# Safety and Opioid Use Following Major Orthopedic Surgery in a Phase 3, Placebo-Controlled Study of Intravenous Meloxicam

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## ABSTRACT

Purpose: Intravenous (IV) meloxicam (also reported as N1539) is a novel IV formulation of NanoCrystal Colloidal Dispersion® meloxicam, being developed for the management of moderate to severe pain. IV meloxicam has been evaluated across a range of doses and patient populations during Phase 2 clinical studies. IV meloxicam 30 mg demonstrated rapid and sustained pain relief throughout the 24-hour dosing interval, along with reductions in opioid use, in 2 recently completed placebo-controlled Phase 3 efficacy studies in subjects with moderate to severe pain following hard and soft tissue surgeries. Dosing with IV meloxicam 30 mg was well tolerated in these studies. The Phase 3 program also included a large, multi-center, placebo-controlled, safety study that enrolled a broad population of subjects undergoing a range of major surgical procedures who received study drug once daily for up to 7 days. Major surgeries performed in this study included orthopedic, abdominal, gynecologic, spinal, and other procedures. This reported safety study included a large population of subjects undergoing orthopedic surgeries, a common surgery type resulting in subjects experiencing moderate to severe postoperative pain lasting multiple days after surgery. This abstract reports study finding in subjects who underwent orthopedic surgeries.

Methods: This was a Phase 3, multi-center, randomized, double-blind, placebo-controlled study in male and female subjects, age 18-80 years scheduled to undergo major elective surgery with an inpatient hospital stay expected to exceed 24 hours. Study participation included a screening visit with written informed consent, an inpatient visit including surgery and study treatment, and two follow-up visits after discharge (one in office and one by phone). Subjects underwent major surgeries according to the standard practice of the institution. Following surgery, eligible subjects were stratified, randomized (3:1), and administered IV meloxicam 30 mg or placebo via IV push over 15-30 seconds every 24 hours for up to 7 doses. Subjects could continue to receive opioid analgesia according to the practice of the investigator to treat uncontrolled pain symptoms; additional NSAIDs were prohibited during inpatient treatment. Opioid use was measured throughout the postoperative inpatient phase and converted to the total IV morphine equivalent dose for summary. Safety assessments included clinical laboratory tests, vital signs, ECGs, surgical wound assessment, total opioid use, and monitoring of adverse events (AEs) and serious AEs (SAEs). The primary objective of the study was to evaluate the safety of IV meloxicam 30 mg compared with placebo according to the collected safety assessments.

Results: The study randomized and treated a total of 379 subjects following major orthopedic surgery; 283 randomized to IV meloxicam 30 mg, and 96 to placebo. Subjects ranged in age from 18 to 80 years, with a mean age of 59 years. The majority of subjects were female (64.4%) and white (88.4%), with demographics similar between the treatments. Surgical procedures included joint replacements, complex foot, bunionectomy, spinal, and other procedures. The mean surgery duration was 1.4 hours, with the mean time to first dose of study drug 2.2 hours following the end of surgery. The majority of subjects (>85%) received 2 or 3 doses of study drug. IV meloxicam 30 mg was well tolerated with no deaths, and a low incidence of SAEs (2.5% of IV meloxicam vs. 4.2% of placebo) and withdrawals due to an AE (0.4% of IV meloxicam vs. 0% of placebo). AEs were generally mild or moderate in intensity, and similar in incidence between treatments. The most common treatment-emergent AEs included nausea, constipation, vomiting, increased gamma-glutamyltransferase, headache, anaemia, insomnia, and pyrexia. Administration of IV meloxicam was well tolerated with no injection site AEs. There was a low incidence of clinically meaningful changes in laboratory, vital sign, and/or ECG assessments during the study, with findings similar between treatments. Investigator assessments of surgical wound healing were favorable and consistent between treatments. Opioid consumption was lower for IV meloxicam 30 mg compared with placebo at all evaluated intervals, reaching statistical significance ($p<0.05$) in the Hour 0-24, Hour 24-48, Hour 0-48, and Hour 0-72 intervals with 27.4%, 26.1%, 26.5%, and 27.2% reductions in opioid use respectively. A lower incidence of nausea and vomiting was observed in the IV meloxicam 30 mg arm, which may have been related to the reduction in opioid use compared with placebo.

