An Evaluation of Safety and Opioid Use in Subjects Receiving Meloxicam IV Following Foot and Ankle Surgeries in a Phase 3, Placebo-Controlled Study

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ABSTRACT

Statement of Purpose: This Phase 3 study was designed to evaluate the safety of meloxicam IV compared with placebo following major surgery.

Methodology: Data from subjects undergoing foot and ankle surgeries (N=124) are presented from a large randomized, double-blind, placebo-controlled trial of the safety of meloxicam IV (N=721). Subjects were randomized 3:1 to meloxicam IV 30 mg or placebo administered once daily starting within 6 hours following surgery.

Procedures: The overall study enrolled subjects undergoing a range of major surgeries. The reported cohort includes subjects who underwent ORIF, osteotomy, ankle stabilization, bunionectomy, and arthrodesis procedures.

Results: The study randomized and dosed a total of 124 subjects following foot and ankle surgeries, age 18 to 77 years (mean 53.2) with demographics similar between treatments. Meloxicam IV 30 mg was generally well tolerated with no deaths, withdrawals due to an adverse event (AE), or serious AEs. The most common treatment-emergent AEs included nausea, vomiting, constipation, and headache. Overall, AEs were reported with greater incidence in placebo vs. meloxicam IV subjects (62.5% vs. 53.3%). Wound healing by investigator evaluation was comparable between treatments. Opioid consumption was lower for meloxicam IV compared with placebo at all evaluated intervals, with a 47.2% reduction observed during the 48 hours following surgery.

Discussion: The safety of dosing with meloxicam IV 30 mg was generally well tolerated in subjects undergoing foot and ankle surgeries, combined with a significant reduction in postoperative opioid utilization. This study supports the safety and tolerability of meloxicam IV 30 mg administered once daily following major foot and ankle surgery.

INTRODUCTION

Meloxicam intravenous (IV) is a novel 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 relatively 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 meloxicam IV 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 meloxicam IV 30 mg in a broad population of subjects undergoing major surgeries, with this poster presenting the results observed in subjects who underwent foot and ankle surgeries.

OBJECTIVE

The primary objective of this study was to evaluate the safety and tolerability of meloxicam IV 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.

Selected exclusion criteria:

- Active or recent gastrointestinal (GI) bleeding or peptic ulcer disease.
- Known bleeding disorder or taking agents affecting coagulation.
- Admission to the ICU following surgery
- 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 meloxicam IV 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 based on specific needs for the procedure and/or patient.
- 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 (IVMED) 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

- 124 subjects undergoing foot and ankle surgeries randomized and dosed; 721 subjects received ≥ 1 dose of study drug overall in the study.
- Study results reported for the safety population including all treated subjects.
- All subjects undergoing foot and ankle surgeries received 2 or 3 study doses during their participation in the study.
- This foot and ankle surgery population included subjects who underwent bunionectomy or complex foot surgeries which included ORIF, osteotomy, ankle stabilization, and arthrodesis procedures.

Table 1: Summary of Subject Demographics and Disposition

Variable	Meloxicam IV 30 mg (N=92)	Placebo (N=32)
Age (yrs) – mean ± SD	53.9 ± 11.63	51.2 ± 12.84
Age > 65 years with Impaired Renal Function, n (%)	15 (16.3%)	3 (9.4%)
Sex, n (%)		
Male	17 (18.5%)	0
Female	75 (81.5%)	32 (100.0%)
Race, n (%)		
White	73 (79.3%)	26 (81.3%)
Black or African American	15 (16.3%)	4 (12.5%)
Asian	3 (3.3%)	1 (3.1%)
Multiple	1 (1.1%)	1 (3.1%)
Ethnicity, n (%)		
Hispanic or Latino	22 (23.9%)	9 (28.1%)
Not Hispanic or Latino	70 (76.1%)	23 (71.9%)
Baseline BMI (kg/m²) – mean ± SD	28.9 ± 4.85	29.0 ± 5.01
Surgery Duration (hr) – mean ± SD	0.9 ± 0.56	1.0 ± 0.55

Safety

- Doses of meloxicam IV 30 mg were generally well tolerated during the study, with all subjects receiving 2 or 3 study doses.
- The incidence and severity of AEs were generally similar between meloxicam IV and placebo 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 meloxicam IV group compared with placebo.

Adverse Events

- AEs were all reported to be of mild or moderate intensity and were similar between treatment groups; AEs were seen with a greater overall incidence in the placebo group compared with meloxicam IV.
- AEs of special interest (including hepatic, renal, cardiovascular, bleeding, wound healing, and injection site events) were infrequent, and generally similar between treatments.
- There were no SAEs reported in subjects undergoing foot and ankle surgeries.
- No subject discontinued due to an AE
- No deaths were reported during or following treatment in the study.

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 incidences of potentially clinically significant changes from normal at baseline to any postdose assessment were infrequent, and are summarized in Table 4.

