2. SYNOPSIS

Sponsor: **Shionogi & Co., Ltd.**	**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 [Naldemedine]**	**Page:**	

Study Title:
A Phase 2b, Randomized, Double-blind, Placebo-controlled, Parallel Group Study of S-297995 for the Treatment of Opioid-induced Constipation (OIC) in Cancer Patients

Investigators and Study Centers: A total of 106 Principal Investigators and 102 study centers (91 in Japan, 11 in Korea)

Publication (reference): none

Studied Period:

[redacted] June 2011 (first patient preliminary enrolled) to [redacted] February 2013 (last patient completed)

Phase of Development: 2

Objectives:

The objective of this study was to evaluate the efficacy and safety of 14-day multiple oral doses of S-297995 in cancer patients with opioid-induced constipation (OIC) in a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Pharmacokinetics of the parent compound and its metabolites were also assessed.

The primary objective of the study was to compare the efficacy of S-297995 with that of placebo using the change in the frequency of spontaneous bowel movements (SBMs) per week from baseline during the 14-day period of once-daily oral administration, as the primary endpoint. An SBM was defined as a bowel movement that occurred without rescue-laxative use within previous 24 hours.

The secondary objectives of the study were as follows:

- To determine the optimal dose of S-297995 from the primary endpoint
- To evaluate the efficacy of S-297995 as compared with the placebo for the secondary endpoints
- To evaluate the safety of S-297995 as compared with the placebo, including transfer to the central nervous system (putative central nervous system affects)
- To assess the pharmacokinetic profiles of S-297995 and its metabolites (Nor-S-297995, S-297995-7-hydroxide, and benzamidine)

Methodology:

This was a Phase 2, multinational (Japan and Korea), multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate 3 dose levels of S-297995 in cancer patients with OIC. The study included a screening period (with a duration of 14

to 28 days), a 14-day treatment period, and a 28-day follow-up period. Patients were randomized in a 1:1:1:1 assignment to receive S-297995 (0.1, 0.2, or 0.4 mg) or placebo once daily during the 14-day treatment period. Subjects were assessed for efficacy, safety, and pharmacokinetics during the treatment period. Final safety assessments were performed at the end of the follow-up period.

Number of Subjects (Planned and Analyzed):
Planned: 212 patients, up to 230 patients

Randomized: 227 patients

Analyzed for Efficacy: 225 patients for the Full Analysis Set (FAS) (55 patients in the 0.1 mg group, 58 in the 0.2 mg group, 56 in the 0.4 mg group, and 56 in the placebo group). The Per Protocol Set (PPS) included 195 patients (49 patients in the 0.1 mg group, 52 in the 0.2 mg group, 47 in the 0.4 mg group, and 47 in the placebo group)

Analyzed for Safety: 226 patients (56 patients in the 0.1 mg group, 58 in the 0.2 mg group, 56 in the 0.4 mg group, and 56 in the placebo group)

Diagnosis and Main Criteria for Inclusion:

The study population included cancer patients ≥18 years of age with opioid analgesic-induced constipation (OIC) receiving opioid analgesics (regular use) for at least 2 weeks prior to Screening, and who were expected to receive opioid analgesics at a stable dose (regular use) for at least 4 weeks after enrollment. Eligible patients were required to have < 5 SBMs during the 14 days prior to enrollment, despite a stable regimen of laxative agents, and experiencing one or more of the following bowel symptoms in 25% or more of bowel movements: presence of straining, feeling of incomplete evacuation, passage of hard stools or small pellets. Patients were required to maintain a stable laxative regimen throughout the study. Female subjects were required not to be pregnant or lactating.

