

2 SYNOPSIS

Sponsor: Shionogi Inc.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Not applicable	Volume:	
Name of Active Ingredient: S-297995	Page:	
Study Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of S-297995 for the Treatment of Opioid-Induced Constipation in Subjects with Non-Malignant Chronic Pain Receiving Opioid Therapy		
Investigators and Study Centers: Multicenter (see Appendix 16.1.4)		
Publication (reference): none		
Study Period: ■ August 2011 (first subject enrolled) to ■ August 2012 (last subject completed)		
Phase of Development: 2		
Objectives: The primary objective of the study was to evaluate the efficacy of oral S-297995 in subjects with non-malignant chronic pain and opioid-induced constipation (OIC) receiving opioid therapy for ≥ 3 months. The secondary objectives of the study were the following: <ul style="list-style-type: none"> • To evaluate the safety of S-297995 • To evaluate the dose response for 3 doses (0.1, 0.2, and 0.4 mg) of S-297995 • To assess the pharmacokinetics (PK) of S-297995 and its metabolite (Nor-S-297995) • To evaluate subject global satisfaction with S-297995 in subjects with OIC • To evaluate potential opioid withdrawal symptoms utilizing the Clinical Opiate Withdrawal Scale (COWS) The exploratory objectives of the study were the following: <ul style="list-style-type: none"> • To assess dehydroepiandrosterone-sulfate and prolactin at baseline and the end of the treatment period • To assess total and free testosterone in male subjects and follicle-stimulating hormone, luteinizing hormone, and estradiol in female subjects at baseline and the end of the treatment period 		
Methodology: This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate 3 doses of S-297995 in the treatment of subjects with non-malignant chronic pain and OIC receiving opioid therapy for ≥ 3 months. The study		

included a screening period (with a duration of 15 to 28 days), a 28-day treatment period, and a 28-day follow-up period. Subjects were randomized in a 1:1:1:1 assignment to receive placebo, S-297995 0.1 mg, S-297995 0.2 mg, or S-297995 0.4 mg once daily during the 28-day treatment period. Subjects were assessed for treatment efficacy, safety, and PK during the treatment period. Final safety assessments were performed at the end of the follow-up period.

Number of Subjects (Planned and Analyzed):

Planned: 240

Randomized: 244

Analyzed for Efficacy: Modified Intent-to-Treat (mITT) Population: 238; Per-Protocol Population: 203

Analyzed for Safety: 243

Diagnosis and Main Criteria for Inclusion:

The study population included subjects ≥ 18 years of age with non-malignant chronic pain and OIC receiving chronic opioid therapy for ≥ 3 months. Eligible subjects were required to have < 3 spontaneous bowel movements (SBMs) per week, despite a stable regimen of laxative agents. Subjects were required to maintain a stable laxative regimen throughout the study, defined as any combination of laxatives taken by the subject on a consistent basis over the past 28 days or no laxative use. Male subjects were required to be sterile or agreed to use an approved method of contraception. Female subjects were required to be not pregnant, non-lactating, postmenopausal, surgically sterile, or agreed to use a barrier method of contraception or a highly effective technique of birth control from the screening visit until 28 days after the last dose of study drug.

Test Product, Dose and Mode of Administration, Lot Number:

S-297995 (0.1 mg tablets) for oral administration; lot numbers [REDACTED] and [REDACTED]

Duration of Treatment: 28 days

Reference Therapy, Dose and Mode of Administration, Lot Number:

Placebo tablets matching 0.1 mg S-297995 for oral administration; lot numbers [REDACTED] and [REDACTED]

Criteria for Evaluation:

Efficacy Assessment:

The primary efficacy variable was the change in the frequency of SBMs per week from baseline to the last 2 weeks of the treatment period.

