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, open-label study of naldemedine in patients with non-malignant chronic pain and opioid-induced constipation receiving S-8117 (oxycodone hydrochloride hydrate)

Investigators and Study Centers: This was a multicenter study conducted at 9 study centers in Japan.

Publication (Reference): Not applicable

Studied Period: [redacted] June 2014 (first patient enrolled) to [redacted] November 2015 (last patient completed)

Phase of Development: 3

Objectives:

The primary objective of the study:

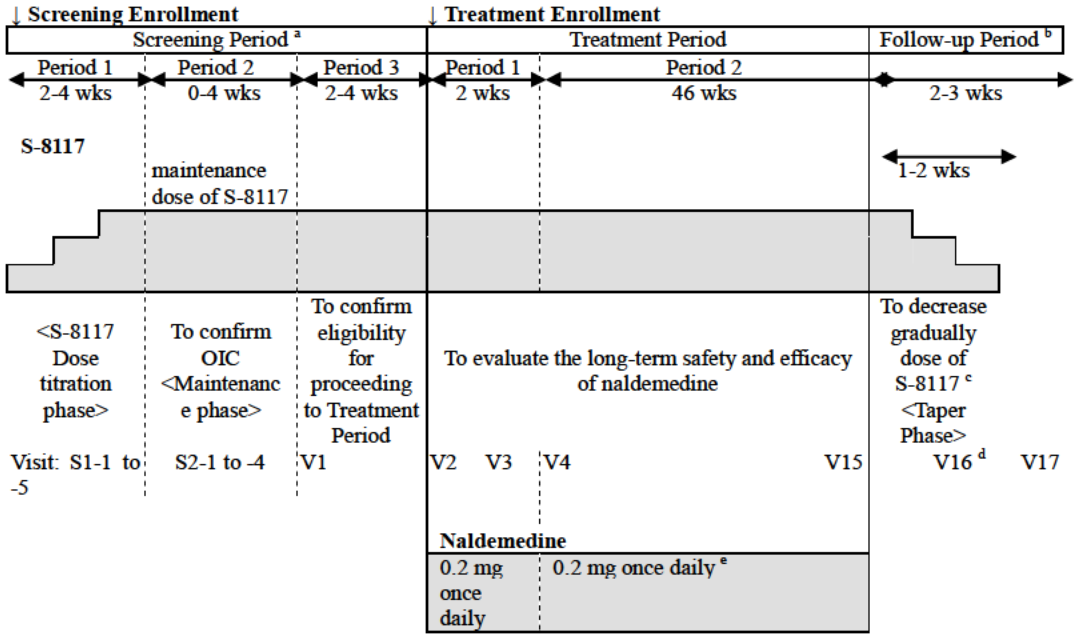
- To evaluate the long-term safety of naldemedine in patients with chronic non-cancer pain and opioid-induced constipation (OIC) receiving S-8117 (oxycodone hydrochloride hydrate).

The secondary objectives of the study:

- To evaluate the efficacy of naldemedine.
- To evaluate the safety and efficacy of S-8117.
- To assess the pharmacokinetic profiles of naldemedine and its metabolite (nor-naldemedine).

Methodology: This was a multicenter, single-arm, open-label study in which 10 patients who had received S-8117 for treatment of chronic non-cancer pain and had confirmed the occurrence of OIC due to S-8117 regimen were to be enrolled. Opioid analgesics other than S-8117 were not allowed. The study consisted of 3 parts: 4- to 12-week Screening Period (Period 1, Period 2, and Period 3), 48-week Treatment Period (Period 1 and Period 2), and 2- to 3-week Follow-up Period.

