



# Safety and Efficacy of Naldemedine for the Treatment of Opioid-Induced Constipation in Patients with Chronic Non-Cancer Pain Receiving Opioid Therapy: A Subgroup Analysis of Patients $\geq 65$ Years of Age

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Published online: 21 February 2020  
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## Abstract

**Background** Opioid-induced constipation (OIC), the most common side effect of opioid treatment, is under-recognized and undertreated in older patients. Naldemedine, an oral, peripherally acting  $\mu$ -opioid receptor antagonist (PAMORA), is approved in Japan, the United States, and the European Union for treatment of OIC in adult patients.

**Objective** This integrated analysis of three phase 3 trials (COMPOSE-1, COMPOSE-2, and COMPOSE-3) evaluated the safety and efficacy of naldemedine for up to 12 weeks in a subgroup of patients aged  $\geq 65$  years.

**Methods** Patients aged 18–80 years with chronic non-cancer pain for  $\geq 3$  months (treated with opioids for  $\geq 3$  months in COMPOSE-1 and COMPOSE-2) and OIC received oral naldemedine 0.2 mg or placebo once daily. Safety assessments included overall incidence of treatment-emergent adverse events (TEAEs), TEAEs in the gastrointestinal disorders System Organ Class, and TEAEs of opioid withdrawal or possible opioid withdrawal. Efficacy was based on the proportion of responders in COMPOSE-1 and COMPOSE-2, defined as having  $\geq 3$  spontaneous bowel movements/week and a  $\geq 1$ -spontaneous bowel movement/week increase from baseline for  $\geq 9$  of 12 weeks and  $\geq 3$  of the last 4 weeks.

**Results** A total of 14.8% (344/2328) of patients were aged  $\geq 65$  years in all studies. The incidence of TEAEs in naldemedine-treated patients aged  $\geq 65$  years (45.9%) was comparable to that in patients aged  $\geq 65$  years receiving placebo (51.6%) and in the overall naldemedine group (47.1%). The incidence of gastrointestinal disorders System Organ Class TEAEs in naldemedine-treated patients aged  $\geq 65$  years (20.2%) was also comparable to that in patients aged  $\geq 65$  years receiving placebo (16.1%) and in the overall naldemedine group (21.8%). The incidence of TEAEs of opioid withdrawal with naldemedine was 1.1% in patients aged  $\geq 65$  years and 1.0% overall, and the incidence of TEAEs of possible opioid withdrawal was 1.1% in patients aged  $\geq 65$  years and 1.7% overall. The proportion of responders was higher in naldemedine-treated patients versus placebo, both overall (50.1% vs 34.1%;  $p < 0.0001$ ) and in those aged  $\geq 65$  years (51.8% vs 37.6%).

**Conclusions** This integrated analysis confirmed that OIC treatment with naldemedine 0.2 mg was generally well tolerated and effective in patients aged  $\geq 65$  years with chronic non-cancer pain. Safety and efficacy results were consistent with the overall patient population.

**ClinicalTrials.gov registration** NCT01965158, NCT01993940, NCT01965652.

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s40266-020-00753-2>) contains supplementary material, which is available to authorized users.

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## Key Points

Individuals aged 65 years or older can safely use naldemedine to treat opioid-induced constipation.

Naldemedine is effective in improving symptoms of opioid-induced constipation in adults, regardless of age.

## 1 Introduction

Opioid analgesic therapy is a common treatment option for chronic moderate-to-severe non-cancer and cancer pain in selected patients [1]. Opioid-induced constipation (OIC) is the most common adverse effect associated with opioid analgesic treatment and results from opioids activating  $\mu$ -opioid receptors that are expressed in the enteric nervous system of the gastrointestinal (GI) tract [2]. Unlike other adverse effects associated with opioid therapy, OIC persists unabated over time, even with use of laxatives [3], and patients may skip or reduce their opioid doses in an attempt to manage such adverse effects, which can lead to inadequate pain relief [4].

Opioids are effective for treating chronic pain in older patients ( $\geq 65$  years of age) [5]; however, evidence suggests the risk of OIC rises with age [6]. In fact, OIC is under-recognized and undertreated in the older population [7], and often does not respond to conventional laxatives [8]. Additionally, studies of nursing home residents show that OIC is associated with worse physical and mental outcomes in older patients [9, 10]. Naldemedine is an oral, once-daily, peripherally acting  $\mu$ -opioid receptor antagonist (PAMORA) approved in Japan, the United States, and the European Union for the treatment of OIC in adults [11–14].

