An Evaluation of the Safety and Efficacy of N1539, a Novel Intravenous Formulation of NanoCrystal Meloxicam, Administered By IV Push in Subjects with Moderate to Severe Pain Following Bunionectomy

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ABSTRACT

Purpose: Previous studies have identified doses of N1539 from 5-60 mg to be well tolerated when administered as an intravenous (IV) push over 1-2 minutes. The current study was planned to evaluate the safety of N1539 administered as a rapid IV push over 15-30 seconds, compared with placebo, in subjects with acute moderate to severe pain following bunionectomy. Additionally, this study sought to evaluate the efficacy of 60 and 30 mg dose levels of N1539 in an orthopedic pain model. N1539 is a novel IV formulation of NanoCrystal Colloidal Dispersion® meloxicam, being developed for the management of moderate to severe pain.

Methods: This was a single-center, randomized, double-blind, placebo-controlled study in male and female subjects, age 18-75 years in otherwise good health, undergoing simple unilateral bunionectomy. 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. Subjects underwent a standardized bunionectomy procedure, and were maintained using a popliteal block until Postoperative Day 1, when they were eligible to qualify for randomization. Qualifying subjects with moderate to severe pain were randomized to receive N1539 60 mg, N1539 30mg, or placebo via IV push over 15-30 seconds every 24 hours for two doses, with an option for a third dose prior to discharge. Safety assessments included clinical laboratory tests, vital signs, ECGs, surgical wound assessment, and monitoring of adverse events (AEs) and serious AEs (SAEs). Efficacy assessments included Pain Intensity (PI) assessed using a 11-point numeric pain rating scale (NPRS), rescue analgesia use, and a patient global assessment (PGA) of satisfaction with analgesia, at intervals over the 48-hour double-blind inpatient phase. Rescue analgesia, oral oxycodone, was available for pain not relieved by the study drug. The primary efficacy objective was to evaluate the effect size of N1539 using the summed PI difference from Hour 0 to 48 ($SPID_{48}$) after dosing. The primary analysis method for $SPID_{48}$ used a last observation carried forward (LOCF) method, with a 2-hour windowed LOCF (W2LOCF) method included as a sensitivity analysis.

Results: This study evaluated 59 subjects ranging in age from 18 to 72 years. The majority of subjects were female (81.4%) and African American (50.8%), with demographics similar across groups. N1539 was tolerated with no deaths, SAEs, or withdrawals due to an AE. AEs were generally mild or moderate in intensity, and similar in incidence across groups. The most common AEs included nausea, headache, dizziness, pruritus, and vomiting. Administration over 15-30 seconds was well tolerated, with no infusion related AEs, and no infusions were slowed or interrupted.

The estimated effect size for $SPID_{48}$ was 0.81 and 0.87 using the LOCF method, and 0.88 and 1.01 using the W2LOCF method for the 60 and 30 mg dose groups respectively. This study demonstrated superior efficacy of N1539 at 60 and 30 mg dose levels versus placebo at all evaluated SPID intervals (6, 12, 24, 48, 12-48, and 24-48 hours), using the LOCF and W2LOCF methods via ANCOVA models. Analysis of SPID results at various intervals revealed no difference between the N1539 60 and 30 mg dose levels. The incidence of subjects achieving 30% and 50% improvement in pain intensity within the first 6 and 24 hours post treatment initiation was statistically significant for the N1539 30 mg dose under the W2LOCF analysis compared with placebo; significant differences were not identified for the 60 mg dose or with other analysis models. Time to first use of rescue medication was statistically significantly longer in N1539 60 mg treated subjects; KM median time to first rescue (95% CI) was 3.10 (1.13-6.35) hours for 60 mg, 1.26 (1.02-2.68) hours for 30 mg, and 1.57 (0.85, 2.51) hours for placebo.

