Efficacy and Safety of N1539, Intravenous Meloxicam, in a Phase 3 Study of Subjects with Moderate to Severe Pain following Abdominoplasty

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ABSTRACT

This Phase 3, multicenter, randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of N1539 in 219 subjects with moderate to severe pain following abdominoplasty. Subjects were enrolled and randomized to treatment (1:1 ratio) with N1539 30 mg or placebo administered via IV push every 24 hours for up to three doses. N1539 is a novel intravenous (IV) formulation of NanoCrystal Colloidal Dispersion® meloxicam, a nonsteroidal anti-inflammatory drug (NSAID), developed for the management of moderate to severe pain.

Baseline characteristics were similar between groups, with a mean pain intensity (numeric pain rating scale, 0-10) of 7.2 in the N1539 group and 7.4 in the placebo group. In the primary efficacy assessment, N1539 demonstrated a statistically significant reduction in the summed pain intensity difference (SPID) through 24 hours following Dose 1 ($SPID_{24}$; p=0.0145) compared to the placebo group. Statistically significant reductions in SPID were also observed through 12 hours ($SPID_{12}$; p=0.0434) and 48 hours post Dose 1 ($SPID_{48}$; p=0.0040) compared with placebo. The study achieved numerous other secondary endpoints, including statistically significant differences in time to perceptible pain relief (p=0.0050), number of subjects with ≥30% improvement in pain reduction at 24 hours (p=0.0178), number of times subjects required rescue analgesia in the first 24 hours (p=0.0275) and from 24 to 48 hours (p<0.0009), along with other pain endpoints.

The safety results demonstrated that N1539 was well tolerated with no difference in adverse event (AE) reporting between the groups. Two serious AEs (SAEs) related to bleeding were reported (one event in each treatment group), with two additional SAEs reported in the placebo group. The most common (≥2%) treatment-emergent AEs (TEAEs) in N1539 treated subjects were nausea, headache, vomiting, and dizziness, which were observed at a lower incidence than in the placebo group. The majority of TEAEs were mild in intensity, with one subject discontinuing treatment due to an SAE of post-procedural bleeding (placebo). Investigator assessments of satisfaction with wound healing and various wound characteristics were comparable between N1539 and placebo groups. There were no meaningful differences between treatment groups in vital signs, ECGs, or clinical laboratory assessments.

The data from this study demonstrated that N1539 provided significant pain relief in subjects with moderate to severe pain following abdominoplasty surgery, with a favorable safety and tolerability profile.

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 currently 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.

The safety and efficacy of IV meloxicam have been evaluated in a range of postoperative settings in Phase 2 studies including dental, abdominal, and orthopedic surgical populations. This Phase 3 study was designed to evaluate the efficacy and safety of dosing with IV meloxicam 30 mg in an adequate and well controlled trial in a soft tissue model of moderate to severe pain.

OBJECTIVE

The primary objective of this study was to demonstrate the analgesic efficacy of IV meloxicam 30 mg compared with placebo, using the summed pain intensity difference over the first 24 hours ($SPID_{24}$) in subjects with moderate to severe pain following abdominoplasty surgery.

Secondary objectives of this study included:

- Evaluating the analgesic effects of IV meloxicam 30 mg versus placebo at various time points using a series of secondary efficacy endpoints for pain intensity, pain relief, and use of rescue medication
- Determine the safety and tolerability of IV meloxicam 30 mg as evaluated with physical examination, vital signs, clinical laboratory tests, ECGs, wound evaluation, and incidence of Adverse Events (AEs) and Serious AEs (SAEs).

METHODS

Subjects

All subjects provided informed consent prior to completing any study activities.

Selected inclusion criteria:

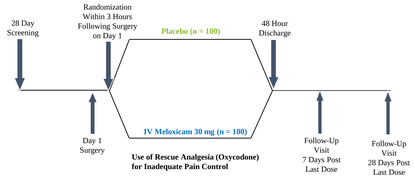
- Healthy males and females aged 18 to 75 years.
- Undergoing abdominoplasty surgery without collateral procedures.
- Moderate to severe pain within 3 hours of the end of surgery (last suture), with a numeric pain rating scale (NPRS) score ≥ 4 out of 10.

