NIHR | Innovation Observatory

# HEALTH TECHNOLOGY BRIEFING
# OCTOBER 2019

# Bupivacaine and meloxicam (HTX-011) for post-operative pain

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| **NIHRIO ID** | 11640 | **NICE ID** | 10228 |
| **Developer/Company** | Heron Therapeutics Inc. | **UKPS ID** | 656577 |

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| **Licensing and market availability plans** | The company submitted a Marketing Authorisation Application to the EMA by centralised procedure in March 2019.[1] |

## SUMMARY


Bupivacaine and meloxicam (HTX-011) in a fixed-dose combination, using a polymer-based Biochronomer® technology to deliver therapeutic levels of the active ingredients over an extended period. It is in development for the management of post-operative pain. Post-operative pain is a typical example of acute pain. Acute pain typically lasts for less than 3-6 months (unlike chronic pain which carries on for longer than 12 weeks) and is provoked by identifiable stimuli and disappears as soon as the tissue injury or damage that had caused it is healed. All surgical procedures are associated with a certain level of post-operative pain. Opioids are often used to manage post-operative pain but carry the risk of harmful side effects, abuse and addiction.

In HTX-011, the inclusion of low-dose meloxicam reduces local inflammation and reverses the acidic environment caused by surgery, allowing enhanced penetration of bupivacaine (a local anaesthetic) into the nerves and thereby increasing bupivacaine's effect. HTX-011 is in development for application into the surgical site and early studies have shown its potential to reduce severe post-operative pain and the need for opioid analgesics for up to 72 hours. If licensed, HTX-011 may offer an additional treatment option for the management of post-operative pain with a potential to reduce the need for opioids.

# PROPOSED INDICATION

HTX-011 is indicated in adults for application into the surgical site to reduce postoperative pain for 72 hours.[2-4]

# TECHNOLOGY

## DESCRIPTION

HTX-011 (ZYNRELEF), which utilizes Heron's proprietary Biochronomer® drug delivery technology, is an investigational, long-acting, extended-release formulation of the local anaesthetic bupivacaine in a fixed-dose combination (33:1) with the low-dose nonsteroidal anti-inflammatory drug (NSAID) meloxicam for the management of post-operative pain.[1]

This Biochronomer® technology was developed by Heron Therapeutics, Inc. specifically for drug delivery applications.[5] Since the polymer formulation is viscous and hydrophilic, HTX-011 can be applied to the affected tissue in the surgical incision without a needle and remains where it is placed, releasing both drugs by controlled diffusion through 72 hours. After bupivacaine and meloxicam have been released from the polymer, hydrolysis causes cleavage of the polymer ester bond, creating small water-soluble polymer fragments that are primarily eliminated via the kidneys.[6]

Bupivacaine is a long acting local anaesthetic of the amide type with both anaesthetic and analgesic effects. Bupivacaine, like other local anaesthetics, causes a reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the cell membrane of the nerve fibres. The sodium channels of the nerve membrane are considered a receptor for local anaesthetic molecules.[7] In order for bupivacaine to pass through the lipid membrane, it must be in the un-ionized state. The pKa (pH where 50% of the molecules are unionized and 50% are ionized) of all local anaesthetics is above the physiologic pH of 7.4).[5]

In addition to causing discomfort in the surrounding tissue, the normal inflammatory process in a surgical incision causes the affected tissues to become acidic. This acidic environment favours the ionized form of bupivacaine thereby further reducing the concentration of bupivacaine molecules available to penetrate into the nerve to block the pain signals.[8,9]

Meloxicam is a NSAID of the oxicam family, with anti-inflammatory, analgesic and antipyretic properties.[10] Inclusion of low-dose meloxicam in HTX-011 reduces local inflammation and reverses the acidic environment caused by surgery, allowing enhanced penetration of bupivacaine into the nerves and thereby potentiating bupivacaine's effect.[4]

HTX-011 is currently in clinical development for management of post-operative pain. In phase IIb and III clinical trials (NCT03295721; EPOCH 1, NCT03237481; EPOCH 2, NCT03974932; HTX-011-306, NCT03907176; HOPE, NCT03015532; HTX-011-209, NCT03718039; HTX-011-218, and NCT03695367; HTX-011-215), the analgesic efficacy and safety of HTX-011 has been assessed in subjects undergoing bunionectomy, total knee arthroplasty, and unilateral open inguinal herniorrhaphy. Details of the dosing regimen and administration schedule assessed in each study are detailed in the clinical trial table section of this briefing.[2,3,11-15]

