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Analgesic Efficacy and Safety of Intravenous Meloxicam in Subjects With Moderate-to-Severe Pain After Open Abdominal Hysterectomy: A Phase 2 Randomized Clinical Trial

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BACKGROUND: An intravenous (IV) formulation of meloxicam was developed for moderate-to-severe pain management. This study evaluated the safety and efficacy of meloxicam IV after open abdominal hysterectomy. Meloxicam IV is an investigational product not yet approved by the US Food and Drug Administration.

METHODS: Women (N = 486) with moderate-to-severe pain after open abdominal hysterectomy were enrolled in this multicenter, randomized, double-blind, placebo- and active-controlled trial. Subjects were randomized to receive a single dose of meloxicam IV (5–60 mg), placebo, or morphine (0.15 mg/kg) in ≤6 hours after morphine dosing on postoperative day 1 and were evaluated for 24 hours. Rescue morphine (≈0.15 mg/kg IV) was available if needed for pain not relieved by the study medication. In an open-label extension (N = 295), meloxicam IV was administered once daily for the remaining hospital stay (or per the investigator's discretion). The coprimary efficacy end points were the summed pain intensity difference ($SPID_{24}$) and total pain relief ($TOTPAR_{24}$) from hour 0 to 24 hours after dosing. Effect size, the standardized difference between means reported in standard deviation (SD) units, was calculated to indicate the magnitude of the difference in the mean analgesic effect measured for different intervention groups.

RESULTS: Subjects who received morphine or meloxicam IV had a median time to first perceptible pain relief within 6–8 minutes. Morphine and meloxicam IV 5–60 mg produced statistically significant differences than placebo in $SPID_{24}$ and $TOTPAR_{24}$. $SPID_{24}$ (standard error [SE]) for meloxicam IV 5–60 mg ranged from −56276.8 (3926.46) to −33517.1 (3930.1; $P < .001$); $SPID_{24}$ (SE) for morphine and placebo were −29615.8 (3869.2; $P < .001$) and 4555.9 (3807.1), respectively. $SPID_{24}$ effect sizes (95% confidence intervals) for the 60, 30, 15, 7.5, and 5 mg meloxicam IV doses and morphine were 1.93 (1.61–2.25), 2.00 (1.65–2.35), 1.70 (1.35–2.05), 1.28 (0.95–1.60), 1.25 (0.90–1.61), and 1.12 (0.77–1.45) SDs, respectively. $TOTPAR_{24}$ (SE) for meloxicam IV 5–60 mg ranged from 3104.5 (155.28) to 4130.4 (191.17; $P < .001$); $TOTPAR_{24}$ (SE) for morphine and placebo were 2723.3 (188.4; $P < .001$) and 1100.6 (185.4), respectively. $TOTPAR_{24}$ effect sizes (95% confidence interval) for the 60, 30, 15, 7.5, and 5 mg meloxicam IV doses and morphine were 2.03 (1.70–2.35), 2.05 (1.70–2.40), 1.78 (1.43–2.13), 1.35 (1.03–1.67), 1.37 (1.01–1.72), and 1.10 (0.75–1.45) SDs, respectively. The mean total opioid consumed (SD) during the double-blind phase was 4.6 (8.17), 5.3 (8.85), 5.9 (7.85), 8.5 (9.67), 9.3 (9.47), 9.6 (8.12), and 16.0 (10.15) mg for patients in the 60, 30, 15, 7.5, and 5 mg meloxicam IV, morphine, and placebo groups, respectively. Generally, meloxicam IV was well tolerated, evidenced by the incidence of adverse events compared to placebo and lack of deaths and treatment-related serious adverse events.

CONCLUSIONS: A meloxicam IV dose of 5–60 mg was generally well tolerated and appeared to reduce opioid consumption in subjects with moderate-to-severe pain after open abdominal hysterectomy. Once-daily administration of meloxicam IV produced analgesic effect within 6–8 minutes postdose that was maintained over a 24-hour dosing interval. (Anesth Analg 2019;128:1309–18)

KEY POINTS

- **Question:** Does the intravenous (IV) formulation of nanocrystal meloxicam provide appropriate analgesia in subjects with moderate-to-severe pain after open abdominal hysterectomy?
- **Findings:** Meloxicam IV at doses of 5–60 mg produced statistically significant improvements in the summed pain intensity difference and total pain relief over the first 24 hours after dosing (coprimary end points) compared with placebo; in addition, there were no deaths or treatment-related serious adverse events.
- **Meaning:** Meloxicam IV was well tolerated and produced analgesic effect for moderate-to-severe pain after open abdominal hysterectomy.

DOI: 10.1213/ANE.0000000000003920

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Accepted for publication October 8, 2018.

Funding: This work was supported by Elan Corp, PLC, Dublin, Ireland. Alkermes Inc (Waltham, MA) merged with Elan Drug Technologies in 2011. Recro Pharma, Inc, entered into a definitive agreement with Alkermes

Meloxicam is a preferential cyclooxygenase-2 inhibitor with analgesic, antipyretic, and anti-inflammatory properties.[1–3] Orally administered meloxicam is indicated for management of chronic conditions, including the relief of signs and symptoms of osteoarthritis and rheumatoid arthritis.[3] Oral meloxicam is not indicated for the management of acute pain largely due to its relatively slow absorption rate; mean maximum plasma concentrations are not achieved until 9–11 hours after oral administration of a 30 mg dose.[2,4]

A nanocrystal formulation of meloxicam (Recro Pharma, Inc, Malvern, PA) was developed for bolus intravenous (IV) administration to provide faster onset of pain relief than can be achieved with oral administration.[5] In a phase 2 study conducted in subjects with moderate-to-severe pain after a standardized bunionectomy procedure, once-daily dosing of meloxicam IV (30 or 60 mg) had a low incidence of adverse events (AEs) and injection-related events and demonstrated onset of analgesia in ≤15 minutes of administration that was maintained throughout 2 sequential 24-hour dosing periods.[6] In another phase 2 study, meloxicam IV (15, 30, or 60 mg) was administered to subjects with moderate-to-severe pain after surgical removal of impacted third molars. In this study, meloxicam IV reduced moderate-to-severe pain compared with placebo and an active control (ibuprofen 400 mg); onset of pain relief began as early as 10 minutes after administration and was maintained throughout the 24-hour inpatient study period.[7] Furthermore, meloxicam IV appeared to have a generally favorable safety profile.[7]

The primary objective of this phase 2 study was to determine the analgesic effect, onset time, duration of effect, and safety of single doses (5–60 mg) of meloxicam IV in subjects after open abdominal hysterectomy, a common surgical procedure typically accompanied by moderate-to-severe postoperative pain.[8–10] Secondary objectives included assessment of the time to first use of opioid rescue analgesia. The safety and tolerability of single doses of meloxicam IV administered once daily for ≤7 days in this population were assessed in an open-label extension study.