Selected exclusion criteria:

- Active or recent gastrointestinal (GI) bleeding or peptic ulcer disease.
- Known bleeding disorder or taking agents affecting coagulation.
- Taking or had taken an opioid chronically (more than one month of routine use) for pain in the past year
- Major surgery within previous 3 months
- Other painful condition that could interfere with pain assessments

Study Design

- Multi-center, randomized, double-blind, placebo controlled study at 4 US sites
- Participation consisted of a screening visit, surgery and inpatient evaluation, and 2 follow-up visits, 7 and 28 days after last study dose.
- Following abdominoplasty, subjects could be maintained using IV fentanyl until eligible to randomize to treatment
- Randomized 1:1 to IV meloxicam 30 mg or placebo
- Study doses were administered as an IV push over approximately 15 seconds every 24 hours for a minimum of two doses, with an optional third dose prior to discharge.



Surgical Procedure

- Surgical approach was to be anterior, with the incision in general to be from one ASIS (anterior superior iliac spine) to the other.
- Midline fascial plication was performed
- Surgical drains were place
- No local or regional anesthesia was used
- No additional modalities such as suction lipectomy were employed

Endpoints

Efficacy

The primary efficacy endpoint was the summed pain intensity difference over the first 24 hours ($SPID_{24}$).

Secondary efficacy endpoints included:

- SPID at various other time points ($SPID_6$, $SPID_{12}$, $SPID_{48}$ and $SPID_{24-48}$)
- Time to perceptible and meaningful pain relief as measured by two stopwatch technique
- Proportion of subjects with improvement ≥ 30% and ≥ 50% within 6 hours and within 24 hours following the first study dose; improvement defined as percent of pain reduction from baseline
- Patient Global Assessment (PGA) of pain control at Hour 24 and Hour 48
- Time to administration of first dose of rescue analgesia and number of times rescue analgesia used during 0-24, 24-48 and 0-48 hours

Safety:

The safety endpoints included the following:

- Incidence of AEs and SAEs
- Change from baseline in laboratory tests; incidence of abnormal clinical laboratory tests, including routine blood chemistry, hematology, urinalysis, and coagulation tests
- Change from baseline in vital signs; incidence of clinically significant changes in vital signs
- Incidence of clinically significant abnormal ECG findings
- Incidence of abnormal wound healing

Statistical Analysis

Efficacy analyses were performed using the Intent-to-Treat (ITT) analysis set, which included all randomized subjects. The safety analysis set includes all subjects treated with study drug. All randomized subjects received study drug, therefore the efficacy and safety populations were the same. Analysis of covariance (ANCOVA) was used to assess the difference between treatment groups for SPID. The ANCOVA model included main effects of treatment and investigational site and a covariate of baseline pain intensity score. Least-squares means (LSmeans) and standard error (SE) of the LSmeans were used to test the difference between groups using 2-sample t-test. Difference in LSmeans and corresponding 95% confidence intervals (CIs) are presented. Difference between groups in the proportion of subjects meeting the improvement criteria and the proportion of subjects who used rescue medication were evaluated with the relative risk (odds ratio) and corresponding 95% CIs. All tests were a 2-sided test at the 0.05 significance level. Nominal p values were reported as is. The primary analysis was the 2 hour windowed last observation carried forward (W2LOCF) where the pain intensity (PI) score obtained prior to a rescue was carried forward to replace PI scores collected within 2 hours following this rescue. Sensitivity analyses included last observation carried forward (LOCF) from the first use of rescue medication, baseline observation carried forward (BOCF) from the first use of rescue medication, and the OBSERVED analysis included all collected PI scores without imputation.

The Medical Dictionary for Regulatory Activities (Version 18.1) was used to classify all AEs with respect to system organ class and preferred term. AEs were summarized by treatment.

RESULTS

Demographics

- A total of 219 subjects were enrolled in this study.
- All enrolled subjects were randomized and treated with study drug, and included in the safety and efficacy analyses.

