

2. SYNOPSIS

Sponsor: Shionogi	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: Naldemedine		
Name of Active Ingredient: Naldemedine		
Study Title: A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter, Phase 3 Study to Evaluate the Long-term Safety of Naldemedine for the Treatment of Opioid-induced Constipation in Subjects with Non-malignant Chronic Pain Receiving Opioid Therapy		
Investigators: Multicenter		
Study Sites: 195 sites in North America (Canada [8] and the United States [133]), Europe (Belgium [3], Denmark [6], Estonia [2], France [2], Germany [5], Hungary [6], Poland [3], Spain [2], Sweden [1], and the United Kingdom [20]), and Africa/Asia Pacific (Australia [3] and South Africa [1]) randomized at least 1 subject		
Publication (Reference): Not applicable		
Phase of Development: 3		
Study Period: ■ September 2013 (first subject enrolled) to ■ January 2016 (last subject last visit)		
Study Objectives: The primary objective of the study was: <ul style="list-style-type: none"> • To assess the overall safety and tolerability of naldemedine in subjects with non-malignant chronic pain receiving a stable opioid therapy regimen for ≥ 1 month and having opioid-induced constipation (OIC) The secondary objective of the study was: <ul style="list-style-type: none"> • To assess the effects of naldemedine on quality of life (QOL) measures, global satisfaction, opiate withdrawal, pain intensity, OIC symptoms, and laxative use The exploratory objective of the study was: <ul style="list-style-type: none"> • To assess the potential impact of naldemedine on testosterone levels in male subjects 		
Methodology: This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the long-term safety of naldemedine 0.2 mg once daily (QD) versus placebo for the treatment of subjects with non-malignant chronic pain and OIC. The study consisted of 3 parts: a 14- to 28-day Screening Period, a 52-week double-blind, placebo-controlled Treatment Period, and a 14-day Follow-up Period. For analysis purposes, data from the Treatment Period were divided into a Core Period Data Set and a Supplemental Period Data Set. The Core Period Data Set included data for all subjects up to the cutoff date of ■ June 2015. Data from the Core Period Data		

Sponsor: Shionogi	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: Naldemedine		
Name of Active Ingredient: Naldemedine		
<p>Set were summarized in a separate Clinical Study Report to support the United States (US) New Drug Application (NDA). The Supplemental Period Data Set included all remaining data; that is, data for all study visits occurring after the Core Period Data Set cutoff date (June 2015) for subjects who remained in the study. The separation of the Treatment Period into the Core Period Data Set and the Supplemental Period Data Set was for analysis purposes and did not have an impact on study conduct. Subjects and study site personnel remained blinded to subject treatment assignment for the entire duration of the study.</p> <p>This is the final report for this study. This report summarizes all data for all subjects throughout the complete study period.</p> <p>Subjects were screened at Visit 1 (Screening) to assess their eligibility to enter the study. To be eligible, subjects must have had self-reported OIC as defined in the inclusion criteria, a documented medical history indicating nonmalignant chronic pain of at least 3 months in duration, and a stable opioid regimen with a total daily dose (TDD) on average of ≥ 30 mg equivalents of oral morphine sulfate for at least 1 month prior to Screening.</p> <p>Eligibility based on frequency of spontaneous bowel movements (SBMs) and other related parameters was assessed on data collected over a 14-consecutive-day qualifying period during the 28-day Screening Period. To be considered for eligibility, subjects must have recorded in the electronic diary (eDiary) at least 4 days of bowel movement (BM) data for each 7-day period that constituted 1 week of the 14-consecutive-day qualifying period. Subjects who did not meet the eligibility criteria during the first 14 days of the Screening Period were allowed to continue for up to 28 days to allow them to meet the eligibility criteria. Eligible subjects were to have had no more than 4 SBMs total over the 14-consecutive-day qualifying period and no more than 3 SBMs in a given week of the qualifying period. Subjects who met these criteria were to be randomized as soon as possible but no more than 7 days of meeting the eligibility requirements.</p> <p>Regular use of laxatives was not required for study participation. At Screening, subjects who were taking laxatives on a routine/regular basis must have provided the investigator with details of their laxative regimen for the previous 28 days. This laxative regimen was used as the subject's stable laxative regimen throughout the Screening Period and every effort was to be made to avoid changes in frequency or dose to prevent fluctuations in OIC severity. Subjects on a stable laxative regimen at Screening were to remain on that regimen throughout the study. During the qualification period, any BMs that occurred while the subject was on the routine/regular laxative regimen were counted as SBMs.</p>		