Conclusions: IV meloxicam 30 mg daily was well tolerated in subjects undergoing orthopedic surgeries compared with placebo, with a low incidence of SAEs and discontinuations due to an AE. AEs were generally mild or moderate in intensity, and similar in incidence between treatment groups. A statistically significant reduction in total opioid use, up to 27.4%, was observed at various intervals during treatment in the IV meloxicam group compared with placebo. This study supports the safety and tolerability of IV meloxicam 30 mg administered once daily as an IV bolus over 15-30 seconds for up to 7 days following major orthopedic surgery.

## INTRODUCTION

N1539 (IV meloxicam) is a novel intravenous (IV) formulation of NanoCrystal Colloidal Dispersion® meloxicam being developed for the management of moderate to severe pain. Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) of the enolic acid class that possesses analgesic, anti-inflammatory, and antipyretic activities, which are believed to be related to the inhibition of cyclooxygenase (COX) and subsequent reduction in prostaglandin biosynthesis (Mobic 2016; Turck 1997; Del Tacca 2002). Oral meloxicam has a slow onset of action, largely due to poor solubility, and is not approved for the treatment of acute pain. The use of proprietary NanoCrystal technology has been shown to provide a rapid onset of action of meloxicam, thus rendering it suitable for the treatment of acute pain via the IV route, as an alternative to, or reducing the requirements for, opioid analgesics.

The safety and efficacy of IV meloxicam have been evaluated in a range of postoperative settings in Phase 2 and Phase 3 studies including dental, abdominal, and orthopedic surgical populations. This Phase 3 study was designed to evaluate the safety of repeated dosing with IV meloxicam 30 mg in a broad population of subjects undergoing major surgeries.

## OBJECTIVE

The primary objective of this study was to evaluate the safety and tolerability of IV meloxicam as evaluated with physical examination, vital signs, clinical laboratory tests, ECGs, wound evaluation, postoperative opioid consumption, and incidence of Adverse Events (AEs) and Serious AEs (SAEs).

## METHODS

**Subjects**

Selected inclusion criteria:

- Males and females aged 18 to 80 years.
- Planning to undergo major elective surgery with a postoperative inpatient course expected to exceed 24 hours; only subjects undergoing orthopedic surgeries presented in this poster.

Selected exclusion criteria:

- Active or recent gastrointestinal (GI) bleeding or peptic ulcer disease.
- Known bleeding disorder or taking agents affecting coagulation.
- Exclusionary surgical procedures included: cranial surgery, open heart procedures, coronary artery bypass graft, organ transplant, or any other surgical procedure in which NSAIDs were contraindicated.
- Moderate to severe renal or hepatic dysfunction.

**Study Design**

- Multi-center, randomized, double-blind, placebo-controlled study at 31 sites in the US, Canada, Australia, and New Zealand.
- Participation consisted of a screening visit, a surgery and inpatient treatment/evaluation visit, and 2 follow-up visits, 7 days (in clinic) and 28 days (telephone contact) after the last study dose.
- Subjects without significant surgical complications who were stable following their procedure were randomized and dosed with study drug within 6 hours following the end of surgery.
- Randomized 3:1 to IV meloxicam 30 mg or placebo
- Study doses were administered as an IV push over approximately 15-30 seconds every 24 hours until their IV was discontinued, the subject was discharged, or the subject had received a maximum of 7 study doses.
- Subjects received peri- and postoperative analgesia per institution standards; additional NSAIDs were not allowed.
- Subjects received anticoagulation therapy per institution standards.
- Blinded safety observations were made throughout the inpatient treatment phase including vital signs, ECG, clinical laboratory testing, surgical wound healing evaluations, monitoring of opioid analgesic use, and monitoring for AEs and SAEs.
- All subjects provided informed consent prior to completing any study activities.

**Study Analysis**

- Postoperative opioid analgesic use in each subject was converted to the IV morphine equivalent dose for summary.
- The Medical Dictionary for Regulatory Activities (Version 18.1) was used to classify all AEs with respect to system organ class and preferred term.

## RESULTS

**Demographics**

- 379 subjects undergoing orthopedic surgeries randomized and dosed with study drug; 721 subjects randomized and dosed in study overall.
- Study results reported for the safety population including all treated subjects.
- The majority of subjects received 2 or 3 study doses during their participation in the study; 87.3% in IV meloxicam 30 mg group, 89.6% in placebo group.

