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Onset of action of naldemedine in the treatment of opioid-induced constipation in patients with chronic noncancer pain: results from 2 randomized, placebo-controlled, phase 3 trials

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Abstract

Opioid-induced constipation (OIC) is a common side effect of chronic opioid therapy. Previously, naldemedine, a peripherally acting μ-opioid receptor antagonist demonstrated efficacy in the treatment of OIC. In this exploratory analysis, the onset of action of naldemedine was evaluated in 2 identically designed phase 3, randomized, placebo-controlled trials. Proportion of patients experiencing a spontaneous bowel movement (SBM) within 24 hours of treatment initiation, time from initial dose to first SBM and weekly SBM frequency were assessed. Naldemedine was associated with significant increases in the proportion of patients experiencing an SBM at 4, 8, 12, and 24 hours after the initial dose compared with placebo (all $P < 0.0001$). Within 24 hours in both studies, statistically significantly ($P < 0.0001$) more patients treated with naldemedine compared with placebo experienced an SBM (61.2% vs 28.3% and 56.5% vs 33.6%, respectively). Median times to first SBM were significantly shorter in the naldemedine group vs placebo (COMPOSE-1, 16.1 vs 46.7 hours; COMPOSE-2, 18.3 vs 45.9 hours; $P < 0.0001$). Naldemedine was also associated with significant increases in weekly SBM frequency vs placebo within 1 week ($P < 0.001$). Most common treatment-emergent adverse events were gastrointestinal-related (abdominal pain, diarrhea, and nausea). Treatment-emergent adverse events were reported most frequently on day 1, followed by a decrease from days 2 to 7. Naldemedine had a timely onset of effect, and gastrointestinal adverse events largely resolved within the first week. These findings should assist clinicians counseling patients with chronic noncancer pain on expectations when initiating naldemedine for OIC.

Keywords: Naldemedine, Opioids, Constipation, Chronic noncancer pain, PAMORA

1. Introduction

Opioid analgesic medications are commonly used for the management of moderate-to-severe chronic pain.[2,13] However, chronic opioid use is associated with a range of adverse events (AEs), including side effects of the gastrointestinal (GI) system, such as nausea, vomiting, and constipation.[15] Opioid-induced constipation (OIC) is one of the more bothersome and frequently experienced AEs.[5,6]

Opioid-induced constipation results from the activation of μ-opioid receptors on the enteric nervous system within the walls of the GI tract. Although μ-opioid receptors in the central nervous system are the primary target of opioid therapy, the activation of similar receptors in the GI tract leads to the symptoms of OIC.[5,6] The hallmark symptoms of OIC are reduced bowel movement (BM) frequency, the development or worsening of straining to pass BMs, a sense of incomplete evacuation, and harder stool consistency.[5,6] Opioid-induced constipation may lead to poorer health-related quality of life and clinically significant physical sequelae such as bowel obstruction and fecal impaction. In addition, patients may modify or be nonadherent to their opioid therapy in an attempt to manage constipation, which has implications for the effectiveness of analgesia.[1,3,5,8,9,19] Thus, a timely and effective response to a treatment, that is well tolerated, is important in minimizing or preventing the negative effects of OIC.

Naldemedine (Symproic, Shionogi, Inc, Florham Park, NJ) is a peripherally acting μ-opioid receptor antagonist (PAMORA) approved in Japan for the treatment of OIC in adults with cancer and chronic noncancer pain and approved in the United States for treatment of OIC in adults with chronic noncancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent dosage escalation.[11,12,16,17] The US approval of naldemedine was based on results from 2 identically designed 12-week, placebo-controlled, phase 3 trials (COMPOSE-1 and COMPOSE-2) in patients with OIC and chronic noncancer pain.[10] The primary efficacy endpoint

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in these trials was the proportion of spontaneous bowel movement (SBM) responders, defined as patients with at least 3 SBMs per week *and* an increase from baseline of ≥1 SBM/week for ≥9 weeks and ≥3 of the final 4 weeks of the 12-week treatment period. Treatment with naldemedine resulted in a significantly ($P \leq 0.002$) higher proportion of responders in COMPOSE-1 and COMPOSE-2 (47.6% and 52.5%, respectively) compared with placebo (34.6% and 33.6%).[10] However, these results did not illustrate how quickly after the first dose of treatment will patients experience a BM or when the AEs that are associated with treatment will occur. Based on the mechanism of action of naldemedine, it was hypothesized that the time to the first BM with naldemedine would be shorter compared with placebo, and that the majority of GI AEs occur shortly after the initiation of treatment when the GI motility is restored.

