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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Methods

N1539 was administered as an IV push over 15-30 seconds every 24 hours for at least two doses. Subjects were randomized to treatment with study drug administered as an IV push over 15-30 seconds every 24 hours for at least two doses. The primary endpoint was the mean change from baseline in pain intensity difference (SPID) at 48 hour. The secondary endpoints included the mean change from baseline in pain intensity difference (SPID) at 6 hours, 12 hours, and 24 hours. The safety endpoints included the following:

- All subjects provided informed consent prior to completing any study activities.
- Underwent primary unilateral first metatarsal bunionectomy repair, without collateral procedures.
- Following bunionectomy, subjects were maintained using a popliteal block and other analgesics until Postoperative Day 1, when subjects were eligible to initiate study medication.
- Study participation included a screening visit with written informed consent, an inpatient visit including surgery and follow-up visits 7 and 28 (telephone visit) days after last study dose.

Ethnicity, n (%)

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>N1539 30 mg   (N=20)</th>
<th>N1539 60 mg   (N=20)</th>
<th>Placebo (N=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Hispanic or Latino</td>
<td>19 (100.0)</td>
<td>17 (85.0)</td>
<td>20 (100.0)</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>0 (0.0)</td>
<td>3 (15.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Statistically significant differences in SPID48 identified for N1539 30 mg and 60 mg dose levels compared with placebo using W2LOCF and LOCF analysis methods.

Dizziness 1 (5.3) 3 (15.0) 2 (10.0)
Constipation 0 1 (5.0) 1 (5.0)
Vomiting 1 (5.3) 3 (15.0) 0

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

Pain

PGA evaluated using 5-point scale of poor (0), fair (1), good (2), very good (3) or excellent (4) pain control

Statistically significant (p<0.01) effect size observed for 30 and 60 mg N1539 doses using the W2LOCF and LOCF analysis methods.

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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>N1539 30 mg   (N=20)</th>
<th>N1539 60 mg   (N=20)</th>
<th>Placebo (N=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>1 (5.3)</td>
<td>3 (15.0)</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>1 (5.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (5.3)</td>
<td>3 (15.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

RESULTS

Analysis Method N1539 30 mg   (N=20) N1539 60 mg   (N=20)

<table>
<thead>
<tr>
<th>Analysis Method</th>
<th>N1539 30 mg</th>
<th>N1539 60 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2,200</td>
<td>2,200</td>
</tr>
<tr>
<td>W2LOCF</td>
<td>-1,655.1</td>
<td>-1,335.0</td>
</tr>
<tr>
<td>LOCF</td>
<td>-1,021.9</td>
<td>-773.9</td>
</tr>
</tbody>
</table>

Analysis of SPID at various time points (SPID6, SPID12, SPID24, SPID48, SPID12-48, and SPID24-48) statistically significant using the W2LOCF analysis method. As a result, the W2LOCF and LOCF analysis methods are presented for all results.

CONCLUSIONS

Once daily dosing with N1539 maintained analgesia over a 24-hour period.

REFERENCES


4. Turk DC, Okifuji A, Cella D, et al. Medians were used to test the difference between the groups using 2 sample t-test. Difference in medians and standard error (SE) of the medians were used to test the difference between the groups using 2 sample t-test. Difference in medians and standard error (SE) of the medians were used to test the difference between the groups using 2 sample t-test.

5. The number and proportion of subjects with abnormal ECG findings at each time point was tabulated by treatment group.

6. The Patient global assessment (PGA) of pain control at Hour 24 and Hour 48. Pain measured using a visual analog scale of 0-100.

7. The proportion of subjects with improvement ≥ 30% and ≥ 50% within 6 hours following the first study dose. Improvement was defined as a percent of pain reduction greater than or equal to 30% and 50%, respectively.

8. SPID at various time points (SPID6, SPID12, SPID24, SPID48, SPID12-48, and SPID24-48) statistically significant using the W2LOCF analysis method. As a result, the W2LOCF and LOCF analysis methods are presented for all results.

9. The efficacy analysis criteria were met in all groups, with the exception of the 60 mg dose group, which did not meet the criteria for the primary endpoint.

10. 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, 12-48-48).

11. Time to first use of rescue medication was statistically significantly longer in N1539 60 mg treated subjects; KM analysis was used to compare the time to first rescue medication use.

12. 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 criteria were met in all groups, with the exception of the 60 mg dose group, which did not meet the criteria for the primary endpoint.