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APPLICATION NUMBER:

211988Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA: 211988; SN0040 Resubmission	Submission Date: 09/26/2019
Link to EDR	\\cdsesub1\evsprod\NDA211988\0040
Relevant IND(s):	IND 125927
Submission Type; Code:	505 (b) (2)
Priority Classification	Priority
Brand Name:	Zynrelef
Generic Name:	Bupivacaine (2.5% bupivacaine base) and Meloxicam (0.075%)
Reference Drugs:	MARCAINE (NDA 016964) and MOBIC (NDA 020938)
Formulation; Strength(s):	Solution; bupivacaine (2.5% bupivacaine base) and meloxicam (0.075%)
Clinical Pharmacology Reviewer:	Suresh B Naraharisetti, Ph.D.
Clinical Pharmacology Team Leader:	Yun Xu, Ph.D.
OCP Division:	Division of Neurology Products
OND Division:	Division of Anesthesiology, Addiction Medicine, Pain Medicine
Sponsor:	Heron Therapeutics, Inc.
Indication:	(b) (4)
Dosage Regimen:	Single dose by instillation

1.0 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Neurology Products (OCP/DNP) has reviewed the Complete Response Resubmission submitted by the applicant on 09/26/19, for NDA 211988; SN0040.

For this NDA, there were no approvability issues from clinical pharmacology perspective in the first review cycle. However, the non-clinical team commented in the complete response (CR) letter that, "Because your drug product exposures above 300 mg of bupivacaine via this drug product will exceed that of the referenced drug product, additional data will be required to support any proposed dose above 300 mg bupivacaine". To address this comment, the applicant

in this resubmission submitted 1) additional pharmacokinetic (PK) information from literature to support clinical bridge for bupivacaine systemic exposure between HTX-011 and literature bupivacaine HCl, 2) bioanalytical information of literature articles, and 3) PK information from the Study BUPI-501, in which 300 mg bupivacaine HCl was infused into surgical wound over 60 hours in herniorrhaphy. In addition, applicant also submitted data based on *in vitro* release assay on percentage of bupivacaine, meloxicam and excipients released from HTX-011. Refer to the biopharmaceutics review in this regard.

As for the meloxicam component of HTX-011, both Cmax and AUC are lower than that of MOBIC, which were concluded in the first review cycle.

Note: In the text, Marcaine and bupivacaine HCl are interchangeably used.

- From the clinical pharmacology perspective, this submission is acceptable. We have the following comments regarding the bupivacaine systemic exposure comparison between HTX-011 and the listed drug, Marcaine, based on the information submitted by the Applicant. Cmax: The mean bupivacaine Cmax value at the highest proposed dose of HTX-011, 400 mg/12 mg, in augmentation mammoplasty is lower than that for bupivacaine HCl in the same surgical procedure. Overall, based on applicant's studies, the highest observed bupivacaine Cmax of HTX-011 is lower than the Marcaine Cmax.
- AUC_{0-24}: Based on observed lower bupivacaine AUC_{0-24} / AUC_{inf} ratio-values of HTX-011 compared to bupivacaine HCl, it is a reasonable estimation that the bupivacaine AUC_{0-24} of HTX-011 at 400 mg/12 mg dose will be lower than that of bupivacaine HCL when given 400 mg /day.
- AUC_{inf}: In comparison to the calculated 400 mg bupivacaine HCl AUC_{inf} values, the observed HTX-011 AUC_{inf} value is lower by ~18% for abdominoplasty (Study 203); while it is higher by ~40% and ~72%, respectively for augmentation mammoplasty (Study 211) and TKA (Study 209). However, in the team meeting held on 03/10/2020, the non-clinical team informed the team that the applicant has submitted new animal data that provides systemic safety coverage up to 400 mg of HTX-011. In such a case, this newly submitted animal data may be adequate to address the non-clinical comment in the CR letter mentioned above, regardless whether the Sponsor has provided adequate PK information to address the systemic exposure of HTX-011 at 400 mg dose. Hence, we defer to non-clinical team on the systemic safety coverage up to 400 mg of HTX-011 based on totality of the data.