The objectives of this exploratory analysis were to assess: (1) the time to onset of action of naldemedine, and (2) the temporal association of the GI AEs in relation of the initial BM in patients with chronic noncancer pain in both trials.

2. Methods

COMPOSE-1 and COMPOSE-2 (ClinicalTrials.gov identifiers NCT01965158 and NCT01993940, respectively) were randomized, multinational, double-blind, placebo-controlled, parallel-group phase 3 trials of identical design conducted between August 2013 and June 2015.[10]

The methodology of the COMPOSE-1 and COMPOSE-2 trials has been previously described.[10] Briefly, adults aged 18 to 80 years with chronic noncancer pain for ≥3 months who were on a stable opioid regimen (≥30 mg morphine equivalents/day) for at least 1 month and who met study entry criteria for OIC were eligible. After discontinuation of laxative use and a 2 to 4 week screening/qualification period to verify OIC symptomatology and eligibility, enrolled patients were randomized in a 1:1 ratio to 12 weeks of once-daily oral treatment with either naldemedine 0.2 mg tablet or matching placebo to be taken with or without food (**Fig. 1**).[10]

Prespecified exploratory endpoints evaluated in the current analysis included the proportion of patients with an SBM/complete spontaneous bowel movement (CSBM) within 24 hours after the initial dose, time to the first SBM/CSBM after the initial dose, and weekly frequency of SBMs. Complete spontaneous bowel movements were defined as SBMs with a feeling of complete evacuation. Safety was assessed using incidences of treatment-emergent adverse events (TEAEs).[10] Adverse events were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 16.0. The proportion of patients who reported GI-related TEAEs on days 1 to 7 after treatment initiation was compared with the proportion of patients who experienced SBMs over the same period.

2.1. Statistical analysis

Efficacy analyses were based on the intent-to-treat population, which included all randomized patients. Safety analyses were based on the safety population, which included all patients in the intent-to-treat population who received at least 1 dose of study medication.[10] The proportion of patients with an SBM/CSBM at specific time points was evaluated using the Cochran–Mantel–Haenszel test adjusted for opioid dose strata. Kaplan–Meier plots of the time to the first SBM/CSBM after first dose were produced by treatment group, and the distribution of time between groups was compared using the generalized Wilcoxon test. A mixed-effect repeat-measures model with opioid dose strata as a covariate and treatment group, time, and time-by-treatment group interaction as fixed effects was used to assess differences between the naldemedine and placebo groups in change from baseline in SBM frequency at each week. All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Inc, Cary, NC).[10]

3. Results

3.1. Study disposition and population

A total of 547 patients were randomized (1:1) to receive naldemedine (n = 274) or placebo (n = 273) in COMPOSE-1, and 553 patients were randomized to receive naldemedine (n = 277) or placebo (n = 276) in COMPOSE-2. Patient demographics and baseline characteristics were generally well matched between groups in each study (**Table 1**).[10]

3.2. Efficacy

A significantly higher proportion of patients in the naldemedine group experienced an SBM at 4, 8, 12, and 24 hours after the initial dose compared with the placebo group ($P < 0.0001$, both studies, all time points) (**Fig. 2**). Similarly, the proportion of patients who had a CSBM at 4, 8, 12, and 24 hours after the initial dose was significantly higher in the naldemedine group

