Phase 3 study to evaluate the efficacy and safety of naldemedine for the treatment of opioid-induced constipation (OIC) in cancer patients.

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Disclosures

- Takaaki Yokota and Yukio Tada are employees of Shionogi & Co., Ltd.
- Nobuyuki Katakami and Toshiyuki Harada were site investigators in the studies.
- Masaru Narabayashi and Narikazu Boku were the medical experts for the studies.

This is an encore presentation from ASCO 2016 and ESMO 2016

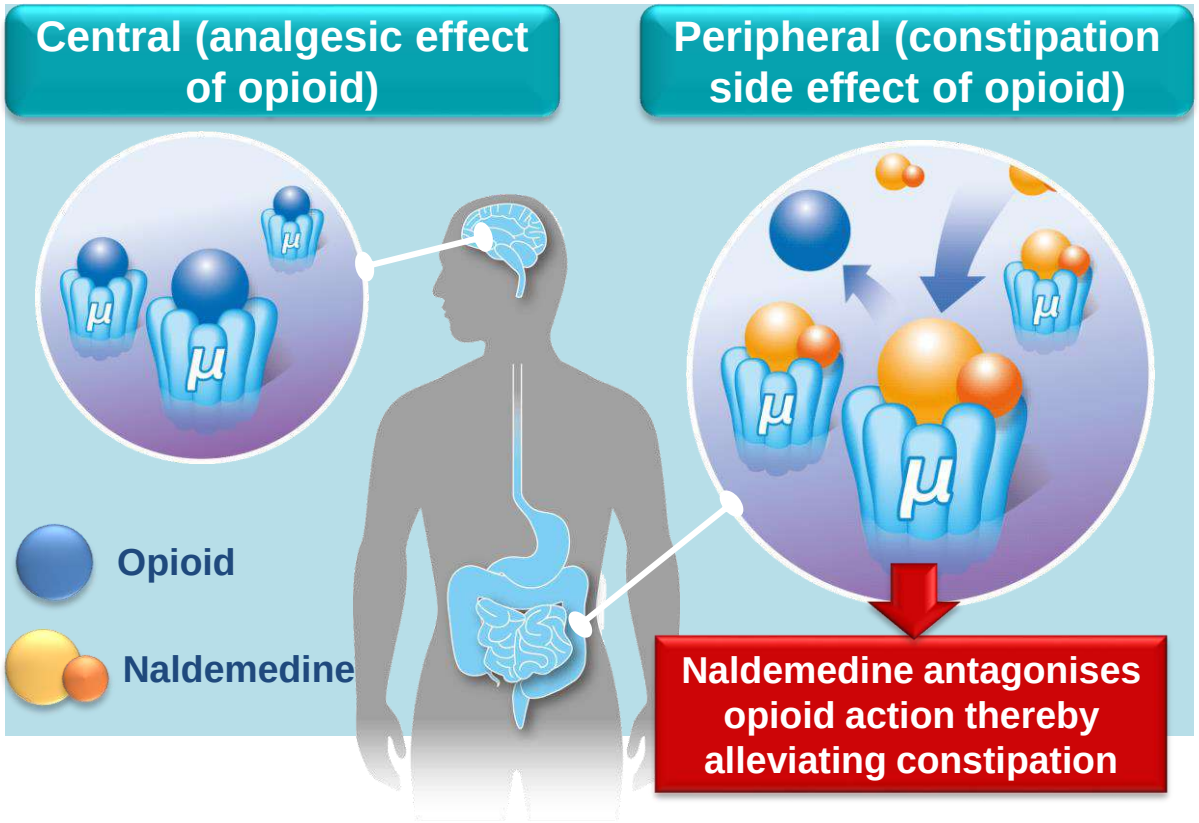
- Harada T et al. J Clin Oncol. 2016; 34: suppl 10016.
- Murata T et al. Annals Oncol. 2016; 27: suppl 1466P.