2. Regulatory Background

For this NDA, Agency issued a CR Letter on 04/30/19 indicating deficiencies related to product-quality and non-clinical teams. A post-action teleconference meeting was held with applicant on 08/07/2019; meeting-minutes of this meeting were posted to DARRTS on 09/06/2019.

In the original NDA submission, there were no clinical pharmacology related deficiencies. The clinical pharmacology review for this NDA is in DAARTS dated 04/10/2019.

In the CR letter, in addition to the deficiencies, Agency also communicated Additional Comments that are not approvability issues, but applicant needs to address them. The additional comment # 1 by non-clinical team was related to $AUC_{0\text{-}24h}$ for proposed maximum dose of 400 mg bupivacaine. It is as follows:

> *"Although the current nonclinical data appear to support the safety of bupivacaine when the product is dosed up to 300 mg, the data do not provide adequate coverage for the maximum $AUC_{0\text{-}24h}$ via this drug product at your proposed maximum dose of 400 mg bupivacaine. Because your drug product exposures above 300 mg of bupivacaine via this drug product will exceed that of the referenced drug product, additional data will be required to support any proposed dose above 300 mg bupivacaine".*

For the above comment, Applicant followed upon in the post-action meeting in Question #7 (Q7). The applicant's Question #7, agency's responses and discussion related to Q7 can be found in meeting minutes (DARRTS, 09/06/2019). For Q7, a part of response was provided by Clinical Pharmacology, for which the highlights are shown below, specifically related to literature-bioanalytical information and bupivacaine-exposure-coverage (e.g., AUC_{inf}) :

> *"You mentioned literature data in the meeting package. If you intend to rely on published literature, you need to provide adequate justification that the results from literature can be used to support your product, considering the potential difference in patient population, drug formulation, route of administration, dosing regimen, etc. To rely on PK data in literature, provide information on whether appropriate bioanalytical information such as precision, accuracy, stability, incurred- sample-reanalysis is available for the bioanalytical methods used for quantifying the drug concentration in those articles. Also, refer to our 505(b)(2) comments regarding 'right of reference' for literature articles. The literature data must provide adequate information to support labeling. You will have to submit a summary and discussion of how the literature supports clinical pharmacology package of the NDA and how it can adequately support the relevant sections of the package insert.*
>
> *You may use observed Cmax values of IR bupivacaine from your completed study to cover the observed Cmax value of HTX-011, providing the dosing regimen and indication of IR bupivacaine are within its label allowed range.*
>
> *You mentioned the maximum of 400 mg total daily dose for IR bupivacaine in the label. In your completed relative bioavailability study between HTX-011 and IR bupivacaine, HTX-011 demonstrated significantly higher total exposure (e.g. AUC0-inf) compared to IR bupivacaine. Therefore, even if a 400 mg dose was used for the IR bupivacaine in the study, it is unlikely that it will cover the total exposure for HTX-011. Also, as a reminder, the systemic safety is associated with observed exposure, not dose-normalized exposure. Only observed exposure will be used for comparison between HTX-011 and IR bupivacaine for systemic safety".*

3. Review of Resubmission:

In the resubmission, for establishing the clinical PK bridge between HTX-011 and bupivacaine HCl for Cmax and AUC (AUC_{0-24} and AUC_{inf}), the applicant provided the data / rationale from their own studies and literature studies. In this review, applicant's provided data / rationale (shown in the italicized text) is followed by the reviewer's comments to each segment.

