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: Naldemedine	**Page:**	

Study Title:
A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of naldemedine in cancer patients with opioid-induced constipation

Investigators and Study Centers: This was a multicenter study conducted at 70 study centers in Japan.

Publication (Reference): Not applicable

Studied Period:
[redacted] November 2013 (first patient enrolled) to [redacted] April 2015 (last patient completed)

Phase of Development: 3

Objectives:

The primary objective of the study:

To evaluate the efficacy of 14-day treatment of naldemedine compared to placebo.

The primary efficacy endpoint was the proportion of spontaneous bowel movement (SBM) responders during the 14-day Treatment Period. An SBM responder was defined as a patient with ≥ 3 SBMs per week and an increase of ≥ 1 SBM per week from baseline.

The secondary objectives of the study:

- To evaluate the efficacy of naldemedine compared to placebo for the secondary endpoint (See Criteria for Evaluation: Efficacy Assessment).
- To evaluate the safety of naldemedine compared to placebo.
- To assess the pharmacokinetic profiles of naldemedine and its metabolite (nor-naldemedine).

Methodology:

This was a phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group study in which 190 cancer patients with opioid-induced constipation (OIC) were to be enrolled. The study consisted of 3 periods: a Screening Period (14 to 28 days prior to first administration of the study drug), a 14-day Treatment Period, and a 4-week Follow-up Period. Patients were to be randomized in a 1:1 ratio to receive a single tablet of either 0.2 mg of naldemedine or placebo (95 patients each) once daily in a double-blind manner during the 14-day Treatment Period. There were no predefined stratification factors at randomization. Patients who discontinued the study, or who were not willing to participate in the extension study, had to have a follow-up visit 4 weeks after the completion or early termination of the Treatment Period and had to have performed the specified physical examinations and safety assessments including monitoring of adverse events (AEs).

Patients who were willing to participate in the extension study after completion of the 14-day Treatment Period, were enrolled directly to the extension study (Study 1332V9237).

Diagnosis and Main Criteria for Inclusion:

The study population included cancer patients ≥20 years of age with OIC receiving opioids regularly for at least 2 weeks prior to Screening , and were treated with a stable opioid regimen for 2 weeks prior to the randomization (100 to 150% of the dose of regular-use opioids on the day of 2 weeks prior to the randomization). Eligible patients were required to have ≤ 5 SBMs during the 14 consecutive days prior to the randomization, and to experience one or more of the following bowel symptoms in an incidence of ≥ 25% of all bowel movements (BMs) regardless of the use of rescue laxatives: presence of straining during bowel movement, feeling of incomplete evacuation, passage of hard stools or small pellets. Patients who were receiving laxatives for OIC, or who had been treated with laxatives and did not receive laxatives due to insufficient efficacy or other reasons, were required to maintain a stable laxative regimen throughout the study. Female patients were required not to be pregnant or lactating.

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

Naldemedine (naldemedine 0.2 mg tablet); 0.2 mg/day; oral; the lot number was [redacted] (Packaged Lot No. [redacted]).

Duration of Treatment: 2 weeks

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

Placebo tablets matching 0.2 mg naldemedine tablets; oral; lot numbers were [redacted] (Packaged Lot No. [redacted]).

Criteria for Evaluation:

Efficacy Assessment:

The primary efficacy endpoint was the proportion of SBM responders during the Treatment Period. An SBM responder was defined as a patient having ≥ 3 SBMs per week and an increase of ≥ 1 SBM per week from baseline.

