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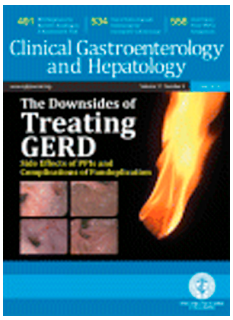

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Establishing Minimal Clinically Important Differences in Quality of Life Measures in Opioid-Induced Constipation

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SHORT TITLE: Clinically meaningful changes in OIC outcomes

CONFLICTS OF INTEREST

Jan Tack has provided scientific advice to Allergan, Kyowa Kirin, Shionogi, and Shire, has been a speaker for Allergan and Kyowa Kirin, and has received a research grant from Kyowa Kirin related to opioid-induced constipation.

Michael Camilleri has provided scientific advice to Shionogi and has received a research grant from AstraZeneca in the field of opioid-induced constipation.

Martin Hale was a clinical trial investigator, consultant to Shionogi Inc. and received a stipend for review of the clinical study report.

Bart Morlion was a clinical trial site investigator for Shionogi Inc.; a consultant for Astellas Pharma Europe Ltd, Boehringer Ingelheim International, Grünenthal, Mundipharma International, Teva Pharmaceuticals Europe, GSK Consumer Healthcare, and Kyowa Kirin; and a speaker for Mundipharma International, Pfizer Inc, Shionogi Inc., Kyowa Kirin, and Procter and Gamble Company.

Srinivas Nalamachu is a consultant for Shionogi Inc. and was a clinical trial site investigator. He is also a consultant and speaker for AstraZeneca, Daiichi Sankyo, Purdue, and Salix.

Lynn Webster is an advisor to Depomed, Inspirion; consultant to Alcobra, Bonti, Charleston Laboratories, Indivior, Insys, Kempharm, Pain Therapeutics, Shionogi, Teva, and Trevi; and has received travel expenses from Alcobra, Bonti, Charleston Laboratories, Depomed, Daiichi Sankyo, Egalet, Indivior, Inspirion, Insys, Kempharm, and Teva.

James Wild received a stipend from Shionogi Inc. for review of the clinical study report.

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Glossary

AE, adverse event; AUC, area under the curve; BM, bowel movement; BMCA, Bowel Movement and Constipation Assessment; BMI, body mass index; CSBM, complete spontaneous bowel movement; GI, gastrointestinal; HRQOL, health-related quality of life; MCID, minimal clinically important difference; MED, morphine equivalent dose; NA, not applicable; OIC, opioid-induced constipation; PAC-QOL, Patient Assessment of Constipation Quality of Life; PAC-SYM, Patient Assessment of Constipation Symptoms; PAMORA, peripherally acting μ-opioid receptor antagonist; PRO, patient-reported outcome; QOL, quality of life; ROC, receiver operating characteristic; SBM, spontaneous bowel movement; SD, standard deviation; SF-36, short form 36 health survey

ABSTRACT

Background & Aims: Opioids have a role in chronic pain management. However, opioid-induced constipation (OIC) may cause patients to skip or reduce opioid doses, leading to inadequate pain relief and negatively impacting quality of life (QOL). We sought to establish a minimal clinically important difference (MCID) to understand whether changes in QOL scores are of value to patients.

Methods: Integrated data from the double-blind, controlled, Phase 3 COMPOSE-1 and COMPOSE-2 trials of naldemedine in chronic non-cancer pain and OIC were used to determine MCIDs using Patient Assessment of Constipation Symptoms (PAC-SYM) and Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaires. Patients completed the questionnaires (5-point Likert scale; pre-dose, weeks 2, 4, and 12), kept a daily log of Bowel Movement and Constipation Assessment (BMCA), and rated satisfaction at end of study. MCIDs were computed using an anchor-based method with 6 anchors: 5 from the BMCA and 1 from patient satisfaction. Threshold values for each anchor were set to define responders versus non-responders based on score definitions. Clinically meaningful cutoff values for changes in PAC-SYM and PAC-QOL scores were determined using receiver operating characteristic (ROC) curves.

Results: Data from 1095 patients (549, naldemedine; 546, placebo) were analyzed. The area under the curve for the ROC curves (ranges: 0.719 to 0.798, PAC-SYM, and 0.734 to 0.833, PAC-QOL) indicated that both instruments can discriminate responders and non-responders for each anchor. PAC-SYM cutoff values ranged from −1.04 to −0.83; PAC-QOL cutoff values ranged from −0.93 to −0.82.

