Naldemedine in Opioid-induced Constipation
三軍總醫院治療經驗分享

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0950-1030

Outline

- Opioid-induced Constipation (OIC)
- Case sharing

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- Case sharing

表 3-1 可能引起便秘的原因[1]

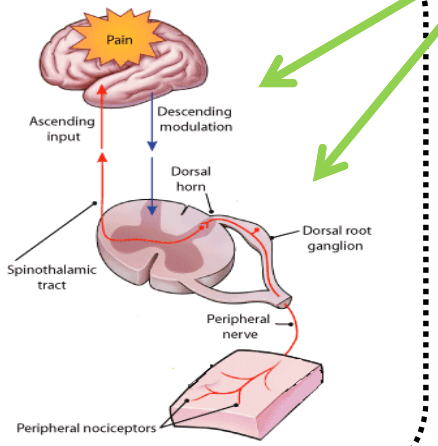
神經/精神性因素	• 自律神經病變 • 脊髓腫瘤或損傷 • 失智症 • 憂鬱症 • 先天性巨結腸病 • 創傷	• 腦血管病變 • 帕金森氏症 • 多發性硬化症 • 飲食障礙（厭食或暴食） • 格林-巴利症候群 • 體化症
內分泌與代謝因素	• 愛迪生氏病 • 糖尿病 • 腦下垂體功能低下 • 嗜鉻細胞瘤	• 尿毒症 • 副甲狀腺機能亢進症 • 甲狀腺機能低下症 • 電解質不平衡（低血鉀、低血鎂、高血鈣）
胃腸道疾病	• 肛門狹窄 • 肛裂 • 痔瘡	• 巨直腸症 • 脫肛 • 憩室症 • 直腸脫垂 • 腸躁症
肌肉、結締組織和發炎性疾病	• 皮肌炎 • 類風濕性關節炎	• 硬皮症 • 全身性紅斑狼瘡
藥物	• 抗膽鹼藥物 • 抗精神病藥物 • 止瀉藥 • 抗焦慮劑 • 抗組織胺 • 降血壓藥物	• 止痛藥／鴉片類藥物 • 鈣離子通道阻斷劑（尤其是 verapamil） • 制酸劑（尤其是含鋁製劑） • 鈣及鐵補充劑
飲食與生活型態	• 纖維攝取不足 • 水分攝取不足 • 坐式生活型態／運動量不足	• 營養（熱量）攝取不足
其他	• 貧血 • 懷孕	• 功能、結構異常 • 接受手術後 • 腫瘤或癌症

Central and Peripheral Actions of Opioids

Opioids act on both CNS and GI tract

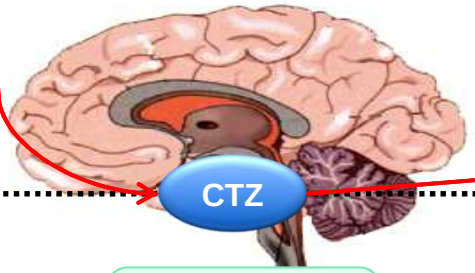
CTZ: Chemoreceptor Trigger Zone
BBB: Blood Brain Barrier

Central (inside of BBB)



Analgesic Effect

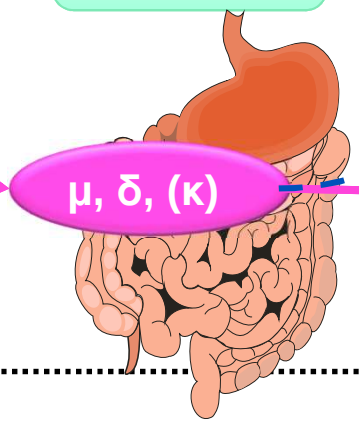
Opioids



CTZ

Emesis (vomiting & nausea)

μ, δ



μ, δ, (κ)

Constipation

Peripheral (outside of BBB)

只要持續使用類鴉片藥物，便祕的情況便會持續的發生

Opioid-induced Constipation (OIC) - Definition

a change in baseline bowel habit or defecatory patterns following initiation, alteration, or increase of opioid therapy

201605

>=2/6

Panel: **The Rome IV diagnostic criteria for opioid-induced constipation***

1 New or escalating symptoms of constipation when initiating, changing, or increasing opioid therapy that must include two or more of the following:
   a) Straining during more than a quarter of defecations — Straining: 用力解便
   b) Lumpy or hard stools (Bristol Stool Form Scale 1–2) more than a quarter of the time — 塊狀或硬的糞便
   c) Sensation of incomplete evacuation more than a quarter of the time — Incomplete: 排便不完全的感覺
   d) Sensation of anorectal blockage or obstruction in more than a quarter of defecations — 肛門直腸堵塞的感覺
   e) Manual manoeuvres to facilitate more than a quarter of defecations — 人工方式協助排便
   f) Fewer than three spontaneous bowel movements per week — 每週少於3 次的自發排便頻率
2 Loose stools rarely present without the use of laxatives — 在不使用緩瀉劑下很難出現稍軟的糞便

*Reproduced from Mearin F and colleagues,[6] by permission of Elsevier.

Lancet Gastroenterol Hepatol. 2018 Mar;3(3):203-212

Diagnosis of OIC

表 3-3　OIC 診斷標準：羅馬準則第四版

1. 當開始使用鴉片類藥物、改變或增加鴉片類藥物的治療時，出現新的便秘症狀或便秘症狀惡化。需符合下列至少 2 項條件：
   - a. 每 4 次排便中有 1 次以上（25%）需要用力解便
   - b. 每 4 次排便中有 1 次以上（25%）糞便呈團塊或硬便（BSFS 第 1 / 2 型）
   - c. 每 4 次排便中有 1 次以上（25%）感覺排便排不乾淨
   - d. 每 4 次排便中有 1 次以上（25%）有肛門直腸阻塞感
   - e. 每 4 次排便中有 1 次以上（25%）需要手動協助解便
   - f. 每週自發性排便小於 3 次
2. 在沒有使用緩瀉劑的情況下，幾乎不會出現鬆軟的糞便。

BSFS, Bristol Stool Form Scale.

布里斯托糞便分類量表（BSFS）

布里斯托糞便分類量表（Bristol Stool Form Scale, BSFS）為目前臨床最常使用的糞便型態分類量表，可供醫師、醫療照護者、病人或一般民眾使用。藉由肉眼觀察糞便的質地及形狀分成共 7 型，由最硬（第 1 型）至最軟（第 7 型）[1,2]。

異常（過硬）	第 1 型		一顆顆分開的硬球，像堅果
	第 2 型		呈團塊的香腸形狀
正常	第 3 型		表面有裂痕的香腸或蛇形狀
	第 4 型		光滑且柔軟的香腸或蛇形狀
	第 5 型		柔軟塊狀，邊緣清楚
異常（過軟）	第 6 型		鬆散、邊緣模糊，呈糊狀
	第 7 型		水狀，無固體塊（完全液態）

Diagnosis of OIC

腸功能指數（Bowel Function Index, BFI）量表僅包含 3 道題目，經確效可用於 OIC 病人，被認為是目前最適合評估 OIC 的量表。

- BFI 量表內容主要依據病人過去 7 天便秘相關的症狀及感覺進行評估，包括**「排便的順暢程度」**、**「排便排不乾淨的感覺」**及**「對便秘的個人感受」**共三個面向。

無症狀或沒有影響為 0 分，最嚴重為 100 分（範圍0–100 分），3 項題目的平均分數即為病人的 BFI 分數。

- **BFI ≥ 30 分**表示病人的症狀符合便秘的情況，若 BFI 分數改變 ≥ 12 分，代表便秘狀況的變化具有臨床顯著意義。

表 3-4　腸功能指數（BFI）量表[*2,5,11]

❶ 排便的順暢程度

在過去 7 天，您認為您的排便順暢程度是幾分？

（0 分為「完全沒有困難」；100 分為「非常困難」）

0 —— 100　_____ 分

❷ 排便排不乾淨的感覺

在過去 7 天，您對於排便排不乾淨的感覺是幾分？

（0 分為「完全沒有排便排不乾淨的感覺」；100 分為「有強烈的排便排不乾淨的感覺」）

0 —— 100　_____ 分

❸ 對便秘的個人感受

在過去 7 天，您覺得您便秘的程度是幾分？

（0 分為「完全沒有便秘」；100 分為「非常嚴重的便秘」）

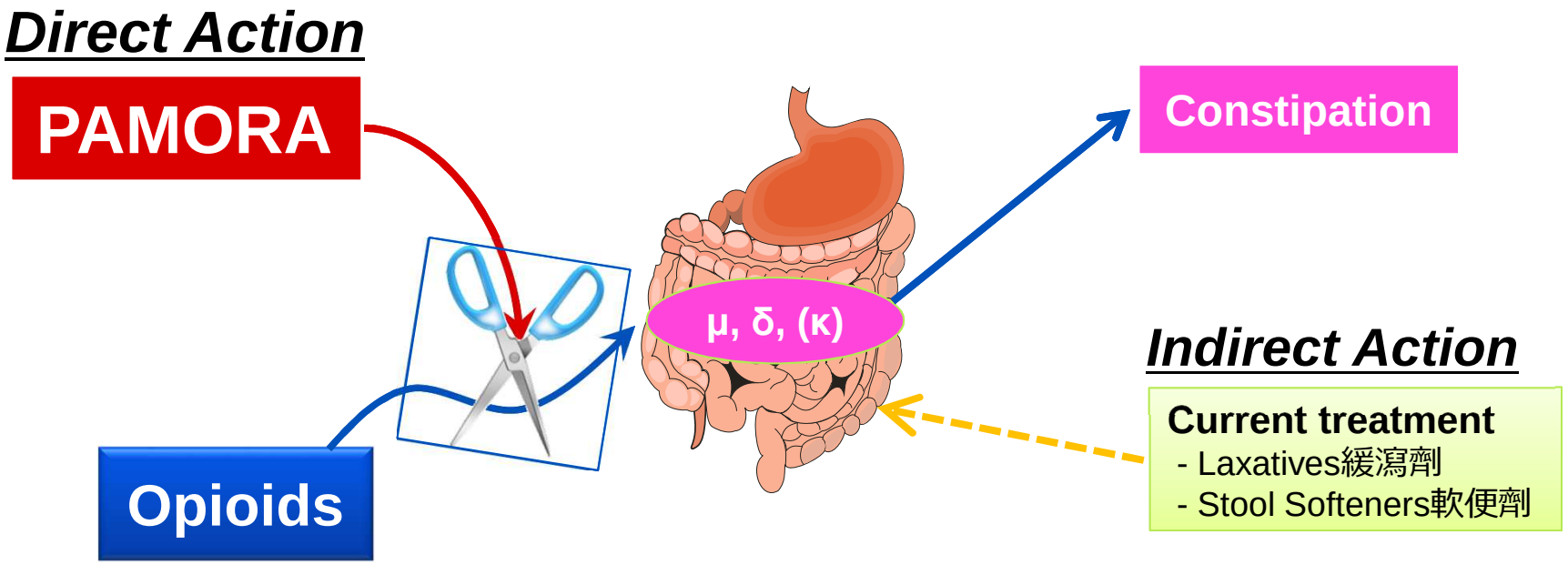
0 —— 100　_____ 分

BFI 評分 = _____（三項分數之平均）

*目前無確效之 BFI 繁體中文翻譯版本，本表之中文翻譯內容僅供參考。

MoA Differentiation among Current Treatments

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

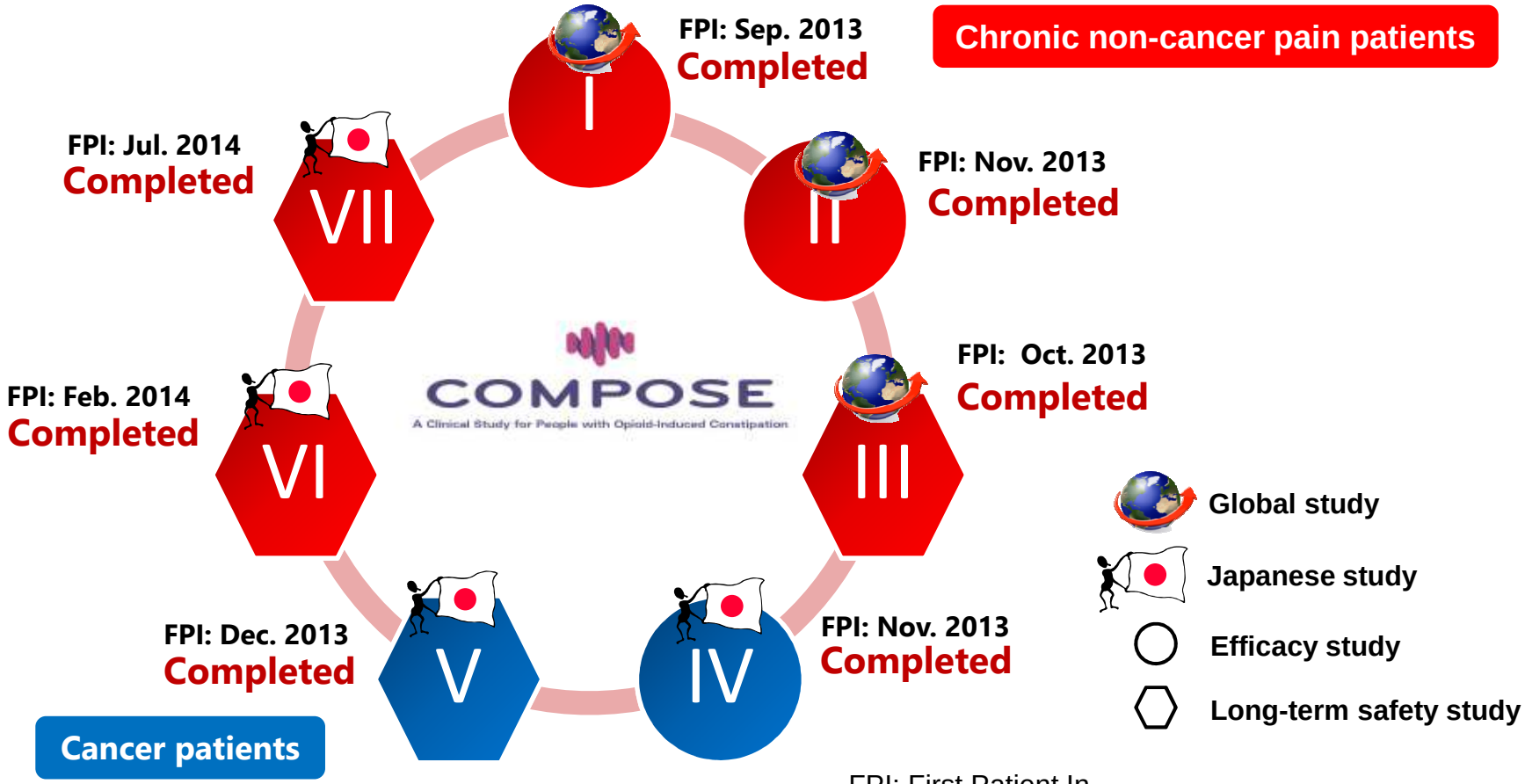


PAMORA: Peripherally-Acting Mu-Opioid Receptor Antagonists

Source: Global OIC market research December 2012

COMPOSE Program (Phase III) of Naldemedine

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



FPI: First Patient In

VOLUME 35 · NUMBER 34 · DECEMBER 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

SONG for you!