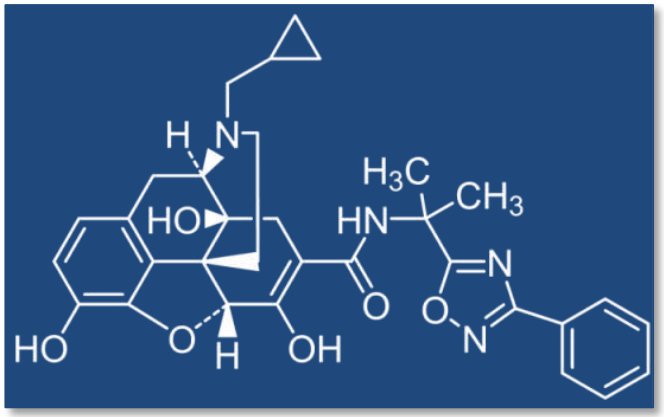
Mechanism of Opioid-Induced Constipation (OIC)

- The clinical benefit of opioid analgesics may be compromised by side effects, including OIC, nausea, and CNS events (eg, confusion, headache, and hallucination)[1,2]
- Opioids act through the μ-opioid receptors located in the enteric nervous system and can cause a reduction in gastrointestinal motility and fluid secretion, resulting in OIC[3]
  - Laxatives, the most commonly used as the first-line treatment for OIC, have limited efficacy and do not address the underlying mechanism of opioids that leads to OIC[2,4]

1. Morlion B et al. *Clin Drug Investig* 2015;35:1-11; 2. Poulsen JL et al. *Therap Adv Gastroenterol* 2015;8:360-72; 3. Camilleri M et al. *Neurogastroenterol Motil* 2014;26:1386-95; 4. Bell TJ et al. *Pain Med* 2009;10:35-42. CNS, central nervous system.