Conclusions: Based on data derived from the anchor method, reductions in PAC-SYM and PAC-QOL scores of >1.0 in patients with chronic non-cancer pain and OIC are clinically meaningful. **ClinicalTrials.gov Registration:** NCT01965158; NCT01993940

Keywords: Opioid-related disorders; PAMORA; naldemedine

WHAT YOU NEED TO KNOW

Background:

The Patient Assessment of Constipation Symptoms and Patient Assessment of Constipation Quality of Life questionnaires are used to measure treatment-related changes in patients with opioid-induced constipation. It is not known whether these changes are of value to the patient.

Findings:

Based on calculations of minimal clinically important differences, reductions in the Patient Assessment of Constipation Symptoms and Patient Assessment of Constipation Quality of Life scores of >1.0 in patients with chronic non-cancer pain and opioid-induced constipation are clinically meaningful.

Implications for Patient Care:

By determining minimal clinically important differences for instruments measuring quality of life, this study establishes how to gauge patient-perceived treatment success and provides rationale for introducing adjustments in treatment.

INTRODUCTION

Opioid analgesic therapy is one treatment option for selected patients with chronic moderate-to-severe non-cancer and cancer pain.[1] The use of opioids, however, is associated with a number of significant adverse events (AEs).[2] Among these, the most frequent is bowel dysfunction, usually opioid-induced constipation (OIC).[3] OIC has been defined as a change from baseline bowel habits after initiating opioid therapy that is characterized by any of the following: a reduction in bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete evacuation, harder stool consistency, or a patient's perception of distress related to bowel habits.[4, 5] Studies of patients with chronic non-cancer pain treated with opioids have reported that as many as 57% experience OIC.[3, 6]

In contrast to many other AEs associated with opioid therapy, OIC is not associated with tolerance and tends to persist unabated over time, even with the use of laxatives.[7] A survey found that constipation was the most prevalent "bothersome" gastrointestinal (GI) side effect for 81% of patients receiving opioids for chronic pain who were taking laxatives.[8] The occurrence of OIC may cause patients to skip or reduce their prescribed opioid doses, leading to inadequate pain relief and a significant negative impact on health-related quality of life (HRQOL).[7-9]

OIC results from the activation of μ-opioid receptors, which are extensively distributed throughout the enteric nervous system in the GI tract. This leads to inhibition of gut motility, enhanced fluid absorption, and reduced intestinal fluid secretion.[4, 10] Peripherally acting μ-opioid receptor antagonists (PAMORAs), which block peripheral μ-opioid receptors in the enteric nervous system without affecting opioid analgesic actions

in the central nervous system, constitute an effective treatment option for patients with OIC.[4] Several PAMORAs have been developed and approved for the treatment of OIC, including naloxegol (oral),[11] methylnaltrexone (oral or subcutaneous),[12] and, most recently, naldemedine (oral).[13]

There are several instruments to assess constipation-related patient-reported outcomes (PROs) that may provide insights into the effectiveness of PAMORAs in OIC. These include the Patient Assessment of Constipation Symptoms (PAC-SYM) and the Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaires.[14-16] The PAC-SYM consists of 12 questions divided into 3 domains (abdominal symptoms, rectal symptoms, and stool symptoms) and has been found to be a reliable, valid, and responsive measure of the presence and severity of OIC.[17, 18] The PAC-QOL consists of 28 questions divided into 4 domains (physical discomfort, psychosocial discomfort, worries and concerns, and satisfaction) and has been validated in patients with chronic functional constipation.[19]

Although the PAC-SYM and PAC-QOL instruments allow measurement of treatment-related changes in PROs in OIC, a key question is whether these changes are deemed to be of value by the patient. A simple comparison of numbers, even if demonstrating statistical significance, does not *per se* imply that the difference in QOL reached a level of benefit perceptible to the patient. Interpreting PROs must therefore consider the concept of minimal clinically important difference (MCID), which is defined as the smallest level of change in a domain score of interest at which patients perceive a benefit.[20] Calculation of the MCID enables researchers comparing 2 treatments to determine the magnitude of benefit, calculate sample size, make cost-effectiveness

comparisons, and infer the proportion of patients receiving benefit.[21] Determining MCID is therefore critical for a patient-centric understanding of outcomes and may constitute important evidence for PRO claims through regulatory agencies.[22] Defining the MCID in QOL is also important to justify treatments, as has been shown, for example, in the context of cholecystectomy,[23] treatment of ulcerative colitis with vedolizumab,[24] Crohn's disease with certolizumab pegol,[25] liver transplant recipients with mycophenolate mofetil,[26] and chronic constipation with prucalopride treatment.[27]

The MCIDs for PAC-SYM and PAC-QOL values in patients with OIC have not yet been established. In order to address this gap, we analyzed data from 2 randomized, Phase 3 clinical studies of naldemedine in patients with chronic non-cancer pain and OIC to determine PAC-SYM and PAC-QOL MCID values for this patient population.