Randomized Phase III and Extension Studies of Naldemedine in Patients With Opioid-Induced Constipation and Cancer

Nobuyuki Katakami, Toshiyuki Harada, Toru Murata, Katsunori Shinozaki, Masakazu Tsutsumi, Takaaki Yokota, Masatsugu Arai, Yukio Tada, Masaru Narabayashi, and Narikazu Boku

COMPOSE-4 & COMPOSE-5 Studies

COMPOSE-4: Randomized, double-blind, parallel-group, placebo-controlled, phase III trial

COMPOSE-5: Open-label, single-arm, 12-week extension study

SHIONOGI

No limitation of laxatives usage during study period

Definition of OIC in COMPOSE-4 & COMPOSE-5

During the 2 weeks before random assignment,

<=5

Five or fewer spontaneous bowel movements

and

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

>=25%

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

Study Objective of COMPOSE-4

Randomized, double-blind, parallel-group, placebo-controlled, phase III trial

Study Objective

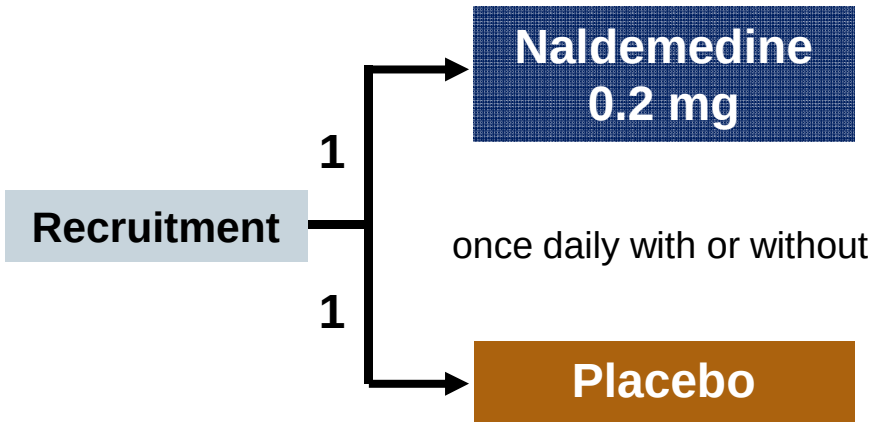
Evaluated the efficacy and safety of once-daily oral **naldemedine 0.2 mg** for 2 weeks in patients with opioid-induced constipation and cancer

- Patients aged ≥ 20 y/o
- ECOG PS ≤ 2
- Any cancer, did not directly affect GI function
- cancer expected to remain stable for the extent of the study
- Patients were on a stable daily dose of opioids for ≥ 2 weeks before screening
- Opioid-induced constipation (OIC)

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

Study Design of COMPOSE-4

2-week screening	**2-week** intervention	**4-week** follow-up*



援救緩瀉劑(rescue laxative)
第一次服用試驗藥品前後的24小時內不得使用外，其他時間病患若有需要皆可使用。

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 – Full Analysis Set (FAS)*

自發排便反應率

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

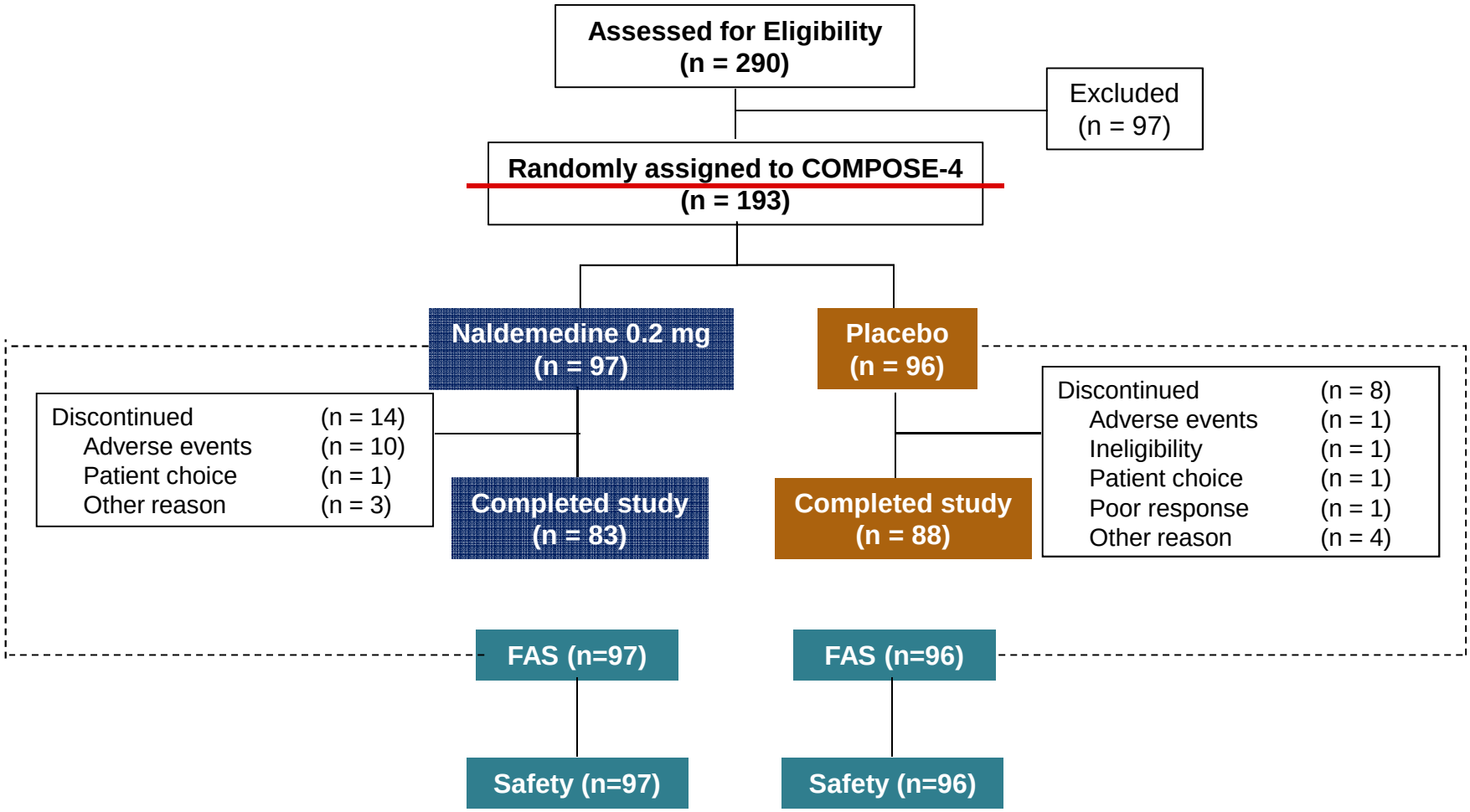
Safety- Patients received at least one dose of study drug

① 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)

* All randomly assigned patients who had at least one dose of study drug and an evaluation of OIC at baseline and post-dose
** 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 Disposition in COMPOSE-4



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

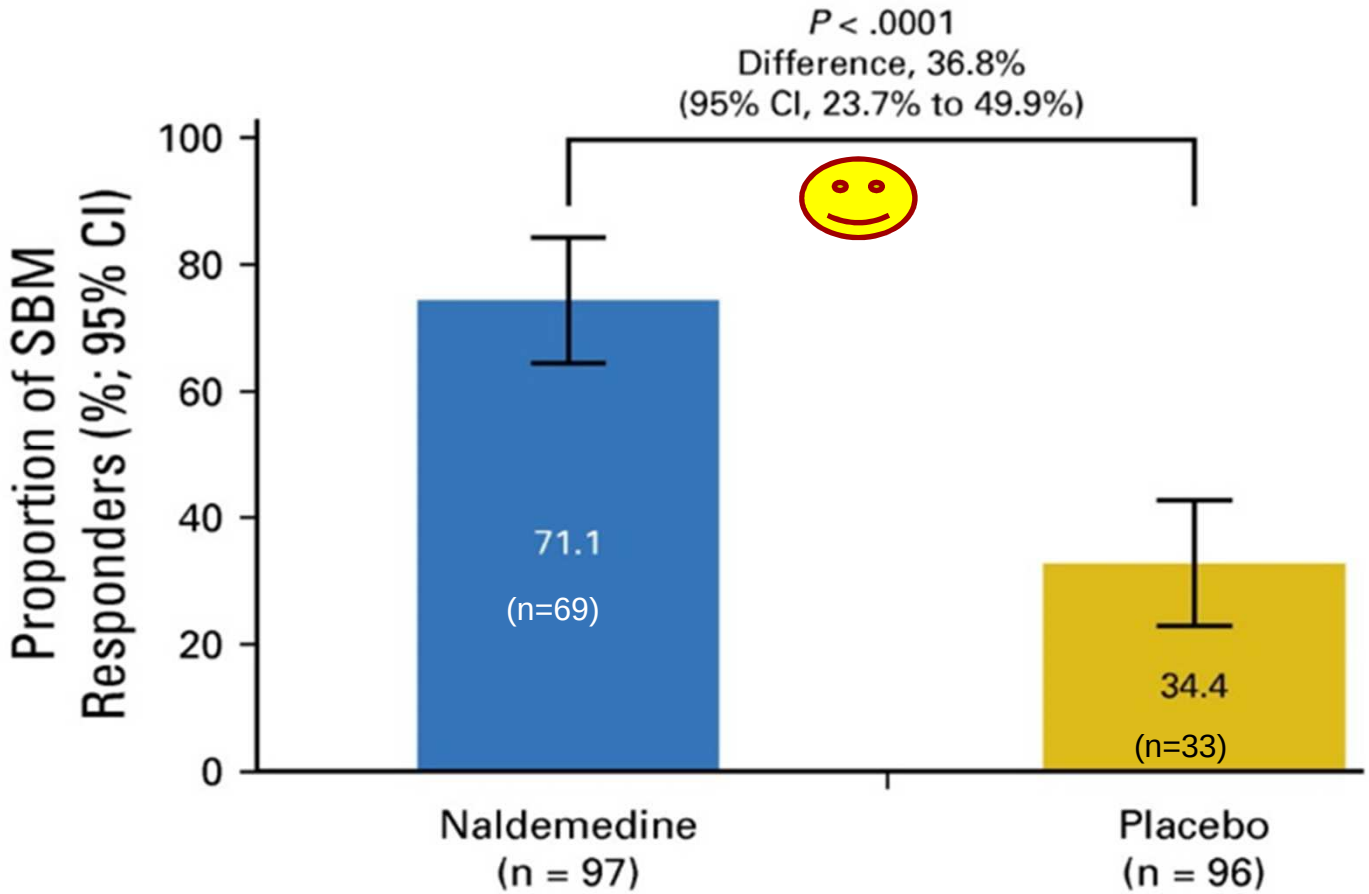
Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

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

Primary Endpoint

自發排便反應率

Proportion of SBM responders during 2-week treatment period



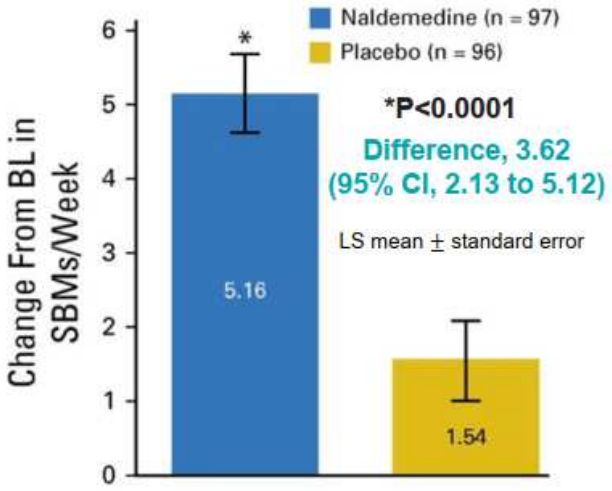
SBMs = spontaneous bowel movements; SBM responder = patients **with >=3 SBMs/week** who had an increase of **>=1 SBM/week from baseline**. Baseline was the average number of SBMs/week during the 2 weeks before random assignment.