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Name of Finished Product: Naldemedine	Volume:	
Name of Active Ingredient: Naldemedine	Page:	
<p>Rescue laxative was allowed and could have been initiated if a subject had not had a BM for any period of more than 72 hours during the Screening or Treatment Periods, regardless of being on a stable laxative regimen or not. A BM occurring within 24 hours after rescue laxative therapy was not considered an SBM. Subjects should also have called the investigator if a BM had not occurred within 5 days.</p> <p>Laxative therapy was provided for those subjects who required laxatives (as a stable regimen or as rescue) during the Screening and Treatment Periods.</p> <p>Approximately 1200 subjects were to be randomized in a 1:1 ratio to receive a single tablet of either 0.2 mg of naldemedine or placebo (600 subjects each) QD in a double-blind manner for 52 weeks. Subjects were to be randomized as soon as possible but within a maximum of 7 days of meeting the eligibility requirements. Randomization was stratified based on the subject's documented opioid use (average TDD during the 14-consecutive-day qualifying period) as follows:</p> <ul style="list-style-type: none"> • 30 to 100 mg equivalents of oral morphine sulfate (average TDD) • > 100 mg equivalents of oral morphine sulfate (average TDD) <p>All subjects who completed the study, withdrew from the study, or terminated the study early were to have had a Follow-up Visit 2 weeks after their last dose of study drug.</p>		
<p>Diagnosis and Main Criteria for Inclusion:</p> <p>The study target population included subjects ≥ 18 to ≤ 80 years of age who had nonmalignant chronic pain and OIC for ≥ 3 months and were receiving a stable opioid regimen for ≥ 1 month.</p> <p>Subjects must have:</p> <ul style="list-style-type: none"> • Been treated with a stable opioid regimen at a total daily dose average of ≥ 30 mg equivalents of oral morphine sulfate for at least 1 month prior to Screening • Had no more than 4 SBMs total over the 14-consecutive-day qualifying period, as well as no more than 3 SBMs in a given week of the qualifying period <p>Male subjects were required to be sterile for 6 months prior to Screening or to agree to use an approved method of contraception. Female subjects were required to be nonpregnant, nonlactating, postmenopausal, surgically sterile, or to agree to use a highly effective method of birth control from the Screening Visit until 28 days after the last dose of study drug.</p>		
<p>Duration of Treatment: 52 weeks</p>		

Sponsor: Shionogi	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Naldemedine	Volume:	
Name of Active Ingredient: Naldemedine	Page:	
Investigational Product, Dose, and Mode of Administration: Naldemedine (0.2-mg tablets) for oral administration; lot numbers [REDACTED] and [REDACTED]		
Reference Product, Dose, and Mode of Administration: Placebo tablets matching naldemedine for oral administration; lot numbers [REDACTED] and [REDACTED]		
<p>Criteria for Evaluation:</p> <p>Primary Endpoint: Assessments of summary measures of treatment-emergent adverse events (TEAEs) were defined as the primary study endpoint.</p> <p>Secondary Safety Endpoints: Safety endpoints included the incidences of TEAEs, serious TEAEs, and TEAEs leading to discontinuation.</p> <p>Other safety endpoints included clinical laboratory evaluations, physical examinations, vital signs, and electrocardiograms (ECGs). Major adverse cardiovascular events (MACE) defined as cardiovascular (CV) death, myocardial infarction, and cerebrovascular accident (stroke), were assessed. Known or suspected CV events were identified, and documentation from these events was sent for review to the an external independent adjudication committee consisting of experienced cardiologists established to provide blinded medical review and adjudicate such events to identify potential MACEs. Clinical safety assessments also included the Clinical Opiate Withdrawal Scale (COWS), the Subjective Opiate Withdrawal Scale (SOWS) to assess opioid withdrawal, opioid dose and an 11-point Numeric Rating Scale (NRS) for pain intensity to assess the potential effect on centrally-mediated analgesia.</p> <p>Secondary Efficacy Endpoints: The secondary endpoints included changes from baseline in efficacy endpoints related to defecation (BMs) and changes from baseline in QOL measures (described below). Although randomization was not stratified by laxative use (ie, on stable laxative regimen versus not on stable laxative regimen), subgroup analyses of each of the secondary endpoints were performed to compare naldemedine and placebo in subjects on a stable laxative regimen and subjects not on a stable laxative regimen.</p> <p>The main efficacy endpoints were:</p> <ul style="list-style-type: none"> • Change in the frequency of BMs from baseline to selected timepoints of the Treatment Period • Change in the Patient Assessment of Constipation Symptoms (PAC-SYM) Overall Score from baseline to each visit • Change in the Patient Assessment of Constipation Quality of Life (PAC-QOL) Overall Score from baseline to each visit • Frequency of Subject Global Satisfaction by treatment group • Number of subjects with laxative use 		