The study schematic is shown below.



a If patients discontinued the S-8117 regimen during Screening Period, they proceeded to Follow-up Period.

b When the investigator/subinvestigator decided not to switch S-8117 treatment to another opioid analgesic after the completion of Treatment Period or early termination of S-8117 regimen (including termination during Screening Period), the patients were to initiate Taper Phase where the dose of S-8117 was decreased gradually and had a follow-up visit 1 week after Taper Phase. When the investigator/subinvestigator decided to switch S-8117 treatment to another opioid analgesic, the patients had a follow-up visit 2 weeks after the completion of Treatment Period or early termination of S-8117 regimen (including termination during Screening Period).

c When the investigator/subinvestigator decided not to switch S-8117 treatment to another opioid analgesic after the completion of Treatment Period or early termination of S-8117 regimen (including termination during Screening Period), the patients initiated a Taper phase where the dose of S-8117 was decreased gradually over a 7-day period. If the investigator/subinvestigator determined that Taper Phase needed to be extended because of high daily dose of S-8117 etc., Taper Phase was allowed to be extended for up to 14 days.

d If patients received the tapered dose of S-8117, patients had the specified examinations at the completion of Taper Phase.

e When the investigator/subinvestigator was concerned about the reduction of patients' QOL by gastrointestinal (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 as below.

First, rescue-use laxatives had not to be used and regular-use laxatives (if used) were to reduce or discontinued.

If the AE persisted even after laxatives had been discontinued, then naldemedine was allowed to be discontinued temporarily (up to 2 weeks) or its dose was allowed to reduce to 0.1 mg at the discretion of the investigator/subinvestigator.

If the AE persisted even after naldemedine had been reduced to 0.1 mg, naldemedine was allowed to be discontinued temporarily (up to 2 weeks).

If the AE resolved after naldemedine had been discontinued, either 0.1 or 0.2 mg of naldemedine

was restarted as promptly as possible.

If constipation worsened during the treatment of naldemedine at the dose of 0.1 mg, the dose was allowed to increase to 0.2 mg after resolution of the AE leading to the dose reduction or temporary discontinuation.

Number of Patients (Planned and Analyzed):

Planned: 10

Enrolled: 12

Full analysis set (FAS)-1 (for analysis of naldemedine): 10

FAS-2 (for analysis of S-8117): 12

Safety Population 1 (for analysis of naldemedine): 10

Safety Population 2 (for analysis of S-8117): 12

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:

Screening Period 1:

1. Patients aged between ≥ 20 and < 80 years at the time of informed consent.
2. Male and female outpatients.
3. Patients who had persistent chronic non-cancer pain for 3 months or longer and who met any of the following criteria:
   - Patients who had to be treated with non-opioid analgesic as an oral, patch, or suppository formulation (including analgesic adjuvants used for analgesia), oral tramadol preparations, oral codeine preparations, or buprenorphine patch preparations for the treatment of chronic non-cancer pain for at least 14 days prior to the Screening enrollment, and who had pain with the average Brief Pain Inventory (BPI) severity score of 4 or higher for the 24 hours prior to the Screening enrollment. If the patients were treated with oral codeine preparations, the doses of codeine had to be 800 mg/day or lower.
   - Patients who had to be treated with oral morphine preparations at the dose of 120 mg/day or lower or fentanyl patch preparations at the dose of 100 μg/hr* or lower for the treatment of chronic non-cancer pain for at least 14 days prior to the Screening enrollment, regardless of the 24-hour average BPI severity score.
     *: Equivalent to Durotep® MT patch 16.8 mg, OneDuro® patch 6.7 mg.
4. Patients who were able to assess condition using the patient's diary (if the patient was capable of assessment using patient's diary but could not record the assessment on the patient's diary, recording by someone on behalf of the patient was allowed).
5. Patients who were able to receive oral intake of drugs, food and beverages.
6. Patients who received explanation about the study and provided written informed consent to participate in the study.

Screening Period 2:

1. Patients who had been confirmed the maintenance dose of S-8117 during Screening Period 1.

Screening Period 3:

1. Patients who had been confirmed the occurrence of OIC due to S-8117 regimen based on patient's spontaneous complain until the end of Screening Period 2.

