Efficacy and Safety of Intravenous Meloxicam in Patients With Moderate-to-Severe Pain Following Bunionectomy

A Randomized, Double-Blind, Placebo-Controlled Trial

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Objective

- To evaluate the analgesic efficacy and safety of a novel intravenous (IV) formulation of meloxicam (30 mg) in patients with moderate-to-severe pain following a standardized, unilateral bunionectomy with first metatarsal osteotomy and internal fixation

The clinical trial described in this publication supported the approval of meloxicam injection as safe and effective for its indicated use, but not all information from these publications is included in the FDA-approved labeling for meloxicam injection.

This study was supported by Recro Pharma, Inc. (now Baudax Bio, Inc.), Malvern, Pennsylvania.

Ira J. Gottlieb is an employee of Chesapeake Research Group, which conducted this trial. Wei Du receives consultancy fees from Recro Pharma Inc. Stewart W. McCallum, Randall J. Mack, and Alex Freyer are employees and security holders of Recro Pharma Inc. Rosemary Keller was an employee of Recro Pharma at the time this study was conducted. The remaining authors declare no conflict of interest.

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Methods

Study Design and Patients

- Phase 3, multicenter, randomized, double-blind, placebo-controlled trial in 201 adult patients with moderate-to-severe pain following standardized, unilateral bunionectomy with first metatarsal osteotomy and internal fixation
  - **Eligibility criteria:** patients were required to have moderate-to-severe pain (≥4 on the 11-point numeric pain rating scale) within 9 hours following discontinuation of popliteal sciatic nerve block at 3 AM on the first postoperative day

Dosing

- Eligible patients were randomized 1:1 to receive ANJESO 30 mg (n=100) or placebo (n=101). Study treatments were administered as a bolus injection lasting ~15 seconds every 24 hours for a minimum of two doses, with an optional third dose prior to discharge at 48 hours
  - Rescue medication (oxycodone 5 mg orally) was provided every 2 hours as needed for pain in both the ANJESO and placebo treatment groups

INDICATION

ANJESO is indicated for use in adults for the management of moderate-to-severe pain, alone or in combination with non-NSAID analgesics.

Limitation of Use: Because of delayed onset of analgesia, ANJESO alone is not recommended for use when rapid onset of analgesia is required.

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Risk

- Non-steroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.
- ANJESO is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.

CONTRAINDICATIONS

ANJESO is contraindicated in patients with:

- Known hypersensitivity (eg, anaphylactic reactions and serious skin reactions) to meloxicam or any components of the drug product.
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs.
- In the setting of coronary artery bypass graft (CABG) surgery.
- Moderate to severe renal insufficiency patients who are at risk for renal failure due to volume depletion.

WARNINGS AND PRECAUTIONS

Hepatotoxicity: Elevations of ALT or AST have been reported in patients with NSAIDs. In addition, rare, sometimes fatal, cases of severe hepatic injury including fulminant hepatitis, liver necrosis, and hepatic failure have been reported. Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue ANJESO immediately if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop.

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Efficacy

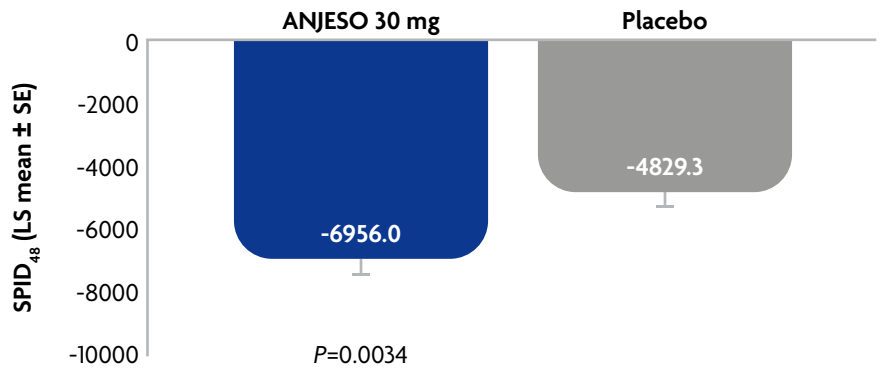
Primary Endpoint

- ANJESO significantly reduced pain by 31% over 48 hours following bunionectomy, as assessed by the sum of pain intensity difference (SPID) from baseline through the first 48 hours, compared with placebo

Secondary Endpoints

- Significantly greater proportion of patients in the ANJESO treatment group had ≥30% reduction in pain at Hour 24 compared with those in the placebo treatment group (37% vs 21%; *P*=0.0107)
- ANJESO provided significantly greater reductions in SPID* at all post-dose intervals (Hour 6, Hour 12, Hour 24, and Hours 24-48 [*P*<0.05])
- Most patients received at least 1 rescue opioid dose within the first 24 hours (83% with ANJESO; 98% with placebo)

ANJESO Provided Significantly Greater Reduction in $SPID_{48}$*



LS, least square; SE, standard error; $SPID_{48}$, summed pain intensity difference from hour 0 to hour 48.
*W2LOCF analysis method (2-hour windowed last observation carried forward).

Safety and Tolerability

- The incidence of treatment-emergent adverse events (AEs) was lower in the ANJESO treatment group than in the placebo treatment group (44% and 54%, respectively, reporting ≥1 treatment-emergent AE)
- No patient was withdrawn from the study due to an AE
- No serious AEs occurred in patients who received ANJESO

Treatment-Emergent AEs Occurring in ≥3% of Patients in Either Study Group

AE	ANJESO 30 mg (n=100) n (%)	Placebo (n=101) n (%)
Patients with ≥1 AE	44 (44%)	54 (54%)
Nausea	20 (20%)	26 (26%)
Headache	8 (8%)	12 (12%)
Pruritus	8 (8%)	3 (3%)
Constipation	4 (4%)	5 (5%)
Vomiting	3 (3%)	9 (9%)
Dizziness	3 (3%)	4 (4%)
Somnolence	3 (3%)	2 (2%)
Flushing	3 (3%)	1 (1%)

Summary

- Once-daily ANJESO significantly reduced pain by 31% versus placebo following bunionectomy (*P*=0.0034)
- The incidence of treatment-emergent AEs was lower in the ANJESO treatment group than in the placebo treatment group, with no serious AEs observed in the ANJESO treatment group

IMPORTANT SAFETY INFORMATION (cont'd)

Hypertension: NSAIDs including ANJESO can lead to new onset of hypertension or worsening of preexisting hypertension, which may contribute to the increased incidence of cardiovascular (CV) events. Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure.

Heart Failure and Edema: NSAID use increased the risk of myocardial infarction (MI), hospitalization for heart failure, and death.Avoid use of ANJESO in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure. If ANJESO is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

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IMPORTANT SAFETY INFORMATION (cont'd)

Post MI Patients: Avoid the use of ANJESO in patients with recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If ANJESO is used in these patients, monitor for signs of cardiac ischemia.

