治療鴉片類藥物所致便祕的最新發展 - Naldemedine

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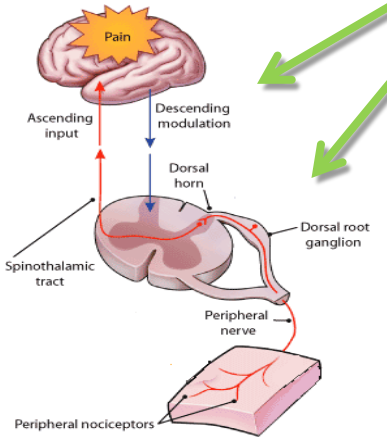
Central and Peripheral Actions of Opioids

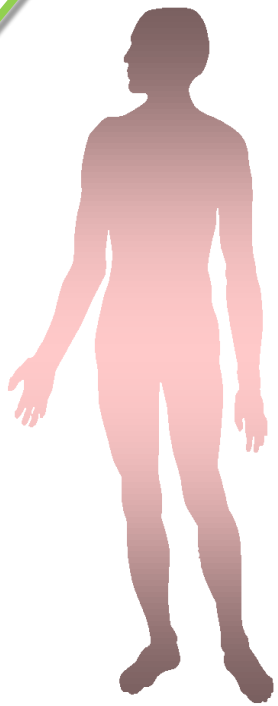
Opioids act on both the Central Nervous System (CNS) and the Gastrointestinal (GI) tract

CTZ: Chemoreceptor Trigger Zone
BBB: Blood Brain Barrier

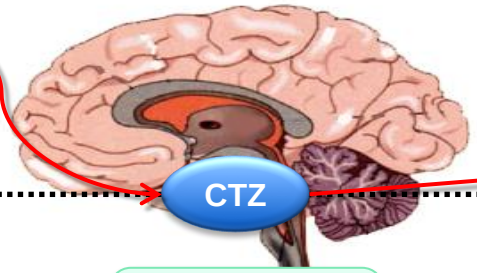
Central (inside of BBB)



Opioids



Analgesic Effect



Emesis (vomiting & nausea)

μ, δ

μ, δ, (κ)

Constipation

Peripheral (outside of BBB)

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台灣疼痛醫學會 TAIWAN PAIN SOCIETY SINCE 1989

台灣癌症安寧緩和醫學會 TAIWAN SOCIETY OF CANCER PALLIATIVE MEDICINE TSCPM

指引手冊電子檔連結: https://pain.org.tw/index.php/pain_page/index/17/3
https://pain.org.tw/index.php/pain_page/index/17/4

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Opioid-induced constipation (OIC)定義

台灣專家建議參考 AGA 的 OIC 定義

- 美國腸胃科醫學會（American Gastroenterological Association, AGA）指出 OIC 顧名思義為「服用鴉片類藥物而引起的便秘」[1]。
- 較具體的OIC定義：「因開始使用鴉片類藥物治療而引起的排便習慣改變，特徵包含排便頻率降低、需要用力解便、感覺到排便排不乾淨，或是出現硬便」[1]。
- 本指引建議以AGA的定義為主要依據。

1. Crockett SD, et al Gastroenterology. 2019;156:218-26. **10.** Larkin PJ, et al. Ann Oncol. 2018;29(Suppl 4):iv111-25.

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OIC流行病學

歐美地區

- **OIC 約影響 40%–80% 的長期鴉片類藥物使用者**[1]。
- 高達 81% 病人因長期服用鴉片類藥物而出現便秘症狀，並認為便秘是所有鴉片類藥物引起的胃腸道症狀中最讓人感到困擾的[11]。
- OIC 出現於 41%–57% 的非癌症慢性疼痛病人，在癌症病人則提高至 51%–87%[12] 。
- **便秘的盛行率會隨著鴉片類藥物的用藥時間增加而上升**[13]。

台灣臨床觀察

- 使用鴉片類藥物後，約每 2 位非癌症慢性疼痛病人中有 1 位會出現 OIC（約50%）。
- 約每 4 位癌症病人中則有 3 位出現 OIC（約75%）。
- 台灣約 46.7% 的非癌症患者因長期使用鴉片類藥物而發生便秘[14]，男性與女性的 OIC 發生率並無顯著不同。(47.9% vs 44.1%)[15]。

1. Crockett SD, et al. Gastroenterology. 2019;156:218-26. **11.** Bell TJ, et al. Pain Med. 2009;10:35-42. **12.** Farmer AD, et al. United European Gastroenterol J. 2019;7:7-20. **13.** Tuteja AK, et al. 2010;22:424-30, e96. **14.** Lin TC, et al. J Formos Med Assoc. 2017;116:257-65. **15.** Lin TC, et al. Medicine (Baltimore). 2018;97:e10805.

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OIC疾病負擔

健康與生活品質相關負擔

- 對病人而言，便秘是 OIBD 中最讓人感到困擾的症狀，無論是整體生活品質或是日常活動，都會造成負面影響[11]。
- 在歐美國家進行的調查發現，非癌症慢性疼痛病人中三成病人的工作表現受到影響，更有高達近四成病人的日常活動受到影響[17]。
- 約 1/3 病人自行減量甚至停用鴉片類藥物，只為了能順利排便[11]。
- 嚴重 OIC 患者經常需使用浣腸劑，對於病人本身及其照護者都會帶來壓力與困擾。
- OIC 也會影響正常社交活動，甚至引發沮喪、焦慮等負面情緒[18]。

醫療負擔

- 回溯性研究指出，相較沒有 OIC 的鴉片類藥物使用者，OIC 患者不僅更頻繁的就醫，住院時間也顯著延長，檢驗及藥事服務的需求也增加，這些狀況也使其醫療支出明顯提高[18]。

11. Bell TJ, et al. Pain Med. 2009;10:35-42. **17.** Gupta A, et al. Pain Med. 2018;19: 2459-68. **18.** Argoff CE. Clin J Pain. 2020;36:716-22.

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OIC致病機轉

- 鴉片類藥物在胃腸道主要作用於腸神經系統（enteric nervous system, ENS）。
- ENS也同時受到交感和副交感神經所控制。鴉片類藥物透過在 ENS 的作用，影響正常胃腸道功能，進而造成便秘[3]。

鴉片類藥物在腸道引起的病生理作用

- 使用鴉片類藥物而引起的便秘副作用，可能發生在用藥期間的任何時間點，並不會隨著使用時間增加而產生耐受性[3]。
- 鴉片類藥物透過多種方式影響胃腸系統正常運作，包括胃腸道的運動（motility）、分泌與吸收功能及括約肌收縮，進而導致排便頻率及效率降低[1,5]。

表 2-1. 鴉片類藥物在腸道引起的病生理作用[1,5]

1. Farmer AD, et al. United European Gastroenterol J. 2019;7:7-20; **3.** Nelson AD, Camilleri M. Ther Adv Gastroenterol. 2015;8:206-20; **5.** Rumman A, et al. Expert Rev Qual Life Cancer Care. 2016;1:25-35.

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介入治療

藥物治療策略

❶治療藥物

- OIC 首選治療藥物為傳統緩瀉劑，建議使用滲透性（例如：氧化鎂）或刺激性（例如：bisacodyl），應由最低劑量開始使用[4]。
- 末梢性 μ 型類鴉片受體拮抗劑（peripherally acting μ-opioid receptor antagonists, PAMORAs）近期已獲得治療 OIC 的適應症，可供 OIC 病人使用，**台灣目前僅有的 PAMORA 類藥物為 naldemedine**。
- 對於確診 OIC 的病人，如果先前已使用過傳統緩瀉劑，但便秘症狀仍持續出現，處置方式包括：
  - 調高劑量或增加一種傳統緩瀉劑
  - 增加 PAMORA 類藥物合併治療
- 若病人未曾使用過緩瀉劑，可選擇給予傳統緩瀉劑或 PAMORA 類藥物。
- **應提醒病人，緩解便秘的藥物需每日規律服用，而非症狀出現時才使用**[4]。

4. De Giorgio R, et al. Adv Ther. 2021;38:3589-621.

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介入治療

藥物治療策略

❷治療評估

- 在給予治療前及藥物治療後 1-2 週，即可依據醫師的臨床經驗及病人的反應判斷治療效果；亦可以 BFI 輔助評估治療效果。
- 若醫師認為治療效果不佳，或 BFI ≥ 30 分或與治療前相比 BFI 減少幅度 < 12分，表示便秘症狀仍存在或改善程度不足，應調整治療藥物。
- 若醫師評估治療效果良好，或 BFI < 30 分或與治療前相比 BFI 降低幅度 ≥ 12分，代表藥物治療反應良好，**在病人無腹瀉或其他不適症狀出現的情況下，則可維持現有的治療處置並持續追蹤觀察**。