## INNOVATION AND/OR ADVANTAGES

HTX-011 is a long-acting, extended-release formulation of bupivacaine with low-dose meloxicam incorporated into a Biochronomer® polymer technology. HTX-011 is viscous and hydrophilic; it can be applied to the affected tissue in the surgical incision without a needle and remains where it is placed, releasing both drugs simultaneously through 72 hours.[a]

In multiple clinical studies, HTX-011 has demonstrated significant reduction in post-operative pain through 72 hours with significant reduction in opioid consumption and significant increase in the proportion of opioid-free patients through 72 hours and at days 10 and 28 during the recovery period, compared with saline placebo and bupivacaine HCl.[a]

By delivering sustained levels of both a potent anaesthetic and a local anti-inflammatory agent directly to the site of tissue injury, HTX-011 was designed to deliver pain relief while reducing the need for systemically administered pain medications such as opioids, which carry the risk of harmful side effects, abuse and addiction.[1]

HTX-011 is ideally suited for needle-free administration. Compared to other local anaesthetics given by injection, simply coating the affected tissue without using a needle: is easier to administer and less invasive, avoids up to 120 needles sticks and reduces the risk of inadvertent intravascular puncture to the patient and accidental needle sticks to the health care professional.[16] In clinical studies, HTX-011 was generally well tolerated with fewer opioid-related adverse events (ORAEs) reported compared to the bupivacaine HCl and placebo and no evidence of local anaesthetic systemic toxicity or NSAID-related toxicity.[a]

Heron considers that the development of HTX 011 represents a significant scientific innovation as it is the application of new scientific knowledge i.e. inclusion of an NSAID to control local tissue inflammation, thereby preventing the tissue acidosis at the surgical site that has enabled the development of a novel medicinal product that provides greater maintenance of bupivacaine efficacy as it is released from the polymer.[a]

## DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

HTX-011 does not currently have Marketing Authorization in the EU for any indication.

Pivotal Phase IIb and Phase III clinical studies of HTX-011 in subjects undergoing a TKA, bunionectomy and herniorrhaphy have been completed to support the HTX-011 marketing authorisation application (MAA). The MAA for HTX-011 was submitted via the Centralised Procedure in March 2019 and is under review. The EMA granted eligibility to the Centralised Procedure for HTX-011 based on it meeting the criteria of a medicinal product constituting a significant scientific innovation.[a]

HTX-011 is currently in phase II and IIIb clinical trials for the treatment of women undergoing a planned C-section (NCT03955211), in adult patients undergoing total knee arthroplasty (NCT03974932) and in paediatric subjects undergoing inguinal herniorrhaphy (NCT03922048).[17] HTX-011 is also being studied in a real-world setting protocol (HOPE project) with non-opioid multimodal analgesia (MMA), an ongoing Phase IIIb multicentre open label study in patients undergoing open inguinal hernia repair surgery (NCT03907176).[11, a]

HTX-011 was granted Fast Track designation, breakthrough therapy designation, and priority review designation from the U.S. Food and Drug Administration (FDA). Heron has resubmitted a New Drug Application (NDA) to the FDA for HTX-011 in 2019.[18] The current Prescription Drug User Fee Act (PDUFA) goal date for HTX-011 is June 26th, 2020.[a]

[a] Information provided by the Heron Therapeutics Inc.

# PATIENT GROUP

## DISEASE BACKGROUND

Acute pain is one of the most common symptoms for which physicians are consulted. The purpose of acute pain is to inform the organism about tissue insult (caused by injury, disease, surgical procedure, or childbirth) in order to prevent further damage. Acute pain is an unpleasant sensory and emotional experience which can lead to behavioural changes. It usually lasts for several hours to days, rarely more than a month.[19]

Post-operative pain is a typical example of acute pain.[19] All surgical procedures are associated with a certain level of post-operative pain. Fear of pain is deeply rooted among patients who are about to have surgery.[20] Satisfactory perioperative pain management is crucial to assuring a good patient experience, optimising post-operative outcomes, and enhancing functional recovery after surgery.[21] Controlling acute pain after surgery is important not only in the immediate post-operative phase but also to prevent chronic postsurgical pain, which can develop in as many as 10% of patients. Pain is a highly personal and subjective experience, which is increasingly recognised to be influenced by life events, mood, fear, anxiety, and anticipation, among other influences.[22]

## CLINICAL NEED AND BURDEN OF DISEASE

According to Core Standards for Pain Management Service in the UK, two-thirds of hospital patients experience pain during their admission. Pain is often poorly relieved, with up to 20% of all inpatients suffering moderate to severe pain at any given time.