MATERIALS AND METHODS

Study Design and Subjects

This 2-part multicenter study was approved by an independent ethics committee. All clinical work was conducted in compliance with current Good Clinical Practices as stated in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guideline E6, local regulatory requirements, and principles of the Declaration of Helsinki. Before patient enrollment, this multicenter study was registered with ClinicalTrials.gov (NCT01084161; principal investigators at each site [Supplemental Digital Content 1, Table S1, http://links.lww.com/AA/C634]; date of registration: March 5, 2010). All study subjects provided written informed consent before participation. The study was performed at 14 sites in 3 countries (Poland, Serbia, and Georgia) from August 6, 2010, to January 4, 2011. Part 1 was a randomized, double-blind, placebo- and active-controlled, single-dose study. Part 2 was a multiple-dose, open-label safety extension.

Women 18–65 years of age who were scheduled to undergo open abdominal hysterectomy with an anticipated incision length of ≥3 inches, who otherwise were in good health (American Society of Anesthesiology class I or II), were considered for study participation. Subjects were eligible for part 1 of the study if they experienced moderate-to-severe pain in ≤6 hours of morphine discontinuation, which took place at ≈6 AM on postoperative day 1 (4-point Likert scale category of moderate or severe and visual analog scale [VAS] score ≥45 mm on a scale of 0–100 mm).

Exclusion criteria included active gastrointestinal bleeding or history of peptic ulcer disease; any known bleeding disorder or use of agents affecting coagulation; history of abdominal surgery, with the exception of inguinal hernia repair, lateral-approach appendectomy, or cesarean delivery performed >1 year before study participation and yielding no postoperative complications; and history of chronic opioid use (>30 consecutive days of use) for pain in the previous 2 years.

Subjects randomized to receive meloxicam IV in part 1 could be enrolled in the open-label extension (part 2) if they did not take rescue medication in the first 18 hours of the double-blind phase (responders). Subjects randomized to receive placebo or morphine in part 1 could be enrolled in part 2 if they used rescue medication within the first 18 hours of the double-blind phase (nonresponders).

Study Procedures

Per the standard of care in each participating institution, open abdominal hysterectomy was performed with subjects under general anesthesia, and postoperative morphine was administered by bolus IV injection or patient-controlled analgesia.

Part 1: Randomized, Double-Blind, Placebo- and Active-Controlled Study. On postoperative day 1 of part 1, at approximately 6 AM, patient-controlled analgesia was discontinued or a dose of IV morphine was administered. Subjects received a single dose of study medication in ≤6 hours after their 6 AM dose of morphine and were monitored for 24 hours. Study medications were meloxicam IV (5, 7.5, 15, 30, or 60 mg), placebo (sterile dextrose 5% in water), and morphine (≈0.15 mg/kg). All medications were administered as an IV push over 1–2 minutes. Morphine 0.15 mg/kg also was used as rescue medication, administered as an IV push or a subcutaneous or an intramuscular injection.

Part 1 consisted of 2 cohorts. Subjects in cohort 1 (n = 206) were randomized using central randomization (block size: 6, 1:1:2:2 ratio) to receive placebo (n = 30), morphine (n = 30), or meloxicam IV 7.5 mg (n = 60) or 60 mg

on March 9, 2015, under which Recro Pharma acquired worldwide rights to Meloxicam intravenous/intramuscular. All subsequent development, including funding for this manuscript, was provided by Recro Pharma, Inc (Malvern, PA).

Conflicts of Interest: See Disclosures at the end of the article.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.anesthesia-analgesia.org).

Trial Registration: ClinicalTrials.gov Identifier: NCT01084161.

Protocol is available on request from Randall J. Mack.

Reprints will not be available from the authors.

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(n = 60). The meloxicam IV 7.5 mg dose was assumed to have a similar treatment effect as morphine 6 mg, with a mean total pain relief (TOTPAR) score of 16 and a standard deviation (SD) of 11.6. There was also an assumption that the mean TOTPAR and SD for the placebo group would be 9 and 9.6, respectively. To provide ≥80% power to detect differences between the placebo and meloxicam IV 7.5 mg groups based on these assumptions, 30 and 60 subjects were required for the placebo and meloxicam IV 7.5 mg groups, respectively. A planned and prespecified interim analysis was performed at the conclusion of cohort 1 to determine dosing for double-blind cohort 2. In cohort 2, subjects (n = 280) were randomized using central randomization (block size: 28) to receive placebo (n = 30), morphine (n = 30), or meloxicam IV 5 (n = 60), 7.5 (n = 20), 15 (n = 60), 30 (n = 60), or 60 mg (n = 20) (3:3:6:2:6:6:2 ratio). The sample size for cohort 2 was based on the same assumptions made for cohort 1 and provided ≥80% power to detect differences between each meloxicam IV group and the placebo group.

Part 2: Open-Label Extension. Meloxicam IV was administered once daily for the remainder of each subject's hospital stay or at the discretion of the investigator based on the subject's needs. Subjects treated with meloxicam IV in part 1 continued on the same dose in part 2. A second computer-generated randomization was created for subjects who received morphine or placebo in part 1 who were eligible to receive meloxicam IV (5, 7.5, 15, 30, or 60 mg) in part 2. Open-label randomization was assigned by the site coordinator or investigator. Subjects were hospitalized for ≥24 hours after the last dose of open-label meloxicam IV to complete safety assessments.

Outcome Measures

Safety and Efficacy Populations. All subjects who received study medication were included in the safety analysis, and all subjects who received study medication and had ≥1 efficacy assessment were included in the efficacy analysis.

End Points. The coprimary efficacy variables were the summed pain intensity difference (SPID) over the first 24 hours postdose ($SPID_{24}$) and the sum of the time-weighted pain relief scores over the first 24 hours postdose ($TOTPAR_{24}$). $SPID_{24}$ and $TOTPAR_{24}$ are accepted regulatory standard measures that combine magnitude and duration of relief into a single score. To assess pain intensity, subjects used a 100-mm VAS anchored at 0 for no pain and 100 for the worst imaginable pain. Pain intensity differences (PIDs) were determined by subtracting the baseline pain intensity score from each postdose pain intensity score. SPID was calculated as the sum of the time-weighted PID (difference between current pain and pain at baseline) multiplied by the interval between ratings. SPID represents the area under the PID curve. More negative SPID scores demonstrate greater cumulative pain reduction.

