治療鴉片類藥物所致便祕的最新發展 - Naldemedine

2022 台灣鴉片類藥物所致便祕之臨床處置指引

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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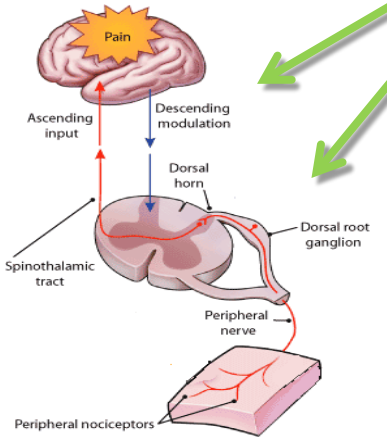
Central and Peripheral Actions of Opioids

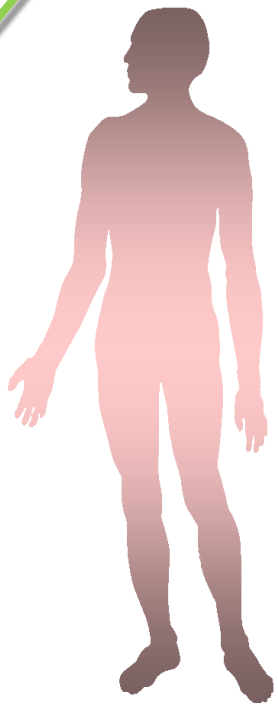
Opioids act on both the Central Nervous System (CNS) and the Gastrointestinal (GI) tract

CTZ: Chemoreceptor Trigger Zone
BBB: Blood Brain Barrier

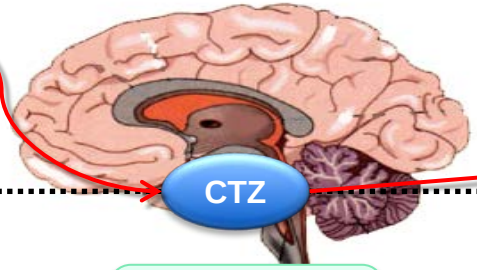
Central (inside of BBB)



Opioids



Analgesic Effect



Emesis (vomiting & nausea)

μ, δ

μ, δ, (κ)

Constipation

Peripheral (outside of BBB)

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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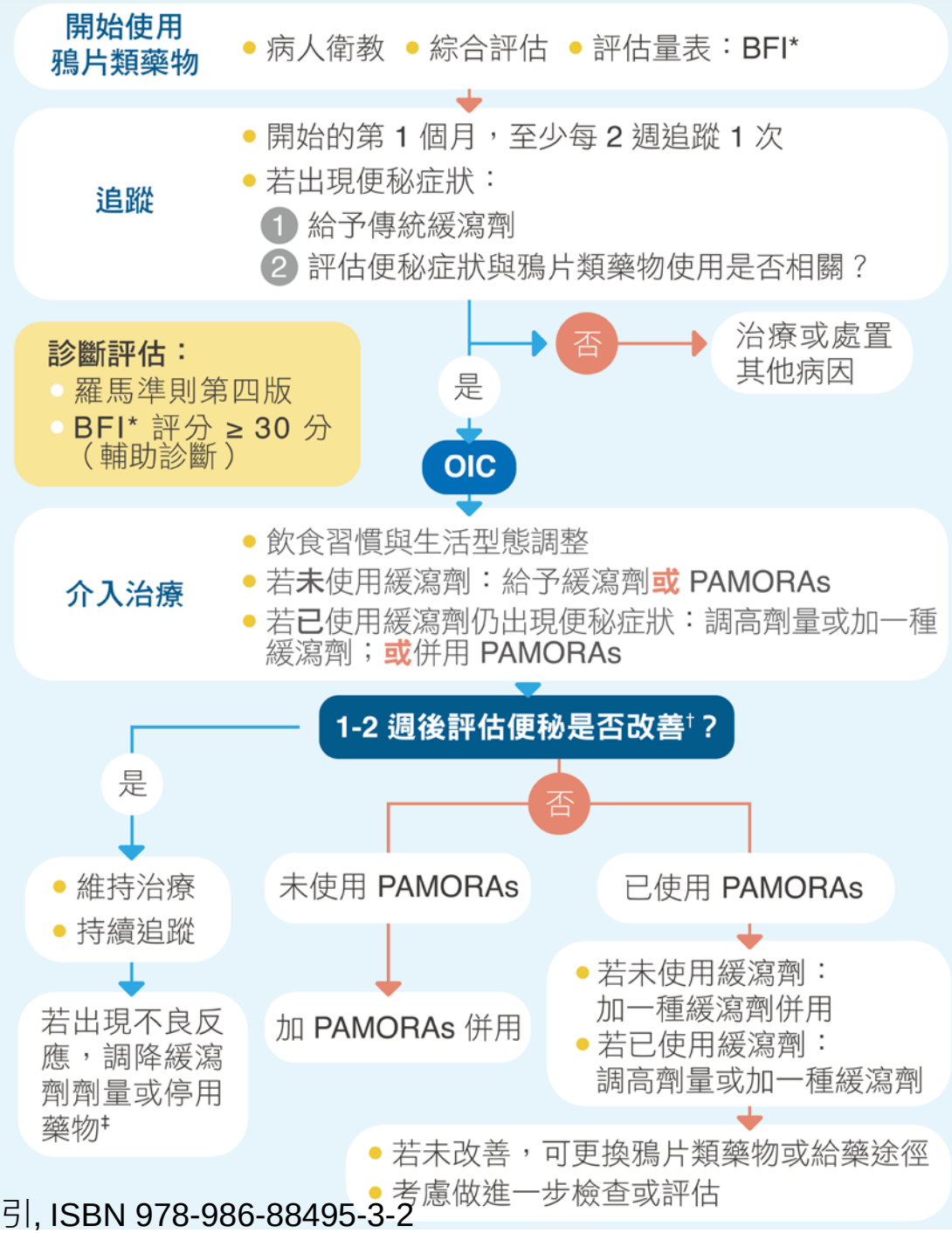
台灣OIC診療流程圖