Even within the surgical population, where the noxious stimulus (the surgery) is well defined and systems are in place to manage acute pain, almost 60% of patients experience severe pain in the post-operative period, with a marked negative impact on health-related quality of life.[23]

The number of surgical procedures performed in England 2017-18 was 11,897,542. If 60% of patients experience severe pain in the postoperative period, this would equate to approximately 7,138,525 of persons who were operated on in 2017-18.[24]

# PATIENT TREATMENT PATHWAY

## TREATMENT PATHWAY

The involvement of patients in pain control is important because pain is such a personal experience. Following the operation, patients should have their pain level assessed using a 0-10 scale. The pain score should be recorded which will help the doctors and nurses know whether pain treatments are working.[25]

Both drug and non-drug treatments can be successful in helping to control pain. In most cases drugs are given to control pain for a few days after surgery. However, non-drug treatments can be just as important in helping to control pain.[25]

**Drug treatment to control pain**
Pain should be treated early rather than allowing it to become worse. The type of drugs should be selected according to the extent of surgery and the amount of pain the patient has. There are many different types of pain killers and the doctors and nurses will choose the best ones to control the pain after talking to the patient about it.[25]

**Non-drug treatment to control pain**

Non-drug treatments include some complementary therapies that can be effective for mild to moderate pain and boost the pain-relief effects of drugs. They include:[25]

- simple relaxation techniques such as abdominal breathing, visualization exercises, and listening to relaxing music
- supporting the wound when coughing, deep breathing and moving after surgery
- massage, which works on the muscles to release excess tension and can help with relaxation

## CURRENT TREATMENT OPTIONS

Painkillers are medicines which relieve pain. There are several types which may be used, depending on how severe is the pain. Some examples are:[26]

- Paracetamol – good for mild to moderate pain and works well with other painkillers e.g. NSAIDs such as ibuprofen and weak opiates, such as codeine.
- Anti-inflammatory painkillers – examples of these are ibuprofen and diclofenac. These work by reducing inflammation and can be used with other painkillers such as paracetamol and codeine.
- Weak opioids – codeine, tramadol for mild to moderate pain.
- Strong opioids – morphine, oxycodone for moderate to severe pain.
- Local anaesthetics – these work by making the area feel numb so that you don't feel any pain.

A combination of the above painkillers may work better than taking one on its own.[26] As recommended, by evidence-based guidelines, multimodal analgesia (MMA) can minimize the use of opioids and associated adverse reactions when treating acute post-operative pain.

## PLACE OF TECHNOLOGY

If licensed, HTX-011 will offer an additional treatment option for the management of post-operative pain with a potential to reduce the need for opioids.

# CLINICAL TRIAL INFORMATION

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| **Trial** | **NCT03907176, HTX-011-304; adults aged ≥18 years; HTX-011 as the foundation of a non-opioid multimodal analgesia (MMA) regimen with Ibuprofen and acetaminophen; phase IIIb** |
| **Sponsor** | Heron Therapeutics Inc. |
| **Status** | Ongoing |
| **Source of Information** | Trial registry[11] and Poster[27] |
| **Location** | United States |
| **Design** | Randomised, active-controlled, open-label<br>There are 2 parts to this study. This table has information for completed part 1. |
| **Participants** | Part 1: Cohort 1 n=46; Cohort 2 n=47; aged ≥18 years old; scheduled and medically fit to undergo an elective unilateral open inguinal herniorrhaphy with mesh under deep sedation or general anaesthesia; no neuraxial technique (e.g., no spinal or epidural). |
| **Schedule** | Patients allocated for both cohort 1 and 2 will receive the HTX-011 at a dose of 300 mg/ 9 mg through luer-lock applicator for instillation, scheduled ibuprofen at |

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| | a dose of 600 mg and acetaminophen at a dose of 1 g either alternating or concurrent.<br>• MMA Cohort 1: alternated taking ibuprofen and acetaminophen every 6 hours, so that one medication was taken every 3 hours while awake after surgery<br>• MMA Cohort 2: took ibuprofen and acetaminophen together, every 6 hours while awake after surgery |
| **Follow-up** | Screening through 15 days |
| **Primary Outcomes** | Proportion of subjects receiving no opioid rescue [Time frame: screening through day 15] |
| **Secondary Outcomes** | • Total post-operative opioid consumption [Time frame: screening through day 15]<br>• Mean total TSQM-9 score [Time frame: screening through day 15] |
| **Key Results** | • Results were similar between MMA cohorts.<br>• 95% of patients receiving HTX-011 with an over the counter (OTC) analgesic regimen did not require opioids to manage their postoperative pain through recovery (Day 15).<br>• 91% of patients receiving HTX-011 with an OTC analgesic regimen were discharged without an opioid prescription, and none of these patients subsequently requested an opioid for postoperative pain (call backs).<br>• On average, patients were discharged between 2-3 hours with a mean NRS pain score of 2.6 (mild pain).<br>• Patients reported high satisfaction with both alternating and concurrent MMA regimens. |
| **Adverse effects (AEs)** | HTX-011 was well tolerated with no serious adverse events or NSAID-related toxicity associated with the addition of the OTC analgesic regimen. |
| **Expected reporting date** | Part 1 of this study was completed in May 2019. |