Pain relief was rated on a numerical rating scale using the following categorical scores: 0 = none, 1 = little, 2 = moderate, 3 = a lot, and 4 = complete. TOTPAR was calculated as the sum of time-weighted pain relief scores in which the weight given to each pain relief score was equal to the elapsed time between assessments. TOTPAR represents the area under the pain relief score curve. A larger TOTPAR value demonstrates greater pain relief. These end points provide a sensitive measure for a relative potency estimate and are used for the evaluation of analgesics.[11]

During the double-blind phase, measurements of pain intensity and pain relief were obtained predose; 10, 20, 30, and 45 minutes postdose; and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hours postdose. Pain intensity was rated on a 100-mm VAS ranging from 0 (no pain) to 100 (worst pain possible). Pain relief was rated on a categorical Likert scale (0 = none, 1 = little, 2 = moderate, 3 = a lot, and 4 = complete).

An interim safety and efficacy analysis was performed after the completion of cohort 1 to determine dose groups in cohort 2. The interim efficacy analysis measured SPID over the first 60 minutes postdose using PID measures assessed 10, 20, 30, 45, and 60 minutes postdose. Findings from SPID over the first 60 minutes postdose were only used to determine the dose levels for cohort 2. No statistical penalty was taken for the interim analysis because this phase 2B study was designed to determine the efficacy trend and possible dose-response trend.

Secondary end points included SPID and TOTPAR for other postdose time intervals, specifically 0–6 and 18–24 hours, time to first use of rescue analgesia, time to first perceptible pain relief, time to meaningful pain relief, and patient-reported global evaluation score (GES).

The time to onset of treatment effect was determined using the 2-stopwatch technique.[12] Stopwatches were started when subjects received study medication. The first watch was stopped when pain relief was first perceptible, and the second watch was stopped when pain relief was considered meaningful.

Subjects rated the pain relief effect of study medication by assigning a GES (0 = poor, 1 = fair, 2 = good, 3 = very good, and 4 = excellent) at the time of rescue medication or 24 hours postdose if rescue medication was not used.

Safety was assessed throughout the study via AE monitoring, with AEs of special interest highlighted based on known association with nonsteroidal anti-inflammatory drugs.[13,14] Additional safety evaluation included clinical laboratory tests, vital sign measurements, physical examinations, 12-lead electrocardiograms, wound-site evaluations, pulse oximetry, and concomitant medication use.

Statistical Analysis

Statistical Methods. An analysis of covariance model, with treatment as a factor and baseline pain intensity as a covariate, was used to analyze $SPID_{24}$ and $TOTPAR_{24}$ to determine treatment effect and analyze various secondary end points. The *P* value indicates the statistical significance in treatment effect between 2 intervention groups, and the effect size (Cohen *d*) reveals the magnitude difference in analgesic effect between groups. Effect size, calculated by subtracting the mean response of placebo from the mean response of the active-treatment group divided by the pooled SD, is reported in units of SDs. An effect size of 1 indicates that the means of the 2 interventions differ by 1 SD; a larger effect size indicates higher assay sensitivity.[11,15] The 95% confidence interval (CI) for each estimated effect size is reported to facilitate interpretation of the effect

intervals; when the CI does not include 0, there is evidence that 1 group has a higher outcome than the other.

Subjects who used rescue medication before 24 hours had their pain intensity score recorded immediately before the rescue dose, and the score was carried forward through 24 hours for PID calculation.

The Kaplan–Meier method was used to evaluate median time to event end points. The Cox proportional hazards model was used to estimate hazard ratios (HRs) of the probability of subjects experiencing pain relief. Subjects who used rescue medication before reporting pain relief were censored at the time of rescue use. The last pain intensity and pain relief scores before rescue medication were carried forward.

Two-sided tests were used to evaluate treatment effects. Statistical significance was declared if the *P* value was <0.05. No adjustment was made for multiple comparisons. All analyses were performed using SAS software, version 9.1.3 (SAS Institute, Cary, NC). Total opioid consumption was tabulated by treatment group, and differences between treatment groups were analyzed using 1-way analysis of variance; subjects who did not use any rescue medication were assigned a zero for the consumption analysis.

Analysis of data from the open-label extension was limited to summary statistics.

RESULTS

All 486 subjects enrolled in the blinded, single-dose study (part 1) received treatment and were included in the efficacy and safety analyses (Figure 1).

Among the 486 enrollees, 228 (46.9%) did not use rescue medication. The group distribution for the 258 subjects who used rescue medication was as follows: placebo, n = 61 (95%); morphine, n = 47 (76%); and meloxicam IV 5 mg, n = 34 (57%);