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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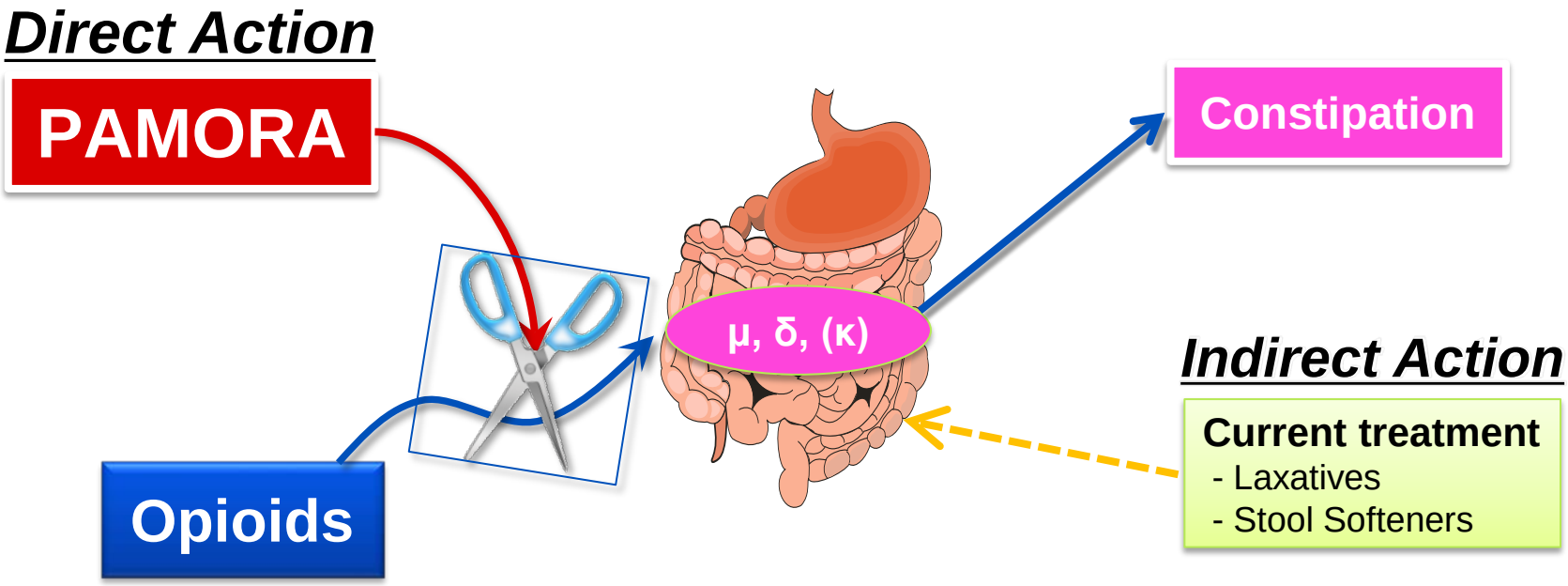
MoA Differentiation among Current Treatments