Test Product, Dose and Mode of Administration, Lot Number:
S-297995 (0.1 mg tablets) for oral administration; lot numbers [redacted], [redacted]

Duration of Treatment: 14 days

Reference Therapy, Dose and Mode of Administration, Lot Number:
Placebo tablets matching 0.1 mg S-297995 for oral administration; lot numbers [redacted], [redacted]

Criteria for Evaluation:

Efficacy Assessment:

The primary efficacy variable was the change in the frequency of SBMs per week from baseline during the 2-week period of administration of the study drug (the 2-week treatment period)

The secondary efficacy variables were as follows:

- The number and proportion of SBM responders in each treatment group, where SBM responder was defined as a patient for whom the frequency of SBMs per week was 3 times or more, and the increase in the frequency of SBM from baseline was 1 or more during the 2-week treatment period and in each week of the treatment period
- The complete spontaneous bowel movement (CSBM) responder rate, where a

CSBM was defined as an SBM with the feeling of complete evacuation.

- Change in the frequency of BM and CSBM per week from baseline during the 2-week treatment period
- Change in the frequency of SBM and CSBM per day from baseline for the 2-week treatment period
- Change in the number of days with the onset of SBM and CSBM per week from baseline during the 2-week treatment period
- Incidence of SBM and CSBM within 24 hours after administration
- Time to the first onset of SBM and CSBM after the initial administration
- Incidence of SBM and CSBM up to 4, 8, and 12 hours after the initial administration
- Change in the frequency of SBM per week rated as 3 or 4 on Bristol Stool Form Scale (BSS) from baseline during the 2-week treatment period
- Change in the frequency of SBM per week without straining (straining score during bowel movement is 0 or 1) from baseline during the 2-week treatment period
- Change in the frequency of use of rescue-laxatives per week from baseline during the 2-week treatment period
- Change in the mean bloating score from baseline along with the change in the abdominal discomfort score in each week of the treatment period
- Overall improvement in the rate of constipation at each visit

Safety Assessment:

- Incidence of adverse events (AEs) and adverse drug reactions (ADRs)
- Change in the pain intensity evaluation (Numerical Rating Scale: NRS) score from baseline (before administration on Visit 2) to each day of administration
- Change in the clinical opioid withdrawal scale (COWS) total score from baseline (before administration on Visit 2) to each visit
- Change in the dose of regular-use opioid analgesics from baseline (before administration on Visit 2) to each visit
- Change from baseline in the daily dose of opioid analgesics for rescue use (rescue drug) during the 2-week treatment period

Pharmacokinetics (PK) Assessment:

Pharmacokinetic blood samples for the analysis of S-297995 and its metabolites (Nor-S-297995, S-297995-7-hydroxide, and benzamidine) were collected from a subset of patients at selected study centers at the following time points:

- Day 1: 1 (± 5 minutes), 2 (± 10 minutes), 4 (± 15 minutes), 8 (± 30 minutes), and 12 (± 60 minutes) hours post-dose
- Day 2: 24 (± 60 minutes, prior to Day 2 dosing) hours post-dose

The following PK parameters were calculated for S-297995 and Nor-S-297995: C_{max}, T_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, λ_z, $t_{1/2,z}$, CL/F, MR_{Cmax}, MR_{AUC}.

Statistical Methods:

Efficacy:

The primary efficacy analysis population was FAS, and PPS was used for the analysis of sensitivity of the primary endpoint. For the primary efficacy analysis, the mean change in frequency of SBMs per week from baseline to the 2-week treatment period was compared between each of the S-297995 dose groups and the placebo group, based on an analysis of covariance model with the 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.

An SBM responder was defined as any patient whose frequency of SBMs per week during the 2-week treatment period was 3 times or more per week and having an average increase in the frequency of SBMs from baseline of 1 or more. A CSBM was defined as an SBM with the feeling of complete evacuation. The SBM and CSBM responder rates were summarized by the treatment group and compared between each of the S-297995 dose groups and the placebo group with a chi-square test. In addition, the pair-wise comparisons between S-297995 dose groups were tested.