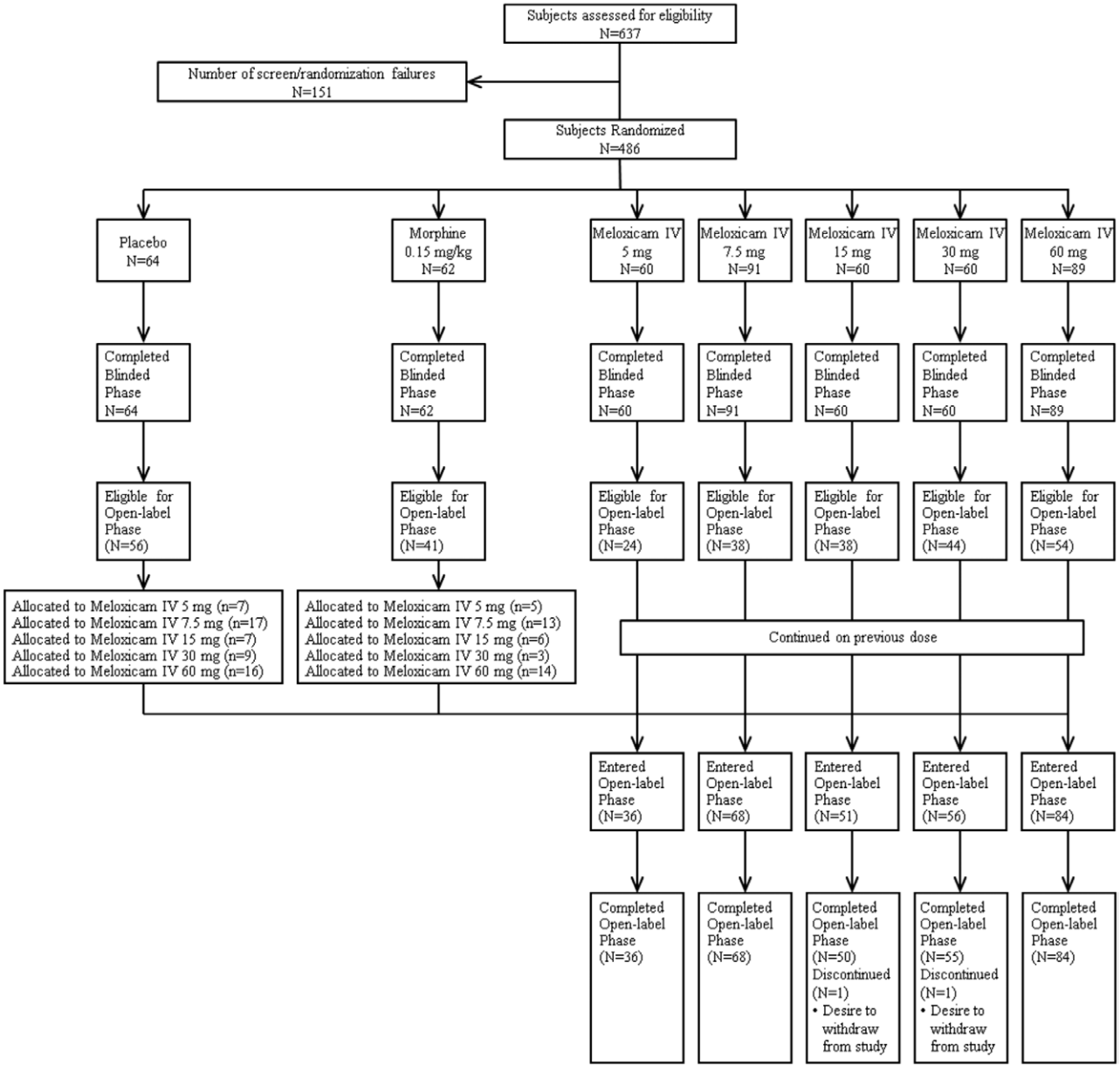

Figure 1. Disposition of study subjects. IV indicates intravenous.

7.5 mg, n = 48 (53%); 15 mg, n = 22 (37%); 30 mg, n = 16 (27%); and 60 mg, n = 30 (34%). No subject discontinued the double-blind phase due to an AE.

A total of 295 enrolled subjects (60.7%) entered the open-label extension, and 293 (99.3%) completed the study. Two subjects discontinued for personal reasons. Data from all 295 subjects were included in the open-label extension safety analyses.

Demographic and baseline clinical characteristics were balanced across treatment groups as summarized in Table 1.

Efficacy Findings

SPID Over the First 24 Hours Postdose. $SPID_{24}$ results are summarized in Figure 2A. $SPID_{24}$ (standard error) for morphine and the meloxicam IV 60, 30, 15, 7.5, and 5 mg doses were −29,615.8 (3869.24), −54,074.4 (3225.48),

Table 1. Demographic and Baseline Clinical Characteristics: Double-Blind Treatment Phase

			Meloxicam IV				
Variable	**Placebo**	**Morphine 0.15 mg/kg**	**5 mg**	**7.5 mg**	**15 mg**	**30 mg**	**60 mg**
Population (n)	64	62	60	91	60	60	89
Age (y)							
Mean (SD)	47.9 (6.46)	48.0 (7.43)	47.7 (6.27)	47.9 (5.67)	46.9 (6.28)	47.4 (7.40)	47.6 (7.12)
Range	32–65	28–63	29–62	36–63	31–65	25–62	29–63
BMI (kg/m^2)							
Mean (SD)	25.79 (3.65)	26.45 (3.14)	25.17 (3.05)	26.02 (3.25)	25.09 (2.87)	25.61 (3.46)	26.50 (3.27)
Range	19.3–31.6	18.8–31.3	19.9–31.3	19.2–31.2	19.7–31.0	18.8–31.2	18.8–31.5
Race (%)							
Caucasian	100	100	100	100	100	100	98.9
Baseline pain score							
Mean (SD)	57.8 (7.49)	57.7 (9.59)	61.1 (11.19)	60.5 (11.10)	60.0 (10.13)	59.4 (10.04)	59.5 (9.68)

Abbreviations: BMI, body mass index; IV, intravenous; SD, standard deviation.

