 2012 (Integrated Summary of Efficacy, Module 5.3.5.3, Table 1.4.22 and Summary of Clinical Efficacy, Table 2.7.3.3-1). From Table 1.4.22, it appears that the actual number of days per week in which subjects had at least one SBM was comparable between placebo subjects and lubiprostone subjects throughout the 12 weeks of study OBD-1033. Thus, the table suggests that in this study, lubiprostone's effect on OIC appears to involve increasing the number of SBMs per day rather than increasing the number of days per week in which subjects are having at least one SBM. This data adequately addresses the second part of the Division's request #5.

As a result, the Division no longer requests that Sucampo present two analyses, one where all multiple daily BMs count towards the weekly average and another in which multiple BMs per day only contribute one BM towards the weekly average.

Please feel free to contact me if you have any questions.

Regards,

Maureen Dewey, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/FDA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
11/29/2012



NDA 21908/S-011

**REVIEW EXTENSION –
EFFICACY SUPPLEMENT**

Sucampo Pharma Americas, LLC.
Attention: Jeffrey Carey
Senior Director, Regulatory Affairs
4520 East-West Highway, Suite 300
Bethesda, MD 20814

Dear Mr. Carey:

Please refer to your Supplemental New Drug Application (sNDA) dated July 20, 2012, received July 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amitiza (lubiprostone) Capsules (8 mcg, 24 mcg).

On November 16, 2012, we received your November 16, 2012, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is April 20, 2013.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by March 29, 2013.

If you have questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DONNA J GRIEBEL
11/27/2012



NDA 21908/S-011

INFORMATION REQUEST

Sucampo Pharma Americas, LLC.
Attention: Jeffrey Carey
Senior Director, Regulatory Affairs
4520 East-West Highway, Suite 300
Bethesda, MD 20814

Dear Mr. Carey:

Please refer to your Supplemental New Drug Application (sNDA) dated July 20, 2012, received July 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amitiza (lubiprostone) Capsules (8 mcg, 24 mcg).

We also refer to your submissions dated August 8, August 24, August 30, September 12, September 25, October 22, and October 26, 2012.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental application.

Efficacy:

- 1) Perform individual trial subgroup analyses by methadone (or congener of methadone) versus non-methadone subjects of the intent to treat (ITT), completer, and per-protocol populations across the two treatment arms for each of the individual trials (OBD-631 and OBD-632) using the primary efficacy endpoint of mean change from baseline in spontaneous bowel movement (SBM) frequency at Week 8 in subjects without dose reduction and the overall SBM response primary endpoint (used in OBD-1033).
- 2) Perform individual trial subgroup analyses by methadone (or congener of methadone) versus non-methadone subjects of the ITT population across the two treatment arms in each of the individual trials (OBD-631, OBD-632) using the mean change from baseline in bowel function parameters endpoint. The table should be similar to that provided in Table 2.7.3.3-33 (page 79 of 119) in Summary of Clinical Efficacy, but should provide separate results for methadone subjects and non-methadone subjects in each treatment arm.
- 3) A true ITT population is defined as all randomized subjects. However, we note that for your efficacy analyses, you defined the ITT population as all randomized subjects who had received at least one study treatment and had at least one post-treatment assessment.

Perform primary and key secondary analyses of the true ITT population (all randomized subjects) for all three efficacy trials (OBD-631, OBD-632, and OBD-1033) using both the primary efficacy endpoint of overall SBM response (as defined for trial OBD-1033) and the primary efficacy endpoint of mean change from baseline in SBM frequency at Week 8 in subjects without dose reduction (as defined for trials OBD-631 and OBD-632).

- 4) Treatment differences between two treatment groups (lubiprostone - placebo) and 95% confidence intervals (CIs) are not presented in the data tables for this sNDA, but means $\pm$ standard deviations and p-values are instead provided. Perform analysis of the ITT population in all three efficacy trials (OBD-631, OBD-632, and OBD-1033) using both the primary efficacy endpoint of overall SBM response (as defined for trial OBD-1033) and the primary efficacy endpoint of mean change from baseline in SBM frequency at Week 8 in subjects without dose reduction (as defined for trials OBD-631 and OBD-632). However, instead of presenting the data as means $\pm$ standard deviations with p-values, present the data as treatment differences with 95% CIs.
- 5) We note that you used an hourly based assessment for SBM frequency calculation rather than a daily based assessment. Please recalculate weekly responder/non-responder rates using a daily based calculation. Present two analyses, one where all multiple daily bowel movements (BMs) count towards the weekly average and another which multiple BMs per day only contribute one BM towards the weekly average.
- 6) We note that you used last observation carried forward (LOCF) for the analysis on the efficacy endpoint of mean change from baseline in SBM frequency at Week 8. For weeks with missing data, conduct sensitivity analyses to further investigate the impact of missing data on the results. Such analyses include BOCF (baseline observation carried forward), worst-case (missing value imputed with worst observation), observed-case, complete-case, and model-based multiple imputation.
- 7) For each of the three individual efficacy trials, provide (via descriptive statistics), the constipation status at baseline by BM frequency and complete BM frequency for subjects in each treatment arm. The table should be similar to Table 2.7.3.3-5, page 29 of 119, Summary of Clinical Efficacy, but rather than presenting SBM frequency per week at baseline, the table should present BM frequency per week at baseline and complete BM frequency per week at baseline. Additionally, provide the BM frequency and complete BM frequency per week for subjects in each treatment arm *prior* to the beginning of the baseline screening period that initiated after Visit 1. More specifically, provide the BM frequency and complete BM frequency at the time of Visit 1 (Day -24 to -21) for subjects in each treatment arm on their usual laxative / rescue medication regimen.
- 8) Explain how the number of subjects in each opioid class/subclass was determined for analyses in Figure 2.7.3.3-11 and Figure 2.7.3.3-12 of the Summary of Clinical Efficacy (pages 104-105). Specifically, if a subject was on more than one opioid from different classes, clarify whether that subject was counted more than once. For example, if a subject was on fentanyl 12.5 mcg patch and hydrocodone as needed for breakthrough,

clarify whether the subject was counted once in the phenylpiperidine class and once in the phenanthrene class.

