SYNOPSIS

Sponsor: Shionogi Inc.	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: S-297995	**Volume:**	
Name of Active Ingredient: S-297995 monotosylate	**Page:**	

Study Title:

A Randomized, Double-blind, Placebo-controlled, Single-ascending Dose Study to Evaluate the Safety and Efficacy of S-297995 for the Treatment of Opioid-Induced Bowel Dysfunction in Subjects With Chronic Pain

Investigators and Study Centers:

[redacted]

Publication (Reference): None

Studied Period:

[redacted] May 2010 (first patient enrolled) to
March 2011 (last patient completed)

Study Phase: 2

Objectives:

The primary objective of the study was:

- To evaluate the safety of single doses of oral S-297995 in subjects physically dependent on opioids.

The secondary objectives of the study were:

- To evaluate incidence of signs and symptoms of withdrawal syndrome
- To evaluate the efficacy of S-297995 on opioid-induced bowel dysfunction (OBD)
- To evaluate the pharmacokinetic (PK) profile of S-297995 and its metabolites with opioid treatment
- To determine the optimal dose of S-297995.

Methodology:

This was a single center, randomized, double-blind, placebo-controlled, single-ascending dose study evaluating 6 dose levels of S-297995 in subjects with chronic pain, OBD and opioid physical dependence. Up to 72 subjects (males and females) between 18 and 65 years of age with chronic pain, OBD and opioid physical dependence were eligible to participate in the study. After meeting eligibility requirements and signing an informed consent form (ICF), subjects were enrolled in the study, randomized to one of two treatment groups (treatment or placebo), screened for a period of 13 days (Days 1 to 13 [± 7 days]), and then admitted to the clinic on Day 14 for pre-admission assessments. Subjects were confined to the clinic for 3 days. They were monitored continuously while

in the clinic (Days 15 to 17) and then monitored as out-patients for an additional 7 days (Days 18 to 25).

A single dose of S-297995 (tablets or oral solution) or matching placebo was administered orally to cohorts of 12 subjects (9 active treatment, 3 placebo) in the morning of Day 15 under fasted conditions. If within 3 days of receiving study drug, 4 subjects experienced any severe study drug-related treatment-emergent adverse events (TEAEs), or dropped from the study based on a Clinical Opioid Withdrawal Scale (COWS) > 8, an unblinded data review was to be triggered. The unblinded safety review was conducted by the Principal Investigator (PI) or sub-Investigator from [redacted] and the Medical Monitor or safety designee from Shionogi Inc. If all 4 subjects were in the active group, no subjects were to be enrolled at the next dose level. Symptoms of gastrointestinal (GI) withdrawal that would cause the PI to employ the stopping rule were: persistent abdominal pain and cramping (nausea and diarrhea could also be present but the pain and cramping would be the indicator that dose escalation should not occur). Symptoms of central nervous system (CNS) penetration that would cause the PI to employ the stopping rule were: chills, arthralgia, muscle pain and/or cramping, nausea, rhinorrhea, and dramatic sympathetic discharge. These symptoms would indicate that the drug had crossed into the CNS (and dose escalation should not occur). Cohorts were to continue to be enrolled until the highest dose level (3 mg) was achieved or until the study was discontinued due to adverse events (AEs) or COWS in excess of those defined above. Cohorts enrolled patients up to the highest dose level without premature discontinuation of the study.

Assessments included monitoring of AEs, physical examinations, vital signs, bowel movement (BM) diary including the Bristol Stool Scale, Bowel Habits Questionnaire, visual analogue scale (VAS) scores, pupillometry, clinical laboratory tests, 12-lead electrocardiograms (ECGs), COWS, Webster Opiate Withdrawal Scale (WOWS), and an examination of the PK profile of S-297995.

Number of Patients (Planned and Analyzed):

Up to 72 subjects were planned; 72 subjects were analyzed for safety; 72 subjects were analyzed for efficacy; 54 subjects who received S-297995 were analyzed for PK.

