

2. SYNOPSIS

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| 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 Study of Naldemedine in the Treatment of Opioid-induced Constipation in Subjects with Non-malignant Chronic Pain Receiving Opioid Therapy | | |
| Investigators: Multicenter (see Appendix 16.1.4) | | |
| Study Sites: 68 sites in North America and Europe randomized subjects: Austria (2), Czech Republic (4), Germany (2), Poland (3), Spain (1), United Kingdom (8), and the United States (48) | | |
| Publication (Reference): Not applicable. | | |
| Phase of Development: 3 | | |
| Study Period: ■ August 2013 (first subject enrolled) to ■ January 2015 (last subject completed) | | |
| <p>Study Objectives:</p> <p>The primary objective of the study was:</p> <ul style="list-style-type: none"> To evaluate the efficacy of naldemedine compared to placebo without concomitant laxative treatment in subjects with non-malignant chronic pain receiving a stable opioid regimen for ≥ 1 month and having opioid-induced constipation (OIC)¹ <p>The secondary objectives of the study were:</p> <ul style="list-style-type: none"> To evaluate the efficacy of naldemedine on the frequency of spontaneous bowel movements (SBMs), complete spontaneous bowel movements (CSBMs), and SBMs without straining To evaluate the safety and tolerability of naldemedine <p>The exploratory objectives of the study were:</p> <ul style="list-style-type: none"> To evaluate the effects of naldemedine on quality of life (QOL) measures, global satisfaction, opiate withdrawal, pain intensity, change in rescue laxative use, CSBMs, and SBMs To determine the potential impact of naldemedine on testosterone levels in male subjects To assess pharmacokinetics (PK) of naldemedine and its metabolite (nor-naldemedine) | | |

¹ Efficacy was assessed over 12 weeks based on the responder rate by treatment group.

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Methodology:

This was a Phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and 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 periods: a minimum 2-week and maximum 4-week Screening Period; a 12-week double-blind, placebo-controlled Treatment Period; and a 4-week Follow-up Period.

Subjects were screened at Visit 1 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 non-malignant chronic pain, opioid use for ≥ 3 months duration, and a stable opioid regimen with a total daily dose (TDD) on average of ≥ 30 mg equivalents of oral morphine sulfate for ≥ 1 month prior to the Screening Visit.

Subjects were to discontinue all laxative use (eg, stool softener, bulking agents, gastrointestinal [GI] tract stimulants/prokinetic agents, suppositories, enemas, or other medications/agents used to treat constipation) from the start of the Screening Period through the end of the Treatment Period. Subjects must have signed the informed consent form prior to any study procedures, including withdrawal of laxatives use.

Rescue laxative therapy was allowed and could have been initiated if a subject did not have a bowel movement (BM) for any period of 72 hours during the Screening or Treatment Periods. Initiation of rescue laxative(s) was to follow the Rescue Laxative Guidelines presented in the Study Protocol ([Appendix 16.1.1](#)). A BM occurring within 24 hours after rescue laxative therapy was not considered an SBM. Every attempt was to be made to limit laxative use during the 24-hour period immediately prior to randomization.

Any number of SBMs rated on the Bristol Stool Scale (BSS) as 1 within a 2-hour period was counted as a single SBM.

The eligibility and baseline BM status were based on a 14-consecutive-day qualifying period during the Screening Period. To be eligible, subjects should 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.

