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Original Reports

ALO-01 (Morphine Sulfate and Naltrexone Hydrochloride) Extended-Release Capsules in the Treatment of Chronic Pain of Osteoarthritis of the Hip or Knee: Pharmacokinetics, Efficacy, and Safety

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Abstract: ALO-01 (EMBEDA [morphine sulfate and naltrexone hydrochloride] extended-release capsules [King Pharmaceuticals, Inc, Bridgewater, NJ]), indicated for chronic moderate-to-severe pain, is designed to release naltrexone upon tampering (eg, by crushing), reducing morphine-induced subjective effects. This multicenter, randomized, double-blind, crossover study assessed pharmacokinetics, efficacy, and safety of ALO-01 and compared them with extended-release morphine sulfate (ERMS, KADIAN [morphine sulfate extended-release] capsules [Actavis US, Morristown, NJ]) in adults (N = 113) with osteoarthritis pain. Study periods included washout until pain flare (intensity ≥ 5 , 0 to 10; 0 = no pain, 10 = worst pain); dose titration with ERMS (20 to 160mg BID); and randomization to 2 (crossover) 14-day treatment periods with ERMS or ALO-01, separated by 7 days of open-label ERMS. Assessments included pharmacokinetics (morphine, naltrexone), pain scores (0 to 10), Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index; Patient Global Assessment of Medication (1 to 5; poor to excellent). Mean score at pain flare was 7.1. Morphine exposure from both formulations at steady state was similar. Plasma naltrexone concentrations were below limit-of-quantification for most patients and, when present, did not impact pain scores. During treatment, mean pain intensity (day 14: ERMS, 2.4; ALO-01, 2.3, $P = .31$), WOMAC change-from-baseline (mean pain, physical function, composite scores), and adverse event frequency were similar. ALO-01 and ERMS provided similar relief of osteoarthritis pain.

Perspective: We present data demonstrating that ALO-01 has steady-state morphine exposure, efficacy, and safety similar to marketed ERMS capsules. Results highlight the potential for morphine in ALO-01 to manage moderate-to-severe osteoarthritis pain, while the sequestered naltrexone does not interfere with efficacy.

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Key words: ALO-01, morphine, naltrexone, chronic pain, tampering, osteoarthritis.

Opioids, the most efficacious analgesic medications, have long been used in pain management, with recent attention focused on patients with

moderate-to-severe pain who are not able to attain relief from or cannot take other analgesic medications.¹⁸ Short-acting opioids provide only about 4 hours of pain relief,¹⁷ with fluctuations in opioid serum levels that can compromise pain control in some patients.¹⁸ Extended-release oral formulations have been developed to release opioids over time and in a controlled manner, thereby providing therapeutic levels of analgesia with minimal fluctuation.⁸

Extended-release oral formulations provide the convenience of once-, twice-, or thrice-daily dosing and

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around-the-clock pain relief. While the availability of larger doses of opioids in a single capsule or tablet has proven attractive for pain management, such products also proved attractive to drug abusers^{14,23,24} and created concern among clinicians and patients over initiating their use for pain control. The concern over abuse has created a need for products that are effective against pain but deter abuse.^{15,16}

Prescription opioid abuse has been defined as “the intentional self-administration of a medication for a non-medical purpose such as altering one’s state of consciousness, eg, getting high.”¹⁵ Tampering with prescription opioids is common, and occurs by chewing or crushing and swallowing, crushing for nasal administration (snorting), dissolving and injecting, smoking, and other less common routes of administration. One strategy to discourage these forms of abuse of extended-release opioids is to include in the formulation a sequestered form of an opioid antagonist that is only released if drug tampering occurs.²⁸

ALO-01 (EMBEDA, [morphine sulfate and naltrexone hydrochloride] extended-release capsules; King Pharmaceuticals, Inc, Bridgewater, NJ), recently approved in the United States for chronic moderate-to-severe pain, is a formulation containing morphine sulfate extended-release pellets, each with a sequestered core of naltrexone. Naltrexone is well established in the literature as a potent, orally active opioid antagonist^{7,19,20} and has been used to block the pharmacologic effects of oral morphine sulfate in normal volunteers.^{3,12} It is also used therapeutically to treat alcohol and opioid addiction.²² ALO-01 was designed on the basis of extended-release technology used in a marketed extended-release morphine sulfate (ERMS) formulation (KADIAN [morphine sulfate extended-release] capsules,¹¹ Actavis US, Morristown, NJ), which contains pellets of ERMS with an inert core. A single-dose study demonstrated bioequivalence of ALO-01 and ERMS (data on file, King Pharmaceuticals, Inc, #ALO-01-07-101).^{25,26}

When ALO-01 is taken as instructed, morphine is released to provide pain relief and the sequestered naltrexone has no clinical effect. If drug tampering occurs (eg, by crushing), the sequestered naltrexone is designed to be released and mitigate the morphine-induced subjective effects, therefore rendering the product less desirable for tampering.