Treatment Period:

1. Patients had to be treated with a stable S-8117 regimen (100% to 150% of the dose of S-8117 taken 14 days prior to the Treatment enrollment) for 14 days prior to the Treatment enrollment.
2. Patients whose frequency of spontaneous bowel movements (SBMs) were 5 times or less during the 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).
3. Patients who were currently receiving laxatives for OIC, or who had been treated with laxatives and did not currently receive laxatives due to insufficient efficacy or other reasons.

Exclusion Criteria:

Screening Period 1:

1. Patients who had 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 and hypothyroidism), irritable bowel syndrome (IBS), inflammatory bowel disease (such as ulcerative colitis, Crohn's disease), active diverticular disease, or pelvic disorder which could cause constipation (such as uterine prolapse, rectal prolapse, and uterine myoma affecting BM). 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 any of the following laboratory test results at the Screening enrollment (for the last tests if several tests had been performed):
   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.
7. Patients with artificial stoma.
8. Patients who had any psychiatric disorder (eg, depression, schizophrenia) that was currently being treated.
9. Patients who had a history of drug abuse, dependence, or alcohol dependence, or might have presence of abuse or dependence.
10. Patients who had been detected phencyclidine, cocaine, stimulant drug or marijuana in urinalysis.
11. Patients who had a history or presence of allergy or hypersensitivity to opium alkaloids.
12. Patients who had absolute or relative contraindications to oxycodone or morphine preparations as follows:
    - Severe respiratory depression or severe chronic obstructive lung disease
    - Current bronchial asthma attacks
    - Heart failure secondary to chronic lung disease
    - Current convulsive status (status epilepticus, tetanus or strychnine intoxication)
    - Acute alcoholism
    - Hemorrhagic colitis
    - Bacterial diarrhea.
13. Patients who had developed clinically significant adverse reactions when they had received opioid analgesic and any of the following drugs, and who were receiving these drugs or were scheduled to receive them during the study period: CNS depressant drugs (phenothiazine derivatives, barbiturates, other antipsychotic drugs, sedative hypnotics, and antiepileptic drugs), inhalation anesthetics, monoamine oxidase (MAO) inhibitors, tricyclic antidepressants, β-blockers, coumarin anticoagulants, anticholinergic drugs, cimetidine, etc.
14. Patients who had severe lactose intolerance.
15. Patients who were found to have medically significant cardiovascular, respiratory, hepatic, or renal functional disorders from the medical history, laboratory tests, ECG, and physical findings, and who had been considered ineligible for the study by the investigator/subinvestigator.
16. Diabetes patients with extremely poor blood glucose control.
17. Patients who were known or suspected to have hypersensitivity to naldemedine, naltrexone, methylnaltrexone, naloxone, or any other opioid antagonists.

18. Patients who were scheduled to receive opioid receptor antagonists or partial agonists by the completion of Treatment Period.
19. Patients who were pregnant or lactating, or who expected own pregnancy or partner's pregnancy during the study period.
20. 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.
21. Patients who had received any other investigational drug(s) within 28 days prior to the Screening enrollment.
22. Patients who had participated in S-8117 or naldemedine (S-297995) trials and had received the study drug.
23. Patients who were considered ineligible for the study by the investigator/subinvestigator based on the concomitant therapy and medical findings.

Screening Period 2:

No exclusion criteria.

Screening Period 3:

1. Patients who had a history of any potential non-opioid cause of bowel dysfunction that might be a major contributor to the constipation.
2. Patients who had never taken laxatives for the treatment of OIC.

Treatment Period:

1. Patients who had reported no BMs for 7 consecutive days prior to the Treatment enrollment.
2. Patients who had fecal disimpaction during Screening Period or who were scheduled to have such treatment by the completion of Treatment Period.

Test Product 1, 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, naldemedine was to be orally administered at a dose of 0.2 mg once daily. For 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.

When S-8117 was temporarily discontinued, naldemedine was also temporarily discontinued. Naldemedine was restarted at the same time as S-8117 was restarted. In case that the discontinuation period of S-8117 was over 28 days, the patient had to be removed from study participation.