介入治療

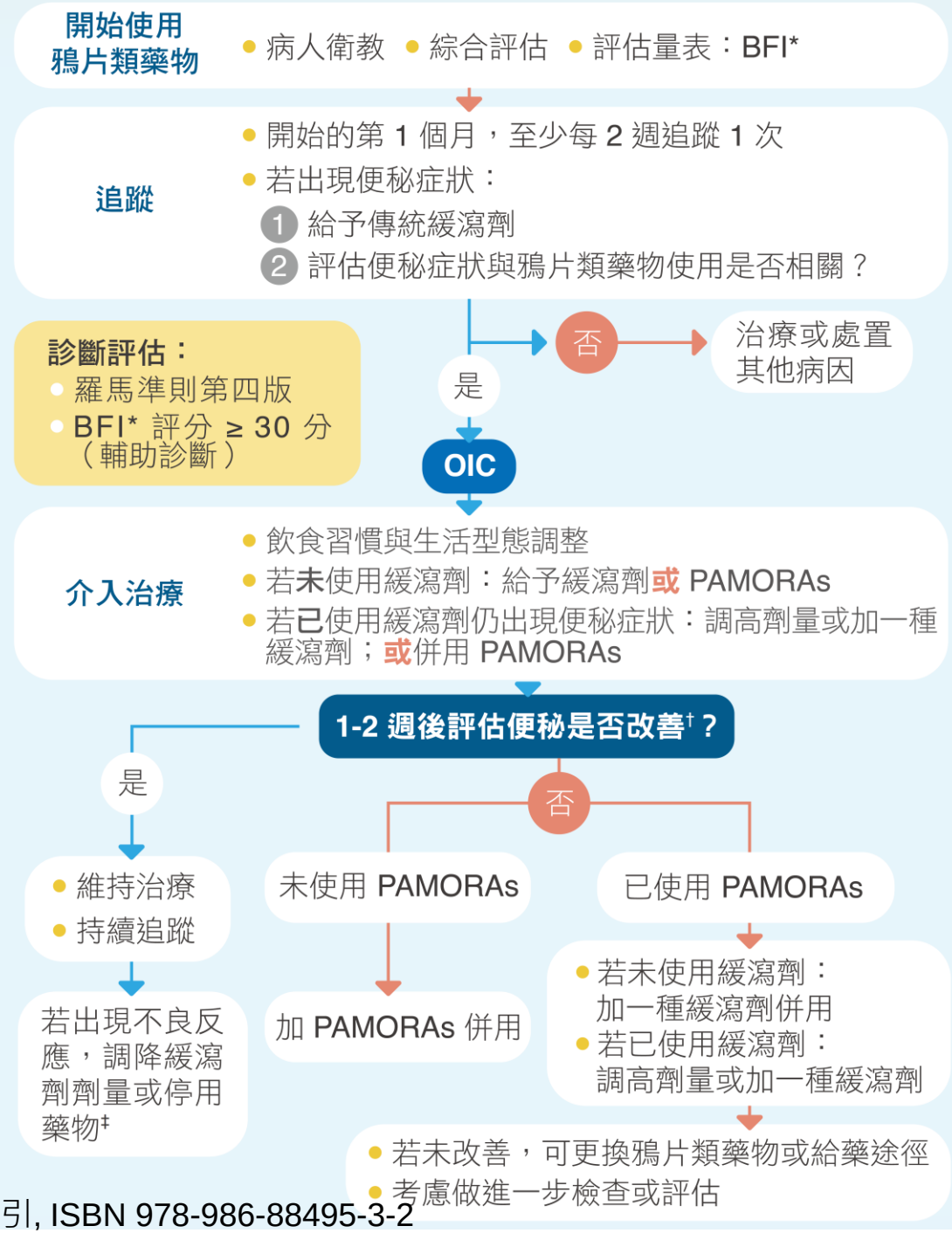
藥物治療策略

❸藥物調整：針對藥物治療後便秘仍無明顯改善的病人

- 在藥物治療後，若便秘症狀仍持續出現未見改善，針對先前未曾使用 PAMORA 類藥物的病人，本指引建議給予 PAMORA 類藥物合併治療。
- 如果病人先前已使用 PAMORA 類藥物，後續處置應考量病人是否已使用傳統緩瀉劑，針對已使用傳統緩瀉劑（刺激性或滲透性）者，建議增加傳統緩瀉劑劑量或給予另一種緩瀉劑合併治療。
- 針對未使用傳統緩瀉劑者，則建議增加一種刺激性或滲透性緩瀉劑合併治療。
- 經過上述藥物處置後，若病人治療反應仍不佳，可考慮更換鴉片類藥物的種類或給藥途徑，並建議諮詢醫療團隊作進一步的評估或檢查。

台灣OIC診療流程圖

圖 4-1. 台灣OIC診療流程圖



*作為輔助工具供評估便秘症狀、治療效果與診斷之用。目前無確效之 BFI 繁體中文翻譯版。
†依醫師臨床經驗與病人反應判定；亦可以 BFI < 30 分或降低 ≥ 12 分輔助評估。
‡先停用緩瀉劑，再停用 PAMORAs。

BFI, Bowel Function Index; OIC, opioid-induced constipation; PAMORAs, peripherally acting μ-opioid receptor antagonists.

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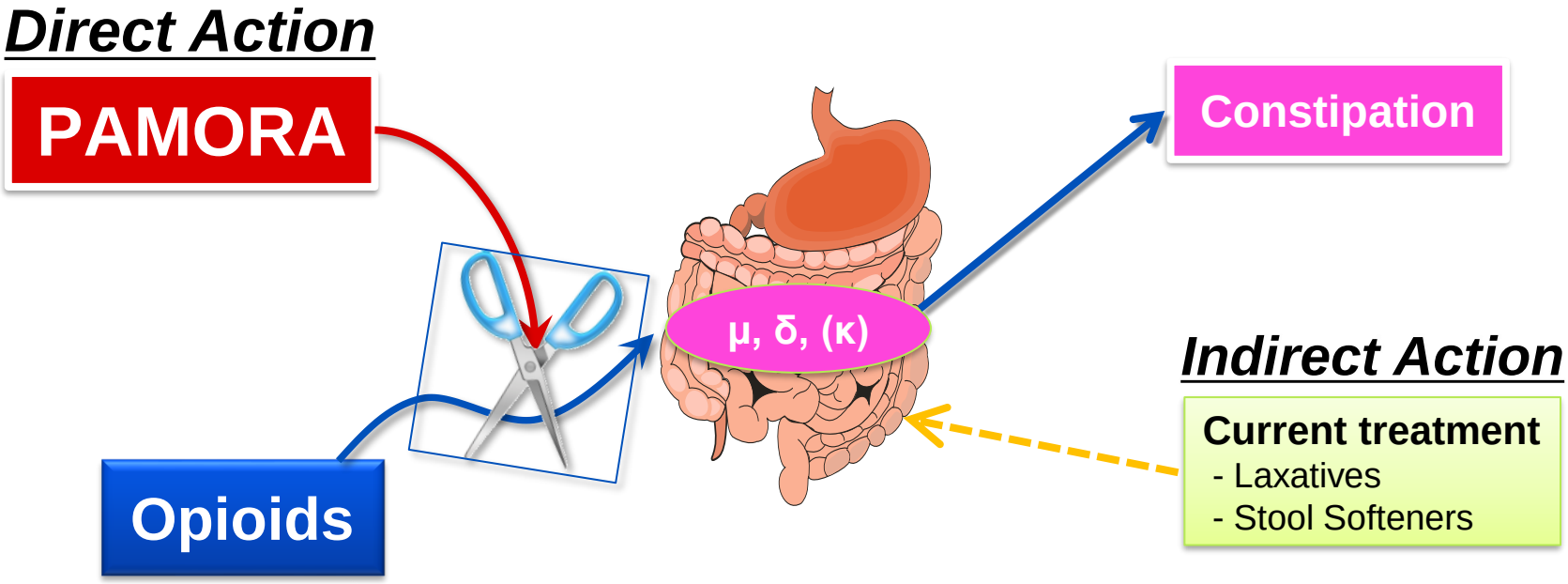
MoA Differentiation among Current Treatments

PAMORA with a new MoA for OIC is an additional treatment option for the current therapies



PAMORA: Peripherally-Acting Mu-Opioid Receptor Antagonists

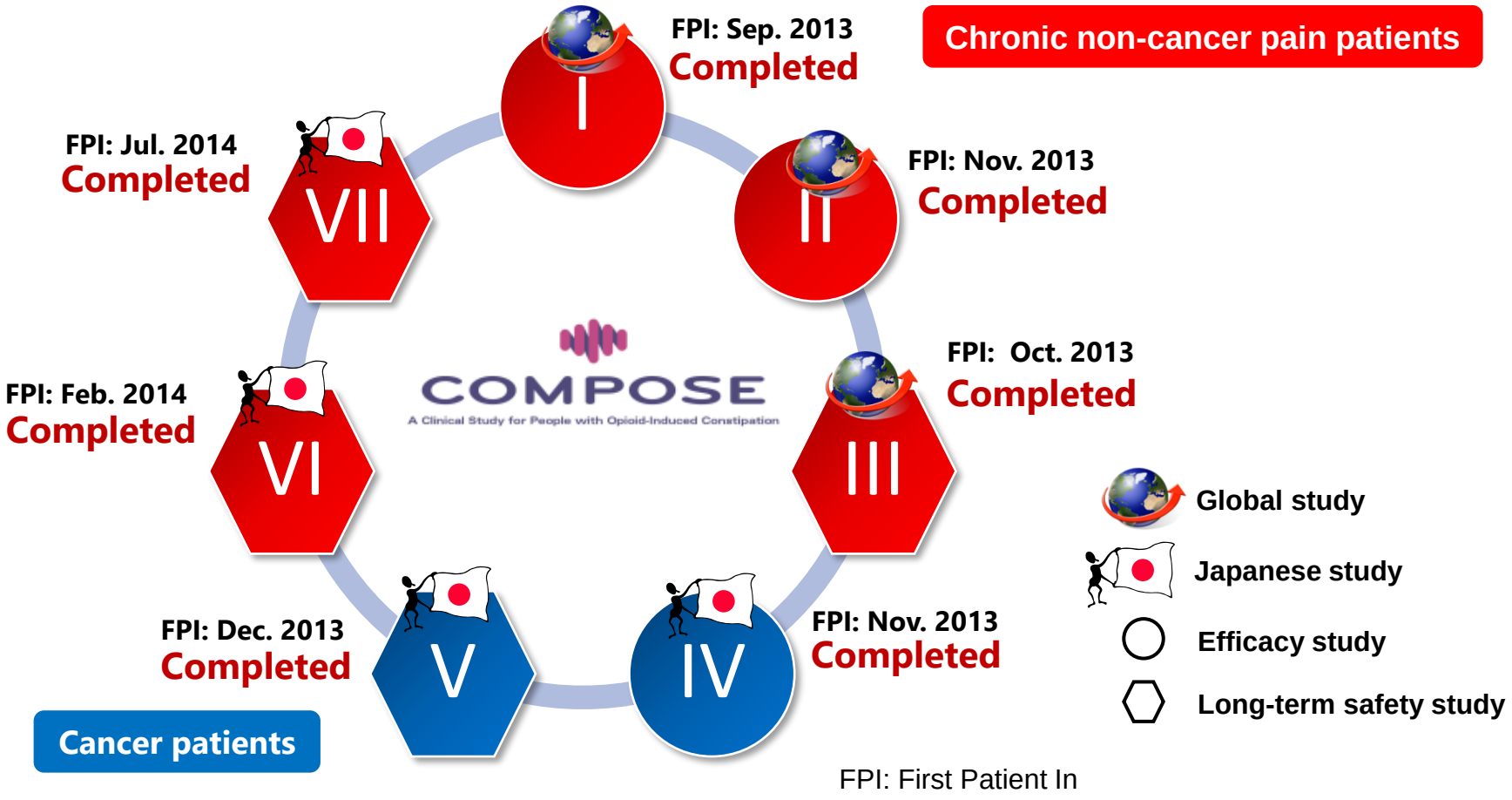
Source: Global OIC market research December 2012

Naldemedine 基本介紹

有效成分	Naldemedine Tosylate
適應症	**治療成人因鴉片類藥物引起之便秘 (Opioid-induced constipation, OIC)**
機轉	**末梢性μ型類鴉片受體拮抗劑(PAMORA)**
使用劑量及頻率	**成人建議劑量為每日口服1次0.2 mg** (膜衣錠) (停止投與類鴉片藥物時，亦應停止投與本藥)
特殊病人族群	1. 輕度至中度肝功能不全病患不需調整劑量，無重度肝功能不全病患相關數據。 2. 腎功能不全病患不需調整劑量。本藥不會以血液透析之方式移除。
禁忌症	1. 對本藥中任一成分曾發生過敏症之病人。 2. 本品禁用於已知或疑似腸胃道阻塞或腸胃道穿孔之病人，或可能具復發性腸胃道阻塞風險之病人，因可能造成腸胃道穿孔。
藥物交互作用	本藥主要經由肝臟代謝酵素CYP3A4代謝。 與CYP3A抑制劑併用時可能會使本藥血中濃度上升，而出現不良反應。