**Table 1: Summary of Subject Demographics and Disposition**

| Variable | IV Meloxicam 30 mg (N=283) | Placebo (N=96) |
|---|---|---|
| Age (yrs) – mean ± SD | 59.7 ± 10.90 | 59.5 ± 12.06 |
| Age ≥ 65 years, n (%) | 109 (38.5) | 37 (38.5) |
| Sex, n (%) | | |
| Male | 105 (37.1) | 30 (31.3) |
| Female | 178 (62.9) | 66 (68.8) |
| Race, n (%) | | |
| White | 249 (88.0) | 86 (89.6) |
| Black or African American | 30 (10.6) | 6 (6.3) |
| Asian | 3 (1.1) | 3 (3.1) |
| Multiple | 1 (0.4) | 1 (1.0) |
| Ethnicity, n (%) | | |
| Hispanic or Latino | 30 (10.6) | 12 (12.5) |
| Not Hispanic or Latino | 253 (89.4) | 84 (87.5) |
| Baseline BMI (kg/m$^2$) – mean ± SD | 30.2 ± 4.7 | 29.8 ± 4.8 |
| Surgery Duration (hr) – mean ± SD | 1.3 ± 0.77 | 1.4 ± 0.95 |
| Time (hr) from End of Surgery to First Dose – mean ± SD | 2.1 ± 1.47 | 2.2 ± 1.46 |
| Surgery Type, n (%) | | |
| Bunionectomy | 40 (14.1) | 13 (13.5) |
| Complex Foot | 52 (18.4) | 19 (19.8) |
| Complex Shoulder Surgery | 6 (2.1) | 2 (2.1) |
| Orthopedic Trauma | 0 | 1 (1.0) |
| Spinal | 10 (3.5) | 3 (3.1) |
| Total Ankle Replacement | 1 (0.4) | 0 |
| Total Hip Replacement | 50 (17.7) | 18 (18.8) |
| Total Knee Replacement | 117 (41.3) | 39 (40.6) |
| Total Shoulder Replacement | 7 (2.5) | 1 (1.0) |

**Safety**

- Doses of IV meloxicam 30 mg were well tolerated during the study, with the majority of subjects receiving 2 or 3 study doses.
- The incidence and severity of AEs were generally similar between groups.
- Wound healing and clinical laboratory assessments were similar between treatment groups.
- No trends for changes in vital signs or ECGs were observed.
- Statistically significant reductions in postoperative opioid use were observed in the IV meloxicam group compared with placebo.

Adverse Events

- AEs were generally reported to be of mild or moderate intensity and occurred with similar frequency between treatment groups.
- There was a low incidence of SAEs, occurring more frequently in the placebo group overall (2.5% of IV meloxicam treated subjects vs. 4.2% of placebo treated subjects).
  - SAEs were all reported as single incidence events in individual subjects with exception of post procedural pulmonary embolism in 2 (0.7%) IV meloxicam treated subjects; both events of post procedural pulmonary embolism were assessed by the investigator as being not related to study treatment.
- There was a low incidence of discontinuations due to an AE (0.4% of IV meloxicam treated subjects vs. 0% of placebo treated).
- No deaths were reported during or following treatment in the study.
- AEs of special interest (including hepatic, renal, cardiovascular, bleeding, wound healing, and injection site events) were generally similar between treatments.
  - Renal events in IV meloxicam subjects included acute kidney injury (2) and blood urea increased (2), and were mild or moderate in intensity and assessed as being not related to study treatment, except one event of blood urea increased considered possibly related.
  - Thrombotic events in IV meloxicam subjects included post procedural pulmonary embolism (2), and deep vein thrombosis (1), and were each assessed as being not related to study treatment.

**Table 2: Summary of Treatment-Emergent AEs in ≥ 4% of Subjects in Either Treatment Group - Number of Subjects (%)**

| Preferred Term | IV Meloxicam 30 mg (N=283) | Placebo (N=96) |
|---|---|---|
| Any AE | 183 (64.7) | 66 (68.8) |
| Nausea | 67 (23.7) | 30 (31.3) |
| Constipation | 35 (12.4) | 13 (13.5) |
| Vomiting | 20 (7.1) | 10 (10.4) |
| Gamma-glutamyltransferase increased | 17 (6.0) | 5 (5.2) |
| Headache | 15 (5.3) | 5 (5.2) |
| Anaemia | 12 (4.2) | 4 (4.2) |
| Insomnia | 8 (2.8) | 5 (5.2) |
| Dizziness | 6 (2.1) | 6 (6.3) |
| Hypotension | 8 (2.8) | 4 (4.2) |
| Pruritus | 8 (2.8) | 4 (4.2) |