We designed this study to assess the steady-state pharmacokinetics (morphine sulfate and naltrexone hydrochloride), efficacy, and safety of ALO-01 compared with ERMS in patients with chronic pain from osteoarthritis (OA) of the knee or hip. Results from this study were presented in poster format at the 27th Annual Scientific Meeting of the American Pain Society, Tampa, FL, May 8 to 10, 2008.¹³

Methods

Patients

We enrolled patients (n = 113) with chronic pain due to OA of the knee or hip, as designated by American Col-

lege of Rheumatology criteria.^{1,2} They required treatment of the affected joint with nonopioid analgesics or had received opioid therapy equivalent to ≤ 40 mg/d of oral morphine. Patients were otherwise required to have generally good health, based on results of a medical history, physical examination, laboratory profile, and 12-lead ECG. Patients were excluded if they had a documented history of drug abuse, dependence, or misuse within 5 years before screening; a positive result on a urine drug test for alcohol or drug abuse at screening; a body mass index >45 kg/m²; physiotherapy without a 4-week stabilization period; inability to discontinue all formulations of prior analgesics during the washout period; active gastrointestinal disease (except gastroesophageal reflux disease); injury at the target joint within 12 weeks before screening; or prior disease other than OA or surgery at the affected joint within the year before enrollment. During the study, use of the following medications was prohibited: corticosteroids, epidural steroids, opioids or combination opioids as rescue medications (including mixed agonist/antagonist opioid analgesics), monoamine oxidase inhibitors, tricyclic antidepressants, central nervous system depressants, muscle relaxants, and nonsteroidal anti-inflammatory drugs.

The study was conducted at 9 clinical sites in the United States in accordance with the provisions of the Declaration of Helsinki and its amendments and Good Clinical Practice. The protocol and the informed consent form were reviewed and approved by each center’s institutional review board/independent ethics committee. Patients provided written informed consent before undergoing any study-related procedures and were compensated for costs related to study visits. The first patients were enrolled on March 20, 2006; the last patient clinic visit occurred on August 18, 2006.

Study Design

This was a phase 2, multicenter, randomized, double-blind, 5-period crossover study (Fig 1). Study periods were as follows:

- Washout: Patients discontinued all pain medications (except acetaminophen used as rescue medication) until a pain flare occurred (pain score of ≥ 5 ; scale 0 to 10; 0 = no pain, 10 = pain as bad as you can imagine).
- Period 1: Dose was titrated with ERMS (ranging from 20 to 160 mg twice daily, approximately every 12 hours) until pain was adequately controlled (pain score of ≤ 3 with the same ERMS dose over 4 consecutive days). The stabilized dose identified during this period was then used throughout periods 2 to 5.
- Period 2: Patients were randomized to the first of the 2 14-day active therapies (ERMS or ALO-01).
- Period 3: Open-label ERMS was administered for 7 days.
- Period 4: Patients crossed over to the other double-blind active therapy (ALO-01 or ERMS) for 14 days.
- Period 5: Patients received open-label ERMS twice daily for 7 days. On day 7 of period 5 (or at early

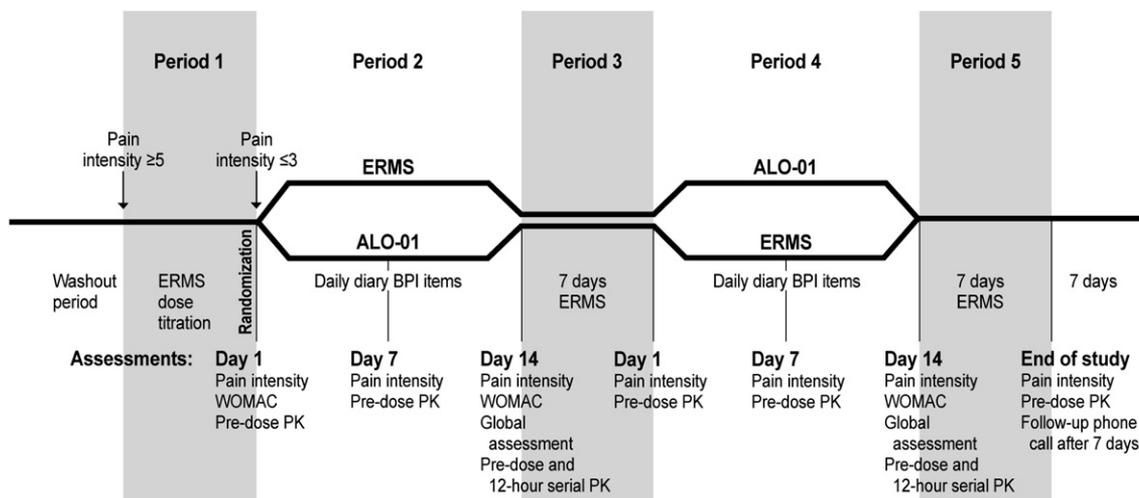


Figure 1. Study design.

termination), patients returned to the clinic for end-of-study procedures and assessments. Investigators were instructed to either continue patients on ERMS or switch them back to their previous analgesic as clinically indicated.

- Follow-up: 7 days after the end of period 5, patients received a follow-up phone call to determine whether any adverse events (AEs) had occurred during the previous week.