Duration of Treatment: 48 weeks

Test Product 2, Dose and Mode of Administration, Lot Number:

S-8117 (S-8117 5-mg tablet), oral, the lot numbers were [redacted] (Packaged Lot No. [redacted]) and [redacted] (Packaged Lot No. [redacted]).

S-8117 (S-8117 10-mg tablet), oral, the lot numbers were [redacted] (Packaged Lot No. [redacted]) and [redacted] (Packaged Lot No. [redacted]).

S-8117 (S-8117 20-mg tablet), oral, the lot numbers was [redacted] (Packaged Lot No. [redacted]).

Screening Period (for 4 to 12 weeks):

Screening Period 1 (for 2 to 4 weeks [14 to 28 days] as a dose titration phase , up to 32 days as needed):

In line with the following switching timing[a] after the final dose of the preceding analgesic (in the case of a patch, after the patch was removed), the opioid treatment was switched from preceding analgesic to S-8117 twice-daily, every 12 hours, at the following initial dose[b] of S-8117 by the day after the Screening enrollment. Fifteen days after receiving the initial dose of S-8117, the dose of S-8117 was titrated up or down for each patient until the investigator/subinvestigator considered that the patient met the criteria[c] to proceed to Screening Period 2 as a dose titration phase based on the dose escalation or reduction criteria. When the patient met the criteria[c] to proceed to Screening Period 2, the patient proceeded to Screening Period 2. The dose of S-8117 treated at the end of Screening Period 1 was defined as a maintenance dose. Patients for whom a maintenance dose had been determined and confirmed the occurrence of OIC (based on patient's claim) due to S-8117 regimen during Screening Period 1 were allowed to proceed to Screening Period 3 directly.

If the patients did not meet the criteria[c] to proceed to Screening Period 2 within 32 days after the initial dose of S-8117, or if the investigator/subinvestigator needed to discontinue the study treatment due to some other reason, the S-8117 regimen was to be discontinued and was to be switched to an appropriate therapy. The patients proceeded to Follow-up Period.

a Switching timing
The initial dose of S-8117 was to be administered after the following length of time depending on the opioid analgesic used most recently.
* Oral morphine preparations: At least 4 hours after the last dose
* Oral tramadol preparations: At least 4 hours after the last dose
* Oral codeine preparations: At least 6 hours after the last dose
* Buprenorphine patch preparations: At least 24 hours after the patch was removed
* Fentanyl patch preparations: At least 17 hours after the patch was removed

b Initial dose
* Patients who were switched from any opioid analgesic:
The initial dose was to be half of the daily dose which was calculated using the attached conversion table based on the regular dose of the opioid analgesic used before S-8117 regimen.
* Patients without any opioid analgesic:
The initial dose was to be 5 mg per administration.

c Criteria to proceed to Screening Period 2 (for decision of maintenance dose of S-8117):
If the patients met all of the following criteria on or after 15 days of the day when the patients received the initial dose of S-8117, the patients proceeded to Screening Period 2.
* The regular dose for 7 consecutive days prior to the assessment had to be treated with a stable opioid regimen.
* The score of the 24-hour average BPI severity score for 3 consecutive days prior to the assessment (the day of assessment, the day before assessment, and before 2 days of assessment) had to have improved to 3 or lower, or by at least 30% compared to that at the Screening enrollment.
* Any AEs experienced for 3 consecutive days prior to the assessment had to have been tolerable.

Screening Period 2 (for 0 to 4 weeks as a maintenance phase):

The patients received S-8117 at the dose which had met the criteria to proceed to Screening Period 2, twice daily, every 12 hours, for up to 4 weeks until the patients met the inclusion/exclusion criteria to proceed to Screening Period 3. If OIC had occurred during Screening Period 1 (based on patient's claim), the patients was allowed to proceed to Screening Period 3 directly without Screening Period 2. The dose of S-8117 was allowed to be titrated up or down at the discretion of the investigator/subinvestigator by the physical examination findings based on the dose escalation or reduction criteria. If the patients did not meet the criteria to proceed to Screening Period 3 within 4 weeks, or if the investigator/subinvestigator needed to discontinue the study treatment due to some other reasons, the S-8117 regimen was to be discontinued and was to be switched to an appropriate therapy. The patients proceeded to Follow-up Period.