METHODS

Data sources

Integrated data from 2 identically designed studies evaluating the efficacy and safety of naldemedine in OIC (COMPOSE-1 and COMPOSE-2) were used for this analysis. Details of the design and methodology for these studies were previously reported.[28] In brief, COMPOSE-1 and COMPOSE-2 were 12-week randomized, multicenter, double-blind, placebo-controlled, parallel-group studies. Adults with chronic non-cancer pain treated with opioid analgesics for ≥3 months, experiencing self-reported OIC, and who were either not using laxatives or had agreed to discontinue laxative use at enrollment were randomized 1:1 to naldemedine 0.2 mg or placebo once daily for 12 weeks. OIC was defined as having no more than 4 spontaneous bowel movements (SBMs) over 14

consecutive days of the study qualifying period; no more than 3 SBMs in a given week of the qualifying period; and at least 1 of the following bowel symptoms with at least 25% of BMs: presence of straining, lumpy or hard stools, sensation of incomplete evacuation or sensation of anorectal obstruction/blockage. The OIC criteria used in the COMPOSE trials were similar to the current Rome IV diagnostic criteria.[5] The studies were conducted in accordance with the principles of the Declaration of Helsinki and in compliance with local Good Clinical Practice guidelines and regulations. Study protocols were approved by independent ethics committees at each site and all relevant institutional review boards.[28] Data from naldemedine and placebo treatment groups were each combined to determine MCID values in the present study. All authors had access to the study data and reviewed and approved the final manuscript.

Outcomes

Exploratory endpoints in COMPOSE-1 and COMPOSE-2 included change from baseline in overall score and in each domain score for the PAC-SYM and PAC-QOL questionnaires (**Supplementary Materials**). Questions in both instruments were rated on a 5-point Likert scale (0=absence of symptoms, 1=mild, 2=moderate, 3=severe, and 4=very severe); lower scores reflect better QOL. The PAC-QOL and PAC-SYM were assessed on day 1 (pre-dose), week 2, week 4, and week 12 or at early termination. In both studies patients also completed a Bowel Movement and Constipation Assessment (BMCA) log daily via eDiary. Patients were asked by the investigator to rate their degree of satisfaction with constipation and abdominal symptoms from the start of study drug dosing to week 12 on a scale of 1 (markedly worsened) to 7 (markedly improved). In

addition, short-form 36 health survey (SF-36) physical and mental component scores, which measure general health status and QOL, were obtained for patients enrolled in COMPOSE-1 and COMPOSE-2 at baseline and week 12.

Definition of anchors for determining MCID

An anchor-based approach was used to calculate estimated MCIDs for PAC-SYM and PAC-QOL scores. As previously described,[27, 29] this approach provides a comparison of changes in a specific PRO of interest, such as the PAC-SYM or PAC-QOL total score, with changes in a different assessment for which a clinically meaningful improvement can be more clearly understood, ie, the "anchor").[27, 30, 31] Generally, 4 to 7 anchor questions are needed to determine MCID based on patients' assessments of treatment response. For this analysis, a total of 6 anchors were utilized: 5 were from the BMCA (3 questions and 2 values calculated from eDiaries) and 1 was patient global satisfaction. Anchors and cutoff scores are summarized in **Table 1**. Anchor questions were selected based on the expert opinion of the authors. Anchor scores were assessed for the last 2 weeks of the study, except for patient global satisfaction, which was assessed at week 12. Threshold values for anchor scores were chosen based on score definitions. For patient global satisfaction, a threshold score >5 (moderately or markedly improved) was chosen to best reflect a meaningful improvement.[32]

Statistical analysis

Receiver operating characteristic (ROC) curves were used to determine MCID cutoff values for the change in total PAC-SYM and PAC-QOL scores at week 12 that best discriminated between responders and non-responders for each anchor.[33] A responder was defined as achieving the cutoff for the anchors described in **Table 1**; conversely, a non-responder was defined as failing to achieve this cutoff. A ROC curve plots sensitivity of the instrument, defined as the proportion of responders correctly identified for each anchor (true positive rate) versus 1−specificity, where specificity is defined as the proportion of non-responders correctly identified for each anchor (false positive rate).[34] Sensitivity and 1−specificity for the change from baseline in PAC-SYM or PAC QOL were calculated for each anchor threshold, and ROC curves were generated. In this system, higher sensitivity and 1−specificity values indicate higher overall accuracy of the instruments, so the minimum PAC-SYM or PAC-QOL change from baseline that is able to effectively discriminate between responders and non-responders with good sensitivity and specificity for each anchor is the MCID. An area under the ROC curve of 1.0 indicates that an instrument is able to discriminate perfectly between responders and non-responders, while a value of 0.5 indicates that an instrument has no discriminating power.[27, 34] The cutoff value is calculated as the point on the curve closest to the top-left most corner of the ROC curve.[34] To assess the association between the constipation-specific PAC-SYM and PAC-QOL and the more general SF-36, the proportions of responders and non-responders and the calculated values for PAC-SYM and PAC-QOL were compared using the MCID for the mental and physical component scores of SF-36 (4.6 and 3.4, respectively, derived from a US

general population sample).[35] Pearson correlation coefficients for SF-36 physical and mental component scores versus PAC-SYM and PAC-QOL were calculated.

