1. TITLE PAGE

CLINICAL STUDY REPORT

A MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLINDED STUDY OF THE EFFICACY AND SAFETY OF LUBIPROSTONE IN SUBJECTS WITH OPIOID-INDUCED BOWEL DYSFUNCTION

Protocol No. SMR/0211OBD-1033

Study Drug Name: Lubiprostone

Phase 3

IND #: 77,771

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Date of First Subject Observation: 07 December 2010
Date of Last Subject Observation: 16 November 2011
Date of Report: 18 April 2012
Date of Previous Report: NA

This study was conducted according to the protocol and in compliance with Good Clinical Practice (GCP) and other applicable regulatory requirements.

Signature Page

STUDY TITLE: A Multicenter, Randomized, Placebo-Controlled, Double-Blinded Study of the Efficacy and Safety of Lubiprostone in Subjects with Opioid-induced Bowel Dysfunction

Study: SMR/0211OBD-1033 Development Phase: 3

I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the study.

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STUDY TITLE: A Multicenter, Randomized, Placebo-Controlled, Double-Blinded Study of the Efficacy and Safety of Lubiprostone in Subjects with Opioid-induced Bowel Dysfunction

I have read this report and confirm that, to the best of my knowledge, Study SMR/0211OBD-1033 was carried out as described in this report.

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2. SYNOPSIS

Sponsor Name:	Sucampo Pharma Americas, Inc.
Study Drug Name:	Lubiprostone
Protocol Number:	SMR/0211OBD-1033

Study Title: A Multicenter, Randomized, Placebo-Controlled, Double-Blinded Study of the Efficacy and Safety of Lubiprostone in Subjects with Opioid-Induced Bowel Dysfunction

Investigators/Study Centers: This was a multicenter study consisting of 105 investigative sites in the United States and European Union. There were 91 sites in the United States and 14 in the European Union.

Study Period: 07 December 2010 to 16 November 2011

Phase of Development: 3

Objectives: The objective of this study was to assess the efficacy and safety of oral lubiprostone at 48 mcg/day (24 mcg twice daily [BID]), as compared to placebo, when administered orally for 12 weeks to subjects with opioid-induced bowel dysfunction (OBD).

Study Design: This study was a 14-week multicenter, double-blinded, randomized, placebo-controlled evaluation of the efficacy and safety of lubiprostone for the treatment of OBD.

Number of subjects (planned and analyzed): Four hundred twenty subjects were planned for this study (210 per treatment group). A total of 447 subjects were randomized, and 353 subjects completed the study.

Diagnosis and main criteria for inclusion: The subjects eligible to participate were ≥18 years of age who had been consistently treated for chronic, noncancer-related pain with any oral, transdermal, intravenous, or subcutaneous opioid for at least 30 days prior to screening, diagnosed with OBD, were capable of utilizing an electronic diary to report their daily spontaneous bowel movements (SBMs), and were willing to continue opioid therapy and discontinue the use of laxatives, stool softeners, and other concomitant medications affecting gastrointestinal motility throughout the study. An SBM was defined as any bowel movement (BM) that did not occur within 24 hours after rescue medication use.

OBD was defined as an average of <3 SBMs/week and at least one 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.

Exclusionary criteria included the use of opioids for the treatment of cancer-related pain, abdominal pain, mechanical bowel obstructions, bowel disorders, and constipation not arising from opioid use, but instead attributable to dietary, neurologic, congenital, or endocrine disorders, scleroderma, and/or for the management of drug addiction.

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Test Product, Dose, and Mode of Administration [including Lot Number(s)]: Lubiprostone 24 mcg (Lot No. 986328) capsules were orally administered BID for a total daily dose of 48 mcg.

Duration of Study: Approximately 18 weeks, including screening and 12 weeks (84 days) for treatment, with another 2 weeks for final follow-up visit.

Reference Therapy, Dose, and Mode of Administration [including Lot Number(s)]: Placebo 0 mcg (Lot No. 1107962) capsules were orally administered BID.

Criteria for Evaluation of Safety: Safety assessments were performed on all subjects who received at least 1 dose of study medication. Assessments were based on incidence of treatment-emergent adverse events (TEAEs), opioid dose adjustments, rescue medication usage, and changes from baseline for clinical laboratory results (including serum chemistry, hematology, and urine analysis) vital signs, physical examinations, and nausea and pain assessments.