- 9) Explain the differences in numbers of subjects at each month (n) between the data presented in Table 2.7.3.5-1 Change from Baseline in SBM Frequency by Month (pages 108-109 of 119, Summary of Clinical Efficacy) and the data presented in Table 14.2.1 of the Clinical Study Report for Study OBD-06S1. The number of subjects in the ITT population of OBD-06S1 in Table 2.7.3.5-1 does not correlate with the number in Table 14.2.1. For example, in Table 2.7.3.5-1, at Month 1, the total n for ITT subjects with measured change from baseline in SBM frequency is 333 (169 +164). In contrast, in Table, 14.2.1, the n is listed as 420. Similar discrepancies in number of subjects at each month exist between Table 14.2.11 (CSR of OBD-06S1) and Table 1.3.19.3 (module 5.3.5.3 of the Integrated Summary of Efficacy), both of which are labeled as reporting the frequency of complete SBMs by month in ITT subjects.
- 10) Verify that n=0 for subjects in the ITT lubiprostone-lubiprostone group at baseline time point in Table 1.3.19.8, module 5.3.5.3 of the Integrated Summary of Efficacy (page 2218 of 2585). If so, explain why there were no subjects in the ITT lubiprostone-lubiprostone group of trial OBD-06S1 to allow for evaluation of change by month in complete SBM frequency.

Safety:

- 1) For the following subjects (listed by unique subject ID number), submit case report forms (CRFs) and patient narratives (if available) that provide details regarding the following adverse events (listed by preferred term and start date), including time of symptom onset in relation to first dose of study medication:
 - **1033-3402-006:** Abdominal pain (8/3/2011, 8/9/2011), hematochezia (10/14/2011, 10/17/2011, 10/21/2011, 10/24/2011, 10/25/2011)
 - **0632-2056-004:** Hematochezia (7/19/2008, 7/26/2008)
 - **06S1-2018-006:** Rectal hemorrhage (1/24/2008)
 - **06S1-2056-005:** Hematochezia (4/27/2009)
 - **06S1-2059-014:** Hematochezia (2/9/2009)
 - **1033-3000-013:** Abdominal pain, nausea, vomiting (7/31/2011)
 - For this subject, above adverse events (AEs) were serious and as such, patient CRF and narrative have already been provided. CRF does NOT need to be re-submitted. However, please provide additional narrative details of patient's hospital presentation and hospital course (i.e., vital signs, other symptoms, treating physician's diagnosis, etc.) if available.
 - **1033-3022-006:** Nausea, abdominal pain upper (3/7/2011)
 - **1033-3044-002:** Hyperhidrosis, tachycardia, nausea (2/4/2011)
 - **1033-3081-004:** Abdominal pain, flushing (3/16/2011)
 - **0631-1028-002:** Abdominal pain, nausea (12/28/2007)
 - **0631-1028-045:** Drug withdrawal syndrome (12/2/2008)

- **0632-2023-018:** Abdominal pain, nausea (12/20/2008)
 - **0632-2080-013:** Agitation, flushing, nausea, tremor (7/17/2008)
 - **0632-2099-005:** Decreased appetite, nausea (10/1/2008); abdominal pain, vomiting (11/1/2008)
 - **06S1-1010-007:** Drug withdrawal syndrome (8/26/2008)
 - **06S1-1051-003:** Nausea, abdominal pain, vomiting (8/25/2008)
 - **06S1-2014-005:** Hyperhidrosis (12/10/2008); cold sweat, nausea (3/17/2009)
 - **06S1-2044-003:** Withdrawal syndrome (5/27/2008)
 - **06S1-2048-006:** Nausea, hyperhidrosis, abdominal pain upper (3/1/2009)
 - **06S1-2067-001:** Abdominal pain, nausea, vomiting (6/18/2009)
- 2) For the following subjects (listed by unique subject ID number), submit case report forms (CRFs) and patient narratives (if available) that provide details regarding the elevations in alanine aminotransferase (ALT), including any comments by investigator regarding relation of laboratory abnormality to study drug:
- **1033-3087-007:** ALT trended from 23 IU/L at screening to 150 IU/L at follow-up with no additional values provided. Was resolution of the subject's ALT elevation (as noted at follow-up visit) documented?
 - **0631-1069-025:** ALT trended from 25 IU/L at screening to 190 IU/L at follow-up open label visit (in study OBD-06S1). Was resolution of the subject's ALT elevation (as noted at open label follow-up visit) documented?
 - **0632-2023-033:** ALT trended from 15 IU/L at screening to 211 IU/L at Visit 4 to 19 IU/L at Visit 6 to 265 IU/L at end-of treatment visit to 24 IU/L at Visit 12 (in study OBD-06S1). Did the investigator provide any explanation for the subject's intermittent ALT elevation?

If you have questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

R. Wes Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD W ISHIHARA
11/09/2012

Eroom for Application and most recent sponsor submitted Label:
http://erom.fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0_2f7b9

COMMENTS/SPECIAL INSTRUCTIONS:

Second Mid-Cycle Meeting: December 17, 2012 3:00 PM

Labeling Planning Meeting: January 8, 2013

Other meetings TBD

SIGNATURE OF REQUESTER
Maureen Dewey

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
11/02/2012

From: [Dewey, Maureen](#)
To: ["Carey, Jeffrey"](#)
Cc: [Dewey, Maureen](#)
Subject: NDA 21909/S011 Amitiza Request for Information
Date: Monday, October 15, 2012 4:48:31 PM

Dear Mr. Carey:

Please refer to your Supplemental New Drug Application (sNDA) dated July 20, 2012, received July 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amitiza (lubiprostone) Capsules (8 mcg, 24 mcg).

We also refer to your submissions dated August 8, August 24, August 30, September 12, and September 25, 2012.

We are reviewing your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your supplemental application.