Sponsor: Shionogi	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Naldemedine	Volume:	
Name of Active Ingredient: Naldemedine	Page:	
Exploratory Endpoint: Total and free testosterone in males		
<p>Statistical Methods:</p> <p>Efficacy: All efficacy analyses were based on the intent-to-treat (ITT) Population, which included all randomized subjects. Subjects were analyzed by the treatment to which they were randomized to, regardless of the actual treatment received. Assessment of naldemedine efficacy was a secondary objective of the study. The significance level of tests was set at 0.05 (two-sided). The analysis of efficacy endpoints was not adjusted for multiplicity; hence, the p-values are purely nominal. Summary statistics for the exploratory efficacy variables (changes in total and free testosterone in males) were calculated by treatment group.</p> <p>Safety: All safety analyses were based on the Safety Population, which included all randomized subjects who received at least 1 dose of study drug. Subjects were analyzed by the treatment actually received. Subjects who took naldemedine at least once were analyzed as naldemedine-treated.</p> <p>Treatment-emergent adverse events (TEAEs) were adverse events (AEs) with a start date after the initial dose of study drug up to 14 days after the final dose of study drug. Incidences of TEAEs, treatment-related TEAEs (adverse drug reactions [ADRs]), TEAEs leading to discontinuation, and serious TEAEs were summarized by System Organ Class (SOC), preferred term (PT), and treatment group. Incidences of TEAEs of abdominal pain (ie, abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort), TEAEs considered for adjudication by the Cardiovascular Adjudication Committee, TEAEs adjudicated as MACE, and TEAEs of opioid withdrawal were summarized in the same manner. Changes in safety laboratory parameters, vital signs, physical examination findings, and ECGs were summarized by treatment group. Summary statistics and change from baseline to each scheduled visit were calculated by treatment group for COWS score, SOWS score, weekly opioid dose, and NRS score.</p>		
<p>Summary of Results:</p> <p>Subject disposition:</p> <p>Screened: 2414 subjects</p> <p>Randomized: 1246 subjects (623 subjects in the naldemedine group and 623 subjects in the placebo group)</p> <p>Randomized but not treated: 1 subject in the naldemedine group (Subject ██████████)</p> <p>A total of 210 subjects in each treatment group discontinued early from the study and 413 subjects in each treatment group completed the 52-week Treatment Period.</p>		

Sponsor: Shionogi	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Naldemedine	Volume:	
Name of Active Ingredient: Naldemedine	Page:	
<p>Reasons for discontinuation were generally similar in both treatment groups.</p> <p>Demographics and baseline characteristics: The study population included a greater proportion of females (63.3%) than males and subjects ≥ 40 to < 65 years of age (74.2%) relative to other age ranges, and 14.3% of subjects were ≥ 65 years of age. Subjects were mainly White (79.7%), and most of the remaining subjects (18.4%) were Black/African American. Eighty-nine (7.2%) subjects were Hispanic or Latino. The study population had a mean weight of 90.27 kg, and the majority of the subjects (83.7%) were overweight or obese (body mass index [BMI] ≥ 25 kg/m²).</p> <p>At baseline, the average daily dose of the opioid analgesic was 123.0 mg morphine-equivalent for the naldemedine group and 121.2 mg morphine-equivalent for the placebo group. The treatment groups were generally balanced with respect to demographic and baseline disease characteristics, including mean number of SBMs per week at baseline and opioid dose strata.</p> <p>Efficacy:</p> <p>All efficacy analyses were conducted on the ITT Population unless stated otherwise. The number of subjects who were on or not on a stable laxative regimen during the study is presented in Table S1.</p>		