COMPOSE Program (Phase III Studies) of Naldemedine

- **Target patients**
  - **US/EU: Chronic non-cancer pain patients**
  - **JP: Cancer patients and chronic non-cancer pain patients**



FPI: First Patient In

Definition of OIC in COMPOSE-4 & COMPOSE-5

During the 2 weeks before random assignment,

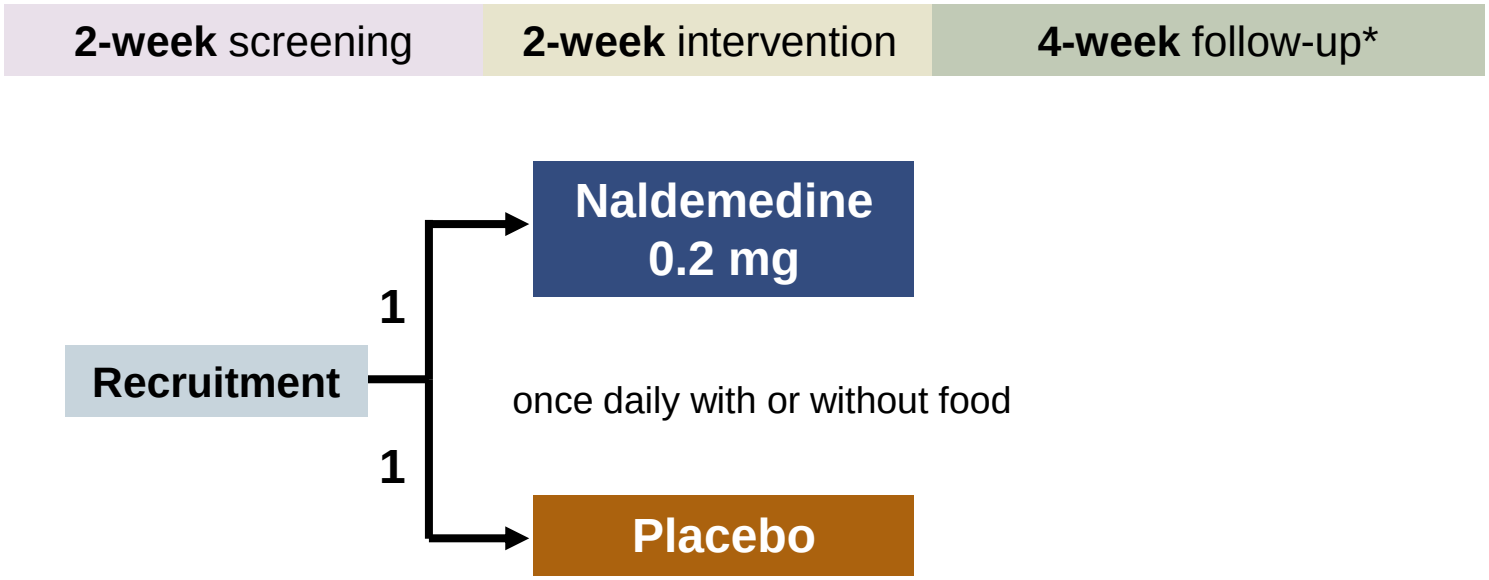
Five or fewer spontaneous bowel movements

and

Experience with straining, incomplete evacuation, and/or hard stools in 25% or more of all bowel movements

Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

Study Design of COMPOSE-4



Statistical Analysis

① Primary endpoint - chi-square test; 95% CI with the Clopper - Pearson method
② Secondary endpoint - evaluated with analysis of covariance
③ Safety - Fisher's exact test (AE); Welch's test (COWS & NRS)

AE = Adverse event; COWS = Clinical opiate withdrawal scale; NRS = Numeric Rating Scale
* Only for patients who did not continue to enter the COMPOSE-5 study

Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

Study Endpoints in COMPOSE-4

Efficacy Analysis – Full Analysis Set (FAS)*

Primary Endpoint – Proportion of SBM responders during the 2-week treatment period

≥ 3 SBMs/week and increase of ≥ 1 SBM/week from baseline

Secondary Endpoint

① Change from baseline in the frequency of SBMs/week
② Change from baseline in the frequency of CSBMs/week
③ Change from baseline in the frequency of SBMs without straining/week

Safety Analysis- Patients received at least one dose of study drug

① Summary measures of treatment-emergent AEs (TEAEs**)
② Opioid withdrawal syndrome at baseline (pre-dose on day 1), at 60 minutes after the first dose, and on days 8 and 15
③ Pain intensity (daily)

SBM, spontaneous bowel movement

Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

Patient Demographic and Baseline Characteristics in COMPOSE-4

Parameter	COMPOSE-4 Naldemedine (n = 97)	COMPOSE-4 Placebo (n = 96)
Mean (SD) age, years	63.8 (9.4)	64.6 (11.8)
Male	59 (60.8)	60 (62.5)
ECOG PS, No. (%)		
0	28 (28.9)	33 (34.4)
1	55 (56.7)	49 (51.0)
2	14 (14.4)	14 (14.6)
Primary tumor, No. (%)		
Lung	42 (43.3)	45 (46.9)
Breast	22 (22.7)	17 (17.7)
Large intestine	3 (3.1)	3 (3.1)
Other	30 (30.9)	31 (32.3)
Mean (SD) SBM frequency/week*	1.01 (0.76)	1.10 (0.85)
Mean (SD) daily dose of opioids, mg†	57.3 (46.4)	69.5 (99.5)
Prior use, No. (%)		
Anticancer drugs	72 (74.2)	62 (64.6)
Routine laxatives‡	72 (74.2)	74 (77.1)
Rescue laxatives§	93 (95.9)	89 (92.7)

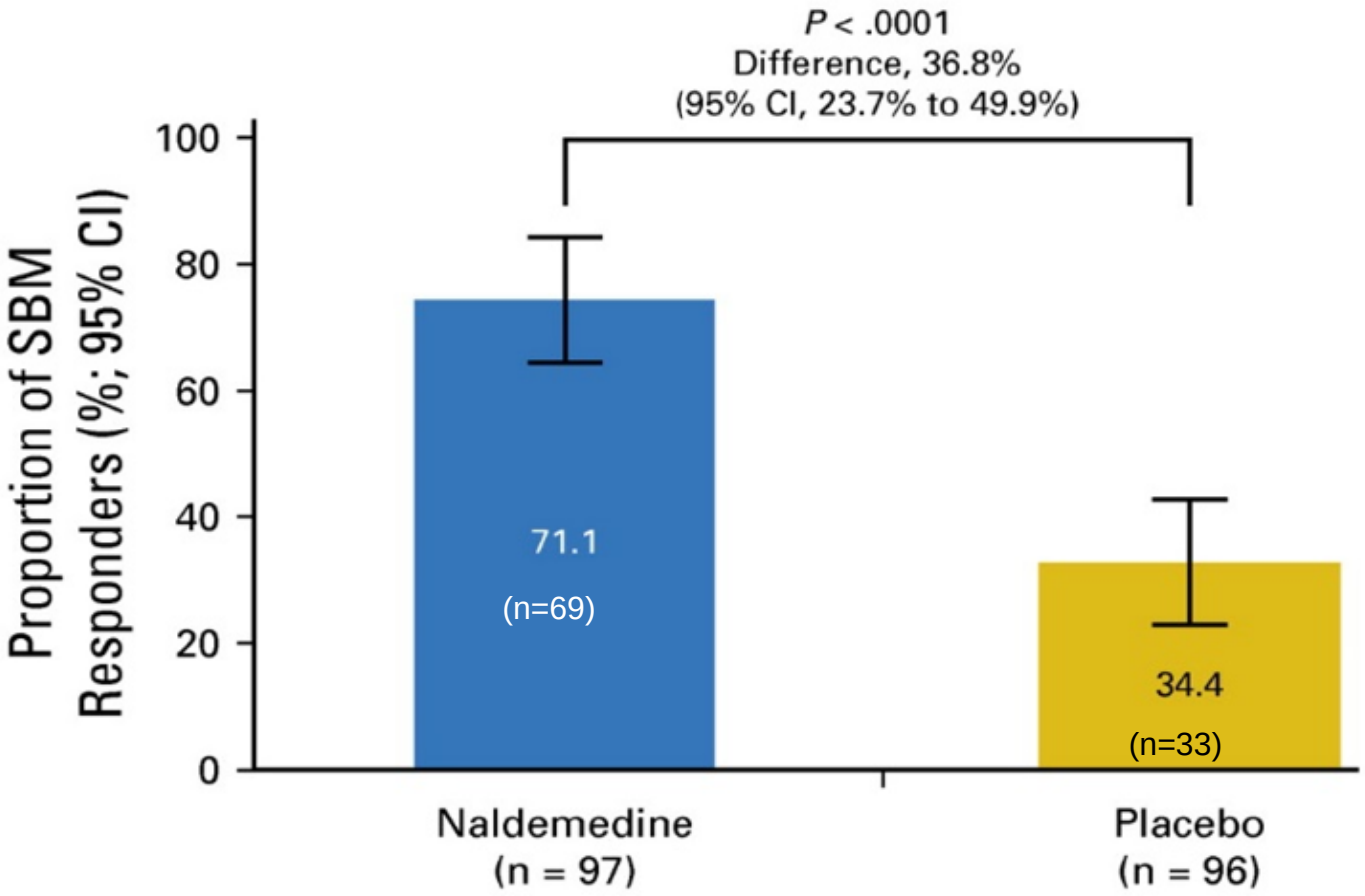
*Before random assignment, the mean SBM frequency/week at baseline was assessed during the 2-week screening period.;
†Oral morphine equivalent.; ‡Patients were routinely using laxatives at the start of the screening period.
§Patients received rescue laxatives only when needed
Rescue laxative was prohibited in 24 hours before and after the first dose of the study drug
ECOG PS, Eastern Oncology Cooperative Group performance status; SBM, spontaneous bowel movement; SD, standard deviation

Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

Proportion of SBM Responders was Significantly Greater with Naldemedine in COMPOSE-4