1. Provide a table summarizing the mean and median duration of opioid use at baseline (using descriptive statistics) for subjects in each treatment arm for each double-blind trial (OBD-631, OBD-632, and OBD-1033). Also present the primary efficacy endpoint for each trial by categories of opioid duration. For example, the table might present overall SBM response and change from baseline in SBM frequency at Week 8 in subjects without dose reduction for lubiprostone and placebo subjects on opioids at baseline for: (1) <3 months; (2) >3 months, but <6 months; (3) >6 months, but <12 months; and (4) >12 months.
- 2) Provide a table summarizing the principal medical diagnoses by treatment arm for which subjects were on chronic opioids for each double-blind trial (OBD-631, OBD-632, and OBD-1033). Additionally, present a tabular analysis of the primary efficacy endpoint for each trial broken down by diagnosis for which subjects were on opioids. For example, the table might present overall SBM response and change from baseline in SBM frequency at Week 8 for lubiprostone and placebo subjects on opioids for: (1) back pain; (2) fibromyalgia; (3) abdominal pain...etc.
- 3) Provide a dataset of the mean weekly and monthly frequency of BMs, SBMs, and complete SBMs over the study period, by individual subject for each double-blind trial (OBD-631, OBD-632, and OBD-1033). Include variables that indicate treatment arm assignment and study.
- 4) For trials OBD-631, OBD-632, include subjects who had dose reduction in the

primary efficacy analysis. That is, present results of mean change from baseline in SBM frequency at Week 8 in all efficacy evaluable subjects, not just those who had no dose reduction. Perform a similar analysis for subjects in trial OBD-1033.

5) Explain discrepancies in reported numbers of subjects with time to first SBM in 24 hours and 48 between numbers provided in Table 2.7.3.3-29, page 69 of 119 Summary of Clinical Efficacy and those in Table 14.2.9.1 (Clinical Study Report of OBD-1033) and Table 14.4.2.1 (Clinical Study Report of OBD-631) for studies OBD-1033 and OBD-631.

If you have questions, please feel free to call me at (301) 796-0845.

Regards,

Maureen Dewey, M.P.H.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/FDA

(301) 796-0845 (office)

(301) 796-9905 (fax)

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0069. Thank you.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
10/15/2012

From: [Dewey, Maureen](#)
To: ["Carey, Jeffrey"](#)
Cc: [Dewey, Maureen](#)
Subject: NDA 21908/S011 Information Request
Date: Friday, October 05, 2012 1:14:01 PM
Attachments: [sNDA 21908 Clinical IR #4 FINAL.pdf](#)

Dear Jeff,

We are reviewing your supplement application for NDA 21908/S011 Amitiza. A request for information is attached to this communication.

Please feel free to let me know if you have any questions. A prompt reply is appreciated.

Regards,

Maureen Dewey, M.P.H.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/FDA

(301) 796-0845 (office)

(301) 796-9905 (fax)

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0069. Thank you.

NDA 21908/S011
Clinical Information Request
10/5/2012

Subject Disposition

- 1) Provide unique subject ID numbers for all subjects in trial OBD-1033 that were misrandomized.
- 2) In Table 14.1.3 of the Clinical Study Report (CSR) for all three efficacy trials (OBD-631, OBD-632, and OBD-1033), the 1st footnote to the table states that “in some cases refined/alternate criteria have been set for other key eligibility criteria (e.g., inclusion criteria # 8, 10 and exclusion criteria #3, 4) and are included under separate violation criteria.” Explain this statement.
- 3) In Table 14.1.3 of the CSR for OBD-1033, the 6th footnote to the table (referring to the protocol violation labeled as “other”) states that “e.g., subject has confounding concurrent medical history diagnosis.” Provide the unique subject ID numbers and confounding concurrent medical history diagnosis for the two listed subjects in the placebo arm and the one listed subject in the lubiprostone arm who were considered to have protocol violations due to “other.”
- 4) Clarify potential inconsistencies in the number of subjects reported in the CSR as excluded from the per-protocol population:
 - a. OBD-1033: Section 10.2 of the CSR (page 46 of 785), indicates that 33 subjects were excluded from the per-protocol population because key eligibility criteria were not met or because they were misrandomized, 23 were excluded due to inconsistent use of prohibited/confounding medications, 14 because of opioid dose adjustments, 15 because of dosing compliance issues, and 3 for other reasons. Based on this information, the total number of subjects excluded from the per-protocol population should be 88 and is consistent with Table 14.1.3 in the CSR. However, in Module 5.3.5.1.18, Listing 16.2.3, the total of protocol violators is 91, which is in keeping with the number of subjects reported in the CSR Section 11. 1 (page 47 of 785) to be in the total per-protocol population (447 randomized subjects minus 91 protocol violators equals 356 per-protocol patients). Explain this discrepancy.
 - b. OBD-631: Table 14.1.3 of the CSR reports a total of 163 subjects with protocol violations (77 placebo and 86 lubiprostone), which should yield a per-protocol population of 275 (438 subjects in ITT minus 163 protocol violators), but Section 11.1 of the CSR (page 50 of 1159) reports 309 per-protocol subjects. Clarify if the discrepancy relates to subjects with multiple violations.
 - c. OBD-632: Table 14.1.3 of the CSR reports a total of 170 subjects with protocol violations (81 placebo and 89 lubiprostone), which should yield a per-protocol population of 265 (435 subjects in ITT minus 170 protocol violators), but Section 11.1 of the CSR (page 52 of 1157) reports 297 per-protocol subjects. Clarify if the discrepancy relates to subjects with multiple violations.
- 5) Provide a detailed listing of all subjects with protocol violations and violation details for trials OBD-631 and OBD-632. This listing should be comparable to listing 16.2.3 entitled “Patients Excluded from Efficacy Analysis” that was provided for trial OBD-1033 in module 5.3.5.1.18. A

comparable listing for trials OBD-631 and OBD-632 in the electronic database was not found. The listings 16.2.2 and 16.2.3 for both trials OBD-631 and OBD-632 do not provide details on subjects with protocol violations.

- 6) In response to Information Request #1, you provided Table 2, entitled “Tabular summary of investigator-decided, sponsor-requested, and other discontinuations from studies OBD-631, OBD-632, OBD-06S1, and OBD-1033.” Review of this table shows that some of the reasons for discontinuation under these three categories duplicate reasons for discontinuation previously provided in Table 2.7.3.3-3, page 23 of 119, Summary of Clinical Efficacy or are unclear. In particular:
- a. Adverse event, lack of efficacy, patient choice, and non-compliance are given as reasons under “other” even though they are each presented separately as a reason for discontinuation in Table 2.7.3.3-3. Similarly, adverse event and non-compliance are listed under “Investigator decision” and also separately as categories in Table 2.7.3.3-3. Explain why some of these reasons are listed under multiple categories.
 - b. Clarify what is meant by “OBD status” in Table 2.
 - c. Clarify what is meant by “drug addiction” and “renal function criteria” in Table 2 under protocol violations. Neither of these terms was listed as a protocol violation in the CSR for the trials.

