Interim Safety and Efficacy of HTX-011 Administered Postpartum to Women Undergoing a Planned Caesarean Section

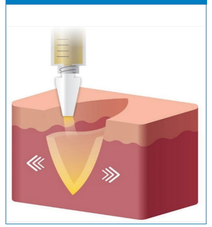
Craig Saffer[1], Chris Storgard[2], Katie Luepke[2], Timothy Melson[3]

[1]West Coast OB/GYN, San Diego, CA; [2]Heron Therapeutics, Inc., San Diego, CA; [3]Shoals Medical Trials, Inc, Sheffield, AL.

INTRODUCTION AND OBJECTIVES

- Over-prescribing opioids is common after Caesarean section (C-section), likely due to concern for inadequate pain management that could decrease the patient's ability to care for their newborn baby[1]. Excess opioid exposure may result in long-term dependence, diversion, and/or opioid-related adverse events (ORAEs) that could predispose to newborn falls (dropping of infant)[2]. Maintaining adequate pain control while minimizing opioid exposure is imperative, thus non-opioid postpartum analgesic therapies are needed.
- HTX-011 (ZYNRELEF®) is comprised of bupivacaine and low-dose meloxicam in an extended-release polymer* that controls the release of active ingredients over 72 hours, which results in enhanced and sustained analgesia[3,4].
  - Meloxicam reduces surgery-related inflammation, thereby normalizing local pH which results in enhanced penetration of bupivacaine into nerves[4].
- HTX-011 is administered via a needle-free Luer-lock applicator into the surgical site prior to closure (**Figure 1**).
- The primary objective of this study was to characterize the pharmacokinetics (PK) of HTX-011 components in expressed breast milk and plasma following postpartum administration of HTX-011 in women undergoing a planned C-section. The secondary objective was to assess safety of HTX-011, and an exploratory objective was to characterize efficacy[5]. Preliminary PK results were previously presented[6]; this presentation is focused on interim safety and efficacy results.

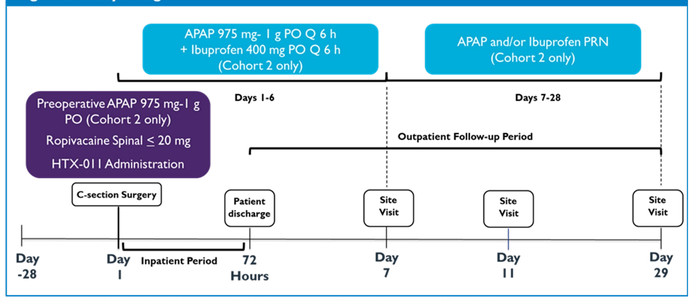
Figure 1. HTX-011 Administered Without Needle



METHODS

- Phase 2, open-label, multi-cohort study of HTX-011 administered intraoperatively with or without scheduled postoperative oral non-opioid multimodal analgesia (MMA) in women undergoing planned C-section (**Figure 2**)[4].
- **Key Inclusion Criteria:** Adult patients (ASA I, II, III) scheduled to undergo planned C-section under spinal anesthesia with low transverse skin incision and refrained from use of breast milk from pregnancy in any manner for 28 days.
- **Key Exclusion Criteria:** Prior full-term pregnancy with unsuccessful breast milk expression, opioid use for ≥ 7 days within 6 months, opioid use prior 24 hours.
- **Safety and Efficacy Endpoints:** Adverse events (AE)s through Day 29 visit, local anesthetic systemic toxicity (LAST) symptoms (vital signs and questionnaire), wound healing assessment using Southampton scale, Numeric rating scale of pain intensity at rest (NRS-R), opioid rescue through 72 hours, opioid discharge prescription (yes/no).
- **Treatment Assignments:**
  - After delivery, a single dose of HTX-011 was administered via instillation into the surgical site (300 mg/9 mg [bupivacaine/meloxicam] in Cohort 1, 400 mg/12 mg in Cohort 2). In Cohort 1, additional intraoperative anesthesia was managed by institutional practice and in Cohort 2 patients received intrathecal morphine sulfate 50 µg and fentanyl 20 µg plus scheduled postoperative oral acetaminophen and ibuprofen through Day 6 (prn thereafter).