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

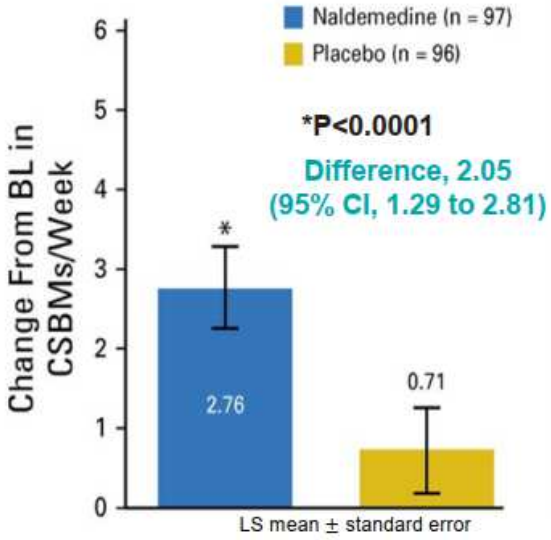
Significantly Greater Change from Baseline with Naldemedine in the Mean Frequency of SBMs, CSBMs, SBMs without Straining/week

Secondary Endpoint

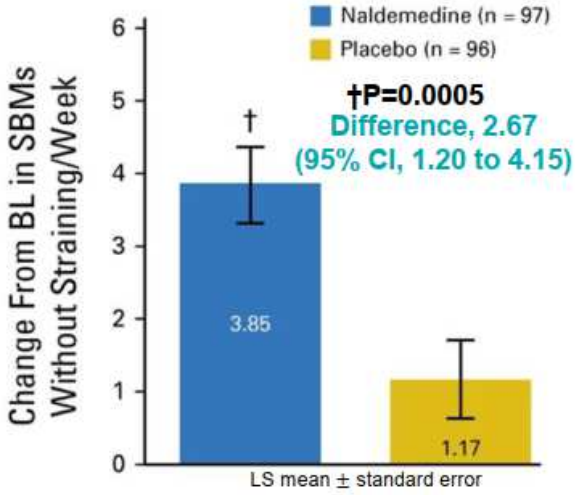
Change from baseline in least squares (LS) mean of frequency of SBMs/week



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



Change from baseline in least squares (LS) mean of the frequency of SBMs without straining/week



CSBMs=complete spontaneous bowel movements

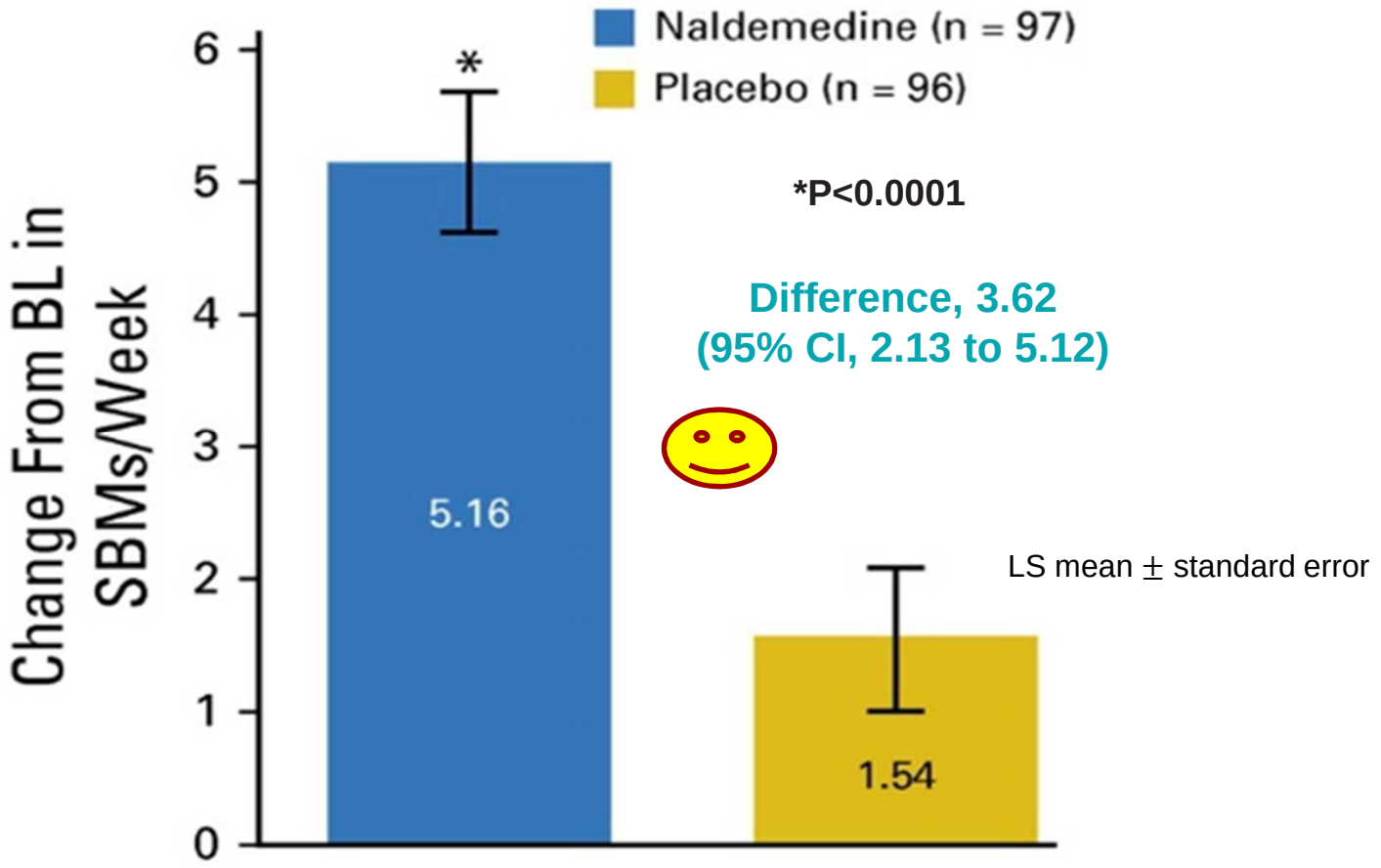
Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

SHIONOGI

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

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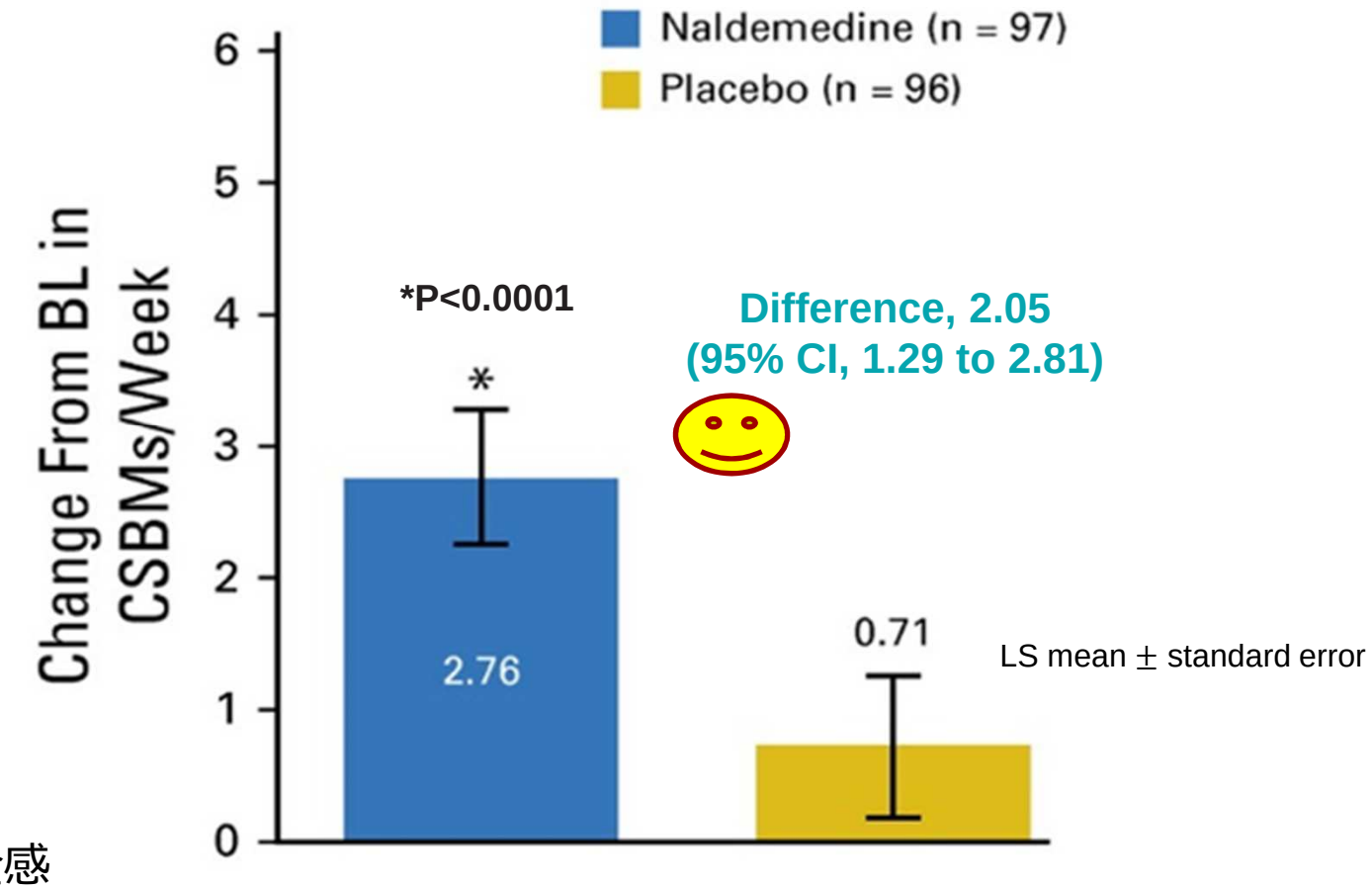
Significantly Greater Change from Baseline with Naldemedine in Mean Frequency of CSBMs/week in COMPOSE-4

Secondary Endpoint

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



排便完全感

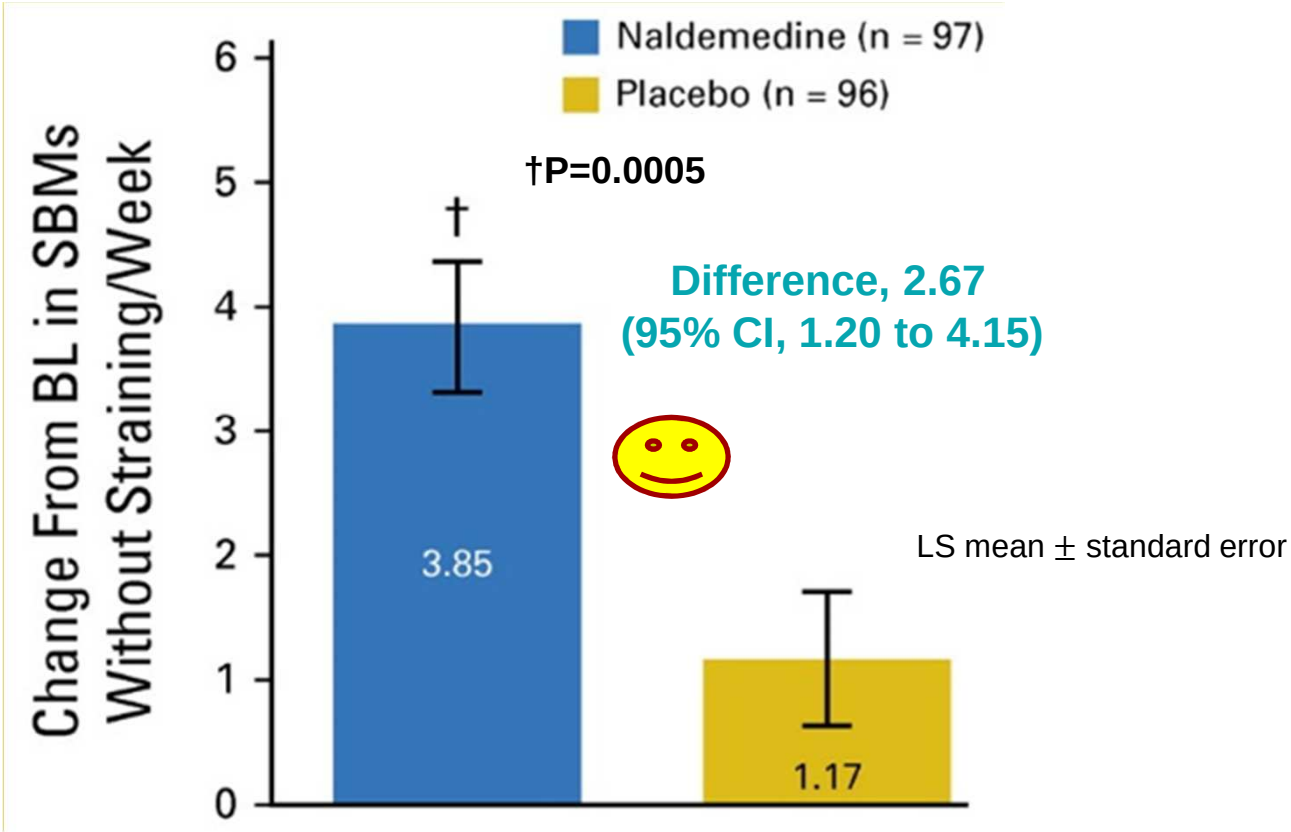
CSBMs=complete spontaneous bowel movements

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

Significantly Greater Change from Baseline with Naldemedine in Mean Frequency of SBMs without Straining/week in COMPOSE-4

Secondary Endpoint

Change from baseline in least squares (LS) mean of the frequency of SBMs without straining/week



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

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

Safety Endpoint

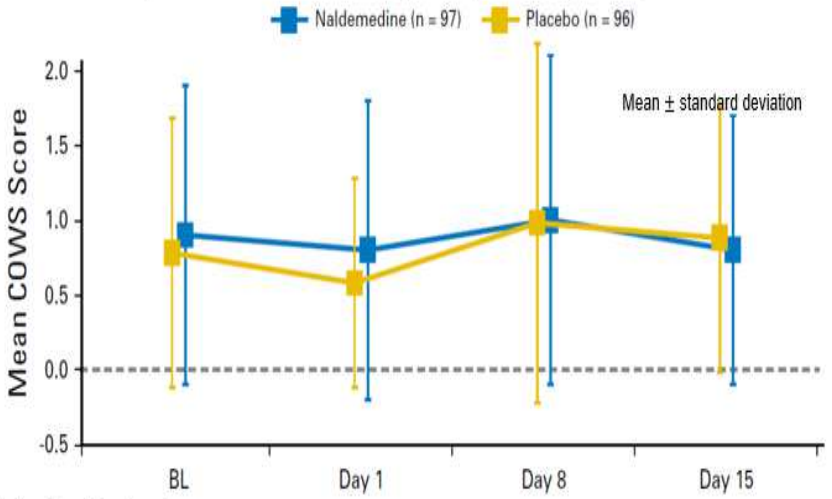
AE	COMPOSE-4* Naldemedine (n = 97)	Placebo (n = 96)
In ≥ 5% of patients		
GI disorders	23 (23.7)	9 (9.4)
Severe	2 (2.1)	0
Diarrhea	19 (19.6)	7 (7.3)
Severe	2 (2.1)	0
Nausea	1 (1.0)	2 (2.1)
Severe	0	0
Vomiting	3 (3.1)	1 (1.0)
Severe	1 (1.0)	0
General disorders	8 (8.2)	5 (5.2)
Severe	1 (1.0)	0
Malaise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

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

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

Safety Endpoint 臨床類鴉片藥物戒斷症狀評估表

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).

