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Morphine Sulfate and Naltrexone Hydrochloride Extended Release Capsules in Patients with Chronic Osteoarthritis Pain

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Abstract

Objective: To assess the efficacy and safety of morphine sulfate and naltrexone hydrochloride extended release capsules (EMBEDA[®]; MS-sNT), which contain morphine sulfate pellets with a sequestered naltrexone core, in treating patients with chronic, moderate-to-severe osteoarthritis (hip or knee) pain. **Patients and Methods:** This phase 3 study had an enriched-enrollment, randomized-withdrawal, double-blind, multicenter design. Patients (N = 547) were titrated to an effective dose of MS-sNT (20–160 mg/day). Responders (n = 344) were randomized to 12 weeks maintenance with an effective MS-sNT dose or were tapered to placebo over 2 weeks. The primary efficacy measure was the change from baseline (CFB) in diary average-pain scores (0–10 scale, Brief Pain Inventory [BPI]) from randomization to the last 7 days of the maintenance period. Secondary efficacy measures included the remaining BPI scores and Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index. Opioid withdrawal symptoms were assessed by the Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS). The study ran from January 10, 2007 through November 8, 2007. **Results:** MS-sNT maintained pain control better than placebo (mean CFB, diary average-pain score, -0.2 ± 1.9 vs $+0.3 \pm 2.1$; $P = 0.045$). Change from baseline for MS-sNT pain-diary score (worst, least, average, current) was superior during the maintenance period visits, weeks 2 to 12 ($P < 0.05$). WOMAC composite score CFB was superior at most visits. MS-sNT was generally well tolerated, with a typical morphine safety profile. No patient taking MS-sNT as directed experienced withdrawal symptoms. **Conclusion:** MS-sNT provided effective analgesia in patients with chronic, moderate-to-severe osteoarthritis pain, with a safety profile typical of morphine-containing products. Naltrexone sequestered in MS-sNT had no clinically relevant effect when MS-sNT was taken as directed.

Keywords: chronic pain; opioids; morphine; extended release; opioid withdrawal

Introduction

Control of chronic pain is an important therapeutic challenge. Suboptimal control of chronic pain can lead to substantial suffering, productivity loss, and increased health care costs, and is a leading reason for disability in working adults.¹ Many patients with moderate-to-severe pain fail to obtain adequate pain relief with nonopioid agents and, as a result, opioid analgesics are frequently used either in monotherapy or as add-on therapy.¹ Because of their analgesic efficacy across multiple pain states, opioids remain a mainstay of chronic pain management.^{2,3} It has been estimated that between February 1998 and September 2006, > 4.3 million adults in the United States regularly used opioids in any given week.^{1,3,4} Immediate-release opioid formulations require dosing every 3 to 4 hours when administered orally, whereas extended-release oral

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formulations can provide effective pain relief over periods up to 24 hours.¹

Despite their demonstrated efficacy, the use of opioid analgesics to treat chronic pain is often limited by the fear of potential abuse and concern among health care providers about being accused of opioid over-prescribing.^{2,3,5} Multiple data sources indicate that the misuse, abuse, and diversion of opioids are increasing. Results from the 2008 National Survey on Drug Use and Health indicated that the number of “current” (within the previous month) abusers of prescription pain relievers (4.7 million) surpassed the number of current abusers of cocaine (1.9 million) and heroin (0.2 million).⁶ In 2008, the specific drug categories with the largest number of past-year initiates among people aged ≥ 12 years were prescription pain relievers and marijuana (approximately 2.2 million initiates each).⁶ The most common routes of administration of abused opioids are oral, snorting, and injection.⁷ Extended-release formulations may be greater targets for abuse compared with shorter-acting, immediate-release formulations due to their higher opioid content. Tampering with extended-release formulations may result in release of the large unit dose of opioid at once, which increases the risk of serious and life-threatening side effects.¹ As a result, several pharmaceutical formulation strategies have been proposed to deter abuse of extended-release opioids.¹ The abuse liability of such products is examined using various methodologies that may include benchtop testing (in vitro) to analyze the robustness of a formulation under various attempts at tampering, preclinical studies (eg, self-administration), and clinical abuse potential testing (commonly referred to as abuse liability or likeability studies) using surrogate markers (eg, reinforcing effects, drug liking, and euphoria). To establish whether any of these products are truly abuse “deterrent” or “resistant,” further post-marketing epidemiological studies are required to determine whether they are less abused in the community compared with similar products that are more readily abused. It also remains important, however, to demonstrate that these formulations are effective in achieving their primary purpose: effectiveness in pain management. Morphine sulfate and naltrexone hydrochloride capsules (EMBEDA[®]) contain polymer-coated pellets of extended-release morphine sulfate, each with a sequestered core of the opioid antagonist naltrexone (morphine sulfate with sequestered naltrexone [MS-sNT]).⁸ MS-sNT was developed based on the extended-release formulation used in morphine sulfate extended-release (KADIAN[®]) capsules, which do not contain naltrexone. The polymer coating of defined thickness and porosity controls the rate of morphine dissolution

in a pH-dependent manner as the pellets pass through the gastrointestinal tract.^{9,10} MS-sNT capsules are indicated for the management of chronic, moderate-to-severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.⁸ When MS-sNT is taken orally as directed, the release of morphine provides analgesic activity, whereas the naltrexone remains sequestered with only trace systemic exposure.⁸ Crushing the pellets and dissolving them in certain solvents releases naltrexone,¹¹ which has been shown to successfully mitigate the morphine-induced, subjective effects in patients with a history of recreational opioid abuse.¹²

When taken whole, as intended, MS-sNT exhibited a comparable pharmacokinetic profile, efficacy, tolerability, and safety in an active-controlled trial compared with a marketed formulation of extended-release morphine sulfate (KADIAN[®])¹⁰ in patients with chronic osteoarthritis (OA) pain.¹³ The current study was designed to evaluate the efficacy and safety of MS-sNT compared with placebo in the treatment of patients with chronic, moderate-to-severe pain associated with OA of the hip or knee.

Patients and Methods

Men and women aged ≥ 21 years with OA of the hip or knee who were otherwise in generally good health were eligible if they required treatment of chronic joint pain within the last 90 days and were unable to consistently control joint pain with either nonopioid analgesics, tramadol, or another opioid at a dose equivalent to ≤ 40 mg/day of oral morphine. Eligible patients had an average 24-hour pain intensity score of ≥ 5 on the 11-point pain scale (0 = no pain; 10 = pain as bad as you can imagine) at the baseline visit following cessation of previous medications, a primary diagnosis of functional class I–III OA of the hip or knee, and also met American College of Rheumatology clinical classification criteria for OA pain of the hip or knee.^{14,15} Patients with ≥ 1 joint pain who met these criteria were asked to choose the most painful area to serve as the target joint for assessing treatment efficacy.

Exclusion criteria included history of drug or alcohol abuse or dependence within the past 5 years; a positive urine toxicology test for illicit drugs or nonprescribed controlled substances at screening; allergy, intolerance, or nonresponsiveness to opioids; established history of uncontrolled major depressive disorder; any condition that would interfere with or confound the study result or pose patient risk; injury to the target joint within 12 weeks prior to screening; and documented history of rheumatoid arthritis, inflammatory arthritis, or nonsteroidal anti-inflammatory drug (NSAID)-dependent

inflammatory arthritis. Women of childbearing potential were required to have a negative urine pregnancy test at screening and be practicing an appropriate method of birth control.

Study Design

This randomized, double-blind, placebo-controlled, multicenter outpatient study (Sponsor study ALO-KNT-301) was conducted in accordance with the principles of the Declaration of Helsinki and its amendments and in compliance with the International Conference on Harmonisation principles of Good Clinical Practice and all national regulatory requirements. The protocol and related study materials were approved by an institutional review board or independent ethics committee for each site before patients were enrolled. All patients provided written informed consent before any study-related procedures were conducted.