Randomization was accomplished using a computer-generated permuted block algorithm that randomly allocated treatment sequence to randomization numbers and was stratified by the stable twice-daily morphine dose established in period 1. Patients, investigators, and study personnel were blinded to the randomized medication, which was encapsulated into matching blank capsules and dispensed in white, high-density polyethylene bottles (with child-resistant closure) containing 30 capsules each of ERMS or ALO-01 (20, 30, 50, or 80 mg) and labeled with a 2-part, tear-off label. The randomization code was retained in a secure location at the clinical research organization and was not revealed to any member of the research team.

Pharmacokinetic Assessments

The primary objective was to evaluate pharmacokinetics of morphine sulfate and naltrexone after multiple doses of ALO-01. In addition, steady-state pharmacokinetics of morphine sulfate after multiple doses of ALO-01 and ERMS were compared. To ensure consistency of study drug exposure between the 2 double-blind periods (periods 2 and 4) and to avoid precipitating opioid withdrawal between treatment periods, patients took open-label ERMS for 1 week as an active treatment during a “washout” period. Plasma was harvested from blood samples (1×10 mL) collected within 45 minutes pre-dose at each clinic visit for the double-blind periods (days 1, 7, and 14; periods 2 and 4) and the second open-label ERMS treatment (day 7; period 5) or at study termination and stored at -20°C or colder until analysis.

Serial blood samples were also obtained at 1, 3, 4, 5, 6, 8, 10, and 12 hours after dosing on day 14 of periods 2 and 4 for steady-state pharmacokinetic assessments. Morphine, naltrexone, and its major metabolite, 6- β -naltrexol, were measured using a highly sensitive, validated bioanalytical method. Limits of quantification for morphine, naltrexone, and 6- β -naltrexol were 0.200 ng/mL, 4.00 pg/mL, and 0.250 pg/mL, respectively. Pharmacokinetic assessments for morphine included maximum plasma concentration at steady state (C_{\max}); time to reach C_{\max} (t_{\max}); steady-state area under the curve during the dosing interval, from time 0 to 12 hours (AUC_{0-12}); minimum plasma concentration at steady state (C_{\min}); time to reach C_{\min} (t_{\min}); average plasma concentration during the dosing interval (C_{avg}); and fluctuation index (FI%).

Efficacy Measures

Secondary objectives were to evaluate efficacy and safety of ALO-01 after multiple doses. Efficacy was assessed by instructing patients to rate their average pain intensity over the past 24 hours during each clinic visit using an 11-point numerical scale (0 to 10; 0 = no pain, 10 = pain as bad as you can imagine), in their daily diaries and during the follow-up phone call. Patients also recorded least and worst pain intensity in the last 24 hours as well as current pain intensity in take-home paper daily diaries, using the pain intensity scales of the Brief Pain Inventory (BPI) Short Form questionnaire, at the same time each day (preferably at bedtime) to maintain consistency of comparisons.⁵ The Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index,⁴ a validated instrument to assess pain and function in OA of the knee or hip, was used to assess pain in the study joint using a visual analog scale (VAS; 0 to 100 mm; 0 mm = no pain, 100 mm = extreme pain) assessing 5 items; stiffness in the study joint during the last 48 hours using a VAS (0 to 100 mm; 0 mm = no stiffness, 100 mm = extreme stiffness) early and later in the day; physical function (degree of difficulty performing 17

tasks, due to arthritis in the study joint) using a VAS (0 to 100 mm; 0 mm = no difficulty, 100 mm = extreme difficulty); and composite index (sum of pain, stiffness, and physical function subscale scores). Higher WOMAC scores indicate greater severity of symptoms. Patients evaluated treatment using a Global Assessment of Study Medication (1 = poor, 5 = excellent) on day 14 of periods 2 and 4. Because this trial has a crossover design, efficacy variables were presented for treatment groups but analyzed using a linear mixed-effects model (described below) accounting for the sequence and period effects. Mean in-clinic pain intensity scores at period 2, day 1, visit 1, and at double-blind days 7 and 14 were determined. Mean pain intensity scores summed for each BPI item and mean scores by day were determined for worst, least, average, and current scores. Mean scores and change from baseline scores for WOMAC subscales were determined for day 14 of periods 2 and 4.

Safety

Adverse events were recorded by the investigator or study personnel during each clinic visit for periods 1, 2, 4, and 5 and at the follow-up phone call; changes in physical examination findings, vital signs, and clinical laboratory tests were determined from baseline to specified time points during or at the end of each treatment period and by ECG recordings, which were made at period 5, day 7, or at study termination.

Statistical Analysis

A sample size of 60 patients was deemed sufficient to achieve a total of at least 50 completed patients to provide $\geq 90\%$ power to demonstrate comparable bioavailability between ALO-01 and ERMS and to detect a difference of 1 point (0 to 10 scale) in mean pain on an 11-point numeric scale between the 2 formulations, assuming $\alpha = 0.05$ and the within-subject standard deviation of pain scores is 1.5.