Safety

- 1) Explain the following discrepancy in number of subjects who discontinued the study due to at least one adverse event:

Table 2.7.4.2-1, page 35 of 167 and Table 2.7.4.2-2, page 36 of 167 in the Summary of Clinical Safety provide the following tabulation:

Overall Summary of TEAEs – Well-controlled Studies Pool and Long-Term Safety Study (Safety Evaluable Subjects)

Subjects With:	Well-controlled Studies Pool		Long-Term Safety Study	
	Placebo (N=652)	Lubiprostone (N=663)	Placebo-Lubiprostone (N=215)	Lubiprostone-Lubiprostone (N=214)
At least 1 AE leading to study discontinuation	16 (2.5%)	36 (5.4%)	15 (6.7%)	8 (3.7%)

The numbers provided in the above table match the numbers provided in Table 2.7.4.1-3, page 15 of 167, and Table 2.7.4.1-5, page 18 of 167 in the Summary of Clinical Safety. However, Table 2.2.9.1.1 in module 5.3.5.3 ISS, which provides a summary of AEs leading to discontinuation of treatment in the safety evaluable population provides the following tabulation:

Number of Participants Reporting:	Well-controlled Studies Pool		Long-Term Safety Study	
	Placebo (N=652)	Lubiprostone (N=663)	Placebo-Lubiprostone (N=215)	Lubiprostone-Lubiprostone (N=214)
At least 1 AE leading to discontinuation of treatment	20 (3.1%)	48 (7.2%)	19 (8.4%)	11 (5.1%)

- 2) In the Postmarketing Data Section of the Summary of Clinical Safety, you indicate that there have been 11 medically confirmed cases of death with 19 events, 11 of which were from postmarketing sources. The table of fatal events provided on page 157 of 167 only provides 10 fatal events (by preferred term). Please clarify the discrepancy.
- 3) Explain how doses of methadone and congeners of methadone were converted to MEDDs. The MEDD Conversion Table you provided (Table 2.7.3.6-3, page 116 of 119 of Summary of Clinical Efficacy) excludes MEDD conversion factors for methadone and congeners of methadone.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
10/05/2012



NDA 21908/S-011

FILING COMMUNICATION

Sucampo Pharma Americas, LLC.
Attention: Jeffrey Carey
Senior Director, Regulatory Affairs
4520 East-West Highway, Suite 300
Bethesda, MD 20814

Dear Mr. Carey:

Please refer to your Supplemental New Drug Application (sNDA) dated July 20, 2012, received July 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amitiza (lubiprostone) Capsules (8 mcg, 24 mcg).

We also refer to your amendments dated August 8, August 24, August 30, September 12, and September 25, 2012.

This supplemental application proposes the following new indication:

“Amitiza is indicated for the treatment of opioid-induced constipation (OIC) [REDACTED] (b) (4)
[REDACTED] in adults with chronic, non-cancer pain.”

During our filing review of your supplemental application, we identified the following potential review issues:

Regarding your sNDA 21908 for lubiprostone in opioid-induced constipation (OIC), we have thus far identified the following issues, which should further explain some of the information requests in this document:

- 1) We note the failure of trial OBD-632 to win on the primary endpoint across all populations (intent-to-treat (ITT), completers, and per-protocol). This has been proposed to be possibly related to a treatment interaction with methadone and higher average dose of methadone (morphine equivalent daily dose (MEDD)) in the treatment arm in study OBD-632. There are also inconsistencies in efficacy across various classes of opioids aside from methadone. You have submitted an analysis that pooled the three efficacy trials and evaluated mean change in SBM frequency from baseline at Week 8 failed to show a significant difference between placebo and lubiprostone in subjects using morphines, oxycodones, or fentanyl (Figure 2.7.3.3-11 and Figure 2.7.3.3-12 of Summary of Clinical Efficacy). We note, however, that these results are based on pooling of

efficacy studies and use of a single primary efficacy endpoint across all three trials. Further analysis will be needed.

- 2) We note the failure of trials OBD-631 and OBD-1033 to win on the primary endpoint in the per-protocol population. You proposed that this lack of a statistically significant difference between the lubiprostone and placebo groups in the per-protocol population was “likely due to the combination of a decrease in the sample size and the difference in distribution of data as compared to the completers population.” Further analysis will be needed.
- 3) No dose-response explorations were done for this sNDA and all subjects in the three efficacy trials randomized to the treatment arm were dosed at 24 mcg BID, which is the current dose used for chronic idiopathic constipation (CIC). If there is an effect modification by baseline opioid dose in the population of subjects with OIC, then a single dose may not be appropriate for all patients receiving opioids.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the supplemental application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your supplemental application.

We request that you submit the following information:

Efficacy

Perform and submit the following additional analyses:

- 1) Individual trial analyses comparing the two treatment arms (placebo vs. lubiprostone) for the ITT, completers, and per-protocol population in trials OBD-631 and OBD-632 using the primary efficacy endpoint employed in trial OBD-1033. This primary efficacy endpoint is overall SBM response, where overall SBM response was defined as at least a moderate response (≥ 1 SBM improvement over baseline SBM frequency) for all treatment weeks for which observed data were available AND a full response (≥ 3 SBMs per week) for at least 9 of the 12 treatment weeks. A new dataset containing the appropriate variables for overall SBM response should be submitted.
- 2) Individual trial subgroup analyses by opioid class and opioid subclass of the ITT, completers, and per-protocol population in each of the individual trials (OBD-631, OBD-632, and OBD-1033) using both the primary efficacy endpoint (overall SBM response) employed in trial OBD-1033 (as described in request #1) and the primary efficacy endpoint used in trials OBD-631 and OBD-632 (mean change from baseline in SBM frequency at week 8).
 - a. The opioid classes of phenylpiperidines, phenanthrenes, and diphenylheptanes should be included for trials OBD-631 and OBD-632. The opioid classes of