RESULTS

Demographics

Demographic and baseline characteristics of the integrated COMPOSE-1 and COMPOSE-2 naldemedine and placebo groups are shown in **Table 2**. The mean age was 53.4 years, and 60.5% of patients were women. Mean duration of opioid use at baseline was approximately 5 years, and the mean number of spontaneous bowel movements (SBMs) per week was 1.24.

ROC analysis

ROC curves for change from baseline in PAC-SYM and PAC-QOL overall score by anchor at week 12 are shown in **Figure 1,** and the corresponding data summarizing these results, including the optimal combination of sensitivity and specificity, are summarized in **Table 3**. The AUC for the ROC curves ranged from 0.719 to 0.798 for PAC-SYM and 0.734 to 0.833 for PAC-QOL, indicating that both instruments have a good ability to discriminate responders and non-responders for each anchor.

Cut-off value analysis

Cutoff values for PAC-SYM based on the 6 anchors ranged from −1.04 to −0.83, indicating an MCID value of −1.00 would include perception of significance by the vast majority of patients in these trials. Similar results were obtained for PAC-QOL, which

had cutoffs ranging from −0.93 to −0.82, again suggesting that a −1.00 change in PAC-QOL should be regarded as clinically important. Based on these data, reductions in PAC-SYM and PAC-QOL scores of >1.0 are clinically meaningful to patients with non-cancer pain and OIC.

Comparison of PAC-SYM and PAC-QOL with SF-36

Figure 2 shows the proportion of patients who achieved the MCID for SF-36 mental and physical component scores and who also achieved clinically meaningful reductions in PAC-SYM and PAC-QOL scores >1.0. There was little relationship between the physical and mental component scores of SF-36 and PAC-SYM or PAC-QOL. This was confirmed by the fact that there was no correlation between the SF-36 physical component score and PAC-SYM and PAC-QOL (Pearson correlation coefficient = −0.14 for both), or between the SF-36 mental component score and PAC-SYM (Pearson correlation coefficient = −0.19). There was a weak correlation between the SF-36 mental component score and PAC-QOL (Pearson correlation coefficient = −0.28).

DISCUSSION

Our study has shown that for both PAC-SYM and PAC-QOL, a difference of 1 point or greater constitutes a perceptible, clinically important difference for patients treated for OIC with a PAMORA. In the COMPOSE-1 and COMPOSE-2 trials, patients with OIC randomized to naldemedine had a significantly higher responder rate than those randomized to placebo (COMPOSE-1: 47.6% vs 34.6%, *P*=.002; COMPOSE-2: 52.5% vs 33.6%, *P*<.0001), with no change in numerical rating scale score for pain at any

study time point.[28] Using PRO data from COMPOSE-1 and COMPOSE-2, the present analysis is the first to determine MCIDs of the PAC-SYM and PAC-QOL in patients with OIC. The analysis was performed using a multi-anchored ROC method.[36] In this method, analogous to that used to assess diagnostic test performance, ROC curves provide the cutoffs at the values of dichotomous responses that minimize false positives and false negatives. The AUC of the ROC curves generated here ranged from 0.719 to 0.798 for PAC-SYM and 0.734 to 0.833 for PAC-QOL. Generally speaking, an AUC of 0.7 to 0.8 suggests that the test can be considered acceptable, and an AUC of 0.8 to 0.9 indicates that the test is excellent.[37] PAC-SYM and PAC-QOL in this setting can be considered to have an acceptable-to-excellent ability to discriminate between responders and non-responders.

Values for all 6 chosen anchors were found to be consistent for both PAC-SYM and PAC-QOL and ranged between −1.04 and −0.83 for PAC-SYM and −0.93 and −0.82 for PAC-QOL. These data indicate that, conservatively, PAC-SYM and PAC-QOL changes of >1.0 are clinically meaningful for patients with chronic non-cancer pain and OIC. Cut-offs at 12 weeks were broadly similar between patients randomized to naldemedine or to placebo. However, there were differences for some anchors, such as CSBM for PAC-SYM, which had a cut-off for naldemedine of −1.08 and for placebo of −0.58, and the change in mean straining score of SBM for PAC-QOL, which had a cutoff for naldemedine of −1.25 and for placebo of −0.82 (data not shown). Similar trends were seen for patients who received an average daily dose of opioid at baseline of 30 to 100 mg or >100 mg. The cut-offs for all 6 anchors were similar for both PAC-SYM and PAC-QOL, except for the change in CSBM after 12 weeks for PAC-SYM (−1.04 and