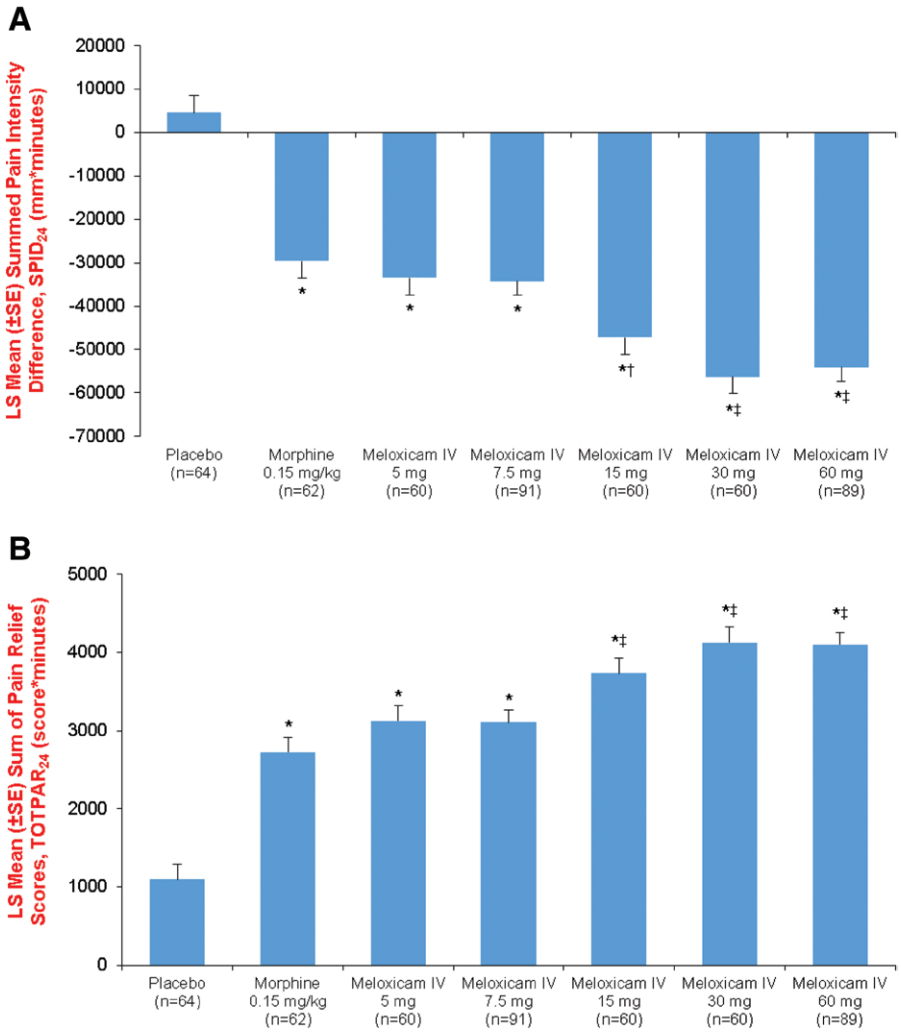

Figure 2. Primary end points: (A) least squares (LSs) mean (± standard error [SE]) summed pain intensity difference at hour 24 ($SPID_{24}$), and (B) LS mean (± SE) sum of pain relief scores at hour 24 ($TOTPAR_{24}$). All meloxicam IV doses significantly reduced acute postoperative pain intensity and improved pain relief during the first 24 h relative to placebo. Meloxicam IV 60, 30, and 15 mg also produced significant reductions in pain intensity and improved pain relief compared with morphine during the same period. *P < .001 versus placebo; †P = .002 versus morphine; ‡P < .001 versus morphine. IV indicates intravenous.

−56,276.8 (3926.46), −47,176.1 (3926.2), −34,241.3 (3189.34), and −33,517.1 (3930.09) mm × minutes, respectively, compared with 4555.9 (3807.05) mm × minutes for placebo ($P < .001$). All meloxicam IV doses significantly reduced acute postoperative pain intensity during the first 24 hours relative to placebo ($P < .001$). The $SPID_{24}$ effect sizes (95% CI) for morphine and meloxicam IV 60, 30, 15, 7.5, and 5 mg doses were 1.12 (0.77–1.47), 1.93 (1.61–2.25), 2.00 (1.65–2.35), 1.70 (1.35–2.05), 1.28 (0.95–1.60), and 1.25 (0.90–1.61) SDs, respectively. Meloxicam IV 60, 30, and 15 mg also produced significant reductions in pain intensity compared with morphine during the same period ($P \leq .002$).

Sum of the Time-Weighted Pain Relief Scores Over the First 24 Hours Postdose. $TOTPAR_{24}$ results are summarized in Figure 2B. $TOTPAR_{24}$ (standard error) for morphine and meloxicam IV 60, 30, 15, 7.5, and 5 mg doses were 2723.3 (188.39), 4101.7 (157.04), 4130.4 (191.17), 3734.3 (191.16), 3104.5 (155.28), and 3124.9 (191.35) score × minutes, respectively, compared with 1100.6 (185.36) score × minutes for placebo ($P < .001$). All meloxicam IV doses significantly improved pain relief during the first 24 hours relative to placebo ($P < .001$). $TOTPAR_{24}$ effect sizes (95% CI) for morphine and meloxicam IV 60, 30, 15, 7.5, and 5 mg doses were 1.10 (0.75–1.45), 2.03 (1.70–2.35), 2.05 (1.70–2.40), 1.78 (1.43–2.13), 1.35 (1.03–1.67), and 1.37 (1.01–1.72) SDs, respectively. Meloxicam IV 60, 30, and 15 mg also significantly improved pain relief compared with morphine during this period ($P < .001$).

PID at Each Time Point. Statistically significant differences from baseline in pain intensity were detected as early as 10 minutes postdose for all active-treatment groups relative to placebo ($P < .001$). Mean PID from baseline (SD) at 10 minutes for placebo, morphine, and meloxicam IV 60, 30, 15, 7.5, and 5 mg doses were −4.7 (14.33), −28.9 (19.69), −21.2 (16.49), −17.5 (15.27), −16.8 (18.28), −16.3 (16.34), and −17.7 (19.47), respectively. Significant differences in pain intensity from baseline were observed throughout the double-blind phase in all active-treatment groups; mean PID (SD) at 24 hours for placebo, morphine, and meloxicam IV 60, 30, 15, 7.5, and 5 mg doses were 7.2 (20.39), −10.7 (28.28), −29.5 (30.13), −29.1 (24.22), −22.3 (25.34), −16.6 (28.87), and −13.4 (24.72), with $P < .001$ for meloxicam IV dose groups only (Figure 3).

SPID and TOTPAR at Various Time Intervals. SPID and TOTPAR for hours 0–6 and 18–24 are presented in Supplemental Digital Content 2, Figure S1A, B, http://links.lww.com/AA/C635. During both intervals, all active treatments were statistically superior to placebo, and meloxicam IV 30 and 60 mg were statistically superior to morphine.

GES at Hour 24. GES was significantly greater for all meloxicam IV dose groups compared with placebo ($P < .001$) and for meloxicam IV doses ≥7.5 compared with morphine ($P \leq .009$) (Supplemental Digital Content 3, Figure S2, http://links.lww.com/AA/C636).

Rescue Medication Use. Compared with placebo, all active treatments reduced the likelihood of requiring rescue medication in the first 24 hours postdose ($P < .001$). Relative to placebo subjects, those who received meloxicam IV 60 or 30 mg were 90% less likely to require rescue medication during the first 24 hours, with an HR of 0.10 (95% CI, 0.06–0.16) for the meloxicam IV 60 mg group and an HR of 0.10 (95% CI, 0.06–0.17) for the meloxicam IV 30 mg group. Those who received meloxicam IV 15, 7.5, or 5 mg were 86% (HR, 0.14; 95% CI, 0.09–0.23), 80% (HR, 0.20; 95% CI, 0.14–0.30), and 81% (HR, 0.19; 95% CI, 0.12–0.29) less likely to require rescue medication in the first 24 hours, respectively.

Compared with morphine, all meloxicam IV doses reduced the likelihood of rescue medication use within the first 24 hours postdose ($P \leq .010$). Relative to morphine, meloxicam IV 60, 30, 15, 7.5, and 5 mg doses reduced the risk of rescue medication use in the first 24 hours by 72% (HR, 0.28; 95% CI, 0.18–0.45; $P < .001$), 73% (HR, 0.27; 95% CI, 0.16–0.45; $P < .001$), 62% (HR, 0.38; 95% CI, 0.23–0.61; $P < .001$), 41% (HR, 0.59; 95% CI, 0.40–0.88; $P = .010$), and 45% (HR, 0.55; 95% CI, 0.35–0.85; $P = .007$), respectively.

The Kaplan–Meier survival curve of time to first use of rescue medication is shown in Figure 4. The median time to first rescue medication use, using the lower bound of the 95% CI for the 50th percentile, was approximately 1.1 hours with placebo, 6.6 hours with morphine, and 21.8, 18.3, 10.1, and 12.2 hours with meloxicam IV 30, 15, 7.5, and 5 mg, respectively. Because <50% of subjects in the meloxicam IV 60 mg group used rescue medication, the median time to the first rescue use could not be estimated for this group.