The efficacy and safety of once-daily naldemedine 0.2 mg in patients with chronic non-cancer pain and OIC have been demonstrated in three placebo-controlled phase 3 studies: two identically designed 12-week studies (COMPOSE-1 and COMPOSE-2) [15] and a 52-week study (COMPOSE-3) [16]. This analysis was conducted to characterize the safety and efficacy of naldemedine 0.2 mg once daily versus placebo for up to 12 weeks in patients aged 65 years or older in the three studies.

## 2 Methods

This subgroup analysis of patients  $\geq 65$  years of age used data from three multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical studies that evaluated the efficacy and safety of naldemedine 0.2 mg once daily in patients with OIC and chronic non-cancer pain (Fig. 1). COMPOSE-1 (NCT01965158) and COMPOSE-2 (NCT01993940) had 12-week treatment periods and were conducted in patients not taking laxatives [15]. COMPOSE-3 (NCT01965652) had a 52-week treatment period and was conducted in patients who could be on stable laxatives [16]. For the purpose of integration, this analysis includes only data from the first dose up to 12 weeks of treatment in all three studies and does not include events reported

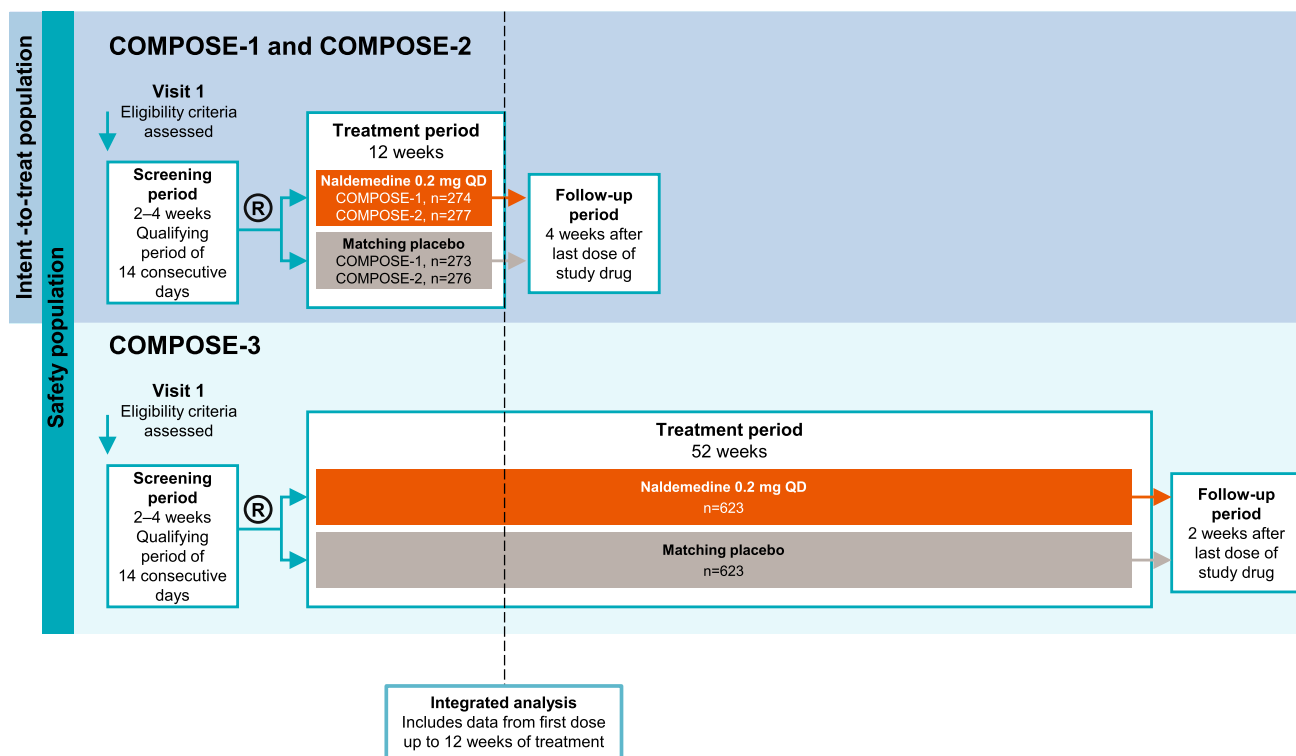


Fig. 1 Study designs. R randomization

during the follow-up periods. The studies were conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki and were approved by the institutional review boards at each study center (see the electronic supplementary material, Online Resource 1). All patients provided written informed consent. Patient disposition profiles for the individual COMPOSE studies have been previously published [15, 16].