The secondary efficacy variables were the following:

- Change in the frequency of SBMs per week from baseline to Weeks 1, 2, 3, and 4
- SBM and complete SBM (CSBM) responder rates
- Change in the frequency of bowel movements, complete bowel movements, and CSBMs per week from baseline
- Change in the number of days of SBMs and CSBMs per week from baseline
- Time to the first SBM and CSBM after the initial administration of study drug
- Incidences of SBMs or CSBMs within 4, 8, 12, and 24 hours after the initial

administration of study drug

- Change in the frequency of SBMs rated as 3 or 4 on the Bristol Stool Scale (BSS) per week from baseline
- Change in the frequency of SBMs without straining per week from baseline
- Change in the frequency of false starts of bowel movements from baseline
- Change in the frequency of rescue use of laxative agents per week from baseline
- The frequency of rescue use of laxative agents during the treatment period
- Changes in the abdominal bloating and abdominal discomfort scores from baseline
- Subject Global Satisfaction score at end of treatment

Pharmacokinetics Assessment:

Pharmacokinetic blood samples for S-297995 and its metabolite (Nor-S-297995) were collected from a subset of subjects at selected study sites at the following time points:

- Day 1: 0 (predose) and 1 (\pm 5 minutes), 2 (\pm 10 minutes), 4 (\pm 15 minutes), and 8 (\pm 30 minutes) hours postdose
- Day 2: 24 (\pm 60 minutes, prior to Day 2 dosing) hours postdose

In addition, 16 subjects (at selected sites) had PK samples collected at the following time points:

- Day 28: 0 (predose) and 1 (\pm 5 minutes), 2 (\pm 10 minutes), 4 (\pm 15 minutes), and 8 (\pm 30 minutes) hours postdose
- Day 29: 24 (\pm 60 minutes) hours postdose

The following PK parameters were calculated for S-297995 and Nor-S-297995: maximum observed concentration (C_{max}); time to maximum concentration (T_{max}); area under the concentration-time curve from hour 0 to the time point of the last measurable concentration within the dose interval (τ , 24 hours) ($AUC_{0-\tau}$); area under the concentration-time curve extrapolated to infinity (AUC_{0-inf}); apparent terminal elimination half-life ($t_{1/2,z}$); apparent total clearance (CL/F); ratio of C_{max} of metabolite to C_{max} of unchanged S-297995, corrected for molecular weight; ratio of $AUC_{0-\tau}$ of metabolite to $AUC_{0-\tau}$ of unchanged S-297995, corrected for molecular weight; accumulation ratio for C_{max} calculated as ratio of Day 28 to Day 1 C_{max} ; accumulation ratio for $AUC_{0-\tau}$ calculated as ratio of Day 28 to Day 1 $AUC_{0-\tau}$.

Safety Assessment:

Safety assessments included adverse events, clinical laboratory safety tests (chemistry, hematology, and urinalysis), vital signs, physical examinations, 12-lead electrocardiograms (ECGs), and questionnaires (COWS and 11-point Numerical Intensity Rating Scale of pain).

Statistical Methods:

Efficacy:

For the primary efficacy analysis, the mean of the change in frequency of SBMs per week from baseline to the last 2 weeks of the treatment period was compared between each of the S-297995 dose groups and the placebo group, based on an analysis of covariance model with frequency of SBMs per week at baseline as a covariate.

A fixed-sequence testing approach was used. The S-297995 dose groups were compared with the placebo group sequentially in descending order of dose. After evaluating the efficacy of S-297995 compared with placebo, the change in the frequency of SBMs per week was compared in pairs between S-297995 dose groups as a secondary analysis to evaluate the differences among the S-297995 dose groups.

The mean of the change in frequency of SBMs per week from baseline was compared at each week between each of the S-297995 dose groups and the placebo group with a mixed-effects model repeated-measure (MMRM), which included the frequency of SBMs per week at baseline as a covariate and treatment group, week, and week-by-treatment group interaction as fixed effects.

An SBM responder was defined as any subject whose frequency of SBMs per week within the last 2 weeks of the treatment period was 3 times or more per week and had an average increase in the frequency of SBMs from baseline of 1 or more. A CSBM was defined as an SBM that was accompanied by the feeling of complete evacuation. The SBM and CSBM responder rates were summarized by treatment group and compared between each of the S-297995 dose groups and the placebo group with a chi-square test.

A Kaplan-Meier plot of the time to the first SBM after the initial administration of study drug was prepared by treatment group. The median of the time to the first SBM and its 95% confidence interval were calculated by treatment group. The distribution of the time was compared between each of the S-297995 dose groups and the placebo group with a generalized Wilcoxon test. The time to the first CSBM after the initial administration of study drug was analyzed in a similar manner.

The changes in the frequency of bowel movements, complete bowel movements, CSBMs, SBMs rated as 3 or 4 on the BSS, and SBMs without straining per week from baseline to the last 2 weeks of the treatment period were analyzed in a manner similar to the primary analysis. The changes in these secondary efficacy variables from baseline to Weeks 1, 2, 3, and 4 were analyzed using an MMRM.