Sponsor: Shionogi	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: Naldemedine		
Name of Active Ingredient: Naldemedine		

Table S1 **Number of Subjects Meeting Each Criterion of Laxative Use Reported from 28 Days Prior to Screening to Last Dose of Study Drug – Intent-to-treat Population**

	Naldemedine 0.2 mg N=621 n (%)	Placebo N=620 n (%)
Subjects not on stable laxatives [a]	186 (30.0)	183 (29.5)
- Subjects who received rescue laxative [b]	13 (7.0)	24 (13.1)
Subjects on stable laxatives [c]	312 (50.2)	335 (54.0)
- Subjects who received rescue laxative [d]	25 (8.0)	47 (14.0)
Other subjects	123 (19.8)	102 (16.5)

Rescue was defined as any laxative taken for the first time during Treatment Period.

[a] Subject not on stable laxatives was defined as a subject who did not have laxative use reported or received only rescue.

[b] The denominator is the number of subjects in [a].

[c] Subject on stable laxatives was defined as a subject who might have at least one/any stable laxative use reported.

[d] The denominator is the number of subjects in [c].

Source: [Table 14.2-1.2](#)

Endpoints Related to Defecation

One secondary endpoint was the change in the frequency of BMs from baseline to selected visits (Weeks 12, 24, 36, and 52) in the Treatment Period. Subjects in the naldemedine group had a greater increase in the frequency of BMs per week from baseline over time than subjects in the placebo group, and the differences between treatment groups in the frequency of BMs per week from baseline to all assessed timepoints were statistically significant (nominal $p \leq 0.0001$).

A subgroup analysis of change from baseline in the frequency of BMs per week over time by laxative use at baseline (on a stable laxative regimen/not on a stable laxative regimen) was performed. In the subgroup of subjects on a stable laxative regimen, subjects in the naldemedine group (N = 312) had a significantly greater increase in the frequency of BMs per week from baseline compared with subjects in the placebo group (N = 335) at each assessed timepoint (nominal $p < 0.0001$). However, in subjects not on a stable laxative regimen, although a trend towards a greater increase in the frequency of BMs per week for subjects in the naldemedine group (N = 186) relative to subjects in the placebo group (N = 183) was observed, the difference between

Sponsor: Shionogi	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Naldemedine	Volume:	
Name of Active Ingredient: Naldemedine	Page:	
<p>treatment groups was statistically significant only at Week 12 (nominal $p = 0.0006$) and Week 36 (nominal $p = 0.0429$).</p>		
<p><u>PAC-SYM Overall Score</u></p>		
<p>The PAC-SYM was assessed at Randomization (Day 1), Weeks 2, 12, 24, 36, and 52, and at Early Termination. Subjects in the naldemedine group had a greater improvement from baseline in the mean overall score for PAC-SYM than subjects in the placebo group. The differences between treatment groups in the mean change in the overall score for PAC-SYM from baseline were statistically significant at all assessed timepoints (nominal $p < 0.0001$).</p>		
<p>In the subgroup analysis of PAC-SYM by laxative use, subjects in the naldemedine group on a stable laxative regimen had significantly larger changes in the PAC-SYM overall score from baseline compared with subjects in the placebo group at all assessed timepoints (nominal $p \leq 0.0184$). Similarly, for subjects not on a stable laxative regimen, the difference between treatment groups in the mean change from baseline in the overall PAC-SYM score was also statistically significant at all assessed timepoints (nominal $p \leq 0.0116$).</p>		
<p><u>PAC-QOL Overall Score</u></p>		
<p>The PAC-QOL was assessed at the same timepoints as the PAC-SYM. Over the 52-week Treatment Period, a greater improvement from baseline in the mean overall score for PAC-QOL was observed in the naldemedine group compared with the placebo group, and the differences between treatment groups were statistically significant at all assessed timepoints (nominal $p < 0.0001$).</p>		
<p>Regardless of laxative use, changes in the PAC-QOL overall score from baseline for subjects in the naldemedine group were statistically significantly greater than those for subjects in the placebo group at all assessed timepoints (nominal $p \leq 0.0015$).</p>		
<p>Exploratory Efficacy Endpoints:</p>		
<p>No difference between treatment groups was observed in total or free testosterone levels in males.</p>		
<p>Safety:</p>		
<p>All safety analyses were conducted on the Safety Population.</p>		
<p>Summary measures of TEAEs are provided in the table below.</p>		