Primary Endpoint

Proportion of SBM responders during 2-week treatment period



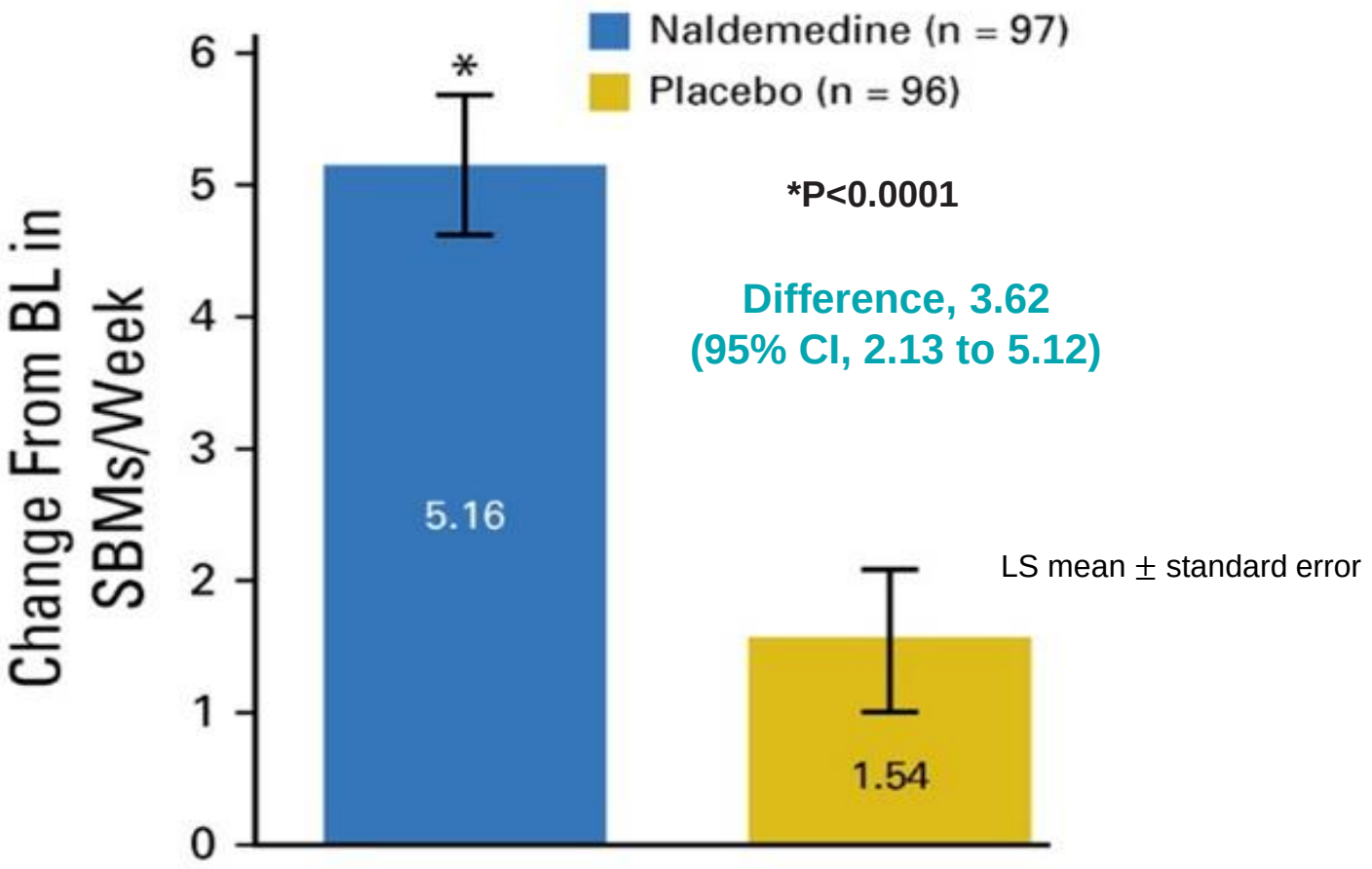
SBMs = spontaneous bowel movements; SBM responder = patients with three or more SBMs/week who had an increase of one or more SBM/week from baseline. Baseline was the average number of SBMs/week during the 2 weeks before random assignment.

Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

Significantly Greater Change from Baseline with Naldemedine in the Mean Frequency of SBMs/week in COMPOSE-4

Secondary Endpoint

Change from baseline in least squares (LS) mean of frequency of SBMs/week



BL= Baseline, the average number of SBMs/week during the 2 weeks before random assignment
SBMs=spontaneous bowel movements

Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

Results of Safety Analysis in COMPOSE-4

Safety Endpoint

AE	COMPOSE-4* Naldemedine (n = 97)	Placebo (n = 96)	*P*
Overall			
TEAEs	43 (44.3)	25 (26.0)	.0103
Severe TEAEs	13 (13.4)	3 (3.1)	—
Treatment-related AEs	18 (18.6)	9 (9.4)	.0957
GI disorders	17 (17.5)	7 (7.3)	—
Study withdrawal**	9 (9.3)	1 (1.0)	.0184
GI disorders	5 (5.2)	0	–
Nonfatal SAEs***	7 (7.2)	2 (2.1)	.1694
Deaths†	2 (2.1)	0	.4974

*Data for COMPOSE-4 are from during the study drug administration (not after)

**The TEAEs of diarrhea (n = 5), vomiting (n = 2), decreased appetite (n = 1), and pyrexia (n = 1) that led to discontinuation in the naldemedine group in COMPOSE-4 were considered related to the study drug by the investigator. The TEAE (somnolence) that led to the single discontinuation in the placebo group was considered unrelated to the study drug.

***In the naldemedine group, four nonfatal serious AEs (SAEs) were considered related to the study drug: diarrhea (n = 2), vomiting (n = 1), and abnormal hepatic function test (n = 1). In the placebo group, one nonfatal SAE of pneumonia was considered related to the study drug.

†None of the deaths in either study was considered by the investigator to be related to the study drug (two patients died as a result of interstitial lung disease and pneumonia (n = 1 each); both patients had primary tumors in the lung

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

Results of Safety Analysis in COMPOSE-4 (cont'd)

Safety Endpoint

	COMPOSE-4*	
AE	Naldemedine (n = 97)	Placebo (n = 96)
In ≥ 5% of patients		
GI disorders	23 (23.7)	9 (9.4)
Severe	2 (2.1)	0
Diarrhea	19 (19.6)	7 (7.3)
Severe	2 (2.1)	0
Nausea	1 (1.0)	2 (2.1)
Severe	0	0
Vomiting	3 (3.1)	1 (1.0)
Severe	1 (1.0)	0
General disorders	8 (8.2)	5 (5.2)
Severe	1 (1.0)	0
Malaise	4 (4.1)	1 (1.0)
Severe	1 (1.0)	0

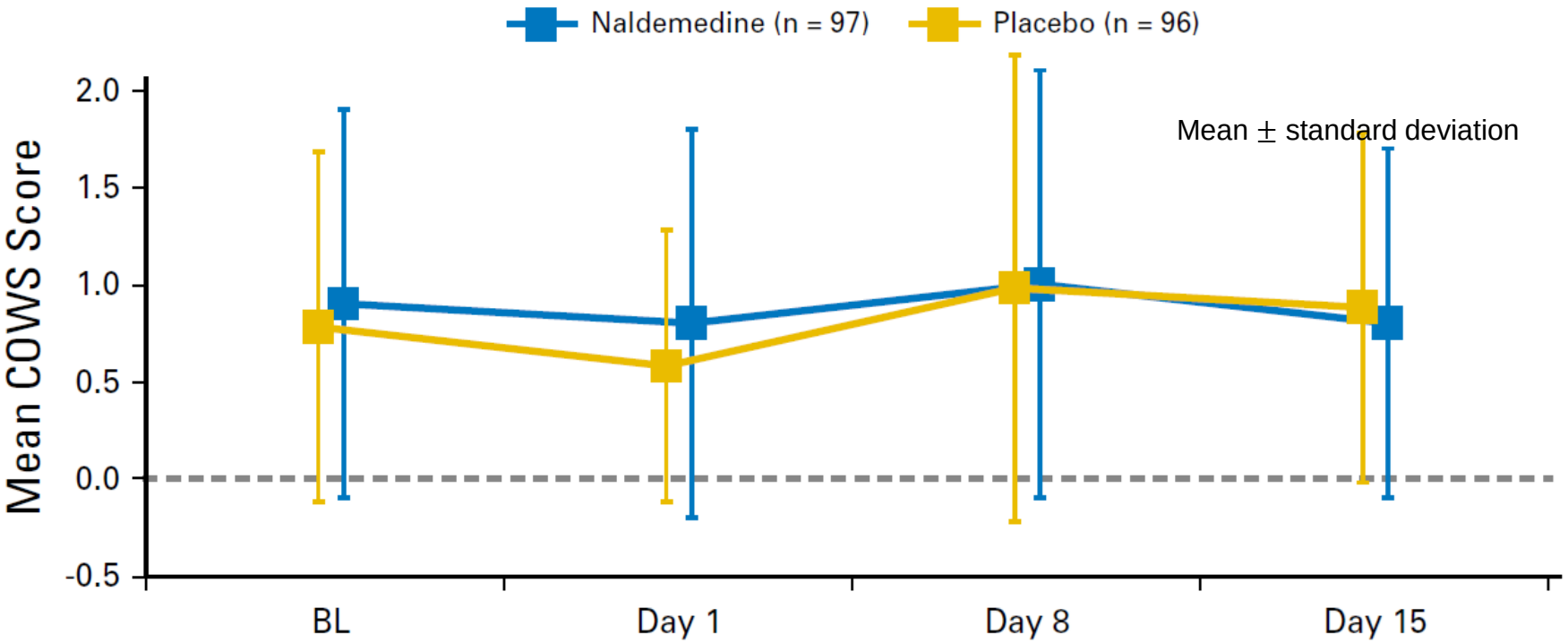
*Data for COMPOSE-4 are from during the study drug administration (not after)

Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

Mean COWS Scores were Similar between Groups and were Generally Low (≤ 2) in COMPOSE-4