The changes in the number of days of SBMs and CSBMs per week from baseline to the last 2 weeks of the treatment period were analyzed in a similar manner as the primary analysis. The changes in the number of days of SBMs and CSBMs per week from baseline to Weeks 1, 2, 3, and 4 were analyzed using an MMRM.

The incidences of SBMs and CSBMs within 4, 8, 12, and 24 hours after the initial administration of study drug and before the second administration were calculated and analyzed in a similar manner as the SBM responder rates.

Summary statistics for the other secondary efficacy variables were calculated by treatment group.

Pharmacokinetics:

Pharmacokinetic parameters were estimated by non-compartmental analysis method. Dose proportionality of PK parameters of S-297995 was assessed for C_{max} and AUC using the power model. Dose proportionality was examined separately for single dose (Day 1) and steady state (Day 28).

Safety:

Treatment-emergent adverse events (TEAEs) were adverse events that occurred after the first dose of study drug. Incidences of TEAEs, treatment-related adverse events, and serious adverse events (SAEs) were summarized by system organ class, preferred term, and treatment group. Changes in safety laboratory parameters, vital signs, physical examination findings, and ECGs were summarized by treatment group. Changes in the Numerical Intensity Rating Scale of pain and the COWS score were compared between each of the S-297995 dose groups and the placebo group with Welch's t-test.

Summary of Results:**Efficacy:**

Treatment with oral S-297995 was effective in relieving constipation in subjects with non-malignant chronic pain and OIC receiving daily opioid therapy for ≥ 3 months. The primary efficacy variable was the change in the frequency of SBMs per week from baseline to the last 2 weeks of the treatment period of individual subjects. A clinically relevant, statistically significant, and dose-dependent increase in the number of SBMs was seen in subjects receiving S-297995 compared to placebo. The least-squares (LS) mean change in the frequency of SBMs during the last 2 weeks of the treatment was 1.42 for the placebo group (61 subjects), 1.98 for the 0.1 mg group (61 subjects), 3.37 for the 0.2 mg group (59 subjects), and 3.64 for the 0.4 mg group (57 subjects). The treatment differences between 0.2 mg and placebo and between 0.4 mg and placebo were statistically significant ($p = 0.0014$ and $p = 0.0003$, respectively). The difference between the 0.1 mg dose and placebo was not statistically significant. In addition, the treatment differences between 0.1 mg and both 0.2 mg and 0.4 mg were statistically significant ($p = 0.0213$ and $p = 0.0071$, respectively). The treatment difference between the 2 higher doses of S-297995 was not statistically significant. Similar results were found for the Per-Protocol Population, except that the treatment difference in LS mean changes in the frequency of SBMs between 0.2 mg and 0.1 mg was not statistically significant ($p = 0.0823$). The results for the frequency of any bowel movement (spontaneous and induced) in the mITT Population were similar to those of SBM.

The results for change in the frequency of SBMs per week from baseline to the last 2 weeks of the treatment period for mITT Population with age, sex, baseline height, and baseline opioid analgesics were similar to the results observed for primary efficacy endpoint. With age as an additional covariate, LS mean change in the frequency of SBMs during the last 2 weeks of the treatment period was 1.44 for the placebo group, 1.95 for the 0.1 mg group, 3.36 for the 0.2 mg group, and 3.67 for the 0.4 mg group. With sex as an additional covariate, the LS mean change in the frequency of SBMs during the last 2 weeks of the treatment period was 1.44 for the placebo group, 2.01 for the 0.1 mg group, 3.35 for the 0.2 mg group, and 3.62 for the 0.4 mg group. With baseline weight as an additional covariate, LS mean change in the frequency of SBMs during the last 2 weeks of the treatment period was 1.44 for the placebo group, 2.01 for the 0.1 mg group, 3.34 for the 0.2 mg group, and 3.63 for the 0.4 mg group. With baseline opioid analgesics as an additional covariate, the LS mean change in the frequency of SBMs during the last 2 weeks of the treatment period was 1.42 for the placebo group, 1.99 for the 0.1 mg group, 3.37 for the 0.2 mg group, and 3.64 for the 0.4 mg group. For each of these analyses, the treatment differences in LS mean change in the frequency of SBMs between S-297995 and placebo

were statistically significant for the 0.2 mg and 0.4 mg groups, but not for the 0.1 mg group. In addition, the treatment differences in LS mean changes in the frequency of SBMs between the low dose of S-297995 (0.1 mg) and the 2 higher doses of 0.2 mg and 0.4 mg were statistically significant, while the difference between 0.4 mg and 0.2 mg was not statistically significant.