Criteria for Evaluation of Efficacy: The intent-to-treat (ITT) subject population was used for the primary efficacy analyses. This population was defined as all randomized subjects who took at least 1 dose of study medication and had at least 1 treatment period diary entry. The primary efficacy endpoint was overall SBM response rate in ITT subjects.

Overall SBM response during the double-blind treatment phase required that a subject have at least 9 weeks of nonmissing weekly SBM rates. Subjects that had at least 1 additional SBM compared to baseline during every week that data were available and a minimum of 3 SBMs per week for at least 9 weeks were considered overall SBM responders. Subjects with <9 weeks of weekly SBM rates were automatically considered nonresponders.

Secondary efficacy endpoints included the following:

- Change from baseline in SBM frequency at Weeks 8, 12, and overall
- Percentage of subjects with a first postdose SBM within 24 hours and within 48 hours of first dose
- Weekly responder rates
- Health-related quality of life
- 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

Additional exploratory analyses included 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, analyses of bowel habit regularity, the frequency of SBMs and BMs, frequency of complete SBMs and BMs, monthly assessment of treatment effectiveness, median time to first SBM, and the proportion of subjects in each treatment group with their first SBM at 4, 8, and 12 hours.

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Statistical Methods: All data listings were summarized by treatment group and subject identification number. Unless otherwise specified, categorical variables were summarized using sample size, frequency, and percentage. Continuous variables were summarized using descriptive statistics, which included sample size, mean, median, standard deviation, and minimum and maximum values. All significance tests were 2-tailed and performed at the $\alpha = 0.05$ level. Subject disposition data, demographics, baseline characteristics, and exposure to study medication were summarized.

***Safety*:**
Adverse events (AEs) were summarized in terms of incidence per treatment group and overall. The incidence of an AE was defined as the number of subjects who experienced at least 1 episode during the study. Incidence rate tabulations (incidence expressed as a percentage of the number of safety-evaluable subjects) were performed for all AEs, including serious adverse events (SAEs), AEs rated as "severe" and those assumed to be at least "possibly related" to treatment, and AEs that resulted in withdrawal from the study. Deaths, SAEs, and AEs leading to discontinuation from the study were listed separately.
Descriptive statistics and pretreatment versus post-treatment cross-tabulations (with classes for below, within, and above normal range) were generated for selected data from clinical laboratory tests.

Additionally, descriptive statistics were used to evaluate changes from baseline for vital signs, weight, and body mass index. Analysis of variance (ANOVA) was used to compare the changes from baseline in nausea scores and in Brief Pain Inventory Short-Form (BPI-SF) scores for pain severity, pain interference, and worst pain across treatment groups. Within-group comparisons were made using paired t-tests.

All medications, including rescue medications used emergently to relieve constipation and the administered opioid treatment's name, dosage parameters, and dose adjustments were captured for all subjects during their participation in the study.

***Efficacy*:**
For the primary efficacy endpoint, baseline was defined as the weekly average SBM frequency from the diary entries during the last 2 weeks of the screening visits. The overall rates comparing treatment groups were analyzed using the Cochran-Mantel-Haenszel (CMH) method, stratifying by pooled site. An additional CMH analysis was conducted using secondary pooling.

For the secondary variable of change from baseline in SBM frequency at Weeks 8, 12, and overall, stratified analysis of covariance (ANCOVA), using the Week 8 and Week 12 values as the dependent variable, controlling for pooled site, was used to compare treatment groups using baseline rate as a covariate. Paired t-tests were used to determine significant changes from baseline within treatment groups.

The Kaplan-Meier life table estimates and Cox proportional hazards regression models were used to describe the proportion of subjects in each treatment group with their first SBM reported within 24 hours of first dose administration. The treatment groups were compared using the likelihood-ratio chi-square test. If the p-value for 24 hours was ≤ 0.05 then the groups were compared at 48 hours as well. The significance level was set at 0.05 in both comparisons.

For mean change from baseline analyses, improvement from baseline within each treatment group was

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generally 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 procedure. Stratified ANCOVA included the baseline value (the covariate). If the model assumptions did not hold, then the van Elteren test was employed.