**Table 3: Summary of AEs of Special Categories - Number of Subjects (%)**

| Event Category | IV Meloxicam 30 mg (N=283) | Placebo (N=96) |
|---|---|---|
| Subjects with ≥ 1 Event | 56 (19.8) | 15 (15.6) |
| Bleeding | 13 (4.6) | 4 (4.2) |
| Cardiovascular | 3 (1.1) | 2 (2.1) |
| Hepatic | 27 (9.5) | 7 (7.3) |
| Injection Site Reactions | 0 | 0 |
| Renal | 4 (1.4) | 0 |
| Thrombotic | 3 (1.1) | 0 |
| Wound Healing | 12 (4.2) | 3 (3.1) |

Clinical Laboratory Assessment

- Clinical chemistry, hematology, urinalysis, and coagulation tests were routinely evaluated during the study.
- Laboratory assessments related to bleeding risk, and renal or hepatic function were of interest due to the known class effects of NSAIDs. The incidence of laboratory changes in these categories were similar between treatment groups.

Wound Healing Assessment

- Surgical wounds were assessed for investigator satisfaction with wound healing rated using a 0-10 scale (0=not satisfied; 10=completely satisfied), along with assessing various characteristics including erythema, drainage, edema, induration, and hematoma.
- Overall satisfaction assessments were similar between IV meloxicam 30 mg and placebo at each assessment
- The incidence of clinically significant wound assessment parameters was low and generally similar between treatment groups.

**Figure 1: Investigator Assessment of Wound Healing – Mean ± SD**

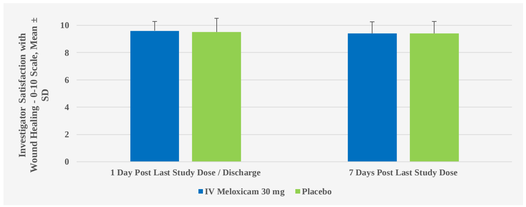


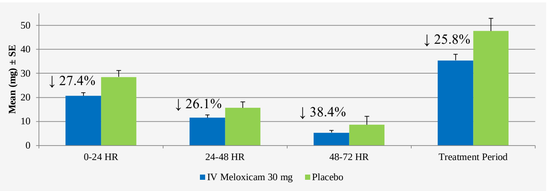

**Table 4: Summary of Clinically Significant Wound Healing Parameters on Investigator Assessment**

| Assessment Parameter | IV Meloxicam 30 mg (N=283) | Placebo (N=96) |
|---|---|---|
| Erythema | 3 (1.1) | 1 (1.1) |
| Drainage | 1 (0.4) | 1 (1.1) |
| Edema | 1 (0.4) | 0 |
| Induration | 1 (0.4) | 0 |
| Hematoma | 1 (0.4) | 0 |

Postoperative Opioid Use

- Opioid analgesics were utilized postoperatively for management of uncontrolled pain symptoms. Opioid analgesic doses were converted to the IV Morphine Equivalent Dose (IVMED) in mg, using a standardized conversion table.
- Opioid consumption was reduced in the IV meloxicam 30 mg group during all measured intervals compared with placebo.
- Statistically significant ($p<0.05$) reductions in opioid use for IV meloxicam 30 mg compared with placebo were observed during the Day 1 (Hour 0-24), Day 2 (Hour 24-48), Day 1-2 (Hour 0-48), Day 1-3 (Hour 0-72), and the Treatment Overall intervals.

**Figure 2: Summary of Postoperative Opioid Analgesic Use (IVMED in mg)**




## CONCLUSIONS

- AEs were mild or moderate in intensity, and similar in incidence between treatment groups.
- There was a low incidence of SAEs, with the overall incidence more frequent in the placebo group compared with IV meloxicam.
- Wound healing assessments were similar between treatment groups.
- A statistically significant reduction in total opioid use was observed at various intervals during treatment in the IV meloxicam group compared with placebo.
- This study supports the safety and tolerability of IV meloxicam 30 mg administered once daily as an IV bolus for up to 7 days following major orthopedic surgery.

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