Naldemedine: A PAMORA for Treating OIC





Naldemedine

PAMORA: peripherally-acting mu-opioid receptor antagonist

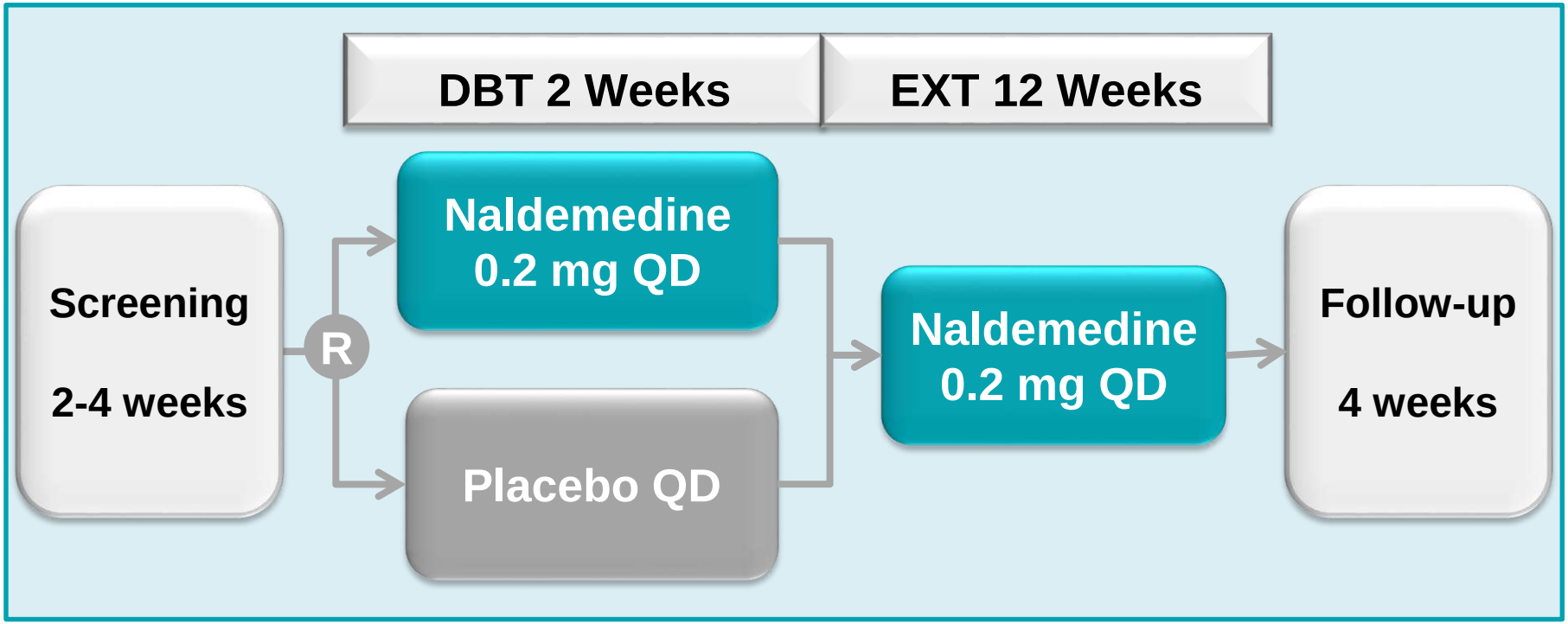
Previous Publication

- Naldemedine was effective and well-tolerated for both population
  - **Chronic non-cancer pain and OIC**
    - 2 replicated 12-week R, D-B, P-C studies
      - M. Hale et al DDW 2016
    - 52-week long term R, D-B, P-C study
      - L. Webster et al PAIN WEEK 2016
  - **Cancer and OIC**
    - 2-week R, P-C, D-B study and 2-week open-label extension study
      - T. Harada et al ASCO 2016, T. Murata et al ESMO 2016

R: randomised, D-B: double-blind, P-C: placebo-controlled

Overall Study Design

- Eligible subjects were randomised 1:1 to receive oral naldemedine 0.2 mg or placebo QD for 2 weeks followed by a 12-week open-label extension study



QD: once daily, R: randomisation, DBT: double-blind study, EXT: extension study

Inclusion & Exclusion Criteria (DBT)

Key Inclusion Criteria

- Age ≥20 years
- Cancer patients and use opioids for ≥2 weeks
- Receiving laxatives for OIC, or had been treated but not currently receiving laxatives due to insufficient efficacy or other reasons
- Met the following definition of OIC:
  - ≤5 SBMs during the 14-day screening period, and
  - ≥1 of the following symptoms in at least 25% bowel movements: straining, lumpy/hard stools, sensation of incomplete evacuation
- ECOG Performance Status (PS) ≤2

Key Exclusion Criteria

- Patients who were receiving or planned to start following therapy
  - New cancer chemotherapy regimen
  - Cancer chemotherapy considered to have obvious effects on GI functions
  - Surgical intervention such as nerve block, or radiotherapy which was considered to have obvious effects on GI functions
  - Manual disimpaction
  - Opioid receptor antagonists or partial agonists
- Significant structural abnormalities of GI
- Ileus within 1 year
- No bowel movements for 7 consecutive days prior to the enrollment

*SBM (Spontaneous Bowel Movement) was defined as a bowel movement that occurred without rescue-laxative use within previous 24 hrs

Endpoints

- **Primary endpoint (DBT)**
  - SBM responder rate for 2-week treatment period*
- **Key secondary endpoints (DBT)**
  - Change from baseline in the frequency of
    - SBM
    - CSBM (SBM accompanied by feeling of complete evacuation)
    - SBM without straining
  - Onset of action after the first dose
    - Time to the first SBM and CSBM
    - Proportion of patients with at least 1 SBM/CSBM within 24 hours after the first dose
- **Safety assessments**
  - Adverse events
  - 11-point numeric rating scale (NRS) pain (DBT)
  - Clinical opiate withdrawal scale (COWS)

*An SBM responder rate was defined as percentage of patients with ≥ 3 SBMs per week and an increase from baseline of ≥ 1 SBM per week