Four analysis populations were defined:

- Pharmacokinetic (PK) population (all patients who completed both periods 2 and 4 and had sufficient plasma samples to characterize a 12-hour pharmacokinetic profile)
- Intent-to-treat population (all randomized patients who received at least 1 dose or portion of a dose of either double-blinded study drug and had at least 1 efficacy observation after period 2, day 1)
- Completer population (all randomized patients who completed both periods 2 and 4)
- Safety population (all patients who received at least 1 dose or portion of a dose of either study drug)

Membership in the analysis populations was determined prior to unblinding.

Using the PK population, the log-transformed value for AUC of morphine concentration was modeled using the linear mixed-effects model described below. From these calculations, 95% confidence intervals (CIs) were determined for the difference in log-transformed AUC between treatments. Comparable bioavailability at steady-state was concluded if the CI of the ratio AUC_{0-12}

ERMS/ AUC_{0-12} ALO-01 was between the boundaries of 80% and 125%.

Baseline was defined as pre-dose of period 2, day 1; at this time, patients had achieved pain relief from titration with a stabilized dose of ERMS. All statistical tests were performed as 2-tailed tests with statistical significance set at $P \leq .05$. Change from baseline to day 14 of periods 2 and 4 for in-clinic pain was modeled using a linear mixed-effects model for a 2-period crossover, including fixed-effect terms for treatment, period, and sequence, with a random effect for subject nested within sequence with day 0 (initiation of titration) and Period 2, Day 1, in-clinic pain as covariates. The 95% CIs were determined; missing in-clinic pain and WOMAC scores were imputed using the last-observation-carried-forward approach. Continuous variables were summarized using descriptive statistics (mean, standard deviation, minimum and maximum, coefficient of variation, and quartiles). Categorical variables were summarized in terms of frequency and percentages.

Results

Patient disposition is shown in Fig 2; 167 patients were assessed for eligibility. Of these, 113 were enrolled and 72 were randomly assigned—35 into sequence 1 (ERMS–ALO-01) and 37 into sequence 2 (ALO-01–ERMS). Of these, 69 (61% of enrolled patients; 96% of randomly assigned patients) completed the study; 2 patients discontinued due to AEs during period 2—constipation in a patient taking ALO-01; and fatigue, crying, headache, somnolence, asthenia, and vomiting in a patient taking ERMS. One patient violated protocol (non-compliance due to a family emergency) during period 4. For the safety population, the patients were predominantly female ($n = 76$, 68.5%) and white ($n = 98$, 88.3%), with a median age of 57.0 years (range, 28 to 83 years). Patients had a mean weight of 90.2 kg and a mean body mass index of 32.4 kg/m². Location of OA pain in order of frequency was right knee (47.7%), left knee (36%), right hip (11.7%), and left hip (4.5%). Demographics for the safety, intent-to-treat, completer, and PK populations were similar, as were characteristics between the treatment sequences. The median daily morphine dose, determined at completion of titration and held constant throughout the remaining treatment periods, was 80 mg (range, 40 to 320 mg).

Pharmacokinetics

Overall, mean morphine concentrations over time from serial blood sampling post-dose on day 14 of periods 2 and 4 were similar for both treatments (Fig 3). Mean morphine C_{max} was 14.1 ng/mL for ALO-01 and 12.4 ng/mL for ERMS. Rate of morphine absorption was similar between the 2 products (median t_{max} , 4.0 and 5.0 hours for ALO-01 and ERMS, respectively). Steady-state plasma morphine exposure over the dosing interval, AUC_{0-12} , demonstrated comparable bioavailability (mean ratio, 0.93; 95% CI, 0.824 to 1.069). Plasma morphine concentrations fluctuated minimally and in