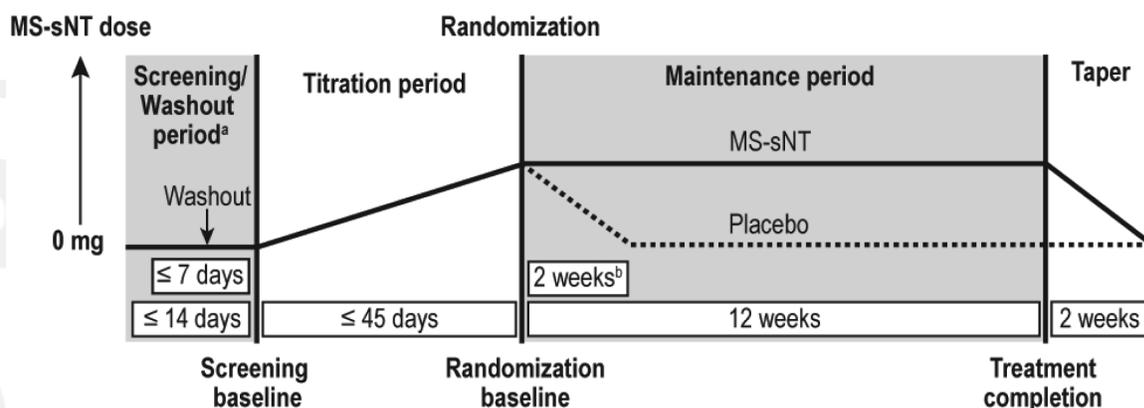
The study followed an enriched-enrollment, randomized-withdrawal (EERW) design.^{16,17} The study consisted of 3 periods: washout, titration, and maintenance (Figure 1). The EERW trial design more closely reflects clinical practice, and differs from that of traditional randomized clinical trials in that all participants undergo open-label dose titration to effective dose prior to randomization.^{16,17} Those patients who did not respond to or did not tolerate the study drug were discontinued from the trial. Patients who reached an optimal effective analgesic dose were randomized either to continued MS-sNT or tapered to placebo. The outcome assessed in the EERW trial design is loss of analgesic efficacy after removal of therapy rather than reduction of pain upon institution of therapy.¹⁸

During each period, rescue medication with acetaminophen (≤ 500 mg every 6 hours) was allowed. Patients were instructed to refrain from taking nonstudy pain medications; however, daily aspirin ≤ 325 mg for cardiovascular prophylaxis was permitted.

Throughout the study, patients used an electronic diary daily to answer questions about their pain intensity and rescue medication use. Patients were screened for eligibility up to 14 days before a baseline assessment, after which they entered a 1- to 7-day washout period, and discontinued all prohibited and pain medications. When the required 24-hour pain intensity was attained (score ≥ 5 on the 11-point pain intensity scale), the patient was instructed to return to the clinic within 72 hours for the baseline assessment, which consisted of standard clinical and laboratory testing and reconfirmation of patient eligibility. Acetaminophen was prohibited during the 24-hour period before this baseline visit. Patients with a pain intensity score of < 5 and those who could not tolerate their pain with the maximum allowed dose of acetaminophen were discontinued from the study.

Eligible patients entered a titration period lasting up to a maximum of 45 days, during which the dose of open-label MS-sNT was titrated until an effective twice-daily regimen was achieved. The starting dose of MS-sNT was 20 mg at bedtime in opioid-naïve patients, and 20 mg twice daily in those previously treated with opioids, although investigator discretion was allowed for the starting dose needed for pain control in opioid-experienced patients. Dose titrations were performed weekly and increases were made in increments of 20 mg/day up to 120 mg/day, with a final increase from 120 to 160 mg/day if needed. A maximum of 2 back-titrations was allowed, if necessary, to establish an effective tolerated dose. During the titration period, patients were seen weekly for pain intensity and safety assessments. Patients were considered responders when their average-pain intensity score on the Brief Pain Inventory (BPI) scale over the last 4 days before the clinic visit was ≤ 4 and had declined by ≥ 2 points from baseline. Once identified as treatment responders,

Figure 1. Study design.



^aWashout period was 1 to 7 days prior to initiation of titration; ^b2-week taper to placebo in double-dummy fashion.

Abbreviation: MS-sNT, morphine sulfate with sequestered naltrexone.

patients were allowed to continue dose titration for increased pain relief provided the maximum MS-sNT dose and titration period duration were not exceeded. Patients who did not achieve an effective analgesic dose after titration to the maximum dose or by 45 days were discontinued.

Treatment responders entered the double-blind maintenance period during which they were randomly assigned to receive the effective dose of MS-sNT determined during titration or dosage titration down to placebo. The outpatient site contacted the Interactive Web Response System to receive a randomization number and treatment assignment (MS-sNT at the effective dose or placebo). Randomization was stratified by target joint (hip or knee), the final total daily dose of the titration period (≤ 80 mg, > 80 mg), and site. Both drug and placebo were packaged so as to be blinded to the investigator, study clinic personnel, and patients.

The minimum dose of MS-sNT allowed at randomization was 20 mg twice daily. Patients randomized to the placebo group were tapered gradually in a blinded manner over 2 weeks using a double-dummy design. During the maintenance period, patients attended clinic visits at weeks 0, 1, 2, 4, 6, 8, 10, and 12 for efficacy, tolerability, and safety assessments. Patients who discontinued prematurely from the titration or maintenance period completed an early termination assessment, which included the same procedures specified for the week 12 clinic visit: vital signs, adverse events (AEs), and efficacy assessments. Patients who completed the maintenance period entered a 2-week tapering period, after which they were transitioned to the standard of care appropriate for their existing OA condition.

Efficacy Assessments

Patients recorded pain intensity daily in their electronic diary using 4 items from the BPI Short Form Questionnaire¹⁹: pain at its worst and least in the last 24 hours, pain on average in the last 24 hours, and the current level of pain, all assessed on a 0-to-10-point scale (0 = no pain; 10 = pain as bad as you can imagine). The primary efficacy outcome was the change in diary average-pain scores from randomization baseline (average of past 24-hour pain scores from the last 7 days before randomization) to completion of the maintenance period (for completers, the final 7 days of the 12-week study).

Prespecified secondary efficacy outcome measures were: in-clinic pain intensity; weekly diary worst-, least-, current-, and average-pain scores over the past 24 hours; diary average-pain scores averaged over the entire maintenance period; and patient-completed assessments on the following instruments: 1) Western Ontario and McMaster Universities (WOMAC)

Osteoarthritis Index, with 3 subscales (pain, stiffness, and physical function) and a composite index score. Each of the 24 items on the WOMAC Osteoarthritis Index has a score of 0 (none) to 4 (extreme); scores were then standardized on a 0-to-100-point scale²⁰; 2) Medical Outcomes Study (MOS) Sleep Scale, consisting of 12 items with 7 subscale scores (score range, 0–100 points); with the exception of sleep adequacy subscale, higher scores indicate greater impairment^{21,22}; 3) Beck Depression Inventory (BDI), a 21-item, multichoice questionnaire to evaluate degree of depression (each item has a scale of 0–3 points; 0 = minimal, 3 = severe; total score range 0–63).²³ The WOMAC Osteoarthritis Index and MOS Sleep Scale were evaluated at screening baseline, last visit of titration (same as first day of maintenance period), and during maintenance. The BDI was administered at screening baseline and at weeks 4, 8, and 12 of the maintenance period. The study protocol included an assessment of Patient Global Impression of Change (PGIC) by a 7-point scale from “very much improved” to “very much worse” since last visit. However, after consideration of the analyses, in which the first reported time was at randomization baseline with values reflecting change from multiple presentations (2, 4, 6, 8, 10, and 12 weeks of maintenance) rather than change from baseline, the data were considered uninterpretable and are not reported here.

A prespecified responder analysis was also performed on in-clinic, 24-hour average-pain intensity scores at the completion of the titration and maintenance periods. For patients who completed the titration period and qualified for randomization, the range of percent decreases for in-clinic, 24-hour average-pain intensity from 0% to 100% (in increments of 10%) between the screening baseline and randomization baseline was calculated. Patients who discontinued during the titration period or who failed to qualify for randomization (ie, patients who did not achieve an effective analgesic dose [defined as an average-pain intensity score of ≤ 4 on the BPI over the last 4 days before the clinic visit and a decline of ≥ 2 points from baseline]) after titration to the maximum dose or by 45 days were considered nonresponders. For patients who entered the maintenance period, the cumulative proportion of responders was based on the percent decrease in in-clinic, 24-hour average-pain intensity from screening baseline to study completion (12 weeks of maintenance). Patients who discontinued from the study during the maintenance period were considered nonresponders.

Use of rescue medication (1 tablet [500 mg] of sponsor-provided acetaminophen every 6 hours, if needed) was

allowed for ethical reasons. The average weekly use of rescue medication was calculated at each visit from pill counts summed over 7-day intervals and was used for descriptive purposes only.

Safety Assessments

Safety was assessed by the incidence of treatment-emergent adverse events (TEAEs) and by changes in vital signs, clinical laboratory parameters, and physical examination findings at clinic visits. Treatment-emergent adverse events were evaluated according to intensity and suspected relationship to study treatment by the investigator, and coded to the Medical Dictionary for Regulatory Activities. In addition, since exposure to naltrexone can precipitate opioid withdrawal in opioid-dependent individuals, the Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS) were used to assess opioid withdrawal during the maintenance period.^{24,25} Investigators used the COWS 11-item scale to assess a patient's level of opioid withdrawal, with total scores of 5 to 12 indicative of mild withdrawal; 13 to 24, moderate withdrawal; 25 to 36, moderately severe withdrawal; and > 36, severe withdrawal. The COWS can be administered serially to identify changes in the severity of the signs and symptoms of opiate withdrawal.²⁴ The COWS was administered at weeks 0, 1, and 2 of the maintenance period, as well as at the final visit of the maintenance period

or an early termination visit. Patients also rated intensity of withdrawal symptoms using the SOWS, which rates 16 withdrawal symptoms on a scale from 0 (not at all) to 4 (extremely).²⁵ Total SOWS scores of 6 to 16 were defined as mild withdrawal; 17 to 32, moderate withdrawal; 33 to 48, moderately severe; and > 48, severe withdrawal. The SOWS was completed daily during the first 2 weeks of maintenance period by electronic diary.