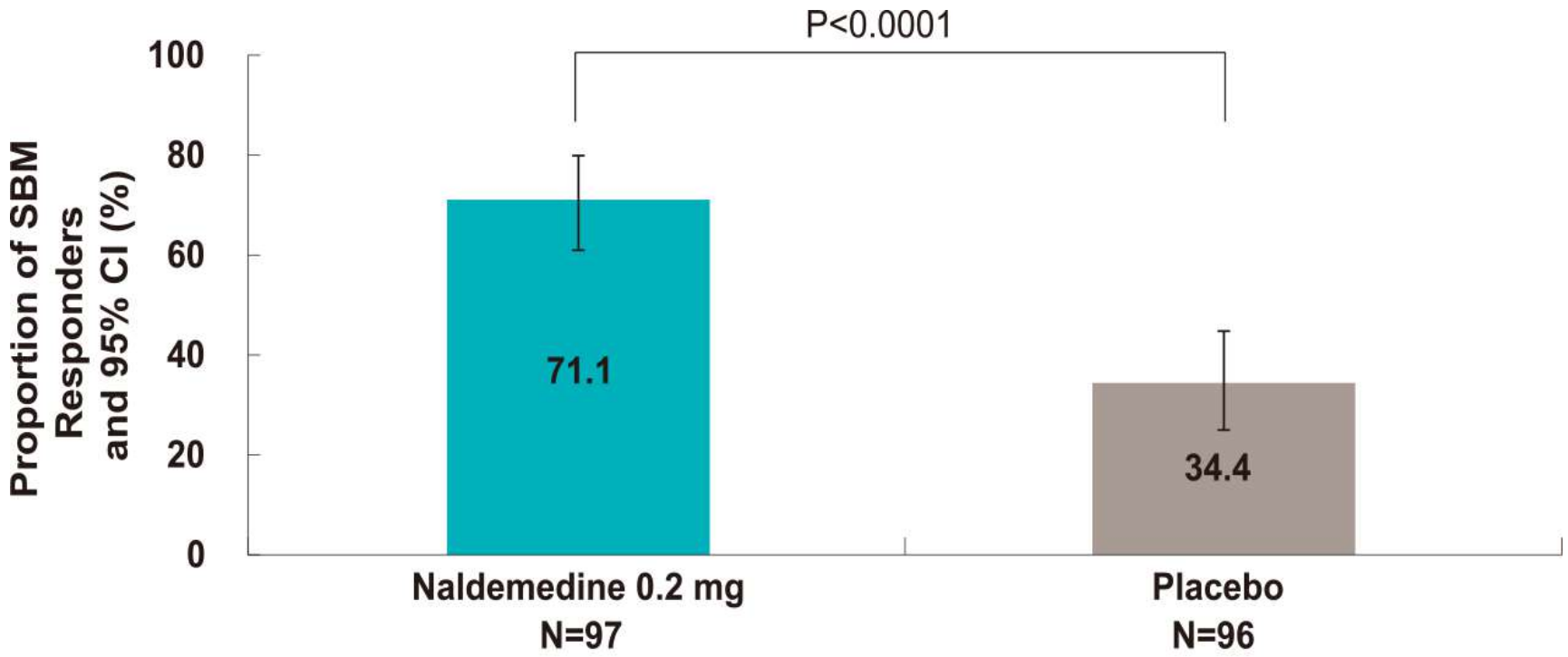
Baseline Characteristics (DBT, FAS)*

		Naldemedine 0.2 mg	Placebo
		N = 97	N = 96
Age (Mean ±SD)		63.8 ± 9.4	64.6 ± 11.8
Gender, n (%)	Male	59 (60.8)	60 (62.5)
BMI (kg/m^2, Mean ±SD)		21.54 ± 3.59	20.82 ± 3.63
ECOG Performance Status, n (%)	0	28 (28.9)	33 (34.4)
	1	55 (56.7)	49 (51.0)
	2	14 (14.4)	14 (14.6)
Inpatient/outpatient, n (%)	Outpatient	77 (79.4)	77 (80.2)
Received anticancer drugs, n (%)		72 (74.2)	62 (64.6)
Primary tumor, n (%)	Lung	42 (43.3)	45 (46.9)
	Breast	22 (22.7)	17 (17.7)
	Colorectal	3 (3.1)	3 (3.1)
	Other	30 (30.9)	31 (32.3)
Baseline SBM frequency /week (Mean ±SD)		1.01 ± 0.76	1.10 ± 0.85
Baseline daily dose of regular opioid (mg, Mean ±SD)**		57.3 ± 46.4	69.5 ± 99.5

*FAS (Full analysis set) was defined as population of patients obtained by excluding those with no baseline or post-baseline efficacy measurements and those having taken no doses of study drug from all randomised patients. ** Oral morphine equivalent dose