Secondary Endpoints:

- Proportion of patients with CSBM (Complete Spontaneous Bowel Movement) response during the 2-week Treatment Period. A CSBM responder was defined as a patient with SBM accompanied by feeling of complete evacuation.
- Proportion of patients with SBM response (or CSBM response) for each week during the Treatment Period
- Change in the frequency of SBMs (or CSBMs) per week from baseline during the Treatment Period
- Weekly change in frequency of SBMs (or CSBMs) per week from baseline during the Treatment Period
- Time to the first SBM (or CSBM) after the first administration of the study drug
- Daily Change in the frequency of SBMs from baseline during the Treatment Period
- Change in the number of Days with at least 1 SBM (or CSBM) per week from baseline during the Treatment Period

- Proportion of patients with at least 1 SBM (or CSBM) for each observation time point within 24 hours after the first administration of the study drug during the Treatment Period
- Change in the frequency of SBMs with Bristol Stool Scale (BSS) score of 3 or 4 per week from baseline during the Treatment Period
- Change in the frequency of SBMs per week without straining (straining score of 0 or 1 during bowel movement) from baseline during the Treatment Period
- Change in the frequency of rescue-use laxatives per week from baseline during the Treatment Period
- Weekly Change in the abdominal bloating and abdominal discomfort scores from baseline during the Treatment Period
- Change in Patient Assessment of Constipation Symptoms (PAC-SYM) and Patient Assessment of Constipation Quality of Life (PAC-QOL) from baseline to each observation time point
- Proportion of patients with PAC-SYM response or PAC-QOL response. A PAC-SYM responder (or PAC-QOL responder) was defined as a patient who achieved an improvement in the overall score on PAC-SYM (or on a domain for dissatisfaction of PAC-QOL) per week of at least 1 point from baseline.

Safety Assessment:

Adverse events (AEs), Numeric Rating Scale (NRS), Clinical Opioid Withdrawal Scale (COWS) assessment, dose of regular-use opioid, vital signs, ECG findings, clinical laboratory tests. Major Adverse Cardiac Events (MACE): cardiovascular (CV) death, myocardial infarction, and cerebrovascular accident (stroke).

Pharmacokinetics Assessment:

Plasma concentrations of naldemedine and its metabolite (nor-naldemedine)

Statistical Methods:

For efficacy and safety analyses, the differences between the groups were tested at a 2-sided significance level of 0.05.

Efficacy:

Full analysis set (FAS) included all randomized patients who received at least 1 actual dose of the study drug and who had an evaluation of OIC at baseline and at least 1 evaluation of OIC after the initiation of the study drug administration. Per protocol set (PPS) included all randomized patients who met all of the following conditions: Patients who met all inclusion criteria and no exclusion criteria, patients with no major deviations from the specified study procedure, and patients with appropriate follow-up. The primary efficacy analysis population was FAS, and PPS was used for the analysis of sensitivity of the primary endpoint. Baseline was defined as the average number of SBMs per week during the 14-day period prior to the Treatment Period. For the primary efficacy endpoint, the proportion of SBM responders was assessed during the 2-week Treatment Period for each treatment group. The proportion of SBM responders was compared between the naldemedine group and the placebo group with the chi-square test. Difference in the proportion of responder between the groups, and its 95% confidence interval (CI) were calculated.

The proportion of patients with SBM response for each week during the 2-week Treatment Period was analyzed in a similar way to the primary endpoint.

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

proportion of CSBM responders was analyzed in a similar way to the primary endpoint.

The changes from baseline in the frequency of SBMs per week during the 2-week Treatment Period were compared between the naldemedine and placebo groups, based on an analysis of covariance (ANCOVA) using the frequency of SBMs per week at baseline as a covariate. The change from baseline in the frequency of CSBMs per week to the 2-week Treatment Period was analyzed similarly.

Summary statistics of frequency of SBMs (or CSBMs) per week for each week during the 2-week Treatment Period and of its change from baseline were calculated for each treatment group. All available data on the change from baseline in the frequency of SBMs per week to Weeks 1 and 2 were used to compare the mean of the change at Weeks 1 and 2 based on the mixed model repeated measures (MMRM) approach. Specifically, the mean of the weekly change in the frequency of SBMs per week (as response variable) was compared between the naldemedine and placebo groups at Weeks 1 and 2, using the MMRM which includes treatment-group, Week, and group by Week interaction as fixed effects, and the frequency of SBMs per week at baseline as a covariate. The weekly change from baseline in the frequency of CSBMs per week was analyzed in a similar way.