Figure 2. Study Design



APAP, acetaminophen; MMA, multimodal analgesia; BMI, body mass index; SD, standard deviation; SE, standard error

*tri(ethylene glycol) poly(orthoester) polymer (TEG POE)

METHODS, cont.

- **Postoperative Rescue Medication (PRN):**
  - Cohort 1: PO ibuprofen ≤600 mg within 6-hour period, PO/IV APAP ≤1 gram within 6 hour period, PO immediate-release oxycodone ≤5 mg within 4-hour period, IV morphine ≤10 mg within 2-hour period.
  - Cohort 2: PO ibuprofen 400 mg once every 12 hours (in addition to scheduled MMA through Day 6), if pain uncontrolled, may administer PO immediate-release oxycodone ≤5 mg within 4-hour period and/or IV morphine ≤10 mg within 2-hour period.

RESULTS

- 25 patients were included, 14 in Cohort 1 and 11 in Cohort 2. Demographics are listed in **Table 1**.

Table 1. Baseline Characteristics

	Cohort 1 HTX-011 300 mg/9 mg N=14	Cohort 2 HTX-011 400 mg/12 mg + MMA N=11	Total N=25
Age, mean (SD)	29.5 (5.6)	25.9 (4.0)	27.9 (5.2)
Race, n (%)			
Black or African American	2 (14.3)	3 (27.3)	5 (20.0)
White	12 (85.7)	8 (72.7)	20 (80.0)
BMI (kg/m^2), mean (SD)	35.4 (7.5)	40.3 (7.4)	37.6 (7.7)

Pharmacokinetics

- Preliminary PK results were previously presented in detail[6]. Overall, a single postpartum dose of HTX-011 resulted in very low (microgram) levels of bupivacaine and meloxicam in breast milk. Levels of the well-known excipient DMSO were barely detectable by 48 hours.

Safety

- Overall, 20 patients (80.0%) reported at least one adverse event (AE); none were considered related to HTX-011. The most common AEs were constipation, flatulence, nausea, pruritis, and anemia. The most common possible NSAID-related AEs were pruritis (n=5, 20%) and postoperative anemia (n=5, 20%) **(Table 2)**.
- Review of vital signs, laboratory parameters, and physical examinations did not reveal any safety concerns. In addition, no symptoms of LAST were reported via the LAST questionnaire.
- The majority of patients (96%) had normal wound healing using the Southampton Wound Scoring System at all assessments. One patient experienced erythema with inflammation around the wound at 72 hours that resolved by Day 7.

Table 2. Summary of Adverse Events

Adverse Events, n (%)	Cohort 1 HTX-011 300 mg/9 mg N=14	Cohort 2 HTX-011 400 mg/12 mg + MMA N=11	Total N=25
Any AE	12 (85.7)	8 (72.7)	20 (80.0)
AE Possibly Related to Study Drug	0	0	0
Severe AE	1 (7.1)	1 (9.1)	2 (8.0)
Serious AE	1 (7.1)	1 (9.1)	2 (8.0)
AE leading to study withdrawal	0	0	0
Opioid-related AE[1]	7 (50.0)	4 (36.4)	11 (44.0)
LAST-related AE[2]	0	0	0
NSAID-related AE[3]	7 (50.0)	6 (54.5)	13 (52.0)
Most common AEs (≥10%)			
Constipation	6 (42.9)	2 (18.2)	8 (32.0)
Flatulence	4 (28.6)	3 (27.3)	7 (28.0)
Pruritis	2 (14.3)	3 (27.3)	5 (20.0)
Anemia	3 (21.4)	2 (18.2)	5 (20.0)
Nausea	3 (21.4)	0	3 (12.0)

2 patients each experienced 1 severe AE (pulmonary hypertension and gestational hypertension), and 2 patients experienced a total of 3 serious AEs (pneumonia, congestive cardiac failure, gestational hypertension).
[1]Opioid-related AEs were prespecified as nausea, vomiting, constipation, pruritus, pruritus generalized, somnolence, respiratory depression, and urinary retention.; [2]Dizziness, tinnitus, metallic taste, and perioral numbness; [3]NSAID-related AEs were identified using a customized list of NSAID toxicity-related preferred terms (>1,800) derived from Essex MN, et al[7].