Renal Toxicity: Long-term administration of NSAIDs has resulted in renal papillary necrosis, renal insufficiency, acute renal failure, and other renal injury. ANJESO is not recommended in patients with moderate to severe renal insufficiency and is contraindicated in patients with moderate to severe renal insufficiency who are at risk for renal failure due to volume depletion. Correct volume status in dehydrated or hypovolemic patients prior to initiating ANJESO. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of ANJESO in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function. If ANJESO is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Anaphylactic Reactions: Meloxicam has been associated with anaphylactic reactions in patients with and without known hypersensitivity to meloxicam and in patients with aspirin-sensitive asthma. Seek emergency help if an anaphylactic reaction occurs.

Exacerbation of Asthma Related to Aspirin Sensitivity: ANJESO is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity).

Serious Skin Reactions: NSAIDs, including ANJESO, can cause serious skin reactions, including exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal and can occur without warning. Discontinue ANJESO at first appearance of skin rash or other signs of hypersensitivity.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Inform patients to stop taking ANJESO immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible.

Hematologic Toxicity: Anemia has occurred in NSAID-treated patients. Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia. NSAIDs, including ANJESO, may increase the risk of bleeding events. Monitor patients for signs of bleeding.

Fetal Toxicity: Limit use of NSAIDs, including ANJESO, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus.

DRUG INTERACTIONS

Drugs That Interfere With Hemostasis (eg, warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking ANJESO with drugs that interfere with hemostasis. Concomitant use of ANJESO and analgesic doses of aspirin is not generally recommended.

ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with ANJESO may diminish the antihypertensive effect of these drugs. Monitor blood pressure.

ACE Inhibitors and ARBs: Concomitant use with ANJESO in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function.

Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to ensure diuretic efficacy including antihypertensive effects.

ADVERSE REACTIONS

The most common adverse reactions in controlled clinical trials occurring in ≥ 2% of patients treated with ANJESO and at a greater frequency than placebo include: constipation, gamma-glutamyl transferase increased, and anemia.

USE IN SPECIFIC POPULATIONS

Pregnancy: Use of NSAIDs, including ANJESO, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of ANJESO use between about 20 and 30 weeks of gestation and avoid ANJESO use at about 30 weeks of gestation and later in pregnancy.

Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of ANJESO in women who have trouble conceiving.

Please see additional Important Safety Information above and full Prescribing Information, including Boxed Warning, at www.anjeso.com.

Reference

Pollak RA, Gottlieb IJ, Hakakian F, et al. Efficacy and safety of intravenous meloxicam in patients with moderate-to-severe pain following bunionectomy: a randomized, double-blind, placebo-controlled trial. *Clin J Pain*. 2018;34(10):918-926.

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ORIGINAL ARTICLE

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Efficacy and Safety of Intravenous Meloxicam in Patients With Moderate-to-Severe Pain Following Bunionectomy

A Randomized, Double-Blind, Placebo-controlled Trial

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Objective: To evaluate the analgesic efficacy and safety of a novel intravenous (IV) formulation of meloxicam (30 mg) in patients with moderate-to-severe pain following a standardized, unilateral bunionectomy with first metatarsal osteotomy and internal fixation.

Materials and Methods: Patients who met the criteria for moderate-to-severe postoperative pain were randomized to receive bolus injections of meloxicam IV 30 mg (n = 100) or placebo (n = 101) administered once daily. The primary efficacy endpoint was the Summed Pain Intensity Difference over 48 hours ($SPID_{48}$). Secondary efficacy endpoints included sum of time-weighted pain intensity differences (SPID) values at other timepoints/intervals, time to first use of rescue analgesia, and number of rescue doses taken. Safety assessments included the incidence of adverse events (AEs), physical examinations, laboratory tests, 12-lead electrocardiography, and wound healing.

Results: Patients randomized to meloxicam IV 30 mg exhibited a statistically significant difference in $SPID_{48}$ versus the placebo group ($P = 0.0034$). Statistically significant differences favoring meloxicam IV over placebo were also observed for secondary efficacy endpoints, including SPID at other times/intervals ($SPID_6$: $P = 0.0153$; $SPID_{12}$: $P = 0.0053$; $SPID_{24}$: $P = 0.0084$; and $SPID_{24\text{-}48}$: $P = 0.0050$) and first use of rescue medication ($P = 0.0076$). Safety findings indicated that meloxicam IV 30 mg was generally well tolerated; no serious AEs or bleeding events were observed. Most AEs were assessed by the investigator to be mild in intensity, and no patients discontinued due to AEs. There were no meaningful differences between the study groups in vital signs, electrocardiographic findings, or laboratory assessments. In most cases, investigators found that wound healing followed a normal course and mean wound-healing satisfaction scores were similar for meloxicam IV 30 mg and placebo.

Discussion: Meloxicam IV doses of 30 mg provided effective pain relief when administered once daily by bolus injection to patients with moderate-to-severe pain following bunionectomy, and had an acceptable safety profile.

Key Words: meloxicam IV, COX-2 inhibitor, postoperative pain, efficacy, safety

(*Clin J Pain* 2018;34:918–926)

Since 2000, when the Joint Commission on Accreditation of Healthcare Organizations revised its standards for assessment and management of pain,[1] treating pain has garnered substantially more attention publicly and in medical care. Current analgesic medications run the gamut in duration of activity, ranging from drugs that provide acute relief for 1 to 2 hours, to formulations that provide as much as 72 hours of analgesia. For patients who undergo surgery, opioid drugs have long been the mainstay of perioperative and postoperative pain management, but overreliance on these drugs in this setting can lead to consequences associated with opioid-related adverse effects, particularly respiratory depression, nausea, vomiting, and constipation, in addition to the risk of opioid dependence and abuse.[2–4] This has led to some changes in recommendations for managing postoperative pain, such as greater support for procedure-specific multimodal analgesic regimens that incorporate nonopioid drugs and other analgesic measures, in an effort to reduce opioid consumption and improve postoperative outcomes for patients.[2,5–7]

Meloxicam, a preferential cyclooxygenase-2 (COX-2) inhibitor nonsteroidal anti-inflammatory drug (NSAID), has analgesic and anti-inflammatory activities that are believed to result from its effect in reducing prostaglandin biosynthesis.[8,9] Meloxicam is associated with better gastrointestinal tolerability than other nonselective NSAIDs.[10] The pharmacokinetic half-life of meloxicam is 20 to 24 hours, which allows for once-daily dosing[11]; however, it is absorbed slowly when given orally, and peak plasma concentrations are not reached until 9 to 11 hours after oral administration of a 30 mg dose.[8,12,13] Consequently, oral meloxicam is not approved for the management of acute pain. To overcome this limitation, an intravenous (IV) nanocrystal formulation of meloxicam is being studied for the management of moderate-to-severe pain.

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R.A.P., I.J.G., F.H., and J.C.Z. managed the patients and contributed to acquisition of data. W.D. provided guidance on data analysis and interpretation.