Diagnosis and Main Criteria for Inclusion:

Males and females between 18 and 65 years of age with chronic pain, OBD and opioid physical dependences were eligible to participate provided they had been chronically treated with opioid therapy for at least 3 months for diagnosis of chronic pain, continued prescribed opioid therapy for the duration of the study, and tested negative on urine drug test. Females had to be non-pregnant, non-lactating, and either postmenopausal or surgically sterile or agreed to effective contraception or birth control methods; males had to agree to use approved methods of contraception.

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

Subject randomized to test product received a single oral dose of S-297995 in a fasted state at approximately 9:30 a.m. (± 2 hours). Each dose varied in composition by treatment cohort, as shown:

Cohort 1: 0.1 mg of S-297995 (one S-297995 tablet 0.1 mg)

Cohort 2: 0.3 mg of S-297995 (three S-297995 tablets 0.1 mg)

Cohort 3: 1 mg of S-297995 (one S-297995 tablet 1.0 mg)

Cohort 4: 3 mg of S-297995 (three S-297995 tablets 1.0 mg)

Cohort 5: 0.03 mg of S-297995 (18 mL of oral solution [0.03 mg])

Cohort 6: 0.01 mg of S-297995 (6 mL of oral solution [0.01 mg]).

S-297995 Monotosylate tablets of 0.1 mg (Batch [redacted]) and 1 mg (Batch [redacted]) were used in this study. Tablets were orally administered with 240 mL of water or as an 18 mL oral solution (0.03 mg) dose 4 hours before breakfast on the first day of the Study Drug Administration period.

Duration of Treatment:

The total duration of treatment for each subject was up to 28 days. Screening assessments occurred within 13 days (Days 1-13) of enrollment (pre-admission) when subjects were admitted to the clinic. Subjects were confined to the clinic for the first 3 days of the Study Drug Administration Period (Days 15 to 17) and then followed for an additional 7 days (Days 18 to 24 [±2]) as out-patients.

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

Subjects randomized to receive placebo received S-297995 placebo tablets (Batch [redacted]) for Cohorts 1 to 4, 18 mL sterile water for Cohort 5, or 6 mL sterile water for Cohort 6, under the same conditions as subjects randomized to test product.

Criteria for Evaluation:

Efficacy:

A daily diary was used by subjects during their in-patient stay at the clinic to record information about BMs and constipation. The Bristol Stool Scale was completed at Screening and as part of the daily diary. The daily diary included the following information: date and time of BM; use of rescue medications, including name, date and time of usage; whether the BM was complete; whether there was any straining with the BM; constipation symptoms severity, including straining during BMs, number of complete BMs, abdominal bloating, abdominal discomfort, consistency of BMs measured by Bristol Stool Scale, number of false start BMs, number of BMs without straining, number of rescue medications used, and number of failed BMs.

The primary efficacy endpoint was the change from baseline to 24 hours post dose in the number of spontaneous bowel movements (SBMs) during the Study Drug Administration Period.

Safety:

Safety was assessed by AEs, clinical laboratory tests, physical examination, vital signs, 12-lead ECG, concomitant medications, COWS assessment, pupillometry, VAS assessment, and WOWS assessment.

Pharmacokinetics:

Blood samples for plasma concentrations of unchanged S-297995 and its metabolites (Nor-S-297995, S-297995 3-*O*-β-D-glucuronide, S-297995 6-*O*-β-D-glucuronide, S-297995-carboxylic acid and benzamidine) were collected for analysis of S-297995 at 0 hour (within 5 minutes prior to dosing), and at 0.25, 0.5, 0.75, 1, 1.5, 2 (± 2 minutes),

2.5, 3, 4, 5, 6 (± 5 minutes), 8, 10, 12 (± 12 minutes), 24, 36, 48 and 72 hours (± 1 hour) post-dose.

Statistical Methods:

The statistical analyses were reported using summary tables, figures, and data listings. Unless otherwise noted, all statistical testing was two-sided and was performed at the 0.05 significance level. Tests were declared statistically significant if the calculated p-value was ≤ 0.05. Continuous variables were summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables were summarized by counts and by percentage of subjects in corresponding categories. All summary tables were presented by dose group and pooled placebo subjects. Baseline summaries also included a total summary column. Individual subject data obtained from the case report forms (CRFs), central clinical lab, central ECG lab, PK data, and any derived data were presented by subject in data listings.