RESULTS

Efficacy

- Mean (SD) area under the concentration curve (AUC) of NRS-R through 72 hours (AUC_{0-72}) was 252.8 (165) for Cohort 1 and 154.0 (138) for Cohort 2. Mean ± SE NRS scores over time are illustrated in **Figure 3**.
- Mean (SD) opioid use over 72 hours was 32.1 (34.3) intravenous morphine milligram equivalents for Cohort 1 and 10.0 (9.76) for Cohort 2, respectively, and majority of opioid use was within first 48 hours **(Table 3)**.
- 7.1% and 27.3% of patients in Cohorts 1 and 2, respectively, had an opioid-free recovery.

Figure 3. Mean (SE) NRS-R Scores at Each Assessed Timepoint Through 72 Hours

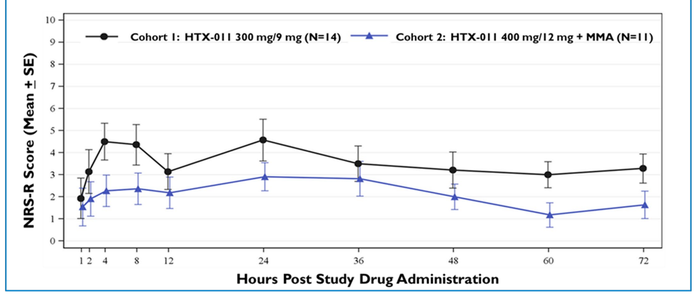


Table 3. Postoperative Opioid Consumption

	Cohort 1[1] HTX-011 300 mg/9 mg N=14	Cohort 2[2] HTX-011 400 mg/12 mg + MMA N=11
Postoperative Opioids (IV MME), Mean (SD)		
0-24 hours	13.6 (12.3)	4.09 (4.07)
24-48 hours	12.3 (16.1)	4.36 (3.61)
0-48 hours	25.9 (27.8)	8.45 (7.49)
48-72 hours	6.15 (7.21)	1.55 (2.70)
0-72 hours	32.1 (34.3)	10.0 (9.76)
24-72 hours	18.5 (22.9)	5.91 (6.00)
Opioid-free Recovery (through 72 hours), n (%)	1 (7.1)	3 (27.3)

MME, morphine milligram equivalents; [1]Intraoperative opioid use was based on institutional practice; 8 (57%) patients received intrathecal fentanyl (20 µg) and 4 (29% received both intrathecal fentanyl (10-25 µg) and morphine (0.1-0.2 mg)
[2]Intraoperative opioid use per protocol, intrathecal fentanyl (20 µg) + intrathecal morphine (0.05 mg)

SUMMARY AND CONCLUSIONS

- In this preliminary safety and efficacy analysis of HTX-011 in planned C-section, treatment was well-tolerated across doses and with scheduled MMA including NSAIDs.
- In Cohort 2, use of protocolized intraoperative anesthesia with HTX-011 400 mg/12 mg in addition to scheduled MMA resulted in mean NRS-R scores within the mild range and 27% of patients with an opioid-free recovery. In addition, reduced opioid consumption in Cohort 2 resulted in fewer ORAEs.
- Preliminary data suggest that HTX-011 400 mg/12 mg may effectively manage postpartum pain and minimize opioid use.

REFERENCES

1. Osmundson SS, et al. Curr Opin Obstet Gynecol. 2019; 31(2): 83–89.
2. Kahn KM, et al. MCN Am J Matern Child Nurs 2021;46(4):190-97.
3. ZYNRELEF (bupivacaine and meloxicam) Extended-Release Solution [Full Prescribing Information].
4. Ottoboni T et al. Reg Anesth Pain Med. 201945:117-123.
5. Clinicaltrials.gov, NCT 03955211.
6. Yamamato A, et al. ASHP Midyear Clinical Meeting 2020 (virtual).
7. Essex MN et al. Expert Opin Drug Saf. 2013;12:465-477.

Funding for this research was provided by Heron Therapeutics, Inc. (San Diego, CA, USA).