Poster #759

Efficacy and Safety of Preoperative Meloxicam IV in Primary Total Knee Arthroplasty

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INTRODUCTION

Intravenous (IV) meloxicam (Meloxicam IV; Anjeso™) is a novel formulation of NanoCrystal Colloidal Dispersion® meloxicam, approved for use in adults for the management of moderate-to-severe pain, alone or in combination with non-NSAID analgesics. To date, nine Phase 2 & 3 clinical studies have been completed in subjects with postoperative pain in the meloxicam IV development program. Previously, studies primarily explored dosing beginning following surgery, after the onset of moderate to severe pain, in order to observe reductions in pain after meloxicam IV administration. In this study, preoperative administration of meloxicam IV was utilized to replicate conditions consistent with current clinical practice, including use of a standardized clinical care protocol based in common best practices for Total Knee Arthroplasty (TKA) procedures, including multimodal analgesia.

OBJECTIVES

Primary Objective: Assess the effect of preoperative administration of meloxicam IV on opioid consumption in subjects undergoing open unilateral TKA compared to placebo.

Secondary objectives were to assess:

- Safety and tolerability of preoperative administration of meloxicam IV compared to placebo
- Effects of preoperative meloxicam IV on postoperative pain and healthcare utilization costs vs. placebo.

METHODS

Subjects

This study was conducted under an FDA IND, IRB approval was obtained prior to study conduct, and all subjects provided written informed consent.

Selected inclusion criteria:

- Males and females aged 35 to 80 years.
- Planning to undergo an elective, primary (no repeat arthroplasties) open unilateral TKA, and be expected to require IV analgesia in an inpatient setting for ≥24 hours.

Selected exclusion criteria:

- Active or recent gastrointestinal (GI) bleeding or peptic ulcer disease.
- Known bleeding disorder or taking agents affecting coagulation.
- Moderate to severe renal or hepatic dysfunction.

Study Design

- Multi-center, randomized, double-blind, placebo-controlled study.
- Participation consisted of a screening visit, surgery/inpatient visit, and 2 follow-up visits after surgery.
- Subjects were randomized 1:1 to meloxicam IV 30 mg or placebo.
- The first study dose was administered prior to the start of surgery, after spinal anesthesia; subsequent doses were administered every 24 hours.
- Subjects received pre-, peri-, and post-operative clinical care per standardized protocol defining medication use and other surgical and recovery activities; including pre-op APAP and Gabapentin, peri-op Bupivacaine, and post-op APAP 650 mg Q8H, etc.
- Subjects utilized opioids postoperatively for analgesia as required; no additional NSAIDs were allowed.

RESULTS

Demographics

- 194 subjects randomized with 181 subjects receiving ≥ 1 dose of study drug.
- The majority of subjects received 2 or 3 study doses during their participation in the study; 87.1% in meloxicam IV 30 mg group, 75.0% in placebo group.

Table 1: Summary of Subject Demographics and Surgery Characteristics

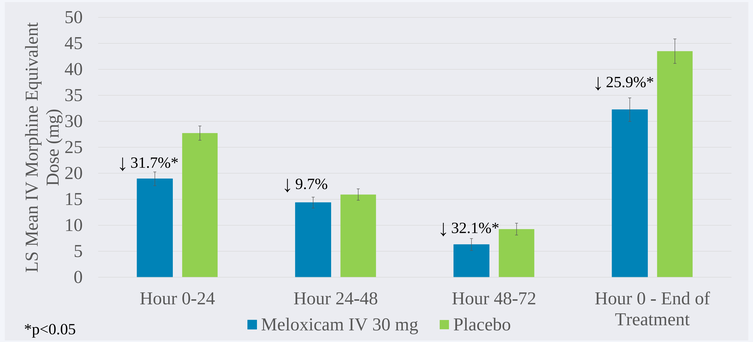
Variable	Meloxicam IV 30 mg (N=93)	Placebo (N=88)	Overall (N=181)
Age (yrs); mean ± SD	66.9 ± 8.23	65.5 ± 8.11	66.2 ± 8.18
Age ≥ 65 years; n (%)	58 (62.4)	54 (61.4)	112 (61.9)
Sex, Male / Female; n (%)	39 (41.9) / 54 (58.1)	37 (42.0) / 51 (58.0)	76 (42.0) / 105 (58.0)
Race; n (%)			
White	74 (79.6)	70 (79.5)	144 (79.6)
Black or African American	18 (19.4)	17 (19.3)	35 (19.3)
Baseline BMI (kg/m^2); mean ± SD	30.6 ± 4.7	31.5 ± 5.1	31.1 ± 4.9
Surgery Duration (hr); mean ± SD	1.27 ± 0.22	1.31 ± 0.24	1.29 ± 0.23
Quadricep Tendon Spared; n (%)	67 (72.0)	58 (65.9)	125 (69.1)