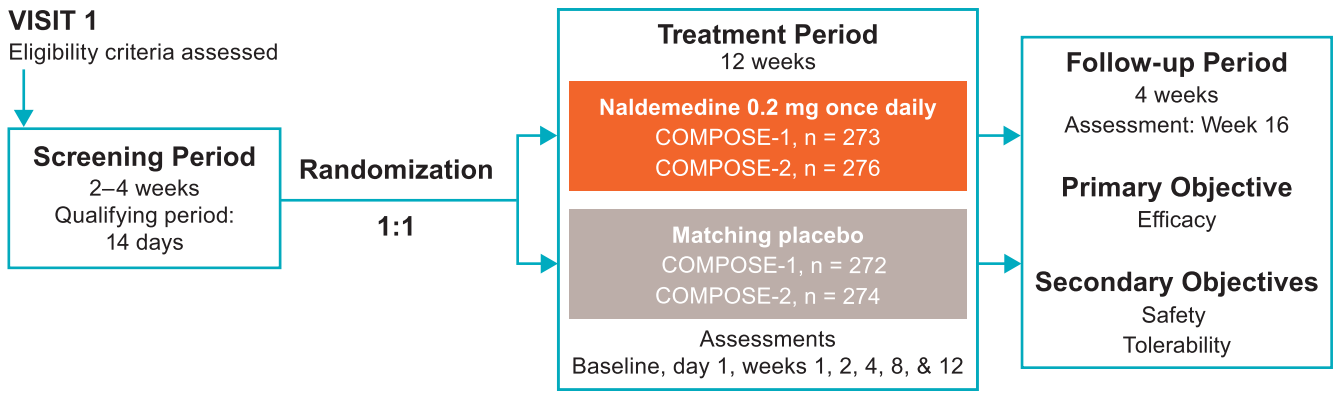

Figure 1. COMPOSE-1 and COMPOSE-2 study design.

Table 1

Summary of patient demographics and baseline characteristics (intent-to-treat population).[10]

Attribute	COMPOSE-1		COMPOSE-2	
	Naldemedine (n = 273)*	Placebo (n = 272)*	Naldemedine (n = 276)*	Placebo (n = 274)†
Mean age, years (SD)	53.3 (10.4)	53.4 (11.0)	54.1 (10.5)	52.9 (11.4)
Female, n (%)	161 (59.0)	168 (61.8)	165 (59.8)	168 (61.3)
Mean BMI, kg/m^2 (SD)	31.4 (7.4)	31.3 (6.8)	31.4 (7.0)	31.3 (7.5)
Region, n (%)				
North America	230 (84.2)	229 (84.2)	241 (87.3)	239 (87.2)
Rest of world	43 (15.8)	43 (15.8)	35 (12.7)	35 (12.8)
Race, n (%)				
White	216 (79.1)	220 (80.9)	222 (80.4)	227 (82.8)
Black	53 (19.4)	48 (17.6)	49 (17.8)	39 (14.2)
Other	4 (1.5)	4 (1.5)	5 (1.8)	8 (3.0)
Mean SBMs/week (SD)	1.3 (0.75)	1.3 (0.71)	1.2 (0.76)	1.2 (0.73)
Mean daily opioid dose, MED, mg (SD)	125.2 (118.0)	139.7 (153.7)	118.0 (122.0)	123.9 (146.1)
Patients with daily opioid dose, n (%)				
30-100 mg	155 (56.8)	153 (56.3)	169 (61.2)	167 (60.9)
>100 mg	118 (43.2)	119 (43.8)	107 (38.8)	107 (39.1)
Types of pain, >5% of patients (by SOC preferred term)				
Arthralgia	13 (4.8)	15 (5.5)	21 (7.6)	22 (8.0)
Back pain	175 (64.1)	163 (59.9)	153 (55.4)	142 (51.8)
Intervertebral disk degeneration	8 (2.9)	12 (4.4)	16 (5.8)	16 (5.8)
Neck pain	27 (9.9)	18 (6.6)	19 (6.9)	22 (8.0)
Osteoarthritis	18 (6.6)	11 (4.0)	16 (5.8)	22 (8.0)
Pain	11 (4.0)	18 (6.6)	30 (10.9)	26 (9.5)
Duration of opioid use before screening in months, mean (SD)	61.10 (62.0)	61.81 (58.3)	61.17 (61.5)	56.7 (55.8)
Duration of opioid use before screening in months, n (%)				
<3	13 (4.8)	7 (2.6)	8 (2.9)	13 (4.7)
≥3 to <6	27 (9.9)	18 (6.6)	29 (10.5)	26 (9.5)
≥6 to <12	21 (7.7)	27 (9.9)	27 (9.8)	31 (11.3)
≥12	212 (77.7)	220 (80.9)	212 (76.8)	204 (74.5)

* One patient was excluded because of duplicate enrollment at different sites.

† Two patients were excluded because of duplicate enrollment at different sites.

BMI, body mass index; MED, morphine equivalent dose; SBM, spontaneous bowel movement; SD, standard deviation; SOC, system organ class.

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compared with placebo ($P < 0.0001$, both studies, all time points) (**Fig. 3**).

The median time to first SBM after the initial dose was significantly shorter in the naldemedine group compared with placebo (COMPOSE-1, 16.1 vs 46.7 hours; COMPOSE-2, 18.3 vs 45.9 hours; $P < 0.0001$, both studies) (**Fig. 4**). The median time to first CSBM after the initial dose was also significantly shorter in the naldemedine group compared with placebo (COMPOSE-1, 49.0 vs 128.9 hours; COMPOSE-2, 49.5 vs 136.8 hours; $P < 0.0001$, both studies).