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

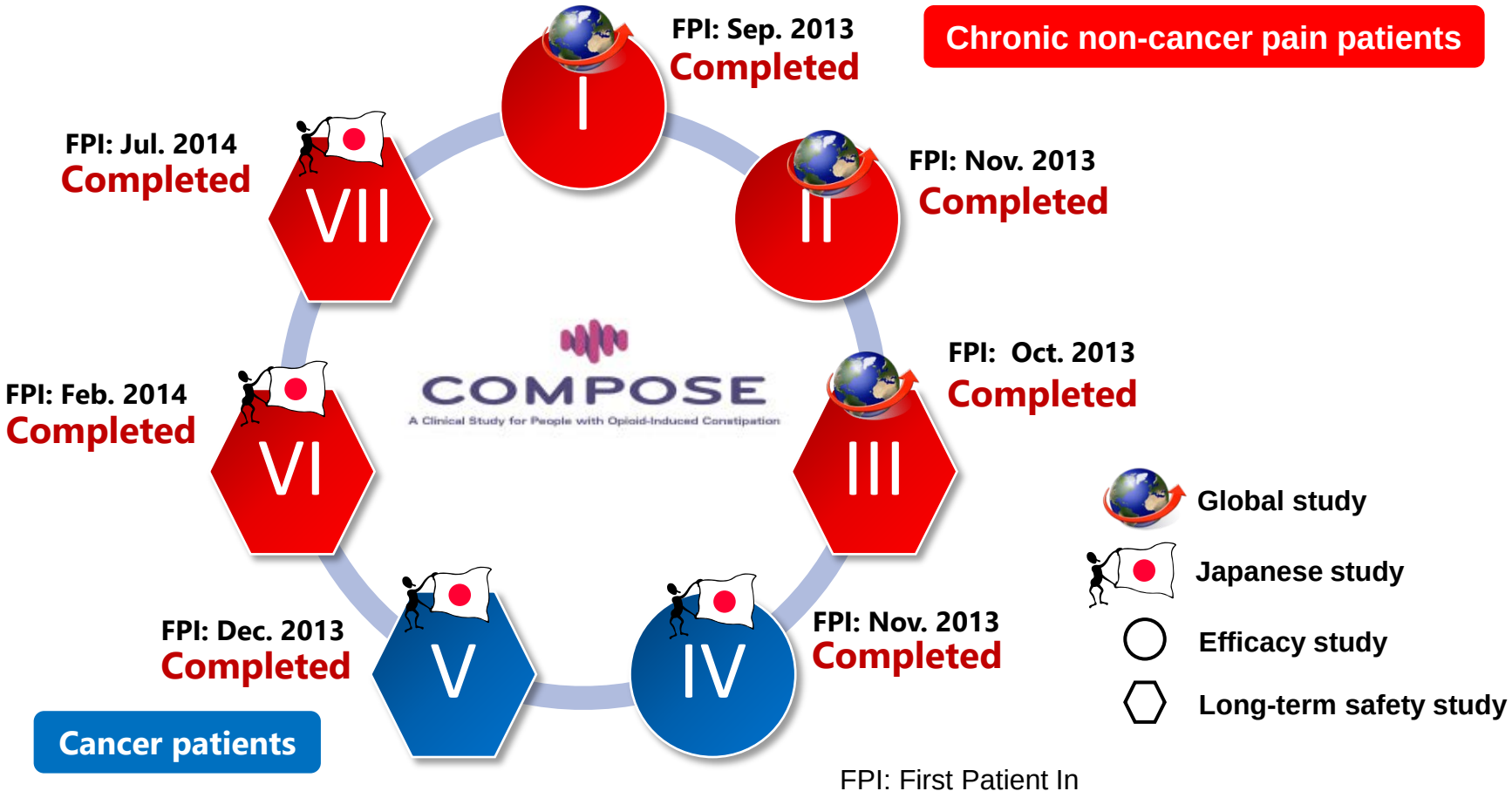


PAMORA: Peripherally-Acting Mu-Opioid Receptor Antagonists

Source: Global OIC market research December 2012

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**

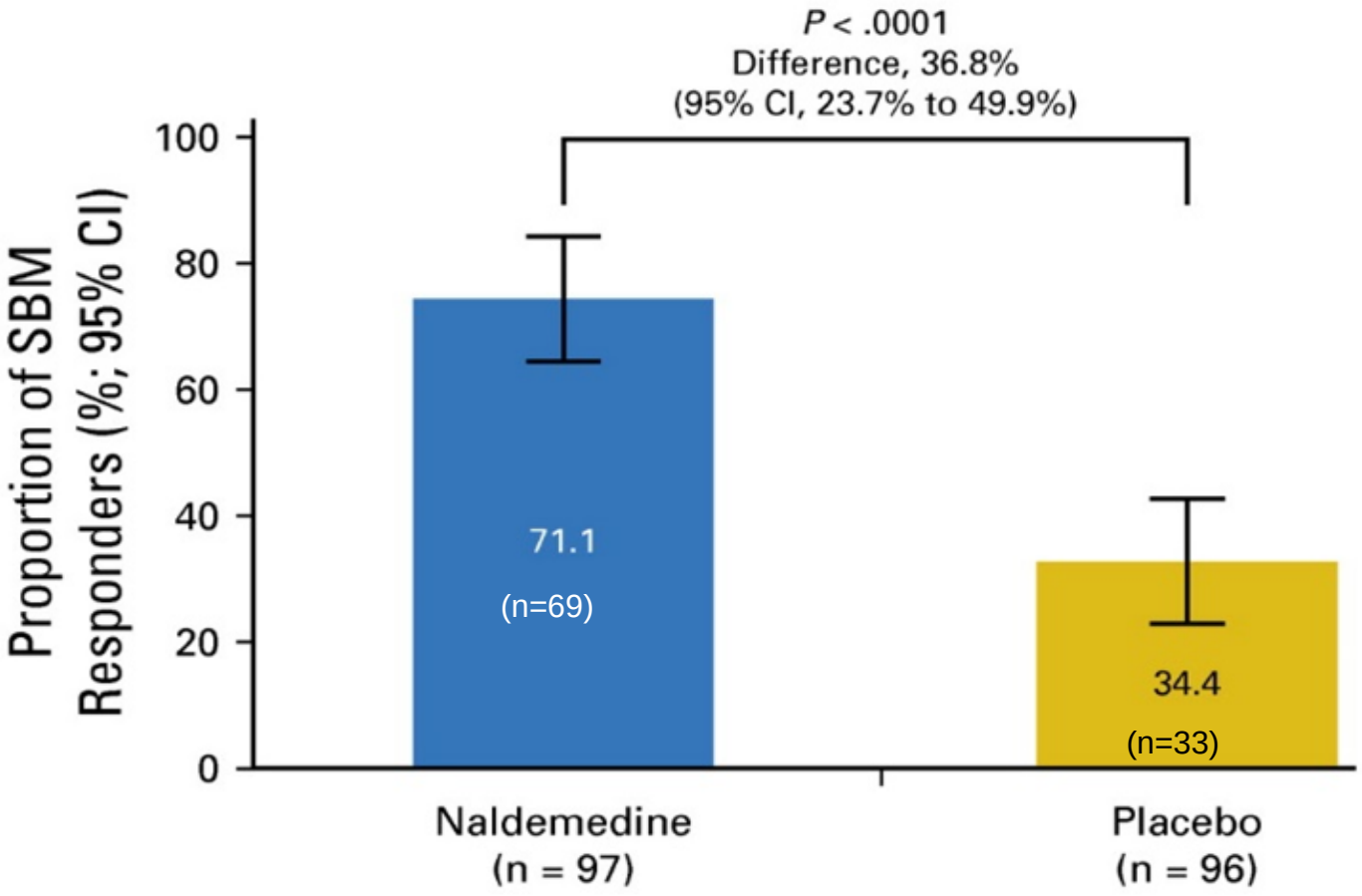


FPI: First Patient In

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