Statistical Analysis

The primary efficacy measure was the change in diary BPI average-pain score from randomization baseline to the last 7 days of the maintenance period. Randomization baseline was defined as the diary average-pain score over the last 7 days of the titration period. For patients who discontinued, pain scores were imputed based on treatment group and reason for discontinuation (Table 1).

The primary efficacy analysis (change from randomization baseline in average-pain scores) was conducted in the intent-to-treat population, defined as all patients who were randomized into the maintenance period and who received ≥ 1 dose of double-blind study medication. Comparisons between the MS-sNT and placebo groups for the primary efficacy measure were made by an analysis of covariance (ANCOVA) with treatment as a categorical factor and the randomization baseline score as covariate. Assuming an

Table 1. Imputation Rules to Account for Patients Who Discontinued From the Study

Reason for Discontinuation	Imputed Value	Effect on Analysis
Primary analysis		
AEs	Screening baseline score	Assigns no benefit to study drug for patients who discontinue due to AEs
Lack of efficacy, administrative reasons	Diary average-pain scores during last 7 days on study drug	Actual last pain scores are carried forward for these dropouts
If discontinued due to withdrawal (COWS at discontinuation > randomization baseline with at least a moderate score [≥ 13]) (patients on placebo)	Randomization baseline score	Assigns full efficacy benefit to patients on placebo who discontinue due to withdrawal
Discontinuation due to withdrawal while taking MS-sNT	Screening baseline score	Assigns no benefit to study drug for patients who discontinued due to withdrawal regardless of pain scores
Additional imputation methods for sensitivity analysis		
Alternative Method 1: All patients who discontinued	Randomization baseline score	Assigns full efficacy benefit to all dropouts
Alternative Method 2: All patients who discontinued due to AE or lack of efficacy	Screening baseline score	Assigns no benefit to study drug for these dropouts
All patients who discontinued for any other reason	Randomization baseline score	Assigns full efficacy benefit to these dropouts
Alternative Method 3: All patients who discontinued	Screening baseline score	Assigns no benefit to study drug

Abbreviations: AE, adverse event; COWS, Clinical Opiate Withdrawal Scale; MS-sNT, morphine sulfate with sequestered naltrexone.

effect size (mean difference between treatments divided by the pooled standard deviation [SD]) of 0.33 and type I error of 0.05 for a 2-tailed test, a sample size of 200 patients per treatment group was estimated to obtain 90% statistical power for the primary efficacy analysis. However, an interim recalculation of power, based on a published study with similar trial design that appeared after the start of the study,¹⁸ indicated that this would have provided > 99% power for the primary efficacy measure with this sample size, which raised ethical concerns about exposing additional patients to the protocol. Therefore, enrollment was discontinued after 344 patients had been randomized.

To account for patients who discontinued, pain scores were imputed based on treatment group and reason for discontinuation. The concern that patients randomized to placebo could experience withdrawal symptoms manifesting as a return of baseline pain, thereby adversely affecting efficacy scores prior to study discontinuation, was addressed with these imputation rules. Screening baseline value was used for patients who discontinued due to AEs and for patients taking MS-sNT capsules who discontinued due to withdrawal symptoms; randomization baseline was used for patients on placebo who discontinued due to withdrawal symptoms; and last-observation-carried-forward methodology was used in all other instances (Table 1). Three additional sensitivity analyses using alternative methods for data imputation (Table 1) were also conducted to consider the possible impact of study discontinuation on the primary efficacy variable. These were designed to be supportive efficacy analyses of the primary endpoint.

Continuous secondary efficacy measures were summarized at each visit by treatment using descriptive statistics and analyzed using a mixed-effects repeated-measures model, with fixed-effects terms including days on study, treatment, and their interaction; randomization baseline value was the covariate. No adjustment for multiple analyses was made because there is only 1 primary efficacy endpoint analysis. Secondary analyses were reported as changes from baseline to parallel the primary outcome.

The cumulative proportion of patients who were responders based on in-clinic, 24-hour average-pain intensity scores was summarized in 10-point increments.²⁶ Differences between the MS-sNT and placebo groups in the proportion of patients who reported $\geq 20\%$, 30% , 40% , or 50% improvement in the maintenance period were assessed using the Fisher exact test.

Safety assessments, including COWS and SOWS, were summarized by treatment using descriptive statistics for all

patients who received double-blind study medication during the maintenance period. The frequency of TEAEs between treatment groups was compared using the Fisher exact test.

In addition, a post hoc determination of the proportion of patients who discontinued during the maintenance period for any reason, for AEs, or for lack of efficacy was performed and displayed graphically over time. The log-rank test was used to test treatment differences in time to discontinuation for each of the above reasons.

Results

Patient Disposition and Baseline Characteristics

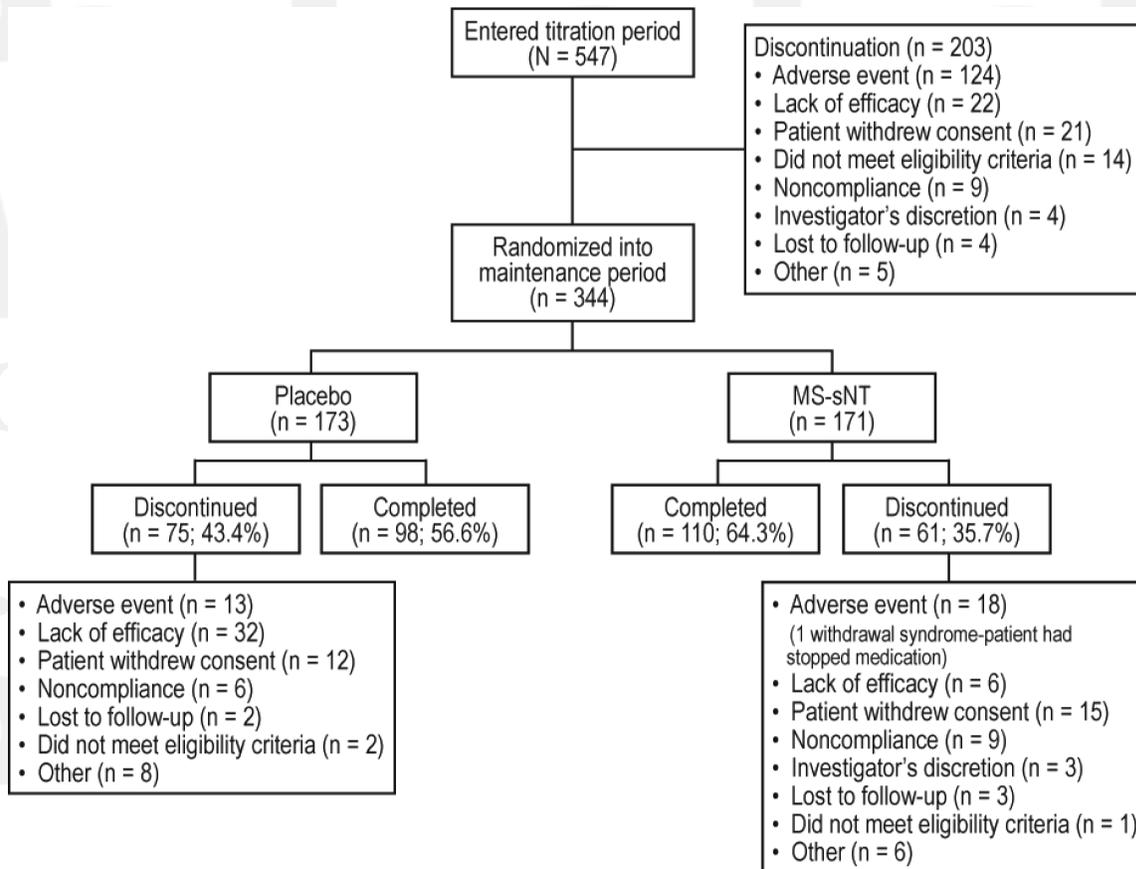
The first patient was enrolled January 10, 2007, and the last patient was completed November 8, 2007. A total of 547 patients entered the titration period and received ≥ 1 dose of MS-sNT. When enrollment was concluded, 344 patients (62.9%) had successfully completed the titration period and proceeded to randomization. During the titration period, the most common reasons for discontinuation were AEs (124/547 patients; 22.7%) and lack of efficacy (22/547; 4%) (Figure 2). At randomization, 173 patients were switched to placebo and 171 patients continued their titrated dose of MS-sNT (Figure 2). During the maintenance period, AEs were also the most common reason for discontinuation in the MS-sNT group (18/171 patients; 10.5%), although the incidence was much lower than in the titration period. In comparison, lack of efficacy (32/173 patients; 18.5%) was the most common reason for discontinuation in the placebo group (Figure 2).