Primary Endpoint

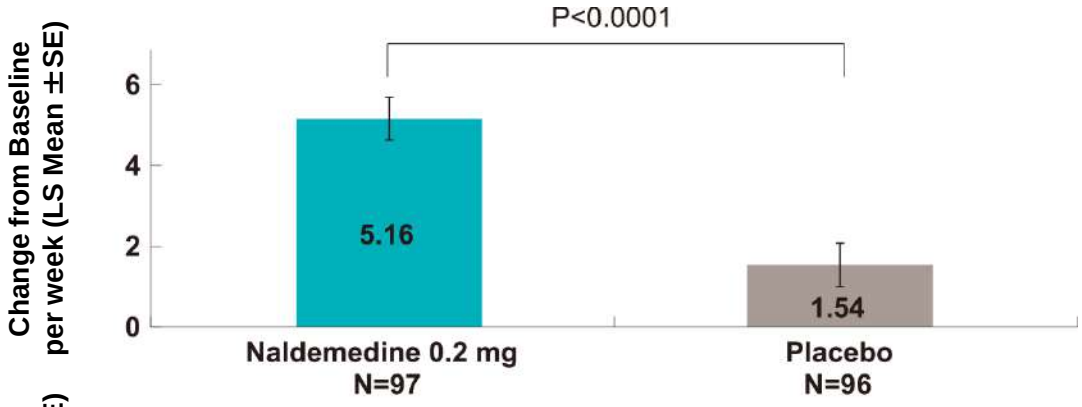
SBM responder rate* for 2-week treatment period (DBT, FAS)



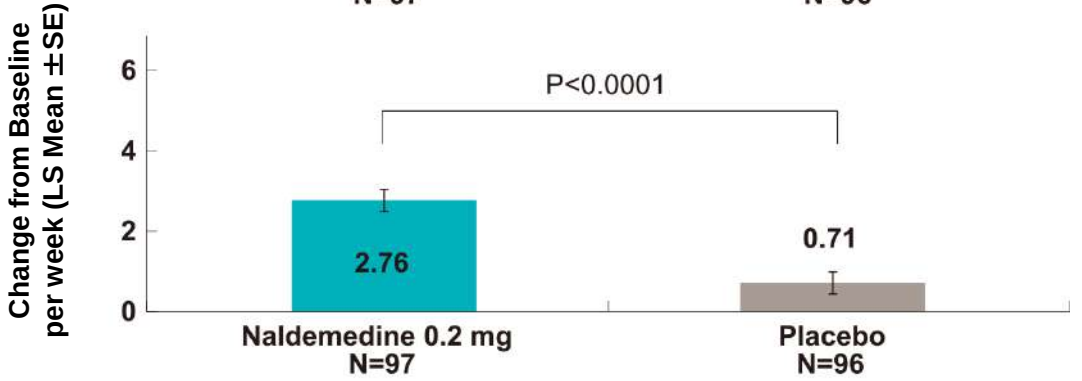
*An SBM responder rate was defined as percentage of patients with ≥ 3 SBMs per week and an increase from baseline of ≥ 1 SBM per week. P-value by Chi-square test, 95% CI was calculated with the Clopper-Pearson method.

Frequency of Bowel Movements (DBT, FAS)