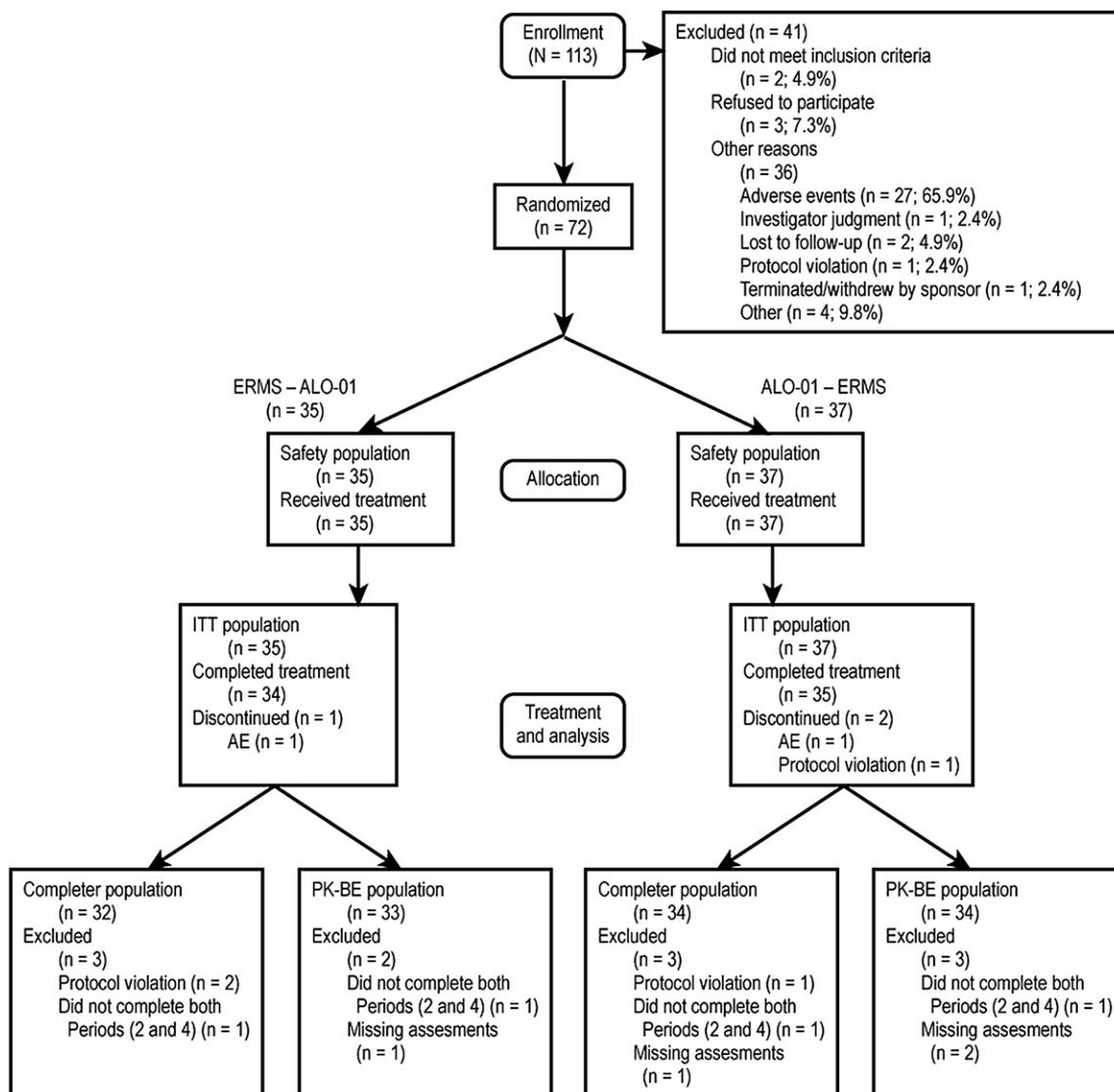


Figure 2. Patient disposition.

a similar fashion during the dosing interval for both products (Table 1).

Plasma naltrexone concentrations were below the limit of quantification (4.00 pg/mL) for most patients (77.6% to 86.6% of patients when taking ALO-01; 86.6% to 91.0% of patients when taking ERMS) when assessed pre-dose on days 1, 7, and 14 and during serial sampling on day 14 (80.6% to 83.6% taking ALO-01 and 88.1% to 91.0% taking ERMS, based on time point). Predose quantifiable naltrexone concentrations ranged from 4.29 to 25.5 pg/mL; serial quantifiable naltrexone concentrations ranged from 4.11 to 21.0 pg/mL and did not increase over time. Given the limited number of quantifiable naltrexone concentrations per patient during the serial sampling interval (<4 quantifiable concentrations in any patient), it was not possible to calculate pharmacokinetic parameters.

Most patients (n = 68) had at least 1 quantifiable 6- β -naltrexol concentration, ranging from 0.3 to 520 pg/mL (mean range: ALO-01, 0.3 to 520 pg/mL; ERMS, 0.3 to

21.0 pg/mL). Fifty-five patients taking ALO-01 had enough quantifiable 6- β -naltrexol concentrations to estimate pharmacokinetic parameters. For these patients, mean C_{max} and AUC_{0-12} of 6- β -naltrexol were

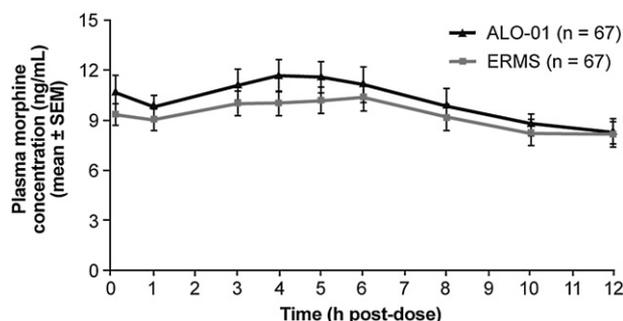


Figure 3. Mean plasma morphine concentration (ng/mL) over time from serial blood sampling post-dose on day 14 of periods 2 and 4 combined: PK population.