Sponsor: Shionogi	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: Naldemedine		
Name of Active Ingredient: Naldemedine		

Table S2 Overall Summary of Treatment-emergent Adverse Events – Safety Population

	Naldemedine 0.2 mg N=621 n (%)	Placebo N=619 n (%)	Difference of Proportion (95% Confidence Interval)
TEAEs	425 (68.4)	446 (72.1)	-3.6 (-8.7, 1.5)
ADRs	149 (24.0)	121 (19.5)	4.4 (-0.1, 9.0)
AE Leading to Discontinuation	39 (6.3)	36 (5.8)	0.5 (-2.2, 3.1)
SAEs	60 (9.7)	73 (11.8)	-2.1 (-5.6, 1.3)
SADRs	3 (0.5)	6 (1.0)	-0.5 (-1.4, 0.5)
SAEs Leading to Discontinuation	7 (1.1)	12 (1.9)	-0.8 (-2.2, 0.6)
Deaths	1 (0.2)	3 (0.5)	-0.3 (-1.0, 0.3)

ADRs were defined as TEAEs that were considered by the investigator to be definitely, probably, or possibly related to study drug.

SADRs were defined as serious ADRs.

CIs based on normal approximation may not be reliable for small counts and should be interpreted with caution.

ADR = adverse drug reaction; AE = adverse event; IMP = investigational medicinal product; SADR = serious adverse drug reaction; SAE = serious treatment-emergent adverse event; TEAE = treatment-emergent adverse event.

Source: [Table 14.3-1.1](#)

The incidences of TEAEs, ADRs, TEAEs leading to discontinuation, serious TEAEs, SADRs, serious TEAEs leading to discontinuation and deaths were generally similar between treatment groups.

A total of 8 subjects (4 in the naldemedine group and 4 in the placebo group) died during the study. In each case, the cause of death was considered not related to the study drug by the investigator.

Four of the subjects who died are not captured in the table above. These subjects died during the study, but more than 14 days after their last study visit, and their study-drug bottles were never returned to the study site for accountability. For this reason, their last dose of study drug was captured in the study database as the last known dose taken – that is, the last dose prior to the last study visit. Therefore, since the dates of death were outside of the study period (ie, from the first dose of study drug until 14 days after the last dose of study drug), these events were not considered TEAEs and do not

Sponsor: Shionogi	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: Naldemedine		
Name of Active Ingredient: Naldemedine		
<p>appear in the table above. However, these 4 subjects were active subjects in the study at the time of death and are summarized in this report with the other subjects who died.</p> <p>The incidence of TEAEs by SOC was generally similar between treatment groups, except for the Gastrointestinal Disorders SOC, in which a higher incidence of TEAEs was observed in the naldemedine group (32.7%) relative to the placebo group (25.5%). The difference observed between treatment groups (7.2%; 95% Confidence Interval [CI]: 2.1, 12.2) in this SOC was mainly due to a higher incidence of TEAEs of abdominal pain (8.2% vs 3.1%, respectively; difference: 5.1% [95% CI: 2.6, 7.7]), diarrhea (11.0% vs 5.3%, respectively; difference: 5.6% [95% CI: 2.6, 8.6]), and vomiting (6.0% vs 3.1%, respectively; difference: 2.9% [95% CI: 0.6, 5.2]) in the naldemedine group relative to the placebo group. Additionally, TEAEs of nausea were reported with a numerically higher frequency in the naldemedine group relative to the placebo group (7.9% vs 5.7%); however, the 95% CI for the difference between treatment groups included zero.</p> <p>The number of TEAEs leading to discontinuation was generally low and reported for a similar proportion of subjects in both treatment groups. A greater proportion of subjects in the naldemedine group (3.7%) discontinued due to TEAEs in the Gastrointestinal Disorders SOC compared with subjects in the placebo group (1.6%) with a difference between treatment groups of 2.1% (95% CI: 0.3, 3.9). Consistent with findings in the assessment of overall TEAEs in the Gastrointestinal Disorders SOC, the difference between treatment groups in TEAEs leading to discontinuation in this SOC was mainly due to a greater proportion of subjects in the naldemedine group than in the placebo group discontinued due to specific TEAEs of abdominal pain (1.8% vs 0%, respectively; difference 1.8% [95% CI: 0.7, 2.8]) and diarrhea (2.1% vs 0.6%, respectively; between-group difference 1.4% [95% CI: 0.2, 2.7]). Other subjects in the naldemedine group discontinued due to different TEAEs each belonging to a different SOC.</p> <p>Cardiovascular TEAEs were adjudicated as MACE for 4 (0.6%) subjects in the naldemedine group (cardiovascular death [1 subject], myocardial infarction [2 subjects]; cerebrovascular accident [1 subject]) and 5 (0.8%) subjects in the placebo group (cardiovascular death [3 subjects]; myocardial infarction [2 subjects]). None of these events was considered related to the study drug by the investigator.</p> <p>Treatment-emergent AEs of opioid withdrawal were reported with a numerically higher frequency in the naldemedine group compared with the placebo group. Although there was a numerical difference, the clinical characteristics of the events, the proportion of TEAEs of opioid withdrawal leading to discontinuation, and the investigator's assessment of severity and causality were considered generally similar for TEAEs of</p>		