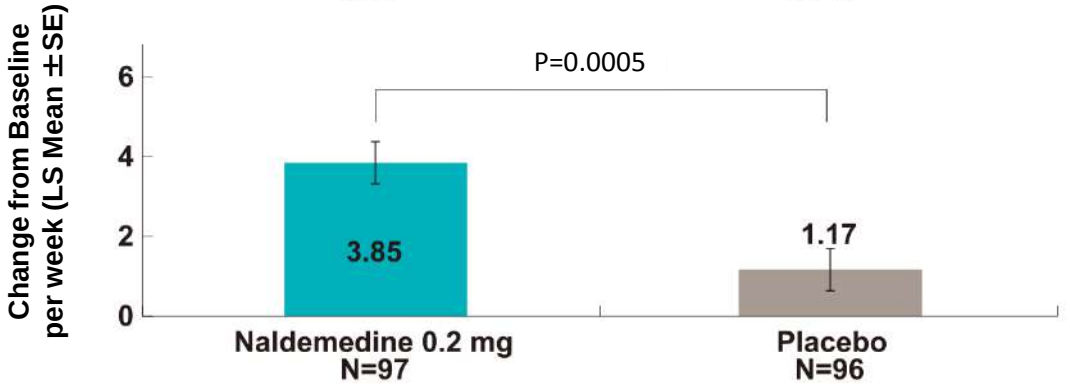
SBM/week



CSBM/week

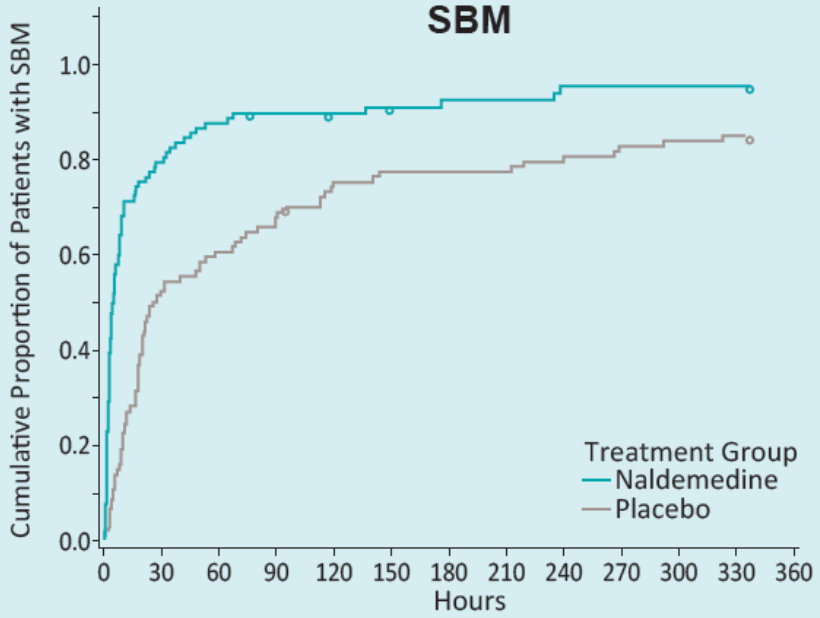


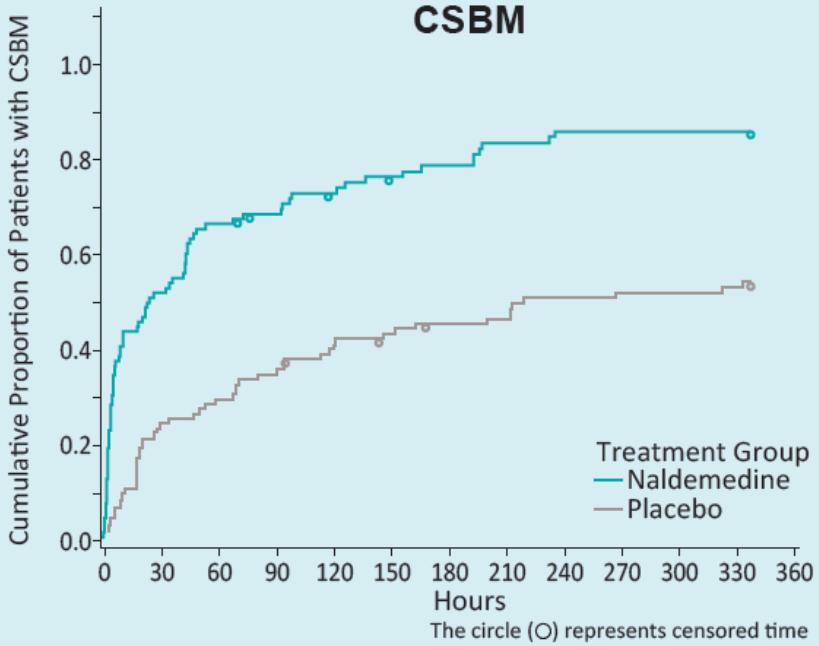
SBM without straining/week



Analysis method: The ANCOVA model has the terms for treatment group, baseline value as fixed effects

Time to First SBM/CSBM (DBT, FAS)