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| **Trial** | **NCT03015532, HTX-011-209; adults aged ≥18 years; HTX-011 vs. HTX-011 + Ropivacaine vs. Bupivacaine HCl vs. placebo; phase IIb** |
| **Sponsor** | Heron Therapeutics Inc. |
| **Status** | Completed |
| **Source of Information** | Trial registry[13] and poster[28] |
| **Location** | United States |
| **Design** | Randomized, double-blind, saline placebo and active-controlled multicentre study |
| **Participants** | n=222 aged ≥18 years old; scheduled to undergo primary unilateral total knee replacement arthroplasty under spinal anaesthesia and has not previously undergone total knee arthroplasty in either knee. |
| **Schedule** | • HTX-011 400 mg/ 12 mg via application into the surgical site (n=58)<br>• HTX-011 400 mg/ 12 mg via application into the surgical site and ropivacaine 0.5% (50 mg, 10 mL) via periarticular injection into the posterior capsule (n=56)<br>• Bupivacaine HCl without epinephrine (0.25%, 125 mg) via periarticular injections into the surgical site (n=55)<br>• Saline placebo via periarticular injection into the surgical site (n=53) |
| **Follow-up** | 72 hours |

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| **Primary Outcomes** | • Mean AUC of NRS pain intensity scores through 48 hours for HTX-011 + low-dose ropivacaine vs. saline placebo<br>• Mean AUC of NRS pain intensity scores through 48 hours for HTX-011 vs. saline placebo |
| **Secondary Outcomes** | • Mean AUC of NRS pain intensity scores through 72 hours for HTX-011 + low-dose ropivacaine vs. saline placebo<br>• Mean AUC of NRS pain intensity scores through 72 hours for HTX-011 vs. saline placebo |
| **Key Results** | • HTX-011 alone significantly reduced mean pain intensity scores versus placebo through 48 and 72 hours (both $p < 0.001$).<br>• Similar results were obtained with the addition of ropivacaine to HTX-011 versus placebo, with only a small additional benefit during the first 8 hours versus HTX-011 alone.<br>• HTX-011 had greater pain reduction through 72 hours compared to bupivacaine ($p=0.0269$) without adjustment for opioids.<br>• Both HTX-011 groups demonstrated numerically lower opioid consumption through 72 hours, and earlier discharge readiness versus placebo.<br>• Mean NRS pain scores were lower for the HTX-011 groups compared with placebo at all timepoints through 72 hours.<br>• The addition of ropivacaine provided a small additional benefit in postoperative analgesia during the first 8 hours. Both HTX-011 groups had fewer patients with severe pain (NRS score ≥ 7) at any time through 72 hours (HTX-011, 81.0%; HTX-011 + low-dose ropivacaine, 76.8%), compared with placebo (92.5%) and bupivacaine HCl (92.7%).<br>• Both HTX-011 groups had lower total opioid consumption through 24, 48, and 72 hours compared with placebo and bupivacaine.<br>• HTX-011 with or without ropivacaine increased the proportion of patients ready for discharge compared with placebo at 8 hours (52% and 55% vs. 26%) and at 12 hours (59% and 68% vs, 36%) using the Modified Postanaesthetic Discharge Scoring System (MPADSS) criteria. |
| **Adverse effects (AEs)** | • The most common TEAEs in the HTX-011 groups were nausea, constipation, and vomiting.<br>• The most common opioid-related TEAEs were nausea and constipation.<br>• The overall incidence of local inflammatory TEAEs was similar in the saline placebo (5.7%), HTX-011 (8.6%), and HTX-011 + ropivacaine (8.9%) groups, while none were reported in the bupivacaine HCl group.<br>• The incidence of potential LAST-related TEAEs in both the HTX-011 and HTX-011 + ropivacaine groups was similar to or lower than the saline placebo group (ie, patients with no exposure to bupivacaine), and no clinically meaningful differences were observed across treatment groups.<br>• Most patients, including 77.4% in the saline placebo group, 83.6% in the bupivacaine HCl group, 89.7% in the HTX-011 group, and 81.8% in the HTX-011 + ropivacaine group, had normal healing (Grade 0) or normal healing with mild bruising or erythema (Grade I) as their worst post baseline assessment. |
| **Expected reporting date** | Study completion date was May 2018. |