Screening Period 3 (for 2 to 4 weeks as an eligibility confirmation phase):

The patients received S-8117 at the dose used at the end of Screening Period 2 twice daily, every 12 hours, for 2 to 4 weeks until the patients met the criteria to proceed to Treatment Period. The dose of S-8117 was allowed to be titrated up or down at the discretion of the investigator/subinvestigator by the physical examination findings based on the dose escalation or reduction criteria. For 14 days prior to Treatment Period, the patients was to be treated with S-8117 dose regimen of 100% to 150% of the dose of S-8117 treated on the day of 14 days prior to the Treatment enrollment, according to the criterion to proceed to Treatment Period. If the patients did not to

meet the criteria to proceed to Treatment Period within 2 to 4 weeks, or the investigator/subinvestigator needed to discontinue the study treatment due to some other reasons, the S-8117 regimen was to be discontinued and was to be switched to an appropriate therapy. The patients proceeded to Follow-up Period.

Treatment Period (for 48 weeks):

Treatment Period 1 (for 2 weeks):

The patients received S-8117 at the dose used at the end of Screening Period 3 twice daily, every 12 hours, for 2 weeks. If the investigator/subinvestigator considered that the patients needed the dose escalation of S-8117 due to reasons such as aggravated pain, the dose of S-8117 was allowed to be titrated up appropriately based on the dose escalation criteria.

Treatment Period 2 (for 46 weeks):

The patients continued to receive S-8117 at the dose used at the end of Treatment Period 1 twice daily, every 12 hours, for 46 weeks. If the investigator/subinvestigator considered that the patients needed the dose change of S-8117 due to reasons such as aggravated pain and AEs, the dose of S-8117 was allowed to be titrated up or down appropriately based on the dose escalation or reduction criteria.

The temporary discontinuation of S-8117 regimen was allowed during Treatment Period 2. When the discontinuation period of the S-8117 regimen was over 28 days, the patient had to be withdrawn from the study.

When the patients discontinued the study during the period of Treatment Period and the investigator/subinvestigator decided not to switch S-8117 treatment to another opioid analgesic, the patients proceeded to Follow-up Period and the dose of S-8117 was decreased gradually. On the other hand, when the investigator/subinvestigator decided to switch S-8117 treatment to another opioid analgesic, the investigator/subinvestigator determined the appropriate dose of another opioid analgesic based on the relevant package insert.

Follow-up Period (for 2 to 3 weeks):

When the investigator/subinvestigator decided not to switch S-8117 treatment to another opioid analgesic after the completion of Treatment Period or early termination of S-8117 regimen (including the termination of Screening Period), the dose of S-8117 was decreased gradually twice daily, every 12 hours, over a 7-day period as Taper Phase based on the dose tapering schedule. However, if the investigator/subinvestigator considered that Taper Phase needed to be extended for some reason, eg, high daily dose of S-8117, Taper Phase was allowed to be extended for up to 14 days. Naldemedine had not to be administered during Taper Phase.

Criteria for Evaluation:

Efficacy Assessments for Naldemedine:

- 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 associated with 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 (or CSBMs) for Treatment Period 1 (2 weeks).
- Time to the first SBM (or CSBM) after the first administration of naldemedine.
- 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 naldemedine.
- 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).
- Change from baseline in the frequency 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 PAC-SYM responder or PAC-QOL responder.

Efficacy Assessments for S-8117:

- Change from baseline to each observation time point in the 24-hour average BPI severity score.
- Change from baseline to each observation time point in the average BPI interference score.

Safety Assessment:

AEs, Major Adverse Cardiac Events (MACE), vital signs, ECG findings, clinical laboratory tests, Clinical Opioid Withdrawal Scale (COWS), the 24-hour average BPI severity score*, dose of S-8117*, Subjective Opioid Withdrawal Scale (SOWS)** assessment, drug dependence/addiction assessments (D-2-A, D-2-B)**

* assessment for naldemedine, ** assessment for S-8117

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 the mean changes from baseline in the frequency of SBMs/CSBMs and their 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 were calculated.