Efficacy:

For the primary efficacy endpoint of change from baseline to 24 hours post dose in the number of SBMs, a non-parametric rank analysis of covariance (ANCOVA) model with dose group and gender as fixed effects, and baseline SBM as a covariate was used to assess the treatment effect. The change from baseline in SBMs for each dose group was compared to that of the pooled placebo group.

The primary efficacy endpoint analyses for SBMs were repeated for secondary efficacy variables of BMs and complete spontaneous bowel movements (CSBMs), with analysis of change from baseline to 24 and 48 hours post-dose in BMs and CSBMs performed. The change from baseline to 48 hours post dose in the number of SBMs was also evaluated as described for the primary efficacy endpoint. The time to first SBM for each dose during the Study Drug Administration Period was summarized using standard survival methods (Kaplan-Meier estimates). Constipation-related symptoms were also analyzed to assess treatment effect. The average symptom (i.e., straining, abdominal bloating and discomfort, Bristol Stool Scale score for consistency) score of all BMs during the specific time point for each patient was calculated, and the change from baseline to 24 and 48 hours post-dose in the mean score between each dose group and pooled placebo group was summarized. The number of false start BMs and number of BMs without straining for 24 hours and 48 hours post dose and the total number of rescue medication taken during the study drug administration period were summarized.

Safety:

All AE summaries were restricted to TEAEs, defined as those AEs that occurred after dosing and those existing AEs that worsened during the study. Verbatim terms on CRFs were mapped to preferred terms and system organ classes (SOCs) using Medical Dictionary for Regulatory Activities (MedDRA) version 13.0. Each AE summary was displayed by dose group. Summaries that were displayed by SOC and preferred terms were ordered by descending order of incidence of SOC and preferred term within each SOC. Summaries of AEs by highest severity, AEs by closest relationship to study drug, and serious adverse events (SAEs) were generated.

Laboratory parameters, vital signs, and ECG parameters were summarized using descriptive statistics at baseline and at each post-baseline time point by dose group and pooled placebo subjects. Changes from baseline were also summarized. Overall interpretation results for ECG were also summarized using shift tables (Normal, Abnormal Not Clinically Significant [NCS], Abnormal Clinically Significant [CS]) comparing baseline to follow-up.

The subject incidences of COWS > 8 and WOWS > 8 during the treatment period were summarized with counts and percentages including an exact 95% confidence interval (CI). Maximum post-dose COWS scores were summarized with descriptive statistics including 95% CIs. The time to first occurrence of COWS > 8 and WOWS > 8 for each dose group during the Treatment Period was summarized using standard survival methods (Kaplan-Meier estimates). Kaplan-Meier curves were generated. Pupillometry and VAS pain scores were listed and summarized using descriptive statistics by dose group and pooled placebo subjects.

Pharmacokinetics:

For each subject, the following plasma PK parameters of S-297995 and its metabolites were determined using a non-compartmental approach: maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration versus time curve from time zero to the last sampling time at which concentrations were at or above the limit of quantitation ($AUC_{0\text{-last}}$), area under the plasma concentration versus time curve from time zero to infinity ($AUC_{0\text{-inf}}$), area under the plasma concentration versus time curve from time zero to X hour ($AUC_{0\text{-Xh}}$), apparent elimination rate constant (λ_Z), apparent elimination half-life ($t_{1/2,z}$), mean residence time (MRT), apparent oral clearance (CL/F), molar ratio of C_{max} for S-297995 metabolites to C_{max} for unchanged S-297995 (MR_{Cmax}), molar ratio of $AUC_{0\text{-inf}}$ for S-297995 metabolites to $AUC_{0\text{-inf}}$ for unchanged S-297995 (MR_{AUC}), and area under the concentration-time curve from Hour 0 to t ($AUC_{0\text{-t}}$).