Primary Endpoint

Proportion of SBM responders during 2-week treatment period



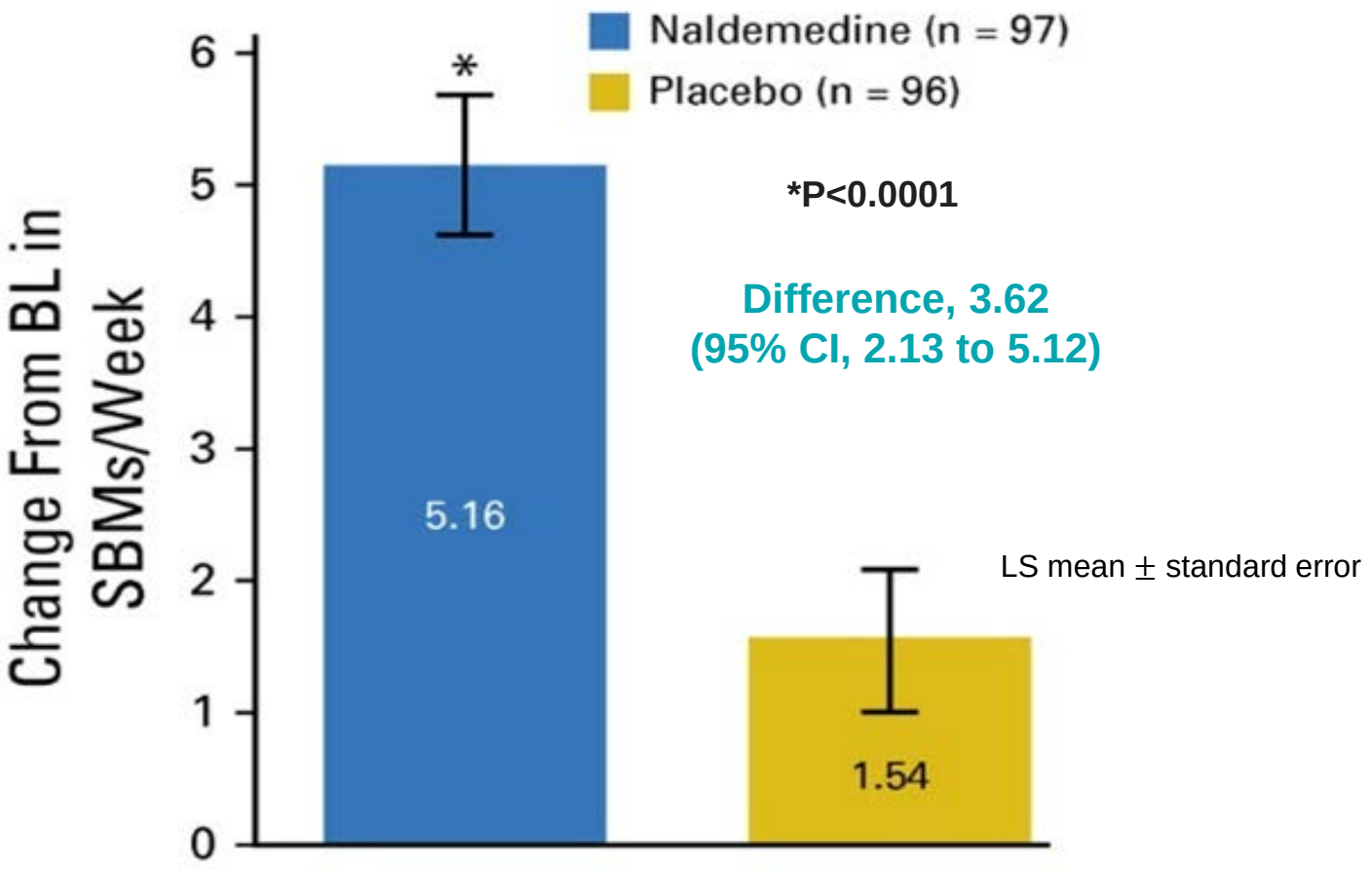
SBMs = spontaneous bowel movements; SBM responder = patients with three or more SBMs/week who had an increase of one or more SBM/week from baseline. Baseline was the average number of SBMs/week during the 2 weeks before random assignment.