3.1 Comparison of bupivacaine Cmax between HTX-011 and Marcaine

3.1a: Applicant's data/ Rationale on Cmax:

To establish the clinical PK bridge to Bupivacaine HCl using Cmax, the observed bupivacaine mean Cmax values for HTX-011 at the proposed highest recommended dose were compared to those from bupivacaine HCl (Table 8). Following administration of HTX-011, the highest mean C_{max} value of bupivacaine was observed in augmentation mammoplasty of 710 ng/mL. In comparison, the observed bupivacaine HCl C_{max} of 150 mg administered via injection or instillation in augmentation mammoplasty (Study BUPI-502, a Phase 4 study) showed a mean C_{max} of 1110 ng/mL for both administration techniques. Based on this, the observed bupivacaine C_{max} from HTX-011 at 400 mg/12 mg is lower than that of bupivacaine HCl when administered in the same surgical model. Hence coverage for bupivacaine Cmax is established.

Table 8: Clinical PK Bridge Established With Mean Plasma C_{max} for HTX-011-56 and Bupivacaine HCl Support the Proposed Maximum Recommended Dose of HTX-011-56 400 mg/12 mg

Treatment	Bupivacaine Dose	Heron Study	Procedure	n	C_{max} (ng/mL)
HTX-011-56	400 mg Instillation	209[a]	TKA	109	672
		211	Augmentation mammoplasty	49	710
Bupivacaine HCl	150 mg Injection or Instillation	BUPI-502	Augmentation mammoplasty	30	1,110

Source 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

In study BUPI-502 (augmentation mammoplasty), 150 mg of bupivacaine HCl was administered by instillation in 15 subjects and by injection in 15 subjects. The mean bupivacaine Cmax observed in both drug administration procedures were 1110 ng/mL. The highest individual concentration of bupivacaine HCl observed in this study was 2170 ng/mL (via injection, at 1 h time point in subject # (b) (6). As can be noted from the Table 8 above, the highest mean bupivacaine Cmax from HTX-011 (Study 211 augmentation mammoplasty) is 710 ng/mL, which is 36% lower compared to the bupivacaine HCl Cmax (cross-study comparison in same surgical procedure).

3.1b: Reviewer's Conclusion for Cmax:

The mean bupivacaine C_{max} value at the highest proposed dose of HTX-011, 400 mg/12 mg in augmentation mammoplasty is lower than that for bupivacaine HCl in the same surgical procedure. Overall, based on applicant's studies, the highest observed bupivacaine Cmax of HTX-011 is lower than the Marcaine Cmax.

3.2 Applicant's attempt to take support of regulatory precedence of 505(b)(2) application-approvals for AUC bridging (AUC_{0-t} and AUC_{inf})

To support the clinical PK bridge between HTX-011 and bupivacaine HCl for AUC parameter (AUC_{0-t} and AUC_{inf}), applicant attempted to evaluate the regulatory precedence of 505(b)(2) application-approvals for test drugs with different exposure profiles from those of the reference drugs.

3.2a. Applicant's proposal on regulatory precedence:

Per Applicant:

- *"To enable the clinical PK bridge, the bupivacaine AUC data for bupivacaine HCl were extrapolated to 400 mg/day for comparison to the bupivacaine AUC data for HTX-011 400 mg/12 mg. Due to the lack of regulatory guidance available for comparison of data for single-dose ER parental products to IR parental products that can be dosed repeatedly, regulatory precedence can be evaluated. There is regulatory precedence for approval of 505(b)(2) applications for new drugs with observed systemic exposure similar to extrapolated values for the reference listed drug (eg, EXPAREL® vs bupivacaine HCl). In addition, there is precedence for new drugs with higher observed systemic exposure than that reported for the reference listed drug (eg, NARCAN® intranasal [IN] spray vs naloxone IM injection)".*
    - *"EXPAREL is the most recently approved local anesthetic and is an extended-release bupivacaine product. In the Clinical Pharmacology and Biopharmaceutics Review(s) of NDA 22-496 for EXPAREL (bupivacaine extended release liposome injection; SKY0402), the FDA reviewer states: "SKY0402 is intended for single-dose administration into the surgical wound. It is impossible and unethical to obtained PK samples in healthy volunteers with SKY0402 administered into surgical wounds. Therefore, only PK in patients with surgical wound is considered relevant and the PK studies in healthy volunteers are not reviewed in detail in the review." Therefore, it is understood that observed data for bupivacaine HCl and EXPAREL should only be obtained at dose levels appropriate for the surgical procedure being studied. To enable comparison between EXPAREL and bupivacaine HCl, extrapolation of observed PK data to the same dose level was performed. The FDA reviewer acknowledges that "The AUC(inf) after the bupivacaine HCl 100 mg dose was 4374 (1561) h×ng/mL… assuming linear PK, a 300 mg dose would have an AUC(inf) of ~13,000 h×ng/mL, similar to those observed for the 225 mg and 300 mg doses of SKY0402 [10,295 (4486) h×ng/mL and 16,758 (6288) h×ng/mL, respectively…]. This suggests that the bioavailability of bupivacaine is comparable whether derived from SKY0402 or from bupivacaine HCl." This shows regulatory precedence for*