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| **Trial** | **NCT03974932, HTX-011-306; adults aged ≥18 years; HTX-011, celecoxib, ibuprofen and acetaminophen; phase IIIb** |
| **Sponsor** | Heron Therapeutics Inc. |
| **Status** | Ongoing |

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| **Source of Information** | Trial registry[12] and poster[29] |
| **Location** | United States |
| **Design** | Single group assignment, open-label |
| **Participants** | n= 51; aged ≥18 years old; scheduled to undergo primary unilateral total knee replacement arthroplasty under spinal anaesthesia and has not previously undergone total knee arthroplasty in either knee. |
| **Schedule** | Patients will receive the HTX-011 at a dose of 400 mg/ 12 mg through luer-lock applicator for instillation, scheduled ibuprofen at a dose of 600 mg days 4-7, scheduled acetaminophen at a dose of 1 g days 1-7 and scheduled celecoxib at a dose of 200 mg days 1-3. |
| **Follow-up** | 12 hours through 29 days |
| **Primary Outcomes** | Mean area under the curve (AUC) of the visual analogue scale (VAS). [Time frame: 12 through 48 hours] |
| **Secondary Outcomes** | • Mean AUC of VAS scores. [Time Frame: 72 hours]<br>• Mean AUC of the NRS of pain intensity at rest (NRS-R). [Time frame: 72 hours]<br>• Proportion of subjects with an NRS-R score ≥7. [Time frame: 10 time points through 72 hours, and day 11 and day 29]<br>• Mean total post-operative opioid consumption (in IV morphine milligram equivalents [MME]). [Time frame: 72 hours]<br>• Proportion of subjects who are opioid-free. [Time frame: through 72 hours, and through Day 11]<br>• Proportion of subjects who are opioid-free through 72 hours who remain opioid-free through 72 hours who remain opioid-free. [Time frame: 72 hours through day 11]<br>• Median time to first opioid rescue medication. [Time frame: 72 hours]<br>• Proportion of subjects who do not receive an opioid prescription at discharge. [Time frame: 72 hours]<br>• Proportion of subjects who do not receive an opioid prescription between discharge and the Day 11 visit. [Time frame: 72 hours through day 11]<br>• Proportion of subjects achieving a score of "good" or better (>1) pain control based on Patient Global Assessment (PGA). [Time frame: 24 hours, 48 hours, 72 hours, day 11]<br>• Median time to first ambulation post-surgery. [Time frame: 72 hours]<br>• Proportion of subjects unable to participate in each rehabilitation session because of pain. [Time frame: 72 hours]<br>• Proportion of subjects who first achieve an MPADSS score ≥9. [Time frame: 10 time points through 72 hours]<br>• Proportion of subjects who are discharged home vs to a skilled nursing facility. [Time frame: 72 hours]<br>• Mean overall benefit of analgesia score (OBAS). [Time frame: 24 hours, 48 hours, 72 hours, day 11]<br>• Mean total TSQM-9 score [Time frame: 72 hours through day 11] |
| **Key Results** | • The mean (SD) AUC12-48 of the VAS was 143.2 (93.5) in patients treated with HTX-011 + MMA.<br>• Mean pain scores remained in the mild range (NRS </=4) through 72 hours post-surgery.<br>• 56.9% of patients did not experience severe pain at any time during the 72-hour inpatient period (VAS scale).<br>• Six patients (11.8%) remained opioid-free through the 72-hour inpatient period. |

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| | • Median opioid consumption was 22.5 mg morphine milligram equivalents (MME; 4-5 oxycodone pills) per patient throughout 72 hours<br>• 68.6% patients (35/51) were deemed ready for discharge within 24 hours.<br>• 74.5% patients were discharged without an opioid prescription. |
| **Adverse effects (AEs)** | • AEs were reported by approximately 75% of patients, were generally mild to moderate in severity, and most were considered related to opioid use.<br>• The most common AEs were nausea, vomiting, and constipation.<br>• There were no deaths or serious adverse events, and no patients discontinued the study due to AEs.<br>• No NSAID-related toxicity was reported. |
| **Expected reporting date** | Estimated primary completion date in December 2020. |