Approximately 540 subjects were to be randomized in a 1:1 ratio to receive a single tablet of either 0.2 mg of naldemedine or placebo (270 subjects each) QD in a double-blind manner during the 12-week Treatment Period. Subjects were to be randomized as soon as possible but within a maximum of 7 days of meeting the eligibility

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| <p>requirements. Subjects were to be stratified based on their 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, or terminated early from the study were to have a Follow-up Visit 4 weeks after their last dose of study drug.</p> | | |
| <p>Diagnosis and Main Criteria for Inclusion: This study population included subjects 18 to 80 years of age, inclusive, with OIC and non-malignant chronic pain receiving chronic opioid therapy for ≥ 3 months. Subjects must have been treated with a stable opioid regimen at a TDD on average of ≥ 30 mg equivalents of oral morphine sulfate for ≥ 1 month prior to Screening, and must have discontinued all laxative use.</p> <p>Subjects must have met the following 3 criteria over a 14-consecutive-day qualifying period during the Screening Period:</p> <ul style="list-style-type: none"> • No more than 4 SBMs total over the 14-consecutive-day qualifying period. In addition, no more than 3 SBMs in a given week of the qualifying period • One or more of the following bowel symptoms in $\geq 25\%$ of BMs: presence of straining, lumpy or hard stools, sensation of incomplete evacuation, or sensation of anorectal obstruction/blockage • Compliance $\geq 78\%$ with daily completion of electronic Diary (eDiary) entries (ie, make 11 of 14 eDiary completions) during the 14-consecutive-day qualification period <p>Male subjects were required to be sterile or agreed to use an approved method of contraception. Female subjects were required to be not pregnant, non-lactating, postmenopausal, surgically sterile, or agreed to use a highly effective technique of birth control from the Screening Visit until 28 days after the last dose of study drug.</p> | | |
| <p>Duration of Treatment: 12 weeks</p> | | |
| <p>Investigational Product, Dose, and Mode of Administration: Naldemedine (0.2 mg tablets) for oral administration; lot numbers [REDACTED] and [REDACTED]</p> | | |
| <p>Reference Product, Dose, and Mode of Administration: Placebo tablets matching 0.2 mg naldemedine for oral administration; lot number [REDACTED]</p> | | |
| <p>Criteria for Evaluation:</p> <p>Efficacy:</p> <p>The primary efficacy endpoint was the proportion of responders, where a responder was defined as having ≥ 9 positive-response weeks out of the 12-week Treatment Period and 3 positive-response weeks out of the last 4 weeks of the 12-week Treatment Period. A</p> | | |

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| <p>positive-response week was defined as ≥ 3 SBMs per week and an increase from baseline of ≥ 1 SBM per week for that week.</p> <p>The secondary efficacy endpoints were the following:</p> <ul style="list-style-type: none"> • Change in the frequency of SBMs per week from baseline to the last 2 weeks of the Treatment Period • Change in the frequency of SBMs per week from baseline to Week 1 of the Treatment Period • Change in the frequency of CSBMs per week from baseline to the last 2 weeks of the Treatment Period • Change in the frequency of SBMs without straining per week from baseline to the last 2 weeks of the Treatment Period <p>The exploratory efficacy endpoints were:</p> <ul style="list-style-type: none"> • Proportion of CSBM responders (Definition similar to that of SBM responders) • Proportion of SBM responders in any 6 weeks • Proportion of SBM responders in any 9 weeks • Proportion of SBM monthly responders • Change in each variable related to defecation per week from baseline to each week of the Treatment Period: <ul style="list-style-type: none"> ○ Frequency of SBMs with BSS of 3 or 4 per week ○ Frequency of SBMs per week ○ Frequency of CSBMs per week ○ Frequency of SBMs without straining per week ○ Frequency of SBMs without blockage per week ○ Number of days with at least 1 SBM per week ○ Number of days with at least 1 CSBM per week • Time to the first SBM and CSBM after initial dose of study drug • Incidences of SBM and CSBM within 4, 8, 12, 24, and 48 hours of initial study drug dose • Change in maximal number of days between SBMs from baseline for each 2-week period of the Treatment Period • Change in each variable related to rescue laxative per week from baseline to each week of the Treatment Period | | |