The change from baseline to the 2-week treatment period in the following efficacy variables was compared between each of the S-297995 dose groups and the placebo group, based on an analysis of covariance model with the corresponding baseline value as a covariate: the frequency of BMs and CSBMs per week, the change in the number of days with an SBM and CSBM per week, the frequency of SBMs per week rated as 3 or 4 on the BSS and SBMs without straining. In addition, the pair-wise comparisons between S-297995 dose groups were tested.

The change from baseline to Weeks 1 and 2 in the following efficacy valuables was compared between each of the S-297995 dose groups and the placebo group with a mixed-effects repeated-measurement model, which included the corresponding baseline value as a covariate and treatment group, week, and week-by-treatment group interaction as fixed effects: the frequency of SBMs, CSBMs, and BMs per week, the number of days with an SBM and CSBM per week, the frequency of SBM rated as 3 or 4 on the BSS and SBM without straining per week, the abdominal bloating score and the abdominal discomfort score. In addition, pair-wise comparisons between S-297995 dose groups were tested.

A Kaplan-Meier plot of the time to the first SBM after initial administration of the study drug was prepared by the treatment group. The median time to the first SBM and its 95% confidence interval were calculated by the 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 initial administration of the study drug was analyzed in a similar manner.

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

The incidence of SBM and CSBM within 24 hours after administration was calculated and analyzed in a similar manner as the SBM responder rates.

Change in the frequency of the use of rescue-use laxatives per week and overall improvement rate of constipation were compared between each of the S-297995 dose groups and the placebo group with a Wilcoxon rank sum test. In addition, the pair-wise comparisons between S-297995 dose groups were tested.

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

Safety:

AEs that occurred during the study drug administration were analyzed separately from those that occurred after completion of study drug administration (during the 28-day follow-up period). The incidences of AEs, ADRs, and serious adverse events (SAEs) were summarized by the system organ class, preferred term, and treatment group. Changes in safety laboratory parameters, vital signs, and ECGs were summarized by the treatment group. Changes in the NRS score 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. The mean dose of daily opioid analgesics and its change were compared between each of the S-297995 dose groups and placebo group with Welch's t test.

Pharmacokinetics:

Pharmacokinetic parameters were estimated by non-compartmental analysis methods. Dose proportionality of pharmacokinetic parameters of S-297995 and Nor-S-297995 were assessed for C_{max} and AUC using the power model.

Summary of Results:

Efficacy:

For the primary endpoint, the least-squares (LS) mean change in the frequency of SBMs during the 2-week treatment period in the FAS population was 3.43 for the 0.1 mg group, 4.75 for the 0.2 mg group, 7.29 for the 0.4 mg group, and 1.50 for the placebo group. The treatment differences in LS mean change in the frequency of SBMs between S-297995 and placebo were statistically significant for all S-297995 dose groups ($p = 0.0465$ for the 0.1 mg group, $P = 0.0007$ for the 0.2 mg group, and $P < 0.0001$ for the 0.4 mg group). In addition, the treatment difference in LS mean changes in the frequency of SBMs between the low and middle doses of S-297995 (0.1 mg and 0.2 mg) and the high dose of 0.4 mg were statistically significant ($P < 0.0001$ and $P = 0.0083$, respectively). The difference between the 0.1 mg group and the 0.2 mg group was not statistically significant ($P = 0.1681$).

With regard to the PPS (the secondary analysis population), the results were similar to those observed for the FAS population, but the difference in LS mean changes in the frequency of SBMs between the placebo group and 0.1 mg group was not statistically significant ($P = 0.0657$). The difference between the 0.2 mg group and the 0.4 mg group was not statistically significant ($P = 0.2475$). In contrast, the difference between the 0.1 mg group and the 0.2 mg group was statistically significant ($P = 0.0232$).