comparison of extrapolated bupivacaine HCl AUC exposures of the reference listed drug to those of the new product, an extended-release bupivacaine product".

- *"In the Clinical Pharmacology and Biopharmaceutics Review(s) of NDA 208411 for NARCAN (naloxone HCl nasal spray), the FDA reviewer states: "The administration of one NARCAN nasal spray in each nostril (8 mg total dose, 0.1 mL of 40 mg/mL naloxone hydrochloride solution) exhibited 1110%, 890% and 878% higher geometric mean ratios (IN/IM) for Cmax, AUCt and AUCinf, respectively compared to the reference 0.4 mg IM injection." Therefore, there is regulatory precedence for approval of a 505(b)(2) application for a product that has higher exposures than those for the reference listed drug. NARCAN is approved for the life-threatening condition of opioid overdose.*

- *"Based on regulatory guidance and precedence for the aforementioned drugs, the bridge for HTX-011-56 to MARCAINE has been adequately demonstrated by the Heron clinical efficacy and safety studies as well as reliance on limited information in the prescribing information for the reference listed drugs and PK and safety data in published literature for bupivacaine HCl.*"

3.2b. Reviewer's comments /conclusions on regulatory precedence:

Overall, applicant's proposed regulatory precedence using Exparel and Narcan to support systemic exposure of proposed product may not necessarily be applicable to this product. Note that when the systemic exposure of the new product is higher than the listed drug, the new product may still be approved if the Sponsor can provide adequate information or risk/benefit assessment to justify the higher systemic exposure.

The applicant's attempt to take support of regulatory precedence using Exparel and Narcan are discussed below:

- Exparel: This applicant quoted the extrapolation language from Exparel's original NDA clinical pharmacology review, dated 09/19/2011. The extrapolation language in the clinical pharmacology review was quoted from Exparel Applicant's (Pacira) Section 2.7.2 of 'Summary of Clinical Pharmacology Studies. Hence, the quoted language is based on Exparel Applicant's view, but not from the clinical pharmacology reviewer. In addition, whether or not the extrapolation of PK parameters for peri-operative products is an appropriate approach will be discussed by this reviewer in later part of the review.
- Narcan: From NDA's clinical pharmacology review of Narcan, the Applicant quoted that, 'naloxone test product's Cmax and AUC are higher than the reference product.' However, since the naloxone test products are indicated for life-threatening condition of opioid overdose, the test product can still be approved based on the risk-benefit evaluation. Considering the difference in the indications and risk/benefit assessment of the two products, the previous experience with Narcan nasal spray may not apply to this product.

3.3 Comparison of bupivacaine AUC_{0-24} between HTX-011 and Marcaine:

From regulatory perspective, for bioavailability comparison between test and reference products, the accepted PK measures are Cmax, AUC_{0-t} and AUC_{inf}. However, as mentioned in section 2 Regulatory Background, in the CR letter dated 4/30/2019, the non-clinical team also asked the sponsor to provide adequate coverage for the maximum AUC_{0-24h}. Therefore, AUC_{0-24h} is also evaluated in this section.