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| <ul style="list-style-type: none"> • Change in the abdominal bloating and abdominal discomfort scores from baseline to each week of the Treatment Period • Change from baseline in overall and each domain for patient assessment of constipation symptom/quality of life questionnaires (PAC-SYM/QOL) • Change from baseline in overall and each domain for Short Form 36 • Frequency of Subject Global Satisfaction • Changes in total and free testosterone in males <p>Pharmacokinetics: Blood samples were collected for determination of plasma concentration of naldemedine and its metabolite (nor-naldemedine) from all subjects at Visit 5 (Week 4), Visit 6 (Week 8), and Visit 7 (Week 12) or at Early Termination.</p> <p>Safety: Safety assessments included adverse events, clinical laboratory evaluations, physical examinations, vital signs, and electrocardiograms (ECGs). Major Adverse Cardiovascular Events (MACE) were also assessed and defined as: cardiovascular (CV) death, myocardial infarction, and cerebrovascular accident (stroke). Suspected CV events were identified and sent to an independent adjudication committee to identify cases of MACE.</p> <p>Clinical safety assessments also included the Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS) to assess possible opioid withdrawal and an 11-point Numeric Rating Scale (NRS) for pain intensity.</p> | | |
| <p>Statistical Methods:</p> <p>Efficacy: The Intent-to-Treat (ITT) Population included all randomized subjects. All efficacy analyses were based on this population. The primary efficacy endpoint was the proportion of responders. The primary efficacy endpoint was summarized by treatment group and analyzed by the Cochran Mantel Haenszel test adjusted by the opioid dose strata for the comparison between naldemedine and placebo. The primary efficacy endpoint was estimated along with its 95% confidence intervals (CIs) by treatment group. The CIs were calculated with the Clopper-Pearson method. In addition, the difference in the responder proportion adjusted by the opioid dose strata between naldemedine and placebo and its 95% CI were calculated. The primary efficacy endpoint was examined for the following subgroups and results were presented descriptively: opioid dose strata, age, body mass index (BMI), gender, race, and region (country and site). Sensitivity analyses were also performed.</p> | | |

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| <p>The mean of the change in frequency of SBM per week from baseline to the last 2 weeks of the Treatment Period was compared between naldemedine and placebo based on an analysis of covariance method using the opioid dose strata as a covariate. Summary statistics of the frequency of SBMs per week and its change from baseline to the last 2 weeks were calculated by treatment group. Change in the frequency of SBMs per week from baseline to Week 1; change in the frequency of CSBMs per week from baseline to the last 2 weeks of the Treatment Period; and change in the frequency of SBMs without straining per week from baseline to the last 2 weeks of the Treatment Period were analyzed in the same manner.</p> | | |
| <p>Pharmacokinetics:</p> <p>The elapsed time between the last dose of naldemedine and PK sampling, elapsed time between the last meal and the corresponding last dose of naldemedine, and plasma concentrations of naldemedine and its metabolite (nor-naldemedine) were listed by subject. Elapsed time between the last dose of naldemedine and PK sampling and plasma concentrations of naldemedine and nor naldemedine were summarized with descriptive statistics by scheduled visit (Week 4, Week 8, and Week 12).</p> | | |
| <p>Safety:</p> <p>Treatment-emergent adverse events (TEAEs) were adverse events with a start date after the initial dose of study drug up to 28 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 (SAEs) were summarized by System Organ Class (SOC), preferred term, and treatment group. Incidences of TEAEs of abdominal pain (ie, abdominal pain, abdominal pain upper, abdominal pain lower and abdominal discomfort), TEAEs of MACE, TEAEs considered for CV adjudication, 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 the COWS score, SOWS score, and the NRS score for pain evaluation.</p> | | |
| <p>Summary of Results:</p> <p>Subject disposition:</p> <p>Screened: 974 subjects</p> <p>Randomized: 547 subjects (274 subjects in the naldemedine group and 273 subjects in the placebo group)</p> <p>Randomized but not treated: 2 subjects in the naldemedine group none in the placebo group</p> | | |