For the analysis of primary endpoint with the opioid analgesics as an additional covariate, the treatment differences in LS mean change in the frequency of SBMs between S-297995 and placebo were statistically significant for all S-297995 dose

groups (P = 0.0493 for the 0.1 mg group, P = 0.0008 for the 0.2 mg group, and P < 0.0001 for the 0.4 mg group).
For the key secondary endpoint, the SBM responder rate during the 2-week treatment period in the FAS population was 56.4% for the 0.1 mg group, 77.6% for the 0.2 mg group, 82.1% for the 0.4 mg group, and 37.5% for the placebo group. The treatment differences in the SBM responder rate between S-297995 and placebo were statistically significant for all S-297995 dose groups (P = 0.0464 for the 0.1 mg group, P < 0.0001 for the 0.2 and 0.4 mg groups). In addition, the treatment difference in the SBM responder rate between the 0.1 mg group and the 0.2 or 0.4 mg groups was statistically significant (P = 0.0163, P = 0.0032, respectively). The treatment difference between the 0.2 mg group and the 0.4 mg group was not statistically significant (P = 0.5445). The results for CSBM responder rate in the FAS population were similar to those of SBM.
The change in the frequency of SBMs per week was higher in the 0.2 and 0.4 mg groups than in the placebo group, for both Weeks 1 and 2. For the 0.1 mg group, the treatment difference from placebo was statistically significant at Week 2 only (P = 0.0348).
The LS mean change in the frequency of BMs during the 2-week treatment period was 1.45 for the 0.1 mg group, 2.42 for the 0.2 mg group, 4.72 for the 0.4 mg group, and 0.26 for the placebo group. The treatment differences in LS mean change in the frequency of BMs between S-297995 and placebo were statistically significant for the 0.2 and 0.4 mg groups (P = 0.0097 and P < 0.0001, respectively), but not for the 0.1 mg group (P = 0.1566). For the LS mean change in the frequency of BMs per week from baseline to Week 1, the treatment differences between S-297995 and placebo were statistically significant for the 0.2 mg and 0.4 mg groups (P = 0.0022 and P < 0.0001, respectively), but not for the 0.1 mg group (P = 0.1407). For the LS mean change in the frequency of BMs per week from baseline to Weeks 2, the treatment differences between S-297995 and placebo were statistically significant for the 0.4 mg group (P < 0.0001), but not for the 0.1 and 0.2 mg groups (P = 0.1860 and P = 0.0556, respectively).
The LS mean change in the frequency of CSBMs during the 2-week treatment period was 1.97 for the 0.1 mg group, 3.09 for the 0.2 mg group, 3.96 for the 0.4 mg group, and 0.60 for the placebo group. The treatment differences in LS mean change in the frequency of CSBMs between S-297995 and placebo were statistically significant for all S-297995 dose groups (P = 0.0146 for the 0.1 mg group, and P < 0.0001 for the 0.2 and 0.4 mg groups). The treatment difference between the 0.2 mg group and the 0.4 mg group was not statistically significant (P = 0.1160). For the LS mean change in the frequency of CSBMs per week from baseline to Weeks 1 and 2, the treatment differences between S-297995 and placebo were statistically significant for the all S-297995 dose groups.

The results of analyses for secondary endpoints to evaluate the change in the frequency of SBM/CSBM were similar to those above.

The median time to first SBM was 9.00 hours for the 0.1 mg group, 4.33 hours for the 0.2 mg group, 2.46 hours for the 0.4 mg group, and 45.43 hours for the placebo group. The median time to first SBM was significantly shorter for all S-297995 dose groups than for the placebo group (P = 0.0005 for the 0.1 mg group, and P < 0.0001 for the 0.2 and 0.4 mg groups). The treatment differences between 0.1 mg and 0.2 or 0.4 mg were statistically significant (P = 0.0059 and P < 0.0001, respectively). The treatment