Safety Endpoint

Clinical Opiate Withdrawal Scale (COWS) score by time point assessed



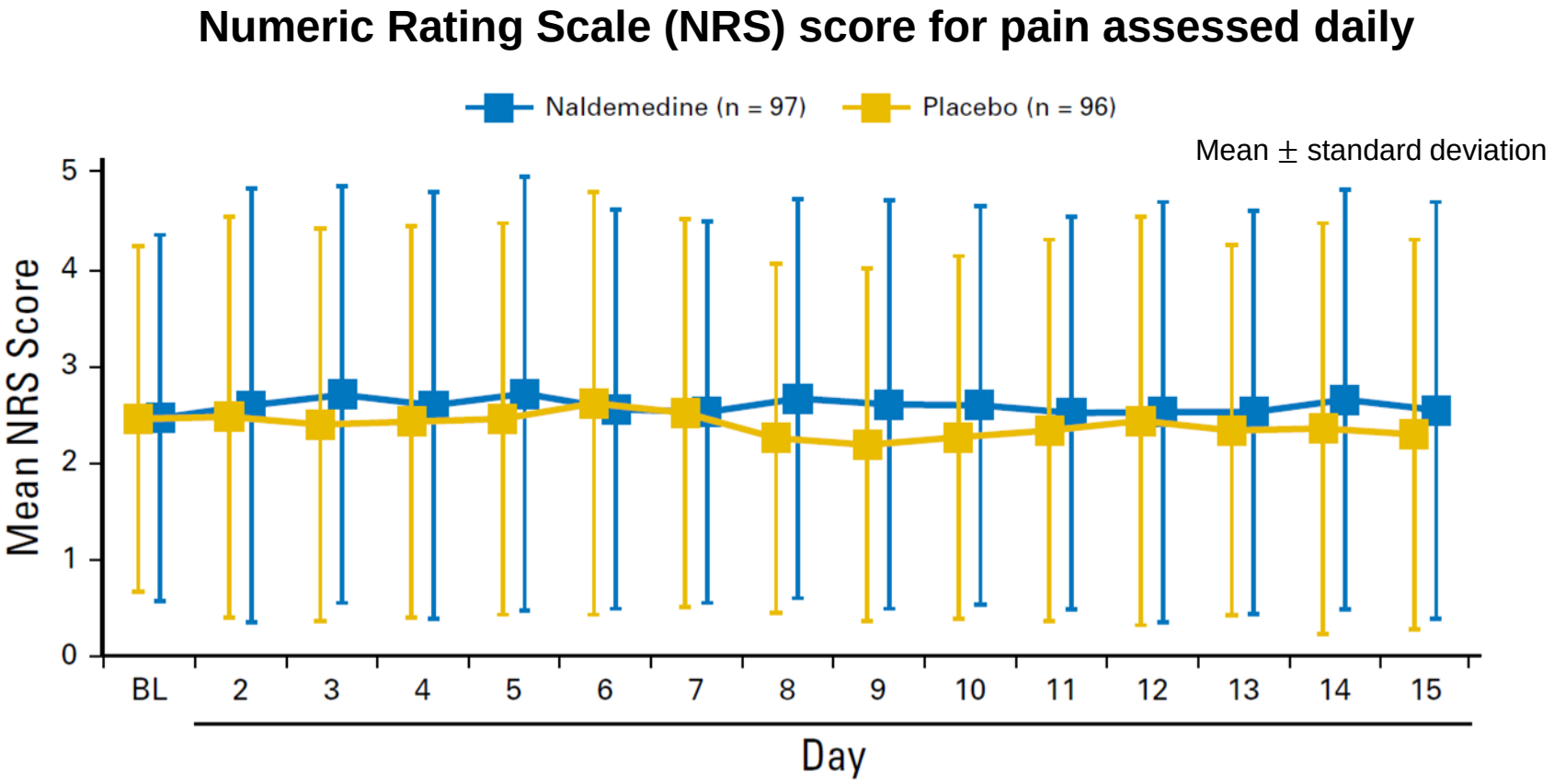
BL= baseline at day 1 pre-dose

A single TEAE of opioid withdrawal syndrome (mild) was reported in the naldemedine group in COMPOSE-4. The occurrence was considered unrelated to the study drug and was probably caused by a reduction of the opioid dose (transdermal fentanyl).

Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

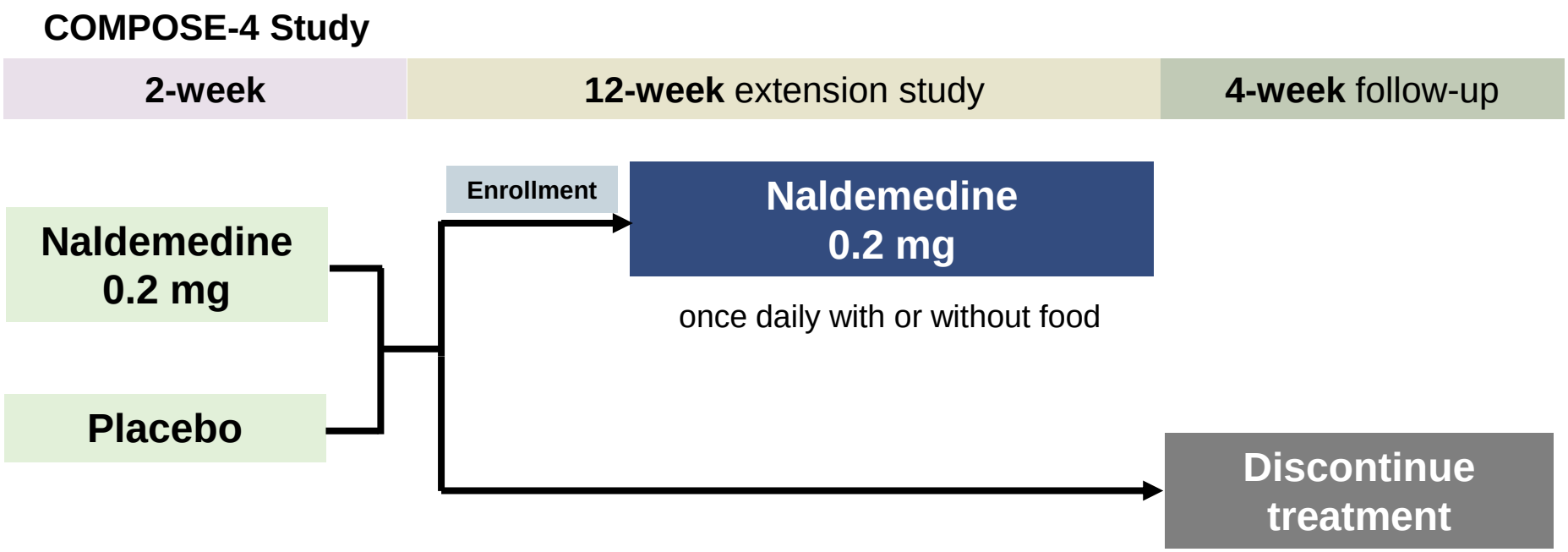
Mean NRS Scores Assessed Daily were Generally Stable and were Similar between Groups in COMPOSE-4

Safety Endpoint



Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

Study Design of COMPOSE-5



Statistical Analysis

Fisher's exact test (AE); Welch's test (COWS)

AE = Adverse event; COWS = Clinical opiate withdrawal scale

Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

Study Endpoints in COMPOSE-5

Safety Analysis - Patients received at least one dose of study drug

Primary Endpoint

① Summary measures of treatment-emergent AEs (TEAEs*)

② Opioid withdrawal syndrome assessed pre- and post-dose on day 1 (last day of treatment of COMPOSE-4) and post-dose on days 15, 29, 57, and 85

*TEAEs were assessed daily during study drug administration and the follow-up period. The severity of a TEAE was graded as mild (grade 1), moderate (grade 2), or severe (grade 3) on the basis of Common Terminology Criteria for Adverse Events (version 4.0) or the impact of the TEAE on the daily activities and clinical status of the patient

Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

Patient Demographic and Baseline Characteristics in COMPOSE-5

Parameter	COMPOSE-5 Naldemedine (n = 131)
Mean (SD) age, years	63.5 (10.4)
Male	74 (56.5)
ECOG PS, No. (%)	
0	43 (32.8)
1	71 (54.2)
2	17 (13.0)
Primary tumor, No. (%)	
Lung	51 (38.9)
Breast	29 (22.1)
Large intestine	5 (3.8)
Other	46 (35.1)
Mean (SD) SBM frequency/week*	0.98 (0.80)
Mean (SD) daily dose of opioids, mg†	64.0 (80.8)
Prior use, No. (%)	
Anticancer drugs	93 (71.0)
Routine laxatives‡	98 (74.8)
Rescue laxatives§	126 (96.2)

*Before random assignment, the mean SBM frequency/week at baseline was assessed during the 2-week screening period.;
†Oral morphine equivalent.; ‡Patients were routinely using laxatives at the start of the screening period.
§Patients received rescue laxatives only when needed

Rescue laxative was prohibited in 24 hours before and after the first dose of the study drug

ECOG PS, Eastern Oncology Cooperative Group performance status; SBM, spontaneous bowel movement; SD, standard deviation

Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

Results of Safety Analysis in COMPOSE-5

Primary Endpoint

AE	COMPOSE-5 Naldemedine (n = 131)
Overall	No. (%)
TEAEs	105 (80.2)
Severe TEAEs	40 (30.5)
Treatment-related AEs	20 (15.3)
GI disorders	14 (10.7)
Study withdrawal*	12 (9.2)
GI disorders**	4 (3.1)
Nonfatal SAEs***	14 (10.7)
Deaths†	15 (11.5)

*3.8% of patients (5/131) were related to complications of the primary cancer; **three patients (3/131, 2.3%) reported diarrhea;
***None of the 23 nonfatal SAEs reported by 14 patients were considered related to the study drug
†None of the deaths in either study was considered by the investigator to be related to the study drug (all 15 deaths were related to cancer progression)

Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

Results of Safety Analysis in COMPOSE-5 (cont'd)