For HTX-011, the maximum proposed bupivacaine dose is 400 mg. For the reference, bupivacaine HCl, the highest label recommended dose is 400 mg/day (MARCAINE USPI, 2011)

3.3a. Applicant's provided data/ information on AUC_{0-24}:

Per applicant, "Mean AUC_{0-24} is most relevant AUC parameter for comparison between HTX-011 (ER) and bupivacaine HCl (IR) because IR bupivacaine HCl is rapidly absorbed and is approved for daily dosing".

Observed AUC_{0-24} values:
For proposed HTX-011 maximum dose of 400 mg/12 mg, the observed bupivacaine AUC_{0-24} values in augmentation mammoplasty and total knee arthroplasty (TKA) are shown in Table 11. For bupivacaine HCl, the observed AUC_{0-24} values in augmentation mammoplasty at 50 and 150 mg doses and TKA at 125 mg dose are also shown in Table 11.

Dose-proportionality for AUC of Bupivacaine HCl in augmentation mammoplasty:
For two studied doses of bupivacaine HCl, 50 and 150 mg in augmentation mammoplasty, dose-proportionality for AUC_{0-24} and AUC_{inf} were observed (Table 9) .

Applicant's extrapolation of bupivacaine HCl AUC_{0-24} data:
From the HTX-011 clinical trials, since observed data for bupivacaine HCl was available only up to 150 mg dose, the applicant extrapolated the mean bupivacaine HCl AUC_{0-24} values to 400 mg dose from the observed AUC_{0-24} values in TKA (125 mg) and augmentation mammoplasty (50 mg and 150 mg) (Table 11). Applicant also extrapolated bupivacaine HCl AUC_{0-24} values from literature studies (Table 11). Based on the extrapolation, applicant tried to show that bupivacaine AUC_{0-24} values of HTX-011 are lower than AUC_{0-24} values of bupivacaine HCl.

Table 9: Dose-Proportional Increase in Bupivacaine AUC_{inf} Following Administration of Bupivacaine HCl in Augmentation Mammoplasty

Surgical Procedure	Study	Bupivacaine HCl Administration Method	Bupivacaine Dose (mg)	Mean AUC_{inf} (h·ng/mL)	Mean AUC_{inf}/Dose
Augmentation Mammoplasty	211	Nerve Block	50	3,060	61.2
	BUPI-502	Instillation or Injection (pooled)	150	9,280	61.9

Table 11: Clinical PK Bridge Established With Bupivacaine Mean AUC_{0-24} for HTX-011-56 at the Proposed Maximum Recommended Human Dose and Bupivacaine HCl From Heron Clinical Studies and Published Literature

Heron Study Data					
Treatment	Surgical Procedure	Heron Study	Bupivacaine Dose	n	AUC_{0-24} (h·ng/mL)
HTX-011-56	TKA	209	400 mg Instillation	108	10,900
	Augmentation mammoplasty	211	400 mg Instillation	49	11,700
Bupivacaine HCl	TKA	209	125 mg Injection	65	4,610
			Extrapolated to 400 mg[a]		*14,800*
	Augmentation mammoplasty	211	50 mg Injection, NB	41	2,440
			Extrapolated to 400 mg[a]		*19,500*
		BUPI-502	150 mg Injection or Instillation (pooled)	30	7,500
			Extrapolated to 400 mg[a]		*20,000*

Table 11: Clinical PK Bridge Established With Bupivacaine Mean AUC_{0-24} for HTX-011-56 at the Proposed Maximum Recommended Human Dose and Bupivacaine HCl From Heron Clinical Studies and Published Literature