Conclusions: This study supports the safety and tolerability of N1539 at a 60 or 30 mg IV dose administered once daily over 15-30 seconds. The efficacy analysis was favorable for both N1539 dose levels compared to placebo with estimated effect size ranged from 0.52 to 1.01 per observed $SPID_{48}$, and statistically significant differences in SPID intervals throughout the study. As no incremental benefit was identified using a higher treatment dose, this study supports the use of N1539 30 mg administered IV once daily in post-operative settings where patients are expected to have moderate to severe pain.

INTRODUCTION

N1539 is a novel intravenous (IV) formulation of NanoCrystal Colloidal Dispersion® meloxicam being developed for the management of moderate to severe acute pain. Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) of the enolic acid class that possesses anti-inflammatory, analgesic, and antipyretic activities, which are believed to be related to the inhibition of cyclooxygenase (COX) and subsequent reduction in prostaglandin biosynthesis (Mobic 2012; Turck1997; 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.

Previous evaluations of N1539 have evaluated IV administration over 2 minutes, while the current study evaluated the safety and tolerability of IV push administration. Additionally, this study evaluated the efficacy of N1539 administered for moderate to severe pain following an orthopedic model of post-operative pain, to support dose selection for future clinical studies.

OBJECTIVE

The primary objective of this study was to evaluate the safety of N1539 administered as an IV push in subjects undergoing bunionectomy surgery as evaluated with physical examination, vital signs, clinical laboratory tests, ECGs, wound evaluation, and incidence of Adverse Events (AEs) and Serious AEs (SAEs).

Secondary objectives of this study included:

- Evaluating the effect size (point estimate with 95% CI) of two dose levels of N1539, using the summed pain intensity difference over the first 48 hours ($SPID_{48}$) in subjects with moderate to severe pain following unilateral bunionectomy
- Evaluating the use of opioid analgesics

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.
- Underwent primary unilateral first metatarsal bunionectomy repair, without collateral procedures.
- Moderate to severe pain within 9 hours of popliteal block discontinuation on Postoperative Day 1, with a NPRS score ≥ 4 out of 10.

Selected exclusion criteria:

- Active gastrointestinal (GI) bleeding, or any history of peptic ulcer disease.
- Known bleeding disorder or was taking agents affecting coagulation.
- Taking or had taken an opioid chronically (more than 30 consecutive days of daily use) for pain in the past years
- Recent bunionectomy surgery within 3 months
- Other painful condition that could interfere with pain assessments

Study Design

- Single-center, randomized, double-blind, placebo controlled study
- Participation consisted of a screening visit, surgery and inpatient evaluation, and 2 follow-up visits 7 and 28 (telephone visit) days after last study dose.
- Following bunionectomy, subjects were maintained using a popliteal block and other analgesics until Postoperative Day 1, when subjects were eligible to randomize to treatment with study drug administered as an IV push over 15-30 seconds every 24 hours for at least two doses.

Endpoints

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

Efficacy: The primary efficacy endpoint was the effect size (point estimate with 95% CI) of two dose levels of N1539 using $SPID_{48}$.

Secondary efficacy endpoints included:

- SPID at various time points ($SPID_6$, $SPID_{12}$, $SPID_{24}$, $SPID_{12-48}$, and $SPID_{24-48}$)
- Proportion of subjects with improvement ≥ 30% and ≥ 50% within 6 hours following the first study dose. Improvement was defined as percent of pain reduction from baseline.
- The 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.

Statistical Analysis

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. Changes in vital signs at each post dosing time point were summarized by treatment using descriptive statistics without formal statistical tests. The number and proportion of subjects with abnormal ECG findings at each time point was tabulated by treatment group.