All three studies had key inclusion criteria, including age 18–80 years, inclusive; chronic non-cancer pain for  $\geq 3$  months (treated with opioid analgesics for  $\geq 3$  months in COMPOSE-1 and COMPOSE-2) and OIC; and receipt of a stable opioid analgesic regimen with a total daily dose of  $\geq 30$  mg oral morphine equivalent for  $\geq 1$  month before screening. In addition, participants in the COMPOSE-1 and COMPOSE-2 studies were not currently using or had discontinued laxatives and met all three of the following criteria during a 14-consecutive-day qualifying period during screening: (1) experienced four or fewer spontaneous bowel movements (SBMs) in the qualifying period; (2) reported three or fewer SBMs in any 7-day period during screening; and (3) had one or more symptoms of OIC in  $\geq 25\%$  of bowel movements, including straining, hard or lumpy stools, sensation of incomplete evacuation, or anorectal obstruction/blockage. In a 14-consecutive-day qualifying period during screening, participants in COMPOSE-3 must have experienced four or fewer SBMs in total and three or fewer SBMs in any 7-day period and patients may or may not have been on a laxative regimen at screening. The proportion of patients either on a routine laxative regimen (naldemedine 50.2%; placebo 54.0%) or not (naldemedine 30.0%; placebo 29.5%) was similar between treatment groups.

Key exclusion criteria in all three studies included evidence or history of bowel structural abnormalities, strictures, and obstructions, or history of bowel surgery; medical conditions affecting GI transit; a history of chronic constipation unrelated to opioid use; and no history of previous laxative use for OIC.

The safety and tolerability of naldemedine were assessed with data up to 12 weeks from all three studies (safety population: all randomized patients who received at least one dose of study drug and were analyzed by the treatment actually received) using the incidence of treatment-emergent adverse events (TEAEs), treatment-related TEAEs (adverse drug reactions), TEAEs in the GI disorders System Organ Class, and TEAEs of opioid withdrawal or possible opioid withdrawal. TEAEs of opioid withdrawal were defined using “drug withdrawal” per standardized Medical Dictionary for Regulatory Activities queries, and possible opioid withdrawal was defined as three or more TEAEs potentially related to opioid withdrawal syndrome with onset on the same date or occurring within 1 day. The efficacy of naldemedine compared with placebo was assessed in

COMPOSE-1 and COMPOSE-2 (intent-to-treat population, including all randomized patients) based on the proportion of responders. Responders were defined as having  $\geq 3$  SBMs per week and a  $\geq 1$ -SBM-per-week increase from baseline for  $\geq 9$  of 12 weeks and  $\geq 3$  of the last 4 weeks. The  $p$  value for the comparison of responders in the naldemedine versus the placebo group for the overall patient population was calculated using the Cochran–Mantel–Haenszel test; no statistical analyses were performed for subgroup comparisons.

## 3 Results

### 3.1 Safety

The integrated safety population included 2328 patients from the COMPOSE-1, COMPOSE-2, and COMPOSE-3 studies. The demographics and baseline medical characteristics of the integrated safety population are summarized in Table 1. Of the 1163 patients treated with naldemedine, 183 (15.7%) were aged  $\geq 65$  years, and of the 1165 patients who received placebo, 161 (13.8%) were aged  $\geq 65$  years. Most patients were white (overall 80.2%;  $\geq 65$  years 87.2%) and female (overall 62.0%;  $\geq 65$  years 57.8%). Patients’ mean duration of opioid use prior to screening was 58.1–61.8 months for the overall population and 57.6–71.3 months for patients aged  $\geq 65$  years, mean daily morphine equivalent dose was 122.2–126.1 mg for the overall population and 84.6–106.4 mg for patients aged  $\geq 65$  years, and 899 patients (38.6%) overall and 89 patients (25.9%) aged  $\geq 65$  years used  $> 100$  mg morphine equivalent dose daily.

The incidence of TEAEs was similar with naldemedine in the overall patient population (47.1%) and in patients aged  $\geq 65$  years (45.9%) (Fig. 2a). The incidence of adverse drug reactions with naldemedine was also similar both overall (20.1%) and in patients aged  $\geq 65$  years (18.6%; Fig. 2b). In patients receiving placebo, the incidence of TEAEs was similar to or greater than that in patients receiving naldemedine, and the incidence of adverse drug reactions was lower than that in patients receiving naldemedine for the overall patient population and for patients aged  $\geq 65$  years of age.