All active treatments reduced total consumption of rescue morphine in the double-blind treatment phase ($P < .0001$ versus placebo). Subjects in the placebo group received a mean (SD) number of rescue doses of 2.2 (1.16). Subjects in the morphine and meloxicam IV 60, 30, 15, 7.5, and 5 mg dose groups received a mean (SD) number of rescue doses of 1.3 (0.96), 0.5 (0.83), 0.6 (0.89), 0.7 (0.84), 0.9 (1.00), and 1.1 (1.09), respectively. Total opioid rescue requirements in the placebo group were 16.0 (10.15) mg. In contrast, total opioid rescue requirements for morphine and meloxicam IV 60, 30, 15, 7.5, and 5 mg recipients were 9.6 (8.12), 4.6 (8.17), 5.3 (8.85), 5.9 (7.85), 8.5 (9.67), and 9.3 (9.47) mg, respectively. The meloxicam IV 60, 30, and 15 mg doses also reduced total rescue opioid consumption relative to morphine ($P = .0008$, $P = .0071$, and $P = .0206$, respectively).

Time to Pain Relief. *Perceptible Pain Relief.* The median time to first perceptible pain relief (based on the point estimate for the 50th percentile) ranged from 6 to 8 minutes among meloxicam IV dose groups, compared with 4 minutes for morphine and 16.9 minutes for placebo. The survival analysis of time to first perceptible pain relief is illustrated in Supplemental Digital Content 4, Figure S3A, http://links.lww.com/AA/C637. Subjects in the active-treatment groups were significantly more likely than those in the placebo group to experience first perceptible pain relief within the first 24 hours ($P < .001$). The HR for morphine was 4.77 (95% CI, 3.04–7.48). HRs (95% CI) for meloxicam IV 60, 30, 15, 7.5, and 5 mg were 3.54 (2.38–5.27), 3.09 (2.03–4.70), 2.80 (1.84–4.26), 2.30 (1.57–3.36), and 2.56 (1.70–3.86), respectively.

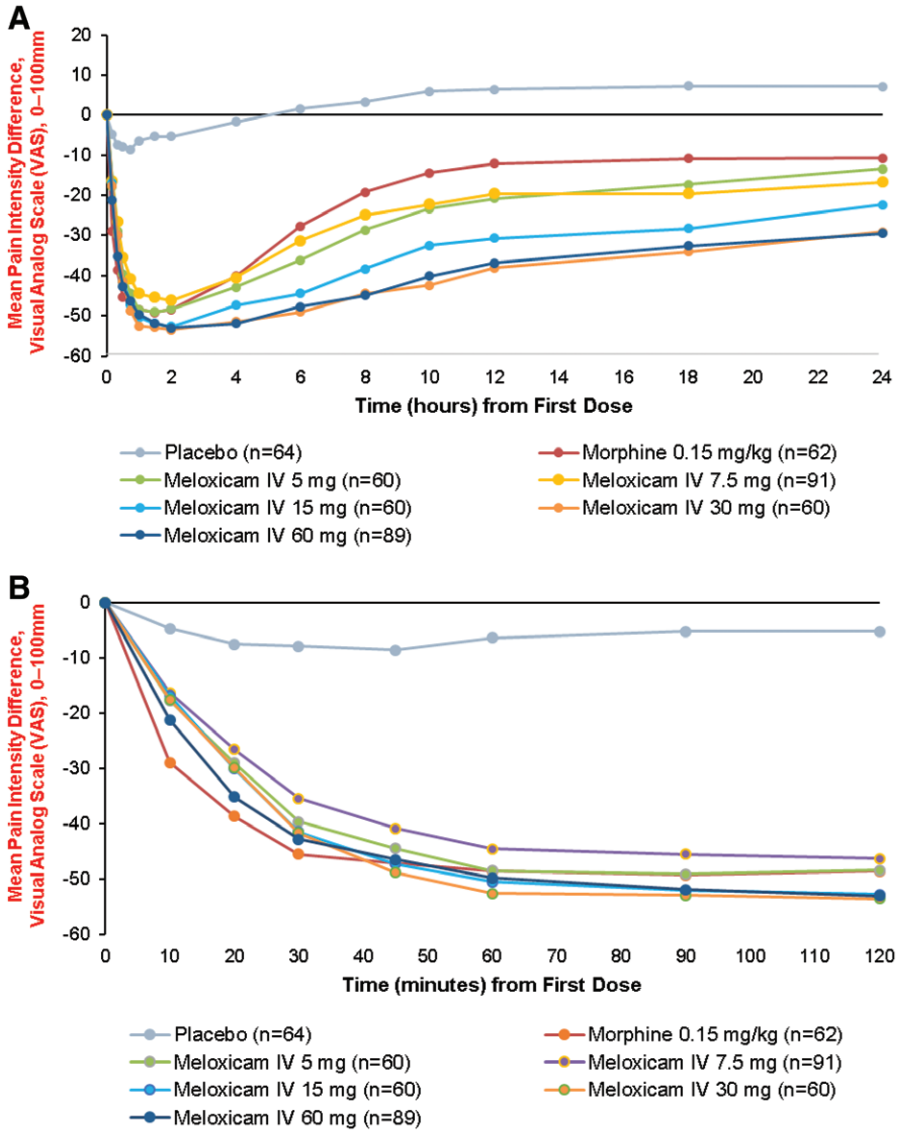

Figure 3. Mean ± SD pain intensity difference over time: (A) hours 0–24, and (B) hours 0–2. Statistically significant differences from baseline in pain intensity were detected as early as 10 min postdose and continued throughout the double-blind phase in all active-treatment groups. IV indicates intravenous; SD, standard deviation; VAS, visual analog scale.

Meaningful Pain Relief. The median time to first meaningful pain relief (based on the point estimate for the 50th percentile) ranged from 17.7 to 26.2 minutes among meloxicam IV dose groups, compared with 16.3 minutes for morphine and 165 minutes for placebo. The survival analysis of time to first meaningful pain relief is illustrated in Supplemental Digital Content 4, Figure S3B, http://links.lww.com/AA/C637. Subjects in active-treatment groups were significantly more likely than subjects who received placebo to experience first meaningful pain relief within the first 24 hours ($P < .001$). The HR for morphine was 6.33 (95% CI, 3.83–10.46). HRs (95% CI) for meloxicam IV 60, 30, 15, 7.5, and 5 mg were 6.17 (3.79–10.03), 6.74 (4.00–11.36), 5.49 (3.27–9.21), 4.25 (2.64–6.86), and 4.37 (2.64–7.24), respectively.