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



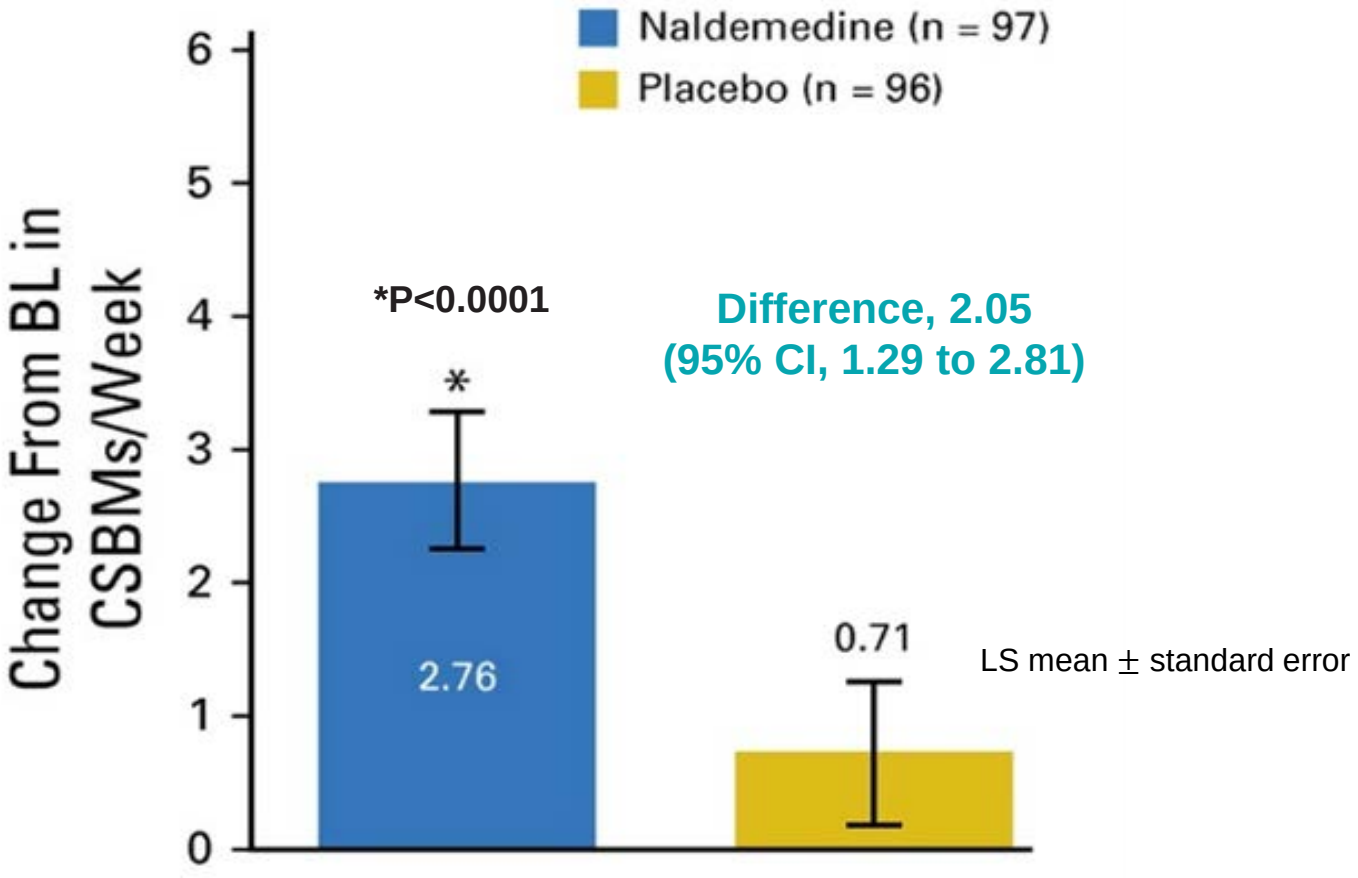
BL= Baseline, the average number of SBMs/week during the 2 weeks before random assignment
SBMs=spontaneous bowel movements

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

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



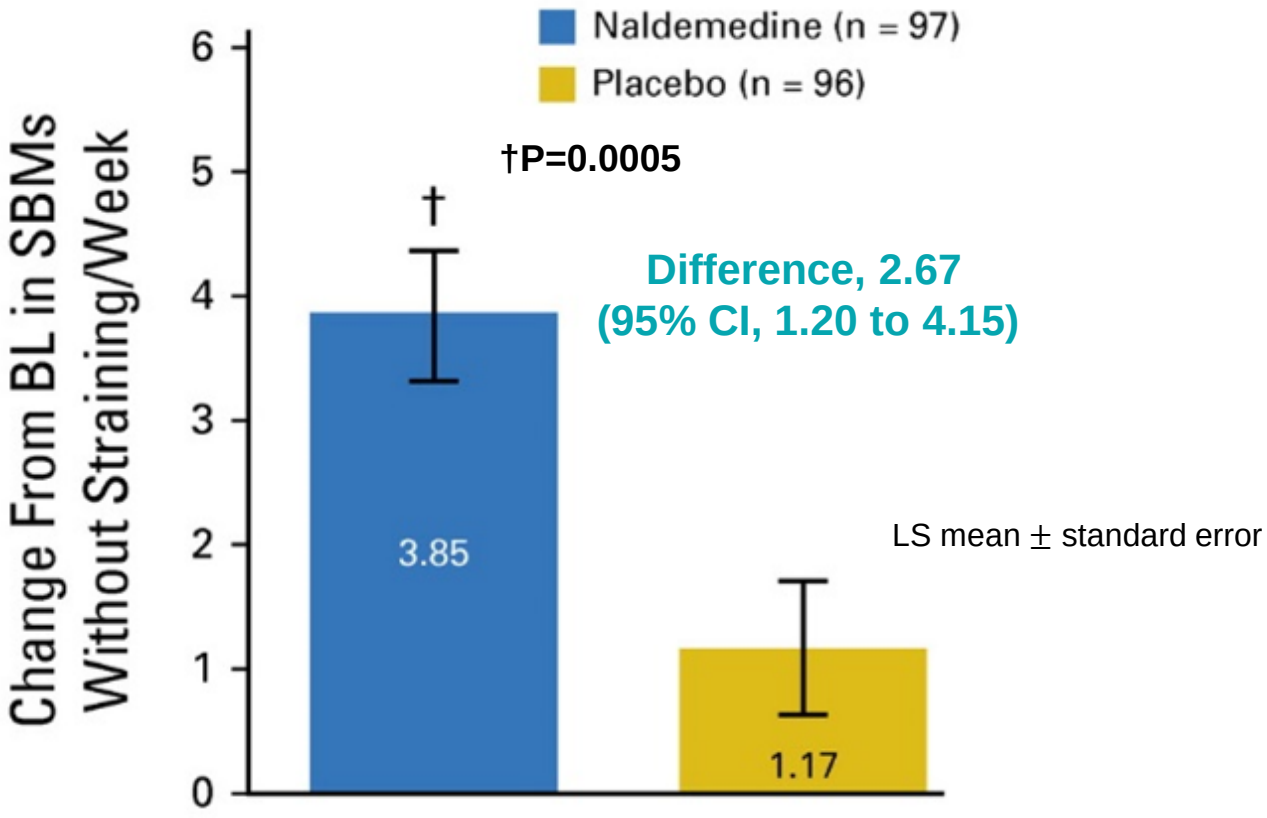
CSBMs=complete spontaneous bowel movements