Table 1. Summary of Morphine Calculated Pharmacokinetic Parameters (PK Population)

| PARAMETER | ERMS N = 67 | ALO-01 N = 67 |
|---|------------------|------------------|
| AUC ₀₋₁₂ , ng•h/mL, mean (±SD) | 111.9 (±72.9) | 122.5 (±88.0) |
| C _{max} , ng/mL, mean (±SD) | 12.4 (±7.7) | 14.1 (±11.0) |
| t _{max} , h, median (minimum, maximum) | 5.0 (0.0, 12.0) | 4.0 (0.0, 12.0) |
| C _{min} , ng/mL, mean (±SD) | 6.7 (±4.6) | 6.9 (±5.4) |
| t _{min} , h, median (minimum, maximum) | 10.0 (0.0, 12.0) | 10.0 (0.0, 12.0) |
| C _{avg} , ng/mL, mean (±SD) | 9.3 (±6.1) | 10.2 (±7.3) |
| Mean fluctuation index, % [C _{max} - C _{min} /C _{avg}] (±SD) | 65.9 (±28.8) | 71.8 (±38.9) |
| 95% CI, AUC ₀₋₁₂ (ERMS)/ AUC ₀₋₁₂ (ALO-01) | 82% to 107% | |

31.3 pg/mL and 308.6 pg•h/mL. Median t_{max} was 3.0 hours.

Efficacy and Safety

After the washout period, the mean in-clinic pain intensity scores were 7.1 ± 1.5 . After dose stabilization on ERMS, mean scores for in-clinic pain were 2.1 ± 1.0 and remained low until study end for both treatment groups (combined analysis, day 14: ERMS, 2.4 ± 1.3 ; ALO-01, 2.3 ± 1.5) (Fig 4A).

Scores from the 4 pain intensity items from the BPI are shown in Fig 4B. At day 14, summed mean scores, mean change from baseline, and daily scores for worst, least, average, and current pain were not appreciably different between treatments. Daily diary scores were also similar between treatments for worst, least, average, and current pain (Fig 5).

WOMAC scores are illustrated in Fig 6. Although patients taking ALO-01 tended to have lower WOMAC scores than when taking ERMS, there were no significant differences between treatments in change from baseline

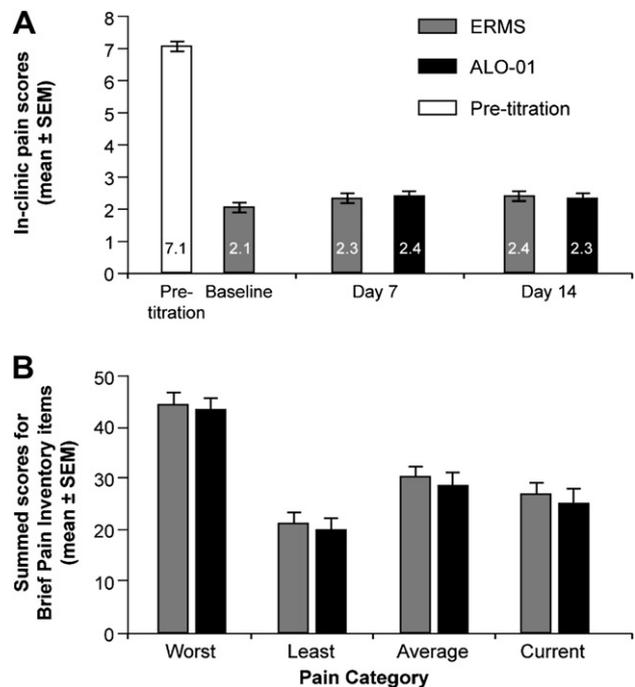


Figure 4. In-clinic and diary pain scores (0 to 10 scale). **A**, In-clinic pain intensity on a scale of 0 (no pain) to 10 (pain as bad as you can imagine) at baseline and on days 7 and 14 of periods 2 and 4 combined. **B**, Daily diary pain scores (0 to 10 scale) summed over the 14 days of treatment periods 2 and 4 combined.

scores for pain, physical function, or composite index subscales. There was a small but statistically significant difference for the stiffness subscale score in favor of ALO-01 (ALO-01, 2.5; ERMS, 12.3, $P = .02$). On the Global Assessment of Study Medication, most patients in both treatment groups rated their treatment as good, very good, or excellent (ALO-01, 65/71, 91.5%; ERMS, 56/71, 78.9%). Rescue medication during treatment was used by 36 of 71 (50.7%) of patients taking ALO-01 and 41 of 71 (57.7%) of patients taking ERMS.