Safety

A total of 486 subjects received ≥1 dose of study medication in the double-blind phase, and 295 received ≥1 dose of study medication in the open-label phase. The majority of subjects in the meloxicam IV 60, 30, and 15 mg groups received ≥2 days of treatment, and approximately one-third of subjects in each of these groups received ≥3 days of exposure. Cumulative exposure was lower in the meloxicam IV 7.5 and 5 mg groups: 47.9% and 40.3% of subjects (respectively) received ≥2 days of treatment, and 28.1% and 16.7% (respectively) had ≥3 days of exposure.

Adverse Events. Generally, meloxicam IV at doses ≤60 mg were well tolerated during the double-blind and open-label phases. Overall, 205 treatment-emergent AEs were reported by 147 subjects during the double-blind treatment phase (Table 2). Most AEs were mild or moderate in severity. Severe treatment-emergent AEs were reported for 3 (4.7%), 6 (9.7%), 5 (8.3%), 7 (7.7%), 9 (15.0%), 5 (8.3%), and 9 (10.1%) patients in the placebo, morphine, and meloxicam IV 5, 7.5, 15, 30, and 60 mg groups, respectively. For 61% of subjects, AEs that occurred during the double-blind treatment phase were considered unrelated to study medication. One subject in the placebo group discontinued the study due to an AE attributed to the use of morphine as rescue medication.

Overall, the type of treatment-emergent AEs reported among subjects treated with meloxicam IV during the

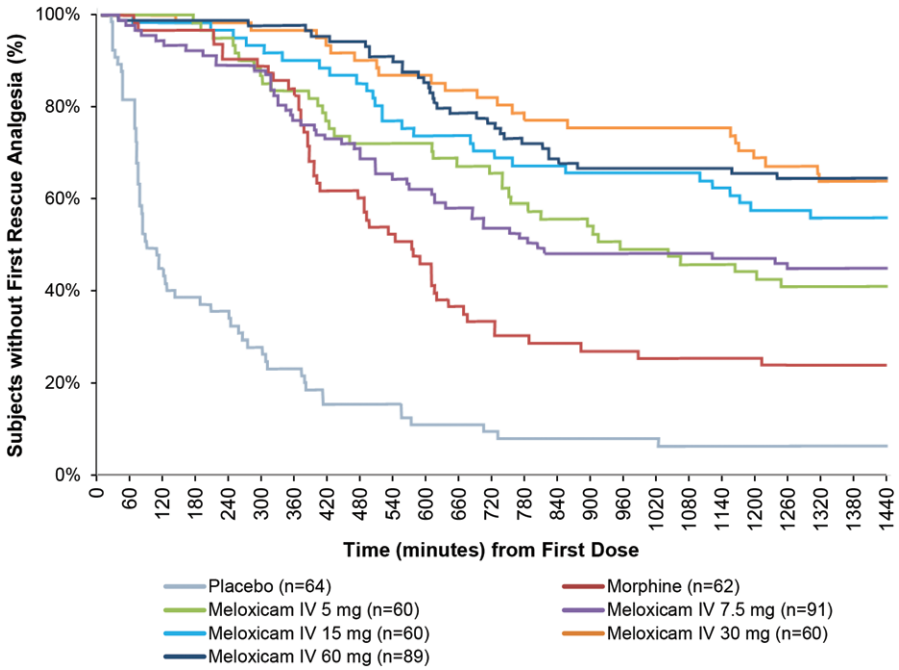

Figure 4. Survival analysis of time to first use of rescue medication. Compared with placebo, all active treatments reduced the likelihood of requiring rescue medication in the first 24 h postdose. Compared with morphine, all meloxicam IV doses reduced the likelihood of rescue medication use within the first 24 h postdose. IV indicates intravenous.

Table 2. Summary of Treatment-Emergent AEs: Double-Blind Treatment Phase

			Meloxicam IV				
AE	Placebo (N = 64), n (%)	Morphine 0.15 mg/kg (N = 62), n (%)	5 mg (N = 60), n (%)	7.5 mg (N = 91), n (%)	15 mg (N = 60), n (%)	30 mg (N = 60), n (%)	60 mg (N = 89), n (%)
Anemia	2 (3.1)	4 (6.4)	2 (3.3)	12 (13.2)	2 (3.3)	3 (5.0)	9 (10.1)
Constipation	–	3 (4.8)	3 (5.0)	1 (1.1)	1 (1.7)	–	–
Flatulence[a]	–	3 (4.8)	1 (1.7)	1 (1.1)	2 (3.3)	–	–
Hypokalemia	–	2 (3.2)	1 (1.7)	1 (1.1)	–	1 (1.7)	–
Insomnia	3 (4.7)	5 (8.1)	6 (10.0)	4 (4.4)	3 (5.0)	3 (5.0)	4 (4.5)
Ketonuria[a]	5 (7.8)	6 (9.7)	4 (6.7)	9 (9.9)	9 (15.0)	6 (10.0)	9 (10.1)
Leukocytosis	–	–	1 (1.7)	–	–	2 (3.3)	–
Pyrexia	1 (1.6)	2 (3.2)	2 (3.3)	2 (2.2)	–	–	–
Sinus tachycardia	–	–	2 (3.3)	–	–	–	1 (1.1)

Abbreviations: AE, adverse event; IV, intravenous.
[a]Considered by the investigator to be a treatment-related AE.

open-label phase was consistent with that reported during the double-blind phase. Most AEs continued to be mild or moderate, and no subject withdrew due to an AE.

Serious AEs. Five serious AEs were reported during the entire study: severe ileus in 1 subject during double-blind treatment with meloxicam IV 5 mg, mild vaginal hemorrhage in 1 patient after receiving rescue medication after double-blind treatment with meloxicam IV 5 mg, mild postprocedural hematoma in 1 patient during open-label treatment with meloxicam IV 7.5 mg, mild wound dehiscence in 1 patient during open-label treatment with meloxicam IV 15 mg, and mild wound infection in 1 patient during open-label treatment with meloxicam IV 15 mg. No serious AE was considered related to study medication.

AEs of Special Interest. During the double-blind phase, 1 (0.2%) meloxicam IV–treated subject had a mild electrocardiogram abnormality that was possibly related to treatment. Hepatic events of interest (abnormal liver function values) were reported for 5 (1.0%) meloxicam IV subjects and 2 (0.4%) placebo recipients. Two (0.4%) meloxicam IV–treated subjects developed mild wound infections unrelated to treatment. During the open-label phase, 11 (2.4%) additional meloxicam IV–treated subjects had hepatic events of interest. The incidence of hepatic events did not appear to increase with increasing doses of meloxicam IV. Cardiovascular and wound healing events among subjects treated with meloxicam IV during the open-label phase were consistent with those reported during the double-blind phase.