COWS總分5~12為輕微；13~24分為中度；25~36分為中度嚴重；35分以上為嚴重戒斷

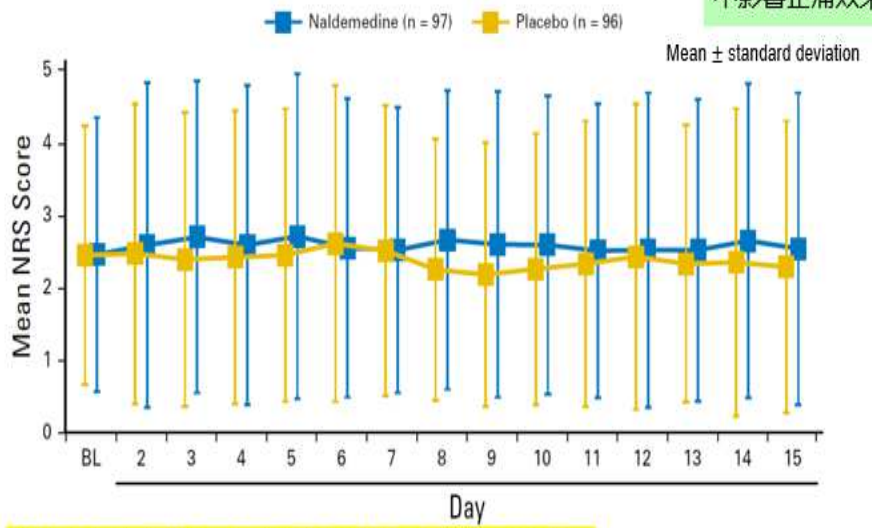
Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

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

Safety Endpoint 疼痛嚴重程度

Numeric Rating Scale (NRS) score assessed daily

不影響止痛效果



NRS: 1~3 mild ; 4~6 moderate ; 7~10 severe

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

Study Objective of COMPOSE-5

Open-label, single arm,12-week extension study following COMPOSE-4 study

Study Objective

Evaluated the **safety** of naldemedine in patients with cancer and opioid-induced constipation

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

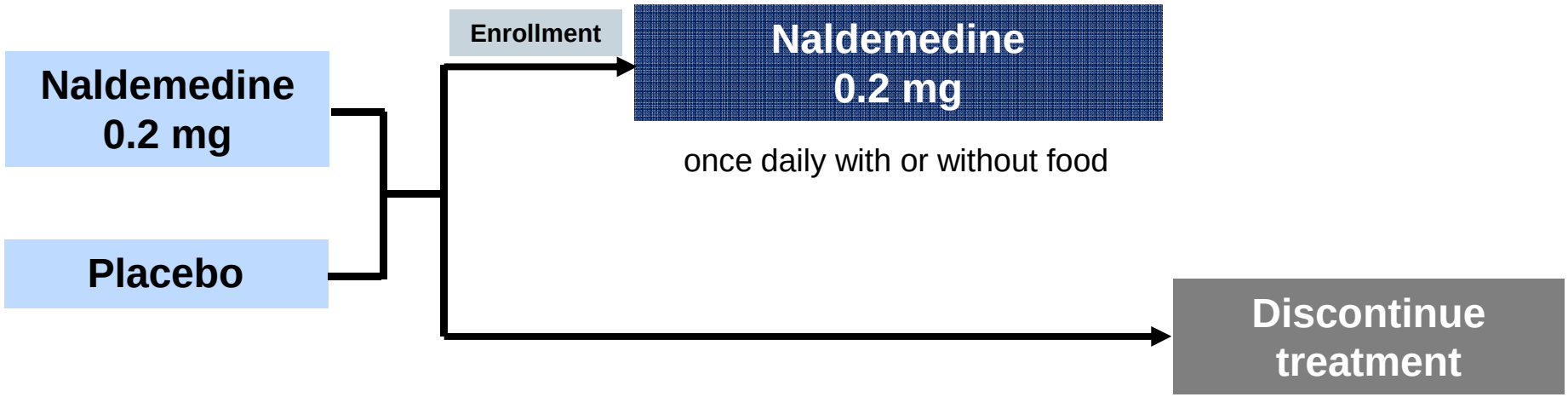
Study Design of COMPOSE-5

用更久有無副作用?

SONG for you!

COMPOSE-4 Study

2-week	12-week extension study	4-week follow-up



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 - Patients received at least one dose of study drug

Primary Endpoint

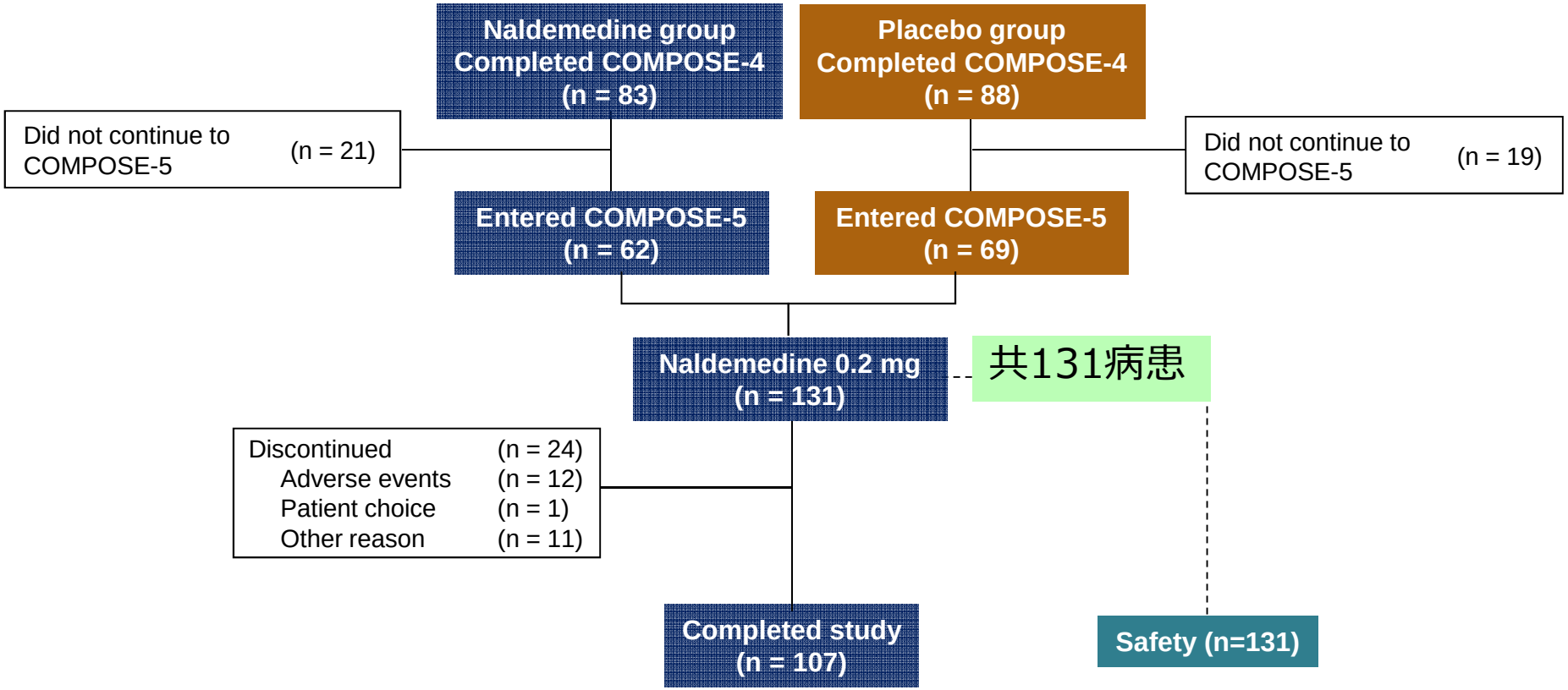
① treatment-emergent AEs (TEAEs*)

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 Disposition in COMPOSE-5



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)

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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

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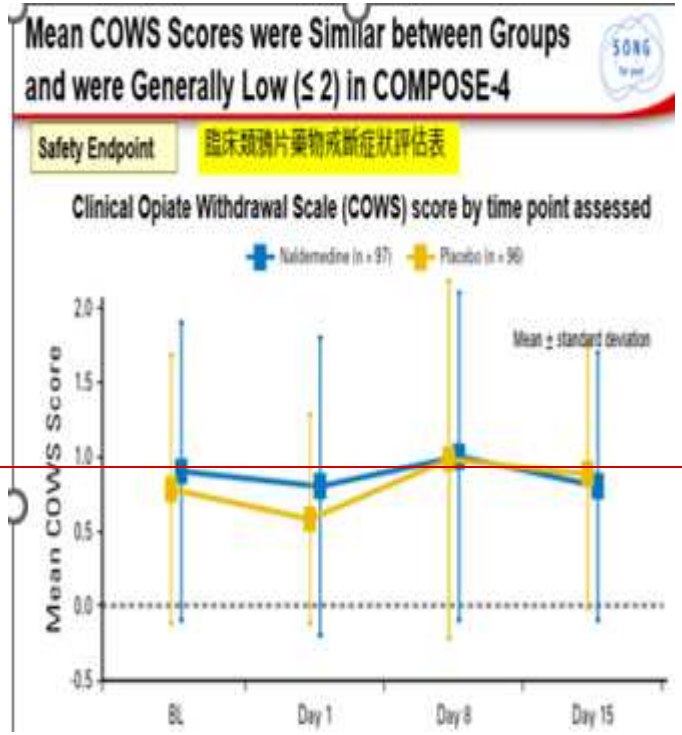
Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

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

Safety Endpoint

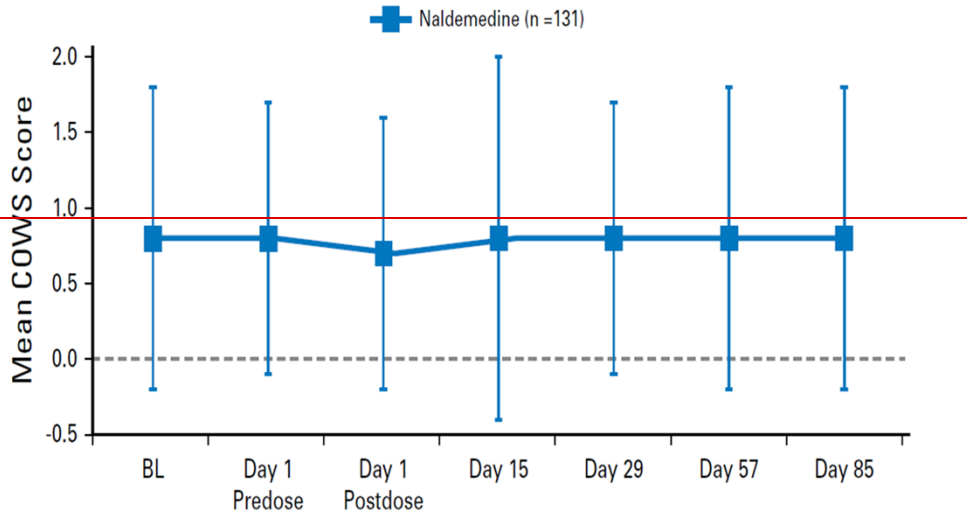
臨床類鴉片藥物戒斷症狀評估表

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



Mean ± standard deviation

COMPOSE-5



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.

Conclusion

- COMPOSE-4 and COMPOSE-5 **the first phase III clinical trials,** efficacy and safety of an oral Peripherally acting mu-opioid receptor antagonists for OIC specifically in cancer.
- the utility of **once-daily oral naldemedine 0.2 mg** taken with or without food as an effective treatment option for patients with OIC and cancer.
- the concomitant use of naldemedine with opioids, well tolerated and **did not impede the analgesic benefits** of opioids or precipitate **opioid-withdrawal syndrome**.