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The safety and efficacy of meloxicam IV were previously investigated in randomized, double-blind, placebo-controlled, phase 2 trials. In one of these trials, meloxicam IV (15, 30 or 60 mg) was administered to patients with moderate-to-severe pain following surgical removal of impacted third molars (NCT00945763).[14] Meloxicam IV was associated with reduced pain in comparison to placebo and an active control (ibuprofen 400 mg) as evidenced by statistically significant differences in the sum of time-weighted pain intensity differences (SPID) throughout the 24-hour dosing period. Onset of pain relief was reported as early as 10 minutes postdose, and was sustained over the 24-hour inpatient study period. In that clinical trial, the safety profile of meloxicam IV was similar to placebo with respect to numbers and frequencies of adverse events (AEs). In a separate study, meloxicam IV (30 or 60 mg) was administered to patients with moderate-to-severe pain following a standardized bunionectomy procedure (NCT02675907).[15] Meloxicam IV had a safety profile comparable to placebo, as evidenced by similar numbers and frequencies of AEs and no reported injection-related events. In addition, meloxicam IV, administered once-daily, showed onset of analgesic effect within 15 minutes after dosing and maintained analgesia throughout 2 sequential 24-hour dosing periods.[15]

The primary objective of the present phase 3, randomized, double-blind, placebo-controlled study was to evaluate the analgesic efficacy of 30 mg doses of meloxicam IV administered once daily by bolus injection, compared with placebo, for 48 hours in patients with moderate-to-severe pain following a unilateral bunionectomy. Secondary objectives included assessment of the analgesic efficacy of meloxicam IV versus placebo at various timepoints during the 48-hour evaluation period, the use of rescue medication (oxycodone) during this time, and evaluation of the safety and tolerability of meloxicam IV. Bunionectomy was selected for this study because it is a well-established research model for evaluating the postsurgical analgesic efficacy of an investigational product.[16,17]

MATERIALS AND METHODS

Study Design and Patients

A phase 3, multicenter, randomized, double-blind, placebo-controlled trial was conducted from January to June 2016 at 4 sites in the United States in healthy patients (American Society of Anesthesiology [ASA] class 1 or 2) aged 18 to 75 years who underwent a primary, unilateral, first metatarsal bunionectomy with first metatarsal osteotomy and internal fixation under regional anesthesia through a popliteal sciatic nerve block. To be eligible for the study, patients were required to have moderate-to-severe pain (determined with a 4-point Likert scale and a score of ≥ 4 on the 11-point numeric pain rating scale [NPRS]).[18] Pain was to be assessed within 9 hours following discontinuation of the popliteal block at 3 AM on the first postoperative day (day 1).

The presence of any of the following excluded a patient from enrollment: body mass index $> 35\ kg/m^2$; history of significant laboratory or 12-lead electrocardiographic (ECG) abnormalities; infection with hepatitis B or C or the human immunodeficiency virus; active or recent gastrointestinal bleeding or peptic ulcer disease; known bleeding disorders or treatment with agents affecting coagulation; other painful conditions that could interfere with pain assessments; and pregnancy or lactation. Moreover, patients with a history of any one of the following criteria did not qualify for entry into the study: respiratory insufficiency; a significant cardiovascular, renal, hepatic, metabolic, neurological, or psychiatric condition; major surgery within the previous 3 months; myocardial infarction or coronary artery bypass graft surgery within the preceding 12 months; known allergies to NSAIDs or aspirin; chronic use of opioid therapy in the last year (> 1 mo of routine use); or abuse of alcohol or any illicit drug. In addition, patients were not eligible to participate if they utilized any concurrent drug therapy that could interfere with the efficacy/safety evaluation of meloxicam IV (including anticonvulsants and antidepressants); any corticosteroid, either systemically or by intra-articular injection (within 6 wk before study entry); lithium; a combination of furosemide with either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; or oral meloxicam within 7 days before surgery. The trial was initially registered with ClinicalTrials.gov on February 1, 2016 (ClinicalTrials.gov identifier, NCT02675907).

The study consisted of a screening visit, surgery, an inpatient 48-hour postoperative treatment period, and 2 follow-up visits (days 7 and 28 after the last study dose). The study was approved by an independent accredited institutional review board (Aspire IRB, Santee, CA) and was conducted in accordance with the principles set forth in the Declaration of Helsinki and its later amendments. All enrolled patients provided written informed consent before undergoing any study procedure. Recro Pharma Inc. was responsible for the overall design, conduct, analyses, and interpretation of data from this study.

Study Procedures and Medication

All patients underwent an Austin bunionectomy, without collateral procedures. After IV propofol induction, both regional anesthesia via a popliteal sciatic nerve block (0.5% ropivacaine) and a local Mayo block using short-acting 2% lidocaine without epinephrine was completed. The maximum duration of the surgical procedure was 2 hours (from first incision to last suture of wound closure), and the surgery was required to be completed by 6 PM on the day of surgery (day –1).

Following the bunionectomy, treatments permitted during the postoperative period included maintenance of the popliteal sciatic nerve block (continuous infusion of 0.2% ropivacaine provided at ~4 to 12 mL/h), other analgesics including ketorolac 30 mg IV administered as required up to 9 PM or morphine 2 to 4 mg IV administered as required up to midnight on the day of surgery, and use of topical ice up to 3 AM on postoperative day 1. Those who experienced moderate-to-severe pain (determined with the 4-point Likert scale and an NPRS score ≥ 4) after discontinuation of the popliteal block and other analgesic measures, and before 12 PM on day 1, were enrolled in the study and immediately (within 15 min) randomized (1:1) to receive meloxicam IV 30 mg or placebo IV (5% dextrose in water), both as a bolus injection lasting ~15 seconds. A computer-generated block randomization procedure, stratified by site, was used to assign patients to a study group. Study doses were prepared in the local site pharmacy and administered by designated unblinded and appropriately qualified member(s) of the health care team at the research site according to the patient's randomization sequence. These unblinded staff members were not involved in the collection of safety or efficacy data. The patient and the investigator and all site staff involved with collection of safety and efficacy data were blinded to the treatment assignment.

A second bolus IV injection of study medication was administered 24 hours after the first dose, and an optional third dose was given before patients' discharge from the

study site, after the final evaluation at hour 48, at the discretion of the investigator.

Efficacy Endpoints

Pain intensity (PI) was assessed via the 11-point NPRS, ranging from 0 (no pain) to 10 (worst pain imaginable). PI scores were determined before and at 0.25, 0.5, 0.75, 1, 2, 4, and 6 hours after administration of the first study dose and every 2 hours thereafter until hour 48. PI scores also were obtained within 5 minutes before administration of each dose of rescue medication (oxycodone 5 mg orally). The primary efficacy endpoint was the Summed Pain Intensity Difference from baseline through the first 48 hours ($SPID_{48}$). The individual Pain Intensity Differences (PID) are calculated by subtracting the PI scores at each observation timepoint from the initial PI score. The PID are then multiplied by the time since the preceding observation. The sum of the time-weighted PID values registered over 48 hours is $SPID_{48}$; a smaller $SPID_{48}$ value denotes a greater treatment effect.[19]

Secondary efficacy endpoints included (1) SPID values at other timepoints, specifically $SPID_6$, $SPID_{12}$, $SPID_{24}$, and for the intervals $SPID_{12\text{-}24}$, $SPID_{12\text{-}48}$, and $SPID_{24\text{-}48}$ during the 48-hour period; (2) the time to perceptible pain relief and to meaningful pain relief (measured by a 2-stopwatch technique); (3) the proportion of patients with overall pain reductions from baseline of $\geq 30\%$ and $\geq 50\%$ within 6 and 24 hours following the first study dose; (4) patients' global assessment (PGA) of pain control at hours 24 and 48 (rated on a 5-point scale);[20] (5) the time to administration of the first dose of rescue analgesia; and (6) the number of times rescue analgesia was used during hours 0 to 24, 24 to 48, and 0 to 48.