Table 1: Summary of Subject Demographics and Disposition

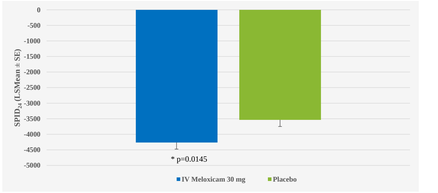
Variable	IV Meloxicam 30 mg (N=110)	Placebo (N=109)	Overall (N=219)
Age (yrs) – mean ± SD	38.9 ± 8.40	41.0 ± 9.63	40.0 ± 9.08
Subjects ≥ 65 Years - n (%)	0	2 (1.8)	2 (0.9)
Sex, n (%)			
Male	1 (0.9)	3 (2.8)	4 (1.8)
Female	109 (99.1)	106 (97.2)	215 (98.2)
Race, n (%)			
White	69 (62.7)	69 (63.3)	138 (63.0)
Black or African American	37 (33.6)	36 (33.0)	73 (33.3)
Asian	3 (2.7)	2 (1.8)	5 (2.3)
American Indian or Alaska Native	0	1 (0.9)	1 (0.5)
Other	1 (0.9)	1 (0.9)	2 (0.9)
Ethnicity, n (%)			
Hispanic or Latino	42 (38.2)	45 (41.3)	87 (39.7)
Not Hispanic or Latino	68 (61.8)	64 (58.7)	132 (60.3)
Baseline BMI (kg/m^2) – mean ± SD	26.5 ± 3.08	26.9 ± 3.16	26.7 ± 3.12
Surgery Duration (hr) – mean ± SD	1.3 ± 0.48	1.4 ± 0.44	1.4 ± 0.46
Time (hr) from End of Surgery to First Dose – mean ± SD	0.85 ± 0.57	0.86 ± 0.53	0.85 ± 0.55
Baseline PI (0-10) – mean ± SD	7.2 ± 1.57	7.4 ± 1.68	-

Efficacy

Primary Efficacy Endpoint – $SPID_{24}$

- Statistically significant difference in $SPID_{24}$ favoring IV meloxicam 30 mg over placebo (p=0.0145); a smaller SPID value demonstrates greater treatment effect.
- Sensitivity analyses of the $SPID_{24}$ each showed that the IV meloxicam 30 mg treated subjects had numerically greater total pain reduction (i.e., a smaller SPID value) compared with placebo.

Figure 1: $SPID_{24}$



SPID At Other Intervals

- SPID assessed at other postdose intervals ($SPID_6$, $SPID_{12}$, $SPID_{48}$, and $SPID_{24-48}$) favored IV meloxicam at all intervals, and reached statistical significance at all but the $SPID_6$ interval (p<0.05).
- End of dose intervals ($SPID_{12-24}$, $SPID_{24-48}$, $SPID_{36-48}$, and $SPID_{24-48}$) numerically favored IV meloxicam 30 mg over placebo at each interval, and achieved statistical significance at all but the $SPID_{12-24}$ interval, suggesting that IV meloxicam 30 mg maintains meaningful analgesia throughout the 24 hours dosing interval

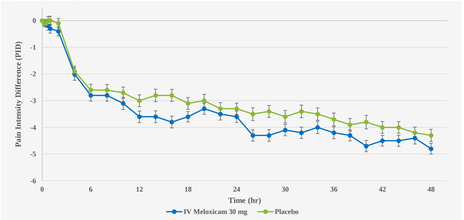
Table 2: SPID (LS Mean ± SE) At Other Intervals

Parameter	IV Meloxicam 30 mg (N=110)	Placebo (N=109)	p-value
$SPID_6$	-607.0 (52.45)	-510.9 (52.66)	0.1841
$SPID_{12}$	-1763.8 (104.77)	−1471.1 (105.18)	0.0434
$SPID_{48}$	-10600.0 (442.31)	-8829.2 (444.08)	0.0040
$SPID_{12-24}$	-2498.3 (123.63)	-2064.7 (124.12)	0.0115
$SPID_{36-48}$	-3276.2 (128.54)	-2827.6 (129.05)	0.0119

Pain Intensity Difference (PID)

- Calculated as the difference in PI at each postdose time point compared with baseline.
- PID was lower in the IV meloxicam 30 mg group compared with placebo at all time points after 30 minutes postdose; PID values were equal prior to 30 minutes post dose.