difference between 0.2 mg and 0.4 mg was also significant (P = 0.0013). The time to the first CSBM was similar to the time to the first SBM, but the difference between the 0.2 mg group and the 0.4 mg group was not statistically significant (P = 0.1066).
The frequency of SBM rated as 3 or 4 on BSS and SBM without straining per week significantly increased from baseline during the 2-week treatment period in the 0.2 and 0.4 mg groups, but not for the 0.1 mg group .
In the 0.2 and 0.4 mg groups, the frequency of rescue laxatives use was reduced significantly from baseline during the 2-week treatment period compared with placebo (P = 0.0028 and P = 0.0006, respectively). However, the difference between 0.1 mg and placebo was not statistically significant (P = 0.0945).
The abdominal bloating score and abdominal discomfort score for the FAS population were significantly improved for all S-297995 dose groups compared with the placebo group from baseline to both Weeks 1 and 2.
For overall improvement rate of constipation for the FAS population at Week 2, the majority of patients in the 0.1, 0.2, and 0.4 mg groups (70.6%, 90.6%, and 81.3%, respectively) reported some level of improvement, while only 42.3% of patients in the placebo group. The treatment difference was significant in all S-297995 dose group (vs. placebo; P = 0.0006, P < 0.0001, and P < 0.0001, respectively). No patients reported worsening of constipation in the 0.2 mg group at Week 2.

Safety:
During the study drug administration, 256 AEs occurred in 120 of 170 patients (70.6%) for the combined S-297995 group: 69 AEs in 37 of 56 patients (66.1%) for the 0.1 mg group, 84 AEs in 39 of 58 patients (67.2%) for the 0.2 mg group, and 103 AEs in 44 of 56 patients (78.6%) for the 0.4 mg group. Sixty-three AEs occurred in 29 of 56 patients (51.8%) for the placebo group. The incidence of AEs during the study drug administration was higher in the combined S-297995 group and the 0.4 mg group than in the placebo group (P = 0.0143 and 0.0052, respectively). During the study drug administration, 122 ADRs occurred in 77 of 170 patients (45.3%) for the combined S-297995 group: 31 in 19 of 56 patients (33.9%) for the 0.1 mg group, 36 in 27 of 58 patients (46.6%) for the 0.2 mg group, and 55 in 31 of 56 patients (55.4%) for the 0.4 mg group. Twenty-seven ADRs occurred in 19 of 56 patients (33.9%) for the placebo group. The incidence of ADRs during the study drug administration was higher in the 0.4 mg group than in the placebo group (P = 0.0361).

The most common SOC of AEs during the study drug administration was gastrointestinal disorders: 19 patients (33.9%) in the 0.1 mg group, 27 patients (46.6%) in the 0.2 mg group, 30 patients (53.6%) in the 0.4 mg group, and 17 patients (30.4%) in the placebo group. The most frequently reported AEs during the study drug administration in the combined S-297995 group were diarrhea (67 patients [39.4%]), followed by white blood cell count decreased (9 patients [5.3%]). The most frequently reported AEs during the study drug administration in the placebo group were diarrhea (14 patients [25.0%]), nausea (4 patients [7.1%]) and white blood cell count decreased (3 patients [5.4%]).

The incidence of AEs after completion of the study drug administration (during the 28-day follow-up period) was approximately 43% to 59% across the treatment groups.

For the incidence of ADRs after completion of the study drug administration, no clear differences were observed between treatment groups.

In the study, 7 deaths occurred in the study: 2 patients in the 0.1 mg group (small cell lung cancer metastatic, lung neoplasm malignant), 2 patients in the 0.4 mg group (bile duct cancer, lung neoplasm malignant), and 3 patients in the placebo group (2 cases of breast cancer and 1 case of lung neoplasm malignant). No deaths occurred in the 0.2 mg group. Of the 7 deaths, 1 patient died (bile duct cancer, in the 0.4 mg group) during the study drug administration and 6 patients died after completion of the study drug administration (during the 28-follow-up period). All deaths were considered not related to the study drug.