−0.58 for opioid doses of 30 to 100 mg and >100 mg, respectively; data not shown). Overall, these data provide further validation of the applicability of PAC-SYM and PAC-QOL. Bearing in mind that MCID values are context dependent,[30] these results are consistent with previous analyses of patients with chronic constipation in clinical trials of prucalopride, which reported that a >0.75-point decrease in PAC-SYM score[27] and a >1-point decrease in PAC-QOL score[29] were clinically meaningful. Additionally, although no MCID was determined, an analysis of pooled data from two Phase 3 studies of naloxegol in patients with non-cancer pain and OIC found that improvements in the frequency of SBMs correlated with improvements in PAC-SYM and PAC-QOL scores.[38] Collectively, these studies underscore the importance of determining PROs in clinical trials of patients with chronic constipation.

Although the present analysis employed an anchor-based method for MCID determination, other methods are also available. In the consensus (ie, Delphi) method, MCID is derived in an iterative process involving a panel of experts.[31] This method has been criticized as not being objectively evidence based.[39] Another approach, the distribution method, arrives at the MCID by analyzing the statistical distribution of outcome scores to determine the magnitude of change required to show that the response is greater than that expected from chance distribution.[40] It has been argued, however, that whereas distribution methods are adequate to determine the lowest change value beyond which random error cannot be expected, they only roughly approximate the MCID.[40] In the anchor-based approach used in the present study, the MCID is determined by associating the numerical scale for a given PRO (the target) with a different, independent health status category (the anchor), thereby "anchoring" each

numerical scale to a more meaningful self-reported categorical assessment.[41] Of these 3 methods, therefore, the anchor-based approach is generally preferred as the only method that is evidence based and fully patient centric.[39] Compared with distribution-based and consensus methods, anchor-based MCID estimates have been found to provide conservative MCID estimates.[30]

SF-36 is a general measure of HRQOL that is commonly used in many different branches of medicine. While the instrument is an effective tool that allows for meaningful comparisons of disease burden across conditions, it lacks specificity.[35] This is borne out in our analysis which found little to no correlation between SF-36 physical and mental component scores and PAC-SYM and PAC-QOL, suggesting that these disease-specific health assessment tools capture aspects of the OIC experience that SF-36 does not. PAC-SYM and PAC-QOL are better instruments for measuring HRQOL in patients with OIC.

Strengths of this study include the uniformity of the clinical trials, the inclusion of more than 1000 patients, and the rigorous choice of anchors based on content experts in the field.

Limitations of the anchor method include choice of anchor and the possibility of variations among patient subgroups, such as those experiencing greater and lesser levels of pain.[31] "Recall bias," the tendency of a patient's current status to influence judgement of the past, cannot be ruled out in any study examining PROs. Nonetheless, the anchor-based method used herein is generally accepted as the most conservative, unbiased approach available.[30, 39] The validity of this result is further strengthened by the fact that the distribution of responses in both the naldemedine and placebo groups

closely approximated a normal distribution. The COMPOSE-1 and COMPOSE-2 trials did not include PRO measures that would allow for the assessment of more generalizable health utilities. Specific measures in this category, such as the EuroQOL, await future studies of naldemedine in OIC. The PAC-QOL, commonly used in studies of treatments for OIC, is validated in patients with chronic functional constipation; efforts to validate PAC-QOL in patients with OIC are warranted. While the PAC-SYM and PAC-QOL instruments are robust PRO tools for use in clinical trials, their length may prohibit use in routine clinical practice.

CONCLUSIONS

The PAC-SYM and PAC-QOL questionnaires are being increasingly utilized for the assessment of PROs in OIC. The current analysis is the first to estimate an MCID for these measures based on naldemedine clinical trial data in patients with chronic non-cancer pain and OIC. Using an anchor-based approach, an MCID value of >1.0 was determined for these questionnaires in this patient population. Establishing such MCIDs for instruments measuring HRQOL is important to understanding patient-perceived treatment success, as well as to help identify when adjustments in treatment may be needed.

AUTHOR CONTRIBUTIONS

Study design: JT, MC, LW

Study investigator: MH, BM, JW

Enrolled patients: MH, BM, SN, JW

Collection and assembly of data: MH

Data interpretation: All authors

Manuscript preparation: All authors

Manuscript review and revisions: All authors

FINAL APPROVAL OF MANUSCRIPT: ALL AUTHORS

FIGURE LEGENDS

Figure 1. Receiver Operating Characteristics Curves for Changes in Baseline in PAC-SYM and PAC-QOL Overall Score at Week 12.