Safety Endpoints

Safety endpoints included the incidence of AEs and serious AEs (SAEs); changes from baseline in laboratory test parameters; the incidence of clinically abnormal results on laboratory tests (including routine blood chemistry, hematology, urinalysis, and coagulation); changes from baseline in vital signs; and the incidence of clinically significant changes in vital signs. The investigator evaluated results from laboratory tests and vital signs that were out of the range of normal and deemed clinically significant and these were subsequently recorded as an AE. In addition, the incidence of clinically significant abnormal ECG findings and abnormal wound healing was recorded. Surgical wound healing was evaluated by investigators on a satisfaction scale of 0 to 10 (0 = not satisfied, 10 = completely satisfied). The following specific characteristics also were assessed: erythema, drainage, edema, induration, and hematoma.

Statistical Analyses

The efficacy analyses were performed on the intent-to-treat study population, which included all randomized patients. Safety analyses were performed on all patients who received at least 1 dose of study medication.

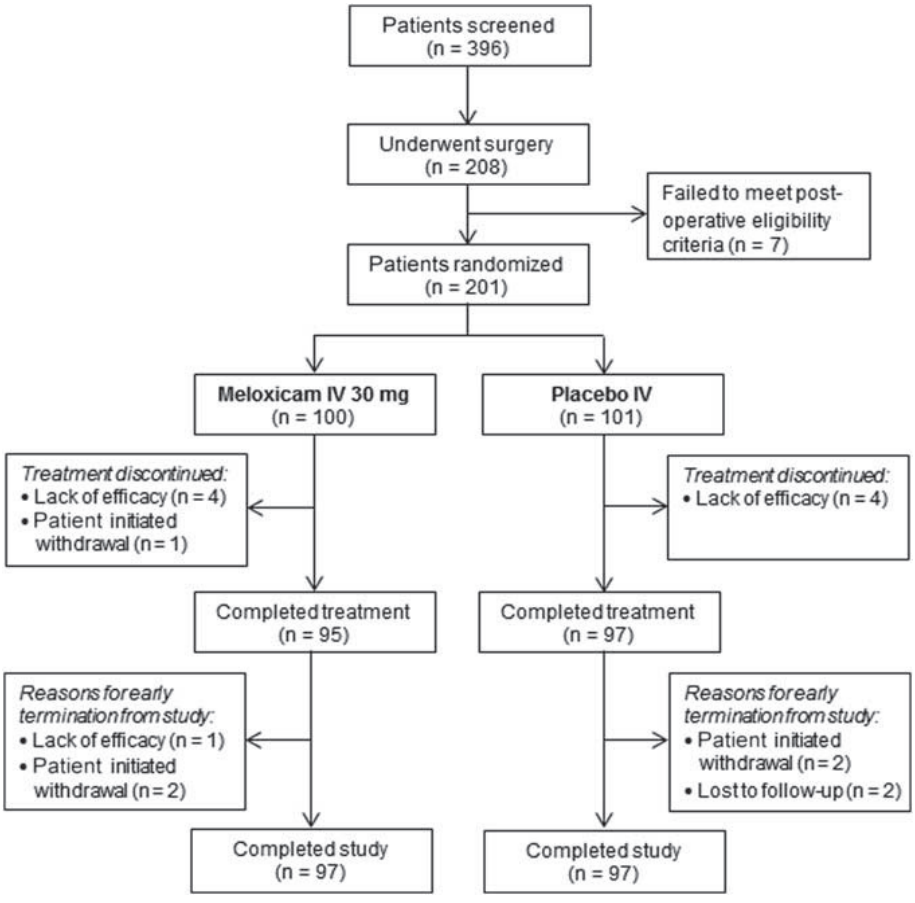

FIGURE 1. Disposition of study patients. IV indicates intravenous.

The sample size for the study was based on an assumption that the difference in $SPID_{48}$ effect size between meloxicam IV 30 mg and placebo would be ≥ 0.40. This determination was based on results from a similar phase 2 meloxicam IV clinical study that also used the bunionectomy model.[15] A 2-group *t* test with a 2-sided significance level of 0.05 determined that the study would have >80% power to detect a difference between meloxicam IV 30 mg and placebo (eg, if the effect size were 0.52, the study's power to detect a difference between meloxicam IV 30 mg and placebo would be 95%).

SPID values were derived using 4 different methods to address the impact of rescue medication on the response to the study medication. The primary analysis method was the 2-hour windowed last observation carried forward (W2LOCF) approach, whereby the PI score obtained before a given rescue dose was carried forward to replace PI scores collected within 2 hours following this rescue dose. Sensitivity analyses incorporated various methods: the last observation carried forward (LOCF) from the first use of rescue medication, the baseline observation carried forward (BOCF) from the first use of rescue medication, and the OBSERVED method, which included all collected PI scores without imputation.

The effect of treatment on SPID was assessed by analysis of covariance (ANCOVA). The ANCOVA model included the study medication received and the investigational site, with the baseline PI score as a covariate. Least-squares (LS) mean values and the standard error (SE) of LS means were determined, as were differences in LS means and corresponding 95% confidence intervals (CIs). Differences between the groups were tested using 2-sample *t* tests based on the LS means. The same approach was used for the number of doses of rescue analgesia. An ad hoc analysis of differences in PGA scores was performed by grouping the responses as positive (pooled ratings of good, very good, and excellent) versus negative (pooled ratings of poor and fair).

Differences between study groups in the proportion of patients who met the criteria for improvement and the proportion who used rescue medication were evaluated by determining the relative risk (odds ratio) and corresponding 95% CIs. Difference in time to events (time to first use of rescue medication, time to perceptible pain relief, and time to meaningful pain relief) were evaluated using a log-rank test. The Kaplan-Meier survival curves were also prepared to graphically display the difference in time to events.

All tests were 2-sided at the 0.05 significance level. Nominal *P*-values were determined without adjustment for multiple comparisons.

AEs, which were classified using the Medical Dictionary for Regulatory Activities (MedDRA), version 18.1, were summarized by treatment. Changes in vital signs at each postdose timepoint were summarized using descriptive statistics without formal statistical tests.

RESULTS

Overall, 201 patients completed the surgery, met the postoperative pain criteria, were enrolled in the study and randomized to receive meloxicam IV 30 mg (n = 100) or placebo (n = 101) (Fig. 1). The demographic and clinical characteristics of the 2 study groups were similar (Table 1). All randomized patients received study medication; therefore, all were included in the efficacy and safety analyses. Five patients in the meloxicam IV group and 4 in the placebo group did not complete the study; the reasons were lack of efficacy (4 patients in each group) and patient-initiated withdrawal (1 patient in the meloxicam IV group).