Time to the first SBM (or CSBM) was defined as the time to appearance of the first SBM (or CSBM) after the first administration of the study drug. The Kaplan-Meier plot of the time to the first SBM was made for each treatment group, and the median time to the first SBM and its 95% CI were calculated for each treatment group. Furthermore, the distribution of the time was compared between the naldemedine and placebo groups with a generalized Wilcoxon test.

The mean of daily change in the frequency of SBMs was compared between the naldemedine and placebo groups on each observation day, using the MMRM which includes treatment-group, day and group by day interaction as fixed effects, and the frequency of SBMs per day at baseline as a covariate.

Summary statistics of the change from baseline in the number of days with SBMs per week to the 2-week Treatment Period were calculated for each treatment group. The change in the number of days with SBMs was compared between the naldemedine and placebo groups based on an ANCOVA using the number of days with SBMs per week at baseline as a covariate. The changes from baseline in the number of days with SBMs to Week 1 and Week 2 were determined, separately. The change from baseline in the number of days with CSBMs to Week 1 and Week 2, was analyzed in a similar manner.

The number and proportion of the patients who experienced an SBM 4, 8, and 12 hours after the first administration of the study drug were calculated for each treatment group. The proportion of patients with at least 1 SBM at each observation time point was defined as the proportion of those who have experienced SBM at each observation time point after the first administration of the study drugs. The difference in proportion of patients with at least 1 SBM between the naldemedine and placebo groups and its 95% CI were calculated for each observation time point. The proportion of patients with at least 1 SBM was compared between the naldemedine and placebo groups with the chi-square test. The incidence of CSBM at each observation time point within 24 hours after the first administration of the study drugs was analyzed in a similar way.

The change from baseline in the frequency of SBMs with BSS score of 3 or 4 per week during the 2-week Treatment Period was calculated for each treatment group. The change from baseline in the frequency of SBMs with BSS of 3 or 4 per week was compared between the naldemedine and placebo groups based on an ANCOVA using the frequency of SBMs with BSS of 3 or 4 per week at baseline as a covariate. Furthermore, the changes from baseline in the frequency of SBMs with BSS of 3 or 4 to Weeks 1 and 2 were analyzed in a similar way.

The change from baseline in the frequency of SBMs per week without straining (straining score of 0 or 1 during BM) during the 2-week Treatment Period was calculated for each treatment group. The change from baseline in the frequency of SBMs without straining per week during the 2-week Treatment Period was calculated for naldemedine and placebo groups based on an ANCOVA using the frequency of SBMs without straining per week at baseline as a covariate. Furthermore, the changes from baseline in the frequency of SBMs without straining to Weeks 1 and 2 were analyzed in a similar way.

Summary statistics of the frequency of rescue-use laxatives per week during the 2-week Treatment Period were calculated for each treatment group. The change from baseline in the frequency of rescue-use laxatives per week in the 2-week Treatment Period was compared between the naldemedine and placebo groups with the Wilcoxon rank-sum test.

Summary statistics of the means of the abdominal bloating and abdominal discomfort scores for each week during the 2-week Treatment Period and the weekly change from baseline in the abdominal bloating and abdominal discomfort scores during the 2-week Treatment Period were calculated for each treatment group. Furthermore, the weekly change in the abdominal discomfort scores was analyzed in a similar way.

Summary statistics of the mean overall score on PAC-SYM and its changes from baseline were calculated for each observation time point. Then, the mean overall score on PAC-SYM was compared between the naldemedine and placebo groups with Welch's t-test. The mean score for each of the domains was analyzed in similar ways. The mean overall score on PAC-QOL and mean score on PAC-QOL for each of the domains were analyzed similarly.

A PAC-SYM responder was defined as a patient who achieved an improvement in the overall score on PAC-SYM per week of at least 1 point from baseline. The proportion of PAC-SYM responders was calculated for each treatment group and was compared between the naldemedine and placebo groups with the chi-square test at Weeks 1 and 2. Furthermore, the difference in the proportion between the naldemedine and placebo groups and its 95% CI were calculated. In addition, the curve of cumulative distribution function based on the change from baseline in the mean overall score on PAC-SYM was plotted for each treatment group. The proportion of responders based on the "dissatisfaction" domain of PAC-QOL was analyzed in similar ways.