Summary statistics and changes in the abdominal bloating and abdominal discomfort scores and the frequency 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 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.

Summary statistics of the 24-hour average BPI severity score and the average BPI interference score, and the change from baseline to each observation time point were calculated.

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 naldemedine administration were termed treatment-emergent adverse events (TEAEs) and the number of patients with TEAEs and the number 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 (TEAEs which were considered related to the study drug by the investigator) were summarized in a similar way. For the AEs occurring

after initiation of S-8117 administration, the number of patients with such AEs as well as the number of such events was separately tabulated. 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

This study defined 2 efficacy analysis populations of the FAS-1 for naldemedine and the FAS-2 for S-8117, and 2 safety analysis populations of the Safety Population 1 for naldemedine and the Safety Population 2 for S-8117. The study results are summarized accordingly below.

Efficacy:

The FAS-1 included all enrolled patients who received at least 1 dose of naldemedine and who had an evaluation of OIC at baseline and at least 1 evaluation of OIC after the initiation of naldemedine administration. The FAS-2 included all enrolled patients who received at least 1 dose of S-8117 and who had an evaluation of BPI-Pain Severity at baseline and at least 1 evaluation of BPI-Pain Severity after the initiation of S-8117 administration. Ten patients were included in the FAS-1and 12 patients were included in the FAS-2.

From the 10 patients in the FAS-1, the following results were obtained:

- The proportion of SBM and CSBM responders for Treatment Period 1 was 90.0% and 50.0%, respectively. The proportion of SBM and CSBM responders for each week were 90.0% at Week 1 and 90.0% Week 2, and 50.0% and 60.0% 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 5.45 SBMs and 3.55 CSBMs, respectively. The mean change in the frequency of SBMs and CSBMs per week from baseline to each week was 6.10 and 4.80 SBMs at Weeks 1 and 2, and 3.70 and 3.40 CSBMs at Weeks 1 and 2, respectively.
- The median time to the first SBM and CSBM after the first administration of naldemedine was 3.35 and 28.19 hours, respectively.
- The mean change from baseline in the frequency of SBMs for each observation day was in the range of 0.31 to 1.71 for Treatment Period 1. The mean change from baseline in the number of days with at least 1 SBM and CSBM per week for Treatment Period 1 was 3.55 and 2.60 days, respectively.
- The proportion of patients with at least 1 SBM at 4, 8, 12 and 24 hours after the first administration of naldemedine was 60.0%, 70.0%, 70.0%, and 80.0%, respectively. The proportion of patients with at least 1 CSBM at 4, 8, 12 and 24 hours after the first administration of naldemedine was 20.0%, 30.0%, 40.0%, and 40.0%, respectively.
- The mean change from baseline in the frequency of SBMs with BSS of 3 or 4 per week for Treatment Period 1 was 2.05 SBMs. The mean change from baseline to each week in the frequency of SBMs with BSS of 3 or 4 per week

was 2.35 SBMs at Week 1 and 1.75 SBMs at Week 2.

- The mean change from baseline in the frequency of SBMs without straining per week for Treatment Period 1 was 4.35 SBMs. The mean change from baseline to each week in the frequency of SBMs without straining per week was 4.90 SBMs at Week 1 and 3.80 SBMs at Week 2.
  The mean change from baseline in the frequency of rescue-use of laxatives per week for Treatment Period 1 was −2.40 times.
- The mean weekly change from baseline in the abdominal bloating scores for Treatment Period 1 was −0.17 at Week 1 and −0.50 at Week 2. The mean weekly change from baseline in the abdominal discomfort scores for Treatment Period 1 was −0.14 at Week 1 and −0.51 at Week 2.
- The changes from baseline in the mean scores for overall, the rectal symptoms domain, and the stool symptoms domain of PAC-SYM significantly improved at almost all observation time points. The changes from baseline in the mean scores for the abdominal symptoms domain of PAC-SYM numerically improved at all observational time points, although there were no statistically significance at several observation time points.
- The changes from baseline in the mean scores for overall, the physical discomfort domain, the psychological discomfort domain, and the worries and concerns domain of PAC-QOL significantly improved at almost all observation time points. The changes from baseline in the mean scores for the dissatisfaction domain of PAC-QOL numerically improved at all observational time points, although there were no statistically significance at several observation time points.
- The proportion of responders for overall PAC-SYM was in the range of 25.0% to 71.4% at each time point throughout the Treatment Period. The proportion of responders for dissatisfaction domain of PAC-QOL was in the range of 25.0% to 71.4% at each time point throughout the Treatment Period.