Demographic characteristics of patients in the titration period and those subsequently randomized to treatment in the maintenance period were comparable (Table 2). Three-quarters of the enrolled patients had not used opioid analgesics within 30 days prior to entering this study; however, nearly all patients had previously used other medications for analgesia, most commonly ibuprofen (32.4%), acetaminophen (23.8%), and naproxen sodium (11.9%). For patients who were randomized, no significant differences in demographic variables or baseline opioid use, pain location, or pain scores were evident between patients in the MS-sNT and placebo groups (Table 2).

Effect of MS-sNT During Titration Period

For randomized patients who reported scores at both screening and randomization baseline, the mean decrease in diary worst-, least-, average-, and current-pain scores is shown in Table 3. Scores for composite index and the 3 subscales of the WOMAC Osteoarthritis Index decreased from titration baseline to final titration visit (Table 3). The MOS Sleep

Figure 2. Patient disposition.



Abbreviations: MS-sNT, morphine sulfate with sequestered naltrexone.

Table 2. Demographic and Clinical Characteristics

Characteristic	Titration Period		Maintenance Period		P Value ^a
	MS-sNT (N = 547)	Placebo (n = 173)	MS-sNT (n = 171)	Placebo (n = 173)	
Sex, n (%)					0.191
Men	215 (39.3)	78 (45.1)	65 (38.0)		
Women	332 (60.7)	95 (54.9)	106 (62.0)		
Mean age, y (SD)	55.7 (12.3)	54.7 (12.9)	54.2 (11.6)		0.703
Race, n (%)					0.336
White	413 (75.5)	121 (69.9)	128 (74.9)		
Black	89 (16.3)	30 (17.3)	29 (17.0)		
Asian	26 (4.8)	15 (8.7)	9 (5.3)		
American Indian or Alaska Native	8 (1.5)	4 (2.3)	2 (1.2)		
Other	11 (2.0)	3 (1.7)	3 (1.8)		
Hispanic ethnicity, n (%)	100 (18.3)	40 (23.1)	36 (21.1)		0.697
Mean BMI, kg/m ² (SD) ^b	32.1 (6.4)	31.8 (6.3)	32.5 (6.9)		0.310
Primary area of OA, n (%)					0.789
Right hip	70 (12.8)	24 (13.9)	20 (11.7)		
Left hip	57 (10.4)	16 (9.2)	17 (9.9)		
Right knee	244 (44.6)	83 (48.0)	77 (45.0)		
Left knee	176 (32.2)	50 (28.9)	57 (33.3)		
Prior opioid use, n (%)		n = 171	n = 167		1.000
Opioid naïve	407 (75.4)	129 (75.4)	125 (74.9)		
Opioid experienced	133 (24.6)	42 (24.6)	42 (25.1)		

^aP value for maintenance period MS-sNT vs placebo from the Fisher exact test for categorical variables and ANOVA for continuous variables. Race was categorized as white vs nonwhite for testing.

^bTitration period, n = 530; maintenance period, n = 167 for both placebo and MS-sNT.

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; SD, standard deviation; MS-sNT, morphine sulfate with sequestered naltrexone; OA, osteoarthritis.

Scale scores at titration baseline and at the final titration visit did not indicate severe sleep problems in these patients at either time (Table 3). The average weekly use of rescue medication (acetaminophen, 500 mg) during the titration period (n = 482) was 12.5 tablets.

There were 317 of 547 (58%) patients who reported scores demonstrating $\geq 30\%$ improvement in in-clinic pain scores; 293 (53.6%) with $\geq 40\%$ improvement; and 247 (45.2%) with $\geq 50\%$ improvement during the titration period.

Primary Efficacy Analysis

Mean average-pain scores at randomization baseline and study completion are shown in Table 4. The mean change from randomization baseline was statistically significant with MS-sNT compared with placebo (-0.2 ± 1.9 vs $+0.3 \pm 2.1$; $P = 0.045$). Patients taking MS-sNT experienced an additional small decline in pain scores, while those taking placebo experienced a small increase compared with randomization baseline.

Treatment group differences from the 3 prespecified alternative methods of imputation, conducted as supportive efficacy analyses to explore the potential impact of opioid withdrawal on the primary outcome measure,

were directionally consistent with the primary analysis (Table 4).

Secondary Efficacy Outcomes During the Maintenance Period

Reduction in average pain from screening baseline was maintained during the maintenance period to a greater degree in patients taking MS-sNT than in those taking placebo (Figure 3). Changes from randomization baseline for each of the 4 pain intensity items statistically favored the MS-sNT group over the placebo group at all visits during the maintenance period ($P < 0.05$, except for the week 1 average-pain score; $P = 0.067$). Patients taking placebo also had a greater increase from randomization baseline in diary average-pain score (0.7 ± 1.5) than those taking MS-sNT (0.1 ± 1.4) when scores were averaged over the entire maintenance period.

Responder analysis at the time of completion of the maintenance period is illustrated in Figure 4. More patients on MS-sNT than on placebo experienced $\geq 30\%$ improvement from the titration baseline visit in-clinic assessment of pain scores (124/171 [72.5%] vs 100/173 [57.8%]; $P = 0.005$). The numerically higher rates for those

Table 3. Effects of MS-sNT During Titration: Mean Change From Screening Baseline Score to Score at Final Titration Visit

Outcome Measure Mean (SD)	n ^a	MS-sNT (N = 547)		
		Screening Baseline	Randomization Baseline (Titration Final)	Change
Weekly diary pain score (score range, 0–10)	277 ^b			
Worst pain in last 24 h		6.8 (1.7)	3.5 (1.7)	–3.3 (2.1)
Least pain in last 24 h		5.3 (2.2)	2.0 (1.3)	–3.3 (2.1)
Average pain in last 24 h		6.1 (1.9)	2.6 (1.3)	–3.4 (2.0)
Current pain		5.9 (2.1)	2.5 (1.6)	–3.5 (2.3)
WOMAC Osteoarthritis Index subscales (score range, normalized, 0–100)	313			
Composite		59.4 (13.0)	30.5 (15.0)	–28.9 (16.2)
Pain		59.4 (13.8)	29.3 (15.4)	–30.1 (17.3)
Stiffness		61.3 (16.6)	34.5 (18.5)	–26.8 (21.7)
Physical function		58.3 (14.9)	29.7 (16.0)	–28.6 (17.7)
MOS Sleep Scale (score range, 0–100)	313			
Sleep disturbance		34.1 (23.7)	22.2 (19.8)	–11.9 (20.9)
Snoring		32.1 (31.4)	27.8 (29.2)	–4.3 (25.3)
Awaken short of breath		13.0 (22.8)	9.5 (19.3)	–3.5 (24.8)
Quantity of sleep		6.6 (1.6)	6.8 (1.6)	0.3 (1.9)
Optimal sleep		0.5 (0.5)	0.5 (0.5)	0.1 (0.5)
Sleep adequacy		58.4 (26.0)	65.5 (25.4)	7.1 (25.8)
Sleep somnolence		24.9 (19.8)	28.5 (23.6)	3.6 (20.5)

^aIncludes only patients with scores reported at both screening baseline and randomization baseline visits.

^bn = 277 except for average pain (n = 278) and current pain (n = 276).

Abbreviations: MOS, Medical Outcomes Study; MS-sNT, morphine sulfate with sequestered naltrexone; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities.

Table 4. Primary Efficacy Outcome: Diary Average-Pain Scores^a and Mean Change From Baseline

Pain Assessment Mean (SD)	Placebo (n = 173)	MS-sNT (n = 170)	P Value
Randomization-baseline pain (score range, 0–10)	3.2 (1.1)	3.3 (1.3)	
Primary imputation method			
Final visit	3.5 (2.1)	3.1 (2.0)	
Change from baseline	0.3 (2.1)	–0.2 (1.9)	0.045
Protocol-specified sensitivity analyses			
Method 1^b			
Final visit	3.1 (1.6)	2.9 (1.6)	
Change from baseline	–0.2 (1.3)	–0.4 (1.3)	0.122
Method 2^c			
Final visit	3.9 (2.4)	3.3 (2.1)	
Change from baseline	0.7 (2.2)	0 (1.9)	0.005
Method 3^d			
Final visit	4.3 (2.5)	3.9 (2.5)	
Change from baseline	1.1 (2.4)	0.6 (2.3)	0.049

^aDiary average-pain scores: 7-day mean of daily average-pain scores.