Safety:

AEs were classified by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) Version 16.1 or higher. AEs that occurred during the Treatment Period and the Follow-up Period, were used in the safety analyses. 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), because the allowable concomitant treatments in the Treatment Period was considered different from those in the Follow-up Period. AEs occurred after the initial administration of the study drug were defined as treatment-emergent adverse events (TEAEs).

The number of patients who experienced AEs in the Treatment Period was tabulated, and the incidence of AEs and its 95% CIs were calculated using Clopper-Pearson method in the Safety Population. Then, the incidence was compared between the naldemedine and placebo groups with Fisher's exact test. Furthermore, fatal AEs, serious (non-fatal) AEs (SAEs), significant AEs, AEs leading to withdrawal, and AEs which were considered related to the study drug by the investigator (ie, treatment-related AEs) were analyzed in a similar way. The above analyses were also made for AEs that occurred in the Follow-up Period. The incidence of each AE related to MACE and its 95% CIs were calculated for each treatment group. MACE and potential MACE were categorized by using standardised MedDRA queries (SMQ).

Pharmacokinetics:

Individual plasma concentrations of naldemedine and its metabolite (nor-naldemedine) were listed by patient with elapsed time from the last meal prior to the corresponding last study drug administration, and the elapsed time from the last study drug administration prior to the corresponding pharmacokinetic (PK) blood sampling. The elapsed time data from the last study drug administration prior to PK blood sampling were summarized at each visit with the number of non-missing observations (N), arithmetic mean, standard deviation and coefficient of variation, median, minimum and maximum values. Plasma concentrations of naldemedine and its metabolite (nor-naldemedine) were summarized at each visit with N, arithmetic mean, standard deviation, coefficient of variation, median, minimum and maximum values, geometric mean and coefficient of variation for geometric mean.

Summary of Results

Patients Disposition:

Planned: 190 patients

Randomized: 193 (97 for the naldemedine group, 96 for the placebo group)

Analyzed for efficacy:

- Full analysis set (FAS): 193 (97 for the naldemedine group, 96 for the placebo group)
- Per protocol set (PPS): 159 (80 for the naldemedine group, 79 for the placebo group)

Analyzed for safety: 193 (97 for the naldemedine group, 96 for the placebo group)

All efficacy analyses were performed on the FAS Population unless stated otherwise. All patients who were randomized in the study were included in the FAS Population. Of the 193 patients randomized, 119 (61.7%) were male and 74 (38.3%) were female. The mean age was in the range of 63.8 to 64.6 years and approximately 50% of patients in each group was 65 years or older. All demographic and baseline characteristics were generally balanced between the treatment groups. In both groups, the most common primary tumor was lung cancer, followed by breast cancer.

Efficacy:

The primary endpoint was the proportion of SBM responders during the 2-week

Treatment Period. The proportion of SBM responders during the Treatment Period was 71.1% (69 of 97 patients) for the naldemedine group and 34.4% (33 of 96 patients) for the placebo group. The difference between the groups was 36.76% and was statistically significant ($P < 0.0001$). The results on the PPS Population as a sensitivity analysis of the primary endpoint were consistent with those of the primary analysis for the FAS Population, and the difference between the groups in the proportion of responders for the PPS Population was 37.06% and was statistically significant ($P < 0.0001$). The proportion of SBM responders was compared between the naldemedine group and the placebo group with Cochran-Mantel-Haenszel test adjusted by the stratified opioid groups (< 60 mg and ≥ 60 mg) based on the specified statistical analysis plan. The difference between the groups in the proportion of SBM responders was 37.39% and was statistically significant ($P < 0.0001$).

The results of secondary efficacy endpoints are described below.