TABLE 1. Demographic and Clinical Characteristics of Enrolled Patients

Characteristics	Meloxicam IV 30 mg (n = 100)	Placebo (n = 101)
Age (mean ± SD) (y)	46.7 ± 12.79	48.4 ± 12.17
Race (n [%])		
White	61 (61.0)	68 (67.3)
Black or African American	32 (32.0)	26 (25.7)
Asian	2 (2.0)	3 (3.0)
Native Hawaiian or other Pacific Islander	2 (2.0)	2 (2.0)
Other	3 (3.0)	2 (2.0)
Ethnicity (n [%])		
Hispanic or Latino	28 (28.0)	36 (35.6)
Neither Hispanic nor Latino	72 (72.0)	65 (64.4)
Baseline BMI (kg/m^2) (mean ± SD)	26.9 ± 4.80	28.3 ± 4.02
Surgery duration (mean ± SD) (h)	0.514 ± 0.240	0.485 ± 0.200
Bunionectomy site (n [%])		
Left foot	50 (50.0)	52 (51.5)
Right foot	50 (50.0)	49 (48.5)
Time from end of surgery to the first dose of study medication (mean ± SD) (h)	18.781 ± 3.346	18.992 ± 3.224
Baseline NPRS score (mean ± SD)	6.7 ± 1.90	7.0 ± 1.82

BMI indicates body mass index; IV, intravenous; NPRS, numeric pain rating scale (score range, 0 to 10); SD, standard deviation.

Efficacy Analyses

Primary Efficacy Endpoint: $SPID_{48}$

According to W2LOCF analysis, patients in the meloxicam IV 30 mg arm experienced a statistically significant reduction in PI compared with the placebo arm (LS mean ± SE values,

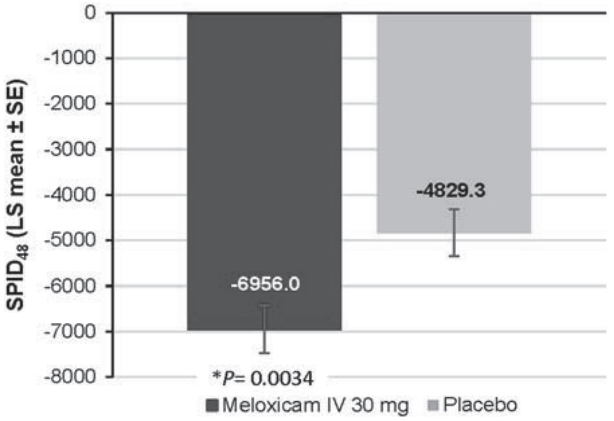

FIGURE 2. LS mean $SPID_{48}$ values for the 2 study groups (W2LOCF analysis method). *Statistically significant difference between the groups. IV indicates intravenous; LS, least-squares; SE, standard error; SPID, sum of pain intensity differences; W2LOCF, 2-hour windowed last observation carried forward.

TABLE 2. SPID Values (LS Means ± SE) at Other Times/Intervals: W2LOCF Analysis Method

Parameters	Meloxicam IV 30 mg (n = 100)	Placebo (n = 101)	*P*
$SPID_6$	−510.78 ± 66.22	−288.33 ± 65.95	0.0153
$SPID_{12}$	−957.83 ± 123.30	−480.15 ± 122.80	0.0053
$SPID_{24}$	−2071.0 ± 247.01	−1167.9 ± 246.00	0.0084
$SPID_{12\text{-}24}$	−1113.1 ± 147.95	−687.76 ± 147.35	0.0376
$SPID_{24\text{-}48}$	−4885.1 ± 313.60	−3661.4 ± 312.32	0.0050
$SPID_{36\text{-}48}$	−2422.4 ± 159.80	−1946.3 ± 159.15	0.0312

IV indicates intravenous; LS, least-squares; SE, standard error; SPID, sum of pain intensity differences; W2LOCF, 2-hour windowed last observation carried forward.

−6956.0 ± 521.69 vs. −4829.3 ± 519.56, respectively; $P = 0.0034$) (Fig. 2). The analgesic effect of meloxicam IV on $SPID_{48}$ values was also shown using the LOCF, BOCF, and OBSERVED approaches (all $P < 0.01$).

SPID Values at Other Times/Intervals

LS mean SPID values at all other postdose times and intervals ($SPID_6$, $SPID_{12}$, $SPID_{24}$, and $SPID_{24\text{-}48}$) were significantly lower with meloxicam IV 30 mg than with placebo using the W2LOCF analysis method ($P < 0.05$) (Table 2). The differences in SPID values between the treatment groups observed during the second 12 hours of each 24-hour dosing interval was statistically significant ($SPID_{12\text{-}24}$: $P = 0.0376$; and $SPID_{36\text{-}48}$: $P = 0.0312$). As with the primary efficacy endpoint, statistically significant differences favoring meloxicam IV 30 mg also were seen with the LOCF, BOCF, and OBSERVED analysis methods for all SPID times/intervals except $SPID_6$, when the difference favored meloxicam IV but did not reach statistical significance with the LOCF or BOCF method.

PID

Mean PI differences from baseline at each postdose timepoint from hours 0 to 6 and hours 0 to 48 for each study group are shown in Figure 3. With the W2LOCF analysis method, the PI difference was lower in the meloxicam IV 30 mg group at all postdose timepoints except 15 minutes after the first dose.

Use of Rescue Analgesia

Most patients (meloxicam IV: 83%; placebo: 98%) used at least 1 dose of rescue medication within 24 hours after the