In the study, 18 cases of SAEs other than death were reported in 16 patients. Four cases of SAEs other than death were reported in 4 patients in the combined S-297995 group during the study drug administration: 1 case (gastrointestinal hemorrhage) in 1 of 56 patients (1.8%) in the 0.1 mg group and 3 cases (pneumonia, anemia, asthenia) in 3 of 56 patients (5.4%) in the 0.4 mg group. No SAEs were reported in the 0.2 mg group or the placebo group during the study drug administration. Ten cases of SAEs other than death were reported in 9 patients in the combined S-297995 group after completion of the study drug administration: 2 cases (febrile neutropenia, delirium) in 2 of 56 patients (3.6%) in the 0.1 mg group, 5 cases (delirium, pneumonia and pyrexia, idiopathic thrombocytopenic purpura, interstitial lung disease) in 4 of 58 patients (6.9%) in the 0.2 mg group, and 3 cases (vena cava thrombosis, ileus, jaundice cholestatic) in 3 of 56 patients (5.4%) for the 0.4 mg group. Four cases of SAEs other than death (toxic skin eruption, febrile neutropenia, ileus and pneumonia) were reported in 3 of 56 patients (5.4%) in the placebo group after completion of the study drug administration (1 patient had 2 SAEs of ileus and pneumonia). All the SAEs other than death were considered not related to the study drug by both the Investigator and the Sponsor, except for 1 SAE of gastrointestinal hemorrhage in the 0.1 mg group. It was considered to be possibly related to the study drug by the Investigator. However, the Sponsor ruled out the causality with the study drug, because pancreatic cancer (primary disease) infiltrated into the duodenum and the Sponsor considered that this infiltration caused the gastrointestinal hemorrhage.

Eight patients discontinued the study due to an AE in the combined S-297995 group: 3 patients (5.4%) in the 0.1 mg group, 1 patient (1.7%) in the 0.2 mg group, and 4 patients (7.1%) in the 0.4 mg group. One patient (1.8%) in the placebo group discontinued the study due to an AE.

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 were noted.

No clinically meaningful changes from baseline during the 2-week treatment period were seen in the pain intensity NRS scores, COWS scores, or the morphine equivalent doses

of opioids.

Pharmacokinetics:

S-297995 was absorbed with median T_{max} approximately 2 hours following the first doses of 0.1 to 0.4 mg S-297995. The C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ of S-297995 increased in a dose-proportional manner over the dose range of 0.1 to 0.4 mg following the first dose of S-297995. The geometric mean C_{max} were 1.32, 2.02, and 4.80 ng/mL following the first dose of 0.1, 0.2, and 0.4 mg of S-297995, respectively. The geometric mean $AUC_{0\text{-last}}$ were 12.04, 21.59, and 45.09 ng·hr/mL following the first dose of 0.1, 0.2, and 0.4 mg of S-297995, respectively. The geometric mean $AUC_{0\text{-inf}}$ of S-297995 were 12.29, 23.79, and 42.20 ng·hr/mL following the first dose of 0.1, 0.2, and 0.4 mg of S-297995, respectively.

Median T_{max} of Nor-S-297995 (a major metabolite of S.297995) was approximately 8 hours and the geometric mean ratios of C_{max} of Nor-S-297995 to that of unchanged S-297995 corrected for molecular weight were less than 10%, following the first dose of 0.1 to 0.4 mg of S-297995. The geometric mean ratio of $AUC_{0\text{-inf}}$ of Nor-S-297995 to that of unchanged S-297995 corrected for molecular weight could not be estimated appropriately because of insufficient data in the elimination phase.

All plasma concentrations of benzamidine (one of minor metabolites of S-297995) were below the limit of quantification (< 0.300 ng/mL) following the first dose of 0.1 to 0.4 mg S-297995.

Conclusions:

S-297995 was effective and generally well tolerated in cancer patients with OIC when given at daily oral doses of 0.1 mg to 0.4 mg. However, the 0.1 mg group did not show a treatment difference compared with placebo for some of the efficacy parameters. For the safety, the incidence of AEs dose-dependently increased from 51.8% for placebo to 66.1% for 0.1 mg, 67.2% for 0.2 mg, and 78.6% for 0.4 mg. Based on these results, 0.2 mg per day was considered the dose with the best risk and benefit balance of efficacy and safety to be tested in future confirmatory clinical trials.