Primary Endpoint

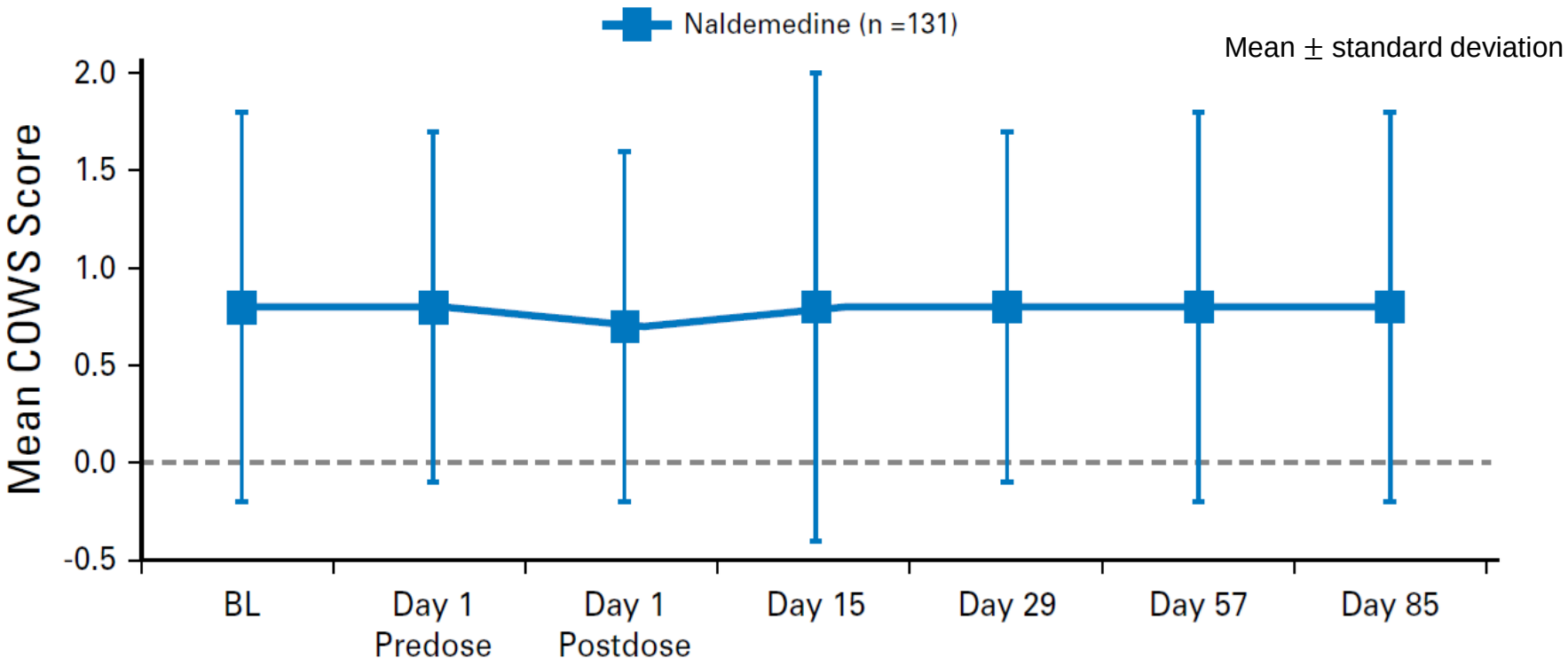
AE	COMPOSE-5 Naldemedine (n = 131)
In ≥ 5% of Patients	
GI disorders	57 (43.5)
Severe	4 (3.1)
Diarrhea	24 (18.3)
Severe	1 (0.8)
Nausea	17 (13.0)
Severe	2 (1.5)
Vomiting	16 (12.2)
Severe	3 (2.3)
General disorders	30 (22.9)
Severe	1 (0.8)
Malaise	13 (9.9)
Severe	0

Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

Mean COWS Scores were Generally Low and Relatively Stable in COMPOSE-5

Safety Endpoint

Clinical Opiate Withdrawal Scale (COWS) score by time point assessed



Although four occurrences of elevated COWS scores were reported, there were no TEAEs of opioid withdrawal

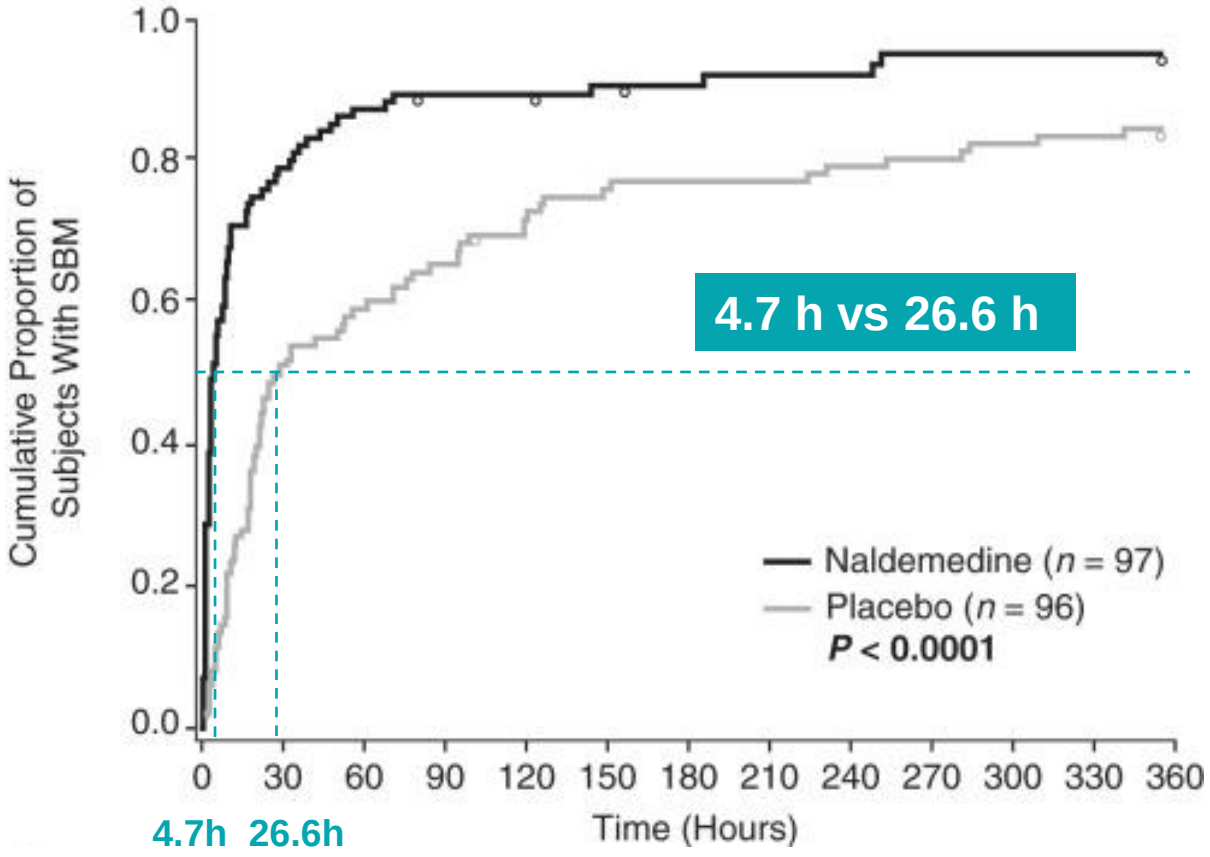
Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

Timely Onset of Relief from OIC with Naldemedine Shown by Median Time to First SBM after the Initial Dose

Efficacy Endpoint

SBM

Kaplan-Meier curve of time to first SBM



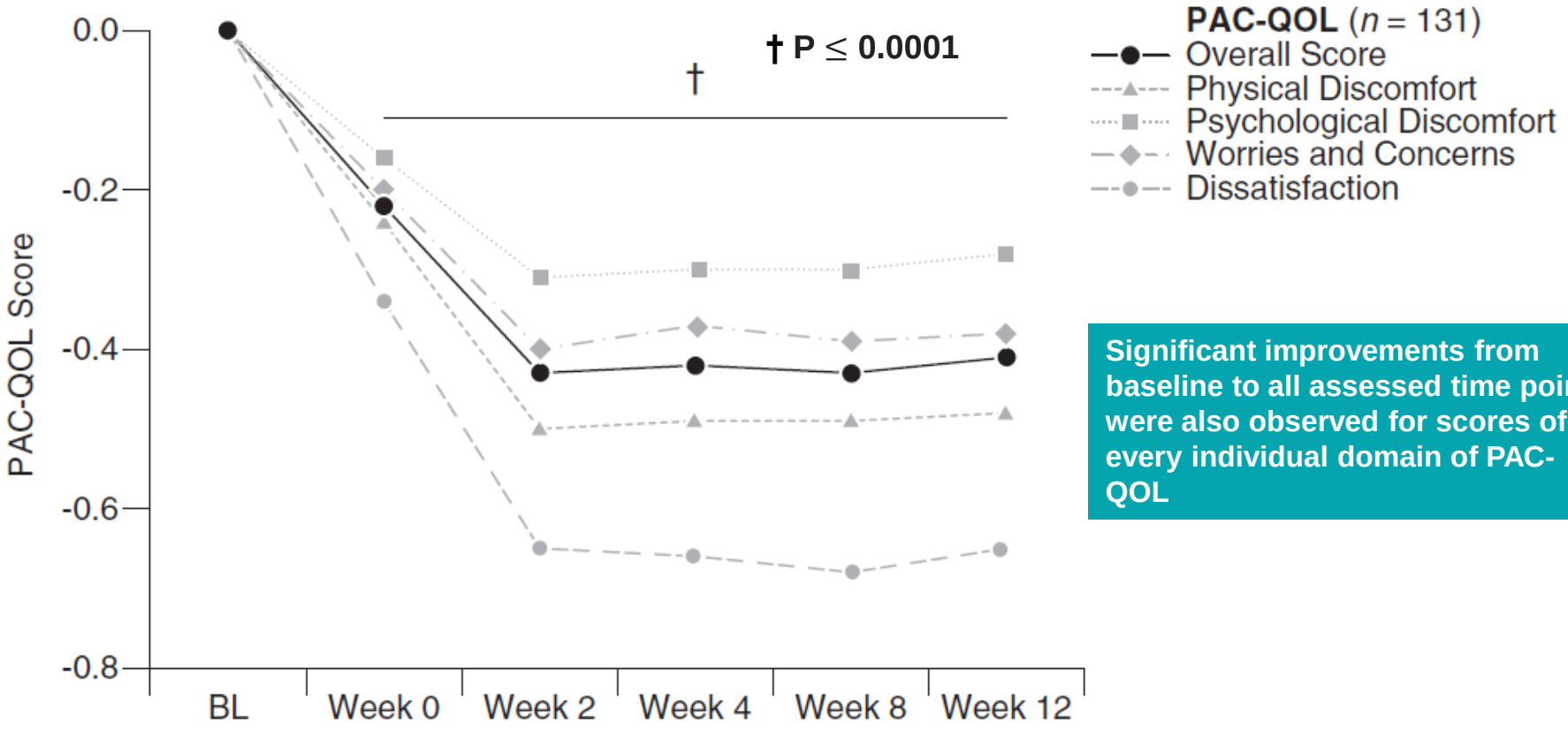
Circles represent censored time. The time to the first SBM was censored for subjects who withdrew from the study before an SBM as observed, or if no SBM occurred during the 2-week treatment period

Katakami et al. Ann Oncol. 2018 Jun;29(6):1461-1467.