- phenylpiperidines, and phenanthrenes should be included for trial OBD-1033. The analysis should be similar to that presented in Table 2.7.3.3-11 (page 104 of the Summary of Clinical Efficacy), but should be broken down by individual trial (rather than pooled trial data).
- b. Within the phenanthrene class, overall SBM response should be analyzed across the two arms for each individual trial (OBD-631, OBD-632, and OBD-1033) with respect to three subclasses of phenanthrenes, namely hydrocodones, morphines, and oxycodones. The analysis should be similar to that presented in Table 2.7.3.3-12 (page 105 of the Summary of Clinical Efficacy), but should be broken down by individual trial (rather than pooled trial data).
- 3) Individual trial subgroup analyses by baseline demographics (specified below) and baseline constipation status of the ITT population in each of the two trials OBD-631 and OBD-632 using the primary efficacy endpoint (mean change from baseline in SBM frequency at week 8) for these trials and using the overall SBM response primary endpoint from trial OBD-1033 (as described in request #1). Each of the following demographics should be separately assessed:
- a. Age
 - b. Age group
 - c. Gender
 - d. Race (white, black, Asian, other)
 - e. Baseline observed morphine equivalent daily dose (MEDD) (mg)
 - f. Geographic region (US vs. non-US)
 - g. Constipation status at baseline (SBM frequency per week, average consistency, hard or very hard stool consistency in $\geq 25\%$ of SBMs, severity of constipation, average degree of straining, moderate or worse straining $\geq 25\%$ of SBMs, sensation of incomplete evacuation $\geq 25\%$ of SBMs, abdominal discomfort, abdominal bloating, bowel habit regularity, and percent days of rescue medication use)
- 4) Explain how the variable “VALUE” in the dataset ADEFFIC is computed.
- 5) Provide a tabular summary of baseline demographics and baseline constipation status (as specified in request #3) for all ITT subjects in trials OBD-631 and OBD-632, stratified by methadone (or congener of methadone) use. These tables should be similar to those presented in Table 2.7.3.3-4 (page 26 of 119) and Table 2.7.3.3-5 (page 29 of 119) of the Summary of Clinical Efficacy, but should be further broken down by subjects on methadone (or congener of methadone) and subjects not on methadone.

Safety

- 1) For each trial (OBD-631, OBD-632, OBD-1033, and OBD-06S1), provide a tabular presentation of number and percentage of subjects on each class of opioids: phenylpiperidines, phenanthrenes, and diphenylheptanes. For the phenanthrene class, provide additional subclassification for morphines, hydrocodones, and oxycodones.

- 2) For trials OBD-631, OBD-632, and OBD-06S1 provide a table that summarizes the number and percentage of subjects on a diphenylheptane opioid (separate by individual opioid, such as methadone, propoxyphene, etc..) in the following populations: (1) randomized; (2) safety-evaluable; (3) ITT; 4) completers; and 5) per-protocol.
- 3) Specify the algorithm used to generate the adverse event incidence tables in Table 2.7.4.2-4 (page 38 of 167) and Table 2.7.4.2-6 (page 43 of 167) of the Summary of Clinical Safety. The clinical reviewer used the ADAE dataset provided in the ISS to generate an AE incidence head count (which counts an AE only once for each subject even if reported more than once by that subject) for the population of subjects where the variable SAFETY=1 and variable AETRTEM=1. This approach, which should generate incidence of adverse events for the safety-evaluable population with treatment-emergent adverse events, did not produce the same numbers presented in the tables described above.
- 4) Provide tabular summary of adverse events (numbers and percentages) by opioid subgroups for the long-term safety study (OBD-06S1) and the overall safety pool in the same format as provided in Tables 2.7.4.5-14 through Table 2.7.4.5-21, pages 139 to 150 in the Summary of Clinical Safety.
- 5) One subject in trial OBD-632, subject 2093002, was reported to be on 1200 mcg transdermal fentanyl, with an MEDD of 95,434 mg. Verify whether this subject was actually on such an opioid regimen. We have noted that this subject, despite being in the ITT population, was excluded from your analysis of baseline observed combined MEDD for trial OBD-632 as presented in Table 2.7.3.3-4, page 27 of 119 of Summary of Clinical Efficacy.
- 6) Provide further cardiovascular information on subject 1040011 in trial OBD-631. This subject, in module 5.3.5.1, OBD-631 Clinical Study Report (CSR), listing 16.2.9, is indicated to have had a normal ECG on screening and an ECG at visit 8 that showed “anterior ischemia.” No additional comment was provided in the CSR and no case report form (CRF) was provided for this subject.
- 7) For all laboratory parameters that were evaluated in trial subjects, provide a tabular listing of the numerical values (and units) used for the reference range lower and upper limits of normal. Specify if different reference ranges were used at specific sites or in various trials.

Statistics

- 8) Provide your well-commented and organized software programming code that was written for each primary analysis dataset and efficacy table created for each pivotal study. In addition, provide the programming code used to analyze the primary variables in the integrated study of efficacy.

Label

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.
2. The length of HL must be less than or equal to one-half page unless a waiver has been granted.

We request that you resubmit labeling that addresses these issues by October 26, 2012. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Maureen Dewey, Senior Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD W ISHIHARA
10/02/2012



NDA 21908/S-011

PRIORITY REVIEW DESIGNATION

Sucampo Pharma Americas, LLC.
Attention: Jeffrey Carey
Senior Director, Regulatory Affairs
4520 East-West Highway, Suite 300
Bethesda, MD 20814

Dear Mr. Carey:

Please refer to your Supplemental New Drug Application (sNDA) dated July 20, 2012, received July 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amitiza (lubiprostone) Capsules (8 mcg, 24 mcg).

We also refer to your amendments dated August 8, August 24, and August 30, 2012.

This supplemental application proposes the following new indication:

“Amitiza is indicated for the treatment of opioid-induced constipation (OIC) [REDACTED] (b) (4)
[REDACTED] in adults with chronic, non-cancer pain.”

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is January 20, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 30, 2012.

If you have any questions, call Maureen Dewey, Senior Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DONNA J GRIEBEL
09/14/2012

Dewey, Maureen

From: Dewey, Maureen
Sent: Friday, September 14, 2012 10:23 AM
To: 'Carey, Jeffrey'
Cc: Dewey, Maureen
Subject: NDA 21908/S011 Request for Information

Dear Jeff,

We are reviewing your supplement application for NDA 21908/S011 Amitiza and have the following request for information:

Clarification of dataset variable corresponding to baseline morphine equivalent daily dose (MEDD) in OBD-631 and OBD-632

For trial OBD-1033, a separate average MEDD variables dataset (called ADOPCALC) was provided with a variable called BASELINE, which gives the MEDD at baseline. No comparable dataset could be found for trials OBD-631 or OBD-632. Instead, both OBD-631 and OBD-632 have an opioid medications variables dataset (called ADOP), with a variable called OPMED that gives the MEDD, but this variable does *not* clearly indicate whether this MEDD is the baseline MEDD or not.