Report Date: 3 July 2013

Prepared in: Microsoft Word 2010 (Word 97-2003 Binary File Format)

6. SECTION 2: SYNOPSIS

Diagnosis and Main Criteria for inclusion:

The study population included cancer patients ≥18 years of age with opioid analgesic-induced constipation (OIC) receiving opioid analgesics (regular use) for at least 2 weeks prior to Screening, and who were expected to receive opioid analgesics at a stable dose (regular use) for at least 4 weeks after enrollment. Eligible patients were required to have ≤ 5 SBMs during the 14 days prior to enrollment, despite a stable regimen of laxative agents, and experiencing one or more of the following bowel symptoms in 25% or more of bowel movements: presence of straining, feeling of incomplete evacuation, passage of hard stools or small pellets. Patients were required to maintain a stable laxative regimen throughout the study. Female subjects were required not to be pregnant or lactating.

Summary of Results:

Efficacy:

For the primary endpoint, the least-squares (LS) mean change in the frequency of SBMs during the 2-week treatment period in the FAS population was 3.43 for the 0.1 mg group, 4.75 for the 0.2 mg group, 7.29 for the 0.4 mg group, and 1.50 for the placebo group. The treatment differences in LS mean change in the frequency of SBMs between S-297995 and placebo were statistically significant for all S-297995 dose groups ($p = 0.0465$ for the 0.1 mg group, $P = 0.0007$ for the 0.2 mg group, and $P < 0.0001$ for the 0.4 mg group). In addition, the treatment difference in LS mean changes in the frequency of SBMs between the low and middle doses of S-297995 (0.1 mg and 0.2 mg) and the high dose of 0.4 mg were statistically significant ($P < 0.0001$ and $P = 0.0083$, respectively). The difference between the 0.1 mg group and the 0.2 mg group was not statistically significant ($P = 0.1681$).

With regard to the PPS (the secondary analysis population), the results were similar to those observed for the FAS population, but the difference in LS mean changes in the frequency of SBMs between the placebo group and 0.1 mg group was not statistically significant ($P = 0.0657$). The difference between the 0.2 mg group and the 0.4 mg group was not statistically significant ($P = 0.2475$). In contrast, the difference between the 0.1 mg group and the 0.2 mg group was statistically significant ($P = 0.0232$).

For the analysis of primary endpoint with the opioid analgesics as an additional covariate, the treatment differences in LS mean change in the frequency of SBMs between S-297995 and placebo were statistically significant for all S-297995 dose groups ($P = 0.0493$ for the 0.1 mg group, $P = 0.0008$ for the 0.2 mg group, and $P < 0.0001$ for the 0.4 mg group).

For the key secondary endpoint, the SBM responder rate during the 2-week treatment period in the FAS population was 56.4% for the 0.1 mg group, 77.6% for the 0.2 mg group, 82.1% for the 0.4 mg group, and 37.5% for the placebo group. The treatment differences in the SBM responder rate between S-297995 and placebo were statistically significant for all S-297995 dose groups ($P = 0.0464$ for the 0.1 mg group, $P < 0.0001$ for the 0.2 and 0.4 mg groups). In addition, the treatment difference in the SBM responder rate between the 0.1 mg group and the 0.2 or 0.4 mg group was statistically significant ($P = 0.0163$ and $P = 0.0032$, respectively). The treatment

difference between the 0.2 mg group and the 0.4 mg group was not statistically significant (P = 0.5445). The results for CSBM responder rate in the FAS population were similar to those of SBM.

The change in the frequency of SBMs per week was higher in the 0.2 and 0.4 mg groups than in the placebo group, for both Weeks 1 and 2. For the 0.1 mg group, the treatment difference from placebo was statistically significant at Week 2 only (P = 0.0111).