Safety Results:

- A total of 120 out of 219 subjects (54.8%) in the lubiprostone group and 108 out of 220 subjects (49.1%) in the placebo group experienced at least 1 AE; the majority of AEs were mild or moderate in severity.
- Significantly more subjects in the lubiprostone group (62/219; 28.3%) experienced treatment-related, treatment-emergent AEs compared to the placebo group (32/220; 14.5%; $p < 0.001$).
- In the lubiprostone group, 3.2% of subjects (7/219) reported an SAE, and 2.7% (6/220) of placebo subjects reported an SAE.
- There was 1 death during the study, in the lubiprostone group; it was not considered treatment related.
- Five out of 220 subjects (2.3%) in the placebo group and 13 out of 219 subjects (5.9%) in the lubiprostone group discontinued study medication due to an AE.
- Changes in laboratory parameters, vital signs, physical examination findings, and weight were not considered clinically meaningful.

Efficacy Results:

- The primary efficacy endpoint, overall SBM response rate in ITT subjects, was statistically significantly higher in lubiprostone-treated subjects than in placebo subjects ($p = 0.035$).
- Lubiprostone-treated subjects had statistically significantly greater mean overall changes from baseline SBM frequency than placebo subjects ($p = 0.002$).
- Statistically significantly more lubiprostone-treated subjects had SBMs within 24 hours ($p = 0.016$) and 48 hours ($p = 0.022$) after the first dose of study medication compared to placebo subjects.
- Lubiprostone-treated subjects had statistically significant overall improvement from baseline in straining ($p = 0.002$), stool consistency ($p < 0.001$), constipation severity ($p = 0.007$), and abdominal discomfort ($p = 0.048$) compared to placebo subjects, even after adjusting for multiplicity. Lubiprostone subjects did not show a statistically significant improvement for abdominal discomfort when adjusted for multiplicity ($p = 0.095$).
- The median time to first SBM was statistically significantly lower in lubiprostone-treated subjects than in placebo subjects (24.25 hours vs. 38.50 hours, respectively; $p = 0.019$).

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Conclusions:

This study demonstrated efficacy of lubiprostone compared to placebo as assessed by several endpoints. The primary efficacy endpoint, overall SBM response rate in ITT subjects, 18.6% for placebo and 26.9% for lubiprostone, was statistically significantly higher in lubiprostone-group subjects than in placebo subjects ($p = 0.035$). Regarding secondary efficacy endpoints, lubiprostone-treated subjects had statistically significantly greater mean overall changes from baseline SBM frequency than did placebo-group subjects and significantly more lubiprostone-treated subjects had SBMs within 24 hours and 48 hours after the first dose of study medication. The onset of treatment effect was rapid, with a statistically significantly larger proportion of lubiprostone subjects reporting a first post-treatment SBM within 4 hours of dose initiation compared to placebo subjects. In addition, lubiprostone-treated subjects had statistically significant overall improvement from baseline in straining, stool consistency, constipation severity, and abdominal discomfort compared to placebo subjects. Median time to first SBM after administration of study medication, an exploratory endpoint, was significantly lower in lubiprostone-treated subjects than in placebo subjects.

Changes in the BPI-SF domains of pain interference, pain severity, and worst pain were not significantly different from baseline values between or within treatment groups at Months 1–3 and at end of treatment, indicating that lubiprostone did not interfere with the analgesic effects of opioids. In addition, there were no statistically significant differences between treatment groups in changes in morphine equivalent daily dose from baseline at Months 1–3.

Lubiprostone was generally safe and well tolerated. Although significantly more subjects in the lubiprostone group (28.3%) experienced treatment-related, treatment-emergent AEs compared to the placebo group (14.5%; $p < 0.001$), the majority of AEs in both treatment groups were mild or moderate in severity. The 1 death occurring during the study, of a lubiprostone-treated subject due to multiple drug toxicity, was not considered related to study drug. Similar numbers of subjects in both treatment groups reported SAEs (3.2% lubiprostone vs. 2.7% placebo). Five subjects (2.3%) in the placebo group and 13 subjects (5.9%) in the lubiprostone group discontinued study medication due to an AE. Results of laboratory tests and changes in vital signs measurements and physical examinations were not of clinical concern.

The safety profile of lubiprostone in this study is similar to that observed in previously conducted Phase 3 studies in subjects with OBD (SPI/0211OBD-0631 and SPI/0211OBD-0632), in which lubiprostone was dosed at the same level (48 mcg) as in the current study. The profile is also similar to that observed in subjects with chronic idiopathic constipation who were treated with the same dose of lubiprostone.

In conclusion, orally administered lubiprostone 24 mcg BID for the treatment of OBD in subjects taking opioids chronically for noncancer pain appears to be effective and well tolerated.

Report Date: 18 April 2012