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

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29: 1461–1467, 2018
doi:10.1093/annonc/mdy118
Published online 18 April 2018

ORIGINAL ARTICLE

Randomized phase III and extension studies: efficacy and impacts on quality of life of naldemedine in subjects with opioid-induced constipation and cancer

N. Katakami[1*], T. Harada[2], T. Murata[3], K. Shinozaki[4], M. Tsutsumi[5], T. Yokota[6], M. Arai[6], Y. Tada[6], M. Narabayashi[7] & N. Boku[8]

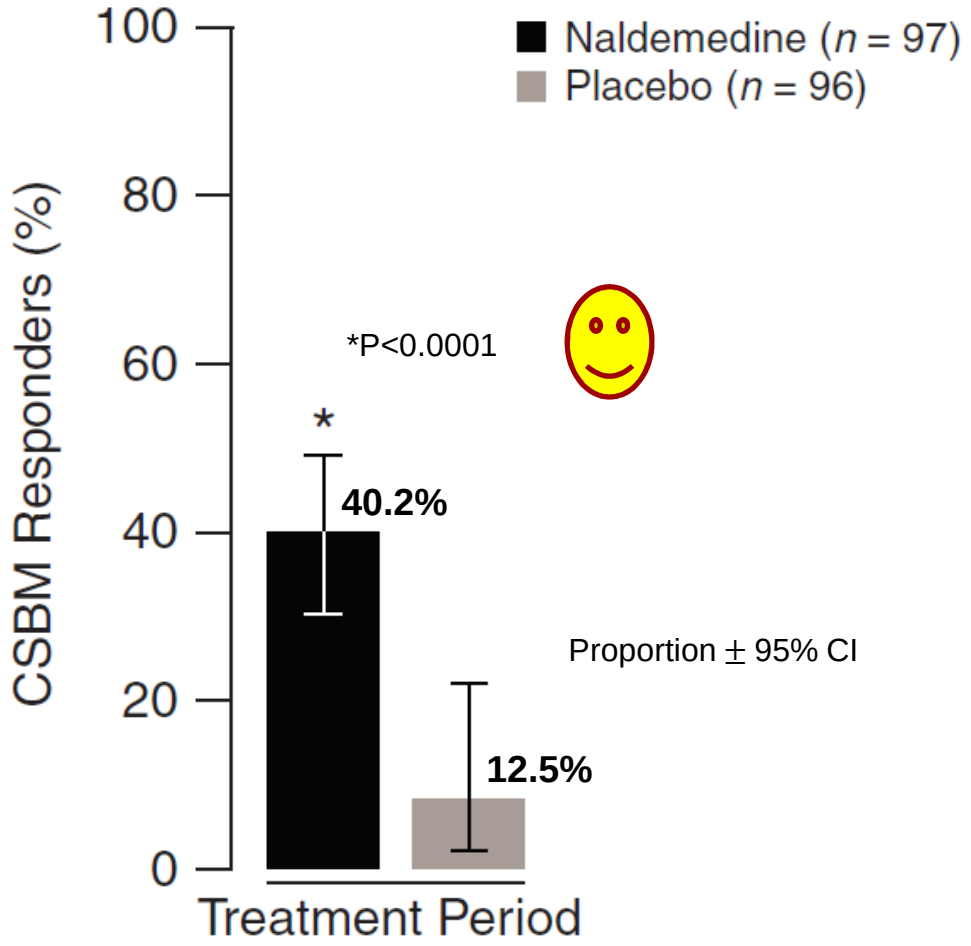
Prespecified secondary efficacy endpoint - evaluate the efficacy, onset of action, and impact on the QOL of naldemedine treatment in subjects with OIC and cancer.

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

Significantly Greater Proportion of CSBM Responders with Naldemedine during 2-week Treatment Period

Efficacy Endpoint

Proportion of CSBM responders over the 2-week treatment period

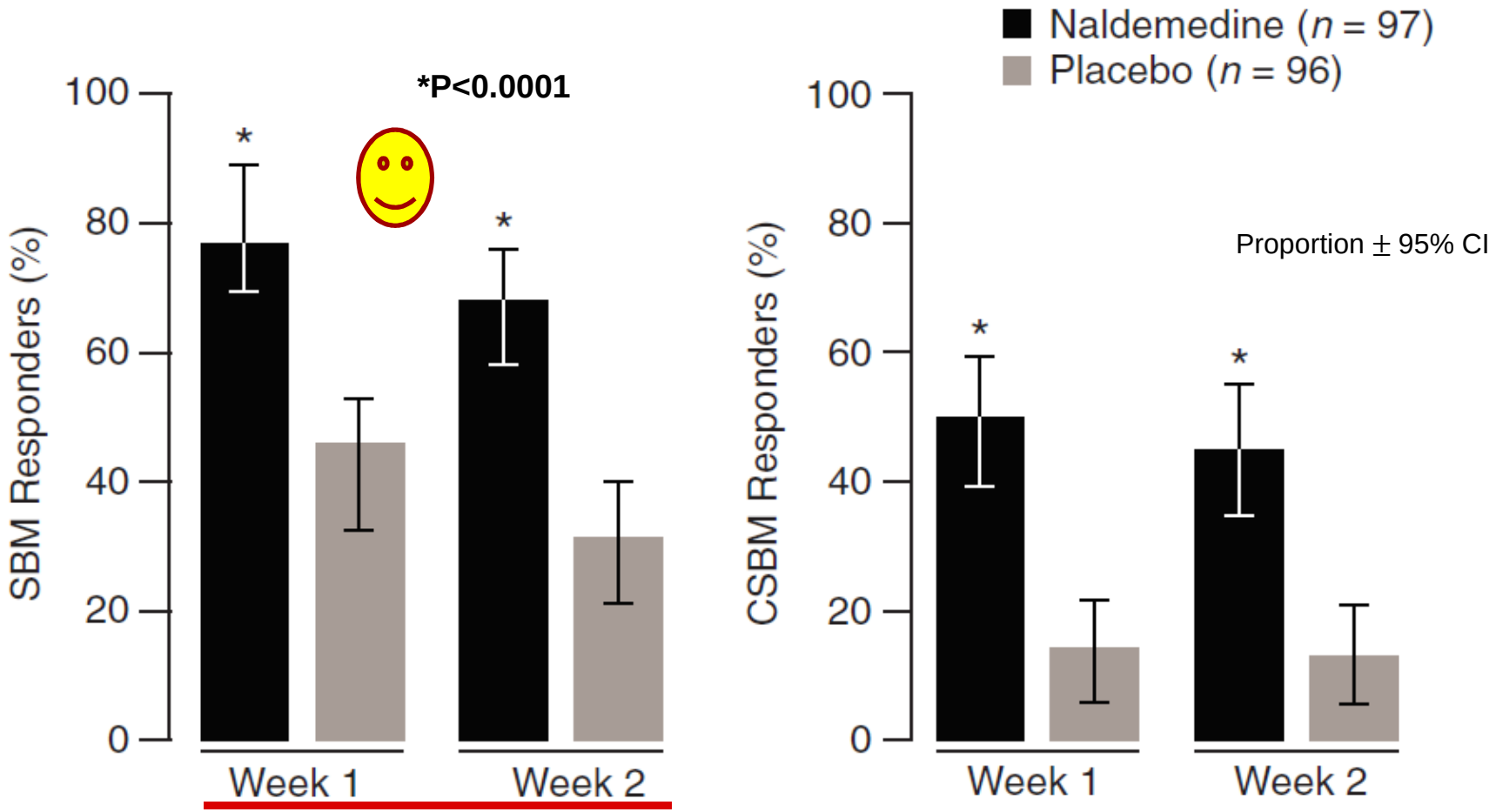


Katakami et al. Ann Oncol. 2018 Jun;29(6):1461-1467.

Significantly Greater Proportions of SBM and CSBM Responders by Week with Naldemedine

Efficacy Endpoint

Proportion of SBM/CSBM responders by week

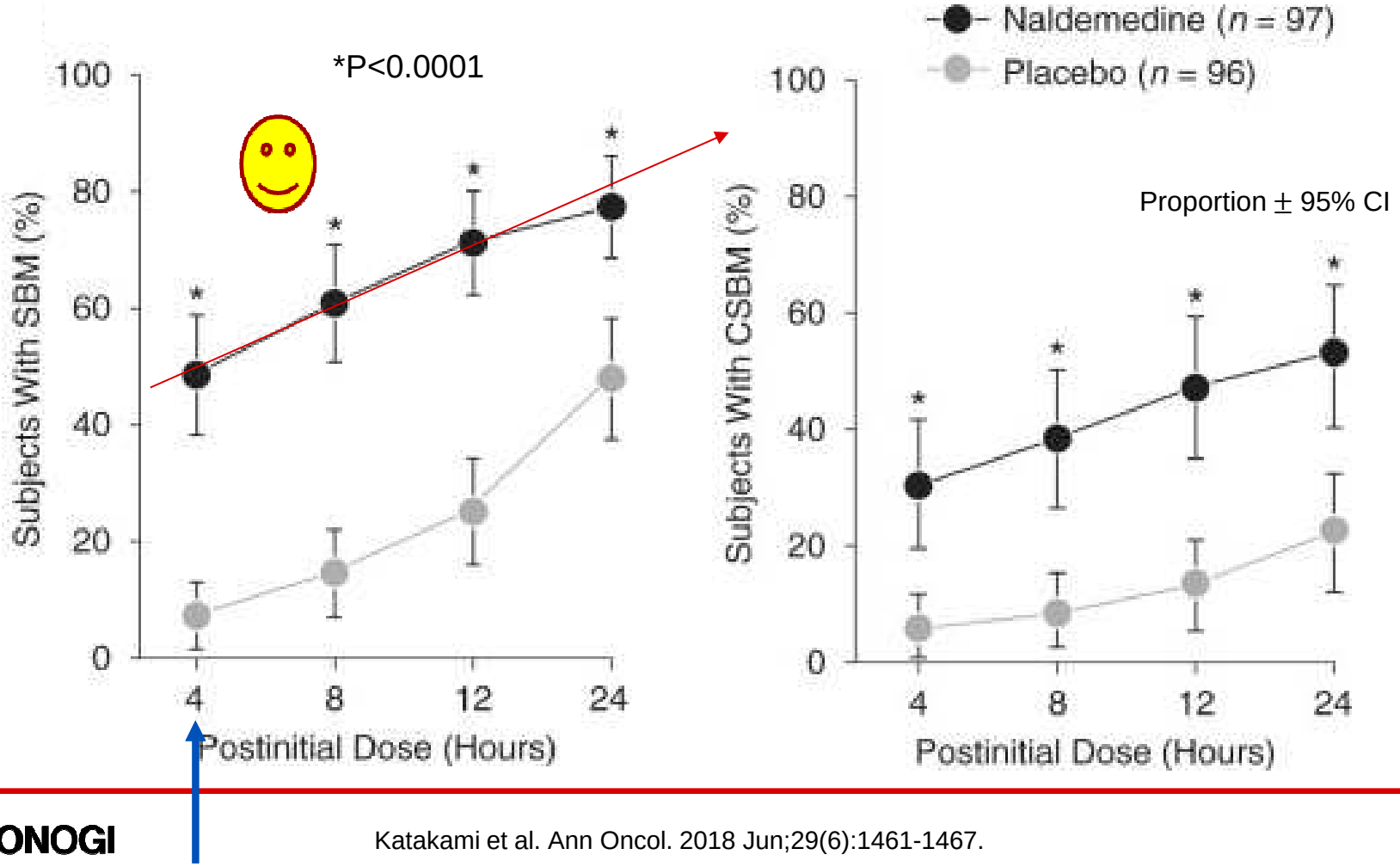


Katakami et al. Ann Oncol. 2018 Jun;29(6):1461-1467.

Significantly Greater Proportion of Subjects had ≥ 1 SBM/CSBM within 24 h after the Initial Dose of Naldemedine

Efficacy Endpoint

Proportion of subjects with ≥ 1 SBM/CSBM at specific time points within 24 h after the initial dose of the study drug



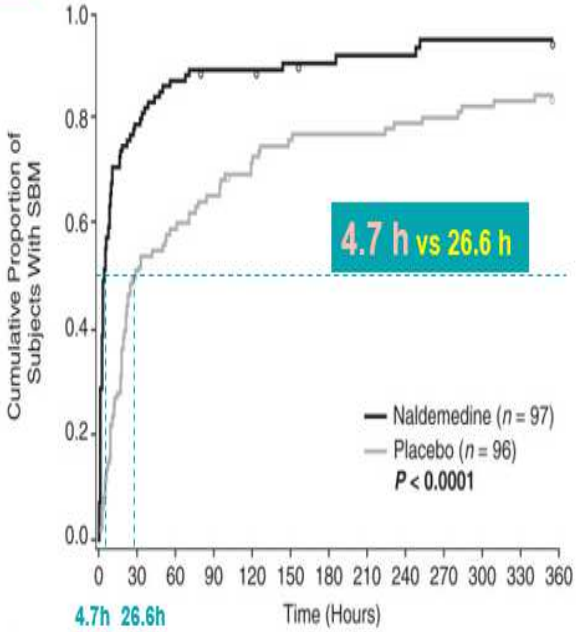
Katakami et al. Ann Oncol. 2018 Jun;29(6):1461-1467.

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

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

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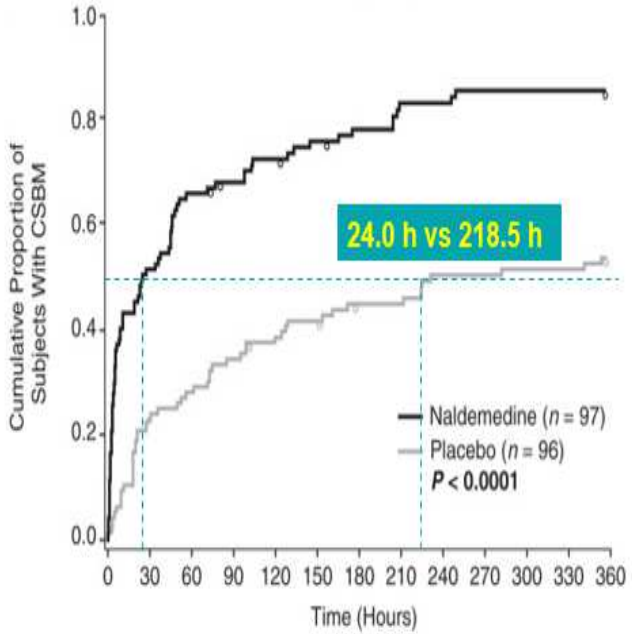
Timely Onset of Relief from OIC with Naldemedine Shown by Median Time to the First CSBM after the Initial Dose

Efficacy Endpoint

CSBM

Kaplan–Meier curve of time to first CSBM



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

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

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Conclusion

- COMPOSE-4 and COMPOSE-5 are especially notable, because they are the first phase III clinical trials to evaluate the efficacy and safety of an oral Peripherally acting mu-opioid receptor antagonists (PAMORA) for opioid-induced constipation (OIC) specifically in patients with cancer.
- These results highlight the utility of once-daily oral naldemedine 0.2 mg taken with or without food as an effective treatment option for patients with OIC and cancer.
- Furthermore, the concomitant use of naldemedine with opioids was generally well tolerated and did not impede the analgesic benefits of opioids or precipitate opioid-withdrawal syndrome in this study population.