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



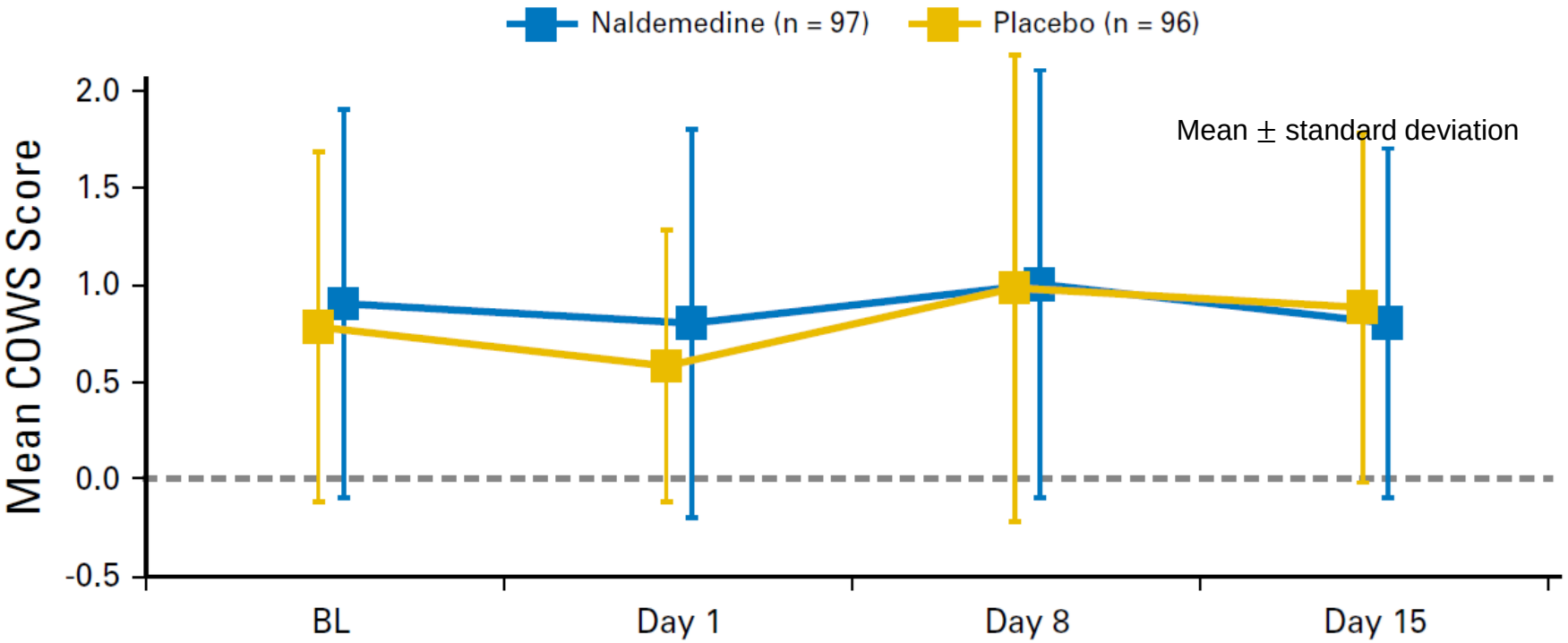
SBMs=spontaneous bowel movements

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

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



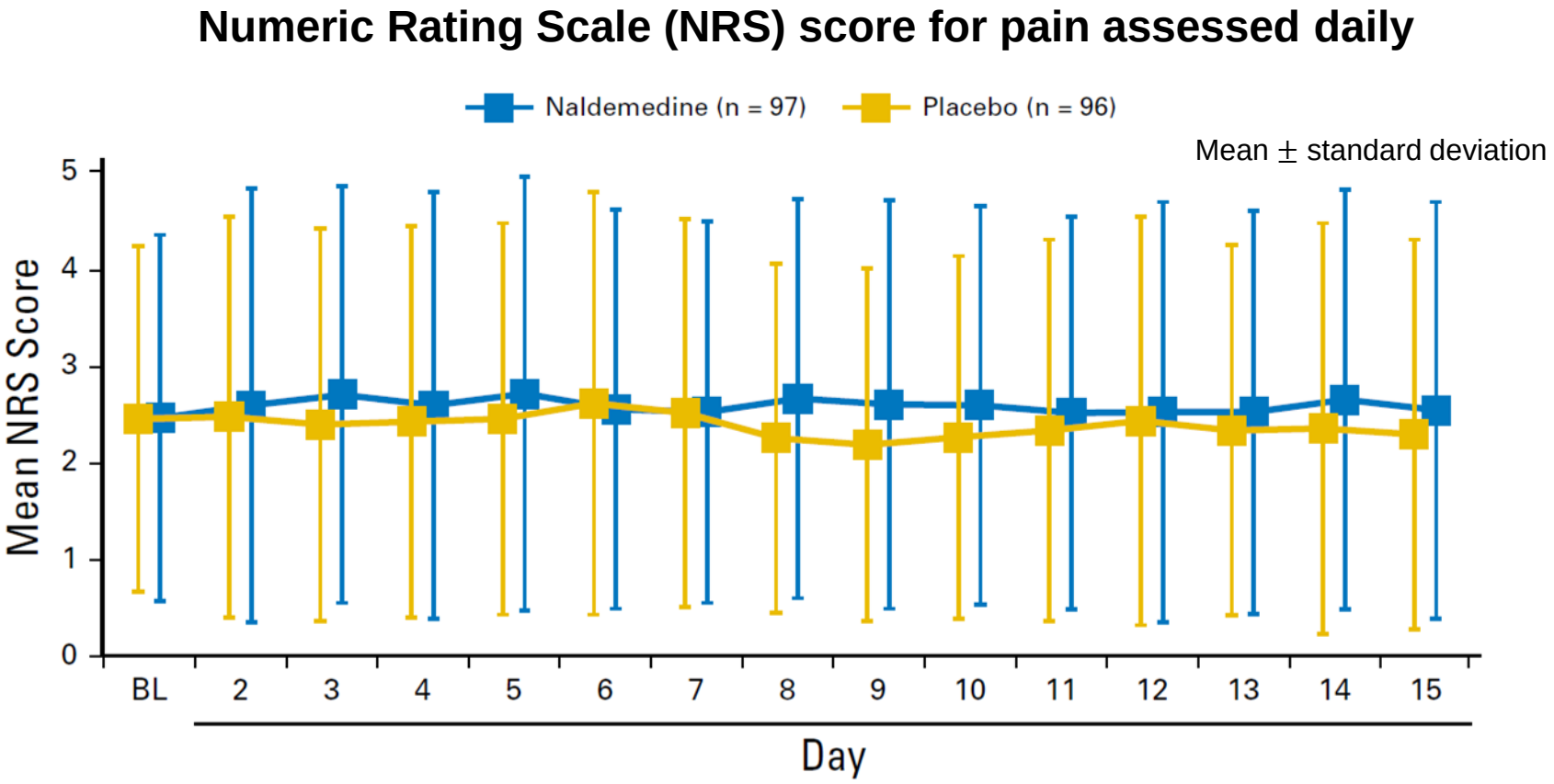
BL= baseline at day 1 pre-dose