From the 12 patients in the FAS-2, the following results were obtained:

- The mean change from baseline in the 24-hour average BPI severity scores during Screening Period 1 was −2.75 and the change after Screening Period 2 and 3 was in the range of −4.50 to −0.71.
- The mean change from baseline in the average BPI interference scores during Screening Period 1 was −1.35 and the change after Screening Period 2 and 3 was in the range of −2.07 to −0.50.

Safety:

All 10 patients enrolled in the study received naldemedine and were included in the Safety Population 1. All 12 patients preliminarily enrolled in the study received S−8117 and were included in the Safety Population 2.

From the 10 patients in the Safety Population 1, the following results were obtained:

- The mean exposure to naldemedine was 254.3 days and the dose of naldemedine in all patients was stable at 0.2 mg.

- No deaths or SAEs were reported. One patient (10.0%) discontinued naldemedine because of malaise occurring 49 days after the initiation of naldemedine administration. The malaise was considered not related to naldemedine by the investigator and recovered/resolved.
- A total of 28 TEAEs were reported in 9 patients (90.0%) after the initiation of naldemedine administration. A total of 5 treatment-related AEs were reported in 5 patients (50.0%) after the initiation of naldemedine administration.
- The most frequent TEAEs for Treatment Period 1 were with respect to the SOC of Gastrointestinal Disorders (40.0%). The most frequently reported TEAEs occurring after the initiation of naldemedine administration were with respect to the SOC of Gastrointestinal Disorders (50.0%), followed by SOC of Infections and Infestations (30.0%). The most frequently reported TEAEs occurring after the initiation of naldemedine administration were diarrhea (40.0%), followed by nasopharyngitis (30.0%). Almost all TEAEs were mild or moderate and recovered/resolved or were recovering/resolving.
- The treatment-related AE for Treatment Period 1 was diarrhea (30.0%). The treatment-related AEs occurring after the initiation of naldemedine administration were diarrhea (40.0%) and weight decreased (10.0%).
- No MACE cases or potential MACE cases were reported.
- No cases of drug withdrawal syndrome were reported. The mean total COWS scores and the mean total COWS scores without GI Upset were almost unchanged from baseline to all the assessed time points. No patients with a total COWS score of ≥ 5 were reported.
- No clinically meaningful findings or changes in laboratory tests, vital signs, or ECG were found. There were no cases of AST or ALT > 3 × ULN and total bilirubin > 2 × ULN, which corresponds “Hy's law case”.
- The mean change from baseline (Visit 2) in the 24-hour average BPI severity scores during Treatment Period was in the range of −0.21 to 2.02, but most of the changes were below 1 at almost all time points. The dose of S-8117 generally stayed unchanged during the study.

From the 12 patients in the Safety Population 2, the following results were obtained:

- No deaths or SAEs were reported. Three patients (25.0%) discontinued S−8117: 2 patients were due to malaise occurring 10 and 93 days after the initiation of S-8117 administration and 1 patient was due to constipation, dehydration, and decreased appetite occurring 18 days after the initiation of S−8117 administration. The 2 cases of malaise and 1 case each of constipation, dehydration, and decreased appetite were considered related to S-8117 by the investigator. One case each of blood triglycerides increased and protein urine present was considered not related to S-8117 by the investigator. These TEAEs recovered/resolved or were recovering/resolving.
- A total of 61 TEAEs were reported in 12 patients (100.0%) after the initiation of S-8117 administration. A total of 33 treatment-related AEs were reported in 10 patients (83.3%) after the initiation of S-8117 administration.