Analysis of covariance (ANCOVA) was used to assess the difference between treatment groups for SPID with baseline pain score as a covariate. Least-squares means (LSmeans) and standard error (SE) of the LSmeans were used to test the difference between the groups using 2 sample t-test. Difference in LSmeans and corresponding 95% confidence intervals (CIs) are presented. Difference between the groups in the proportion of subjects meeting the improvement criteria and the proportion of subjects who used rescue medication are evaluated with the relative risk (odds ratio) and corresponding 95% CIs. All tests are a 2-sided test at the 0.05 significance level. Nominal p-values were reported without adjustment for multiple comparisons. The primary efficacy endpoint $SPID_{48}$ was derived using different methods to address the impact of rescue medication on the response to study drug. In the LOCF analysis (primary analysis), PI score collected prior to the first use of rescue medication was to be carried forward to replace all PI scores collected following the rescue. In the W2LOCF analysis (sensitivity analysis), the PI score obtained prior to each rescue was to be carried forward to replace PI scores collected within the following 2 hour window.

RESULTS

Demographics

- A total of 59 subjects enrolled in this study.
- All enrolled subjects were randomized and treated with study drug, and included in safety and efficacy analyses.

Table 1: Summary of Subject Demographics and Disposition

Variable	Placebo (N=19)	N1539 30 mg (N=20)	N1539 60 mg (N=20)	Overall (N=59)
Age (yrs)				
Mean ± SD	49.2 ± 12.81	47.6 ± 12.66	44.9 ± 16.67	47.2 ± 14.06
Median	50.0	51.0	48.5	51.0
Range (min, max)	18, 68	20, 69	18, 72	18, 72
Gender - n (%)				
Male	5 (26.3)	4 (20.0)	2 (10.0)	11 (18.6)
Female	14 (73.7)	16 (80.0)	18 (90.0)	48 (81.4)
Race, n (%)				
White	8 (42.1)	10 (50.0)	10 (50.0)	28 (47.5)
Black or African American	11 (57.9)	10 (50.0)	9 (45.0)	30 (50.8)
Multiple	0	0	1 (5.0)	1 (1.7)
Ethnicity, n (%)				
Hispanic or Latino	0	3 (15.0)	0	3 (5.1)
Not Hispanic or Latino	19 (100.0)	17 (85.0)	20 (100.0)	56 (94.9)
Surgery Duration (hr) – mean ± SD	0.775 ± 0.1918	0.852 ± 0.1068	0.747 ± 0.0965	0.792 ± 0.1423
Bunionectomy Surgery Site: n (%)				
Left Foot	10 (52.6)	10 (50.0)	11 (55.0)	31 (52.5)
Right Foot	9 (47.4)	10 (50.0)	9 (45.0)	28 (47.5)
Baseline Pain Score (NPRS, 0-10) - Mean ± SD	7.684 ± 2.2374	7.700 ± 2.0026	7.400 ± 1.9029	

Safety

- Doses of 30 and 60 mg N1539 were well tolerated during the study.
- Adverse events were generally reported as mild with no meaningful differences evident between treatment groups.
- No deaths, SAEs or discontinuations due to an AE occurred during the study.
- No infusion related events were reported, and no infusions were required to be discontinued or prolonged.
- There was no apparent trend in clinically meaningful abnormal laboratory results between treatment groups.
- There was a minor decrease in blood pressure and heart rate observed in N1539 treated subjects compared with placebo; no dose related effect was observed.
- Two subjects had abnormal findings in wound healing
  - One N1539 60 mg treated subject had erythema, edema, and local cellulitis observed associated with an AE of cellulitis that was determined to be not related to treatment
  - One placebo treated subjects wound was assessed as being slightly macerated, but was determined to be not clinically significant.
- No clinically significant abnormal ECGs were observed in the study.