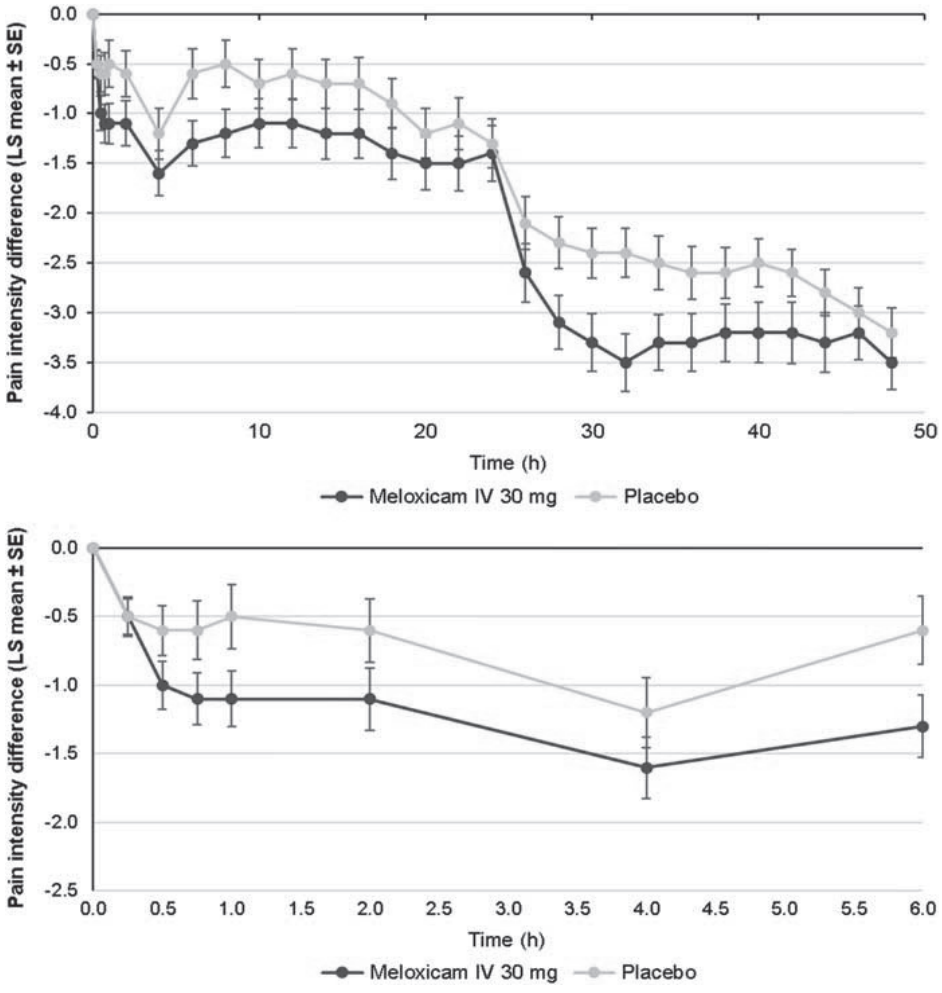

FIGURE 3. Mean pain intensity differences from baseline over 0 to 6 and 0 to 48 hours in the 2 study groups (W2LOCF analysis). IV indicates intravenous; LS, least-squares; W2LOCF, 2-hour windowed last observation carried forward.

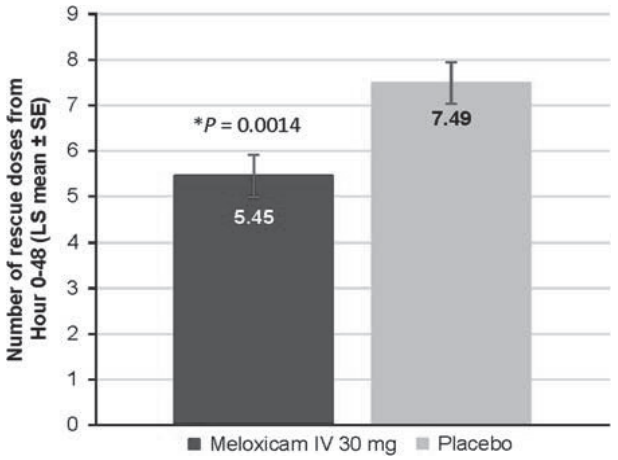

FIGURE 4. LS mean numbers of rescue analgesia doses from hour 0 to 48 in the 2 study groups. *Statistically significant difference between the groups. IV indicates intravenous; LS, least-squares.

initial dose of study medication, and 50% of patients took their first rescue dose within the first 2 hours. Although the median time to first dose of rescue medication was ~2 hours in both groups, the Kaplan-Meier estimated 75th percentile time to first rescue dose was significantly longer ($P = 0.0076$) in the meloxicam IV 30 mg group (8.65 h; 95% CI, 5.06-14.91; vs. placebo: 5.73 h; 95% CI, 4.61-7.23). In addition, during each assessment interval (hours 0 to 24, 24 to 48, and 0 to 48), the number of patients utilizing rescue analgesia was significantly lower in the meloxicam IV 30 mg group ($P < 0.001$), and the mean number of rescue analgesia doses per patient was also significantly lower in the meloxicam IV 30 mg group ($P < 0.05$). For the entire evaluation period (hours 0 to 48), the LS mean number of doses required per patient was 5.45 ± 0.46 in the meloxicam group and 7.49 ± 0.46 in the placebo group ($P = 0.0014$) (Fig. 4).

Time to Perceptible Pain Relief and Meaningful Pain Relief

According to Kaplan-Meier estimates, the median time to perceptible pain relief was numerically shorter in the meloxicam IV 30 mg group than in the placebo group (0.52 vs. 1.59 h), as was the median time to meaningful pain relief (2.16 vs. 3.19 h) (Fig. 5). However, the between-group differences were not statistically significant.

PGAs of Pain Control

PGAs of pain control were performed at hours 24 and 48. The percentage of patients who reported good or better pain control (scores of 2+ in the PGA assessment) was significantly higher in the meloxicam IV 30 mg group than in the placebo group at both hour 24 (57.9% vs. 43.3%, respectively; $P = 0.0452$) and hour 48 (84.2% vs. 65.6%, respectively; $P = 0.0043$). The estimated odds ratio (95% CI) was 1.80 (1.02-3.19) at 24 hours and 2.79 (1.40-5.59) at 48 hours (Fig. 6).

Response Analysis

Response analyses were performed for overall pain reduction from baseline of $\geq 30\%$ and $\geq 50\%$ within the first 6 and 24 hours after the first dose of study medication. Within both 6 hours and 24 hours, a significantly larger percentage of patients in the meloxicam group had $\geq 30\%$ reduction in pain compared with patients in the placebo

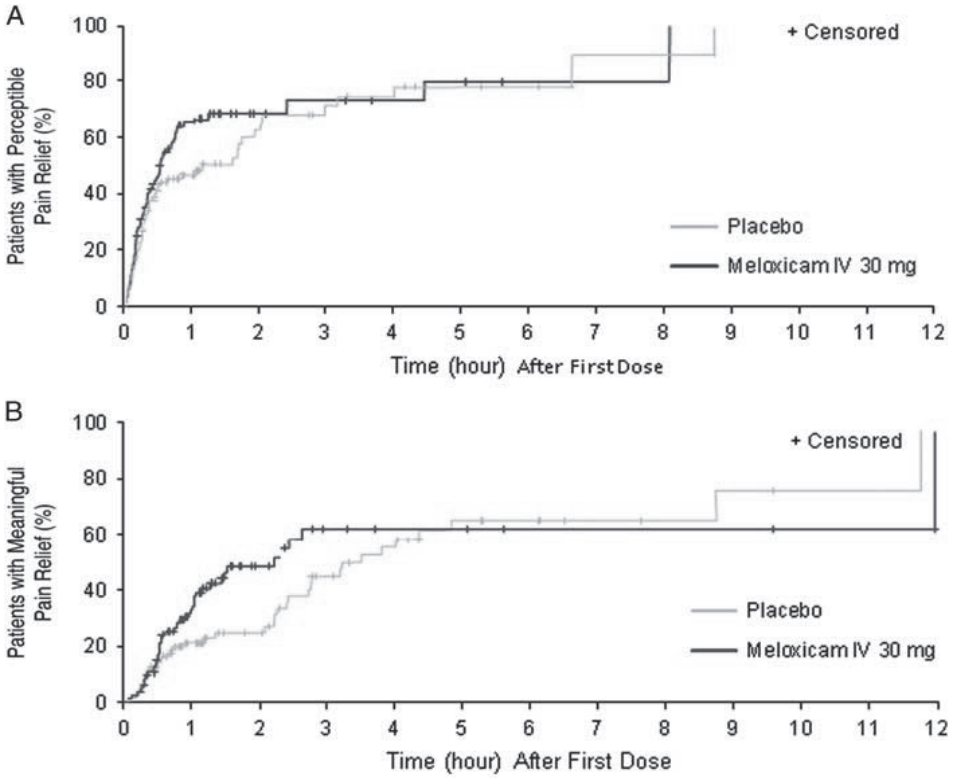

FIGURE 5. Kaplan-Meier estimates of the time to achieve (A) perceptible and (B) meaningful pain relief. IV indicates intravenous.