- The most frequently reported TEAEs occurring after the initiation of S-8117 administration were with respect to the SOC of Gastrointestinal Disorders (83.3%). The most frequently reported TEAEs occurring after the initiation of S-8117 administration were nausea (66.7%), followed by constipation (50.0%), somnolence, and diarrhea (33.3% each). Almost all TEAEs were mild or moderate and recovered/resolved or were recovering/resolving.
- The most frequently reported treatment-related AEs occurring after the initiation of S-8117 administration were with respect to the SOC of Gastrointestinal Disorders (75.0%). The most frequently reported treatment-related AEs occurring after the initiation of S-8117 administration were nausea (66.7%), followed by constipation (50.0%), decreased appetite, somnolence, vomiting, and malaise (25.0% each). These treatment-related AEs are known to be adverse reactions of opioid analgesics.
- Three patients (25.0%) experienced constipation, nausea, or urine glucose positive during Screening Period which did not recover/not resolve. The constipation and nausea were considered related to S-8117 by the investigator.
- Two patients proceeded to Tapering Period. Only 1 case of nasopharyngitis was reported during Tapering Period.
- No clinically meaningful findings or changes in laboratory tests, vital signs, or ECG were found. There were no Hy's law cases.
- The mean total COWS scores were almost unchanged from baseline to all the assessed time points. No patients with a total COWS score of ≥ 5 were reported. The mean total SOWS score did not increase.
- Based on the drug dependence/addiction assessments (D-2-A, D-2-B), 2 patients (Patient ID [redacted] and [redacted]) met the criteria of possible drug dependence/addiction at several time points and were reported to the IDSMB for S-8117. At every evaluation, the IDSMB judged that it was appropriate to continue the study since the symptoms of these patients were within the physiological reactions, considered due to the effect of S-8117, or were related to the patient's expectation for the analgesic effect of S-8117, and were not due to drug dependence/addiction. Therefore, no drug dependence/addiction for S-8117 was found.

Pharmacokinetics:

At Visit 3 (Day 15), the mean (minimum – maximum) elapsed time from dosing to PK sampling time was 17.92 (12.50 – 24.75) hours and the mean (minimum – maximum) plasma concentration was 1.01 (0.00 – 1.97) ng/mL for naldemedine and 0.238 (0.00 – 0.466) ng/mL for nor-naldemedine for the PK Concentration Population.

CONCLUSIONS

Of the 12 patients preliminarily enrolled in the study, 10 patients completed Screening Period and enrolled in the study. Of the 10 patients enrolled in the study, 7 patients completed the study.

For the naldemedine evaluation, the efficacy endpoints associated with SBM and CSBM showed that naldemedine was effective during the 2-week Treatment Period 1. In addition, the PAC-SYM and PAC-QOL scores showed the durability of efficacy over 48-week Treatment Period. No deaths, SAEs, or MACE cases were reported. No clinically meaningful findings or changes were observed in the safety measurement parameters including laboratory measurements, ECG, vital signs, COWS score, the 24-hour average BPI severity score, and the dose of S-8117.

For the S-8117 evaluation, the efficacy endpoints of the 24-hour average BPI severity score and the average BPI interference score showed an analgesic effect of S-8117 throughout the study. No deaths or SAEs were reported. No clinically meaningful findings or changes were observed in the safety measurement parameters including laboratory measurements, ECG, vital signs, COWS score, SOWS score, D-2-A, and D-2-B.

Overall, the study objectives were achieved in this long-term study. The oral daily dose of 0.2 mg naldemedine was generally well tolerated and effective in patients with chronic non-cancer pain and OIC receiving S-8117. S-8117 was also generally well tolerated and effective in patients with chronic non-cancer pain.

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