GI TEAEs were reported in 37 of 183 patients (20.2%) aged  $\geq 65$  years who received naldemedine and 253 of 1163 patients (21.8%) in the overall patient population who received naldemedine; a lower incidence of GI TEAEs was reported in patients receiving placebo for both the overall patient population and patients aged  $\geq 65$  years (Fig. 2c). The incidence of the most common GI disorders reported in patients who received naldemedine, including abdominal pain, diarrhea, nausea, and vomiting, was similar in patients aged 65 years or older to the incidence in the overall patient population (Fig. 3). Again, a lower incidence

**Table 1** Baseline demographics and medical characteristics

Attribute	Integrated safety population (COMPOSE-1/COMPOSE-2/COMPOSE-3)				Intent-to-treat population (COMPOSE-1/COMPOSE-2)			
	Overall		≥ 65 years of age		Overall		≥ 65 years of age	
	Naldemedine 0.2 mg/day (n = 1163)	Placebo (n = 1165)	Naldemedine 0.2 mg/day (n = 183)	Placebo (n = 161)	Naldemedine 0.2 mg/day (n = 549)	Placebo (n = 546)	Naldemedine 0.2 mg/day (n = 83)	Placebo (n = 85)
<b>Age</b>								
Mean age, years (SD)	53.6 (11.1)	52.9 (10.9)	70.3 (4.1)	69.8 (4.0)	53.7 (10.5)	53.1 (11.2)	70.1 (4.1)	69.9 (4.1)
< 65 years, % (n)	84.3 (980)	86.2 (1004)	–	–	84.9 (466)	84.4 (461)	–	–
≥ 65 years, % (n)	15.7 (183)	13.8 (161)	–	–	15.1 (83)	15.6 (85)	–	–
Female, % (n)	60.6 (705)	63.3 (738)	56.8 (104)	59.0 (95)	59.4 (326)	61.5 (336)	56.6 (47)	58.8 (50)
Mean BMI, kg/m <sup>2</sup> (SD)	31.5 (7.4) <sup>a</sup>	31.4 (7.4) <sup>a</sup>	30.5 (6.9)	30.4 (5.6) <sup>b</sup>	31.4 (7.2) <sup>c</sup>	31.3 (7.2) <sup>d</sup>	30.8 (7.3)	30.6 (6.1) <sup>e</sup>
<b>Region, % (n)</b>								
North America	85.8 (998)	86.4 (1007)	76.0 (139)	77.6 (125)	85.8 (471)	85.7 (468)	78.3 (65)	74.1 (63)
Rest of world	14.2 (165)	13.6 (158)	24.0 (44)	22.4 (36)	14.2 (78)	14.3 (78)	21.7 (18)	25.9 (22)
<b>Race, % (n)</b>								
White	79.4 (924)	80.9 (943)	87.4 (160)	87.0 (140)	79.8 (438)	81.9 (447)	89.2 (74)	84.7 (72)
Black	19.0 (221)	16.7 (195)	11.5 (21)	11.2 (18)	18.6 (102)	15.9 (87)	8.4 (7)	12.9 (11)
Other	1.5 (18)	2.3 (27)	1.1 (2)	1.9 (3)	1.6 (9)	2.2 (12)	2.4 (2)	2.4 (2)
<b>Opioid use</b>								
Mean duration of opioid use, months (SD)	61.8 (65.3)	58.1 (56.4)	71.3 (88.2)	57.6 (58.0)	61.1 (61.7)	59.2 (57.1)	55.6 (65.4)	58.9 (63.8)
Mean daily opioid dose, MED, mg (SD)	122.2 (134.5)	126.1 (157.3)	84.6 (80.4)	106.4 (140.9)	121.6 (120.0)	131.8 (150.0)	81.5 (73.8)	122.6 (177.2)
<b>Patients with daily opioid dose, % (n)</b>								
30 to 100 mg	61.7 (717)	61.1 (712)	76.5 (140)	71.4 (115)	59.0 (324)	58.6 (320)	74.7 (62)	69.4 (59)
> 100 mg	38.3 (446)	38.9 (453)	23.5 (43)	28.6 (46)	41.0 (225)	41.4 (226)	25.3 (21)	30.6 (26)
Mean duration of treatment exposure, days (SD)	76.6 (20.8)	77.2 (18.8)	76.9 (20.6)	77.6 (19.1)	77.5 (22.0) <sup>f</sup>	77.9 (20.4)	76.1 (23.1) <sup>g</sup>	77.7 (21.1)

