2. SYNOPSIS

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Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: Naldemedine	**Page:**	

Study Title:

A phase 3, open-label study of naldemedine in patients with non-malignant chronic pain and opioid-induced constipation

Investigators and Study Centers: This was a multicenter study conducted at 21 study centers in Japan.

Publication (Reference): Not applicable

Studied Period:

[redacted] February 2014 (first patient enrolled) to [redacted] September 2015 (last patient completed)

Phase of Development: 3

Objectives:

The primary objective of the study:

- To evaluate the long-term safety of naldemedine in patients with chronic non-cancer pain and opioid-induced constipation (OIC).

The secondary objectives of the study:

- To evaluate the efficacy of naldemedine.
- To assess the pharmacokinetic profiles of naldemedine and its metabolite (nor-naldemedine).

Methodology:

This was a multicenter, single-arm, open-label study in which 40 patients with chronic non-cancer pain and OIC were to be enrolled. The study consisted of 3 parts: 2- to 4-week Screening Period, 48-week Treatment Period (2-week Treatment Period 1 followed by 46-week Treatment Period 2), and 2-week Follow-up Period. Eligible patients received a single tablet of 0.2 mg of naldemedine once daily during 48-week Treatment Period.

Number of Patients (Planned and Analyzed):

Planned: 40

Enrolled: 43

Full analysis set (FAS): 42

Safety Population (for analysis of naldemedine): 43

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Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: Naldemedine	**Page:**	

Diagnosis and Criteria for Inclusion:

Patients with chronic non-cancer pain and OIC who satisfied the following criteria were included in the study.

Inclusion Criteria:

1. Patients aged 20 years or older at the time of informed consent.
2. Men and women, outpatients.
3. Patients whose pain had persisted for 3 months or longer and who had been diagnosed with any kind of chronic non-cancer pain.
4. Patients had to be treated with opioids (regular-use) for at least 2 weeks prior to the Screening enrollment, and be treated with a stable opioid regimen for 14 days prior to the Treatment enrollment (100% to 150% of the dose of regular-use opioids 14 days prior to the day of Treatment enrollment).
5. Patients who were currently receiving laxatives for OIC, or who had been treated with laxatives and were not currently receiving laxatives due to insufficient efficacy or other reasons.
6. Patients whose frequency of SBMs was 5 times or less during 14 consecutive days prior to the Treatment enrollment and those who experienced one or more of the following bowel symptoms in 25% or more of all bowel movements (BMs) without regard to the use of the rescue-use laxatives. A BM occurring within 24 hours after rescue-use laxative therapy was not considered an SBM.
   - Straining during BM (2 [moderate] or above on the straining symptom score)
   - Feeling of incomplete evacuation
   - Passage of hard stools or pellets (1 or 2 on Bristol Stool Form Scale)
7. Patients who were able to receive oral intake of drugs, food and beverages.
8. Patients who were able to assess condition using the patient's diary (if the patient was capable of assessment using patient's diary but cannot record the assessment on the patient's diary, recording by someone on behalf of the patient will be allowed).
9. Patients who received explanation about the study and provided written informed consent to participate in the study.

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Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: Naldemedine	**Page:**	

Exclusion Criteria:

1. Patients who had a history of active treatment for cancer within the last 2 years prior to the Screening enrollment (except for basal cell or squamous cell carcinoma of the skin that had been successfully resected).
2. Patients who had evidence of significant structural abnormalities of the gastrointestinal (GI) tract (such as mechanical ileus), diseases affecting intestinal transit (such as paralytic ileus, uncontrolled hyperthyroidism or hypothyroidism), irritable bowel syndrome (IBS), inflammatory bowel disease (such as ulcerative colitis, Crohn's disease), active diverticular disease, pelvic disorder which could cause constipation (such as uterine prolapse, rectal prolapse, and uterine myoma affecting bowel movement). Patients whose medical histories were considered to have an effect on GI function by the investigator/subinvestigator, even if the patients had been cured of these diseases.
3. Patients who had undergone surgery or intervention (such as nerve block) which was considered to have effects on the GI functions within 28 days prior to the Screening enrollment, or who were scheduled to receive such surgery or intervention from Screening Period to the completion of Treatment Period.
4. Patients who had undergone radical surgery for pain site within 28 days prior to the Screening enrollment, or who were scheduled to receive such surgery or intervention from Screening Period to the completion of Treatment Period.
5. Patients who had evidence of ileus within 1 year prior to the Screening enrollment.
6. Patients who had history of any potential non-opioid cause of bowel dysfunction that might be a major contributor to the constipation.
7. Patients who had never taken laxatives for the treatment of OIC.
8. Patients who had reported no BMs for 7 consecutive days prior to the Treatment enrollment.
9. Patients with any of the following laboratory test results within 7 days prior to the Treatment enrollment:
   a. >2 × upper limit of normal (ULN) for alanine aminotransferase (ALT) or aspartate aminotransferase (AST)
   b. >1.5 × ULN for total bilirubin
   c. >1.5 × ULN for serum creatinine.

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Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: Naldemedine	**Page:**	

10. Patients who had fecal disimpaction during Screening Period or who were scheduled to have such treatment by the completion of Treatment Period.
11. Patients with artificial stoma.
12. Patients who were found to have medically significant cardiovascular, respiratory, hepatic, or renal functional disorders based on the medical history, laboratory tests, ECG, and physical findings, and who were considered ineligible for the study by the investigator/subinvestigator.
13. Patients who were known or suspected to have hypersensitivity to naldemedine, naltrexone, methylnaltrexone, naloxone, or any other opioid antagonist.
14. Patients who were currently receiving opioid receptor antagonists or partial agonists, or who were scheduled to receive such medicine by the completion of Treatment Period.
15. Patients who were pregnant or lactating, or who expected own pregnancy or partner's pregnancy during the study period.
16. Patients who were considered to be unable or unwilling to use appropriate birth control methods from the Screening enrollment to 30 days after the last dosing of the study drug.
17. Patients who had received any other investigational drug(s) within 28 days prior to the Screening enrollment.
18. Patients who had participated in naldemedine (S-297995) trials and had received the study drug.
19. Patients who were considered ineligible for the study by the investigator/subinvestigator based on the concomitant therapy and medical findings.

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]).

Naldemedine (naldemedine 0.1 mg tablet); 0.1 mg/day; oral; the lot number was [redacted] (Packaged Lot No. [redacted]).

During Treatment Period 2, when the investigator/subinvestigator was concerned about the reduction of patients' QOL by GI adverse event (AE) (as a guide, moderate or severe GI AE) such as diarrhea and abdominal pain, temporary discontinuation or dose reduction of naldemedine was allowed according to the AE handling procedure.

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Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: Naldemedine	**Page:**	

When the opioids were temporarily discontinued, naldemedine was also temporarily discontinued. Naldemedine was restarted at the same time as the opioids were restarted. When the discontinuation period of opioid was over 28 days, the patient had to be removed from study participation.

Duration of Treatment: 48 weeks

Reference Therapy, Dose and Mode of Administration, Lot Number:
Reference therapy was not set.

Criteria for Evaluation:

Efficacy Assessments:

- Proportion of SBM responders for Treatment Period 1 (2 weeks): An SBM responder was defined as a patient with 3 or more SBMs per week and an increase of 1 or more SBM per week from baseline.
- Proportion of complete spontaneous bowel movement (CSBM) responders for Treatment Period 1 (2 weeks): A CSBM responder was defined as a patient with SBM accompanied by feeling of complete evacuation.
- Proportion of SBM responders (or CSBM responders) in each week for Treatment Period 1 (2 weeks).
- Change from baseline in the frequency of SBMs (or CSBMs) per week for Treatment Period 1 (2 weeks).
- Weekly change from baseline in frequency of SBMs for Treatment Period 1 (2 weeks).
- Time to the first SBM (or CSBM) after the first administration of the study drug.
- Daily change from baseline in the frequency of SBMs for Treatment Period 1 (2 weeks).
- Change from baseline in the number of days with at least 1 SBM (or CSBM) per week for Treatment Period 1 (2 weeks).
- 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.
- Change from baseline in the frequency of SBMs with Bristol Stool Form Scale (BSS) score of 3 or 4 per week for Treatment Period 1 (2 weeks).
- Change from baseline in the frequency of SBMs per week without straining (straining score of 0 or 1 during BM) for Treatment Period 1 (2 weeks).

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Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: Naldemedine	**Page:**	

- Change from baseline in the frequency of the use of rescue-use laxatives per week for Treatment Period 1 (2 weeks).
- Weekly change from baseline in the abdominal bloating or abdominal discomfort scores for Treatment Period 1 (2 weeks).
- Change from baseline to each observation time point in Patient Assessment of Constipation Symptoms (PAC-SYM) or Patient Assessment of Constipation Quality of Life (PAC-QOL).
- Proportion of patients with PAC-SYM responder or PAC-QOL responder.

Safety Assessment:

AEs, Major Adverse Cardiac Events (MACE), pain intensity (Numeric Rating Scale [NRS]), Clinical Opioid Withdrawal Scale (COWS) assessment, dose of regular-use opioid, vital signs, ECG findings, clinical laboratory tests.

Pharmacokinetics Assessment:

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

Statistical Methods:

Unless otherwise noted, continuous variables were summarized by using the number of subjects with non-missing observations, arithmetic mean (mean), standard deviation (SD), median, minimum, and maximum values as descriptive statistics; categorical variables were summarized by using the frequency count and the percentage of patients in each category as descriptive statistics.

All statistical tests were performed at the 0.05 significance level using two-sided tests, except where otherwise noted. No multiplicity adjustment was applied for the statistical tests.

Efficacy Analyses:

Proportion of SBM/CSBM responder and changes in the frequency of SBMs/CSBMs and its 95% confidence interval (CI) were calculated for Treatment Period 1 (2 week).

Kaplan-Meier plot of the time to the first SBM/CSBM was made, and the median of the time to the first SBM/CSBM and its 95% CI was calculated.

Summary statistics and changes in the abdominal bloating and abdominal discomfort scores and the frequency of the use of rescue-use laxatives per week were calculated for Treatment Period 1.

The mean of overall score of PAC-SYM was summarized by scheduled time point, and change from baseline was also summarized. The mean overall score at each Visit and

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Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: Naldemedine	**Page:**	

last observation time point (Visit 15 or early termination visit) was compared with baseline by using the paired t-test.

The change in the mean score for each domain of PAC-SYM, the mean overall score for PAC-QOL and the mean score for each domain of PAC-QOL were analyzed in a similar way.

A responder for PAC-SYM was defined as a patient who achieved an improvement in the mean overall score of at least 1 point from baseline. The proportion of responders for overall PAC-SYM was summarized at each Visit and last observation time point. The proportion of responders for the dissatisfaction domain of PAC-QOL was analyzed in a similar way.

Safety Analyses:

AEs were classified by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) Version 16.1. AEs which occurred/worsened after initiation of the study were termed treatment-emergent adverse event (TEAEs) and the number of patients with TEAEs and that of TEAEs were tabulated. The incidence of TEAEs and the 95% CI were calculated. The CI for the incidence was calculated using the Clopper-Pearson method. Treatment-related AEs (AEs which were considered related to the study drug by the investigator) were summarized in a similar way. The fatal TEAEs (deaths), serious (non-fatal) TEAEs (SAEs), TEAEs leading to the withdrawal of study drug, the significant TEAEs, and treatment-related AEs were tabulated in a similar fashion. The incidence of MACE and its 95% CI were calculated. MACE were categorized by using Standardised MedDRA Queries (SMQ).