In both studies, the change from baseline in frequency of SBMs per week was significantly higher in the naldemedine group vs the placebo group at week 1 ($P < 0.001$ for both between-group comparisons), with significant increases maintained at each week through week 12 (**Fig. 5**).

A greater proportion of patients in the naldemedine group (45%-47%) experienced an SBM on day 1 compared with the placebo group (16%-19%; **Fig. 6**). The proportion of patients who experienced an SBM remained higher in the naldemedine group from days 2 to 7 compared with the placebo group (41%-52% vs 29%-39%, respectively).

3.3. Safety

As previously reported, the overall incidence of TEAEs during the studies was similar between the naldemedine groups and the placebo groups (COMPOSE-1, 49% vs 45%, respectively; COMPOSE-2, 50% vs 48%, respectively). Treatment-related TEAEs were reported more commonly in the naldemedine groups compared with the placebo groups (COMPOSE-1, 22% vs 17%, respectively; COMPOSE-2, 17% vs 11%, respectively), likely driven by a higher incidence of GI TEAEs.[10]

In the naldemedine group, GI TEAEs occurred most frequently on day 1, although the incidence was low (6%-7%), and then decreased in occurrence from days 2 to 7 (0%-3%). In the placebo group, the incidence of GI TEAEs was similar from days 1 to 7 (0%-1%) (**Fig. 6**). The 3 most common GI TEAEs during the studies, abdominal pain, diarrhea, and nausea,[10] were generally mild to moderate in severity. During the first week of treatment, these occurred most frequently on day 1 and then decreased in occurrence from days 2 to 7 in the naldemedine group (**Fig. 7**).

During the first 7 days of the study, there were 6 discontinuations in each study in the naldemedine group and 2 discontinuations in each study in the placebo group. None of the discontinuations in the naldemedine group were due to GI TEAEs.

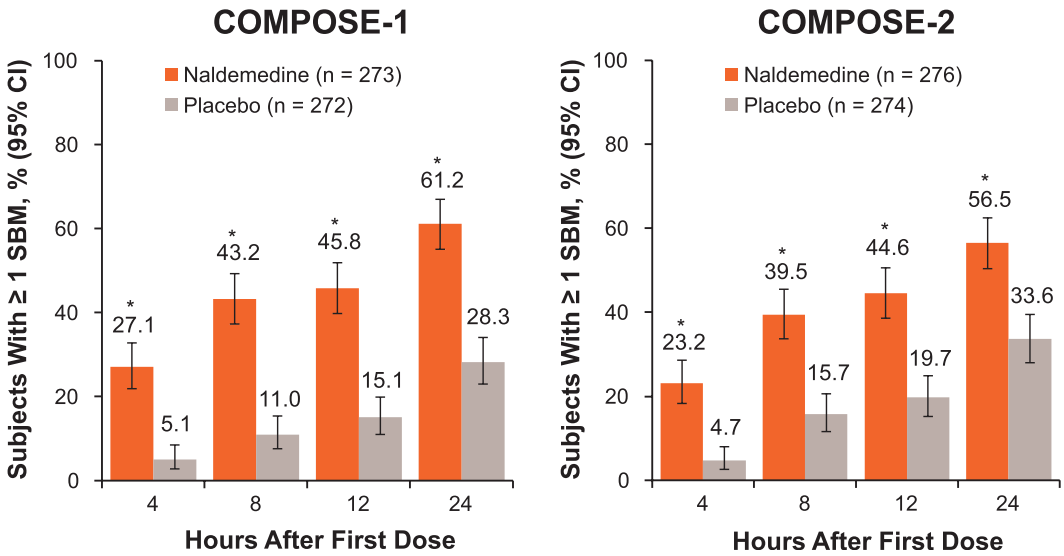

Figure 2. Patients with ≥1 spontaneous bowel movement after the first dose. *$P < 0.0001$; naldemedine vs placebo; Cochran–Mantel–Haenszel test adjusted by opioid dose stratum. SBM, spontaneous bowel movement.