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

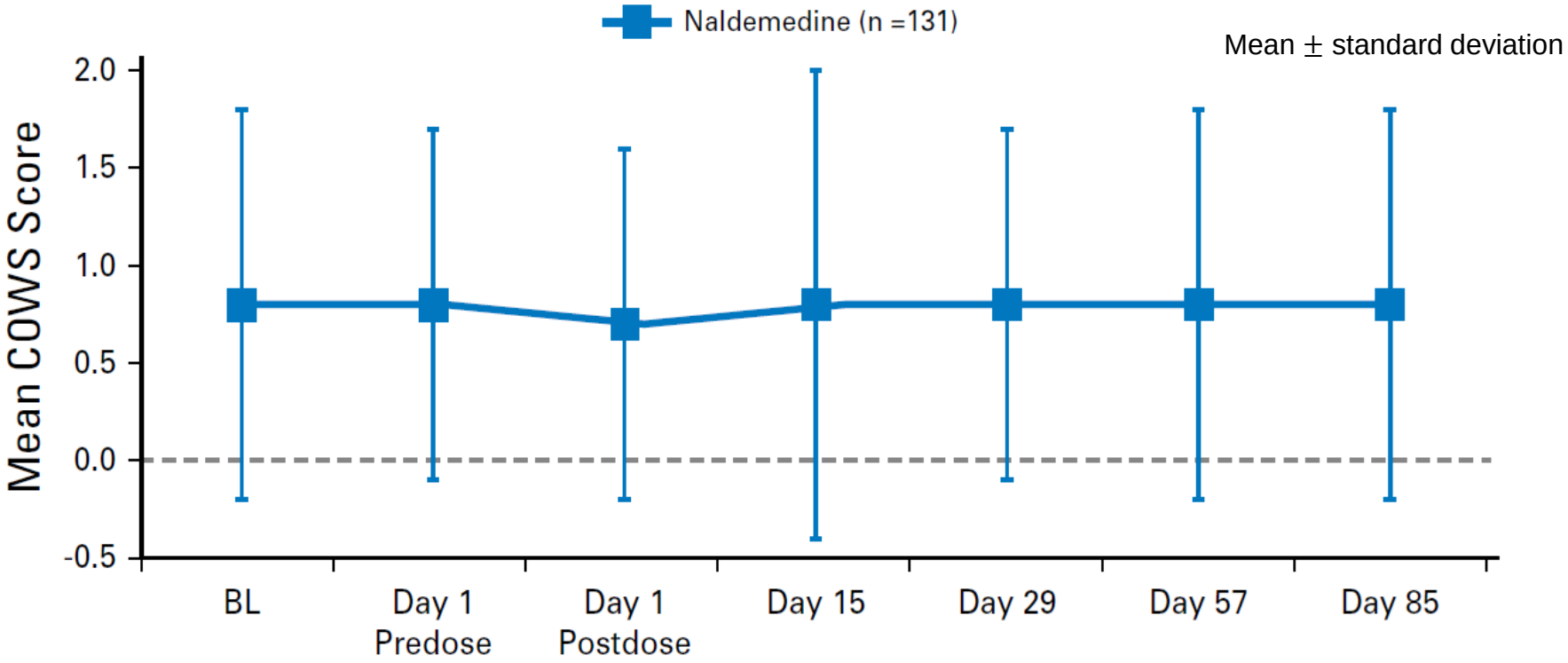


Katakami N et al. J Clin Oncol. 2017 Dec 1;35(34):3859-3866.

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

Safety Endpoint

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



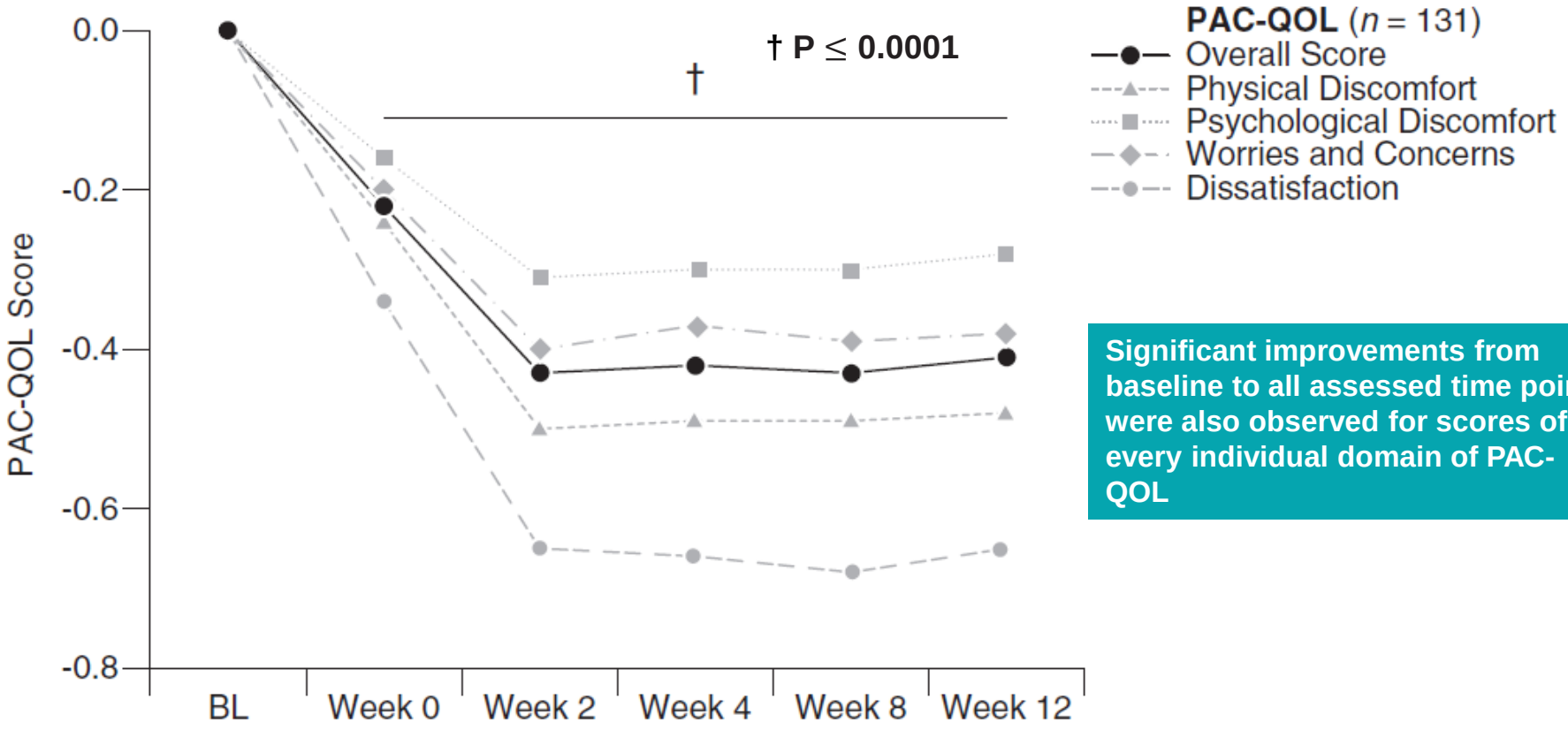
Although four occurrences of elevated COWS scores were reported, there were no TEAEs of opioid withdrawal

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

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.

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。

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)

為了精進未來的課程安排，
懇請 您撥冗回覆問卷，感謝您!

SHIONOGI