
HTX-011 – Hope or Hype?

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The Case Against HTX-11

HTX-011 (Heron Therapeutics, Inc) is an investigational drug granted fast track status by the FDA for use directly into incision sites, which claims to be a long acting local (LAL). The drug is a biochronomer, a bio-erodible polyorthoester, that allows for a controlled, continuous breakdown to release its drug payload. Its maker, Heron, states that the drug is comprised of the local anesthetic bupivacaine and the NSAID meloxicam in a thick viscous solution that can be delivered without a needle directly into a surgical wound for postoperative pain relief. Here are some key things clinicians should consider:

Investigational drug - Unknown dosage

Heron states that HTX-011 contains bupivacaine and the NSAID meloxicam in a fixed ratio, but the published literature does not reveal the dosage of each drug within that ratio. There is also no published standard dose of HTX-011 given that this is an investigational drug and there are limited data. Until those data are published, it cannot be effectively compared to standard doses of bupivacaine and liposomal bupivacaine.

Meloxicam: instill or inject, is there a difference?

Meloxicam is an NSAID commonly used to treat arthritis and administered after surgery. Heron's reasoning behind adding meloxicam to the bupivacaine is founded on legitimate science—meloxicam, in essence may reduce inflammation at the wound site, which allows the analgesic effect of the bupivacaine to more effectively work. However, there is no published research effectively demonstrating a benefit to instilling meloxicam in a wound versus giving it in an IV or injection. Additionally, there are no data that explore the potential negative side effects of instilling meloxicam directly into the wound. This is particularly important in hip or joint replacement surgeries, where it is essential to prevent infection and promote wound healing to protect the joint.

Data analysis aimed at investors

The limited data that are currently available on HTX-011 appear to be aimed at investors and organized and analyzed in such a way that can be misleading. Since it is described as an opioid-sparing treatment (though not clearly demonstrated by current data), it appears to be an effort to get a hold of a market for financial gain. Close examination of the available data and the discrete data points does not show a clinically significant reduction in pain scores and/or opioid use beyond 24 hours.

There are problems with four of the studies that Heron has released on the investigational drug, which are briefly reviewed here:

Study 301, EPOCH 1

Over 400 Bunionectomy patients took part in multi-center study, randomized control. Patients received either HTX-011 at 60 mg, bupivacaine-HCl at 50 mg, or saline.

The primary endpoint was the area under the curve to 72 hours for HTX-011 versus saline. It is worth noting that while this primary endpoint has little to no clinical relevance, it does ensure that unless HTX-011 fails as a local anesthetic, it will provide a “positive” study with statistical difference demonstrated in the primary outcome.

Additionally, this study not only compared HTX-011 to bupivacaine without epinephrine (which is expected to last a shorter duration than the formulations with epinephrine), but they also underdosed the bupivacaine-HCl. An equivalent dose would have been 67mg, not the 50mg that were studied. The inequivalent dosing as well as using a formulation without epinephrine would be expected to produce subpar results compared to HTX-011. That said, there was no clinically relevant difference between the HTX-011 and bupivacaine-HCl groups beyond 12-24 hours and the only clinically significant difference, where HTX-011 “performed” better at lowering pain scores compared to bupivacaine-HCl existed between 8-12 hours.

Study 2, EPOCH 2

This study had the same criteria as EPOCH1 but was performed in patients undergoing hernia repair. The doses were different from EPOCH 1 and remarkably dissimilar, with patients receiving either 300mg HTX-011 or 75mg bupivacaine-HCl. In all fairness, they cannot provide an equivalent dose for the bupivacaine-HCl as that would be a dose of greater than 300mg bupivacaine and would put the patient at risk for local anesthetic systemic toxicity (LAST). Presuming that none of the patients that received HTX-011 experienced signs of symptoms of LAST, the much higher dose allowed with HTX-011 is noteworthy and indicates there may be some protection from LAST in the biochronomer formulation, but this disparate dosing must be considered when evaluating the data. Interestingly, despite such a dose discrepancy, there was no clinically relevant difference between HTX-011 and bupivacaine-HCl beyond 8-12 hours, with both treatment groups experiencing equivalent moderate pain.

Study 209: TKA

This study is less straightforward than the EPOCH studies. They enrolled 222 total knee replacement patients who were randomized to receive 1 of 4 different treatments: 1. 400mg HTX-011 instilled at the incision alone; 2. 400mg HTX-011 instilled at the incision plus 50mg ropivacaine injected in the posterior capsule; 3. 125mg bupivacaine-HCl periarticular injection; and 4. Saline injection alone.

Comparing 4 different treatment agents with 3 different treatment protocols creates some confusion when examining the data as it is unclear whether to attribute any observed difference to the drug or to the specific protocol or both. This makes it challenging to make any firm conclusions from this data. Upon review of the plotted data though, it is clear that all patients, regardless of their treatment arm experienced moderate pain out to 36 hours, with no clinically significant or relevant difference between them beyond 24 hours (with the exception of the saline group).

Study 215 Herniorraphy

Finally, Heron recently included a new study in their released corporate update—a cohort study of 63 patients following hernia repair. Both cohorts received preoperative Tylenol, HTX-011 in the incision, followed by routine postoperative Tylenol and ibuprofen, however only one cohort received intraoperative Ketorolac. Since the only difference between the 2 cohorts is the addition of IV Ketorolac, this study only demonstrates whether the addition of IV Ketorolac improves pain scores or not. In fact, they found no significant difference between the 2 cohorts at all time points

out to 72 hours, which reveals that adding IV Ketorolac to the postoperative analgesia cocktail provides no benefit when HTX-011 is used intraoperatively. It is unclear what, if any clinical value this study provides.

Conclusion

A clinically relevant study that was either not done or has not been made available would be to compare HTX-011 to bupivacaine-HCl with epinephrine either alone or in conjunction with an IV NSAID such as Ketorolac. Until such a study is done, we cannot make an informed decision as to whether HTX-011 or a similar formulation would provide a significant enough benefit to outweigh the added cost.

These four studies raise significant concerns about HTX-011. The Epoch 1 study manipulated data to present an inaccurately “positive” result and didn’t compare clinical drug equivalents. The Epoch 2 study is ineffective at demonstrating that HTX-011 has a superior pain relieving effect to bupivacaine-HCl. The TKA study’s results are muddled by multiple treatment agents and treatment protocols, which make it difficult to determine any clinically relevant effects of HTX-011. The Herniorraphy study does not demonstrate any clinically relevant data about whether HTX-011 provides long lasting pain relief.

In conclusion, the available data on HTX-011 do not give me confidence that it is worth the potential risk and unknown costs that it may come with.

Heron Therapeutics - Corporate Update (Jan 7, 2019). Retrieved from <https://herontherapeutics.gcs-web.com/static-files/7a7ec637-9158-4949-a09d-1bdcdd1f6c37> Accessed Feb 2019.