4. Discussion

In patients with OIC, producing a BM soon after treatment initiation combined with the ability to tolerate treatment may be important in effectively managing the symptoms of OIC. This exploratory analysis provides temporal characterization of the time to relief from OIC with naldemedine treatment in patients with chronic noncancer pain. Significant differences in all measurements of onset of effect, including the proportion of patients with an SBM/CSBM within 24 hours after the initial dose, time to the first SBM/CSBM after the initial dose, and the weekly frequency of SBMs, were observed in the naldemedine group compared with placebo. A majority of patients experienced an SBM within 24 hours after the first dose of naldemedine, with a median time to first SBM of 16 to 18 hours, and approximately one-quarter of patients experienced an SBM within 4 hours after first dose. Furthermore, a significant increase in SBM frequency was observed by the end of week 1 that was durable and maintained throughout the 12-week treatment period. Collectively, these data support the timely onset of action of naldemedine and consistency and durability of treatment effect over time.

Although direct comparisons are difficult to make due to differences in study methodologies, the results of our analysis generally align with those previously reported for other PAMORAs. The median time to first postdose laxation with naloxegol (12.5 and 25 mg doses) was 6 to 20 hours,[7] and the occurrence of laxation within 4 hours of the first dose was 24% to 25% for oral methylnaltrexone (300 and 450 mg doses)[14] and 34% for subcutaneous methylnaltrexone.[20]

Naldemedine was generally well tolerated in these phase 3 trials, with an overall incidence of TEAEs similar to placebo. Gastrointestinal side effects were the most frequently reported TEAEs, which is consistent with the mechanism of action of naldemedine, being a PAMORA, and primarily blocking the effects of opioids on μ-opioid receptors in the GI tract.[17] Most GI TEAEs were mild to moderate in severity and occurred early in

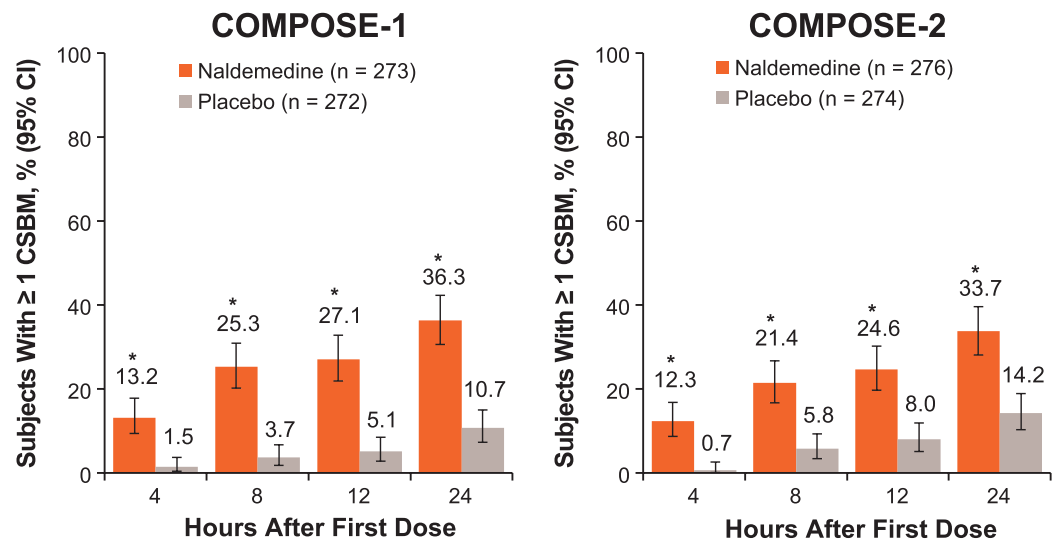

Figure 3. Patients with ≥1 complete spontaneous bowel movement after the first dose. *$P < 0.0001$; naldemedine vs placebo; Cochran–Mantel–Haenszel test adjusted by opioid dose stratum. CSBM, spontaneous bowel movement with a feeling of complete evacuation.