Table 2: Summary of Treatment-Emergent AEs in > 1 Subject in Either Treatment Group - Number of Subjects (%)

Preferred Term	Meloxicam IV 30 mg (N=92)	Placebo (N=32)
Subjects with ≥ 1 AE	49 (53.3)	20 (62.5)
Nausea	14 (15.2)	9 (28.1)
Vomiting	10 (10.9)	5 (15.6)
Headache	9 (9.8)	3 (9.4)
Constipation	4 (4.3)	4 (12.5)
Dermatitis contact	6 (6.5)	1 (3.1)
Pruritus generalised	7 (7.6)	0
Gamma-glutamyltransferase increased	4 (4.3)	2 (6.3)
Alanine aminotransferase increased	2 (2.2)	2 (6.3)
Aspartate aminotransferase increased	1 (1.1)	2 (6.3)
Blood alkaline phosphatase increased	1 (1.1)	2 (6.3)
Infusion site extravasation	3 (3.3)	0
Cellulitis	2 (2.2)	0

Table 3: Summary of Treatment-Emergent AEs of Special Interest - Number of Subjects (%)

Preferred Term	Meloxicam IV 30 mg (N=92)	Placebo (N=32)
Subjects with ≥ 1 Event	11 (12.0)	4 (12.5)
Gamma-glutamyltransferase increased	4 (4.3)	2 (6.3)
Alanine aminotransferase increased	2 (2.2)	2 (6.3)
Aspartate aminotransferase increased	1 (1.1)	2 (6.3)
Blood alkaline phosphatase increased	1 (1.1)	2 (6.3)
Cellulitis	2 (2.2)	0
Incision site erythema	0	1 (3.1)
Incision site rash	1 (1.1)	0
International normalised ratio abnormal	1 (1.1)	0
Localised infection	1 (1.1)	0
Postoperative wound infection	1 (1.1)	0
Prothrombin time abnormal	1 (1.1)	0

Table 4: Potentially Clinically Significant Change in Laboratory Assessments from Normal at Baseline – Number of Subjects (%)

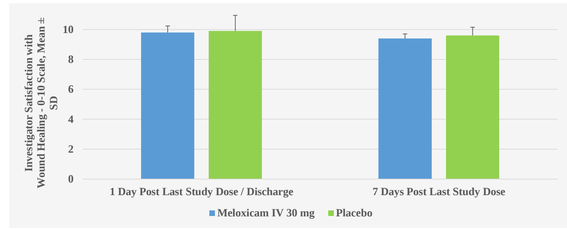
Parameter	Potential Significance Criteria	Meloxicam IV 30 mg	Placebo
Hematocrit	< 30%	-	-
Hemoglobin	< 10 g/dL	-	-
Creatinine	>1.5x ULN	-	-
ALT	3-10x ULN	-	1 (3.1)
	≥10x ULN	-	-
AST	3-10x ULN	-	2 (6.3)
	≥10x ULN	-	-
GGT	≥3x ULN	2 (2.2)	3 (9.4)
Alkaline Phosphatase	1-3x ULN	15 (16.3)	5 (15.6)
	3-10x ULN	-	-
Total Bilirubin	> 2x ULN	-	-
aPTT	≥ 55 seconds	-	-
INR	> 1.5	1 (1.1)	-

ULN=Upper Limit of Normal range

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 meloxicam IV 30 mg and placebo at each assessment
- The incidence of clinically significant wound assessment parameters was low and generally similar between treatment groups.

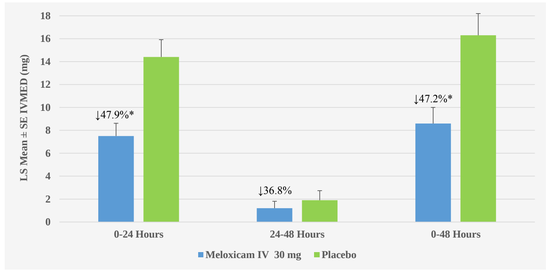
Figure 1: Investigator Assessment of Wound Healing – Mean ± SD



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 meloxicam IV 30 mg group during all measured intervals compared with placebo.
- Statistically significant ($p<0.05$) reductions in opioid use for meloxicam IV 30 mg compared with placebo were observed during the Day 1 (Hour 0-24) and Day 1-2 (Hour 0-48) intervals.

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



* $P < 0.005$

CONCLUSIONS

- AEs were mild or moderate in intensity, and similar in incidence between treatment groups.
- There was a low incidence of SAEs, with events reported more frequently in the placebo group compared with meloxicam IV.
- Wound healing assessments, as performed by the investigator, were similar between treatment groups.
- A statistically significant reduction in total opioid use was observed at various intervals during treatment in the meloxicam IV group compared with placebo.
- This study supports the safety and tolerability of meloxicam IV 30 mg administered once daily as an IV bolus in subjects undergoing foot and ankle surgery

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