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Name of Finished Product: Naldemedine	Volume:	
Name of Active Ingredient: Naldemedine	Page:	
<p>opioid withdrawal reported for subjects in either group.</p> <p>Events of possible opioid withdrawal were identified with higher frequency in the naldemedine group relative to the placebo group. Except for 1 subject in the placebo group, all events of possible opioid withdrawal included at least 1 PT from the Gastrointestinal Disorders SOC. Furthermore, in the naldemedine group, approximately 50% of the events of possible opioid withdrawal included only PTs from the Gastrointestinal Disorders SOC, which was expected given the mechanism of action of naldemedine. No clinically meaningful changes from baseline over time were observed for COWS scores, SOWS scores, NRS scores, or opioid analgesics doses.</p> <p>No clinically meaningful differences were observed between treatment groups with respect to changes from baseline in safety laboratory or endocrinology parameters.</p> <p>No clinically meaningful safety findings or trends were identified based on vital signs or ECG parameters.</p>		
<p>Conclusions:</p> <ul style="list-style-type: none"> • Treatment with naldemedine 0.2 mg QD was generally well tolerated in this 52-week study in subjects with non-malignant chronic pain and OIC. • Treatment with naldemedine 0.2 mg QD for up to 52 weeks had a similar adverse event profile to that of placebo, except for a higher frequency of TEAEs, ADRs, and TEAEs leading to discontinuation of abdominal pain, diarrhea, and vomiting that is expected given the mechanism of action of the drug. • Treatment with naldemedine 0.2 mg QD for up to 52 weeks was associated with a low incidence of TEAEs of opioid withdrawal that was similar to that observed with placebo. Events of possible opioid withdrawal were identified more frequently with naldemedine than with placebo; however, the overall incidence was low, and all events included 1 or more PT from the Gastrointestinal Disorders SOC. Furthermore, approximately 50% of events of possible opioid withdrawal identified in the naldemedine group included only PTs from the Gastrointestinal Disorders SOC, mainly abdominal pain, abdominal pain upper, diarrhea, nausea and/or vomiting. • The incidences of all-cause mortality and MACE were low and generally similar in both treatment groups. • Treatment with naldemedine resulted in a significantly greater increase from baseline in the frequency of BMs per week compared with treatment with placebo. This greater increase was observed at the first assessed timepoint, and the difference between treatment groups was maintained over 52 weeks. 		

Sponsor: Shionogi	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: Naldemedine		
Name of Active Ingredient: Naldemedine		
<ul style="list-style-type: none">• The effect of naldemedine on the frequency of BMs was consistently observed in subgroups of subjects on or not on stable laxative regimens, although, in the subgroups of subjects not on a stable laxative regimen, the difference between treatment groups was not statistically significant at some timepoints.• The improvement of constipation with naldemedine 0.2 mg QD relative to placebo had a positive effect on symptoms associated with constipation and measures of QOL, as demonstrated by statistically significant and clinically meaningful improvements in the overall scores of PAC-SYM and PAC-QOL, as well as in the assessment of Subject Global Satisfaction.		
Date of the Report: 23 January 2017		