^bRandomization baseline score for those who discontinued.

^cScreening baseline score if due to AEs/lack of efficacy; randomization baseline score if due to other.

^dScreening baseline score.

Abbreviations: AE, adverse event; SD, standard deviation; MS-sNT, morphine sulfate with sequestered naltrexone.

with $\geq 20\%$ (133/171 [77.8%] vs 118/173 [68.2%]), 40% (110/171 [64.3%] vs 96/173 [55.5%]) and 50% (97/171 [56.7%] vs 82/173 [47.4%]) improvement were not statistically significant.

Significant differences from randomization baseline favoring MS-sNT versus placebo ($P < 0.05$) were observed at most visits during the maintenance period for the composite index and physical function subscale scores of WOMAC. Changes from randomization baseline in WOMAC composite index and pain subscale scores significantly favored MS-sNT over placebo ($P = 0.031$ and $P = 0.023$, respectively) at week 12 of maintenance (Table 5). At week 12 of maintenance, changes from randomization baseline in stiffness and physical function subscale scores were not significantly different from the placebo group (Table 5).

Mean changes from baseline to week 12 of the maintenance period were not significantly different between treatment groups for MOS Sleep Scale (randomization baseline to week 12) or BDI scores (titration baseline to week 12). The BDI scores at titration baseline and all assessments during the maintenance period were < 6 , indicating only mild depression throughout the study (Table 5).

During the maintenance period, 127 patients (74.3%) in the MS-sNT group and 125 patients (72.3%) in the placebo group used rescue medication (acetaminophen) for breakthrough pain. In both groups, the number of tablets per week was low (mean \pm SD, 5.3 ± 6.1 vs 6.2 ± 5.7 tablets; median, 2.4 vs 4.4 tablets).

Figure 5 demonstrates a post hoc analysis of the proportion of patients who discontinued during the maintenance

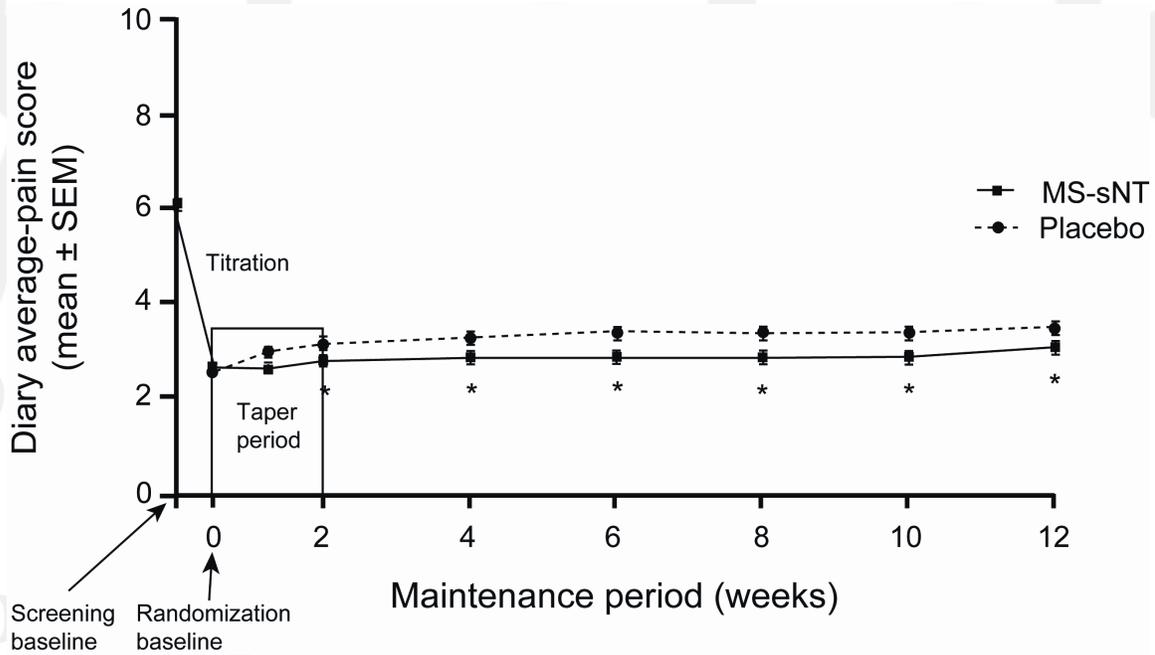
period for any reason over time overall (A), as well as those who discontinued due to AEs (B), or lack of efficacy (C). Time to discontinuation due to any reason or AEs did not differ between the MS-sNT and placebo groups, but the time to discontinuation for lack of efficacy was shorter for placebo versus MS-sNT ($P < 0.001$, log-rank test). This difference was consistent with the higher proportion of patients who discontinued due to lack of efficacy during the maintenance period in the placebo group (18.5%) versus those taking MS-sNT (3.5%; $P < 0.0001$, Fisher exact test).

Safety and Tolerability

The titration period with MS-sNT lasted for 19.6 ± 13.8 days (mean \pm SD). Patients started MS-sNT at an average daily dose of 25.3 ± 9.7 mg (range, 20–120 mg) and ended at an average daily dose of 43.5 ± 31.7 mg (range, 20–160 mg). After entering the maintenance period, exposure to double-blind treatment was numerically longer in the MS-sNT group than in the placebo group (mean, 74.2 vs 66.4 days).

The majority of patients (347/547, 63.4%) experienced ≥ 1 AE during the titration period, most commonly constipation, nausea, and somnolence (Table 6). Three patients (0.5%) had serious AEs (SAEs) during the titration period; of these, 1 event (hypotension) was considered by the investigator to be possibly or probably related to the study drug. Of the other 2 events, atrial fibrillation was considered unrelated to study treatment and concussion was considered unlikely to be treatment related. During the titration period, 38 patients (6.9%) had AEs that were judged to be severe, most frequently constipation (1.8%) and somnolence

Figure 3. Mean diary average-pain scores from baseline through the maintenance period (imputation method 1).



* $P < 0.01$, MS-sNT vs placebo, change from randomization baseline.

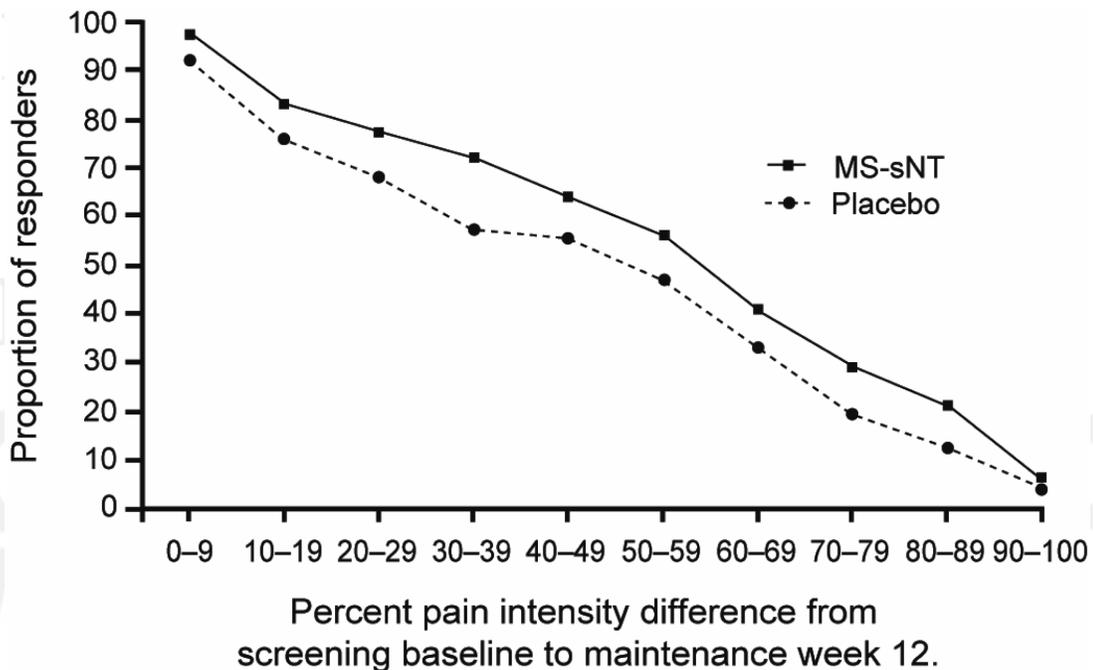
Abbreviations: MS-sNT, morphine sulfate with sequestered naltrexone; SEM standard error of mean.

(1.5%). A total of 130 patients (23.8%) discontinued from the study during the titration period due to AEs, most commonly nausea (4.2%), constipation (3.7%), somnolence (2.7%), and vomiting (2.7%).

