HTX-011, a Proprietary, Unique, Long-Acting Local Anesthetic, Reduces Acute Postoperative Pain Intensity and Opioid Consumption Following Bunionectomy

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Disclosures

• Erol Onel is an employee of Heron Therapeutics, Inc.
HTX-011, a Novel, Long-Acting Local Analgesic for Non-Opioid Postoperative Pain Management

Postoperative Pain and the Opioid Crisis

- Overreliance on opioids for postoperative pain can lead to increased:
  - Risk of opioid-related adverse events for patients
  - Costs for hospitals
  - Societal impact of opioid addiction

Current Local Analgesic Options Have Limited Efficacy in Postoperative Pain

- Bupivacaine is commonly used; however, even ER formulations have limited efficacy beyond 12-24 hours after surgery
- The normal postoperative inflammatory process impairs the ability of local anesthetics to block sensory nerve conduction

HTX-011

- HTX-011’s unique formulation of ER bupivacaine and meloxicam in proprietary Biochronomer® technology is designed to overcome the challenges of the local inflammatory process, potentiating a synergistic pain reduction effect postoperatively through 72 hours

ER, extended-release.
Although it Can Be Injected Like Bupivacaine, HTX-011 is Ideally Suited for Needle-Free Administration

- HTX-011 is easy to apply and stays in place at the surgical site after application
- HTX-011 releases its active ingredients simultaneously
- HTX-011’s release is controlled by diffusion from the polymer, not modulated by the environment
- Compared to injection, simply coating the affected tissue without using a needle:
  - Is easier to administer and less invasive
  - Avoids up to 120 needle sticks
  - Reduces the risk of inadvertent intravascular puncture and accidental needle sticks
Bunionectomy Study: Phase 2 Clinical Study Design

**Screening**

**Key Inclusion Criteria**
- Male or female ≥18 years old
- Able to undergo a lidocaine Mayo block for primary unilateral first metatarsal bunionectomy repair

**Key Exclusion Criteria**
- ASA Physical Status classification category ≥4
- Clinically significant renal or hepatic abnormalities
- Current use of analgesics for a chronic pain condition, use of long-acting opioids within 3 days of surgery, or use of any opioids within 24 hours of surgery

**Study Treatments**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTX-011 200 mg</td>
<td>Bupivacaine HCl 50 mg</td>
</tr>
<tr>
<td>HTX-011 120 mg</td>
<td>Saline Placebo</td>
</tr>
<tr>
<td>HTX-011 60 mg</td>
<td>Bupivacaine ER 60 mg</td>
</tr>
<tr>
<td>HTX-011 30 mg</td>
<td>Meloxicam ER</td>
</tr>
</tbody>
</table>

**Endpoints**

**Efficacy Endpoints (assessed through 72 hours)**
- AUC of mean pain intensity score
- Total opioid rescue medication used (MME)
- Proportion of opioid-free subjects

**Safety Endpoints**
- TEAEs, serious TEAEs
- Vital signs, clinical laboratory evaluations, ECG

ASA, American Society of Anesthesiologists; AUC, area under the curve; ECG, electrocardiograph; MME, intravenous morphine milligram equivalent; TEAE, treatment-emergent adverse event.

*Dose being carried forward in Phase 3 studies.*
## Bunionectomy Study: Baseline Demographics and Characteristics Comparable Across Cohorts

<table>
<thead>
<tr>
<th></th>
<th>HTX-011 60 mg&lt;sup&gt;a&lt;/sup&gt; n = 52</th>
<th>Bupivacaine HCl 50 mg n = 25</th>
<th>Bupivacaine ER 60 mg n = 23</th>
<th>Meloxicam ER n = 30</th>
<th>Saline Placebo n = 104&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>45 (86.5)</td>
<td>22 (88.0)</td>
<td>21 (91.3)</td>
<td>27 (90.0)</td>
<td>91 (87.5)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>7 (13.5)</td>
<td>3 (12.0)</td>
<td>2 (8.7)</td>
<td>3 (10.0)</td>
<td>13 (12.5)</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>52.2 (15.13)</td>
<td>52.7 (11.81)</td>
<td>50.2 (12.89)</td>
<td>49.9 (13.41)</td>
<td>50.0 (13.46)</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (SD)</td>
<td>29.20 (5.89)</td>
<td>31.75 (5.83)</td>
<td>29.39 (5.54)</td>
<td>29.20 (6.11)</td>
<td>30.26 (6.75)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race, n (%)</th>
<th>Asian</th>
<th>Black or African American</th>
<th>White</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>2 (3.8)</td>
<td>0</td>
<td>2 (8.7)</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>17 (32.7)</td>
<td>7 (28.0)</td>
<td>3 (13.0)</td>
<td>10 (33.3)</td>
</tr>
<tr>
<td>White</td>
<td>33 (63.5)</td>
<td>17 (68.0)</td>
<td>18 (78.3)</td>
<td>17 (56.7)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1 (4.0)</td>
<td>0</td>
<td>1 (3.3)</td>
</tr>
</tbody>
</table>

BMI, body mass index, SD, standard deviation.
<sup>a</sup>Dose being carried forward in Phase 3 studies.
<sup>b</sup>Numbers of subjects represent those in the safety population. Slight differences in numbers of subjects from those in the efficacy results are due to mis-dosed subjects.
Bunionectomy Study: HTX-011 Significantly Reduced Pain Compared with Bupivacaine or Saline Placebo Through 72 Hours

Mean Pain Intensity (NRS) vs. Hours After Study Drug Administration

- HTX-011 60 mg (n = 52)
- Bupivacaine HCl 50 mg (n = 25)
- Saline Placebo (n = 103)

**AUC**
- **AUC**<sub>0-24</sub>:
  - 60 mg v P: p < 0.0001
  - 60 mg v B: p = 0.0020
- **AUC**<sub>0-48</sub>:
  - 60 mg v P: p < 0.0001
  - 60 mg v B: p = 0.0020
- **AUC**<sub>0-72</sub>:
  - 60 mg v P: p = 0.0003
  - 60 mg v B: p = 0.0166

**Notes:**
- NRS: numeric rating scale; P: placebo.
- Pain was assessed using an 11-point (0, no pain–10, worst pain imaginable) numeric rating scale.