CSBM, complete spontaneous bowel movement; PAC-QOL, Patient Assessment of Constipation Quality of Life; PAC-SYM, Patient Assessment of Constipation Symptoms; SBM, spontaneous bowel movement.

Figure 2. Proportion of Patients Who Achieved the MCID for SF-36 Mental and Physical Component Scores and Who Also Achieved Clinically Meaningful Reductions in PAC-SYM and PAC-QOL Scores >1.0 for: A) SF-36 and PAC-SYM; and B) SF-36 and PAC-QOL.

PAC-QOL, Patient Assessment of Constipation Quality of Life; PAC-SYM, Patient Assessment of Constipation Symptoms; SF-36, short form 36 health survey.

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TABLES

Table 1. Description of Anchors Used for Determining the Minimal Clinically Important Difference of the PAC-SYM and PAC-QOL

Anchor Used in MCID Analysis	Question	Definition/Scale
Bowel movement and constipation assessment during the last 2 weeks relative to baseline		
Change in SBMs of >3 per week without the use of laxatives in the prior 24 hours,	NA*	BMs without the use of rescue laxative in the past 24 hours
Change in CSBMs of >2 per week without the use of laxatives in the prior 24 hours	NA*	SBMs with a perception of complete evacuation
Change of <-1 in mean abdominal bloating	Please rate your abdominal bloating for the past 24 hours on a scale of 0–4	0=Absent 1=Mild 2=Moderate 3=Severe 4=Very severe
Change of <-1 in mean abdominal discomfort	Please rate your abdominal discomfort for the past 24 hours on a scale of 0–4	0=Absent 1=Mild 2=Moderate

		3=Severe 4=Very severe
Change of <-1 in mean straining score	Please rate the severity of straining with the bowel movement	0=No straining 1=Mild straining 2=Moderate straining 3=Severe straining 4=Very severe straining
Patient global satisfaction at 12 weeks (end of study)		
Patient global satisfaction score of >5	Investigator or designee asked the patient about the degree of satisfaction of constipation and abdominal symptoms from the start of study drug dosing to week 12	1=Markedly worsened 2=Moderately worsened 3=Slightly worsened 4=Unchanged 5=Slightly improved 6=Moderately improved 7=Markedly improved

*Value calculated from daily eDiary entries.

BM, bowel movement; CSBM, complete spontaneous bowel movement; MCID, minimal clinically important difference; NA, not applicable; PAC-QOL, Patient Assessment of Constipation Quality of Life; PAC-SYM, Patient Assessment of Constipation Symptoms; SBM, spontaneous bowel movement.

Table 2. Demographic and Baseline Characteristics of the Integrated COMPOSE-1 and COMPOSE-2 Intent-to-Treat Study Population

	Naldemedine 0.2 mg/day (n=549)	**Placebo (n=546)**	**Total (N=1095)**
Age, years			
Mean (SD)	53.7 (10.5)	53.1 (11.2)	53.4 (10.8)
Sex, % (n)			
Female	59.4 (326)	61.5 (336)	60.5 (662)
Male	40.6 (223)	38.5 (210)	39.5 (433)
BMI (kg/m^2)			
Mean (SD)	31.35 (7.20)	31.31 (7.16)	31.33 (7.18)
Region, % (n)			
North America	85.8 (471)	85.7 (468)	85.8 (939)
Europe	14.2 (78)	14.3 (78)	14.2 (156)
Race, % (n)			
American Indian or Alaska native	0.7 (4)	0.9 (5)	0.8 (9)
Asian	0.7 (4)	0.7 (4)	0.7 (8)
Black or African American	18.6 (102)	15.9 (87)	17.3 (89)
Native Hawaiian or other Pacific Islander	0.2 (1)	0.5 (3)	0.4 (4)

White	79.8 (438)	81.9 (447)	80.8 (885)
SBMs per week, mean (SD)	1.24 (0.75)	1.23 (0.72)	1.24 (0.74)
Mean overall PAC-SYM (SD)	1.89 (0.74)	1.81 (0.74)	1.85 (0.74)
Mean overall PAC-QOL (SD)	2.07 (0.75)	2.05 (0.75)	2.06 (0.75)
Total daily opioid use, MED Mean (SD)	121.6 (120.0)	131.8 (150.0)	126.7 (135.8)
Patients with daily opioid use, % (n)			
<30 mg	1.1 (6)	0.5 (3)	0.8 (9)
30 to 100 mg	56.8 (312)	56.6 (309)	56.7 (621)
>100 to ≤200 mg	25.3 (139)	24.7 (135)	25.0 (274)
>200 to ≤400 mg	13.1 (72)	13.4 (73)	13.2 (145)
>400 mg	3.6 (20)	4.8 (26)	4.2 (46)
Duration of opioid use (months) Mean (SD)	61.1(61.7)	59.2 (57.1)	60.2 (59.4)