The proportion of CSBM responders during the Treatment Period was 40.2% (39 of 97 patients) for the naldemedine group and 12.5% (12 of 96 patients) for the placebo group. The difference between the groups was 27.71% and was statistically significant ($P < 0.0001$).

The differences between the groups in the proportion of SBM responders per week for each observation week during the 2-week Treatment Period were 32.53% at Week 1 and 34.73% at Week 2 and were both statistically significant ($P < 0.0001$ for both). Consistently, the differences between the groups in the proportion of CSBM responders per week for each observation week during the 2-week Treatment Period were 33.86% at Week 1 and 29.75% at Week 2 and were both statistically significant ($P < 0.0001$ for both).

The least squares (LS) mean change from baseline in the frequency of SBMs per week during the 2-week Treatment Period was 5.16 SBMs in the naldemedine group relative to 1.54 SBMs in the placebo group. The difference between the groups was 3.62 SBMs and was statistically significant ($P < 0.0001$). Consistently, the LS mean change from baseline in the frequency of CSBMs per week during the 2-week Treatment Period was 2.76 CSBMs in the naldemedine group relative to 0.71 CSBMs in the placebo group. The difference between the groups was 2.05 CSBMs and was statistically significant ($P < 0.0001$).

In the MMRM approach, the differences between the groups in the LS mean change in the frequency of SBMs were 3.97 SBMs at Week 1 and 2.73 SBMs at Week 2 and were both statistically significant ($P < 0.0001$ for both). Consistently, the differences between the groups in the LS mean change in the frequency of CSBMs were 2.52 CSBMs at Week 1 and 1.37 CSBMs at Week 2 and were both statistically significant ($P < 0.0001$ and $P = 0.0002$, respectively).

The median time to the first SBM after the initial administration of the study drug was 4.67 hours for the naldemedine group and 26.58 hours for the placebo group. The median time to the first SBM in the naldemedine group was significantly shorter than that in the placebo group ($P < 0.0001$). Consistently, the median time to the first CSBM after the initial administration of the study drug was 24.00 hours for the naldemedine group and 218.50 hours for the placebo group. The median time to the first CSBM in the naldemedine group was significantly shorter than that in the placebo group ($P < 0.0001$).

In the MMRM approach, the differences between the groups in the LS mean change

from baseline in the frequency of SBMs per day were statistically significant on each observation day except Days 5 and 14.

The LS mean change from baseline in the number of days with at least 1 SBM per week during the 2-week Treatment Period was 2.60 days in the naldemedine group relative to 0.98 days in the placebo group. The difference between the groups was 1.63 days per week and was statistically significant ($P < 0.0001$). Consistently, the LS mean change from baseline in the number of days with at least 1 CSBM per week during the 2-week Treatment Period was 1.75 days in the naldemedine group relative to 0.52 days in the placebo group. The difference between the groups was 1.23 days per week and was statistically significant ($P < 0.0001$). In the MMRM approach, the differences between the groups in the LS mean change from baseline in the number of days with at least 1 SBM per week were 1.72 days at Week 1 and 1.54 days at Week 2 and were both statistically significant ($P < 0.0001$ for both). Consistently, the differences between the groups in the LS mean change from baseline in the number of days with at least 1 CSBM per week were 1.47 days at Week 1and 0.98 days at Week 2 and were both statistically significant ($P < 0.0001$ and $P = 0.0002$, respectively).

The differences between the groups in the proportion of patients with at least 1 SBM at predefined time points (4, 8, 12 and 24 hours after the initial administration of the study drug) were statistically significant at all observation time points ($P < 0.0001$ for all). Consistently, the differences between the groups in the proportion of patients with at least 1 CSBM at the same predefined time points were statistically significant at all observation time points ($P < 0.0001$ for all).

The LS mean change from baseline in the frequency of SBMs per week with BSS of 3 or 4 during the 2-week Treatment Period was 1.38 SBMs in the naldemedine group relative to 0.74 SBMs in the placebo group. The difference between the groups was 0.64 SBMs and was statistically significant ($P = 0.0140$). In the MMRM approach, the differences between the groups in the LS mean change from baseline were 0.72 SBMs at Week 1 and 0.60 SBMs at Week 2 and were both statistically significant ($P = 0.0364$ and $P = 0.0379$, respectively).