Table 2: Summary of Treatment-Emergent Adverse Events – Number of Subjects (%)

Preferred Term	Placebo (N=19)	N1539 30 mg (N=20)	N1539 60 mg (N=20)
Nausea	4 (21.1)	6 (30.0)	4 (20.0)
Headache	4 (21.1)	2 (10.0)	3 (15.0)
Dizziness	1 (5.3)	3 (15.0)	2 (10.0)
Pruritus	0	1 (5.0)	2 (10.0)
Vomiting	1 (5.3)	3 (15.0)	0
Decreased appetite	2 (10.5)	0	1 (5.0)
Erythema	1 (5.3)	2 (10.0)	0
Constipation	0	1 (5.0)	1 (5.0)
Gamma-glutamyltransferase increased	2 (10.5)	0	0
Muscle spasms	0	2 (10.0)	0
Somnolence	0	1 (5.0)	1 (5.0)

Efficacy

While the LOCF analysis was defined as the primary analysis method for this study, subsequent guidance from FDA and other literature sources has identified the W2LOCF analysis as a more appropriate method for imputation. As a result, the W2LOCF is presented for all results, with the LOCF presented as support.

$SPID_{48}$

- Statistically significant ($p<0.01$) effect size observed for 30 and 60 mg N1539 doses using the W2LOCF and LOCF analysis methods.
- Statistically significant differences in $SPID_{48}$ identified for N1539 30 mg and 60 mg dose levels compared with placebo using W2LOCF and LOCF analysis methods ($P<0.01$)

Figure 1: $SPID_{48}$ Effect Size (W2LOCF)

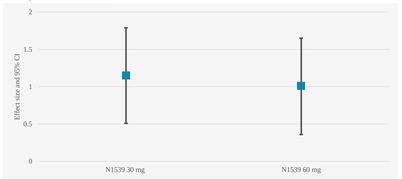
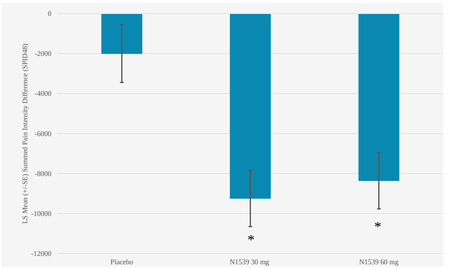


Table 3: Effect Size (95% CI) By Analysis Method

Analysis Method	N1539 30 mg (N=20)	N1539 60 mg (N=20)
W2LOCF	1.15 (0.51, 1.79)*	1.01 (0.36, 1.65)*
LOCF	0.94 (0.30, 1.58)*	0.89 (0.25, 1.53)*

* p≤0.01 vs. placebo

Figure 2: $SPID_{48}$ (W2LOCF)



* p≤0.01 vs. placebo

Table 4: $SPID_{48}$ By Analysis Method – LS Mean (SE)

Analysis Method	Placebo (N=19)	N1539 30 mg (N=20)	N1539 60 mg (N=20)
W2LOCF	-1991.3 (1448.20)	-9241.9 (1411.74)*	-8350.6 (1413.30)*
LOCF	3668.1 (1145.58)	-1021.9 (1116.74)*	-773.9 (1117.97)*

* p≤0.01 vs. placebo

SPID at Various Intervals

- SPID was evaluated using each analysis method at various post-dose intervals including: 0-6, 0-12, 0-24, 12-24, 12-48, 24-48 hours
- SPID values were statistically significant for both N1539 dose levels versus placebo at all intervals using the LOCF and W2LOCF analysis methods ($P< 0.05$).
- Statistically significant effect size was observed for both N1539 dose levels using the W2LOCF ($P<0.01$) and LOCF ($P<0.05$) analysis methods at the $SPID_{12}$, $SPID_{24}$, and $SPID_{48}$ intervals.