Summary statistics for plasma concentrations and PK parameters of S-297995 and its metabolites were presented by dose group. Dose proportionality of PK parameters was also examined between dose groups. The PK parameters C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of S-297995 were assessed for dose proportionality using the power model.

Summary of Results

Efficacy:

The primary and multiple secondary efficacy endpoints were achieved in this study. The following results are based on the results of efficacy analyses for the ITT Population:

- Results for the primary efficacy endpoint, change from baseline to 24 hours in the number of SBMs during the Study Drug Administration Period (Day 16), were highly significant and dose-related in the 0.3, 1, and 3 mg cohorts, with mean increases of 1.83, 3.76, and 4.77 SBMs, respectively, compared with an increase of 0.29 SBMs in the pooled placebo cohort ($p < 0.0001$). Mean increases of 0.42 and 0.43 SBMs in the 0.03 and 0.1 mg cohorts, respectively, were not significantly different compared with placebo ($p \geq 0.6373$). The mean decrease in the 0.01 mg cohort (-0.09) was not statistically significant compared with placebo ($p = 0.0767$).

- Changes from baseline to 48 hours in the number of SBMs (Day 17) were statistically significant in the 0.3, 1, and 3 mg cohorts, with mean increases of 0.88, 2.15, and 2.44 SBMs, respectively, compared with an increase of 0.21 SBMs in the placebo cohort ($p = 0.0047$ for 0.3 mg; $p < 0.0001$ for 1 and 3 mg). Mean changes in number of SBMs in the 0.01, 0.03, and 0.1 mg cohorts were not significantly different than the change in the placebo cohort ($p \geq 0.4946$).
- Changes from baseline to 24 hours in the number of BMs were statistically significant and dose-related in the 0.3, 1, and 3 mg cohorts, with mean increases of 1.67, 3.60, and 4.62 BMs, respectively, compared with an increase of 0.15 BMs in the placebo cohort ($p = 0.0002$ for 0.3 mg; $p < 0.0001$ for 1 and 3 mg). Changes from baseline to 48 hours were statistically significant in the 0.3, 1, and 3 mg cohorts, with mean increases of 0.72, 1.99, and 2.29 BMs, respectively, compared with an increase of 0.15 BMs in the placebo cohort ($p = 0.0283$ for 0.3 mg; $p < 0.0001$ for 1 and 3 mg). Mean changes in number of BMs in the 0.01, 0.03, and 0.1 mg cohorts were not significantly different than the change in the placebo cohort at 24 hours ($p \geq 0.1334$) or 48 hours ($p \geq 0.7143$).
- Changes from baseline to 24 hours in the number of CSBMs were statistically significant in the 1 and 3 mg cohorts, with mean increases of 2.42 and 2.90 CSBMs, respectively, compared with an increase of 0.02 CSBMs in the placebo cohort ($p < 0.0001$ for 1 mg; $p = 0.0002$ for 3 mg). Changes from baseline to 48 hours were statistically significant in the 1 and 3 mg cohorts, with mean increases of 1.36 and 1.51 CSBMs, respectively, compared with an increase of 0.05 CSBMs in the placebo cohort ($p < 0.0001$ for 1 mg; $p = 0.0018$ for 3 mg). Mean changes in number of CSBMs in the 0.01, 0.03, 0.1, and 0.3 mg cohorts were not significantly different than the change in the placebo cohort at 24 hours ($p \geq 0.1968$) or 48 hours ($p \geq 0.6131$).
- Kaplan-Meier median estimates of time to SBM were 37.0, 13.9, N/A, 4.7, 1.4, and 0.7 hours for subjects in the 0.01, 0.03, 0.1, 0.3, 1, and 3 mg cohorts, respectively, and 27.2 hours in the pooled placebo cohort. The probability of occurrence of an SBM was significantly higher in the 0.3 (hazard ratio [HR] = 7.52; $p = 0.0005$), 1 (HR = 9.93; $p < 0.0001$), and 3 mg (HR infinite; $p < 0.0001$) cohorts compared with occurrence of the event in the pooled placebo cohort. Estimates for median time to BM were 28.4, 13.9, 25.1, 4.7, 1.4, and 0.7 hours for subjects in the 0.01, 0.03, 0.1, 0.3, 1, and 3 mg cohorts, respectively, and 27.2 hours in the placebo cohort. The probability of occurrence of a BM was significantly higher in the 0.3 (HR = 7.36; $p = 0.0005$), 1 (HR = 9.54; $p < 0.0001$), and 3 mg (HR infinite; $p < 0.0001$) cohorts compared with placebo. Estimates for median time to CSBM were 1.7 and 0.8 hours for subjects in the 1 and 3 mg cohorts, respectively. The probability of occurrence of a CSBM was significantly higher in the 1 (HR = 59.34; $p < 0.0001$) and 3 mg (HR =10.99; $p = 0.0007$) cohorts compared with placebo.
- Assessment of seven constipation symptoms generated the following conclusions:
  - At 24 hours post-dose, mean scores for straining during BMs decreased slightly in all S-297995 cohorts (Range: -0.9 to -0.1) and increased in the placebo cohort (0.8). At 48 hours post-dose, mean scores decreased in the 0.1, 1, and 3