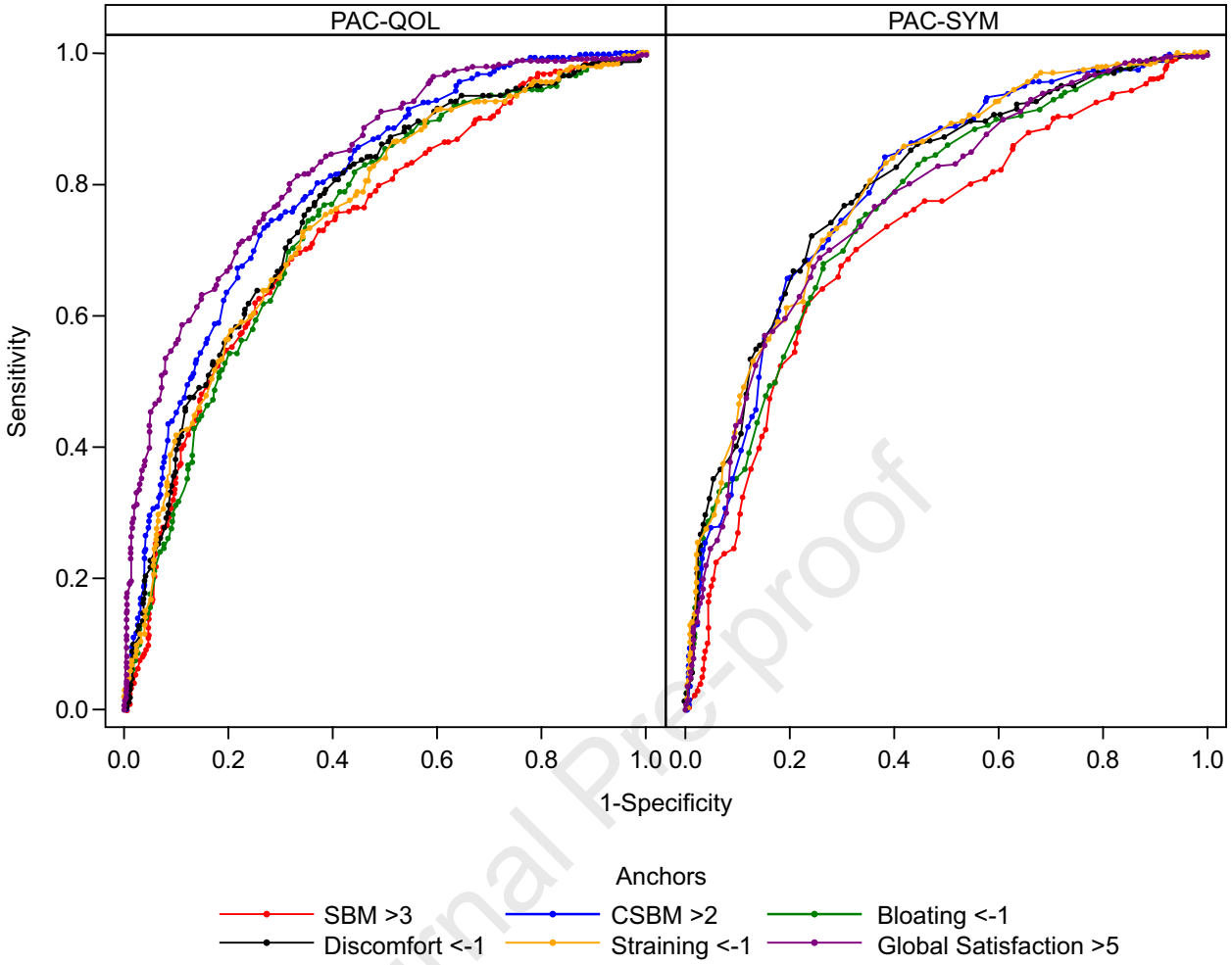
BMI, body mass index; MED, morphine equivalent dose; PAC-QOL, Patient Assessment of Constipation Quality of Life; PAC-SYM, Patient Assessment of Constipation Symptoms; SBM, spontaneous bowel movement; SD, standard deviation.