Please provide clarification of the variable in the datasets for studies OBD-631 and OBD-632 that corresponds to average MEDD *at baseline* for all subjects in those 2 trials.

Your prompt response to this request is appreciated.

Regards,

Maureen Dewey, M.P.H.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/FDA

(301) 796-0845 (office)
(301) 796-9905 (fax)

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0069. Thank you.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
09/14/2012

REQUEST FOR CONSULTATION

TO (Office/Division):
ODE I
Division of Cardiovascular and Renal Products
Attn: Norman Stockbridge, M.D.

FROM (Name, Office/Division, and Phone Number of Requestor):
Maureen Dewey, Regulatory Project Manager
Division of Gastroenterology & Inborn Errors Products
WO 22, Room 5159
(301) 796-0845

DATE September 11, 2012	IND NO. 77771	NDA NO. 21908/011	TYPE OF DOCUMENT Efficacy Supplement/Juvenile Tox Study	DATE OF DOCUMENT 7/20/2012 Efficacy Suppl 5/22/2012 (SD #109)

NAME OF DRUG Amitiza (lubiprostone)	PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG Cathartics and Laxatives	DESIRED COMPLETION DATE 12/10/2012

NAME OF FIRM: **Sucampo**

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE-NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END-OF-PHASE 2a MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ END-OF-PHASE 2 MEETING	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ RESUBMISSION	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☒ SAFETY / EFFICACY	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE / ADDITION	☐ PAPER NDA	☒ OTHER (SPECIFY BELOW):
☐ MEETING PLANNED BY	☐ CONTROL SUPPLEMENT	

II. BIOMETRICS

☐ PRIORITY P NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END-OF-PHASE 2 MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER (SPECIFY BELOW):
☐ OTHER (SPECIFY BELOW):	

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILITY STUDIES	☐ PROTOCOL - BIOPHARMACEUTICS
☐ PHASE 4 STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☒ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

Questions for CardioRenal:

DGP is requesting a nonclinical consult to review the cardiovascular (CV) effects of lubiprostone in juvenile rats. Lubiprostone is a prostaglandin analog and caused significant increases in heart rate and blood pressure in juvenile rats following oral administration of the drug. The sponsor plans to conduct studies in pediatric patients with lubiprostone to fulfill the PREA requirements. Please review the data on CV effects of lubiprostone in juvenile rats and provide feedback whether there is any significant CV risk in pediatric subjects treated with the drug, and if any precautions/monitoring would be required while conducting studies in pediatric patients.

EDR Location:

\\CDSESUB1\EVSPROD\NDA021908\0109

Eroom for Application and Label:

http://erom.fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0_2f7aa

SIGNATURE OF REQUESTOR

Maureen Dewey on behalf of Sushanta Chakder, Ph.D.

METHOD OF DELIVERY (Check one)

DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
09/13/2012

DGCPC/OSI CONSULT: Request for Clinical Inspections

Date: September 6, 2012

To: Lauren Iacono-Connors, Ph.D., Acting Division Director, DGCPC
Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB
Susan Thompson, M.D., Acting Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
Susan Leibenhaut, M.D. Acting Team Leader, GCPAB
CDER OSI PM Track
Dr. Malik [OSI Primary Reviewer]
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through:

From: Farrokh Sohrabi, MD, Medical Officer
Division of Gastroenterology and Inborn Errors Products
Center for Drug Evaluation & Research
Bldg 22, Rm 5161

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 021908/S-011
IND#: 77771

Applicant/ Applicant contact information (to include phone/email):

Sucampo Pharms Americas, LLC.
Regulatory Contact: Jeff Carey, Senior Director, Regulatory Affairs
4520 East-West Highway, Suite 300
Bethesda, MD 20814
(301) 961-3400

Drug Proprietary Name: Amitiza
Generic Drug Name: Lubiprostone
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No
DGCPC/OSI Consult
version: 07/9/2012

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s):

"Treatment of opioid-induced constipation and associated signs and symptoms in adults with chronic, non-cancer pain"

PDUFA: January 18, 2013

Action Goal Date: January 18, 2013

Inspection Summary Goal Date: December 21, 2012

II. Protocol/Site Identification

Site # (Name, Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
3098 (Eric Wolfson; 6803 W. Tropicana, Suite 100, Las Vegas, NV 89106; fax # 1-702-869-0270)	SMR/021 1OBD-1033	19	Opioid induced constipation
3019 (Karamo Chilombo; 1530 E. South Street, Long Beach, CA 90805; fax # 1-888-586-3444 [X 2])	SMR/021 1OBD-1033	10	Opioid induced constipation
1069 (Nelson Sandoval, Fabia Kwiecinski, Pam Laubscher, Michael Dao; 5390 E. Erickson Dr Tucson, AZ 85712; fax # 1-520-829-6839)	SMR/021 1OBD-0631	25	Opioid induced constipation
1018 (Harvey Leslie, Howard DeHaven; 3009 Rainbow Drive, Suite 146, Decatur, GA 30034; fax # 1-404-244-0608)	SMR/021 1OBD-0631	28	Opioid induced constipation

(b) (4)

III. Site Selection/Rationale

Site 3098: Highest % of lubiprostone responders (32%) for a site with ≥ 10 subjects

Site 3019: Highest % of placebo non-responders (60%) for site with ≥ 10 subjects. In the Study Report for OBD-1033, the Sponsor indicated that routine monitoring and subsequent audit of data collected at site 3019 led the sponsor to question the suitability of the data. As a result, the modified intent-to-treat population excluded data from site 3019. Further information on the nature of the issue at site 3019 was requested. The Sponsor responded that during the study, a representative from the monitoring team of the CRO vendor expressed concerns regarding source documentation at site 3019. Improvement in the site's organization and record keeping was noted during subsequent monitoring visits to the site. The CRO vendor conducted a routine audit at site 3019 on October 19-20, 2011. Although one major issue (maintenance of inadequate case histories) and some minor issues were identified, the auditor had no concerns about the integrity of the data collected at the site. Corrective action was taken to address the issues identified during the audit. Despite the results of the audit report, the Sponsor decided to have an independent third party vendor (b) (4) perform "for-cause audits" at site 3019. These audits were conducted on December 12-13, 2011. Because of the pending database lock (December 8, 2011), the Sponsor decided to include the analysis of a modified ITT population in the event major GCP violations indicative of compromised data were confirmed. Again, the independent auditor concluded that there were no concerns related to the integrity of the data collected at the site.

