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 cancer patients with opioid-induced constipation – extension study –

Investigators and Study Centers: A total of 75 Principal Investigators and 70 study centers

Publication (Reference): none

Studied Period:

[redacted] December 2013 (first patient enrolled) to
April 2015 (last patient completed)

Phase of Development: 3

Objectives:

The primary objective of the study:

To evaluate the long-term safety of naldemedine in cancer patients with opioid-induced constipation (OIC)

The secondary objective of the study:

To evaluate the long-term efficacy of naldemedine in cancer patients with OIC

Methodology: This was an open-label, single-arm study. The patients who participated in the preceding naldemedine phase 3 study in cancer patients with OIC, – randomized, double-blind, placebo-controlled study – (Protocol No. 1331V9236) and completed the treatment period were enrolled.

The target number of subjects who completed the 12-week treatment period was 100. All of the target number of subjects was enrolled in the extension study from the preceding double-blind trial (DBT) study. The direct enrollment to this extension study was planned but was not implemented.

In the Case of Patients Completing the Preceding DBT Study

Patients who had completed the 2-week treatment period in the preceding DBT study and who were willing to participate in the extension study received a full explanation of the study, and written informed consents were obtained from the patients. Eligible patients to enter the extension study were confirmed by the tests and physical examination performed at the End of Treatment in the preceding DBT study (Visit 4 in the preceding DBT study).

The eligible patients received naldemedine 0.2 mg, once daily for 12 weeks (Extension Treatment Period) to evaluate the safety and quality of life (QOL) as an efficacy endpoint. If adverse events (AEs) including diarrhea reduce the patients'

QOL, the temporary discontinuation or dose reduction of naldemedine to 0.1 mg was allowed.

The AEs were followed up for 4 weeks after completion of the Extension Treatment Period as a Follow-up Period.

Diagnosis and Main Criteria for Inclusion:

Cancer patients with OIC who met the following eligibility criteria were included.

1. Patients who had received explanation about the study and provided written informed consent to participate in the study.
2. Patients who participated in the preceding DBT study and completed the 2-week treatment period.
3. Male and female patients, on treatment with regular opioids as inpatients or outpatients.
4. Patients who were capable of oral intake of drugs, food and beverages.
5. Patients who were capable of walking and carrying out daily activities without assistance [2 or below on Performance Status (PS) of Eastern Cooperative Oncology Group (ECOG)].

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

Naldemedine (0.2 mg tablet) for oral administration; lot number was [redacted] (Packaged Lot No. [redacted]).

Naldemedine (0.1 mg tablet) for oral administration; lot number was [redacted] (Packaged Lot No. [redacted]).

Duration of Treatment: 12 weeks

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

Not applicable as this was an open-label study.

Criteria for Evaluation:

Safety Assessment:

Adverse events (AEs), Clinical Opioid Withdrawal Scale (COWS) assessment, major adverse cardiac events (MACE), vital signs, ECG findings, clinical laboratory tests.

Efficacy Assessment:

The change from baseline in score of Patient-Assessment of Constipation Symptoms (PAC-SYM) and Patient-Assessment of Constipation Quality of Life questionnaire (PAC-QOL).

Pharmacokinetics Assessment:

The pharmacokinetics (PK) of naldemedine was not assessed in the study.

Statistical Methods:

Unless otherwise noted, continuous variables were summarized by using the number of subjects with non-missing observations, arithmetic 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.

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 which occurred/worsened after initiation of the extension study are termed TEAEs and the number of patients with TEAEs and that of TEAEs were tabulated. The incidence of TEAEs and the 95% confidence interval were calculated. The confidence interval 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. For the AEs which had persisted from the preceding DBT study, 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 TEAEs related to study drug (treatment-related AEs) were tabulated in a similar fashion. The incidence of MACE and its 95% confidence interval were calculated. MACE were categorized by using Standardised MedDRA Queries (SMQ).

Efficacy:

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 8 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 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 of Results

Enrolled: A total of 131 patients were enrolled in this study (107 patients completed the study treatment and 24 patients were withdrawn from the study). Of the 131 patients enrolled in this study, 62 patients were randomized to the naldemedine group and 69 patients to the placebo group in the preceding DBT study.

Analyzed for safety: 131 patients for safety population.