The LS mean change from baseline in the frequency of SBMs per week without straining during the 2-week Treatment Period was 3.85 SBMs in the naldemedine group relative to 1.17 SBMs in the placebo group. The difference between the groups was 2.67 SBMs and was statistically significant ($P = 0.0005$). In the MMRM approach, the differences between the groups in the LS mean change from baseline in the frequency of SBMs without straining per week during the 2-week Treatment Period were 3.13 SBMs at Week 1 and 1.53 SBMs at Week 2 and were both statistically significant ($P < 0.0001$ and $P = 0.0017$, respectively).

The mean change from baseline in the frequency of rescue-use laxatives per week was −2.98 times for the naldemedine group and −1.13 times for the placebo group. The difference between the groups was statistically significant during the 2-week Treatment Period ($P < 0.0001$).

In the MMRM approach, the differences between the groups in the LS mean changes from baseline in the abdominal bloating score were −0.15 at Week 1 and −0.14 at Week 2 and were statistically significant at Week 1, but not at Week 2 ($P = 0.0469$ and $P = 0.0864$, respectively). Consistently, the differences between the groups in the LS mean changes from baseline in the abdominal discomfort score were −0.16 at Week 1 and −0.11 at Week 2 and were statistically significant at Week 1, but not at

Week 2 (P = 0.0389 and P = 0.1608, respectively).

The changes from baseline in the PAC-SYM mean score for stool symptoms in the naldemedine group was statistically significantly improved relative to those in the placebo group at Visit 4 and the last observation (Visit 4 or early termination). However, the changes from baseline in the PAC-SYM mean scores for overall and for the other 2 domains in the naldemedine group were not statistically significantly different from those in the placebo group. The changes in the PAC-QOL mean scores except for dissatisfaction at Visit 4 (Day 15) in the naldemedine group were not statistically significantly different from those in the placebo group. The change from baseline in the PAC-QOL mean score for overall in the naldemedine group was not statistically significantly different from that in the placebo group.

The differences between the groups in the proportion of responders for overall PAC-SYM were 7.48% at Visit 4 and 7.59% at the last observation and were statistically significant at Visit 4 and the last observation (P = 0.0383 and P = 0.0402, respectively). On the other hand, the differences between the groups in the proportion of responders for dissatisfaction domain of PAC-QOL were 15.96% at Visit 4 and 12.24% at the last observation and were statistically significant at Visit 4, but not at the last observation (P = 0.0176 and P = 0.0527, respectively).

Pharmacokinetics:
At Visit 4 (Day 15), the mean (minimum – maximum) elapsed time from dosing to PK sampling time was 27.93 (10.60 – 121.33) hours and the mean (minimum – maximum) plasma concentration was 0.660 (< 0.0100 – 2.42) ng/mL for naldemedine and 0.217 (< 0.0400 – 0.749) ng/mL for nor-naldemedine for the PK Concentration Population.

Safety:

All randomized patients received the study drug and were included in the Safety Population.

The proportion of deaths and other (non-fatal) SAEs were generally similar between the groups. Three patients (3.1%) died in the naldemedine group relative to 4 patients (4.2%) in the placebo group after the initial administration of the study drug. No deaths were considered related to the study drug. Ten other SAEs were reported in 7 patients (7.2%) in the naldemedine group relative to 8 other SAEs in 7 patients (7.3%) in the placebo group after the initial administration of the study drug. Of them, 4 SAEs (diarrhea, vomiting, and liver function test abnormal reported in 1 patient, and serious diarrhea in 1 patient) in the naldemedine group and 1 SAE (pneumonia) in the placebo group were considered related to the study drug by the investigator.

A higher proportion of patients in the naldemedine group (10/97, 10.3%) discontinued the study due to TEAEs relative to patients in the placebo group (1/96, 1.0%) after the initial administration of the study drug.