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| **Trial** | **EPOCH 1, NCT03295721, HTX-011-301; adults aged ≥18 years; HTX-011 vs placebo or bupivacaine HCl; phase III** |
| **Sponsor** | Heron Therapeutics Inc. |
| **Status** | Completed |
| **Source of Information** | Trial registry[2] and Publication[30] |
| **Location** | United States |
| **Design** | Randomised, placebo and active controlled, triple blind |
| **Participants** | n= 412; aged ≥18 years old; scheduled to undergo a primary unilateral, distal, first metatarsal bunionectomy with osteotomy and internal fixation under regional anaesthesia. |
| **Schedule** | Patients were randomised in three different groups. Patients assigned to the experimental group received HTX-011 at a dose of 60 mg/ 1.8 mg through luer-lock applicator for instillation. Subjects assigned to the placebo group received saline placebo through luer-lock applicator for instillation and subjects assigned to the active comparator group received bupivacaine injection without epinephrine at a dose of 50 mg. |
| **Follow-up** | 72 hours |
| **Primary Outcomes** | Mean area under the curve (AUC) of the Numeric Rating Scale of pain intensity scores with activity (NRS-A) for HTX-011 compared with saline placebo. [Time frame: 72 hours] |
| **Secondary Outcomes** | Time frame 72 hours:<br>• Mean AUC of the NRS-A pain intensity scores for HTX-011 compared with bupivacaine HCl.<br>• Mean total post-operative opioid consumption (in morphine equivalents) for HTX-011 compared with saline placebo.<br>• Proportion of subjects who are opioid-free for HTX-011 compared with bupivacaine HCl.<br>• Mean total post-operative opioid consumption (in morphine equivalents) for HTX-011 compared with bupivacaine HCl. |
| **Key Results** | • Patients who received HTX-011 showed a reduction in mean pain intensity over 72 hours of 27% compared with saline placebo (323.3 vs 445.3; p<0.001) and 18% compared with bupivacaine HCl (323.3 vs 393.5; p<0.001).<br>• Compared with saline placebo, mean NRS pain intensity scores were lower in the HTX-011 group at all timepoints through 72 hours.<br>• Over the course of 72 hours after treatment, total opioid consumption was significantly reduced by 37% in those who received HTX-011 when |

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| | compared with saline placebo (p<0.001) and by 25% vs those who received bupivacaine HCl (p=0.002).<br>• Overall, 29% of subjects who received HTX-011 were opioid free after 72 hours, whereas 11% of those who received bupivacaine HCl (p<0.001) and 2% of those who received placebo (p<0.001) were opioid free.<br>• Among the 45 HTX-011 subjects who were opioid free during the 72 hours after surgery, 41 (91.1%) stayed opioid free though day 10 and 37 (82.2%) stayed opioid free though day 28. |
| **Adverse effects (AEs)** | • The most common treatment-emergent AEs in the HTX-011 group were nausea and dizziness.<br>• A lower proportion of subjects experienced ORAEs in the HTX-011 group compared with the saline placebo and bupivacaine HCl groups (43.9% vs 53.5% and 50.6%, respectively).<br>• The incidence of local inflammatory TEAEs was higher in the HTX-011 and bupivacaine groups compared with the placebo group. The most common local inflammatory TEAEs in the HTX-011 group were incision site edema and incision site erythema.<br>• No evidence of drug-related local anaesthetic systemic toxicity (LAST) based on a comprehensive review of TEAEs, vital signs, ECGs and bupivacaine plasma concentrations (highest concentration observed was 190 ng/mL).<br>• The proportion of patients reported to have any wound-healing findings was similar across treatment groups.<br>• There was no evidence of drug-related delayed bone healing based on X-rays through day 42 for all treatment groups. |
| **Expected reporting date** | Study completion date was in March 2018. |

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| **Trial** | **NCT03718039, HTX-011-218; adults aged ≥18 years; HTX-011 as part of a schedule non-opioid MMA regimen; phase II** |
| **Sponsor** | Heron Therapeutics Inc. |
| **Status** | Completed |
| **Source of Information** | Trial registry and Poster[31] |
| **Location** | United States |
| **Design** | Open label, multi cohort study |
| **Participants** | n= 31; aged ≥18 years old; scheduled to undergo a primary unilateral, distal, first metatarsal bunionectomy with osteotomy and internal fixation under regional anaesthesia. |
| **Schedule** | Patients received HTX-011 60 mg/1.8 mg intraoperatively and a scheduled non-opioid OTC MMA regimen for 72 hours following surgery:<br>• HTX-011 doses were individualized; surgeons coated all pain-generating tissues but did not allow excess that could be expressed onto the skin<br>• The maximum allowed HTX-011 dose was 60 mg/ 1.8 mg<br>• A scheduled non-opioid OTC MMA regimen was taken postoperatively for 72 hours: ibuprofen 600 mg every 6 hours (q6h) orally (PO) alternated every 3 hours with acetaminophen 1 g q6h PO |
| **Follow-up** | 72 hours through 28 days |
| **Primary Outcomes** | Mean AUC of the NRS of pain intensity scores through 72 hours (AUC 0-72) |
| **Secondary Outcomes** | • Total postoperative opioid consumption (in morphine equivalents) through 72 hours |