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| <p>Completed: 471 subjects (233 subjects in the naldemedine group and 238 subjects in the placebo group)</p> | | |
| <p>Discontinued: 76 subjects (41 subjects in the naldemedine group and 35 subjects in the placebo group)</p> | | |
| <p>Demographics and baseline characteristics: The study population was characterized by having a larger proportion of females (60.4% of subjects) and subjects ≥ 40 to < 65 years of age (74.9% of subjects); additionally, 86/545, 15.8% of subjects were ≥ 65 years of age. Subjects were mainly White (80.0% of subjects), with Black/African American subjects composing most of the remainder of the subjects (18.5% of subjects). Fifty-three (9.7%) subjects were Hispanic or Latino. The study population had a mean weight of 89.91 kg and the majority of subjects (approximately 80%) were overweight or obese (BMI ≥ 25 kg/m²).</p> | | |
| <p>At baseline, the mean daily dose of the opioid analgesic was 125.21 mg morphine-equivalent for the naldemedine group and 139.66 mg morphine-equivalent for the placebo group. The observed difference between groups in the mean opioid dose was driven by a few outliers in the placebo group receiving an opioid morphine-equivalent dose > 400 mg. When the mean daily dose at baseline was calculated for subjects taking up to 400 mg, no difference between groups was observed. A slightly higher proportion (53.8%) of subjects was taking a morphine-equivalent dose of opioids between 30 to 100 mg relative to subjects taking > 100 mg (~45%). The mean number of SBMs per week at baseline was 1.31. Five (1.8%) subjects in the naldemedine group and 1 (0.4%) subject in the placebo group were randomized, despite having a mean dose of opioids of < 30 mg, morphine-equivalent.</p> | | |
| <p>Efficacy:</p> | | |
| <p>All efficacy analyses were conducted on the ITT population unless stated otherwise.</p> | | |
| <p>The primary endpoint of the study was the proportion of responders during the Treatment Period. There was a significantly ($p=0.002$) greater proportion of responders in the naldemedine group (47.6%) relative to the placebo group (34.6%), meeting the primary objective of the study.</p> | | |
| <p>The proportion of responders by subgroups defined by opioid dose strata (30 to 100 mg; > 100 mg), age (< 40 years; ≥ 40 to < 65 years; ≥ 65 years; ≥ 75 years), BMI (< 18.5 kg/m²; ≥ 18.5 to < 25 kg/m²; ≥ 25 to < 30 kg/m²; ≥ 30 kg/m²), gender, and race was numerically higher for the naldemedine group than the placebo group in all subgroups except for that of subjects < 40 years of age. The differences between groups in these subgroups were not tested for statistical significance.</p> | | |

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| <p>Six different sensitivity analyses of the primary endpoint were conducted: observed case, complete case, worst case, modified worst case, Modified Intent-to-Treat Population, and the Per-Protocol Population. Consistent with the primary analysis, a greater proportion of responders was observed in the naldemedine group than in the placebo group in each of these analyses. The differences between groups in the proportion of responders in all of these sensitivity analyses were statistically significant ($p \leq 0.022$).</p> <p>To further characterize the effect of naldemedine in subjects with non-malignant chronic pain who have OIC, 4 secondary efficacy endpoints were predefined including assessments of durability of effect (up to 12 weeks) and speed of onset of action, as well as measures of quality of SBMs including frequency of CSBMs and SBMs without straining. Results of all 4 secondary efficacy endpoints were consistent with the primary outcome measure.</p> <p>Treatment with naldemedine was associated with a statistically significant ($p < 0.0001$) increase in frequency of SBMs per week from baseline to the last 2 weeks of treatment relative to placebo, demonstrating durability of the treatment effect.</p> <p>Additionally, a statistically significant ($p < 0.0001$) increase from baseline in the frequency of SBMs per week to Week 1 of the study period was observed in the naldemedine group (3.48 SBMs per week) relative to the placebo group (1.36 SBMs per week).</p> <p>Consistent with the observed changes in frequency of SBMs, the frequency of CSBMs per week increased significantly ($p < 0.0001$) from baseline to the last 2 weeks in the naldemedine group relative to the placebo group, as did the frequency of SBMs without straining per week, which also increased significantly from baseline to the last 2 weeks ($p = 0.0003$) in the naldemedine group relative to the placebo group.</p> <p>In general, the results from the analysis of exploratory parameters further demonstrated the efficacy of naldemedine on constipation. Importantly, the median time to the first SBM after the initial dose of study drug was 16.07 hours in the naldemedine group and 46.73 hours in the placebo group and was statistically significant (nominal $p < 0.0001$). Consistently, median time to the first CSBM after the initial dose of study drug was 48.95 hours for the naldemedine group and 128.92 hours for the placebo group and was statistically significant (nominal $p < 0.0001$).</p> <p>Subjects tended to use less rescue laxatives with naldemedine than with placebo, although the difference did not reach statistical significance. This numerical trend suggests that the improvement in constipation by naldemedine was due directly to drug effect, not rescue medication use.</p> | | |