Efficacy

Primary Efficacy Endpoint – Opioid Consumption on First Postsurgical Day

- Meloxicam IV 30 mg group had significantly lower opioid consumption during the first postsurgical day, with a 31.7% reduction vs. placebo (LS Mean 18.94 mg vs. 27.73 mg; p<0.0001).
- Significant reductions in opioid use observed on subsequent days and throughout treatment

Figure 1: Summary of Opioid Consumption



*p<0.05

Secondary Efficacy Endpoints

- Summed Pain Intensity (SPI): Meloxicam IV 30 mg had a significantly lower SPI on the first postsurgical day and throughout their inpatient course (p≤0.0001; see Table 2).
- Opioid Free Subjects: Most subjects received at least one opioid medication on the first postsurgical day, with no difference in the incidence of opioid free subjects between treatment groups.
- Opioid Rescue: Meloxicam IV 30 mg treated subjects had a significantly longer time to first opioid rescue after surgery compared with placebo (see Table 2).

Other Efficacy Findings

- A significant difference was noted on Day 1 for Patient Global Assessment (PGA) and Overall Benefit of Analgesia scores (OBAS) favoring meloxicam IV (p=0.0105 and 0.0027), but was not present on subsequent days.
- No significant differences were identified in the time to first ambulation or PI on ambulation.
- Meloxicam IV 30 mg treated subjects had numerically lower incidences of all cause hospital readmissions, fewer subjects discharged to skilled nursing facilities, and fewer ER visits and doctor calls related to pain during the follow-up period (see ASRA 2020 ePoster #651).

Table 2: Efficacy Endpoints

Efficacy Parameter	Meloxicam IV 30 mg (N=93)	Placebo (N=88)	P-value
SPI; LS Mean (SE)			
Post Surgical Day 1 (Hour 0-24)	5328 (238.1)	6854 (248.6)	<0.0001
Inpatient Period (Hour 0-DC)	10541 (993.0)	15670 (1045)	0.0001
Opioid Free Subjects			
Post Surgical Day 1 (Hour 0-24)	1 (1.1)	0	0.2482
Opioid Rescue; median			
Time to first rescue, hours	3.38	2.78	0.0021

Safety

- AEs were primarily mild or moderate in intensity and not related to study treatment, with a higher incidence of AEs reported in the placebo group.
- The incidence of SAEs was generally higher in the placebo group (3 meloxicam IV subjects [3.2%] vs. 9 placebo subjects [10.2%]), with all events in the meloxicam IV group assessed as not related to study treatment; no subject discontinued due to an AE.
- AEs of special interest (AEOSI; events related to concerns associated with NSAIDS) including bleeding, cardiovascular, hepatic, injection site reactions, renal, thrombotic, and wound healing events are summarized in Table 3.
- Laboratory and surgical wound healing assessments were similar between treatment groups.

Table 3: Adverse Events of Special Interest in >1 Subject in either treatment – N (%)

AEOSI Category / Preferred Term	Meloxicam IV 30 mg (N=93)	Placebo (N=88)
Any AE	65 (69.9)	81 (92.0)
Any AEOSI	9 (9.7)	19 (21.6)
Bleeding	4 (4.3)	3 (3.4)
Anaemia	3 (3.2)	2 (2.3)
Cardiovascular	0	8 (9.1)
Hypertension	0	7 (8.0)
Hepatic	3 (3.2)	3 (3.4)
GGT increased	2 (2.2)	2 (2.3)
Renal	1 (1.1)	1 (1.1)
Thrombotic	0	4 (4.5)
Pulmonary embolism	0	2 (2.3)
Wound Healing	1 (1.1)	4 (4.5)
Cellulitis	0	3 (3.4)

CONCLUSIONS

- Preoperative administration of meloxicam IV 30 mg demonstrated efficacy with significant reductions in opioid consumption (primary endpoint) and summed pain intensity, along with a longer time to first opioid rescue vs. placebo.
- Safety profile for preoperative administration of meloxicam IV 30 mg demonstrated a lower overall incidence of AEs and SAEs compared with placebo.
- This study supports the efficacy and safety of meloxicam IV 30 mg administered IV once daily, with administration beginning prior to surgery, as part of a multimodal regimen in subjects undergoing primary unilateral TKA. Additional research is required to further evaluate use in this setting.