During the maintenance period, the incidence of AEs was similar between the MS-sNT and placebo groups (53.2%

and 48.6%, respectively, $P = 0.391$), with the most common events being diarrhea and nausea (Table 6). Compared with the titration period, the most common AEs, except for diarrhea, occurred at lower rates during the maintenance period. Six patients taking MS-sNT experienced SAEs (pancreatitis and renal cell carcinoma, malignant lung

Figure 4. Proportion of responders from screening baseline through completion of the maintenance period.



Abbreviations: MS-sNT, morphine sulfate with sequestered naltrexone.

Table 5. Summary of Prespecified Secondary Efficacy Outcomes: Mean Change From Baseline^a to Maintenance Week 12

Scores Mean (SD) ^b	Placebo (n = 173)			MS-sNT (n = 171)			P Value ^{c,d} vs Placebo ^d
	Baseline	Week 12	Change	Baseline	Week 12	Change	
Diary pain scores (score range, 0–10)							
Worst pain	3.5 (1.6)	4.4 (2.3)	0.9 (2.0)	3.6 (1.6)	3.9 (2.1)	0.3 (2.0)	0.003
Least pain	1.9 (1.3)	2.7 (2.0)	0.8 (1.8)	2.1 (1.4)	2.4 (1.9)	0.3 (1.8)	0.036
Average pain	2.6 (1.2)	3.5 (2.1)	0.9 (1.9)	2.8 (1.3)	3.1 (2.0)	0.3 (1.9)	0.003
Current pain	2.4 (1.5)	3.3 (2.2)	0.9 (2.1)	2.6 (1.6)	3.0 (2.1)	0.4 (2.0)	0.026
In-clinic pain (score range, 0–10)	2.8 (1.5)	4.3 (2.5)	1.5 (2.3)	2.8 (1.4)	3.5 (2.2)	0.7 (2.3)	0.002
Diary average-pain score averaged over the entire maintenance period	2.6 (1.2)	3.3 (1.7)	0.7 (1.5)	2.7 (1.3)	2.9 (1.5)	0.1 (1.4)	0.001
WOMAC subscales (score range, normalized, 0–100)							
Composite index	30.4 (15.4)	36.2 (18.3)	5.8 (16.8)	31.2 (15.3)	32.8 (20.0)	1.6 (18.0)	0.031
Pain	29.4 (15.6)	35.1 (18.3)	5.7 (17.1)	29.7 (15.5)	31.1 (19.9)	1.4 (18.9)	0.023
Stiffness	34.5 (18.9)	39.8 (21.0)	5.3 (22.0)	35.1 (18.4)	36.2 (22.5)	1.1 (21.1)	0.063
Physical function	29.3 (16.4)	35.5 (19.8)	6.2 (17.8)	30.7 (16.3)	32.9 (21.1)	2.3 (18.4)	0.064
MOS Sleep Scale (score range, 0–100)							
Sleep disturbance	22.7 (19.1)	28.3 (22.2)	5.6 (17.7)	23.0 (21.1)	25.3 (22.0)	2.4 (15.3)	0.068
Snoring	30.1 (29.9)	32.8 (31.8)	2.8 (22.6)	26.7 (28.8)	29.2 (31.8)	2.5 (20.6)	0.687
Awaken with shortness of breath/headache	12.3 (23.1)	11.8 (23.0)	–0.5 (25.3)	8.5 (16.4)	10.7 (21.0)	2.2 (17.9)	0.699
Sleep quantity	6.8 (1.5)	6.6 (1.4)	–0.2 (1.3)	6.8 (1.7)	6.8 (1.8)	0.0 (1.9)	0.079
Optimal sleep	0.5 (0.5)	0.4 (0.5)	–0.1 (0.5)	0.5 (0.5)	0.5 (0.5)	0.0 (0.5)	0.325
Sleep adequacy	62.9 (25.7)	57.5 (27.4)	–5.4 (24.5)	65.8 (25.8)	63.6 (26.9)	–2.2 (21.4)	0.068
Somnolence	29.4 (24.3)	26.9 (23.2)	–2.5 (17.9)	27.8 (22.5)	27.0 (24.0)	–0.7 (13.8)	0.407
BDI (score range, 0–63)	4.7 (4.3)	3.7 (4.5)	–0.9 (3.9)	5.5 (5.5)	4.0 (4.8)	–1.4 (4.5)	0.675

^aFor pain, in-clinic pain, WOMAC Osteoarthritis Index, and MOS Sleep Scale, baseline visit is randomization baseline visit; for BDI baseline is screening baseline visit day 0.

^bImputation rules used for missing secondary endpoints were the same as those used for primary endpoints.

^cChange from baseline.

^dP value is based on based on mixed-effects, repeated-measures model.

Abbreviations: BDI, Beck Depression Inventory; MOS, Medical Outcomes Study; MS-sNT, morphine sulfate with sequestered naltrexone; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities.

neoplasm, cholelithiasis, intestinal blockage, viral gastroenteritis, and basal cell carcinoma); 3 patients on placebo experienced SAEs (chest pain, abdominal pain, and transient ischemic attack). Only 1 SAE (abdominal pain in a patient taking placebo) was considered by the investigator to be treatment related. Twenty patients, including 11 patients (6.4%) in the placebo group and 9 patients (5.3%) in the MS-sNT group, had severe AEs. During the maintenance period, 18 patients (10.5%) in the MS-sNT group and 13 patients (7.5%) in the placebo group indicated AEs as the reason for discontinuation; however, 11 patients (6.4%) in the placebo group and 14 patients (8.2%) in the MS-sNT group had premature discontinuation of study drug indicated as the action taken on the AE case report form. The most common AEs leading to discontinuation were nausea (3 MS-sNT [1.8%], 2 placebo [1.2%]) and vomiting (1 MS-sNT [0.6%], 2 placebo [1.2%]). Two patients each (1.2%)

discontinued due to constipation and somnolence in the MS-sNT group.

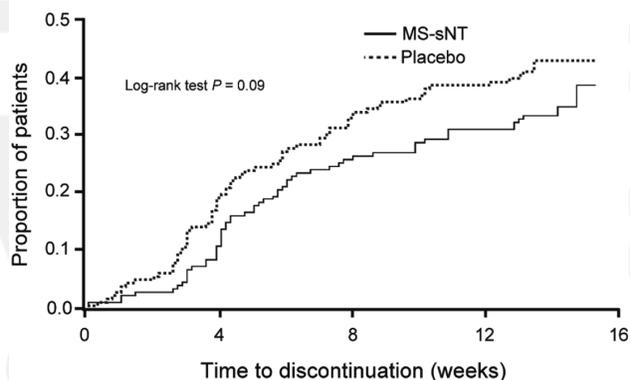
Overall, the majority of AEs in the titration and maintenance periods were judged by the investigators to be mild to moderate in intensity. Analysis of laboratory and vital signs data revealed no clinically relevant results with MS-sNT compared with placebo.

Withdrawal Symptoms

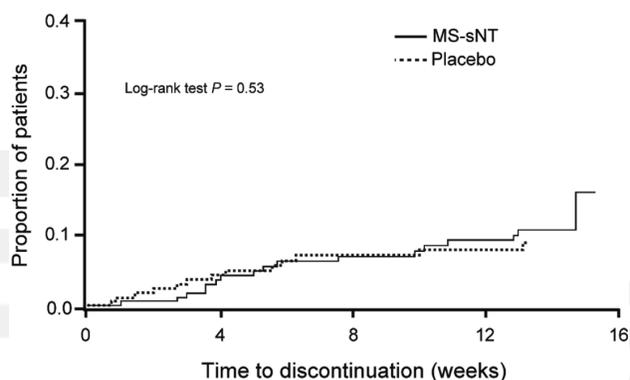
Symptoms and signs of opioid withdrawal were evaluated using COWS and SOWS and analyzed according to the dose of MS-sNT (≤ 80 and > 80 mg/day) at randomization. In both subsets, the mean COWS score at the randomization baseline was low (≤ 0.7). During the study, no patient experienced opioid withdrawal while taking MS-sNT as directed. During titration, an opioid-naïve patient taking a daily dose of MS-sNT 160 mg had a single COWS assessment with a score of 16 at an early termi-

Figure 5. Proportion of patients who discontinued during the maintenance period due to (A) any reason, (B) AEs, or (C) lack of efficacy.

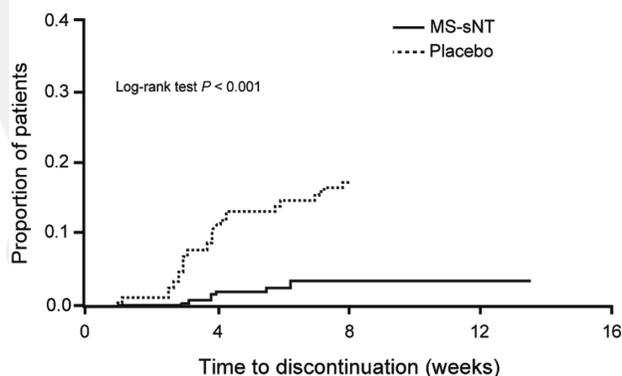
(A) Any Reason



(B) AEs



(C) Lack of efficacy



Duration of trial for some patients was extended beyond 12 weeks based on the actual time of the nominal 12-week visit.