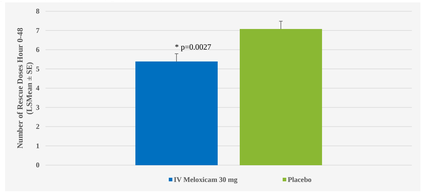
Figure 2: Pain Intensity Difference Over Time



Rescue Analgesia Use

- Rescue analgesia (oxycodone 5 mg PO) was available to subjects with inadequately controlled pain during the treatment phase.
- The number of rescue doses utilized per subject was significantly lower in each assessed study interval (Hour 0-24, Hour 24-48, and Hour 0-48) in the IV meloxicam 30 mg group compared with placebo (p<0.05).
- The number of subjects utilizing rescue in each assessed study interval (Hour 0-24, Hour 24-48, and Hour 0-48) was numerically lower in the IV meloxicam 30 mg group compared with placebo.
- No difference was observed in the time to first rescue use.

Figure 3: Number of Rescue Analgesia Doses from Hour 0-48



Time to Perceptible and Meaningful Pain Relief

- Kaplan-Meier estimates of median time to perceptible pain relief were significantly shorter for the IV meloxicam 30 mg group compared with placebo (0.76 vs. 1.28 hours; p=0.005), however a statistical difference in time to meaningful pain relief was not achieved.

Patient Global Assessment of Pain Control

- Subjects were asked to evaluate how well their pain was controlled in the study according to a 5-point scale with categories of 0-poor, 1-fair, 2-good, 3-very good, or 4-excellent.
- No significant difference in PGA was identified at Hour 24, however, a statistical improvement in PGA for the IV meloxicam 30 mg treatment group was identified at Hour 48 (p=0.0027)

Response Analysis

- Response analysis was performed with thresholds of ≥30% and ≥50% improvement in pain scores over the first 6 and 24 hours following Dose 1
- The IV meloxicam 30 mg group showed a numerically greater proportion of responders in each category, using each SPID imputation method, compared with placebo. A significantly higher proportion of subjects reported a ≥ 30% improvement over the first 24 hours following treatment with IV meloxicam 30 mg versus placebo (71.8% vs. 56.9%; p=0.0178); a significant response was not identified for other categories.

Safety

- Doses of IV meloxicam 30 mg were well tolerated during the study, with the majority of subjects receiving 3 study doses (79.1%).
- AEs were generally reported to be of mild intensity and occurred with greatest overall frequency in the placebo group.
- No deaths or discontinuations due to an AE occurred in the IV meloxicam 30 mg group.
- Four subjects experienced an SAE in the study (1 IV meloxicam 30 mg, 3 placebo): 2 events of post procedural haemorrhage (1 on IV meloxicam 30 mg and 1 on placebo); 1 event of post procedural pulmonary embolism (placebo); 1 event of postoperative wound infection (placebo)
- AEs of special interest (including hepatic, renal, cardiovascular, bleeding, wound healing, and injection site events) were infrequent, with a greater incidence overall in the placebo group.
- No trends for changes in vital signs or ECGs were observed.

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

Preferred Term	IV Meloxicam 30 mg (N=110)	Placebo (N=109)
Any AE	58 (52.7)	80 (73.4)
Nausea	30 (27.3)	41 (37.6)
Headache	13 (11.8)	18 (16.5)
Vomiting	5 (4.5)	10 (9.2)
Dizziness	4 (3.6)	10 (9.2)
Decreased appetite	2 (1.8)	3 (2.8)
Alanine aminotransferase increased	2 (1.8)	2 (1.8)
Constipation	2 (1.8)	2 (1.8)
Hypotension	2 (1.8)	2 (1.8)
Aspartate aminotransferase increased	2 (1.8)	1 (0.9)
Hyperhidrosis	2 (1.8)	1 (0.9)
Pruritus generalized	2 (1.8)	1 (0.9)
Induration	2 (1.8)	0
Injection site pain	2 (1.8)	0
Tachycardia	2 (1.8)	0

Table 4: Summary of Treatment-Emergent AEs of Special Interest - Number of Subjects (%)