Anemia was reported for 28 meloxicam subjects (5.8%) and 2 placebo recipients (0.4%) during the double-blind phase. The incidence of anemia did not appear related to the meloxicam IV dose. Investigators were instructed to report the following as AEs: any postsurgical hemoglobin value <8.0 g/dL and any postsurgical hemoglobin value of 8.0–9.9 g/dL that decreased by ≥0.5 g/dL since screening. Further evaluation demonstrated that none of the shifts in hemoglobin, for any treatment group (including the placebo group), was clinically meaningful (Supplemental Digital Content 5, Figure S4, http://links.lww.com/AA/C638).

There was an unexpected incidence of ketonuria events in all study groups (Supplemental Digital Content 6, Table S2, http://links.lww.com/AA/C639). Forty-eight of the 486 subjects experienced ketonuria during the double-blind treatment phase. Further investigation showed that all ketonuria AEs occurred at the same study center where nonsteroidal anti-inflammatory drugs were not typically first-line treatment for postoperative pain management; rather, parenteral acetaminophen was used. The anomaly of ketonuria may reflect differences in the timing of resumption of adequate oral caloric intake and/or the use of glucose-containing electrolytes. According to the site investigator, the occurrence of ketonuria was more frequent than he typically had seen and therefore was reported as an AE possibly related to treatment with meloxicam and morphine.

DISCUSSION

Results of the present study demonstrate that meloxicam IV provided significant analgesic effect and, in general, was well tolerated in subjects with moderate-to-severe pain after open abdominal hysterectomy. The onset of pain relief after the administration of meloxicam IV occurred within 6–8 minutes postdose, and analgesic effects were maintained for 24 hours after dosing. Doses of 5–60 mg produced statistically significant improvements in $SPID_{24}$ and $TOTPAR_{24}$ relative to placebo; the 30 mg dose produced the greatest treatment effect. Moreover, meloxicam IV doses of ≥15 mg significantly improved $SPID_{24}$ and $TOTPAR_{24}$ relative to morphine. Beneficial effects on secondary outcome measures were also observed, and patient-reported GES suggested a preference for meloxicam IV over morphine for all but the lowest dose of meloxicam IV.

Importantly, meloxicam IV was associated with a significantly reduced need for rescue medication; total rescue opioid consumption was 42%–71% lower with meloxicam IV versus placebo during the double-blind phase. Meloxicam IV doses of 15, 30, and 60 mg were also associated with significantly lower overall rescue opioid consumption versus morphine. Opioid monotherapy has been a mainstay and standard of care for postoperative pain management and has demonstrated adequate pain reduction in a variety of soft-tissue surgical procedures. Morphine was a rigorous comparator in this surgical model; it is highly effective, acts rapidly with clearly defined efficacy, and does not require dose adjustment for renal impairment, unlike other current nonopioid IV analgesics.

Other studies have evaluated the preoperative administration of meloxicam formulations, including suppositories or oral tablets for reducing postoperative pain after hysterectomy.[16–18] In these studies, meloxicam appears to provide effective analgesia; however, in some cases, investigators observed that morphine consumption was not significantly reduced for subjects who received meloxicam compared with placebo. The relatively poor solubility and slow absorption rate of these meloxicam formulations[2,4] may not provide maximum analgesia in the immediate postoperative period. Bolus IV injections of meloxicam administered postoperatively provided onset of analgesia as early as 6 minutes postdose, and the IV formulation provides a useful alternative in the immediate postoperative period.

Meloxicam IV generally was well tolerated in this study, with a low incidence of AEs, 2 discontinuations (due to "a desire to withdraw from the study"), no deaths, and no serious treatment-related AEs. In the combined treatment phases, the most commonly reported AE was anemia. This outcome likely reflects the procedure for reporting anemia in the study protocol and was not deemed clinically meaningful by the principal investigators.

Potential limitations of this study include the use of only single doses of morphine in the double-blind phase (morphine typically can be administered every 4 hours as needed[19]) and the lack of comparators in the open-label extension. Furthermore, methods of imputation may have influenced the findings. For efficacy analyses, missing data were imputed using the last observation carried forward approach. The scores for pain intensity and pain relief for any time points after the administration of rescue medication were imputed using the last score before the rescue dose. For the analyses of time to first perceptible pain relief, time to first meaningful pain relief, and time to first rescue analgesic, data from patients who withdrew prematurely or took rescue medication were right censored. Last, subjects who were nonresponders in the meloxicam IV treatment arms in the double-blind phase and subjects who received morphine or placebo and did not require rescue medication were not eligible to enter the open-label extension phase.

In summary, meloxicam IV at doses of 5–60 mg produced statistically significant improvement in pain intensity and pain relief compared with placebo in subjects with moderate-to-severe pain after open abdominal hysterectomy. Onset of pain relief with meloxicam IV ranged from 6 to 8 minutes and was comparable to that of morphine; analgesic effect was maintained for ≤24 hours. Meloxicam IV was generally well tolerated and reduced opioid consumption. Findings of this study support further (phase 3) studies of the efficacy and safety of the IV formulation of meloxicam in subjects with moderate-to-severe postoperative pain.

ACKNOWLEDGMENTS

The authors thank Mary Tom, PharmD, and Susan Martin, PhD, of The Medicine Group for assistance with manuscript preparation and Recro Pharma, Inc, for funding.

DISCLOSURES

Name: Tomasz Rechberger, MD.
Contribution: This author helped manage subjects; helped with data acquisition and study design and its implementation; helped draft the article and/or critically reviewed it for important intellectual content; and approved the final article.
Conflicts of Interest: T. Rechberger is a consultant and paid investigator for Allergan plc, Astellas Pharma Inc, and Bayer AG.
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Contribution: This author helped provide guidance on data interpretation, helped draft the article and/or critically review it for important intellectual content, and approved the final article.
Conflicts of Interest: R. J. Mack is an employee of Recro Pharma, Inc.
Name: Stewart W. McCallum, MD.
Contribution: This author helped provide guidance on data interpretation, helped draft the article and/or critically review it for important intellectual content, and approved the final article.
Conflicts of Interest: S. W. McCallum is an employee of Recro Pharma, Inc.
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Contribution: This author helped provide guidance on data analysis and interpretation, helped design the study and its implementation, helped draft the article and/or critically review it for important intellectual content, and approved the final article.
Conflicts of Interest: W. Du receives consultancy fees from Recro Pharma, Inc.
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Contribution: This author helped provide guidance on data analysis and interpretation, helped draft the article and/or critically review it for important intellectual content, and approved the final article.
Conflicts of Interest: A. Freyer is an employee of Recro Pharma, Inc.
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