Supportive Care in Cancer
https://doi.org/10.1007/s00520-022-06807-y

ORIGINAL ARTICLE

Post-marketing surveillance of the safety and effectiveness of naldemedine in the management of opioid-induced constipation in patients with cancer pain in Japan

Keiko Takata[1] · Masami Nakazawa[1] · Keiichi Honda[1] · Sayo Hashimoto[2]

Received: 29 September 2021 / Accepted: 31 December 2021

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

Patient Demographics and Baseline Characteristics

Parameter	Safety analysis set (n = 1177)	Effectiveness analysis set (n = 953)
Mean (SD) age, years	69.0 (12.8)	68.9 (12.9)
ECOG-PS, n (%)		
0	119 (10.1%)	96 (10.1%)
1	356 (30.2%)	283 (29.7%)
2	320 (27.2%)	266 (27.9%)
3	298 (25.3%)	247 (25.9%)
4	83 (7.1%)	60 (6.3%)
Unknown	1 (0.1%)	1 (0.1%)
Previous use of laxatives (including prophylactic), n (%)	854 (72.6%)	747 (78.4%)

the surveillance included patients who were excluded from clinical trials (without previous use of laxatives, ECOG-PS 3 or 4)

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

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Patient Demographics and Baseline Characteristics -1

Parameter	Safety analysis set (n = 1177)	Effectiveness analysis set (n = 953)
Primary focus, n (%)		
Lung cancer	199 (16.9%)	157 (16.5%)
Pancreatic cancer	149 (12.7%)	119 (12.5%)
Breast cancer	90 (7.6%)	70 (7.3%)
Gastric cancer	79 (6.7%)	67 (7%)
Colon cancer	53 (4.5%)	46 (4.8%)
Others	617 (52.4%)	502 (52.7%)
History of GI disease, n (%)	220 (18.7%)	182 (19.1%)

the surveillance included patients who were excluded from clinical trials (GI cancer)

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

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Table 1 Patient demographics, baseline characteristics and treatment factors

Parameter	Safety analysis set ($n = 1177$)	Effectiveness analysis set ($n = 953$)
Mean (SD) age, years	69.0 (12.8)	68.9 (12.9)
Sex male/female, n (%)	672 (57.1)/505 (42.9)	543 (57.0)/410 (43.0)
Eastern Cooperative Oncology Group performance status, n (%)		
0	119 (10.1)	96 (10.1)
1	356 (30.2)	283 (29.7)
2	320 (27.2)	266 (27.9)
3	298 (25.3)	247 (25.9)
4	83 (7.1)	60 (6.3)
Unknown	1 (0.1)	1 (0.1)
Primary focus, n (%)		
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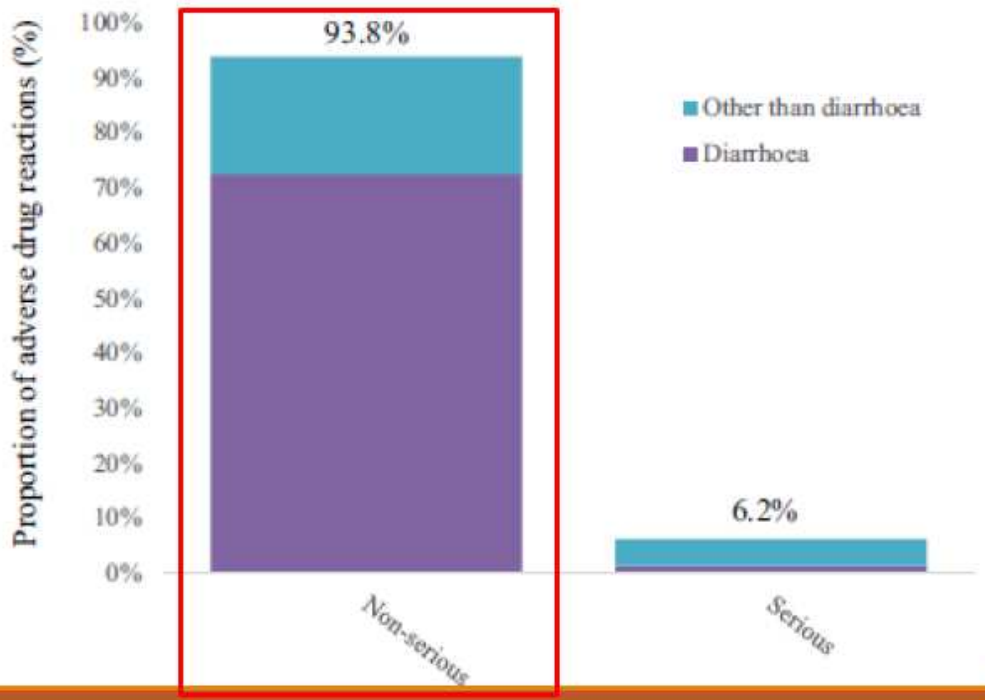
Breast cancer	90 (7.6)	70 (7.3)
Gastric cancer	79 (6.7)	67 (7.0)
Colon cancer	53 (4.5)	46 (4.8)
Others	617 (52.4)	502 (52.7)
Hepatic function abnormalities, n (%)	114 (9.7)	91 (9.5)
Renal function abnormalities, n (%)	74 (6.3)	56 (5.9)
Complications (complications excluding cancer and its metastasis), n (%)	755 (64.1)	622 (65.3)
History of GI disease, n (%)	220 (18.7)	182 (19.1)
Treatment factors		
Duration of naldemedine treatment (days), Median (Q1, Q3)	42.0 (17.0, 85.0)	47.0 (21.0, 85.0)
Duration of naldemedine treatment, n (%)		
< 2 weeks	220 (18.7)	139 (14.6)
2– < 4 weeks	215 (18.3)	183 (19.2)
4– < 6 weeks	142 (12.1)	124 (13.0)
6– < 8 weeks	81 (6.9)	62 (6.5)
8– < 10 weeks	83 (7.1)	73 (7.7)
10– < 12 weeks	53 (4.5)	44 (4.6)
≥ 12 weeks	383 (32.5)	328 (34.4)
Time from opioid administration to starting naldemedine, n (%)		
1–2 days	219 (18.6)	95 (10.0)
3–4 days	105 (8.9)	95 (10.0)
5–6 days	69 (5.9)	63 (6.6)
7–13 days	134 (11.4)	117 (12.3)
≥ 14 days	634 (53.9)	577 (60.5)
Unknown	16 (1.4)	6 (0.6)
Types of opioid analgesics when naldemedine was started, n (%)		
Weak	91 (7.7)	77 (8.1)
Strong	1032 (87.7)	833 (87.4)
Weak + strong	47 (4.0)	42 (4.4)
Unknown	7 (0.6)	1 (0.1)
Opioid exposure within 2 weeks before the start of naldemedine (morphine equivalent), Median (Q1, Q3)	265.0 (90.0, 630.0)	262.5 (90.0, 630.0)
Previous use of laxatives (including prophylactic*), n (%)	854 (72.6)	747 (78.4)
Concomitant laxatives, n (%)	950 (80.7)	811 (85.1)
Osmotic laxatives/saline laxatives	744 (63.2)	647 (67.9)
Stimulant laxatives/Colorectal stimulant laxatives	396 (33.6)	344 (36.1)
Chloride channel activators	82 (7.0)	75 (7.9)

Post-Marketing Surveillance of Naldemedine in Japan – Safety Result

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.

Proportion of serious and non-serious ADRs

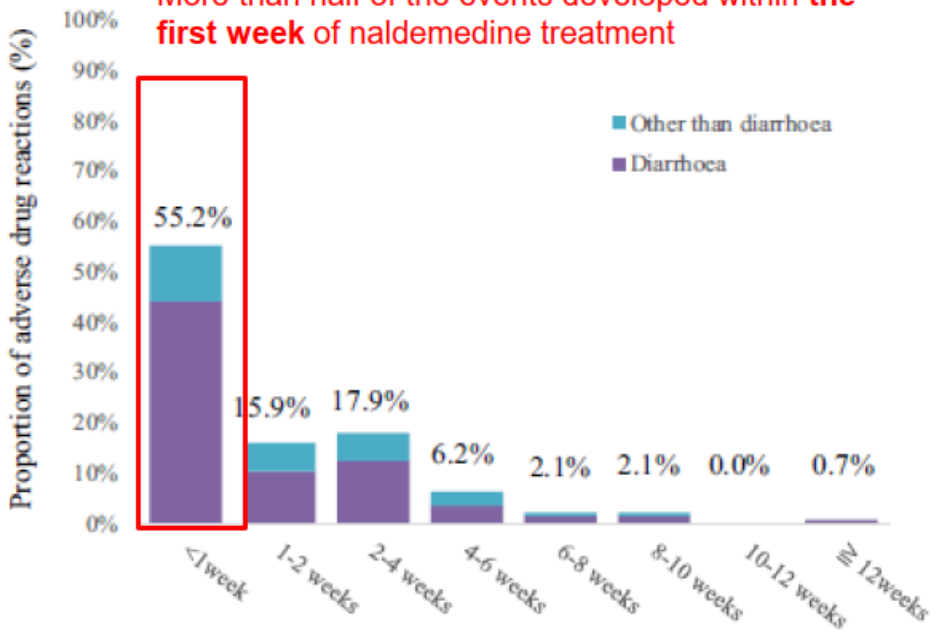


Takata K et al. Support Care Cancer. 2022 May;30(5):3943-3954.

Post-Marketing Surveillance of Naldemedine in Japan – Safety Result

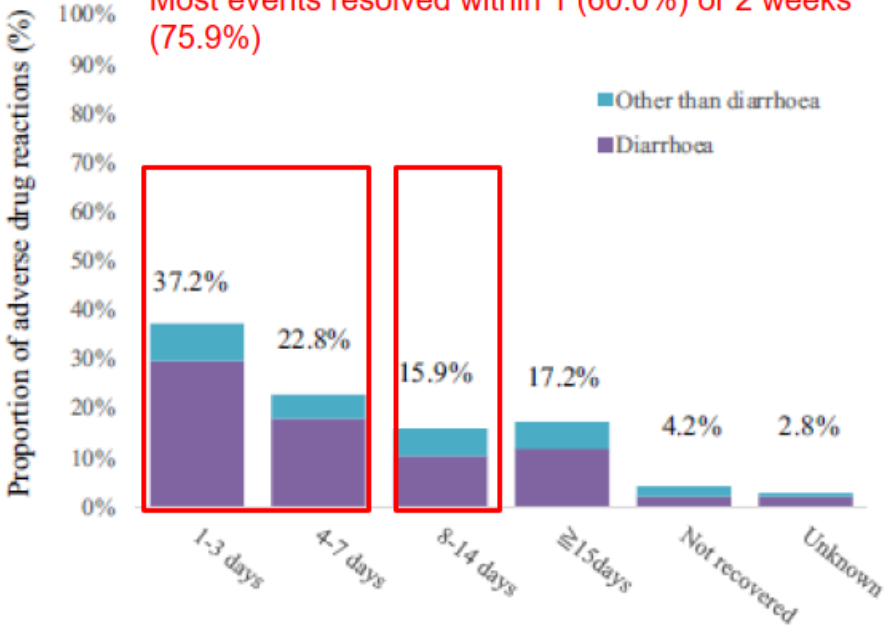
Time to onset of ADR after the start of naldemedine treatment

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



Time to recover 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 for Opioid-Induced Constipation in Patients With Cancer: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial

Jun Hamano, MD, PhD[1]; Takahiro Higashibata, MD, PhD[2]; Takaomi Kessoku, MD, PhD[3,4,5]; Shinya Kajiura, MD, PhD[6]; Mami Hirakawa, MD, PhD[7]; Shunsuke Oyamada, PhD[8]; Keisuke Ariyoshi, MMedSci[9]; Takeshi Yamada, MD, PhD[10]; Yoshiyuki Yamamoto, MD, PhD[11]; Yasuyuki Takashima, MPharm[12]; Kosuke Doki, PhD[13]; Masato Homma, PhD[13]; Bryan J. Mathis, PhD, MS[14]; Tsumugi Jono, MD[3,15]; Tomoki Ogata, MD[3]; Kosuke Tanaka, MD[3,4]; Yuki Kasai, MD[3]; Michihiro Iwaki, MD, PhD[3]; Akiko Fuyuki, MD, PhD[3,16]; Atsushi Nakajima, MD, PhD[3]; Ryuji Hayashi, MD, PhD[6]; Takayuki Ando, MD, PhD[17]; Naoki Izawa, MD, PhD[18]; Yuko Kobayashi, MSc[19]; Yoshiki Horie, MD, PhD[18]; and Tatsuya Morita, MD[20,21]

J Clin Oncol. 2024 Sep 10:JCO2400381.

Study Highlights

Background	Multicenter, double-blinded, randomized, placebo-controlled, confirmatory trial
Objective	Clarify the **preventive effect** of naldemedine versus placebo for constipation in patients with cancer starting regularly dosed therapy with strong opioids.
Location	Four university hospitals in Japan
Duration	2021/07/02 ~ 2023/05/30
Subject	103 patients
Methods	1. Patients with cancer **starting a first-time regularly dosed strong opioid for cancer pain** and age 20+ years. 2. **Primary end point** - the proportion of patients with a Bowel Function Index (BFI) of <28.8 on day 14. 3. **Secondary end points** - Frequency of spontaneous bowel movements (SBM), quality of life (QOL), and frequency of opioid-induced nausea and vomiting (OINV).

- Naldemedine **prevented constipation** and **improved constipation-related QOL**, with **possible preventive effect on OINV** in patients with cancer starting regularly dosed opioids therapy.

J Clin Oncol. 2024 Sep 10:JCO2400381.

Constipation-Related Outcomes

- The proportion of patients with a **BFI of <28.8 on day 14** was **significantly greater with naldemedine** than with placebo.