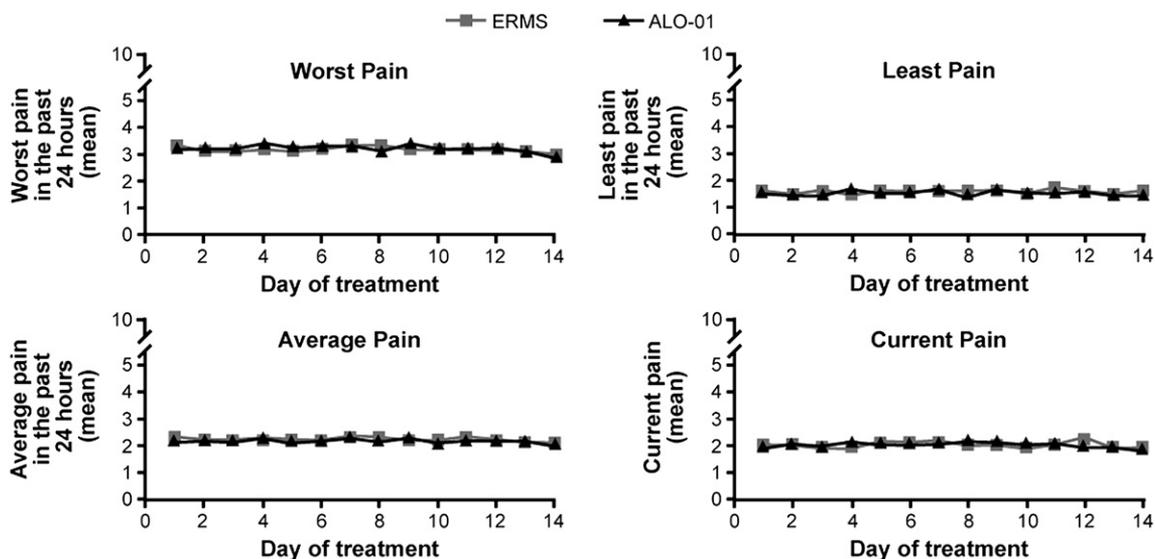


Figure 5. Brief Pain Inventory items daily diary scores (0 to 10 scale) during treatment periods 2 and 4 combined.

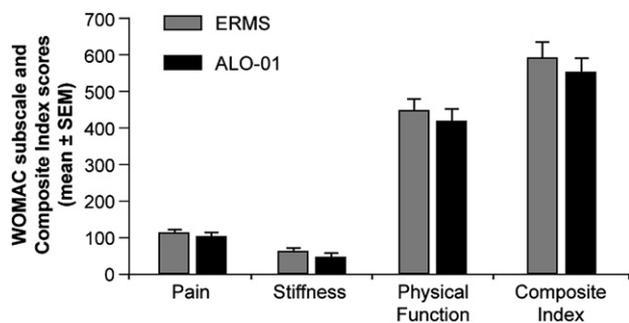


Figure 6. Mean Western Ontario and McMaster Universities (WOMAC) subscale and composite index scores on day 14 of periods 2 and 4 combined.

A post hoc analysis was performed to assess the impact of quantifiable levels of naltrexone and 6-β-naltrexol on pain scores. Analysis of pain scores at baseline following ERMS run-in and for the duration of each double-blind treatment period for patients who had quantifiable concentrations of naltrexone and/or 6-β-naltrexol did not reveal any positive correlation toward increased pain (Fig 7). Therefore, the quantifiable levels of naltrexone and 6-β-naltrexol recorded in this study had no observable clinical effect on the ability of extended-release morphine from ERMS or ALO-01 to reduce pain.

The most common AEs during the open-label and double-blind treatment periods are shown in Table 2. The 3 most common AEs were constipation, nausea, and somnolence. The proportion of patients who experienced AEs was 83.8% during open-label ERMS, 45.1% during double-blind ERMS, and 46.5% during double-blind ALO-01. For each study drug, most AEs were mild to moderate in intensity. More patients experienced severe AEs during open-label ERMS (13/111, 11.7%; constipation, nausea, vomiting, headache, chest pain, somnolence, dizziness) than either double-blind ERMS (1/71, 1.4%; constipation) or ALO-01 (0.0%). There were no deaths, and there was no evidence of any AE on laboratory parameters, vital signs, or ECGs with either study treatment. There were no unexpected AEs; most events that occurred are those well documented after

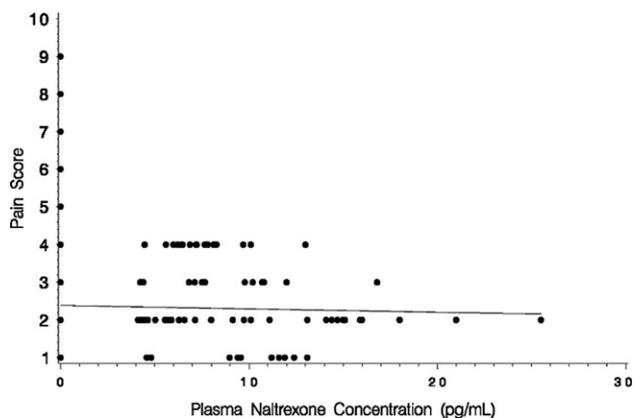


Figure 7. Time-matched naltrexone concentration and pain score for patients with quantifiable naltrexone.

morphine administration. Chest pain was the 1 serious AE that occurred and was considered unlikely to be related to study drug.

Discussion

The results of this study demonstrate that ALO-01 was efficacious and generally safe in the treatment of patients with chronic pain caused by OA of the hip or knee, as evidenced by maintenance of pain control in patients who had been stabilized taking ERMS to a similar degree in patients taking ALO-01. Efficacy outcomes, including in-clinic pain, daily diary BPI, and WOMAC scale scores (change from baseline for pain, physical function, and composite index) were similar for ALO-01 and marketed ERMS. Most patients rated both treatments as good, very good, or excellent.