The results for the change in the frequency of SBMs per week from baseline to Weeks 1, 2, 3, and 4 for the mITT Population were similar to those observed from baseline to the last 2 weeks of the treatment period. The change in frequency from baseline to each time point also increased with increasing doses of S-297995. At each time point, the treatment differences between 0.2 mg and placebo and between 0.4 mg and placebo were statistically significant, while the treatment difference between 0.1 mg and placebo was not statistically significant at any time point.

A responder analysis showed positive results for the 2 higher doses of S-297995. An SBM responder was defined as a subject whose frequency of SBMs within the last 2 weeks of the treatment period was 3 or more times per week and had an increase of at least 1 or more per week. The proportion of SBM responders during the last 2 weeks of the treatment period was 39.3% (24/61) for the placebo group, 52.5% (32/61) for the 0.1 mg group, 71.2% (42/59) for the 0.2 mg group, and 66.7% (38/57) for the 0.4 mg group. These differences were statistically significant for the 0.2 mg and 0.4 mg groups ($p = 0.0005$ and $p = 0.0030$, respectively), but not for the 0.1 mg group. Similar findings were seen for CSBM responders. A CSBM was defined as an SBM that was accompanied by the feeling of complete evacuation. The proportion of CSBM responders during the last 2 weeks of the treatment period was 21.3% (13/61) for the placebo group, 29.5% (18/61) for the 0.1 mg group, 45.8% (27/59) for the 0.2 mg group, and 45.6% (26/57) for the 0.4 mg group. These differences were statistically significant for the 0.2 mg and 0.4 mg groups ($p = 0.0045$ and $p = 0.0050$, respectively).

Complete spontaneous bowel movements also increased after using S-297995 in a dose-dependent manner. The LS mean change in the frequency of CSBMs per week from baseline to the last 2 weeks of the treatment period was 0.99 for the placebo group, 1.49 for the 0.1 mg group, 2.69 for the 0.2 mg group, and 2.44 for the 0.4 mg group. Again these differences were statistically significant only in the 0.2 mg and 0.4 mg groups ($p = 0.0007$ and $p = 0.0039$, respectively). Similar results were seen with all complete bowel movements (spontaneous and induced); however, the difference was not significant for the 0.4 mg group compared with the placebo group ($p = 0.0888$).

Subjects who received S-297995 experienced more days with SBMs and CSBMs per week than those on placebo. The LS mean change in number of days with SBMs per week from baseline to the last 2 weeks of the treatment period was 0.88 for the placebo group, 1.46 for the 0.1 mg group, 2.10 for the 0.2 mg group, and 2.42 for the 0.4 mg group. These differences were statistically significant for the 0.2 mg and 0.4 mg groups ($p = 0.0002$ and $p < 0.0001$, respectively).

The LS mean change in the number of days with CSBMs per week from baseline to the last 2 weeks of the treatment period was 0.83 for the placebo group, 1.25 for the 0.1 mg group, 1.93 for the 0.2 mg group, and 2.02 for the 0.4 mg group. These differences were statistically significant for the 0.2 mg and 0.4 mg groups ($p = 0.0004$ and $p = 0.0001$, respectively).

Time to the first SBM and CSBM after the initial administration of study drug was significantly decreased by S-297995 compared to placebo. The median time to first SBM was 49.57 hours for the placebo group, 28.15 hours for the 0.1 mg group, 11.08 hours for the 0.2 mg group, and 21.33 hours for the 0.4 mg group. These differences were statistically significant in all S-297995 dose groups compared with placebo ($p = 0.0118$, $p < 0.0001$, and $p = 0.0004$, respectively). The median time to first CSBM was 223.92 hours for the placebo group, 82.50 hours for the 0.1 mg group, 44.83 hours for the 0.2 mg group, and 32.93 hours for the 0.4 mg group. These differences were statistically significant in all S-297995 dose groups compared with placebo ($p = 0.0079$, $p = 0.0011$, and $p < 0.0001$, respectively).