Primary Endpoint

Day 14				
End Point	Naldemedine Group (n=48)	Placebo Group (n=47)	Differerence Between Groups (Naldemedine-Placebo)	*p*
BFI<28.8				
Number of patients	31	8		
Point estimate of the percentage (95%CI)	**64.6** (51.1 to 78.1)	**17.0** (6.3 to 27.8)	47.6 (30.3 to 64.8)	<.0001
BFI	25.4 6 ± 27.1	55.1 ± 6 29.5		
Difference from day 1	7.1 (–0.2 to 14.3)	38.5 (26.6 to 50.4)	–31.5 (–44.9 to –18.0)	<.0001

預防性使用naldemedine 14天後，近65%患者便秘症狀較輕或不存在

J Clin Oncol. 2024 Sep 10:JCO2400381.

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Constipation-Related Outcomes

- The proportion of patients with a **BFI of <28.8 on day 7** was **significantly greater with naldemedine** than with placebo.

Day 7				
End Point	Naldemedine Group (n=48)	Placebo Group (n=47)	Differerence Between Groups (Naldemedine-Placebo)	*p*
BFI<28.8				
Number of patients	28	8		
Point estimate of the percentage (95%CI)	**58.3** (44.4 to 72.3)	**17.0** (6.3 to 27.8)	41.3 (23.7 to 58.9)	<.0001
BFI	27.2 6 ± 28.8	50.9 6 ± 25.1		
Difference from day 1	9.8 (1.4-18.2)	33.1 (22.1-44.2)	–23.4 (–36.9 to –9.8)	<.0001

並且在投藥後7天就已顯示出明顯的效果

J Clin Oncol. 2024 Sep 10:JCO2400381.

Constipation-Related Outcomes

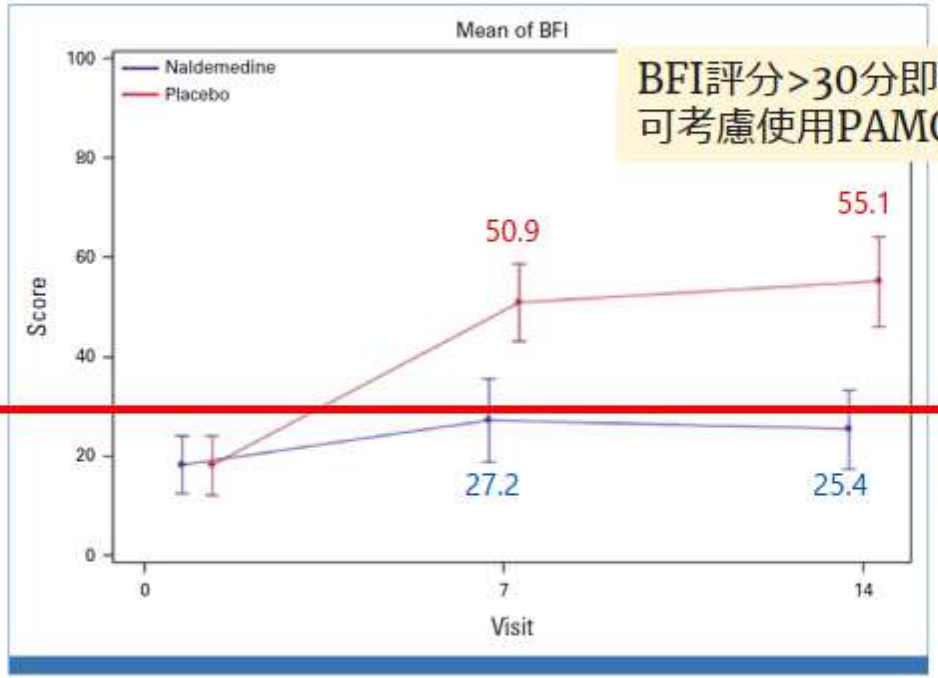


FIG A1. Line plot of mean BFI for naldemedine group and placebo group at days 1, 7, and 14. Bar indicated the mean of BFI with 95% CI. BFI, Bowel Function Index.

BFI評分>30分即可判定瀉藥治療失敗，
可考慮使用PAMORA進行OIC治療 [1]

對接受定期強效鴉片類藥物治療的癌症患者，
預防性給予naldemedine具防止OIC發生的效果

J Clin Oncol. 2024 Sep 10:JCO2400381.

OINV-Related Outcomes

- The proportion of **antiemetic drug use** during the 72-hour period from days 1 to 3 was **significantly lower with naldemedine** than with placebo.

End point	Naldemedine Group (n=48)	Placebo Group (n=47)	Differerence Between Groups (Naldemedine-Placebo)	*p*
Patients who used antiemetic drugs between days 1 and 3	**10.6** (1.8-19.5)	**51.1** (36.5-65.7)	–40.47 (23.41-57.53)	<.0001
Patients with at least one episode of nausea and/or vomiting				
Day 1	2.1 (0.0-6.3)	35.6 (21.6-49.5)	–33.4 (18.9-48.0)	<.0001
Day 2	6.4 (0.0-13.4)	46.6 (32.1-61.2)	–40.3 (24.1-56.5)	<.0001
Day 3	6.4 (0.0-13.4)	43.2 (28.6-57.8)	–36.8 (20.6-53.0)	<.0001

① 預防性給予naldemedine有效減少止吐藥的使用

QOL Measures

- The changes in EORTC QLQ-C15-PAL **global QOL scale** on day 7 and day 14 from day 1 were **significantly higher in the naldemedine group** than in the placebo group, indicative of better QOL.

	Day 7				Day 14			
End point	Naldemedine Group (n=48)	Placebo Group (n=47)	Differerence Between Groups (Naldemedine-Placebo)	*p*	Naldemedine Group (n=48)	Placebo Group (n=47)	Differerence Between Groups (Naldemedine-Placebo)	*p*
EORTC QLQ-C15-PAL								
Global QOL	69.1 (25.5)	69.6 (20.8)			73.2 (23.3)	71.4 (19.3)		
Difference from day 1	**16.0** (4.5-27.5)	**−3.2** (−12.1 to 5.7)	19.1 (4.5-33.7)	.0108	**15.6** (3.4-27.8)	**−2.0** (−13.6 to 9.6)	17.6 (0.9-34.3)	.0390

預防性給予naldemedine能大幅度改善患者的整體生活品質

Use Frequency of Rescue Laxatives

Day	Naldemedine Group, No (%) (n=48)	Placebo Group, No (%) (n=47)	*p*
Day 14			
0	46 (95.8)	38 (80.9)	
1	2 (4.2)	4 (8.5)	
2	0	0	
3	0	0	
4	0	0	
Missing	0	0	
Total, n	48	45	
Mean (SD)	**0.6 (1.5)**	**2.0 (3.0)**	.0059

次/14天

Abbreviation: SD, standard deviation.

而且預防性給予naldemedine也可減少對瀉藥的依賴

Safety Outcomes

- During the treatment period, **no patient** treated with naldemedine had diarrhea, nausea, or vomiting causally related to protocol treatment.

	Naldemedine Group (n=48), No. (%)			Placebo Group (n=47), No. (%)		
Adverse Event	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Abdominal distension	0	0	0	2 (4.3)	0	0
Abdominal pain	0	0	0	2 (4.3)	0	0
Diarrhea	2(4.2%)	0	0	3 (6.4)	0	0
Nausea	9(18.8%)	0	0	18(38.3%)	0	0
Vomiting	6(12.5%)	0	0	18(38.3%)	0	0

相較COMPOSE-4 phase III 的結果，
預防性給予naldemedine可以防止不必要的腹瀉

The safety and effectiveness of naldemedine for opioid-induced constipation in patients with advanced cancer in real-world palliative care settings: a multicenter prospective observational study

Masaki Shimizu[1] · Isseki Maeda[2] · Takaomi Kessoku[3,4] · Hiroto Ishiki[5] · Tetsuya Matsuura[6] · Yusuke Hiratsuka[7,8] · Yoshinobu Matsuda[9] · Takaaki Hasegawa[10] · Kengo Imai[11] · Shunsuke Oyamada[12] · Eriko Satomi[5] · On behalf of the Phase-R OIC Study Group

Support Care Cancer 32, 504 (2024).

Study Highlights

Background	Multicenter prospective observational study
Objective	Evaluate the **safety** and **effectiveness** of naldemedine for treating opioid-induced constipation (OIC) in patients with advanced cancer, who are receiving palliative care, and particularly explored its early effects.
Location	14 hospital palliative care teams and inpatient palliative care units in Japan.
Duration	2018.04~2018.12
Subject	204 patients
Methods	1. The eligibility criteria : (1) adult cancer patients receiving palliative care either in a hospital, outpatient setting, or inpatient palliative care unit; (2) patients administered naldemedine for the treatment of OIC; (3) patients with a stable opioid and laxative regimen not expected to change within the next three days. 2. The exclusion criteria : (1) The suspected malignant bowel obstruction; (2) previous history of malignant bowel obstruction, and a high recurrence risk. 3. **Primary endpoint** - The spontaneous bowel movement (SBM) within 24 h after the first dose of naldemedine. 4. **Secondary endpoint** - Weekly changes in SBM frequency and adverse events.

Support Care Cancer 32, 504 (2024).

Patient characteristics

	Values
Total	204
Age	63±14
Sex	
Men	103 (50.5%)
Women	101 (49.5%)
Primary cancer site	
Lung	**48 (23.5%)**
Gastrointestinal	**28 (13.7%)**
Hepatobiliary	9 (4.4%)
Pancreas	16 (7.8%)
Breast	14 (6.9%)
Gynecological	16 (7.8%)
Urological	19 (9.3%)
Others	54 (26.5%)
Comorbidities	
Partial malignant bowel obstruction	**8 (3.9%)**
Peritonitis carcinomatosa	**12 (5.9%)**
History of gastrointestinal resection	**27 (13.2%)**
History of abdominal irradiation	**18 (8.8%)**
Primary or metastatic brain tumors	14 (6.9%)
Meningitis carcinomatosa	1 (0.5%)

- Lungs were the most common primary cancer site, followed by the gastrointestinal tract, presenting 13.7% of the total cases analyzed.

本次研究包含腹部癌症或腹部病變患者，也納入具原發性或轉移性腦腫瘤患者。

Support Care Cancer 32, 504 (2024).

Treatment outcomes

- **SBMs within 24 h** after the initial dose of naldemedine were observed in 146 patients (71.6%, 95% confidence interval 65.4–77.8%).

	Values
SBM within 24 h after the initial naldemedine administration	146 (**71.6%,** 95% CI 65.4–77.8%)

服用naldemedine 24小時內，大於 70%晚期癌症患者發生自發性排便

Treatment outcomes

- The **weekly SBM counts increased** in 62.7% of the participants.

		SBMs per week (**post**-treatment)		
		5 or more	3-4	2 or fewer
SBMs per week (**pre**-treatment)	5 or more	26 (12.9%)	2 (1.0%)	4 (2.0%)
	3-4	37 (**18.1%**)	13 (6.4%)	4 (2.0%)
	2 or fewer	43 (**21.1%**)	48 (**23.5%**)	25 (12.3%)

Values are *N* (%)
SBM Spontaneous bowel movement

且服藥後一週內，大於 60%晚期癌症患者排便總次數提升

Adverse events

- **No serious adverse events**, such as gastrointestinal perforation, bleeding, or death were reported.

	Incidence	
	CTCAE grade*	
	Grade 1-2	Grade 3
Diarrhea	35 (17.2%)	1 (0.5%)
Abdominal pain	10 (4.9%)	1 (0.5%)
Gastrointestinal perforation	0 (0.0%)	0 (0.0%)
All cause death	0 (0.0%)	0 (0.0%)

Values are N (%)
* Common Terminology Criteria for Adverse Events
Adverse events with a causality of possible or higher, according to the Japan Clinical Oncology Group criteria.

除此之外，在原發性或轉移性腦腫瘤或癌性腦膜炎患者中未檢測到疼痛加劇。

Support Care Cancer 32, 504 (2024).