The LS mean change in the frequency of BMs during the 2-week treatment period was 1.45 for the 0.1 mg group, 2.42 for the 0.2 mg group, 4.72 for the 0.4 mg group, and 0.26 for the placebo group. The treatment differences in LS mean change in the frequency of BMs between S-297995 and placebo were statistically significant for the 0.2 and 0.4 mg groups (P = 0.0097 and P < 0.0001, respectively), but not for the 0.1 mg group (P = 0.1566). For the LS mean change in the frequency of BMs per week from baseline to Week 1, the treatment differences between S-297995 and placebo were statistically significant for the 0.2 and 0.4 mg groups (P = 0.0021 and P < 0.0001, respectively), but not for the 0.1 mg group (P = 0.1401). For the LS mean change in the frequency of BMs per week from baseline to Weeks 2, the treatment differences between S-297995 and placebo were statistically significant for the 0.2 and 0.4 mg groups (P = 0.0158 and P < 0.0001, respectively), but not for the 0.1 group (P = 0.0870).

The LS mean change in the frequency of CSBMs during the 2-week treatment period was 1.97 for the 0.1 mg group, 3.09 for the 0.2 mg group, 3.96 for the 0.4 mg group, and 0.60 for the placebo group. The treatment differences in LS mean change in the frequency of CSBMs between S-297995 and placebo were statistically significant for all S-297995 dose groups (P = 0.0146 for the 0.1 mg group, and P < 0.0001 for the 0.2 and 0.4 mg groups). The treatment difference between the 0.2 mg group and the 0.4 mg group was not statistically significant (P = 0.1160). For the LS mean change in the frequency of CSBMs per week from baseline to Weeks 1 and 2, the treatment differences between S-297995 and placebo were statistically significant for all S-297995 dose groups.

The results of analyses for secondary endpoints to evaluate the change in the frequency of SBM/CSBM were similar to those above.

The median time to first SBM was 9.00 hours for the 0.1 mg group, 4.33 hours for the 0.2 mg group, 2.46 hours for the 0.4 mg group, and 45.43 hours for the placebo group. The median time to first SBM was significantly shorter for all S-297995 dose groups than for the placebo group (P = 0.0005 for the 0.1 mg group, and P < 0.0001 for the 0.2 and 0.4 mg groups). The treatment differences between 0.1 mg and 0.2 or 0.4 mg were statistically significant (P = 0.0059 and P < 0.0001, respectively). The treatment difference between 0.2 mg and 0.4 mg was also significant (P = 0.0013). The time to the first CSBM was similar to the time to the first SBM, but the difference between the 0.2 mg group and the 0.4 mg group was not statistically significant (P = 0.1066).

The frequency of SBM rated as 3 or 4 on BSS and SBM without straining per week significantly increased from baseline during the 2-week treatment period in the 0.2 and 0.4 mg groups, but not for the 0.1 mg group.

In the 0.2 and 0.4 mg groups, the frequency of rescue laxatives use was reduced significantly from baseline during the 2-week treatment period compared with placebo (P = 0.0028 and P = 0.0006, respectively). However, the difference between 0.1 mg and placebo was not statistically significant (P = 0.0945).

The abdominal bloating score and abdominal discomfort score for the FAS population were significantly improved for all S-297995 dose groups compared with the placebo group from baseline to both Weeks 1 and 2.

For overall improvement rate of constipation for the FAS population at Week 2, the majority of patients in the 0.1, 0.2, and 0.4 mg groups (70.6%, 90.6%, and 81.3%, respectively) reported some level of improvement, while only 42.3% of patients in the placebo group. The treatment difference was significant in all S-297995 dose group (vs. placebo; P = 0.0006, P < 0.0001, and P < 0.0001, respectively). No patients reported worsening of constipation in the 0.2 mg group at Week 2.