A total of 77 TEAEs during the study drug administration were reported in 43 patients (44.3%) in the naldemedine group relative to 40 TEAEs in 25 patients (26.0%) in the placebo group. A total of 26 treatment-related AEs during the study drug administration were reported in 18 patients (18.6%) in the naldemedine group relative to 11 treatment-related AEs in 9 patients (9.4%) in the placebo group during the study drug administration. The incidence of overall TEAEs and treatment-related AEs during the study drug administration in the naldemedine group was higher than that in

the placebo group.

The most frequent TEAEs reported during the study drug administration were associated with the SOC of Gastrointestinal Disorders (23 patients [23.7%] in the naldemedine group and 9 patients [9.4%] in the placebo group). The higher incidence of TEAEs associated with the SOC of Gastrointestinal Disorders with naldemedine treatment was due to a higher incidence of TEAEs of diarrhea relative to placebo.

The most common TEAE during the study drug administration was diarrhea: 19 patients (19.6%) in the naldemedine group and 7 patients (7.3%) in the placebo group. Most cases of diarrhea reported in the naldemedine group were mild in severity (except for 2 cases reported as severe for Patient IDs [redacted] and [redacted]). Other more frequent TEAEs during the study drug administration were malaise (4.1% for naldemedine vs. 1.0% for placebo), vomiting (3.1% for naldemedine vs. 1.0% for placebo), decreased appetite and white blood cell count decreased (for both 3.1% for naldemedine vs. 0.0% for placebo). The incidence of treatment-related AEs except diarrhea during the study drug administration was generally similar between the groups.

No MACE cases were reported in the naldemedine group. Two cases (monoparesis in Patient ID [redacted] and blood creatine phosphokinase increased in Patient ID [redacted]) were categorized as MACE cases in the placebo group.

No patients reported a total COWS score of ≥ 5 in the naldemedine group. One patient (Patient ID [redacted]) reported a total COWS score of ≥ 5 (COWS score of 1 at baseline to 7 at Day 8) in the placebo group. This case was considered caused by aggravated general conditions due to the primary disease and not related to opioid withdrawal syndrome by the investigator. Withdrawal syndrome was reported in 1 patient (Patient ID [redacted]) in the naldemedine group. The case was mild and was considered not related to the study drug by the investigator because the symptom occurred by a decrease in concomitant medication (transdermal fentanyl) after completion of the study drug administration.

There were no cases reported of AST or ALT > 3 × ULN, and total bilirubin > 2 × ULN, termed "Hy's law case", in either treatment group. One SAE of liver function test abnormal (Patient ID [redacted]) was reported in the naldemedine group. The patient had received many concomitant medications when the events occurred; however, the event was considered related to the study drug by the investigator because these findings occurred after administration of the study drug.

No abnormal findings in ECG or abnormal changes in vital signs were found.

The mean changes from baseline in the laboratory measurements were generally small and no clinically relevant changes were observed.

The change from baseline in the mean NRS score in the naldemedine group was statistically significantly higher than that in the placebo group at some time points. These difference between the groups resulted mainly from decrease of NRS score in the placebo group. The changes from baseline in the mean NRS score in the naldemedine group were small and were not clinically meaningful at all of the time points. The change in the mean regular-use opioid dose in the naldemedine group was not statistically significantly different from that in the placebo group.

CONCLUSIONS

Treatment with naldemedine 0.2 mg given orally once daily was effective and demonstrated a statistically significant improvement over placebo in the treatment of OIC in cancer patients, regardless of the opioids dosage. The incidence of overall TEAEs and treatment-related AEs during the study administration was higher with naldemedine compared to placebo. However, most of these AEs were mild or moderate in severity. In addition, the results of the small changes from baseline in the mean NRS score and regular-use opioid dose suggested that naldemedine did not affect the analgesic effect of opioids. Overall, oral daily dose of 0.2 mg naldemedine was effective and generally well tolerated in cancer patients with OIC.

Final Report Date: 30 September 2015

Date of Revision: 2 November 2016