Site 1069: Large number of subjects with disproportionately high responder status (~20%)

Site 1018: Site with largest number of subjects

Optional - Site 3028: Site with largest number of subjects. OSI had indicated that this investigator has 46 INDs in the OSI database and has never been inspected.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects: At site 3028, site 1018
- High treatment responders (specify): At site 3098, site 1069
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): High placebo non-responders: At sites 3019

International Inspections:

There are no international site inspections recommended.

Five or More Inspection Sites:

We have requested 4 domestic sites for inspection and 1 optional because of the following reasons: OSI review team had indicated Site 3028 as a potential inspection site for the reasons described above. DGIEP defers to OSI if they would like to inspect this site, but DGIEP does not consider this site a priority over the other 4 sites.

IV. Tables of Specific Data to be Verified (if applicable)

Should you require any additional information, please contact *Maureen Dewey* at 301-796-0845 or *Farrokh Sohrabi, MD* at 301-796-0966.

Concurrence: (as needed)

Robert Fiorentino Medical Team Leader
Farrokh Sohrabi Medical Reviewer

Division Director (for foreign inspection requests or requests for 5 or more sites only)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
09/11/2012

DONNA J GRIEBEL
09/11/2012



NDA 21908/S-011

INFORMATION REQUEST

Sucampo Pharma Americas, LLC.
Attention: Jeffrey Carey, Senior Director
Regulatory Affairs
4520 East-West Highway, Suite 300
Bethesda, MD 20814

Dear Mr. Carey:

Please refer to your Supplemental New Drug Application (sNDA) dated July 20, 2012, received July 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amitiza (lubiprostone) Capsules (8 mcg, 24 mcg).

We also refer to your submissions dated August 8, August 24, and August 30, 2012.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental application.

- 1) Clarify whether any female subjects enrolled in any of the four OBD trials (0631, 0632, 1033, or 06S1) became pregnant at any time during the trial or by last follow-up visit. If so, provide brief patient narratives for each of these subjects that includes the outcome of the pregnancy.
- 2) For OBD-06S1, provide a tabular listing of the original treatment arm (in trial 0631 or 0632) for all subjects who experienced death, a serious adverse event, or an adverse event leading to discontinuation of medication. For example, if subject #1 was originally enrolled in OBD-0631 and subsequently participated in the open-label trial OBD-06S1, indicate whether subject #1 was in the placebo or the lubiprostone arm of trial OBD-631.
- 3) With reference to reasons for discontinuation (subject disposition) discussed for all four trials (0631, 0632, 1033, or 06S1), clarification is requested of the following terms:
 - a. Discontinuation due to "other": Provide the specific "other" reasons for discontinuation and the number of subjects discontinued for each of the "other" reasons. Tabulate by treatment arm and study.
 - b. Discontinuation due to "investigator decision": Provide the specific reasons for discontinuation by the investigator and the number of subjects discontinued for

each of those investigator decision-based reasons. Tabulate by treatment arm and study.

- c. Discontinuation due to “sponsor request”: Provide the specific reasons for discontinuation by the sponsor and the number of subjects discontinued for each of those sponsor request-based reasons. Tabulate by treatment arm and study.

If you have questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

R. Wes Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD W ISHIHARA
09/07/2012

REQUEST FOR Patient Reported Outcomes (PRO) ENDPOINTS CONSULTATION

TO: Study Endpoints and Labeling Development (SEALD) CDER/OND-IO White Oak Bldg 22, Mail Drop 6411 SEALD.ENDPOINTS@FDA.HHS.GOV	FROM: Review Division: Division of Gastroenterology Products Medical Reviewer: Farrokh Sohrabi, M.D. Project Manager: Maureen Dewey

DATE OF CONSULT REQUEST	Application# IND/NDA/BLA#	LETTER # OR SUBMISSION #	TYPE OF DOCUMENT (Meeting; Protocol/SPA; PDUFA Product Review)	REQUESTED SEALD COMPLETION DATE*
08/23/2012	IND 77771 NDA 21908/S011		Efficacy Supplement	November 1, 2012

DRUG ESTABLISHED NAME	DRUG TRADE NAME	NAME OF SPONSOR	SPONSOR SUBMIT DATE
Amitiza	Lubiprostone	Sucampo	July 20, 2012

DEVELOPMENT PHASE (E.G., pre-IND/NDA/BLA; IND/BB-IND Phase 1, 2, 3; NDA/BLA): Efficacy Supplement
GOAL DATE (if NDA/BLA./SPA): January 20, 2013

ELECTRONIC LINK (if applicable): EDR Location: <\\CDSESUB1\EVSPROD\NDA021908\0112>
 Gateway Location: <\\chdc9681\cderesub\inbound\ectd\ci1342793395601.882550@llnap12.te>

MEETINGS (if applicable) (please send invite to SEALD.ENDPOINTS@FDA.HHS.GOV)
 21st Century Review Meetings TBD

PLEASE make certain the background-briefing package is included with this consult. It should contain the following applicable information needed to start Study Endpoints Review: Protocol or Study ID; Endpoint Concept(s); Instrument(s); Indication(s); Study population(s); Prior related reviews. Division please provide the following specific information on this consult form:

Indication(s):

"Treatment of opioid-induced constipation (b)(4) in adults with chronic, non-cancer pain"

Specific Questions/Comments for SEALD:

The Sponsor is seeking labeling for lubiprostone "for the treatment of opioid-induced constipation (OIC) (b)(4) in adults with chronic, non-cancer pain." (b)(4)

Questions: (b)(4)

Requester

Maureen Dewey on behalf of Dr. Farrokh Sohrabi, primary medical officer

Name/Phone number/email address/office location

Glossary:

Concept: The specific goal of a measurement (i.e. the *thing* that is to be measured by a PRO instrument).

Instrument: A means to capture data (e.g. questionnaire, diary) plus all the information and documentation that supports its use. Generally, Reference ID: 3182729

that includes clearly defined methods and instructions for administration or responding, a standard format for data collection, and well-documented methods for scoring, analysis, and interpretation of results.