Abbreviations: AE, adverse event; MS-sNT, morphine sulfate with sequestered naltrexone.

nation visit prior to randomization; the patient had been compliant until titration week 5, then took 5 capsules in 10 days between the week 5 visit and the early termination visit (Table 7). During the maintenance period, 2 patients had scores of 23 (moderate withdrawal) during taper to placebo: an opioid-experienced patient taking 120 mg/day who had a COWS score of 23 at week 2 of maintenance, continued in the study, then discontinued at week 6 of maintenance due to lack of efficacy (COWS score at that time was 1); and an opioid-naïve patient taking 60 mg/day who had a COWS score of 23 at week 1 of maintenance

and discontinued due to lack of efficacy. The latter patient was handled as a dropout due to opioid withdrawal during the imputation process, per prespecified rules. An additional opioid-naïve patient tapering from 160 mg/day to placebo had a COWS score of 13 (moderate) during week 1 of taper, which was reduced to 8 (mild) at week 2. This patient completed the study. One opioid-naïve patient taking 120 mg/day of MS-sNT abruptly stopped treatment on day 49 of maintenance, experienced drug withdrawal symptoms on day 52, and had a score of 28 (moderately severe withdrawal) on day 54. The event resolved on the same day after the patient was discontinued from the study and treated with lorazepam. As was prespecified for the efficacy analysis, pain scores were imputed using the screening baseline value (Table 7).

SOWS data were collected during the first 2 weeks of the maintenance period. At the randomization baseline, the mean SOWS scores in the placebo and MS-sNT groups averaged 4.7 and 4.4, respectively, in the subset with a randomization dose of ≤ 80 mg, and 6.7 and 7.9, respectively, in the subset with a randomization dose of > 80 mg. Over days 4 to 6, the mean worst score on SOWS increased to 9.3 and 8.8 in the placebo and MS-sNT groups, respectively, in the subset with a randomization dose of ≤ 80 mg, and to 11.9 in both groups in the subset with a randomization dose of > 80 mg. Overall, the SOWS scores did not differ appreciably between the MS-sNT and placebo groups.

Three additional patients reported individual symptoms consistent with withdrawal as an AE during the study (Table 7). One patient reported withdrawal symptoms during the week 4 titration visit. The patient had taken rescue medication instead of study drug during the previous week, and was discontinued from the study due to noncompliance. The COWS score was 7 for this patient at the study termination visit 1 week later. Two patients reported symptoms noted as drug withdrawal symptoms beginning on the second day of tapering after completion of the 12-week maintenance period, which therefore did not influence the analyses of any outcome measures. One of these patients had been taking MS-sNT 20 mg twice daily and experienced diarrhea, vomiting, and restless legs syndrome; all classified as mild and unrelated to study drug. She was treated with 10 mg oral morphine sulfate as needed for 3 days. The COWS score had been 0 the prior day. The second patient had been taking placebo over the 12-week maintenance period and reported withdrawal symptoms of moderate intensity identified as

Table 6. TEAEs During the Titration and Maintenance Periods^a

AE, n (%)	Titration	Maintenance	
	MS-sNT (N = 547)	Placebo (n = 173)	MS-sNT (n = 171)
Patients with TEAEs	347 (63.4)	84 (48.6)	91 (53.2)
Patients with drug-related TEAEs ^b	313 (57.2)	45 (26.0)	56 (32.7)
Patients with SAEs	3 (0.5)	3 (1.7)	6 (3.5)
Patients with drug-related SAEs ^b	1 (0.2)	1 (0.6)	0
TEAEs leading to discontinuation	130 (23.8)	11 (6.4)	14 (8.2)
Most common TEAEs			
Constipation	167 (30.5)	7 (4.0)	12 (7.0)
Nausea	115 (21.0)	13 (7.5)	20 (11.7)
Somnolence	78 (14.3)	5 (2.9)	2 (1.2)
Vomiting	50 (9.1)	4 (2.3)	12 (7.0)
Dizziness	47 (8.6)	3 (1.7)	3 (1.8)
Pruritus	38 (6.9)	1 (0.6)	1 (0.6)
Headache	33 (6.0)	6 (3.5)	12 (7.0)
Dry mouth	31 (5.7)	2 (1.2)	3 (1.8)
Diarrhea	15 (2.7)	21 (12.1)	21 (12.3)
Rhinorrhea	2 (0.4)	12 (6.9)	4 (2.3)

^aAll TEAEs occurring in $\geq 5\%$ of patients during the titration period or in $\geq 5\%$ of patients in either group of the maintenance period.

^bDrug-related events were judged to be possibly, probably, or definitely related to study treatment by the investigator.

Abbreviations: AE, adverse event; MS-sNT, morphine sulfate with sequestered naltrexone; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Table 7. All Patients With Potential Opioid Withdrawal

Patient Description	Total MS-sNT Daily Dose (mg)	Treatment Period at Occurrence	COWS Score ^a	Outcome
Withdrawal assessment based on COWS score^a				
Opioid-naïve man, aged 58 years; noncompliant with dose prior to termination	160	Titration period (Early termination visit)	16	Discontinued medication after day 37 of titration; AE of severe worsening of anxiety
Opioid-naïve woman, aged 56 years	60 tapering to placebo	Maintenance period (Week 1 taper to placebo)	23	Premature discontinuation on maintenance day 7; lack of efficacy
Opioid-naïve man, aged 42 years	160 tapering to placebo	Maintenance period (Week 1 taper to placebo)	13	Completed study (week 2 taper to placebo, COWS = 8; week 12, COWS = 1)
Opioid-experienced man, aged 45 years	120 tapering to placebo	Maintenance period (Week 2 taper to placebo)	23	Premature discontinuation on maintenance day 42; lack of efficacy (COWS = 1 on day of discontinuation)
Opioid-naïve woman, aged 51 years; abruptly stopped taking dose on day 49 of maintenance	120	Maintenance period (Early termination visit)	28	Discontinued; experienced withdrawal symptoms reported as AE on maintenance day 52
Withdrawal reported as an AE				
Opioid-experienced man, aged 69 years; reported withdrawal symptoms and drug withdrawal syndrome	80	Titration period (Early termination visit), 1 week after study withdrawal	7 ^b	Discontinued due to noncompliance (failed to take study drug)
Opioid-naïve woman, aged 55 years; reported mild diarrhea, vomiting, nighttime restless legs syndrome, and withdrawal symptoms	40	Day 2 of tapering at completion of maintenance week 12	0 ^c	Treated with 10 mg morphine sulfate as needed; vomiting resolved, but diarrhea and restless legs syndrome were ongoing
Opioid-naïve woman, aged 49 years; reported moderate-intensity drug withdrawal syndrome	Placebo over the maintenance	Day 2 of tapering at completion of maintenance week 12	0 ^c	Symptoms resolved

^aCOWS score 5–12 = mild withdrawal; 13–24 = moderate withdrawal; 25–36 = moderately severe withdrawal; > 36 = severe withdrawal.

^bWithdrawal as an AE lasted 6 days and was first reported 7 days prior to the last COWS score.

^cWithdrawal as an AE was reported 1 day after the last COWS score was taken.

Abbreviations: AE, adverse event; COWS, Clinical Opiate Withdrawal Scale; MS-sNT, morphine sulfate with sequestered naltrexone.

definitely related to study drug. The patient's COWS score had been 0 throughout the study. The symptoms resolved the following day.

Discussion

This study demonstrated that MS-sNT is significantly more efficacious than placebo in maintaining relief of chronic, moderate-to-severe pain associated with OA of the hip and knee in patients who had not been able to consistently control their pain with previous medications, including NSAIDs, COX-2 inhibitors, tramadol, and low-dose opioids.

In this study, patients were first titrated to an effective dose of MS-sNT and then randomized to continue MS-sNT or switch to placebo. The open-label titration period allowed for slow dose increases over a prolonged period (up to 45 days). Using this protocol, the treatment was effective in 62.9% of patients (344/547), based on prespecified efficacy criteria and tolerability. The relatively high rate of responders during titration was similar to that in other trials of opioids in which there was a gradual process to stabilize patients on the optimal dose.^{18,27} The diary average-pain score in the last 24 hours was reduced from 6.1 at the beginning of the titration to 2.6 at randomization. Similar reductions were seen in the worst, least, and current pain scores, and decreases in WOMAC Osteoarthritis Index subscale and composite scores were observed. It is important to note, however, that these results are reported for only those patients who satisfactorily completed titration (ie, proceeded to randomization), and do not represent the mean score for the entire group entering titration.