The proportion of subjects with SBMs and CSBMs within 4, 8, 12, and 24 hours after the initial administration of study drug was higher in all S-297995 dose groups, reaching statistical significance at all time points in the 0.2 mg and 0.4 mg groups for SBMs and CSBMs. Within 12 hours of administering the first dose of study drug, 50.8% of subjects taking 0.2 mg had a SBM and 23.7% had a CSBM, 43.9% of subjects taking 0.4 mg had SBM and 33.3% had a CSBM, and 18.0% of subjects taking placebo had an SBM and 6.6% had a CSBM.

Treatment with S-297995 resulted in a normalization of the consistency of stool measured by the frequency of SBMs rated as 3 or 4 on the BSS. The LS mean change in the frequency of SBMs rated as 3 or 4 on BSS per week from baseline to the last 2 weeks of the treatment period was 0.54 for the placebo group, 1.08 for the 0.1 mg group, 2.05 for the 0.2 mg group, and 1.87 for the 0.4 mg group. The differences were statistically significant in the 0.2 mg and 0.4 mg groups ($p < 0.0001$ and $p = 0.0003$, respectively). As a result of the normalization in the stool consistency, the number of SBMs without straining was also increased. The LS mean change in the frequency of SBMs without straining per week from baseline to the last 2 weeks of the treatment period was 0.85 for the placebo group, 1.54 for the 0.1 mg group, 2.92 for the 0.2 mg group, and 3.21 for the 0.4 mg group. The differences were statistically significant in the 0.2 mg and 0.4 mg groups ($p = 0.0002$ and $p < 0.0001$, respectively).

The frequency of false starts of bowel movements from baseline to the last 2 weeks of the treatment period was decreased in all treatment groups. The mean change in the frequency of false starts of bowel movements from baseline to the last 2 weeks of the treatment period was -2.71 for the placebo group, -3.06 for the 0.1 mg group, -3.75 for the 0.2 mg group, and -2.80 for the 0.4 mg group.

The frequency of rescue laxative use increased in the placebo and 0.2 mg groups and decreased in the 0.1 mg and 0.4 mg groups. The mean change in the frequency of rescue use of laxative agents per week from baseline to the last 2 weeks of the treatment period was 0.94 for the placebo group, -0.47 for the 0.1 mg group, 0.15 for the 0.2 mg group, and -1.24 for the 0.4 mg group. The treatment comparisons between S-297995 and placebo were statistically significant for the 0.4 mg group ($p = 0.0272$), but not for the 0.1 mg or 0.2 mg group.

There were no meaningful changes in the abdominal bloating or abdominal discomfort scores from baseline to the last 2 weeks of the treatment period in any of the treatment groups with the exception of the differences in change from baseline for the abdominal bloating score between the 0.4 mg group and placebo at Weeks 1 and 2. The treatment

differences for abdominal bloating scores between the 0.4 mg group at Weeks 1 and 2 and placebo were statistically significant ($p = 0.0196$ and $p = 0.0173$, respectively).

Significantly more patients in the 0.1 mg, 0.2 mg, and 0.4 mg groups (72.4% [42/58], 91.2% [52/57], and 83.0% [44/53], respectively) reported improvement in their level of Global Satisfaction at Visit 6 compared with placebo (50.0% [29/58]). The differences in Global Satisfaction Score at Visit 6 between the S-297995 groups and placebo were statistically significant ($p = 0.0290$, $p < 0.0001$, and $p < 0.0001$, respectively).

Pharmacokinetics:

S-297995 was rapidly absorbed following multiple doses of 0.1 to 0.4 mg S-297995, with median T_{max} 1.0 hours on both Days 1 and 28.

The median (range) accumulation ratio of C_{max} and $AUC_{0-\tau}$, of S-297995 on Day 28 to those on Day 1 were 1.060 (0.593 to 2.102) and 1.202 (0.719 to 2.112), respectively, indicating slight C_{max} and AUC accumulation in S-297995 following multiple doses of 0.1 to 0.4 mg of S-297995.

The geometric mean C_{max} and $AUC_{0-\tau}$ of S-297995 increased in a dose-proportional manner over the dose range of 0.1 to 0.4 mg following single and multiple doses of S-297995.