Summary of Results

Efficacy:

A total of 42 patients were included in the FAS.

The proportion of SBM and CSBM responders for Treatment Period 1 was 81.0% and 42.9%, respectively. The proportion of SBM and CSBM responders for each week were 85.7% and 76.2% at Weeks 1 and 2, and 52.4% and 40.5% at Weeks 1 and 2, respectively.

The mean change from baseline in the frequency of SBMs and CSBMs per week for Treatment Period 1 was 5.42 SBMs and 2.74 CSBMs, respectively. The mean change from baseline to each week in the frequency of SBMs and CSBMs per week was 6.24 and 4.60 SBMs at Weeks 1 and 2, and 3.19 and 2.29 CSBMs at Weeks 1 and 2, respectively

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Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: Naldemedine	**Page:**	

The median time to the first SBM and CSBM after the first administration of the study drug was 8.41 and 28.22 hours, respectively.

The mean change from baseline in the frequency of SBMs on each observation day for Treatment Period 1 was in the range of 0.47 to 1.49. The mean change from baseline in the number of days with at least 1 SBM and CSBM per week for Treatment Period 1 was 3.20 and 1.98 days, respectively.

The proportion of patients with at least 1 SBM at 4, 8, 12 and 24 hours after the first administration of the study drug was 40.5%, 47.6%, 57.1%, and 78.6%, respectively. The proportion of patients with at least 1 CSBM at 4, 8, 12 and 24 hours after the first administration of the study drug was 19.0%, 33.3%, 40.5%, and 50.0%, respectively.

The mean change from baseline in the frequency of SBMs with BSS of 3 or 4 per week for Treatment Period 1 was 1.93 SBMs. The mean change from baseline to each week in the frequency of SBMs with BSS of 3 or 4 per week was 1.86 SBMs at Week 1 and 2.00 SBMs at Week 2.

The mean change from baseline in the frequency of SBMs without straining per week for Treatment Period 1 was 2.86 SBMs. The mean change from baseline to each week in the frequency of SBMs without straining per week was 3.24 SBMs at Week 1 and 2.48 SBMs at Week 2.

The mean change from baseline in the frequency of rescue-use of laxatives per week for Treatment Period 1 was −2.08.

The weekly change from baseline in the abdominal bloating scores for Treatment Period 1 was −0.33 at Week 1 and −0.37 at Week 2. The weekly change from baseline in the abdominal discomfort scores for Treatment Period 1 was −0.21 at Week 1 and −0.35 at Week 2.

The PAC-SYM mean scores for overall and the 3 domains of PAC-SYM significantly improved from baseline at all observation time points.

The PAC-QOL mean scores for overall and the 4 domains of PAC-QOL significantly improved from baseline at all observation time points.

The proportion of responders for overall PAC-SYM was in the range of 23.8% to 48.5% at each time point throughout Treatment Period. The proportion of responders for dissatisfaction domain of PAC-QOL was in the range of 48.6% to 66.7% at each time point throughout Treatment Period.

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Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: Naldemedine	**Page:**	

Safety:

A total of 43 patients were enrolled in the study. All of them received the study drug and were included in the Safety Population.

There was 1 patient (2.3%) who died after the initiation of study drug administration. An administrative autopsy could not reveal the cause of death. As the patient had medical conditions of venous thrombosis in the lower extremities and pulmonary embolism prior to the study enrollment, the death was suspected to be associated with these conditions by the investigator. In addition, because of the mechanism of action of naldemedine and the long dosing duration, the investigator considered that the death was not related to the study drug. Five other SAEs in 4 patients (9.3%) were reported after the initiation of study drug administration: urethral stenosis, ileus, and urinary tract infection in 1 patient each; and cerebral infarction and cholelithiasis in 1 patient. The SOCs of these events were different from each other. All SAEs were considered not related to the study drug by the investigator.