During the titration period, the mean decrease from titration baseline in the diary worst, least, average, and current pain scores was ≥ 3.3 , a difference generally accepted as clinically meaningful.²⁸ Because of the randomized withdrawal design, the lowest mean pain scores in both treatment groups were expected at the randomization baseline; pain scores were expected to increase over time during the maintenance period in the placebo group. In the primary efficacy analysis, average pain scores (over the last 24 hours, averaged over the last 7 days of treatment) declined by 0.2 (6.1% decrease) from the randomization baseline to the final week of the maintenance period in the MS-sNT group, whereas it increased by a mean of 0.3 (9.4% increase) in the placebo group ($P = 0.045$). This difference between treatments indicated that the ability to maintain established pain relief with MS-sNT is superior to that of placebo.

Prespecified alternative imputation methods, used to account for patients who discontinued during the study, supported the efficacy findings of the primary analysis. Methods 2 and 3, which assigned poor efficacy responses for discontinuations due to lack of efficacy (screening baseline imputation) provided more appropriate estimates than Method 1, which assigned good efficacy responses for discontinuations due to lack of efficacy.

The robustness of the primary efficacy finding was supported by the secondary outcomes, which favored MS-sNT over placebo for both pain and function. These outcomes included diary pain scores (worst, least, average, and current pain) and WOMAC composite index and pain subscale scores during the maintenance period, with trends observed for the physical function and stiffness subscales. Differences in rescue medication usage did not account for the difference between treatment group efficacy responses, since patients in the MS-sNT group used numerically fewer tablets of rescue medication per week than those in the placebo group.

The MOS Sleep Scale and BDI scores at baseline and subsequent evaluations indicated that, overall, patients did not experience depression, nor did they have severe sleep problems during the study. Therefore, it is not surprising that differences between treatment groups were not observed during the maintenance period. Because patients were asked to report global improvement on the PGIC at each visit compared with the previous visit, the differences in PGIC between MS-sNT and placebo during the maintenance period were not interpretable. Ideally, studies should assess PGIC at study endpoint compared with study entry.

This study used an EERW design, which identified patients who appeared to benefit from and tolerate the active drug in an open-label setting and excluded those who did not tolerate the treatment acceptably or failed to respond to the drug.¹⁶ Using this trial design, study drug is titrated to an effective, tolerated dose individually tailored, rather than assigned a fixed dose that would not be optimal for all patients. The open-label portion of the EERW methodology may more accurately reflect clinical practice when compared with a parallel treatment design comparing a set dose of active therapy versus placebo.²⁹ In clinical practice, individualized adjustments to therapy are made to attain optimal pain control, side effects are managed appropriately before discontinuing therapy, and patients are aware that they are receiving active treatment and not placebo. In this study, 53.6% of the initial cohort of patients reported $\geq 40\%$ improvement with treatment, similar to response rates identified in other opioid trials.^{18,27}

Following the titration period of a study using EERW methodology, patients are randomized to their customized dose of study drug or placebo during the double-blind maintenance period.^{16,18,29} The randomized withdrawal period is used to determine whether the improvement in the titration period was related to study drug, rather than to nonspecific factors. In an analgesic trial, patients would detect return of pain after removal of an effective analgesic rather than onset of pain relief after initiation of analgesic treatment.¹⁸ In the current trial, statistically significant separation in change from baseline was seen between patients who continued on MS-sNT and those who tapered to placebo. Patients taking placebo had a small increase in average-pain score, while those taking MS-sNT had a small reduction. This is particularly noteworthy because more patients on placebo discontinued due to lack of efficacy than those on MS-sNT (18.5% vs 3.5%; $P < 0.0001$).

The results of this study were similar to those of 2 studies evaluating the efficacy and safety of another opioid, oxymorphone extended release, using an EERW method in patients with chronic low back pain. In these studies, patients randomized to both active and placebo treatment groups experienced increases in pain score, but with a greater degree of separation between active treatment and placebo than seen in the current trial.^{18,27} It is possible that the careful withdrawal of opioid during the tapering period in the current trial may have lessened the impact of the switch to placebo and suggests an improved methodology for tapering patients during future trials of opioids. Alternatively, the effect size of therapy in patients with OA may be smaller than those seen in back pain in EERW studies of opioids.

The study design, whereby patients who failed to attain adequate treatment response during the titration period did not continue, was designed to minimize exposure of patients to ineffective treatment (placebo or study drug) during randomization and the maintenance period. In addition, the EERW methodology lowers the possibility that patients may become unblinded due to recognizable AEs because most occur during the titration period before randomization, as seen in this study in which AEs after randomization were similar in the MS-sNT and placebo groups. Just as in clinical practice, the EERW design maximizes the potential benefit for the individual patient. Because a large minority of patients will discontinue during the enrichment period, it is important that the initial sample size be large enough to account for these patients.¹⁶

The overall safety and tolerability of MS-sNT during the titration and maintenance periods were consistent with other opioid products, including a marketed polymer-coated, extended-release morphine sulfate capsule formulation (KADIAN[®]), which contains similarly designed morphine pellets but with an inert core.^{30,31} The most frequently reported AEs during titration were constipation, nausea, somnolence, and vomiting, while the most common during the maintenance period were diarrhea, nausea, and constipation. In both periods of the study, the majority of AEs were judged to be mild to moderate in intensity by the investigator. Except for diarrhea, the frequency of the most common AEs was lower during the maintenance period than during the titration period. This profile might have reflected the discontinuation of a substantial proportion of patients during the titration period due to AEs and/or the development of tolerance to the AEs of morphine over time.

In this trial, evaluations were performed to determine if patients experienced opioid withdrawal, either when they were switched to placebo or due to the presence of naltrexone within the MS-sNT formulation. Withdrawal was assessed through 2 instruments, COWS and SOWS, as well as by capturing AEs that could be reported by investigators as opioid withdrawal. No patient taking MS-sNT as directed experienced withdrawal symptoms, suggesting that the presence of naltrexone within the MS-sNT formulation did not lead to withdrawal. The report of withdrawal symptoms during the post-maintenance period by 1 patient who had been taking placebo during the previous 12 weeks suggested that opioid withdrawal symptoms can be a result of a nocebo effect, such that anticipation of AEs can lead to reports of their occurrence.³² To our knowledge, the frequency with which this happens in clinical practice in patients who are discontinuing opioids is not known.

Scores from the SOWS, assessed daily during the first 2 weeks of the maintenance period, indicated little evidence of withdrawal. Although COWS and SOWS are considered to be validated instruments for the measurement of opioid withdrawal,^{24,25} and were considered to be the most appropriate instruments available for this study, no instruments have been validated for the measurement of opioid withdrawal in the setting of opioid therapy for chronic pain.

The current study was designed to assess the efficacy and safety of MS-sNT compared with placebo in maintaining pain control in patients with chronic, moderate-to-severe pain due to OA of the hip or knee. In a separate study in patients with chronic OA pain, MS-sNT demonstrated comparable efficacy with extended-release morphine sulfate

(KADIAN[®]),¹³ suggesting that the presence of naltrexone within MS-sNT did not affect response. The current study was not designed to evaluate the potential for misuse or abuse of the MS-sNT formulation. A study designed to assess the subjective effects among recreational opioid abusers when MS-sNT was tampered with and taken orally indicated reduced drug liking and euphoria compared with those from morphine taken in solution.¹² A second study, in which morphine and naltrexone were administered intravenously in the ratio present in MS-sNT, indicated a similar reduction in subjective effects compared with administration of morphine alone.³³ Large epidemiology studies in the community are warranted to better assess the abuse potential of MS-sNT and other formulations incorporating features designed to deter abuse.

Conclusion

In summary, this study demonstrated that 12 weeks of treatment with MS-sNT is significantly more effective than placebo in maintaining pain relief provided by initial dosing of MS-sNT in patients with chronic, moderate-to-severe pain due to OA of the hip or knee. MS-sNT demonstrated a safety profile typical of other morphine-containing products. The presence of sequestered naltrexone in the MS-sNT formulation did not cause withdrawal symptoms when used as directed for pain management.

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Conflict of Interest Statement

Nathaniel Katz, MD, MS, has served as a consultant and has received research funding from King Pharmaceuticals[®], Inc. Martin Hale, MD, served as a principal investigator for the trial reported. David Morris, PhD, is an employee

of WebbWrites, LLC and has provided consulting services to King Pharmaceuticals[®], Inc. Joseph Stauffer, DO, MBA, was an employee of, owned stock in, and has a patent pending with Alpharma Pharmaceuticals, LLC, a wholly owned subsidiary of King Pharmaceuticals[®], Inc. The opinions and discussion contained in this article do not reflect the opinion of Johns Hopkins University.

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