*For voluminous study endpoint submissions (e.g. PRO “dossier” or content validity documentation greater than 50 pages), SEALD requests 60 days after receiving the background/briefing package document to complete the review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
08/30/2012

**REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW
CONSULTATION**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-DDMAC-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Maureen Dewey Division of Gastroenterology & Inborn Errors Products WO 22, Room 5159 (301) 796-0845

REQUEST DATE August 23, 2012	IND NO. 77771	NDA/BLA NO. 21908/S011	TYPE OF DOCUMENTS Full Prescribing Information submitted with Efficacy Supplement

NAME OF DRUG Amitiza (lubiprostone)	PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG Cathartics and laxatives	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) November 5, 2012

NAME OF SPONSOR Sucampo	PDUFA Date: January 20, 2013

TYPE OF LABELING: (Check all that apply) ☒ PACKAGE INSERT (PI) ☐ PATIENT PACKAGE INSERT (PPI) ☐ CARTON/CONTAINER LABELING ☐ MEDICATION GUIDE ☐ INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION ☐ ORIGINAL NDA/BLA ☐ IND ☒ EFFICACY SUPPLEMENT ☐ SAFETY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ PLR CONVERSION	REASON FOR LABELING CONSULT ☐ INITIAL PROPOSED LABELING ☒ LABELING REVISION

ELECTRONIC LINK (if applicable): EDR Location:
<\\CDSESUB1\EVSPROD\NDA021908\0112>
 Gateway Location: <\\chdc9681\cderesub\inbound\ectd\ci1342793395601.882550@llnap12 te>
 Eroom for Application and Label:
http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0_2f7aa

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:
 Mid-Cycle Meeting: ~ October 26, 2012
 Labeling Meetings: TBD
 Wrap-Up Meeting: TBD

SIGNATURE OF REQUESTER: Maureen Dewey, M.P.H.

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

eMAIL

HAND

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
08/28/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			Pediatric and Maternal Health Staff Request for Consultation	
TO: CDER Pediatric and Maternal Health Staff (<i>please check</i>) Pediatrics ☒ Maternal Health ☐ Both ☐			FROM (<i>Name, Office/Division, and Phone Number of Requestor</i>): Maureen Dewey, RPM Division of Gastroenterology and Inborn Errors Products WO 22, RM 5159 (301) 796-0845	
DATE 08/17/2012	IND NO. 77771	NDA/BLA NO. 21908	TYPE OF DOCUMENT Prior Approval Efficacy Supplement	DATE OF DOCUMENT 07/20/2012
NAME OF DRUG Amitiza (lubiprostone)		NAME OF FIRM Sucampo	CLASSIFICATION OF DRUG Chloride Channel Activator Cathartic/Laxatives	PDUFA Goal Date 1/20/2013
Requested Consult Completion Date: October 19, 2012		☐ Urgent* (< 14 days)	☐ Priority (14-29 days)	☒ Routine $\geq$ 30 days October 19, 2012
*Note: Any consult requests with a desired completion date of < 14 days from receipt must receive prior approval from PMHS team leaders. Also, please check one of the three boxes above and also put in a due date.				
REASON FOR REQUEST				
Pediatrics: ☐ Labeling Review ☐ Written Request/PPSR ☐ PREA PMR/General Regulatory Question ☐ SPA ☐ Action Letter Review ☐ 30-day IND Review ☐ Other Protocol Review ☐ Meeting Attendance ☒ PeRC Preparation Assistance ☒ Other (please explain):			Maternal Health Team: ☐ Labeling Review ☐ Pregnancy Exposure Registry (protocol or report) ☐ Clinical Lactation Study (protocol or report) ☐ Pregnancy PK (protocol or report) ☐ 30-day IND Review ☐ Risk Management – Pregnancy Prevention and Planning ☐ Evaluation of possible safety signal ☐ Guidance development ☐ Other (please explain):	
Link to electronic submission (if available): EDR Location: \CDSESUB1\EVSPROD\NDA021908\0112 EDR Location: \CDSESUB1\EVSPROD\NDA021908\0113 (pediatric plan)			Materials to be reviewed: Waiver of Pediatric Studies and Deferral of Pediatric Studies	
1. Please briefly describe the submission including drug's indication(s): Indication proposed: "Treatment of opioid-induced constipation (b) (4) in adults with chronic, non-cancer pain" OIC Request for Waiver of Pediatric Study (Module 1, 1.9.1), and the OIC Request for Deferral of Pediatric Study (Module 1, 1.9.2) which contains the OIC Pediatric Plan. 2. Describe in detail the reason for your consult. Include specific questions: DGIEP kindly requests assistance with scheduling of PeRC and subsequent preparation for PeRC. 3. Meeting dates: Filing Meeting: August 23, 2012 9:00 a.m. Planning Meeting: September 10, 2012 4. DARRTS Reference ID # for Prior Peds or Maternal Health consults for this product (within the last 3 years): IND 77771 or NDA 21908				
Review team: Project Manager: Maureen Dewey Clinical reviewer & Team Leader: Farokh Sohrabi, Robert Fiorentino Pharmacology/Toxicology reviewer & Team Leader: Sushanta Chakder Clinical Pharmacology reviewer & Team Leader: Sandhya Apparaju, Sue Chih Lee				

Other: Freda Cooner/Mike Welch (Stats)

PRINTED NAME or SIGNATURE OF REQUESTOR:

METHOD OF DELIVERY (Please check)

DARRTS EMAIL HAND OTHER

Version: [DARRTS 06/01/2011](#)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
08/17/2012



NDA 21908/S-011

**ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT**

Sucampo Pharma Americas, Inc.
Attention: Jeffrey Carey, Senior Director
Regulatory Affairs
4520 East-West Highway, Suite 300
Bethesda, MD 20814

Dear Mr. Carey:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 21908
SUPPLEMENT NUMBER: 011
PRODUCT NAME: Amitiza (lubiprostone) Capsule 24 mcg, 8 mcg
DATE OF SUBMISSION: July 20, 2012
DATE OF RECEIPT: July 20, 2012

This supplemental application proposes the following change:

Indication for the treatment of opioid-induced constipation (OIC) [REDACTED] (b) (4)

[REDACTED] in adults with chronic, non-cancer pain.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 18, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/ct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 21908/S-011** submitted on July 20, 2012, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey, M.P.H.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
08/07/2012