mg cohorts (Range: -1.4 to -0.4) and increased in the 0.01, 0.03, and 0.3 mg cohorts (Range: 0.1 to 0.4) and in the placebo cohort (0.5). No dose-related trends were observed. The largest reduction in mean score was observed in the 3 mg cohort at 24 hours (-0.9) and 48 hours (-1.4).

- Changes from baseline to 24 hours in the number of complete bowel movements (CBMs) were statistically significant in the 1 and 3 mg cohorts, with mean increases of 2.32 and 2.81 CBMs, respectively, compared with a slight decrease (-0.07 CBMs) in the placebo cohort ($p = 0.0001$ for 1 mg; $p = 0.0006$ for 3 mg). Changes from baseline to 48 hours were statistically significant in the 1 and 3 mg cohorts, with mean increases of 1.27 and 1.42 CBMs, respectively, compared with a slight decrease (-0.04 CBMs) in the placebo cohort ($p < 0.0001$ for 1 mg; $p = 0.0006$ for 3 mg). Mean changes in number of CBMs in the 0.01, 0.03, 0.1, and 0.3 mg cohorts were not significantly different than the change in the placebo cohort at 24 hours ($p \geq 0.5054$) or 48 hours ($p \geq 0.3441$).
- Small or no changes in mean abdominal bloating scores were reported across all cohorts at 24 hours (Range: -0.5 to 0.7) and 48 hours (Range: -0.8 to 0.4) post-dose, with no dose-related trends. Small changes in abdominal discomfort scores were reported across all cohorts at 24 hours (Range: -0.8 to 1.3), with the largest increase at 3 mg, and at 48 hours (Range: -1.1 to 1.1) post-dose, with no dose-related trends.
- At 24 hours post-dose, mean scores for stool consistency increased in the 0.3, 1, and 3 mg cohorts (1.5, 1.9, and 4.1, respectively) and decreased in the placebo cohort (-1.4). Mean scores decreased or did not change in the 0.01 (-3.0), 0.03 (-0.0), and 0.1 (-1.4) mg cohorts. At 48 hours post-dose, mean scores increased in the 0.01, 0.3, 1, and 3 mg cohorts (0.2, 0.6, 0.7, and 2.5, respectively) and decreased in the placebo cohort (-1.0) and in the 0.03 (-0.3) and 0.1 (-1.0) mg cohorts. At both time points, stool consistency improved at the three highest dose levels, with the largest effect at 3 mg.
- A wide range of changes in mean number of false start BMs was observed at 24 hours (Range:-0.11 to 2.56) and 48 hours (Range: -0.06 to 1.61) post-dose, with no dose-related trends. Mean number of false start BMs increased modestly in the placebo cohort at 24 hours (0.28) and 48 hours (0.25) post-dose. No apparent improvements were observed at any dose or time period, as indicated by the small decreases in number of false start BMs reported in few cohorts.
- At 24 hours post-dose, the mean number of BMs without straining increased in the 0.3, 1, and 3 mg cohorts (0.28, 0.41, and 3.37, respectively) and decreased slightly in the placebo cohort (-0.03). At 48-hours post-dose, the mean number increased in the 0.3, 1, and 3 mg cohorts (0.12, 0.19, and 1.76, respectively) and decreased slightly in the placebo cohort (-0.01). At both time points, the increase was largest in the 3 mg cohort, and improvements were smaller and similar in the 0.3 and 1 mg cohorts. Small changes were reported in the other cohorts at 24 hours (Range: -0.09 to 0.06) and 48 hours (Range: -0.03 to 0.01).