BMI body mass index, MED morphine equivalent dose, SD standard deviation

<sup>a</sup>n = 1162

<sup>b</sup>n = 160

<sup>c</sup>n = 547

<sup>d</sup>n = 543

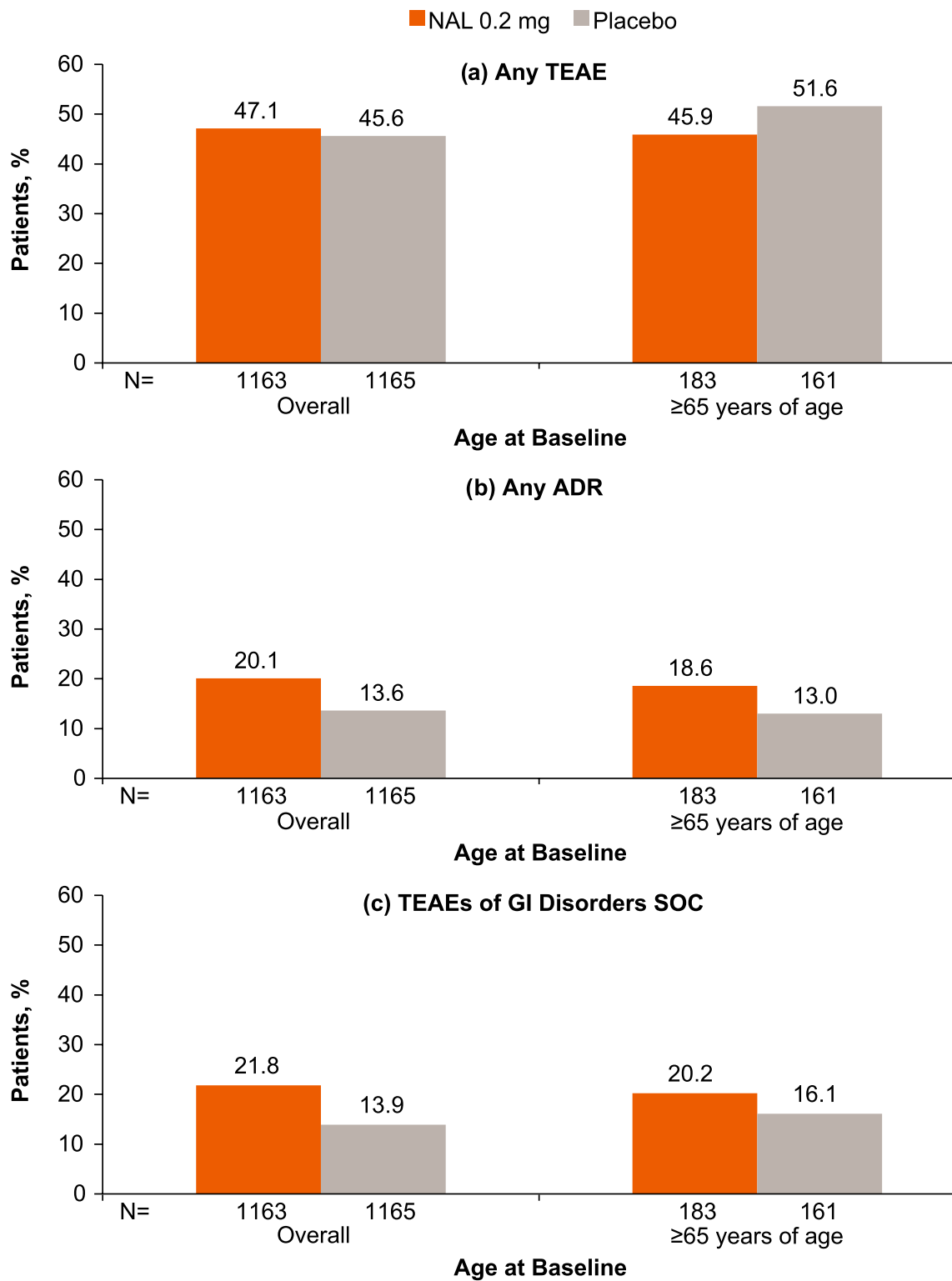
<sup>e</sup>n = 84

<sup>f</sup>n = 542

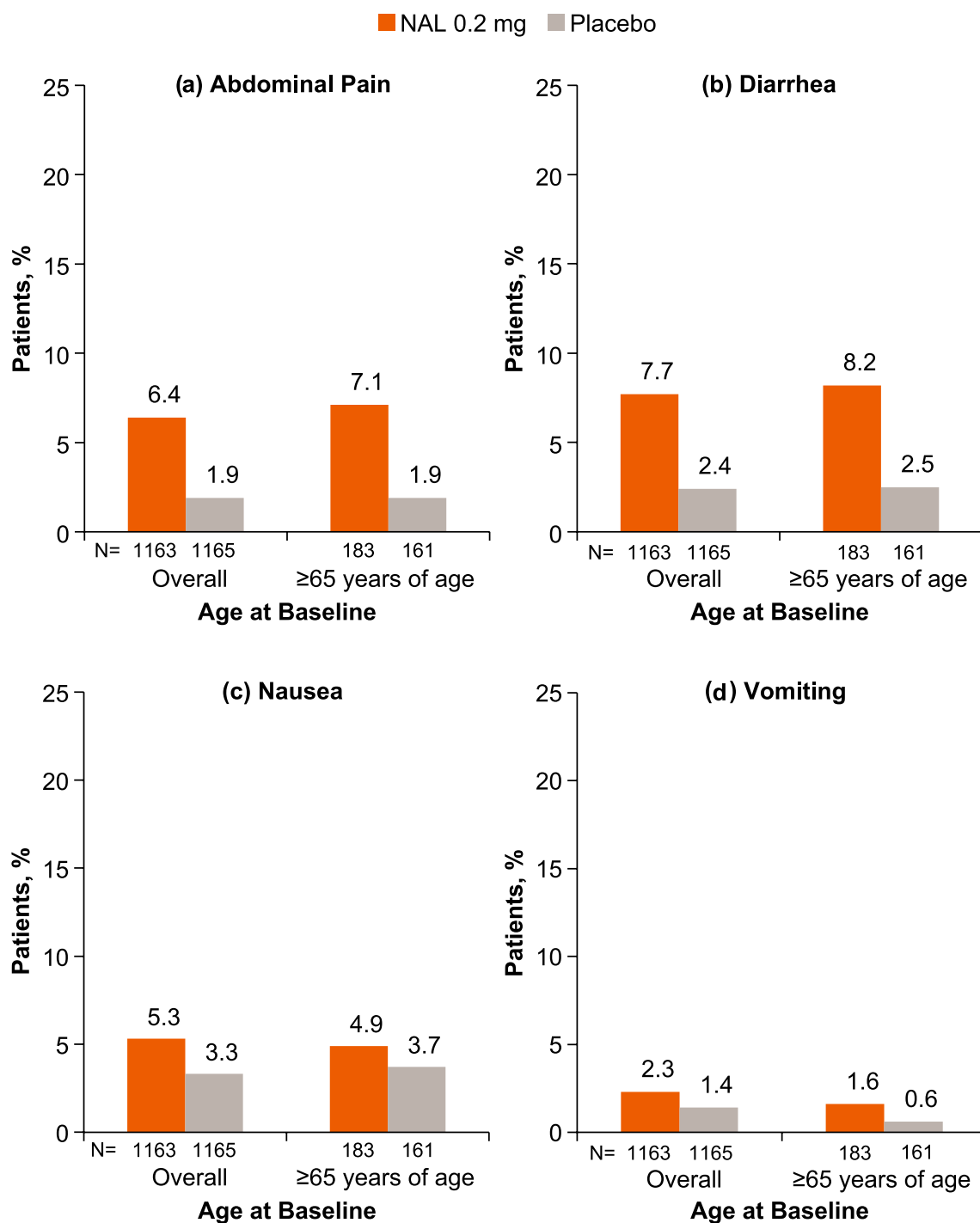
<sup>g</sup>n = 82

of these GI disorders was reported in patients receiving placebo for both the overall patient population and patients aged ≥ 65 years.

The incidence of TEAEs of opioid withdrawal and possible opioid withdrawal is shown in Fig. 4. Opioid withdrawal was reported in 12 of 1163 patients (1.0%) treated