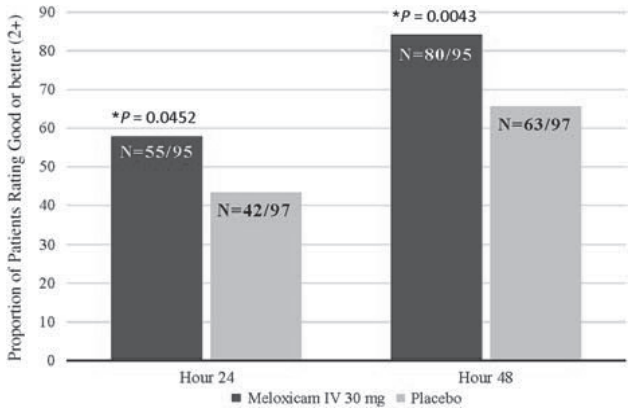

FIGURE 6. Percentages of patients who reported good or better pain control at 24 and 48 hours. *Statistically significant difference between the groups. IV indicates intravenous.

group (hour 6: 32.0% vs. 19.8, respectively; $P = 0.0451$; hour 24: 37.0% vs. 20.9%, respectively; $P = 0.0107$) (Fig. 7A). In addition, within 24 hours, significantly more patients in the meloxicam IV 30 mg group had $\geq 50\%$ reduction in pain compared with patients in the placebo group (13.0% vs. 5.0%, respectively; $P = 0.0430$). The difference between active treatment and placebo for $\geq 50\%$ pain reduction within 6 hours was not statistically significant ($P = 0.0781$) (Fig. 7B).

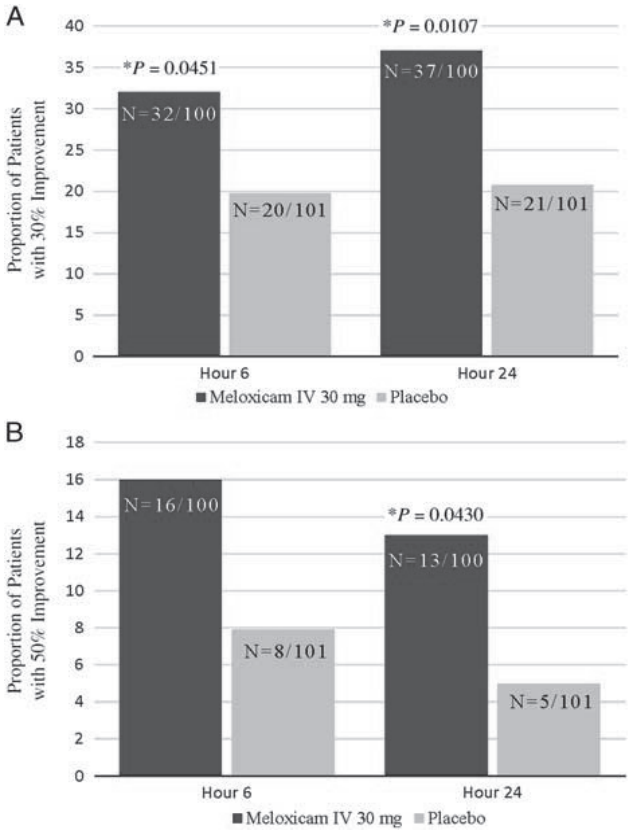

FIGURE 7. Percentages of patients whose improvement in pain from baseline was $\geq 30\%$ (A) and $\geq 50\%$ (B) at 6 and 24 hours. *Statistically significant difference between the groups. IV indicates intravenous.

Safety Analysis

All randomized patients received at least 1 dose of study medication, and most received 3 doses (meloxicam IV group, 73.0%; placebo group, 75.2%). Meloxicam IV doses of 30 mg were well tolerated during the study. The majority of treatment-emergent AEs (TEAEs) were reportedly of mild intensity, no patient was withdrawn from the study due to an AE, and no SAEs occurred in patients who received meloxicam IV 30 mg (Table 3). Two SAEs were reported in the placebo group—a fracture and a sudden death (1 patient each). Death occurred 55 days after the last dose of study drug. Autopsy reported the cause of death was due to complications of the toxic effects of methamphetamines use.

TABLE 3. Summary of TEAEs Occurring in Each Study Group: Number (%) of Patients

AE (Preferred Term)	Meloxicam IV 30 mg (n = 100)	Placebo (n = 101)
All AEs	44 (44.0)	54 (53.5)
Intensity		
Mild	39 (39.0)	44 (43.6)
Moderate	14 (14.0)	21 (20.8)
Severe	2 (2.0)	6 (5.9)
Serious AEs	0	2 (2.0)
Withdrawals due to AEs	0	0
TEAEs occurring in $\geq 3\%$ of patients in either group		
Nausea	20 (20.0)	26 (25.7)
Headache	8 (8.0)	12 (11.9)
Pruritus	8 (8.0)	3 (3.0)
Constipation	4 (4.0)	5 (5.0)
Vomiting	3 (3.0)	9 (8.9)
Dizziness	3 (3.0)	4 (4.0)
Somnolence	3 (3.0)	2 (2.0)
Flushing	3 (3.0)	1 (1.0)
AEs of special interest		
Patients with ≥ 1 event	7 (7.0)	12 (11.9)
Injection-site reactions	2 (2.0)	4 (4.0)
Injection-site pain	1 (1.0)	2 (2.0)
Phlebitis at vessel puncture site	1 (1.0)	0
Injection-site erythema	0	2 (2.0)
Injection-site induration	0	1 (1.0)
Injection-site infection	0	1 (1.0)
Wound-healing events/ reactions	5 (5.0)	4 (4.0)
Cellulitis	2 (2.0)	0
Postprocedural discharge	1 (1.0)	0
Wound	1 (1.0)	0
Wound dehiscence	1 (1.0)	0
Wound infection	0	2 (2.0)
Incision-site cellulitis	0	2 (2.0)
Hepatic reactions	0	4 (4.0)
ALT increased	0	3 (3.0)
AST increased	0	2 (2.0)
Alkaline phosphatase increased	0	2 (2.0)
GGT increased	0	1 (1.0)
Liver function test: abnormal result	0	1 (1.0)

AE indicates adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; IV, intravenous; TEAE, treatment-emergent adverse event.

TABLE 4. Potentially Clinically Significant Changes in Laboratory Parameters From Normal Values at Baseline: Number (%) of Patients

Parameters	Criterion of Potential Significance	Meloxicam IV 30 mg	Placebo
Hematocrit	< 30%	0	0
Hemoglobin	< 10 g/dL	1 of 100 (1.0)	0
BUN	1.5-3×ULN	1 of 89 (1.1)	0
Creatinine	1.5-3×ULN	1 of 96 (1.0)	0
ALT	3-10×ULN	0	3 of 89 (3.4)
	≥ 10×ULN	0	1 of 89 (1.1)
AST	3-10×ULN	0	3 of 85 (3.5)
	≥ 10×ULN	0	0
GGT	1-3×ULN	6 of 89 (6.7)	5 of 83 (6.0)
	3-10×ULN	0	2 of 83 (2.4)
Alkaline phosphatase	1-3×ULN	6 of 80 (7.5)	8 of 74 (10.8)
Total bilirubin	> 2×ULN	0	0
aPPT	≥ 55 s	0	0
INR	> 1.5	0	0

ALT indicates alanine aminotransferase; aPPT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; GGT, gamma-glutamyltransferase; IV, intravenous; INR, international normalized ratio; ULN, upper limit of normal.