Three patients (7.0%) discontinued the study drug because of death, ileus, or anal fissure after the initiation of study drug administration. These TEAEs were considered not related to the study drug by the investigator. The ileus and anal fissure recovered/resolved.

A total of 136 TEAEs were reported in 38 patients (88.4%) and a total of 20 treatment-related AEs were reported in 12 patients (27.9%) after the initiation of study drug administration.

The most frequent TEAEs for Treatment Period 1 were with respect to the SOC of Gastrointestinal Disorders (18.6%). The most frequently reported TEAEs occurring after the initiation of study drug administration were with respect to the SOC of Gastrointestinal Disorders (53.5%), followed by SOC of Infections and Infestations (41.9%). The most frequently reported TEAEs occurring after the initiation of study drug administration were nasopharyngitis (25.6%), followed by diarrhea (23.3%).

The most frequent treatment-related AEs for Treatment Period 1 were with respect to the SOC of Gastrointestinal Disorders (16.3%). The treatment-related AEs occurring after the initiation of study drug administration were similar to those for Treatment Period 1. The most frequently reported treatment-related AEs occurring after the initiation of study drug administration were diarrhea (14.0%), followed by abdominal pain (7.0%).

Three TEAEs (cerebral infarction in 1 patient and blood creatine phosphokinase increased in 2 patients) were categorized as MACE cases. The cerebral infarction was

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Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: Naldemedine	**Page:**	

severe and serious. The cerebral infarction was considered not related to the study drug by the investigator since the patient had concurrent condition of old myocardial infarction, hypertension, and hyperlipidemia and the event recovered/resolved with continuing the administration of naldemedine. Both cases of blood creatine phosphokinase increased were mild and considered not related to the study drug by the investigator.

One case of drug withdrawal syndrome was reported. The drug withdrawal syndrome was considered due to a dose reduction of concomitant opioid and not related to the study drug by the investigator. The drug withdrawal syndrome recovered/resolved with a dose increase of the concomitant opioid. All patients reported a total COWS score of < 5 at all scheduled time points. One patient reported a total COWS score of 6 at an unscheduled time point (Day 5). The investigator considered that the COWS escalation was due to the patient's physiological variations and environmental condition and that there was no relationship with opioid withdrawal syndrome.

The mean changes from baseline in the laboratory measurements were generally small and no clinically relevant changes were observed. There were no cases of AST or ALT > 3 × ULN, and total bilirubin > 2 × ULN, which would correspond to "Hy's law case".

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

The changes from baseline in the mean NRS score were small and were not clinically meaningful at all of the time points. The dose of regular-use opioids generally stayed unchanged during the study.

Pharmacokinetics:
At Visit 3 (Day 15), the mean (minimum – maximum) elapsed time from dosing to PK sampling time was 18.49 (2.53 – 35.77) hours and the mean (minimum – maximum) plasma concentration was 1.02 (0.0256 – 3.27) ng/mL for naldemedine and 0.200 (0.00 – 0.397) ng/mL for nor-naldemedine for the PK Concentration Population.

CONCLUSIONS

Of the 43 patients enrolled in the study, 31 (72.1%) patients completed the study. Most of the enrolled patients received the study drug at the stable dose of 0.2 mg during the study treatment. None of fatal, non-fatal SAEs, MACE cases were considered related to the study drug. No clinically meaningful findings or changes were observed in the safety measurement parameters including laboratory measurements, ECG, vital signs, COWS score, NRS score, or the dose of regular-use opioids.

The efficacy endpoints based on SBM and CSBM showed that naldemedine was effective during the 2-week Treatment Period 1. In addition, the PAC-SYM and PAC-

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Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: Naldemedine	**Page:**	
QOL scores significantly improved from baseline at all observation time points throughout the 48-week Treatment Period, showing the durability of efficacy. Overall, the oral daily dose of 0.2 mg naldemedine was generally well tolerated and effective in patients with chronic non-cancer pain and OIC in this long-term study.		
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