Preferred Term	IV Meloxicam 30 mg (N=110)	Placebo (N=109)
Subjects with ≥1 Event	12 (10.9)	17 (15.6)
Anaemia Postoperative	1 (0.9)	1 (0.9)
Post Procedural Haemorrhage	1 (0.9)	1 (0.9)
Hypertension	0	3 (2.8)
Alanine Aminotransferase Increased	2 (1.8)	2 (1.8)
Aspartate Aminotransferase Increased	2 (1.8)	1 (0.9)
Hepatic Enzyme Increased	1 (0.9)	3 (2.8)
Injection Site Pain	2 (1.8)	0
Blood Creatinine Increased	1 (0.9)	1 (0.9)
Incision Site Cellulitis	1 (0.9)	1 (0.9)
Induration	2 (1.8)	0
Postoperative Wound Infection	1 (0.9)	1 (0.9)
Seroma	0	2 (1.8)

Wound Healing Assessment

- Surgical wounds were assessed for investigator satisfaction 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 Hour 48, 7 days post last study dose, and at 28 days post last study dose.
- Clinically significant wound assessment parameters were more common in the placebo group compared with IV meloxicam 30 mg.

Table 5: Investigator Satisfaction with Surgical Wound Healing (0-10 NRS)

Time Point	IV Meloxicam 30 mg (N= 110)	Placebo (N=109)
Hour 48	9.1 ± 1.08	9.2 ± 0.99
Last Study Dose +7 Days	9.4 ± 0.77	9.4 ± 1.03
Last Study Dose +28 Days	9.7 ± 0.74	9.6 ± 0.90

Table 6: Summary of Clinically Significant Wound Healing Assessment Parameters

Assessment Parameter	Time Point	IV Meloxicam 30 mg (N=110)	Placebo (N=109)
Erythema	Last Study Dose +7 Days	1 (0.9)	1 (0.9)
	Last Study Dose +28 Days	0	1 (1.0)
Drainage	Last Study Dose +7 Days	0	2 (1.9)
	Last Study Dose +28 Days	1 (1.0)	1 (1.0)
Edema	Last Study Dose +7 Days	0	0
	Last Study Dose +28 Days	0	0
Induration	Last Study Dose +7 Days	0	0
	Last Study Dose +28 Days	2 (1.9)	1 (1.0)
Hematoma	Last Study Dose +7 Days	0	1 (0.9)
	Last Study Dose +28 Days	0	0

Clinical Laboratory Assessment

- Clinical chemistry, hematology, urinalysis, and coagulation tests were routinely evaluated during the study.
- Laboratory assessments related to renal and hepatic function, and bleeding risk were evaluated due to the known class effects of NSAIDs.
- There was no apparent trend in clinically meaningful abnormal laboratory results between treatment groups

Table 7: Potentially Clinically Significant Change in Laboratory Assessments from Normal at Baseline

Parameter	Potential Significance Criteria	IV Meloxicam 30 mg	Placebo
Hematocrit	< 30%	3 (2.7)	-
Hemoglobin	< 10 g/dL	5 (4.5)	3 (2.8)
BUN	≥ 1.5x ULN	-	-
Creatinine	≥ 1.5x ULN	-	-
ALT	3-10x ULN	2 (1.8)	3 (2.8)
	≥10x ULN	1 (0.9)	-
AST	3-10x ULN	2 (1.8)	1 (0.9)
	≥10x ULN	-	-
GGT	1-3x ULN	8 (7.3)	11 (10.1)
	3-10x ULN	-	1 (0.9)
Alkaline Phosphatase	1-3x ULN	10 (9.1)	8 (7.3)
Total Bilirubin	> 2x ULN	-	-
aPTT	≥ 55 seconds	-	-
INR	> 1.5	-	-

ULN=Upper Limit of Normal range

CONCLUSIONS

- IV meloxicam 30 mg administered as an IV push once daily, was well tolerated with a low incidence of AEs, SAEs, and infusion events.
- Dosing with IV meloxicam 30 mg was demonstrated to provide a significant reduction in pain, as evidenced by $SPID_{24}$ results, and the reduction in opioid rescue use.
- Once daily dosing with IV meloxicam maintained analgesia over the 24-hour dosing interval
- Assessments of wound healing demonstrated no differences between IV meloxicam and placebo treated subjects
- The study supported the efficacy and safety of IV meloxicam 30 mg administered IV once daily in subjects with moderate to severe pain following abdominoplasty surgery.

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