Symproic® (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。

Symproic TFDA Label

Symproic® (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)

圖 4-1 台灣 OIC 診療流程圖

†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.
*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。

Thanks for your attention

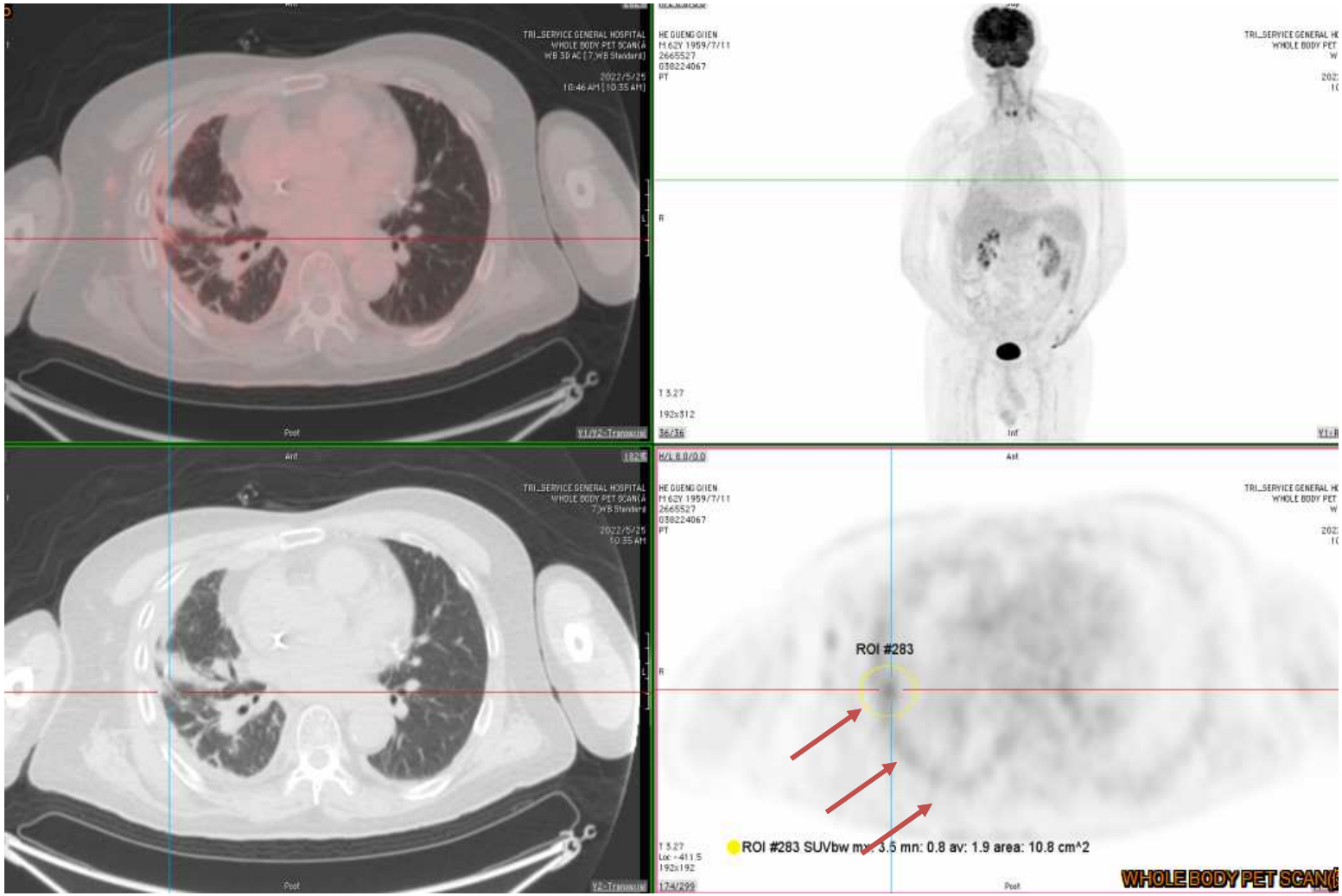
HOPE therapy
20220701 出版

Double heart stone (empathy)

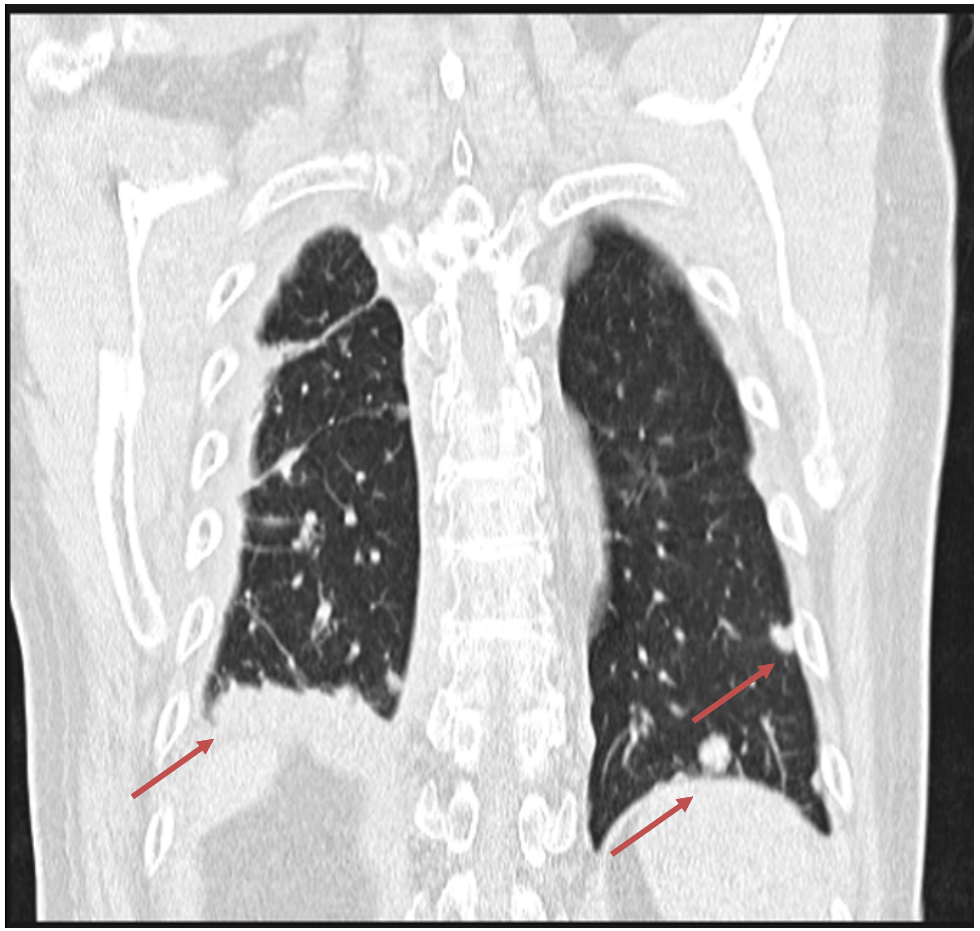
Case sharing: case 1:M/60

- *. Adenoid cystic carcinoma of hard palate pT2Nx, status post excision of palate tumor(20200110), status post wide excision of adenoid cystic carcinoma of hard palate, left(20200205), status post radiotherapy (2020/02/05)
- bilateral lung metastasis, status post uniportal non-intubated video-assisted thoracic surgery with wedge resection of right middle lobe of lung and pleura biopsy (20200922), under weekly PF (cisplatin + 5-FU) (20200924 - 20201222, 7 courses), s/p SD, shift to keytruda + Lenvima (20201104 - 20220112, 19 courses), shift to keytruda + triweekly PF(20220218), cisplatin+Lipo-dox+endoxan+bavencio (20220310, 20220408, 20220429, 20220623, 20220720).
- *. History of Coronary artery disease status post percutaneous coronary intervention (PCI) with stenting to LMCA-LAD and LMCA-LCx, middle LCx (201812, DESx3) with recurrent non-ST elevation myocardial infartion status post PCI with stenting to LMCA and DEB to LMCA-LCx (20190713)

20220525 PET



20230824 CHEST CT



OXYCONTIN 20 MG Q12H
FENTANYL 25 MCG/HR Q3D

MORPHINE 75 MG

床號	入院日期	出院日期
51 - 123	1111003	1111202
21 - 042	1110815	1110927
51 - 041	1110719	1110726
32 - 171	1110622	1110630
52 - 271	1110522	1110602
21 - 072	1110428	1110506
52 - 241	1110406	1110411
62 - 111	1110309	1110318
21 - 071	1110207	1110222
52 - 022	1110112	1110121
32 - 201	1101203	1101227
51 - 032	1101111	1101118
52 - 061	1101021	1101027
52 - 161	1100930	1101006
62 - 191	1100909	1100915
52 - 042	1100818	1100825
21 - 071	1100727	1100802
51 - 081	1100708	1100712
73 - 221	1100608	1100623
51 - 031	1100519	1100523
52 - 151	1100427	1100501
32 - 081	1100406	1100410
51 - 082	1100316	1100319

OPD FOLLOW UP

藥　　名	用　法	頻率	次劑量	天數	總量
自備					
OXYCONTIN CR TAB 20 MG (***)	PO	Q12H	2.000	25	100.00
N					
FENTANYL TD PATCH 25 MCG/HR PP	TD	Q3D	1.000	25	9.000
N					
CELEBREX CAP 200 MG	PO	BID	1.000	25	50.000
N					
KENTAMIN CAP	PO	TIDPC	1.000	25	75.000
N					
GATY FC TAB 600 MG	PO	Q12H	1.000	25	50.000
N					
FENTORA BUCCAL TAB 100 MCG	B	Q2HPRN	2.000	4	96.000
N					
SYMPROIC FC TAB 0.2 MG	PO	QD	1.000	25	25.000
N					
ACLOVIR CREAM 50 MG/G 5 G	EXT	PRN	999.00	25	10.000
N					
ENOXOLONE GINGIVAL PASTE 80 G	EXT	BID	999.00	25	10.000
N					
OXYNORM IR CAP 5 MG	PO	Q6HPRN	2.000	10	80.000
N					
ANTIBIOPHILUS CAP 250 MG	PO	PIDPRN	4.000	25	500.00
N					
FLUR DI FEN PATCH 40MG/12G	TD	Q12HPRN	2.000	25	100.00
N					

Conclusion

- once-daily, oral naldemedine 0.2 mg significantly improves bowel movement function in a timely manner, and positively impacts the QOL of subjects with OIC and cancer.

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

Definition of Terminology in COMPOSE Studies

1. Rescue laxative
   - In COMPOSE-1 to COMPOSE-3, rescue laxative was used **if a patient had not have a bowel movement for a period of 72 hours**
   - In COMPOSE-4 to COMPOSE-7, patients were allowed to receive rescue laxative **as-needed**, however, their use was prohibited 24 hours before and after the first dose of the study drug
2. Spontaneous bowel movement (SBM) – No rescue laxative use within 24 hours prior to the bowel movement (BM)
3. SBM responder – ≥ 3 SBMs/week and increase of ≥ 1 SBM/week from baseline (14-consecutive-day qualifying period during the Screening Period)
4. Complete spontaneous bowel movement (CSBM) – SBM with a feeling of complete evacuation
5. Treatment-emergent adverse event (TEAE) – Adverse events occurring after the first dose of study drug administration were considered treatment emergent
6. TEAE of opioid withdrawal – Defined by Medical Dictionary for Regulatory Activities standardized Query "drug withdrawal"
7. TEAE of possible opioid withdrawal syndrome – ≥ 3 events possibly related to opioid withdrawal occurred within the same day (or the next day)
8. Death not considered TEAE – Patient died >14 days after their last visit and the bottles of pills were never returned for accountability

Hale M et al. Lancet Gastroenterol Hepatol. 2017 Aug;2(8):555-564; Webster L.R. et al. Pain. 2018 May;159(5):987-994; Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866; Saito Y et al. J Pain Res. 2018 Dec 24;12:127-138.

Correspondence to Comments - 1

What kinds and amount of drugs were used for a routine laxative regimen and for rescue laxatives? Whether the frequency of rescue laxative use was decreased after naldemedine treatment?

The top three concomitant routine laxative*

	Naldemedine	Placebo
Magnesium oxide osmotic	64.9%	69.8%
Sennoside A+B stimulant	17.5%	18.8%
Pantethine stimulant	4.1%	3.1%

The top three rescue laxative*

	Naldemedine	Placebo
Sennoside A+B stimulant	18.6%	39.6%
Sodium picosulfate stimulant	17.5%	17.7%
Magnesium oxide osmotic	17.5%	34.4%

Mean change from baseline in the frequency of using rescue laxative/week

	Naldemedine	Placebo
Mean Change	- 2.98	- 1.13
P < 0.001		

*A routine laxative regimen was maintained throughout the study, and a bowel movement within 24 hours of using a rescue laxative was not counted as a spontaneous bowel movement (SBM); therefore, the impact of routine or rescue laxatives on SBMs was limited

Katakami N et al. J Clin Oncol. 2018 Apr 1;36(10):pp1049-1050.

Overview of Symproic® (Naldemedine)

Mechanism	Orally active, Peripherally-Acting Mu-Opioid Receptor Antagonists (**PAMORA**)
Target Disease	Opioid-induced Constipation (OIC)
Development Status	**COMPOSE** program (Global Ph3 studies) in **chronic non-cancer pain and cancer** patients with positive data already reported
Approved	March, 2017 in Japan and US February, 2019 in EU

表 4-2 NCCN 之 OIC 三階段處置建議[8]

- 病人衛教及設立治療目標
- 每日服用鴉片類藥物的病人幾乎都需使用便秘治療藥物
- 預防性藥物：刺激性緩瀉劑、polyethylene glycol。增加鴉片類藥物劑量時也須增加緩瀉劑劑量

- 評估便秘的原因與嚴重程度
- 排除阻塞的可能性
- 調整緩瀉劑劑量，以達每 1-2 天自發性排便 1 次的目標
- 考慮使用輔助的止痛劑，以降低鴉片類藥物的劑量

- 重新評估便秘的原因及嚴重程度
- 考慮加上其他藥物
- 如果對緩瀉劑的治療反應不理想，可考慮使用 PAMORAs
- 對於棘手的慢性便秘，考慮轉換為經皮吸收的鴉片類藥物
- 考慮其他介入方式以減輕疼痛、緩解便秘或（及）降低鴉片類藥物的劑量

PAMORAs, peripherally acting μ-opioid receptor antagonists.

表 5-2 國際 OIC 治療藥物之建議

2019 AGA OIC 藥物治療指引[1]

建議	建議強度	證據等級
針對難治型 OIC 病人，建議使用 naldemedine 優於不治療	強	高
針對難治型 OIC 病人，建議使用 naloxegol 優於不治療	強	中
建議使用緩瀉劑作為 OIC 病人的第一線治療	強	中
針對難治型 OIC 病人，可使用 methylnatrexone 優於不治療	有條件	低
針對 lubiprostone 和 prucalopride 在 OIC 的使用無建議	無建議	證據不足

建議強度：強（strong）= 絕大多數病人願意接受此建議；絕大多數醫師應接受此建議，較不須決策輔助工具來協助作出符合其價值觀與偏好的醫療決策。有條件（conditional）= 多數病人願意接受此建議，但也有部分病人不願意；不同病人適合不同選擇，決策輔助工具有助於作出符合價值觀與偏好的醫療決策，決策時醫師須花費更多時間與病人討論。無建議（no recommendation）= 對於療效的信心不足，任何建議均屬於推測性。

2018 ESMO 臨床指引：晚期癌症病人之便秘的診斷、評估與處置[2]

建議	建議強度	證據等級
除非病人有腹瀉禁忌症，否則所有接受鴉片類藥物治療的病人均應同時處方緩瀉劑	B	V
緩瀉劑治療包含第一線藥物；通常優先考慮使用滲透性緩瀉劑或刺激性緩瀉劑	B	V
不建議使用膨脹性緩瀉劑（如 psyllium）治療 OIC	D	V
臨床研究顯示併用鴉片類藥物和 naloxone 可降低 OIC 發生風險	B	II