At steady state, the rate of morphine absorption (T_{max}) was slightly higher for ALO-01, but overall exposure (AUC_{0-12}) indicated comparable bioavailability between ALO-01 and marketed ERMS. Naltrexone was adequately sequestered, as plasma concentrations of naltrexone and its major metabolite, 6-β-naltrexol, were low or below the limit of quantification for most patients. The presence of 6-β-naltrexol indicates exposure to trace amounts of naltrexone in most patients. Quantifiable 6-β-naltrexol levels in the plasma of some patients taking ERMS were attributed to carryover effect.

Plasma levels of 6-β-naltrexol were higher and more prevalent than those of naltrexone due to well-known rapid and extensive first-pass metabolism of the parent compound; however, 6-β-naltrexol has only a small fraction of the antagonistic activity of the parent compound.^{7,27} Even the highest level of 6-β-naltrexol recorded in this study (520.0 pg/mL, or 0.52 ng/mL) was well below the level attained with a single dose of naltrexone 50 mg (99.3 ng/mL), which is used for opioid blockade.²¹ The results of this study also indicate that even when quantifiable, neither naltrexone nor 6-β-naltrexol plasma concentrations showed any correlation with

Table 2. Most Common Adverse Events (≥5%) in the Open-Label Portion of Study and Either Double-Blind Treatment Group

| ADVERSE EVENT N (%) | OPEN-LABEL ERMS (N = 111) | DOUBLE-BLIND | |
|------------------------|------------------------------|------------------|--------------------|
| | | ERMS (N = 71) | ALO-01 (N = 71) |
| Constipation | 52 (46.8) | 9 (12.7) | 11 (15.5) |
| Nausea | 45 (40.5) | 6 (8.5) | 7 (9.9) |
| Somnolence | 32 (28.8) | 6 (8.5) | 7 (9.9) |
| Vomiting | 27 (24.3) | 3 (4.2) | 6 (8.5) |
| Dizziness | 23 (20.7) | 5 (7.0) | 1 (1.4) |
| Headache | 18 (16.2) | 6 (8.5) | 3 (4.2) |
| Dry mouth | 17 (15.3) | 1 (1.4) | 0 (0.0) |
| Pruritus | 16 (14.4) | 1 (1.4) | 1 (1.4) |
| Fatigue | 10 (9.0) | 0 (0.0) | 2 (2.8) |
| Pruritus generalized | 7 (6.3) | 2 (2.8) | 0 (0.0) |
| Muscle spasms | 6 (5.4) | 3 (4.2) | 3 (4.2) |

Abbreviation: ERMS, extended-release morphine sulfate.

pain scores and therefore did not have any negative clinical effects on pain treatment.

During this study, alcohol was prohibited but dosing was allowed without regard to meals. The results of a previous single-dose pharmacokinetic study indicated that when ALO-01 was taken after a high-fat meal, morphine had a lower rate and extent of bioavailability (C_{max}) but total exposure similar to when taken after a fast. The frequency and extent of quantifiable naltrexone concentrations were somewhat greater in the fed condition.⁹ While the current study did not specifically control for meals, no effects on pain scores were observed in those patients with quantifiable levels of naltrexone or its metabolite 6- β -naltrexol.

The development of ALO-01 was prompted by the need for a medication that is effective in managing pain but less desirable to those who tamper with opioid medications. An ideal antagonist-containing product of this type should retain safety, efficacy, and bioavailability of a conventional product for pain management and should release sufficient naltrexone after being crushed (a common method of tampering) to meaningfully reduce or eliminate euphoria via common routes of administration (eg, intravenous, nasal, oral).^{6,15,29} The results of this study indicate that ALO-01, used as directed, was effective in the management of chronic OA pain, with morphine exposure, efficacy, and safety comparable to that of currently marketed ERMS. Most patients taking ALO-01 in this study did not demonstrate quantifiable naltrexone levels. In those with quantifiable levels, there was no apparent effect on pain scores. Although no specific withdrawal measures were assessed, no AEs related to opioid withdrawal syndrome were reported.

A recent study assessed the pharmacodynamic response (drug-liking, euphoria) and pharmacokinetics of ALO-01 whole versus crushed after oral ingestion, compared with morphine sulfate in solution and placebo. Pharmacokinetic analysis indicated that the morphine levels were similar in subjects whether they took morphine solution or crushed ALO-01, with maximum concentration occurring at approximately 1 hour. Naltrexone concentration from crushed ALO-01 also

peaked at approximately 1 hour. Pharmacodynamic results indicated that the morphine solution produced significantly more euphoria than the crushed ALO-01 despite similar plasma morphine levels. Although the disposition of plasma morphine was similar following morphine solution and crushed ALO-01, the released naltrexone from the crushed product mitigated the effect of the immediately available morphine.¹⁰ Further research is needed to determine reduction of euphoria when ALO-01 is tampered with in other ways and taken via other routes.

The results reported in this study provide evidence that treatment of patients with OA of the hip or knee with ALO-01 results in morphine exposure, efficacy, and safety similar to marketed ERMS. The naltrexone contained in the core of each pellet remained adequately sequestered when used as intended and did not appear to alter the safety or efficacy of the morphine sulfate. Additional studies on the efficacy and safety of ALO-01 are needed to demonstrate the usefulness of this product in balancing the need for appropriate pain management with the need to deter tampering with extended-release opioids.

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