- Mean daily rescue medication use remained consistent and similar to baseline in the pooled placebo and 0.1 mg cohorts during the 48-hour post-dose period. Rescue medication use was not required at all in the 0.3 and 3 mg cohorts during the 48-hour post-dose period. In the 0.01, 0.03, and 1 mg cohorts, rescue medication use was not required in the 24-hour post-dose period but was required in the 24-to-48-hour post-dose period. The resulting mean number of rescue medications used in the 48-hour post-dose period was smaller compared with corresponding baseline values in these cohorts.

- For analyses of mean number of SBMs, BMs, CSBMs, and CBMs, statistically significant changes were not observed for any cohort at the 24-to-48 hour post-dose period. Therefore, statistically significant changes at 48 hours post-dose were entirely attributable to significant changes observed at 24 hours post-dose.

Pharmacokinetics:

The following results are based on PK analyses:

- Plasma concentrations of S-297995 and its metabolites (Nor-S-297995, S-297995 3-*O*-β-D-glucuronide, S-297995 6-*O*-β-D-glucuronide, S-297995 carboxylic acid, and benzamidine) were measured serially in subjects over 72 hours after dose administration. The parent compound was the predominant analyte found in plasma. Quantifiable concentrations of only two metabolites (Nor-S-297995 and S-297995 3-*O*-β-D-glucuronide) were identified in plasma, at significantly lower concentrations than the parent.
- Peak concentrations of the parent compound (S-297995) were achieved relatively quickly after oral administration (median T_{max} range: 0.75 to 2.5 hours). The geometric mean C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ estimates increased in an approximately dose-proportionate manner and exhibited a modest amount of inter-individual variability (geometric coefficient of variation [CV]% range: 21% to 44%). The geometric mean $t_{1/2,z}$ values ranged from 7.46 to 12.6 hours, with the lowest values of 7.46 and 8.13 hours occurring in the 0.01 and 0.03 mg dose groups, respectively.
- For Nor-S-297995, PK parameters for subjects receiving 0.01 or 0.03 mg of S-297995 were not calculated due to a lack of quantifiable concentrations. In the higher dose groups, Nor-S-297995 concentrations were much lower overall compared with S-297995 concentrations, as evidenced by the geometric mean MR_{AUC} estimates (range: 15.6% to 28.8%). Median T_{max} for Nor-S-297995 occurred later than that for the parent compound (range: 4.1 to 8 hours). Geometric mean C_{max} and $AUC_{0\text{-last}}$ estimates increased in an approximately dose-proportionate manner. The geometric mean $t_{1/2,z}$ of Nor-S-297995 was prolonged as compared to S-297995 (range: 16.0 to 25.7 hours).
- Based on the statistical analysis of dose proportionality using the power model, S-297995 PK parameters (C_{max}, $AUC_{0\text{-last}}$, or $AUC_{0\text{-inf}}$) increased in a dose proportional manner over the range of doses examined (0.01 to 3 mg).