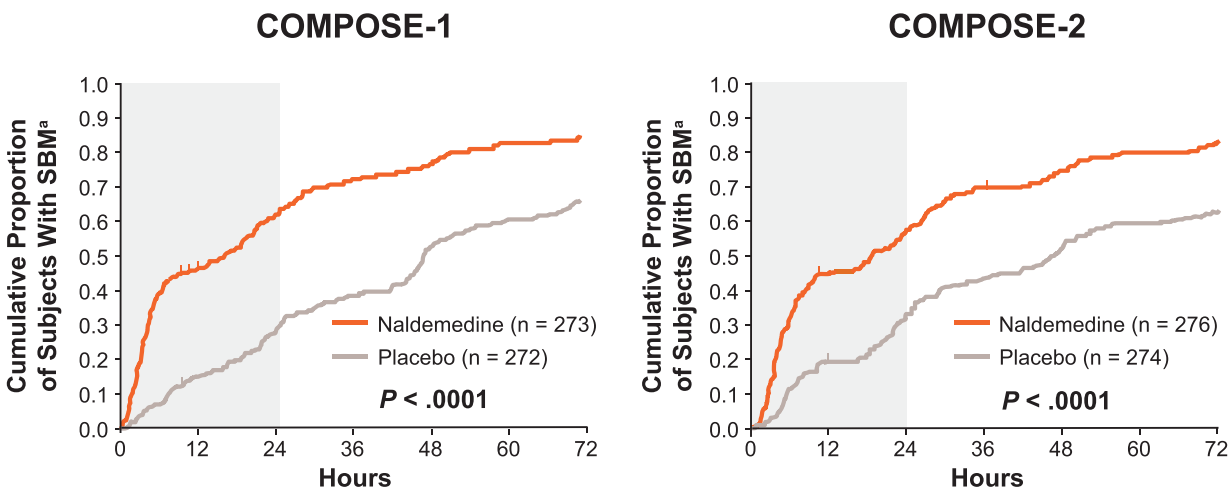

Figure 4. Time to first spontaneous bowel movement. [a]Kaplan–Meier analysis of time to first SBM was conducted in the intent-to-treat population, including patients who might have discontinued within 72 hours of the initial dose. SBM, spontaneous bowel movement.

treatment (on day 1) before decreasing in frequency from days 2 to 7. The increase in GI TEAEs of abdominal pain and diarrhea in the naldemedine group compared with placebo are likely due to the increase in GI motility as demonstrated by the large proportion of patients in the naldemedine group (45%-47%) who experienced an SBM on day 1. This temporal association of the GI AEs with the time of the first BM after initiation of therapy was expected, given the mechanism of action of naldemedine, and the observed speed of onset is consistent with the pharmacokinetic profile of naldemedine as previously reported.[16]

Nonetheless, the overall incidence of abdominal pain with naldemedine during the 12-week treatment periods of COMPOSE-1 and COMPOSE-2 was relatively low (5%-6%)[10] compared with other PAMORAs (7%-19%),[7,10,14,18] and the incidence of diarrhea was similar (7%-9% vs 3%-9%, respectively).[7,10,14,18] These findings may guide clinicians in counseling patients about what to expect after initiation of naldemedine treatment. Informing patients in advance of commencing treatment on common adverse effects, how likely they are to occur, and whether they will self-resolve without intervention may help avoid nonadherence to medication[4] and alleviate any potential fears or concerns that may arise.

Limitations of the analysis include the use of exploratory outcomes to evaluate onset of action; however, it should be noted that each of the outcomes used for this analysis were prespecified in the original clinical trial protocols, with the relevant data collected prospectively. In addition, these analyses were performed in patients who were not being treated concurrently with over-the-counter laxatives. This was in accordance with the regulatory mandate for such clinical trials; however, further studies in patients who are also on laxatives should be performed. Finally, analyses of clinical data to better elucidate the relationship between improvement in GI function after treatment with naldemedine and the patients' perceptions of OIC disease burden are warranted.

In conclusion, this analysis of multiple efficacy measures of time to onset of effect from 2 phase 3 trials of naldemedine in the treatment of OIC in patients with chronic noncancer pain demonstrated that naldemedine quickly improved symptoms of OIC, with most patients experiencing an SBM within 24 hours of the first dose, and that improvement was sustained for the duration of treatment. Furthermore, the occurrence and resolution of the relatively low incidence of GI-related AEs within the first week of treatment parallel the timely onset of action of