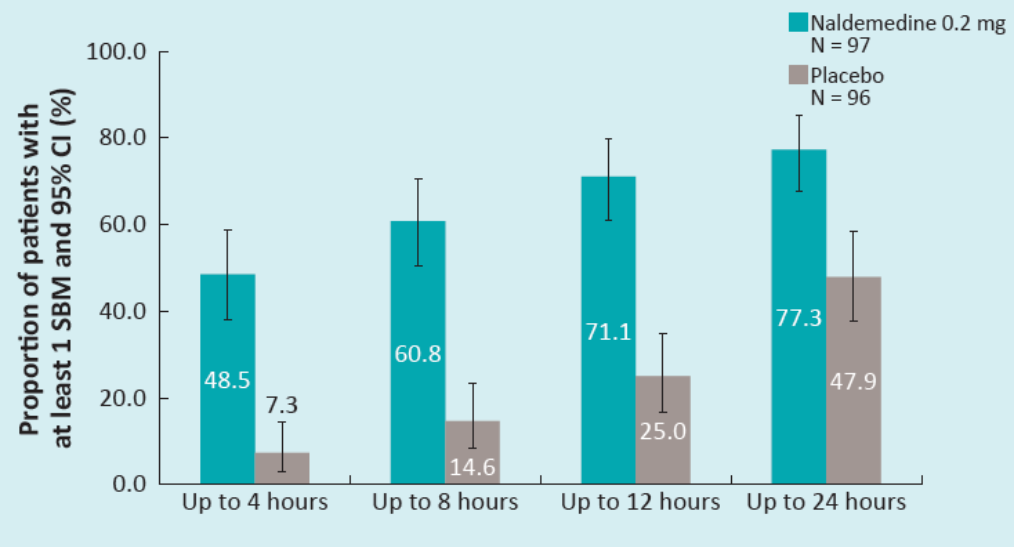


	SBM		CSBM	
	Naldemedine 0.2 mg N = 97	Placebo N = 96	Naldemedine 0.2 mg N = 97	Placebo N = 96
Median time to BM after the initial dose, hour (95% CI)	4.67 (3.00, 7.58)	26.58 (19.65, 58.17)	24.00 (9.00, 43.25)	218.50 (117.75, -)
p-value vs placebo	< 0.0001		< 0.0001	

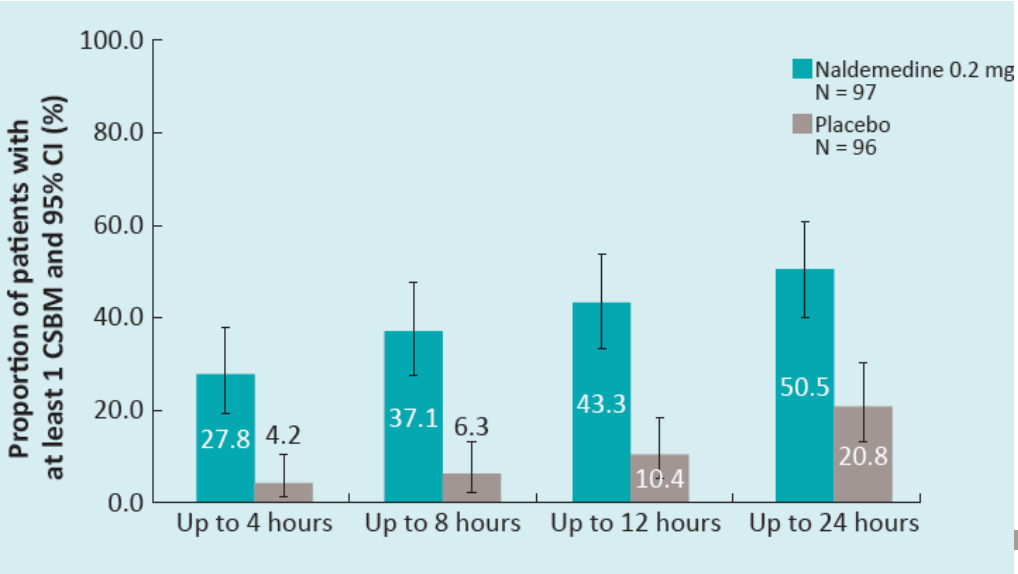
Median and 95% CI for Median were based on Kaplan-Meier estimates of time to first event. P-value was from the generalised Wilcoxon test.

Incidence of Patients with At Least 1 SBM/CSBM for Each Observation Point (DBT, FAS)