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| <p>This study also assessed the impact of treatment of OIC with naldemedine in measures of QOL. Over the 12-week Treatment Period, a greater reduction from baseline in overall score for PAC-SYM was observed in the naldemedine group relative to the placebo group. The differences between groups in change in the overall score for PAC-SYM from baseline were statistically significant at all assessed time points (nominal $p \leq 0.0001$). Consistently, the overall score for PAC-QOL decreased more from baseline over time for the naldemedine group relative to the placebo group. The differences between groups in changes in the overall score for PAC-QOL from baseline were statistically significant at all assessed time points (nominal $p \leq 0.0014$).</p> <p>The results of the SF-36 questionnaire in the naldemedine group were generally similar to the placebo group. Of the subjects who completed a Subject Global Satisfaction evaluation at their last study visit (140 subjects in the naldemedine group and 107 subjects in the placebo group), the degree of satisfaction with constipation and abdominal symptoms improved markedly, moderately, or slightly in 75.7% and 57.2%, respectively.</p> <p>No difference between treatment groups was observed in testosterone levels.</p> <p>Pharmacokinetics:</p> <p>At Visit 7 (Week 12), the mean (minimum – maximum) elapsed time from dosing to PK sampling time was 12.72 (0.25 – 44.00) hours and the mean (minimum – maximum) plasma concentration was 1.03 (0.00 – 6.37) ng/mL for naldemedine and 0.125 (0.00 – 0.531) ng/mL for nor-naldemedine for the PK Concentration Population.</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> | | |

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Table S1 Overall Summary of Treatment-Emergent Adverse Events – Safety Population

| | Naldemedine 0.2 mg (N = 271) n (%) | Placebo (N = 272) n (%) | Difference of Proportion (95% Confidence Interval) |
|---------------------------------|--|-------------------------------|--|
| TEAEs | 132 (48.7) | 123 (45.2) | 3.5 (-4.9, 11.9) |
| ADRs | 59 (21.8) | 45 (16.5) | 5.2 (-1.4, 11.8) |
| AE leading to discontinuation | 13 (4.8) | 4 (1.5) | 3.3 (0.4, 6.2) |
| SAEs | 14 (5.2) | 5 (1.8) | 3.3 (0.2, 6.4) |
| SADRs | 2 (0.7) | 0 (0.0) | 0.7 (-0.3, 1.8) |
| SAEs leading to discontinuation | 3 (1.1) | 0 (0.0) | 1.1 (-0.1, 2.4) |
| Deaths | 0 (0.0) | 0 (0.0) | 0.0 (---, ---) |

ADRs were defined as TEAEs that were considered by the Investigator to be definitely, probably, or possibly related to IMP.

SADRs were defined as serious ADRs.

CI 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 adverse event; TEAE = treatment-emergent adverse event.