Significant Improvement from Baseline in Mean Overall Scores of PAC-QOL with Naldemedine at All Time Points

Efficacy Endpoint

Change from baseline over time in PAC-QOL overall scores and scores for each domain

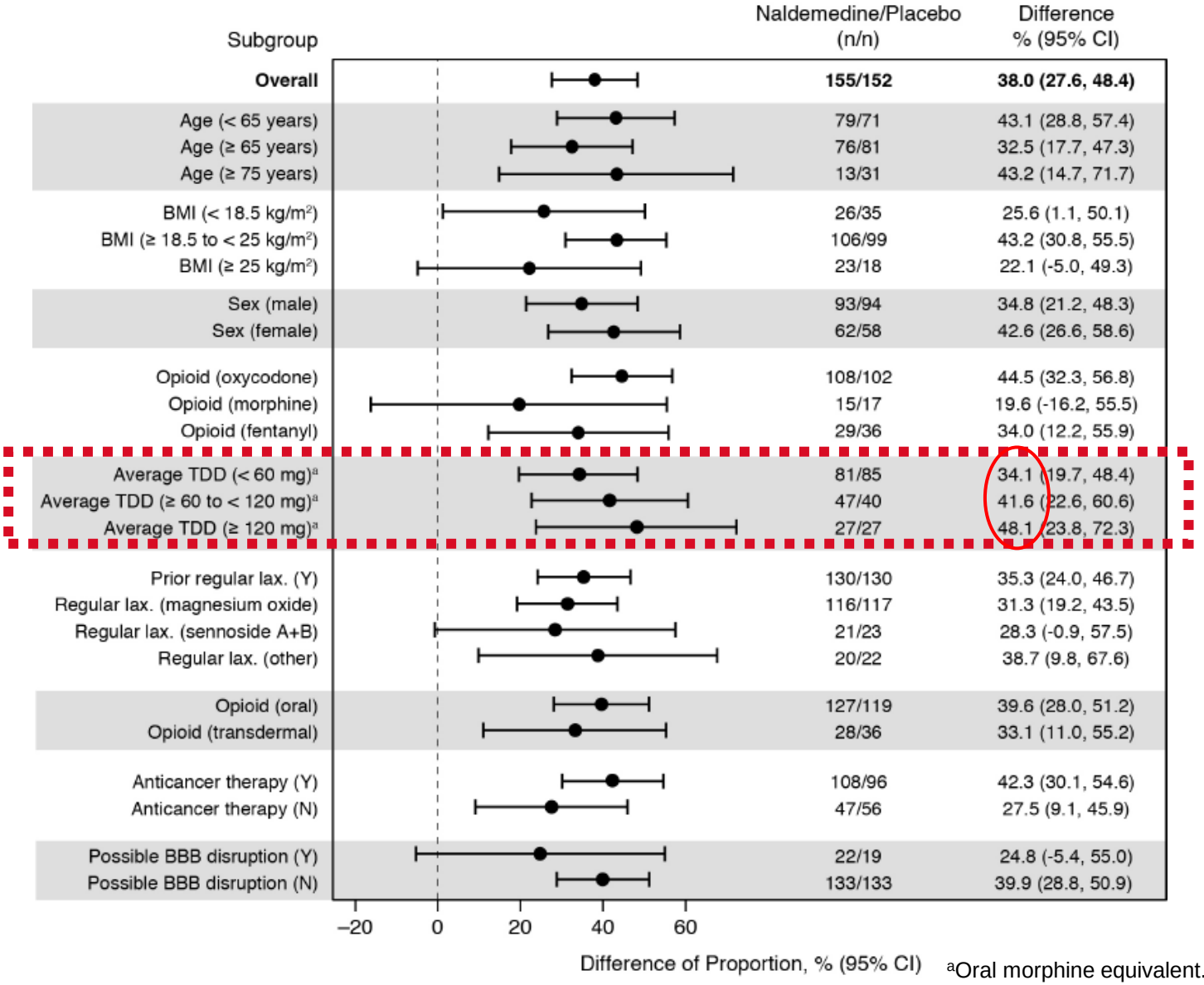


Significant improvements from baseline to all assessed time points were also observed for scores of every individual domain of PAC-QOL

PAC-QOL, Patient Assessment of Constipation Quality of Life

Katakami et al. Ann Oncol. 2018 Jun;29(6):1461-1467.

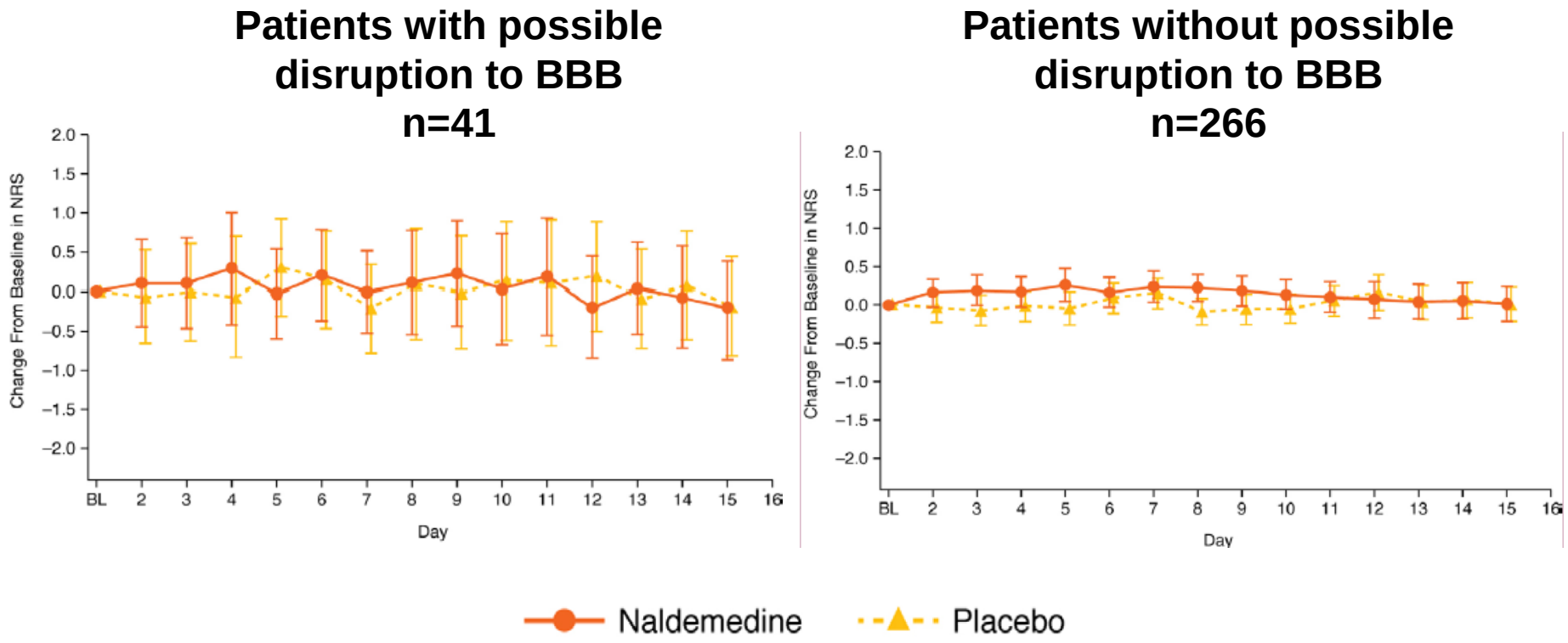
Differences in the Proportions of SBM Responders by Subgroups



Osaka I et al. ESMO Open. 2019 Jul 31;4(4):e000527.

[a]Oral morphine equivalent. BBB, blood–brain barrier; BMI, body mass index; LAX; laxative; N, no; SBM, spontaneous bowel movement; TDD, total daily dose at baseline; Y, yes

Change from Baseline in NRS Scores in the Subgroup of Patients with a Possible BBB Disruption



Osaka I et al. ESMO Open. 2019 Jul 31;4(4):e000527.

Post-Marketing Surveillance of Naldemedine in Japan — Safety Result

The prospective PMS study collected data on the safety and effectiveness of naldemedine for up to 12 weeks in OIC and cancer pain in Japan (N = 1177)

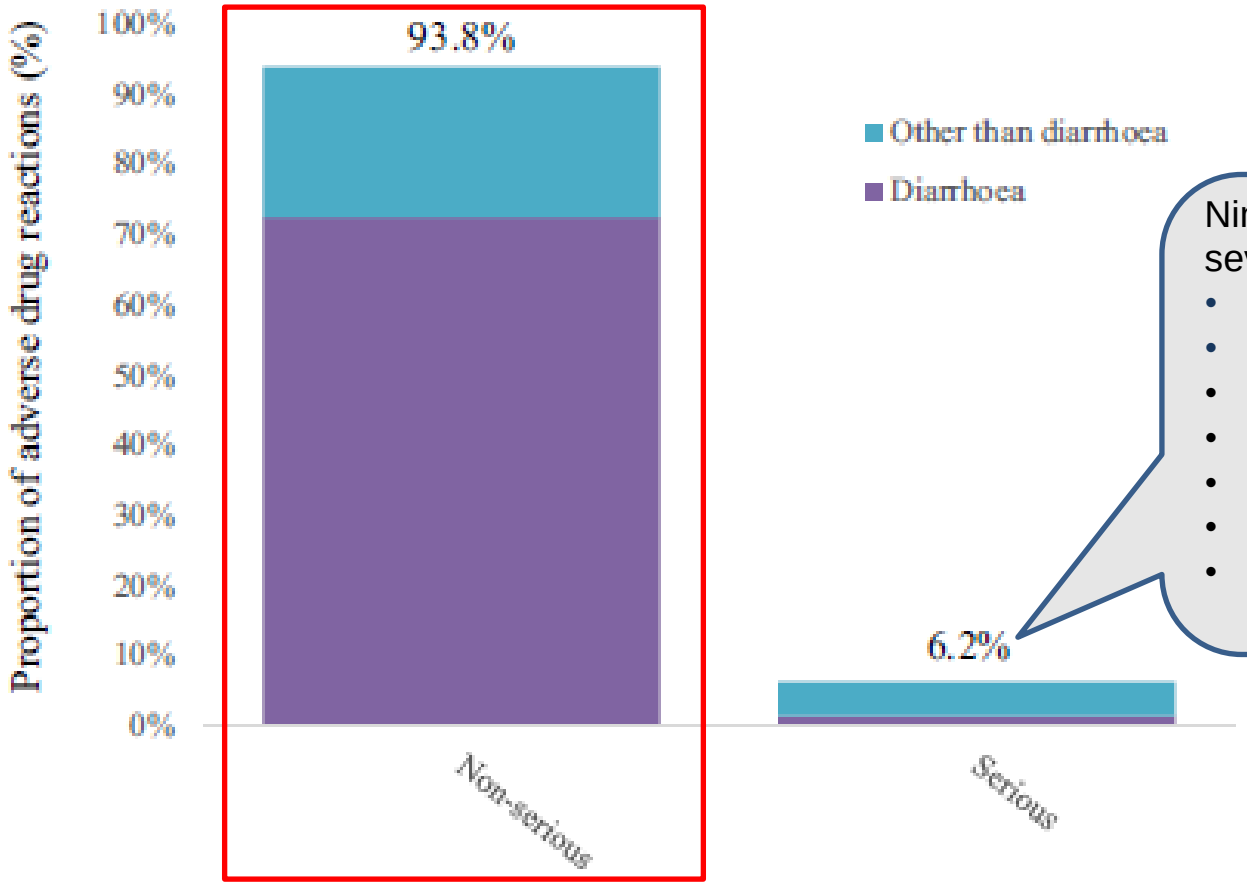
Cases with Adverse Drug Reactions, total		n (%) 133 (11.30)
System Organ Class	Preferred Term	
Infections and infestations		1 (0.08)
	Pneumonia	1 (0.08)
Metabolism and nutrition disorders		4 (0.34)
	Dehydration	1 (0.08)
	Hyperkalemia	1 (0.08)
	Hypokalemia	1 (0.08)
	Decreased appetite	1 (0.08)
Psychiatric disorders		4 (0.34)
	Delirium	2 (0.17)
	Insomnia	2 (0.17)
Gastrointestinal disorders		121 (10.28)
	Abdominal discomfort	1 (0.08)
	Abdominal pain	8 (0.68)
	Abdominal pain lower	1 (0.08)
	Constipation	1 (0.08)
	Diarrhea	107 (9.09)
	Gastrointestinal pain	1 (0.08)
	Nausea	3 (0.25)
	Vomiting	1 (0.08)
	Large intestinal hemorrhage	1 (0.08)
	Feces soft	3 (0.25)
	Anal incontinence	1 (0.08)
Hepatobiliary disorders		1 (0.08)
	Hepatic function abnormal	1 (0.08)
Skin and subcutaneous tissue disorders		3 (0.25)
	Drug eruption	1 (0.08)
	Hyperhidrosis	1 (0.08)
	Rash	1 (0.08)
General disorders and administration site conditions		2 (0.17)
	Inadequate analgesia	1 (0.08)
	Edema peripheral	1 (0.08)
Investigations		1 (0.08)
	Alanine aminotransferase increased	1 (0.08)
	Aspartate aminotransferase increased	1 (0.08)