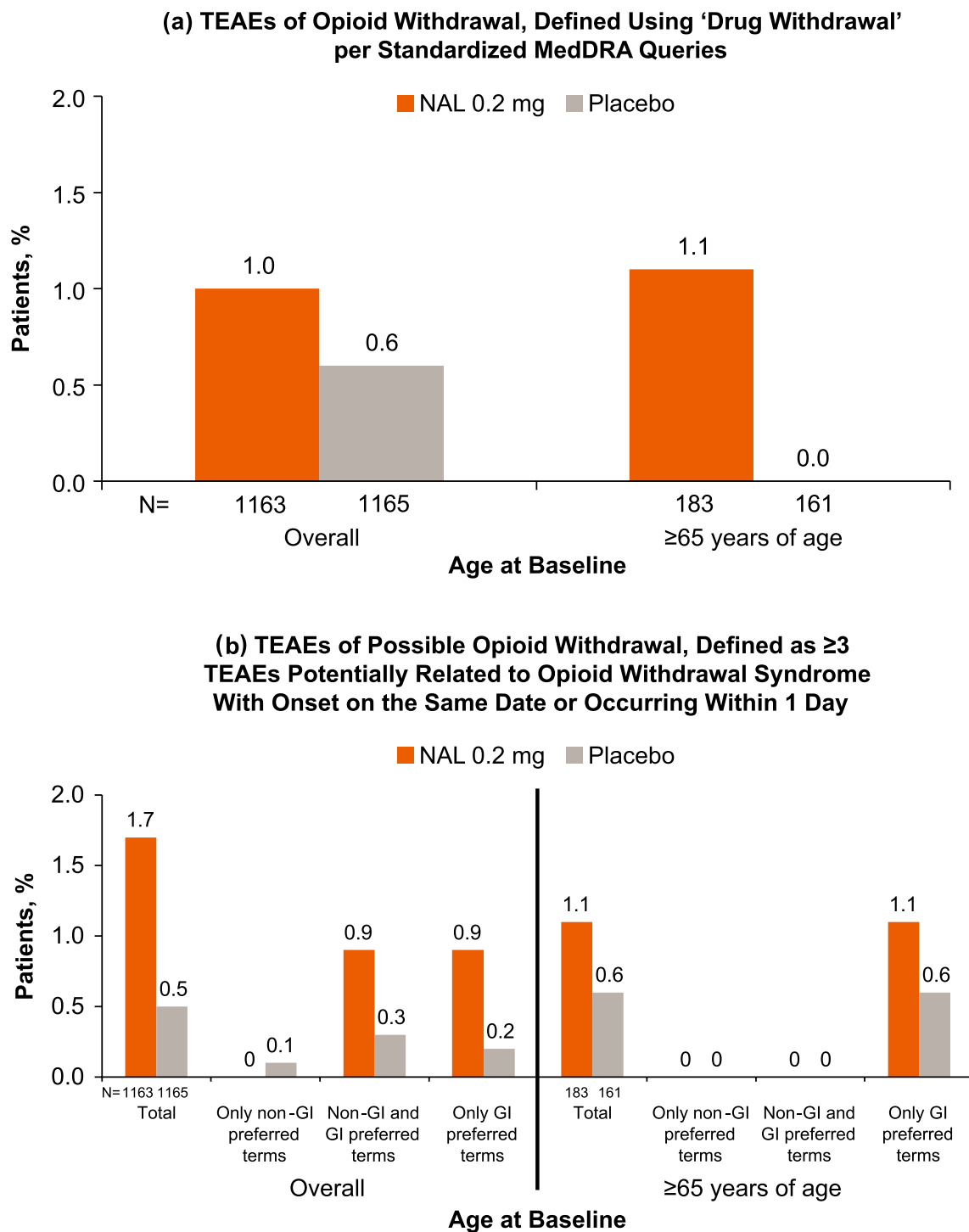
**Fig. 2** Incidence of any TEAE (a), any ADR (b), and TEAEs of GI disorders SOC (c) by age at baseline (safety population). *ADR* adverse drug reaction, *GI* gastrointestinal, *SOC* system organ class, *TEAE* treatment-emergent adverse event



**Fig. 3** Incidence of abdominal pain (a), diarrhea (b), nausea (c), and vomiting (d) by age at baseline (COMPOSE-1, COMPOSE-2, and COMPOSE-3 safety population). *NAL* naldemedine

with naldemedine overall and in two of 183 patients aged  $\geq 65$  years (1.1%); the incidence in the placebo groups ranged from 0% to 0.6%. Overall, possible opioid withdrawal was identified in 20 of 1163 naldemedine patients (1.7%), all of which were characterized either solely or at least partially by GI symptoms.

There were two cases of possible opioid withdrawal identified in patients aged  $\geq 65$  years receiving naldemedine (1.1%), both of which were characterized solely by GI symptoms. The incidence of possible opioid withdrawal in patients receiving placebo was 0.5% in the overall patient population and 0.6% in patients aged  $\geq 65$  years.



**Fig. 4** TEAEs of opioid withdrawal (a) and possible opioid withdrawal (b) (COMPOSE-1, COMPOSE-2, and COMPOSE-3 safety population). *GI* gastrointestinal, *MedDRA* Medical Dictionary for Regulatory Activities, *NAL* naldemedine; *TEAE* treatment-emergent adverse event

### 3.2 Efficacy

The intent-to-treat population included 1095 patients from the COMPOSE-1 and COMPOSE-2 studies. The distribution of demographics and baseline medical

characteristics in the intent-to-treat population was similar to that of the integrated safety population (Table 1). Of the 549 patients treated with naldemedine, 83 (15.1%) were aged ≥ 65 years, and of the 546 patients who received placebo, 85 (15.6%) were aged ≥ 65 years. Most patients

were white (overall 80.8%;  $\geq 65$  years 86.9%) and female (overall 60.5%;  $\geq 65$  years 57.7%). Patients' mean duration of opioid use prior to screening was 59.2–61.1 months for the overall population and 55.6–58.9 months for patients aged  $\geq 65$  years, mean daily morphine equivalent dose was 121.6–131.8 for the overall population and 81.5–122.6 for patients aged  $\geq 65$  years, and 451 patients (41.2%) overall and 47 patients (28.0%) aged  $\geq 65$  years used  $> 100$  mg morphine equivalent dose daily.

Overall, there were significantly more responders in the naldemedine group [50.1% (275/549)] than in the placebo group [34.1% (186/546); difference (95% confidence interval) 16.0% (10.2–21.8);  $p < 0.0001$ ]. Likewise, among patients aged  $\geq 65$  years, more patients in the naldemedine group [51.8% (43/83)] were responders compared with the placebo group [37.6% (32/85); difference (95% confidence interval) 12.6% (–2.3 to 27.5)].