Source: [Table 14.3-1.1](#)

The incidence of TEAEs, ADRs, and treatment-related SAEs were generally similar between groups, and the 95% CIs for the differences between groups included zero. A higher proportion of subjects in the naldemedine group discontinued due to a TEAE relative to the placebo group (13/271, 4.8% vs. 4/272, 1.5%, respectively). Of the 13 subjects in the naldemedine group who discontinued due to a TEAE, 8 subjects discontinued due to a TEAE in the GI disorders SOC. Gastrointestinal AEs (eg, abdominal pain, diarrhea, and nausea) were expected with naldemedine treatment, given its mechanism of action, and its effect on reverting the agonistic effect of opioids in μ receptors in the GI tract. The remaining 5 subjects in the naldemedine group discontinued due to different TEAEs each belonging to a different SOC.

A slightly higher number of SAEs were reported for subjects in the naldemedine group relative to the placebo group (5.2% vs 1.8%, respectively). These events were distributed across multiple SOCs and no specific event was reported in more than 1 subject. No subjects died during the study. Only 1 subject, a subject in the naldemedine group, had a TEAE adjudicated as a MACE.

The TEAEs reported more frequently with naldemedine than with placebo were abdominal pain, diarrhea, and peripheral edema. The 95% CIs for the differences between groups in the incidences of these AEs excluded zero. Abdominal pain was reported for 6.3% of subjects in the naldemedine group and 1.8% of subjects in the

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| <p>placebo group. Diarrhea was reported for 6.6% of subjects in the naldemedine group and 2.9% of subjects in the placebo group. As mentioned above, a higher proportion of adverse events of abdominal pain and diarrhea were expected with naldemedine due to its mechanism of action. Additionally, TEAEs of peripheral edema were reported for 1.5% of subjects in the naldemedine group and none in the placebo group.</p> <p>Low and similar frequencies of TEAEs of opioid withdrawal or possible opioid withdrawal were observed in both treatment groups. No clinically meaningful changes from baseline over time were observed for COWS scores, SOWS scores, NRS scores, or opioid analgesics doses.</p> <p>There were no clinically meaningful differences between the treatment groups with respect to changes from baseline in safety laboratory or endocrinology parameters.</p> <p>No clinically meaningful safety findings or trends in vital signs or ECG parameters were observed.</p> | | |
| <p>Conclusions:</p> <p>In this 12-week study in subjects with non-malignant chronic pain and OIC, treatment with naldemedine resulted in a significantly greater proportion of SBM responders than treatment with placebo.</p> <p>Improvement in constipation with naldemedine was observed early in treatment as demonstrated by a significant increase in the frequency of SBMs per week from baseline to the first week of the study period relative to placebo. Early effect of naldemedine on constipation was also demonstrated by the median time to first SBM, which was almost one-third of that with placebo.</p> <p>The effect of naldemedine on constipation was durable with a generally stable increase in the number of SBMs per week from baseline through Week 12 relative to placebo that was statistically significant.</p> <p>The frequency of both CSBMs and SBMs without straining increased from baseline with naldemedine more than with placebo, consistent with the results for the frequency of SBMs.</p> <p>The improvement in constipation with naldemedine relative to placebo had a generally positive effect on 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.</p> <p>Naldemedine was generally well tolerated in subjects with non-malignant chronic pain and OIC. The incidence of TEAEs was generally similar between the naldemedine group and the placebo group. A slightly higher proportion of subjects discontinued due</p> | | |

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| <p>to TEAEs in the naldemedine group relative to the placebo group. This was generally due to a higher incidence of TEAEs in the Gastrointestinal Disorders SOC that were expected due to the mechanism of action of naldemedine. A slightly higher number of SAEs were reported for subjects in the naldemedine group relative to the placebo group. These events were distributed across multiple SOCs and no specific event was reported in more than 1 subject.</p> <p>Treatment with naldemedine for 12 weeks was not associated with signs or symptoms of opioid withdrawal and the analgesic effect of opioids was not affected by treatment with naldemedine.</p> | | |
| Date of the Report: 13 October 2015 | | |