Safety:

The following results are based on safety analyses:

- Treatment-emergent AEs were reported in 50.0% of subjects receiving placebo and in 81.5% of subjects receiving any dose of S-297995 (66.7%, 66.7%, 55.6%, 100.0%, 100.0%, and 100.0% of subjects receiving 0.01, 0.03, 0.1, 0.3, 1, and 3 mg, respectively).
- The most frequently reported TEAEs in subjects treated with S-297995 (> 10% incidence) were abdominal pain, nausea, diarrhea, hyperhidrosis, vomiting, chills, dizziness, flatulence, and headache. Over half of the frequently reported AEs were GI disorders. Dose-related trends were apparent in the incidences of diarrhea, vomiting, chills, and hyperhidrosis, but not for nausea, flatulence, dizziness, or headache.
- Treatment-related TEAEs were reported in 33.3% of subjects receiving placebo and in 64.8% of subjects receiving any dose of S-297995 (55.6%, 33.3%, 11.1%, 100.0%, 88.9%, and 100.0% of subjects receiving 0.01, 0.03, 0.1, 0.3, 1, and 3 mg, respectively).
- The most frequently reported treatment-related TEAEs in subjects treated with S-297995 (> 10% incidence) were abdominal pain (44.4%), nausea (29.6%), diarrhea (24.1%), vomiting and hyperhidrosis (16.7% each), chills (14.8%), and dizziness (11.1%). The incidence of each of these AEs was higher in subjects treated with S-297995 than in placebo-treated subjects. Treatment-related abdominal pain was most frequent at the 0.3, 1, and 3 mg dose levels; nausea, diarrhea, vomiting, and hyperhidrosis were most frequent at the 1 and 3 mg dose levels; and chills and dizziness were most frequent at 3 mg.
- The majority of subjects experienced mild to moderate TEAEs. Severe TEAEs were reported by 7 subjects, including 1 (11.1%) subject in the 1 mg cohort (drug withdrawal syndrome of nausea and stomach cramping) and 6 (66.7%) subjects in the 3 mg cohort (abdominal pain, diarrhea, nausea, vomiting, oxygen saturation decreased, and chills; some subjects had several of each of the AEs). All severe TEAEs resolved and all were considered definitely related to treatment.
- There were no deaths, SAEs, or AEs that led to study discontinuation.
- Shifts from normal laboratory baseline values to high or low post-baseline values were observed in all cohorts, including the placebo cohort, during the study. Sporadic abnormal hematology, chemistry, or urinalysis values were reported by most subjects, but none were considered CS. Two subjects, one each in the placebo and 0.1 mg cohorts, had mild blood glucose decreased AEs that were considered not related to treatment. One subject in the 0.1 mg cohort had a moderate blood prolactin increased AE that was considered possibly related to treatment and was associated with an abnormal, CS prolactin value.
- No clinically significant results were reported for vital signs, physical examination results, or ECG readings during the study. As expected per protocol, use of concomitant opioid, analgesic, and rescue laxative medications was most commonly reported.

- Mean maximum post-dose COWS scores were higher in the 1 and 3 mg cohorts (4.44 and 10.89, respectively) compared with means reported in the placebo cohort (1.33) and in the lower dose cohorts (range 0.56-2.11). Seven subjects, including 1 (11.1%) and 6 (66.7%) subjects in the 1 and 3 mg cohorts, respectively, reported COWS scores > 8. The subject in the 1 mg cohort experienced the elevated COWS score at 1.5 hours post-dose; this subject experienced multiple concurrent drug withdrawal syndrome AEs, including concurrent severe stomach cramping and severe nausea several hours after the COWS score elevation. The median time to event for the six subjects in the 3 mg cohort was 4.1 hours. All individual scores returned to a stable value < 8 within 3 hours after the first COWS > 8 score for 5 of the 6 subjects. The COWS score for Subject [redacted] increased to > 8 three separate times post-dose and returned to a stable value < 8 within 8 hours after the first COWS > 8 score.
- Only one subject (0.3 mg) experienced a WOWS score > 8 during the study, a score of 11 at 24 hours post-dose due to symptoms of mild perspiration/diaphoresis, runny nose or tearing, and multiple episodes of diarrhea, nausea, and abdominal cramping. The score decreased to 0 at 48 hours post-dose, indicating a resolution of all opioid withdrawal symptoms.
- Mean changes in pupil size were small and similar in the 0.01 mg to 1 mg dose cohorts and in the placebo cohort at 1 (range -0.17 to 0.17 mm), 2 (range -0.22 to 0.28 mm), and 3 hours (-0.29 to 0.28 mm) post-dose. The changes were larger in magnitude in the 3 mg cohort at 1, 2, and 3 hours post-dose (-1.00, -0.75, and -0.61 mm, respectively) compared with the other cohorts. At 4 to 8 hours post-dose, mean changes in pupil size were similar across all cohorts.
- No dose-related trends were observed with respect to mean changes in VAS scores from 1 to 8 hours post-dose.