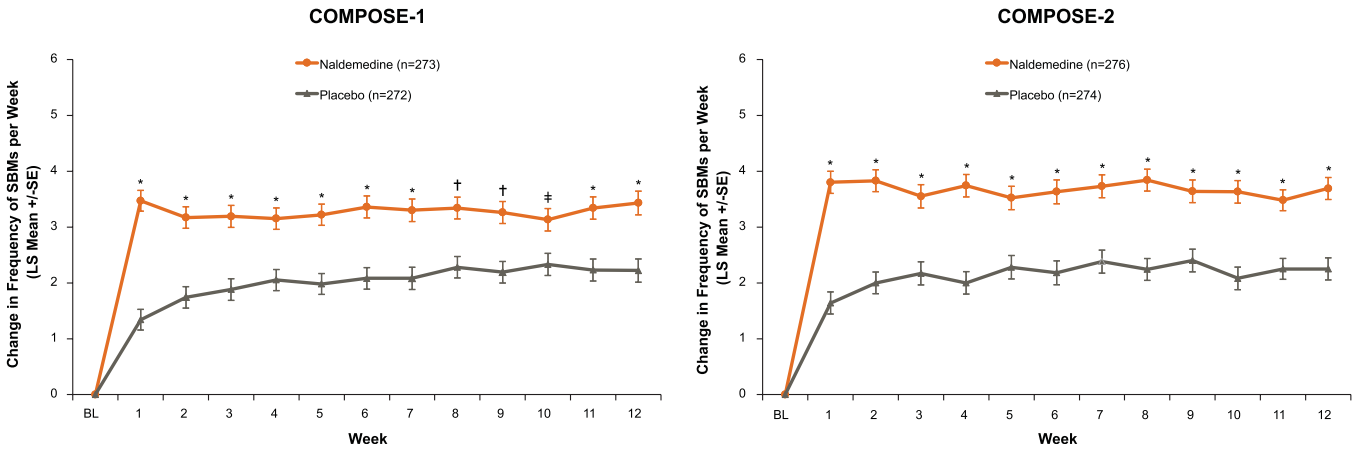

Figure 5. Change from baseline in frequency of spontaneous bowel movements per week (mixed-effect repeat-measures model with terms for treatment group, time, treatment-by-time as a fixed effect, and the opioid dose strata as a covariate). *Nominal $P < 0.0001$; †Nominal $P = 0.0001$; ‡Nominal $P < 0.005$. BL, baseline; LS, least squares; SBM, spontaneous bowel movement; SE, standard error.

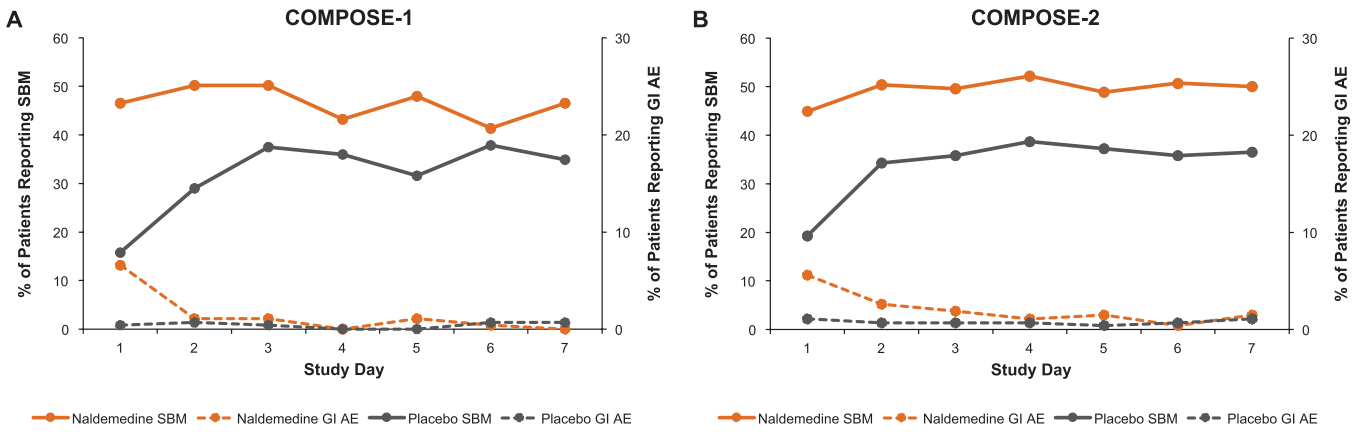

Figure 6. Incidence of spontaneous bowel movements and gastrointestinal treatment-emergent adverse events during study days 1 to 7. (A) COMPOSE-1. (B) COMPOSE-2. AE, adverse event; GI, gastrointestinal; SBM, spontaneous bowel movement.

naldemedine. This suggests that naldemedine exerts its effect by restarting the motility of the GI tract and it is likely that this initial increase in motility leads to these GI-related AEs. These results provide valuable information regarding what to expect when initiating treatment with naldemedine in patients with chronic noncancer pain and OIC; counseling patients on the expected onset of action and side-effect profile of naldemedine could help to improve adherence to treatment.

Conflict of interest statement

J. Wild received a stipend from Shionogi, Inc, for review of the clinical study report. M. Hale was a consultant to Shionogi, Inc, and received a stipend for review of the clinical study report. J.C. Arjona Ferreira was an employee of Shionogi, Inc, at the time this study was conducted. T. Yamada is an employee of Shionogi, Inc, who may or may not own stock options.