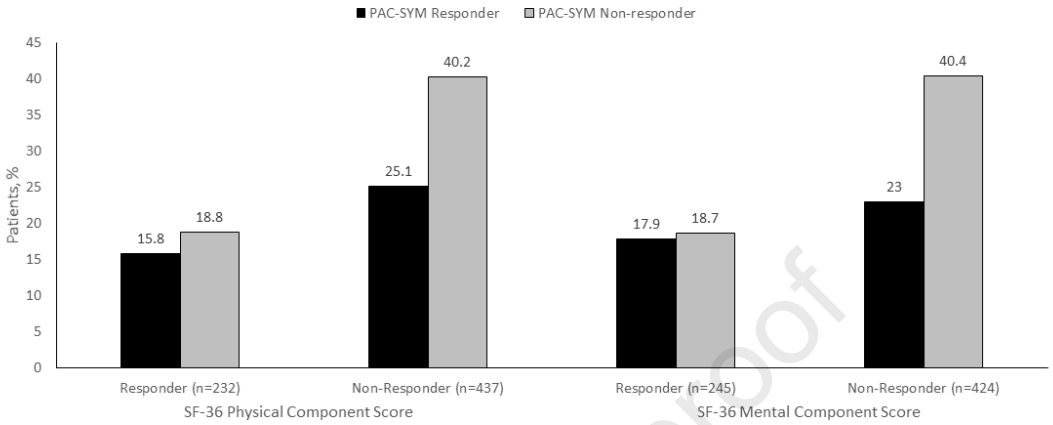
Table 3. Receiver Operating Characteristics Curve Analysis for Change From Baseline in PAC-SYM and PAC-QOL Overall Score at Week 12

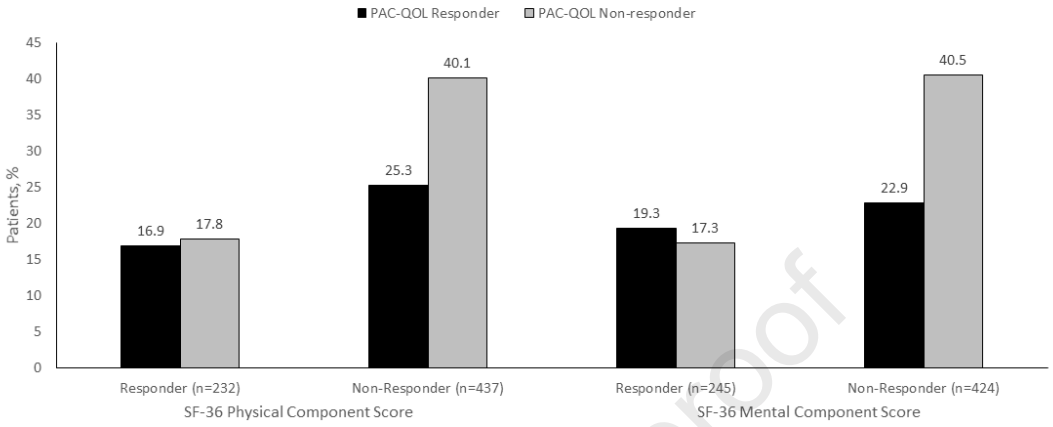
	SBM >3	CSBM >2	Bloating <−1	Discomfort <−1	Straining <−1	Global Satisfaction >5
PAC-SYM (overall N=1095)						
AUC	0.719	0.793	0.765	0.795	0.798	0.772
Cutoff	−1.00	−1.04	−1.00	−1.00	−0.92	−0.83
Sensitivity, %	61.2	65.8	67.8	72.3	71.6	68.7
Specificity, %	77.1	80.4	73.6	75.8	73.8	74.3
PAC-QOL (overall N=1095)						
AUC	0.734	0.799	0.745	0.763	0.752	0.833
Cutoff	−0.93	−0.93	−0.89	−0.86	−0.82	−0.89
Sensitivity, %	67.6	73.4	74.4	76.2	72.8	71.5
Specificity, %	69.7	73.5	65.1	64.9	66.0	77.5

Sensitivity is defined as the proportion of responders correctly identified based on anchors; specificity is defined as the proportion of non-responders correctly identified based on anchors. Cutoff is the value that maximizes sensitivity and specificity. Responders were defined as those achieving the threshold for the anchors described in Table 1, and non-responders were defined as those failing to achieve this threshold.

AUC, area under the curve; CSBM, complete spontaneous bowel movement; PAC-QOL, Patient Assessment of Constipation Quality of Life; PAC-SYM, Patient Assessment of Constipation Symptoms; SBM, spontaneous bowel movement.







Background:

The Patient Assessment of Constipation Symptoms and Patient Assessment of Constipation Quality of Life questionnaires are used to measure treatment-related changes in patients with opioid-induced constipation. It is not known whether these changes are of value to the patient.

Findings:

Based on calculations of minimal clinically important differences, reductions in the Patient Assessment of Constipation Symptoms and Patient Assessment of Constipation Quality of Life scores of >1.0 in patients with chronic non-cancer pain and opioid-induced constipation are clinically meaningful.

Implications for Patient Care:

By determining minimal clinically important differences for instruments measuring quality of life, this study establishes how to gauge patient-perceived treatment success and provides rationale for introducing adjustments in treatment.