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| | • Proportion of patients who are opioid-free through 72 hours<br>• AUC 0-72 of the NRS pain intensity scores<br>• Proportion of patients who are opioid-free through 72 hours who remain opioid-free through Day 10 and Day 28 |
| **Key Results** | • Mean pain intensity remained within the mild range (NRS <4) at all times through 72 hours.<br>• Twenty-four (77.4%) patients treated with HTX-011 and non-opioid MMA required no opioids through 72 hours after surgery.<br>• Only one (3.2%) patient who received HTX-011 with MMA in this study was discharged with an opioid prescription.<br>• Of the 24 patients who did not take opioids during the first 72 hours, all (100%) remained opioid-free through Day 28 of recovery.<br>• Mean pain scores did not reach the severe pain range (NRS score ≥7) at any time during the study. |
| **Adverse effects (AEs)** | • Overall, 20 (64.5%) patients reported at least one AE, none of which were severe or considered related to study drug.<br>• The most common AEs were nausea (22.6%) and vomiting (9.7%).<br>• There was one local inflammatory AE (impaired healing), which was mild in severity and resolved.<br>• Opioid-related AEs (ORAEs) occurred in 9 (29%) patients.<br>• There were no reports of cardiac, renal, or hepatobiliary AEs in the EPOCH-1 Follow-on study.<br>• There was no evidence of NSAID- or acetaminophen-related toxicity when HTX-011 was administered with the MMA regimen as determined from AEs and clinical laboratory tests. |
| **Expected reporting date** | Study completion date was in Mar 2019. |

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| **Trial** | **EPOCH 2, NCT03237481, HTX-011-302; adults aged ≥18 years; HTX-011 vs placebo or bupivacaine HCl; phase III** |
| **Sponsor** | Heron Therapeutics Inc. |
| **Status** | Completed |
| **Source of Information** | Trial registry[3] and Publication[32] |
| **Location** | United States and Belgium |
| **Design** | Randomised, placebo and active controlled, triple blind |
| **Participants** | n= 418; aged ≥18 years; scheduled to undergo a unilateral open inguinal herniorrhaphy with mesh under general anaesthesia. |
| **Schedule** | Patients were randomised in three different groups. Patients assigned to experimental group received HTX-011 at a dose of 300 mg/ 9 mg through luer-lock applicator for instillation. Subjects assigned to the placebo group have saline placebo through luer-lock applicator for instillation and subjects assigned to the active comparator group received bupivacaine HCl without epinephrine at a dose of 75 mg injection. |
| **Follow-up** | 72 hours |
| **Primary Outcomes** | Mean area under the curve (AUC) of the Numeric Rating Scale of pain intensity scores with activity (NRS-A) for HTX-011 compared with saline placebo. [Time frame: 72 hours] |
| **Secondary Outcomes** | Time frame 72 hours: |

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| | • Mean AUC of the NRS-A pain intensity scores for HTX-011 compared with bupivacaine HCl.<br>• Mean total post-operative opioid consumption (in morphine equivalents) for HTX-011 compared with saline placebo.<br>• Proportion of subjects who are opioid-free for HTX-011 compared with bupivacaine HCl.<br>• Mean total post-operative opioid consumption (in morphine equivalents) for HTX-011 compared with bupivacaine HCl. |
| **Key Results** | • HTX-011 subjects showed a 23% reduction in mean pain intensity over 72 h compared to saline placebo (269.39 versus 350.82; $p < 0.0001$). At all timepoints through 72 h, the mean NRS pain intensity scores were lower in the HTX-011 group when compared with saline placebo.<br>• A significant reduction of 21% for pain intensity over 72 h was observed when HTX-011 was compared to bupivacaine (269.39 versus 341.88; $p < 0.0001$).<br>• Total opioid consumption through 72 h in the HTX-011 group was significantly reduced by 38% when compared with saline placebo ($p < 0.0001$) and by 25% when compared with bupivacaine HCl ($p = 0.024$).<br>• Overall, 51% of HTX-011 subjects were opioid-free through 72 h versus 40% for bupivacaine HCl ($p = 0.0486$) and 22% in saline placebo ($p < 0.0001$).<br>• Fewer patients receiving HTX-011 experienced severe pain (i.e., NRS score ≥ 7) at any time. Specifically, fewer than half the subjects in the HTX-011 group (48.8%) experienced severe pain at any time point over 72 h compared with the 60.5% in the bupivacaine HCl group ($p = 0.0372$) and 81.7% in the saline placebo group ($p < 0.0001$).<br>• The proportion of patients who did not require any opioid rescue medication over the 72-hour postoperative period was significantly higher in the HTX-011 group compared with placebo and bupivacaine.<br>• Of the 84 subjects in the HTX-011 group who were opioid-free through 72 h, 80 (95.2%) and 71 (84.5%) subjects remained opioid-free though Day 10 and Day 28, respectively. |
| **Adverse effects (AEs)** | • The most common treatment-emergent AEs (TEAEs) in the HTX-011 group were nausea, constipation, and dizziness.<br>• A lower incidence of ORAEs was reported for HTX-011 (32.5%) compared with saline placebo (43.9%) and bupivacaine HCl (42.2%).<br>• The incidence of local inflammatory TEAEs was higher in the HTX-011 and bupivacaine groups compared with the placebo group. The most common local inflammatory TEAEs in the HTX-011 group were incision site swelling and incision site infection.<br>• Across all arms, the incidence of local inflammatory AEs was low and there was no evidence of delayed wound healing.<br>There was no evidence of local anaesthetic systemic toxicity (LAST) based on a comprehensive review of potential LAST-related AEs, vital signs, ECGs, and bupivacaine plasma concentrations. |
| **Expected reporting date** | Study completion date was in January 2018. |