## 4 Discussion

This integrated analysis evaluated the safety and efficacy of naldemedine 0.2 mg once daily for 12 weeks in patients aged  $\geq 65$  years with chronic non-cancer pain and OIC using data from the phase 3 clinical studies. Treatment with naldemedine was shown to be generally well tolerated compared with placebo in aged patients  $\geq 65$  years from the COMPOSE-1, COMPOSE-2, and COMPOSE-3 clinical studies. The incidence of overall TEAEs, adverse drug reactions, and TEAEs in the GI disorders System Organ Class in patients  $\geq 65$  years of age was consistent with that in the overall patient population, and GI-related TEAEs occurred more frequently in the naldemedine group compared with the placebo group in the overall patient population and in patients  $\geq 65$  years of age. This observation is expected due to the mechanism of action of naldemedine, which reverses the effects of opioids on  $\mu$ -opioid receptors in the GI tract [11]. The overall incidence of TEAEs of opioid withdrawal or possible opioid withdrawal was low in both the naldemedine and placebo treatment groups in the overall patient population and in patients  $\geq 65$  years of age, and all TEAEs of possible opioid withdrawal in the naldemedine group were solely or partially related to GI symptoms.

These results compare favorably with other orally available PAMORAs currently approved for the treatment of OIC. A pooled safety analysis of naloxegol studies suggested no increase in adverse events in patients aged  $\geq 65$  years [17], but data in Japanese patients showed higher exposure in older patients than in younger patients, although no dose adjustment is recommended [18]. Likewise, available information indicates oral methylnaltrexone is effective in patients aged  $\geq 65$  years, but a higher incidence of diarrhea (data not specified) was reported in older patients [19].

Results from our analysis found that diarrhea was the most commonly occurring GI disorder in patients aged  $\geq 65$  years receiving naldemedine; however, the incidence of diarrhea in the subgroup of patients aged  $\geq 65$  years (8.2%) was similar to that in the overall patient population (7.7%), which suggests that the occurrence of this adverse event in patients receiving naldemedine is not influenced by age.

Integrated data from the COMPOSE-1 and COMPOSE-2 studies showed that the proportion of responders in patients  $\geq 65$  years of age was consistent with the overall patient population and that the percentage of responders was higher with naldemedine than with placebo both in patients aged  $\geq 65$  years and in the overall patient population.

A limitation of this analysis is that it is a post hoc subgroup analysis. However, the large sample size for the integrated safety population ( $n = 2328$ ), which includes patients across the COMPOSE-1, COMPOSE-2, and COMPOSE-3 clinical studies, provides a robust data set for comparison of safety and tolerability in the overall patient population versus patients aged  $\geq 65$  years ( $n = 344$ ). The sample size for the intent-to-treat population from COMPOSE-1 and COMPOSE-2 was smaller (overall  $n = 1095$ ;  $\geq 65$  years of age  $n = 168$ ); however, the results in the subgroup of patients  $\geq 65$  years of age were also consistent with the overall patient population.

The results of this integrated analysis support the safety and efficacy of naldemedine in the treatment of OIC. An increase in age does not result in different tolerability and a different safety profile for naldemedine, nor is the efficacy of naldemedine affected by an increase in age.

**Acknowledgements** Editorial and writing support was provided by Bina Patel, PharmD, of Peloton Advantage, LLC, an OPEN Health company.

## Compliance with Ethical Standards

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committees (see the electronic supplementary material, Online Resource 1) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the studies.

**Funding** These studies were sponsored by Shionogi Inc., Florham Park, NJ. BDSI owns full rights to commercialize Symproic® (naldemedine) tablets 0.2 mg in the US for opioid-induced constipation. Editorial and writing support was funded by Shionogi Inc.

**Conflict of interest** James Wild received a stipend from Shionogi Inc. for review of the clinical study report. Lynn R. Webster has received honoraria for consultation from Daiichi Sankyo, Insys, Mallinckrodt, Merck, Pain Therapeutics, Pfizer, Shionogi, Teva, Trevena, and Valion; honoraria for work on advisory boards from BDSI, Ensysce Biosciences, Mallinckrodt, Neurana Pharmaceuticals, Pfizer, and Trevena; and travel expenses from BDSI, Daiichi Sankyo, Ensysce, Elysium,



Insys, Mallinckrodt, Pain Therapeutics, Pfizer, Shionogi, Teva, and Trevena. Martin Hale was a consultant to Shionogi Inc. and received a stipend for review of the clinical study report. Tadaaki Yamada is an employee of Shionogi Inc. who may or may not own stock options.

**Data availability statement** All data generated or analyzed during this study are included in this published article and its supplementary information files.

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