- No ADRs concerning opioid withdrawal syndrome, GI perforation, and cardiovascular events.
- One patient required an increase in the opioid dose after the administration of naldemedine, but underlying disease or complications were also possible factors to have caused the event.

Takata K et al. Support Care Cancer. 2022 May;30(5):3943-3954.

Post-Marketing Surveillance of Naldemedine in Japan — Safety Result

Proportion of serious and non-serious ADRs



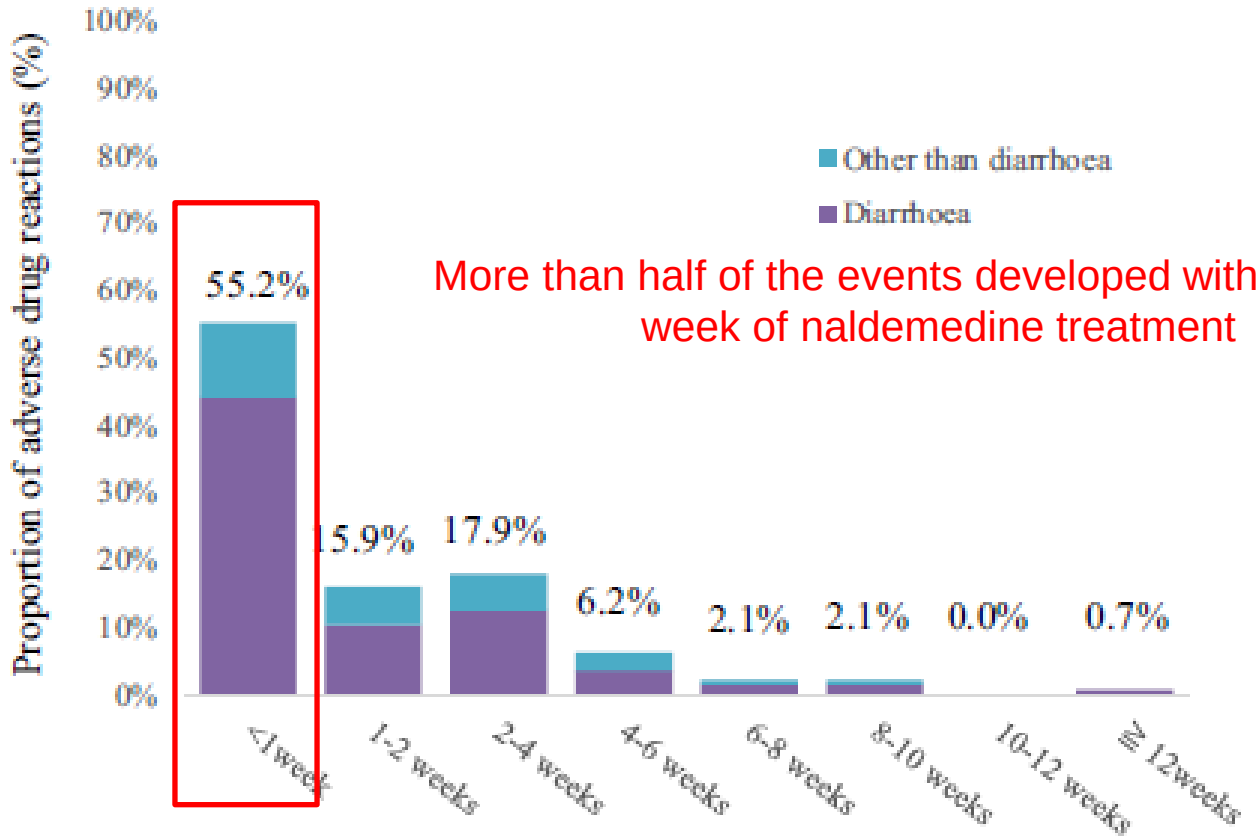
Nine serious ADRs in seven patients

- **Diarrhea**
- **Dehydration**
- Delirium
- Pneumonia
- Hyperkalemia
- Vomiting
- Large intestinal hemorrhage

Takata K et al. Support Care Cancer. 2022 May;30(5):3943-3954.

Post-Marketing Surveillance of Naldemedine in Japan – Safety Result

Time to onset of ADR after the start of naldemedine treatment

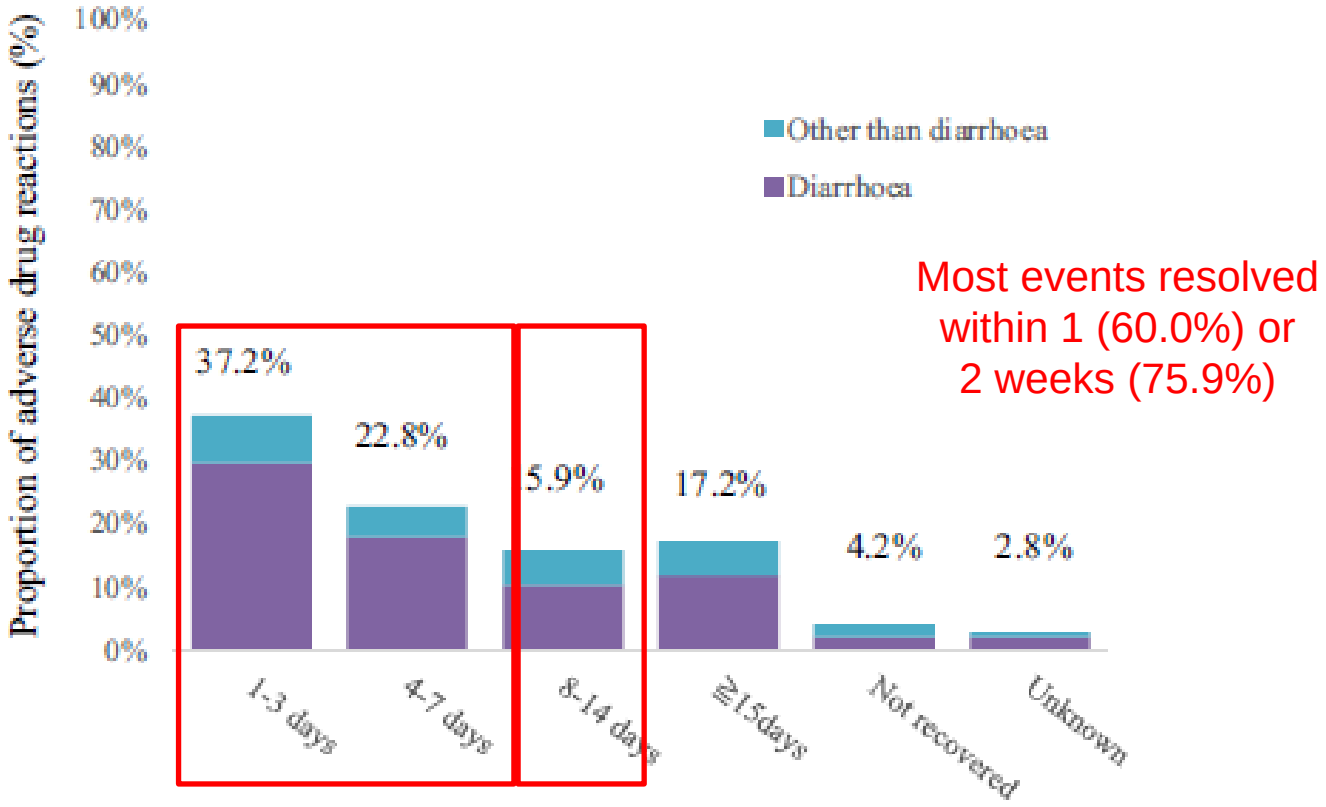


More than half of the events developed within the first week of naldemedine treatment

Takata K et al. Support Care Cancer. 2022 May;30(5):3943-3954.

Post-Marketing Surveillance of Naldemedine in Japan — Safety Result

Time to recovered and recovering after onset of ADR



Most events resolved within 1 (60.0%) or 2 weeks (75.9%)

Takata K et al. Support Care Cancer. 2022 May;30(5):3943-3954.

Naldemedine 不良反應

Naldemedine發生的不良事件(AE)通常是輕度和短暫的

表1 在安慰劑對照之第三期臨床試驗中通報的不良反應(慢性非癌症疼痛病人及OIC)

器官系統分類	非常常見	常見	不常見	罕見	非常罕見
胃腸消化系統異常		腹瀉，腹痛，噁心，嘔吐			

非常常見(≥1/10)；常見(≥1/100 to <1/10)；不常見(≥1/1,000 to <1/100)；罕見(≥1/10,000 to <1/1,000)；非常罕見(<1/10,000).

表2 在安慰劑對照之臨床試驗中通報的不良反應(慢性癌症病人及OIC)

器官系統分類	非常常見	常見	不常見	罕見	非常罕見
胃腸消化系統異常	腹瀉	腹痛			

非常常見(≥1/10)；常見(≥1/100 to <1/10)；不常見(≥1/1,000 to <1/100)；罕見(≥1/10,000 to <1/1,000)；非常罕見(<1/10,000)