SBM

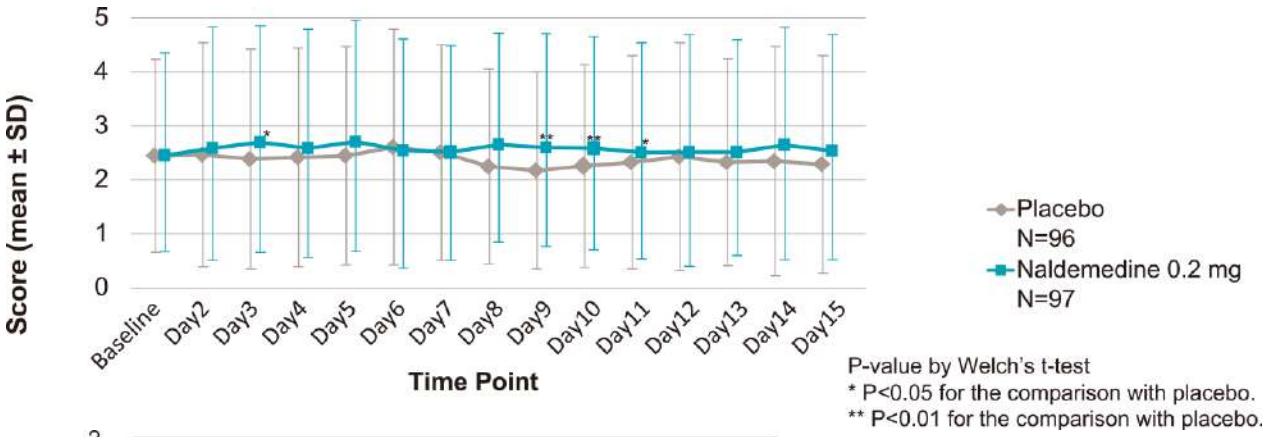


CSBM

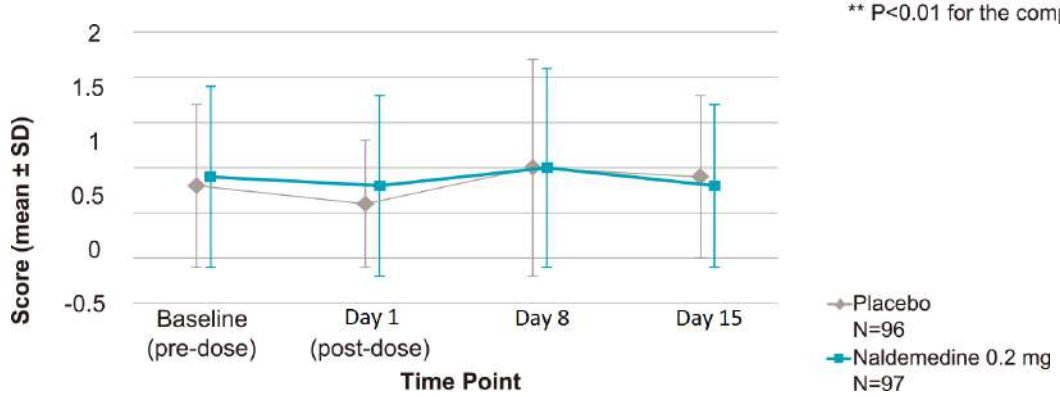


Safety Assessments (Safety population)*

11-point NRS score for pain evaluation (DBT)



Total COWS score (DBT)



Total COWS score (EXT)

* Safety population was obtained by excluding the patients who have not received the study drug at all, from all randomised (for DBT)/enrolled (for EXT) patients.

Summary of Adverse Events (Safety population)

n (%)	DBT[1]		EXT[2]
	Naldemedine 0.2 mg, N = 97	Placebo N = 96	Naldemedine 0.2 mg, N = 131
Any adverse events (AEs)	43 (44.3)	25 (26.0)	105 (80.2)
Death	2 (2.1)	0	15 (11.5)
Serious AEs except death	7 (7.2)	2 (2.1)	14 (10.7)
AEs leading to withdrawal	9 (9.3)*	1 (1.0)	12 (9.2)
GI AEs ≥2% of patients in naldemedine group in DBT or EXT			
Diarrhoea	19 (19.6)	7 (7.3)	24 (18.3)
Vomiting	3 (3.1)	1 (1.0)	16 (12.2)
Abdominal pain	2 (2.1)	1 (1.0)	3 (2.3)
Stomatitis	2 (2.1)	0	6 (4.6)
Nausea	1 (1.0)	2 (2.1)	17 (13.0)
Abdominal pain upper	0	0	3 (2.3)

[1]Events reported during treatment period, [2]Events reported after initiation of extension treatment period.
*One more patient withdrew the study by AE but not summarised in the table due to the data handling standard.

Conclusion

- Treatment with naldemedine 0.2 mg given orally once daily was effective and significantly improved the symptoms of OIC in cancer patients.
- Naldemedine was generally well tolerated with the most commonly observed adverse events being GI disorders over 12 weeks.
- Naldemedine is a potential new treatment option for OIC in cancer patients.