Table 5: SPID at Other Intervals By Analysis Method – LS Mean (SE)

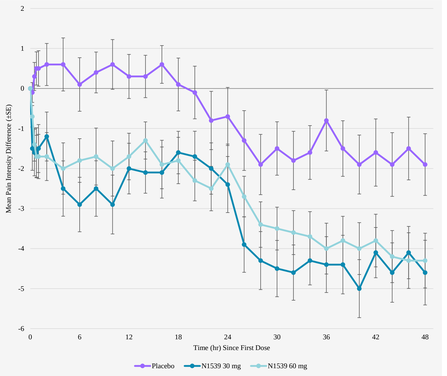
Analysis Method / SPID Interval	Placebo (N=19)	N1539 30 mg (N=20)	N1539 60 mg (N=20)
W2LOCF			
$SPID_6$	146.22 (176.91)	-793.87 (172.45) *	-663.17 (172.64) *
$SPID_{12}$	319.67 (347.53)	-1655.1 (338.78) *	-1334.9 (339.15) *
$SPID_{24}$	276.46 (661.28)	-3024.0 (644.63) *	-2793.3 (645.34) *
LOCF			
$SPID_6$	277.92 (174.77)	-328.52 (170.37) †	-413.68 (70.56) *
$SPID_{12}$	761.69 (304.45)	-448.14 (296.78) *	-475.49 (297.11) *
$SPID_{24}$	1727.51 (574.01)	-637.70 (559.56) *	-552.40 (560.18) *

† p≤0.05 vs. placebo
* p≤0.01 vs. placebo

Pain Intensity Differences at Each Time Point

Statistically significant PID from baseline were detected as early as 15 minutes post-dose.

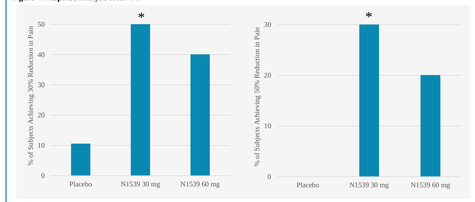
Figure 3: Pain Intensity Difference Over Time (W2LOCF)



Response Analysis

- Response analysis was performed using each analysis method with thresholds of ≥30% and ≥50% improvement in pain scores over the first 6 and 24 hours following Dose 1.
- The N1539 30 mg treatment group had a statistically significant greater number of subjects experiencing 30/50% improvement in pain through Hour 6 and Hour 24 using the W2LOCF analysis; no significant results were observed for the N1539 60 mg group or using other analysis methods

Figure 4: Response Analysis Hour 0-24

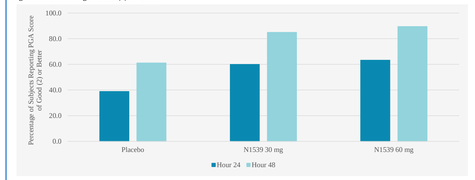


* p≤0.05 vs. placebo

Patient Global Assessment (PGA) of Pain Control

- PGA evaluated using 5-point scale of poor (0), fair (1), good (2), very good (3) or excellent (4) pain control
- No statistical differences was identified between the treatment groups; a numerically greater incidence in the number of subjects reporting pain control of "Good" or better (2+) in the N1539 treatment groups compared with the placebo group

Figure 5: PGA Rating of Good (2) or Better



Rescue Analgesia

- Rescue (oral oxycodone 5 mg) was utilized by ≥90% of subjects in each treatment group during Hour 0-24.
- Time to first rescue was longer for N1539 60 mg compared with placebo, no difference was identified for N1539 30 mg.
- Subjects treated with N1539 30 mg or 60 mg used numerically fewer doses of rescue per subject (8.2 and 6.9 doses respectively) compared with placebo (11.1 doses), however this difference was not significant.

CONCLUSIONS

- N1539, at doses of 30 and 60 mg administered as an IV push once daily, was well tolerated with no SAEs, and a low incidence of AEs and infusion events.
- Both studied doses of N1539 produced meaningful effect sizes using W2LOCF and LOCF analysis methods, as well demonstrating significant differences in $SPID_{48}$ values compared to placebo.
- Once daily dosing with N1539 maintained analgesia over a 24-hour period
- The study supported the use of N1539 doses of 30 and 60 mg administered IV once daily in post-operative settings where patients are expected to have moderate to severe pain.

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