The investigator considered the death to be not related to study medication.

In general, TEAEs occurred more frequently in the placebo group (Table 3). The most common TEAEs (≥ 5% of patients) in the meloxicam IV 30 mg group were nausea (20% of patients), headache (8%), and pruritus (8%). Hepatic and injection-site TEAEs were infrequent in both groups, with a greater incidence overall in the placebo group (Table 3). AEs of special interest (AEOSI) included injection-site reactions, bleeding, cardiovascular, hepatic, renal, thrombotic, and wound-healing events. No renal, cardiovascular, bleeding, or thrombotic AEOSIs were observed in either treatment group. Nor was there any apparent trend in clinically meaningful abnormal laboratory results between the study groups (Table 4), and no trends for changes in vital signs or ECGs.

Wound-healing Assessment

Mean investigator satisfaction scores for wound healing were similar for meloxicam IV 30 mg and placebo at hour 48 (9.7 ± 0.61 vs. 9.6 ± 0.60, respectively), at 7 days after the last study dose (9.4 ± 1.14 vs. 9.6 ± 1.03, respectively), and at 28 days after the last study dose (9.7 ± 0.77 vs. 9.6 ± 0.86, respectively). Seven days after the last dose of study medication, the incidence of clinically significant abnormalities in wound healing were more common in the placebo group (n = 8) than the meloxicam IV group (n = 1). On day 28, no patient in the placebo group and 1 patient in the meloxicam IV group had a wound-healing abnormality. Overall, 4 patients in the placebo group reported 4 wound healing AEOSI and 5 patients in the meloxicam IV group reported 5 wound-healing AEOSI (Table 3).

DISCUSSION

This randomized, double-blind, placebo-controlled study of meloxicam IV was conducted in patients with moderate-to-severe postbunionectomy pain, which has proven a useful model of postoperative pain for assessing the efficacy of analgesic drugs.[17] The study design was consistent with research design recommendations of the IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) group for trials involving patients with short-duration acute pain.[21] Meloxicam IV administered once daily appeared effective in providing rapid and sustained relief of moderate-to-severe postoperative pain throughout the 48-hour assessment period. In comparison to placebo, bolus IV doses of 30 mg meloxicam, administered once daily over ~15 seconds, produced a statistically significant reduction in the primary pain endpoint ($SPID_{48}$ values) according to the W2LOCF method ($P = 0.0034$), as well as statistically significant reductions in SPID values at other times/intervals ($SPID_6$, $SPID_{12}$, $SPID_{24}$, and $SPID_{24\text{-}48}$), greater proportions of patients with overall pain reductions from baseline of ≥ 30% and ≥ 50% within 6 and 24 hours after dosing, and greater proportions of patients with good or better pain control at 24 and 48 hours after dosing.

Other key findings included a rapid onset of analgesia, which was evident as early as 15 to 30 minutes after administration of meloxicam IV 30 mg (Fig. 3), and a sustained analgesic effect over its 24-hour dosing interval, as evidenced by statistically significant differences in $SPID_{12\text{-}24}$ and $SPID_{36\text{-}48}$ values versus placebo ($P = 0.0376$ and 0.0312, respectively). Moreover, an opioid-sparing effect was apparent for meloxicam IV 30 mg, indicated by the significantly longer time to first use of rescue analgesia ($P = 0.0076$ vs. placebo), the significantly lower number of patients utilizing rescue analgesia in each assessment interval ($P < 0.001$ vs. placebo), and the significantly lower mean number of per-patient rescue doses at each assessment interval ($P < 0.05$ vs. placebo).

Efficacy sensitivity results attained with other analysis methods (ie, LOCF, BOCF, and OBSERVED) were consistent with those of the primary analysis method (W2LOCF), suggesting that the efficacy conclusions were not affected by missing data or by the use of rescue medication. Results attained with other analysis methods supported the finding that meloxicam IV 30 mg was superior to placebo in terms of analgesic efficacy.

In terms of safety, meloxicam IV doses of 30 mg were well tolerated, with no associated SAEs or withdrawals due to AEs. The majority of TEAEs in the meloxicam IV 30 mg group were reported as mild or moderate in intensity. The incidence and intensity of these TEAEs were comparable to, or lower than, those in the placebo group. The most common TEAEs occurring with meloxicam IV 30 mg were nausea (20% of patients), headache (8%), and pruritus (8%). AEOSIs (including hepatic, wound-healing, and injection-site events) were infrequent in both groups, with a greater incidence overall in the placebo group. Inhibition of COX-2 may produce a reduction in prostacyclin, which could increase thrombotic risk.[22] Short-duration use has a lower probability of risk for thrombotic events, and no clinically significant shift in coagulation parameters were identified in this trial, which is consistent with the phase 2 clinical trial findings.[14,15] No clinically meaningful vital sign changes or ECG results were reported during the study, and there was a low incidence of clinically significant laboratory findings, which were more common in the placebo group. In general, results of wound-healing satisfaction scores were similar for meloxicam IV 30 mg and placebo and investigators determined that wound healing followed a normal course. Seven days after the last study dose, the incidence of clinically

significant wound status observations was lower in the meloxicam group.

The principal limitations of this study include possible variance from normal clinical practice, in that patients were required to remain in the clinic for an extended period (48 h) for clinical assessment, analgesia was administered after pain escalated (not preemptively), and patients did not have access to multimodal analgesic regimens to manage postoperative pain. In addition, the use of rescue medication could impact the response to the study medication, although various imputation methods utilized were to address the effect of rescue medication on efficacy conclusions. The surgical procedure, anesthesia protocol, and initial postoperative management regimens were standardized as much as possible to minimize intersubject variability in this study, but it is possible that hemodynamic fluctuations and other intraoperative events may have necessitated some deviations from the standard regimen and been responsible for a degree of intersubject variability.

In summary, once-daily IV bolus doses of meloxicam IV 30 mg produced a significant analgesic effect in patients with moderate-to-severe pain after bunionectomy, as evidenced by $SPID_{48}$ data, SPID values at other times/intervals, times to perceptible and meaningful pain relief, PGA pain-control findings, pain reductions from baseline of $\geq 30\%$ and $\geq 50\%$, and reductions in opioid rescue use in comparison to placebo. Once-daily dosing of meloxicam IV 30 mg showed rapid onset of analgesia, an analgesic effect that was sustained throughout the 24-hour dosing interval, and a favorable tolerability profile that included a low incidence of AEs that was comparable to placebo, few injection-related events, and no SAEs. Results from this clinical trial indicate that meloxicam IV may be useful in treating postbunionectomy pain and may permit a longer dosing interval than is associated with other NSAIDs without an increased risk of side effects commonly associated with nonselective NSAIDs or opioid analgesics. This bunionectomy study was designed to evaluate analgesic effectiveness in a hard-tissue model; additional studies are planned to investigate the use of meloxicam IV in other surgical models.

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