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| **Trial** | **NCT03695367, HTX-011-215; adults aged ≥18 years; HTX-011 as part of a schedule non-opioid MMA regimen; phase II** |
| **Sponsor** | Heron Therapeutics Inc. |
| **Status** | Completed |

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| **Source of Information** | Trial registry and Poster[33] |
| **Location** | United States |
| **Design** | Open label study |
| **Participants** | n= 63; aged ≥18 years old; scheduled to undergo a unilateral open inguinal herniorrhaphy with mesh under general anaesthesia. |
| **Schedule** | All patients (Cohorts 1 and 2) received a single dose of HTX-011 300 mg/ 9 mg administered via needle-free application to the surgical site prior to closure in addition to non-opioid MMA therapy consisting of:<br>• Preoperative oral acetaminophen 1 g<br>• Postoperative oral ibuprofen 600 mg and oral acetaminophen 1 g every 6 hours, alternating, so that patients received an analgesic every 3 hours<br>Cohort 2 also received a single dose of intravenous (IV) ketorolac intraoperatively (15-30 mg, per prescribing information) |
| **Follow-up** | 72 hours through 28 days |
| **Primary Outcomes** | Proportion of opioid-free patients through 72 hours |
| **Secondary Outcomes** | • Total postoperative opioid consumption through 72 hours<br>• Proportion of patients who were opioid-free through 72 hours that remained opioid-free through Day 10 and Day 28<br>• Proportion of patients in severe pain (NRS ⩾ 7) at any point in the first 72 hours postoperatively |
| **Key Results** | • Efficacy results were generally similar in the 2 cohorts; i.e., with or without ketorolac – the results of both cohorts were therefore combined.<br>• In this follow-on study, 90.5% of patients (57/63) receiving HTX-011 with a non-opioid MMA regimen remained opioid-free through 72 hours following surgery, and 96.5% of them (55/57) remained opioid-free through Day 10 and 91.2% (52/57) remained opioid-free through Day 28 of recovery.<br>• Mean pain intensity was mild (NRS < 4) at every assessment timepoint during the 72-hour inpatient period.<br>• In total, 82.5% of patients (52/63) did not experience severe pain (NRS ⩾7) at any time following surgery. Among patients who experienced severe pain (11/63), all initially reported it within the first 24 hours following surgery.<br>• 6 patients (10%) requested an opioid medication during the 72-hour postoperative period reported an NRS score of ⩾6 within 1 hour following surgery; 4 of these patients reported severe pain (NRS ⩾7) within the first 2 hours following surgery. All patients who took an opioid during the 72-hour inpatient period reported severe pain and/or received an opioid within 2 hours following surgery |
| **Adverse effects (AEs)** | • Thirty-eight percent of patients (24/63) experienced an AE; none of these were serious or led to study withdrawal.<br>• Eleven percent of patients (7/63) reported opioid-related AEs in this study. This was lower than the prior phase 3 study, concordant with the decreased use of opioids.<br>• There was no evidence of nonsteroidal anti-inflammatory drug (NSAID)-related toxicity with the addition of an MMA regimen (which included NSAIDs) to HTX-011. |
| **Expected reporting date** | Study completion date was December 2018. |

# ESTIMATED COST

The cost of HXT-011 is not known yet.

# RELEVANT GUIDANCE

## NICE GUIDANCE

- No relevant guidance identified.

## NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified.

## OTHER GUIDANCE

- Chou R. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. 2016.[38]
- European Association of Urology. Guidelines of Pain Management. 2012.[39]
- American Society of Anesthesiologists. Practice Guidelines for Acute Pain Management in the Perioperative Setting: An Updated Report by the American Society of Anesthesiologists Task Force on Acute Pain Management. 2012.[40]

# ADDITIONAL INFORMATION

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