All plasma concentrations of Nor-S-297995 on Day 1 were below the limit of quantification (< 0.0806 ng/mL) following single dose of 0.1 mg S-297995. The median (range) metabolic ratio of C_{max} and $AUC_{0-\tau}$ of Nor-S-297995 on Day 1 to those of unchanged S-297995 corrected for molecular weight were 0.043 (0.000 to 0.106) and 0.041 (0.000 to 0.194), respectively, following a single dose of 0.2 to 0.4 mg of S-297995.

The median (range) metabolic ratio of C_{max} and $AUC_{0-\tau}$ of Nor-S-297995 on Day 28 to those of unchanged S-297995 corrected for molecular weight were 0.088 (0.000 to 0.136) and 0.088 (0.005 to 0.230), respectively, following multiple doses of 0.1 to 0.4 mg of S-297995.

Safety:

The overall incidence of TEAEs was similar for treatment groups (50.8% for the placebo group and 48.9% for the S-297995 total group [41.0% for the 0.1 mg group, 50.0% for the 0.2 mg group, and 55.7% for the 0.4 mg group]). The most frequently reported TEAEs were abdominal pain and diarrhea (17 [9.3%] subjects each), flatulence, nausea, and urinary tract infection (8 [4.4%] subjects each), abdominal pain upper (7 [3.8%] subjects), and headache (6 [3.3%] subjects) for the S-297995 total group and arthralgia and back pain (4 [6.6%] subjects each) and diarrhea (3 [4.9%] subjects) for the placebo group.

The incidence of treatment-related adverse events was higher in the 0.2 mg and 0.4 mg groups (25.0% and 39.3%, respectively) than in the 0.1 mg and placebo groups (16.4% for both groups); however, only the 0.4 mg group was statistically significantly different from the placebo group. The most frequently reported treatment-related adverse events for the S-297995 total group were abdominal pain (16 [8.8%] subjects), diarrhea (12 [6.6%] subjects), and flatulence and nausea (8 [4.4%] subjects each). The most frequently reported treatment-related adverse events for the placebo group were diarrhea and flatulence (2 [3.3%] subjects each).

No subject died during the study. Three subjects had an SAE: 2 subjects in the 0.1 mg group (chest pain and appendicitis) and 1 subject in the 0.4 mg group (left ventricular dysfunction). The SAE of chest pain led to discontinuation from the study. None of the

SAEs were considered by the Investigators to be related to study treatment. Ten subjects were discontinued from the study due to an adverse event: 1 subject in the 0.1 mg group (chest pain); 4 subjects in the 0.2 mg group (flatulence, abdominal pain upper, diarrhea, and abdominal pain); 5 subjects in the 0.4 mg group (3 subjects with diarrhea; 1 subject with dyspnea; and 1 subject with 2 events of abdominal pain and 2 events of diarrhea). All adverse events except 1 (chest pain) were considered by the Investigators to be related to study treatment.

There were no clinically relevant differences between the treatment groups with respect to changes from baseline in safety laboratory or endocrinology parameters.

No clinically meaningful safety findings or trends in vital signs or ECG parameters were noted.

No clinically meaningful changes from baseline to Visit 6/Early Termination were seen in the pain intensity Numerical Rating Scale scores, COWS scores, or the morphine equivalent doses of opioids.

Conclusions:

S-297995 was highly effective, safe, and well tolerated in patients with OIC when given at daily oral doses of 0.2 mg or 0.4 mg. Treatment with 0.2 mg or 0.4 mg resulted in robust increases in the frequency of SBMs per week from baseline compared with placebo and 0.1 mg of S 297995 with statistically significant p-values of 0.0014 and 0.0003, respectively, when compared with placebo. The effect of 0.4 mg on the primary outcome measure was not statistically different from that of 0.2 mg. The incidence of treatment-related adverse events increased as the dose increased from 16% for placebo and 0.1 mg to 25% for 0.2 mg and 40% for 0.4 mg. None of the 3 SAEs in the study were considered related to study drug. Adverse events leading to discontinuation from the study for 0.2 mg and 0.4 mg were gastrointestinal in nature. Opiate withdrawal symptoms were rare; of the 244 randomized subjects, only 4 had opiate withdrawal symptoms that were mild and 1 had symptoms that were moderate. There were no changes in opiate doses or pain indices during the study. Based on these results, 0.2 mg per day was identified as the dose to be tested in future confirmatory clinical trials.

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