Analyzed for efficacy: 131 patients for full analysis set (FAS).

Safety:

- One hundred and eighteen patients received the study drug at a stable dose of 0.2 mg during the study treatment (99 patients completed the study treatment, 19 patients were withdrawn from the study). Thirteen patients were temporarily discontinued (8 patients completed the study treatment, 5 patients ended up withdrawal from the study). Four patients were reduced to 0.1 mg during the study treatment.
- A total of 431 TEAEs were reported in 105 (80.2%) of 131 patients enrolled. The incidence was similar between the naldemedine group and the placebo group allocated in the preceding DBT study.

- Forty-four treatment-related AEs were reported in 20 patients (15.3%).
- Fifteen patients (11.5%) died during the study. None of deaths reported were considered related to the study drug. Twenty-three cases of non-fatal SAEs were reported in 14 patients (10.7%). None of the SAEs reported were considered by the investigator to be related to the study drug. Seventeen AEs leading to withdrawal were reported in 12 patients (9.2%). Of these, 4 AEs in 4 patients (3.1%) were considered treatment-related AEs.
- Only 1 case of dysarthria was categorized as MACE by using SMQ. However, it was considered by investigator not related to the study drug but related to increasing the opioid.
- Although 4 COWS elevated cases were reported, none were considered opioid withdrawal by the investigators. The mean change in the total COWS score from baseline to each time point was small and no clinically relevant changes were observed. The similar results were obtained for the analysis of total COWS score excluding the score tied to the question related to gastrointestinal AEs (ie, "GI Upset").
- Hy's Law criteria were defined as AST or ALT > 3 × upper limit of normal (ULN) and total bilirubin > 2 × ULN or PT-INR > 1.5, if PT-INR was measured. Two cases were reported to meet these criteria which were considered not related to the study drug by the investigators.
- The mean changes from baseline in laboratory measurements and vital signs were generally small and no clinically relevant changes were observed.

Efficacy:

A total of 131 patients were included in the FAS.

- The PAC-SYM mean scores at the last observation significantly improved compared to baseline for overall and the 3 domains (abdominal symptoms, rectal symptoms, and stool symptoms). In addition, at each Visit, PAC-SYM mean scores for overall and the 3 domains significantly improved compared to baseline. PAC-SYM mean scores for overall and the 3 domains also significantly improved at the last observation in both naldemedine and placebo groups allocated in the preceding DBT study compared to baseline. In the group treated with placebo in the preceding DBT study, with the exception of Abdominal symptoms at Visit 4, all other scores at each Visit significantly improved compared to baseline. In the group treated with naldemedine 0.2 mg QD in the preceding DBT study, with the exception of Abdominal symptoms at Visit 4 and Rectal symptoms at Visit 4 and Visit 6, all other scores at each Visit significantly improved compared to baseline.
- The PAC-QOL mean scores at the last observation significantly improved compared to baseline for overall and the 4 domains (physical discomfort, psychological discomfort, worries and concerns, and dissatisfaction). In addition, at each Visit, PAC-QOL mean scores for overall and the 4 domains significantly improved compared to baseline. PAC-QOL mean scores for overall and the 4 domains significantly improved at the last observation in both naldemedine and placebo groups allocated in the preceding DBT study compared to baseline. In the group treated with placebo in the preceding DBT study, with the exception of dissatisfaction at Visit 4, all other scores at each Visit significantly improved compared to baseline. In the group treated with naldemedine 0.2 mg QD in the preceding DBT study, all scores at each

Visit significantly improved compared to baseline.

- The proportion of responders for mean overall PAC-SYM score and mean PAC-QOL dissatisfaction score were 18.5% and 35.3%, respectively, at the last observation.

CONCLUSIONS

Naldemedine administered once daily at 0.2 mg for 12 weeks was generally well tolerated in cancer patients with OIC. The safety and tolerability profiles of naldemedine appeared similar to those observed in the cancer population [Phase 2b study (Study 1108V9222) and preceding DBT study (Study 1331V9236)]. The OIC related symptoms evaluated by PAC-SYM and QOL by PAC-QOL improved compared to the baseline. These results suggest that 12-week treatment with naldemedine continues improving OIC symptoms in cancer patients and has a positive effect on QOL.

Final Report Date: 30 September 2015

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