CONCLUSIONS

Efficacy Conclusions:

S-297995 taken as single oral doses of 0.3, 1, and 3 mg effectively reversed OBD in a dose-dependent manner, as measured by statistically significant increases in number of SBMs in the 24-hour post-dose period compared with the change in the placebo cohort. In the 0.3, 1, and 3 mg cohorts, the number of SBMs in the 48-hour post-dose period and the number of BMs in the 24- and 48-hour post-dose periods also significantly increased when compared with placebo. Significant changes in these parameters were not observed in the 24-to-48 hour post-dose period, suggesting that efficacy was achieved primarily during the 24-hour post-dose period. Changes were not statistically significant at the 0.01, 0.03, or 0.1 mg dose levels for any tested efficacy variable when compared with placebo. Improvements in stool consistency score and number of BMs without straining as well as the reduced requirement for rescue laxatives provided support for efficacy at the 0.3, 1, and 3 mg dose levels.

Pharmacokinetic Conclusions:

Plasma samples obtained serially up to 72 hours after subjects ingested a single dose of S-297995 contained predominantly the parent compound as well as quantifiable but lower

concentrations of the metabolites Nor-S-297995 and S-297995 3-*O*-β-D-glucuronide. Peak concentrations S-297995 were achieved relatively quickly after oral administration (median T_{max} range: 0.75 to 2.5 hours). S-297995 PK parameters of C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ increased in a dose proportional manner over the range of doses examined (0.01 to 3 mg). Quantifiable concentrations of Nor-S-297995 were only observed in samples from subjects in the 0.1, 0.3, 1, and 3 mg cohorts. Concentrations of this metabolite peaked later compared with parent concentrations (median T_{max} range: 4.1 to 8 hours). Geometric mean C_{max} and $AUC_{0\text{-last}}$ estimates for Nor-S-297995 increased in an approximately dose-proportionate manner. Geometric mean $t_{1/2,z}$ values for S-297995 ranged from 7.46 to 12.6 hours, and were prolonged for Nor-S-297995 (range: 16.0 to 25.7 hours).

Safety Conclusions:

S-297995 was safe and well-tolerated in subjects with OBD at doses up to 3 mg, and was most tolerable at doses up to 0.3 mg. The most frequently reported treatment-related AEs in subjects receiving S-297995 were abdominal pain, nausea, diarrhea, vomiting, hyperhidrosis, chills, and dizziness. Most related AEs occurred with the highest incidence at the 1 and 3 mg dose levels. GI disorders were identified as clinically significant AEs that occurred frequently, were generally treatment related, represented approximately half of severe AEs, and had the highest incidence in the 1 and 3 mg dose cohorts. Across all dose cohorts, most AEs were mild or moderate. Severe AEs were only reported at the 1 and 3 mg dose levels, with most observed at the highest dose; all were considered treatment related and all resolved. Only one subject (1 mg dose level) reported drug withdrawal syndrome AEs, including two severe withdrawal AEs of nausea and stomach cramping. Six other subjects (3 mg dose level) reported severe AEs, most of which were GI disorders. Drug withdrawal symptoms, as assessed by the validated COWS tool, were reported within 8 hours post-dose in the 1 and 3 mg cohorts; incidence was highest at 3 mg and all symptoms appeared transient in nature. Pupillometry results did not show evidence of CNS entry of S-297995 and VAS score results did not show evidence of attenuated efficacy of opioid therapy. With the exception of one subject with transient CS elevated prolactin, there were no CS findings for laboratory evaluations, vital signs, physical examinations, or ECG results.

The 0.3 mg dose demonstrated the best combination of safety, tolerability, and efficacy in the treatment of OBD.

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