AUC<sub>x</sub>, area under the curve from 0 to x hours after study drug administration; B, bupivacaine; NRS, numeric rating scale; P, placebo.
Bunionectomy Study: HTX-011 60 mg Significantly Reduced Pain Through 72 Hours Compared with Bupivacaine

AUC\(^a\) LSMD (vs Saline Placebo)  

- Time Interval After Study Drug Administration, Hours
- Greater Pain Reduction

HTX-011 60 mg (n = 52)  Bupivacaine HCl 50 mg (n = 25)

- p = 0.0020
- p = 0.0020
- p = 0.0166

LSMD, least squares mean difference.
\(^a\)Pain was assessed using an 11-point (0, no pain-10, worst pain imaginable) numeric rating scale.
## Bunionectomy Study: HTX-011 Significantly Reduced the Use of Opioid Medication Through 72 Hours Compared with Bupivacaine or Saline Placebo

### Mean Opioid Rescue Medication, MME

<table>
<thead>
<tr>
<th>Time Interval After Study Drug Administration, Hours</th>
<th>HTX-011 60 mg (n = 52)</th>
<th>Bupivacaine HCl 50 mg (n = 25)</th>
<th>Saline placebo (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-24</td>
<td>8.33</td>
<td>14.68</td>
<td>16.75</td>
</tr>
<tr>
<td>0-48</td>
<td>16.44</td>
<td>25.36</td>
<td>26.6</td>
</tr>
<tr>
<td>0-72</td>
<td>21.73</td>
<td>32.28</td>
<td>32.67</td>
</tr>
</tbody>
</table>

- **p < 0.0001** for HTX-011 vs. Bupivacaine HCl
- **p = 0.0008** for HTX-011 vs. Saline Placebo
- **p = 0.0002** for Bupivacaine HCl vs. Saline Placebo
- **p = 0.0131** for 0-24 vs. 0-48 for HTX-011
- **p = 0.0047** for 0-24 vs. 0-48 for Bupivacaine HCl
- **p = 0.0382** for 0-24 vs. 0-48 for Saline Placebo
HTX-011 Significantly Increased the Proportion of Opioid-Free Subjects vs Saline Placebo

0-72 Hours After Study Drug Administration

<table>
<thead>
<tr>
<th>Group</th>
<th>Proportion of Opioid-free Subjects, %</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTX-011 60 mg</td>
<td>17.3%</td>
<td>52</td>
</tr>
<tr>
<td>Bupivacaine HCl 50 mg</td>
<td>8.0%</td>
<td>25</td>
</tr>
<tr>
<td>Saline placebo</td>
<td>3.9%</td>
<td>103</td>
</tr>
</tbody>
</table>

p = 0.4877
p = 0.0106
## Bunionectomy Study: Summary of TEAEs

### TEAEs Occurring in >10% of Subjects in Any Group, n (%)

<table>
<thead>
<tr>
<th></th>
<th>HTX-011 60 mg (n = 52)</th>
<th>Bupivacaine HCl 50 mg (n = 25)</th>
<th>Saline Placebo (n = 104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one TEAE</td>
<td>33 (63.5%)</td>
<td>20 (80.0%)</td>
<td>76 (73.1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (30.8%)</td>
<td>11 (44.0%)</td>
<td>44 (42.3%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (15.4%)</td>
<td>5 (20.0%)</td>
<td>27 (26.0%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7 (13.5%)</td>
<td>4 (16.0%)</td>
<td>8 (7.7%)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (9.6%)</td>
<td>5 (20.0%)</td>
<td>19 (18.3%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (7.7%)</td>
<td>1 (4.0%)</td>
<td>20 (19.2%)</td>
</tr>
</tbody>
</table>
Bunionectomy Study: A Synergistic Effect on Pain Reduction Was Observed with HTX-011

Pain was assessed using an 11-point (0, no pain–10, worst pain imaginable) numeric rating scale.

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\(^{a}\)Pain was assessed using an 11-point (0, no pain-10, worst pain imaginable) numeric rating scale.
Conclusions

• HTX-011’s unique formulation significantly reduced pain intensity through the first 72 hours after bunionectomy compared with either bupivacaine HCl or saline placebo
  – Mean pain scores remained well below the severe pain threshold through the entire 72-hour study period after treatment with HTX-011

• HTX-011 significantly reduced opioid use following bunionectomy and increased the number of opioid-free subjects through 72 hours

• HTX-011 had an adverse event profile similar to that of bupivacaine HCl or saline placebo

• HTX-011 provided a synergistic effect, demonstrating greater pain reduction than its individual components (bupivacaine ER plus meloxicam ER)

• HTX-011 may represent a significant advance in the treatment of postoperative pain