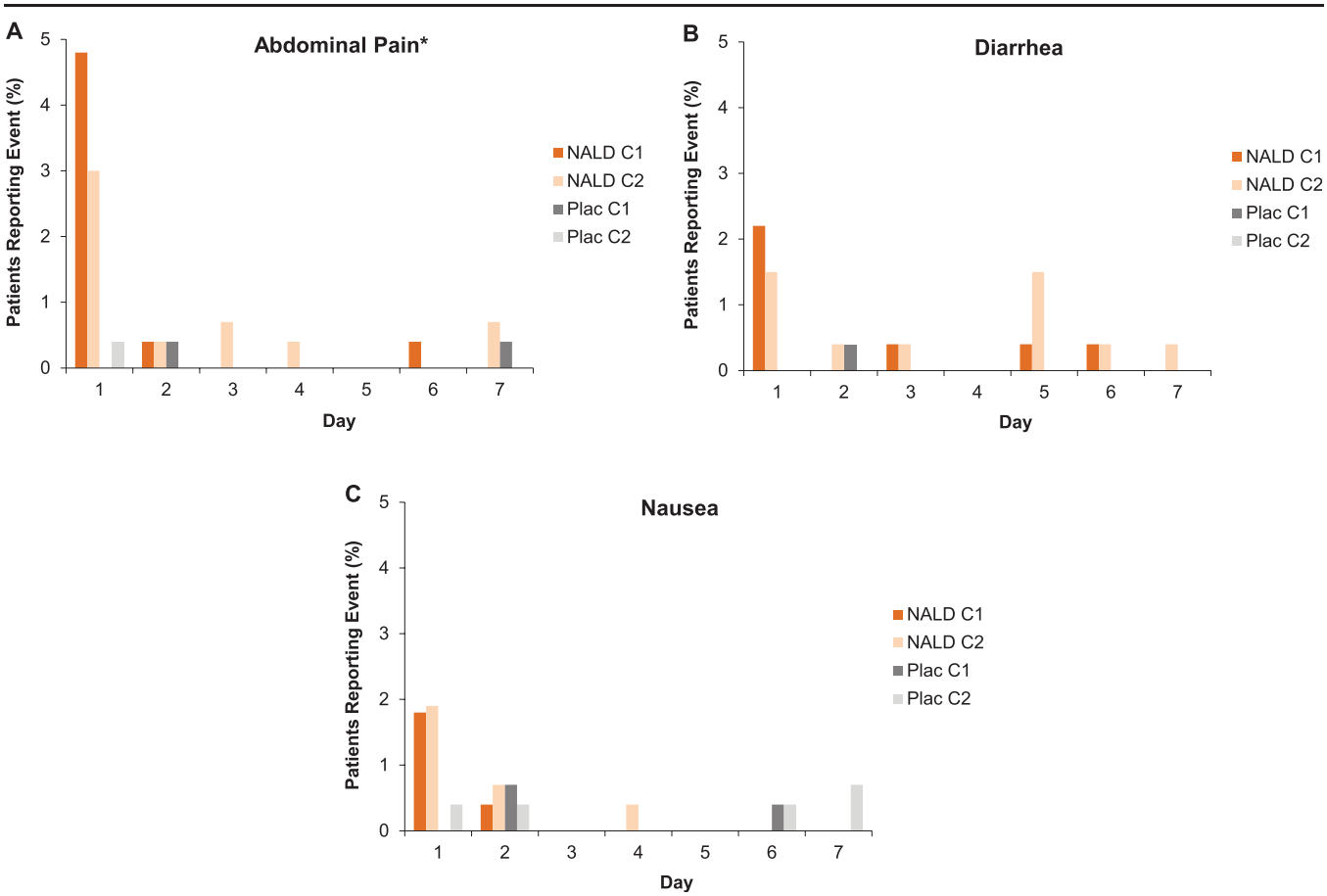

Figure 7. Number of patients reporting the 3 most common gastrointestinal treatment-emergent adverse events during study days 1 to 7. (A) Abdominal Pain. (B) Diarrhea. (C) Nausea. *Abdominal pain includes treatment-emergent adverse events of "abdominal pain," "abdominal pain lower," "abdominal pain upper," and "abdominal discomfort." C1, COMPOSE-1; C2, COMPOSE-2; Nald, naldemedine; Plac, placebo.

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