Literature Study Data					
Treatment	Procedure	Study	Bupivacaine Dose	n	AUC_{0-24} (h·ng/mL)
Bupivacaine HCl	Cholecystectomy	(Kastrissios 1991)	Interpleural infusion of 8 mL/h 0.25% bupivacaine + 20 mL bolus of 0.5% bupivacaine HCl (100 mg) with epinephrine at start and repeated 5 hours later. Total of 680 mg on first day.	12	~24,000[b]
	Not applicable (healthy male volunteers)	(Emanuelsson 1995)	Epidural bolus of 25 mg bupivacaine followed by infusion of 25 mg/h for a total of 550 mg over 21 hours.	8	~16,000[c]
	Chronic Pain	(Denson 1983)	Epidural, brachial plexus, or lumbar sympathetic chain block and continuous infusion of 0.125%, 0.25%, or 0.5% bupivacaine HCl up to 30 mg/h. Up to 720 mg/day.	50	~24,000[d]
	Shoulder	(Tuominen 1989)	Interscalene block 1.25 mg/kg of 0.5% bupivacaine with continuous infusion of 0.25% bupivacaine at 0.25 mg/kg/h. Mean dose 536.5 mg/day.	18	~15,000[e]
	Shoulder	(Tuominen 1987)	Interscalene block 1.25 mg/kg of 0.5% bupivacaine with continuous infusion of 0.25% bupivacaine at 0.25 mg/kg/h for a total of 493 mg/day over 24 hours. Mean dose 493 mg/day.	20	~20,000[f]

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-24}, area under the plasma concentration-time curve from Time 0 to 24 hours postdose; AUC_{inf}, area under the plasma concentration-time curve from Time 0 extrapolated to infinity; C_{ss}, concentration at steady state; NB, nerve block; PK, pharmacokinetic(s); TKA, total knee arthroplasty.

[a] Estimated bupivacaine HCl AUC data are extrapolated based on the bupivacaine HCl mean data in dose levels administered in the clinical studies.

[b] Estimated AUC_{0-24} of approximately 24,000 h·ng/mL and AUC_{inf} of >70,000 h·ng/mL were calculated based on concentrations observed over time in Figure 1 in Kastrissios 1991. Steady plasma concentration of at least approximately 1,000 ng/mL was observed through 24 hours and up to approximately 70 hours.

[c] Estimated AUC_{0-24} was calculated based on concentrations observed over time in Figure 1 in Emanuelsson 1995. AUC_{inf} was calculated as Dose/Clearance based on clearance of 423 mL/min and dose of 550 mg for bupivacaine (Table 1 of literature).

[d] Estimated C_{min} was calculated as Infusion rate/Clearance. Estimated AUC_{0-24} of approximately 24,000 h·ng/mL was calculated based on the C_{ss} of approximately 1,000 ng/mL over 24 hours. Estimated AUC_{inf} of >120,000 h·ng/mL was calculated based on the C_{ss} of approximately 1,000 ng/mL over 120 hours.

[e] Estimated AUC_{0-24} was calculated based on mean concentrations reported over time in Tuominen 1989: 680 ng/mL, 620 ng/mL, 520 ng/mL, and 760 ng/mL at 30, 60, and 180 minutes, and 24 hours, respectively.

[f] Estimated AUC_{0-24} was calculated based on concentrations observed over time in Figure 1 in Tuominen 1987.

Source 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

3.3b. Reviewer's Analyses and Conclusions on AUC_{0-24} :

Per applicant, *"Mean AUC_{0-24} is most relevant AUC parameter for comparison between HTX-011 (ER) and bupivacaine HCl (IR) because IR bupivacaine HCl is rapidly absorbed and is approved for daily dosing"*.

To compare systemic exposure on Day 1 to the overall systemic exposure between HTX-011 and bupivacaine HCl, the ratios of AUC_{0-24} to AUC_{inf} were compared between two products from NDA clinical trials. The data are shown in Tables A and Table B, respectively.

For HTX-011, AUC_{0-24} to overall AUC (AUC_{inf}) range between 29 to 51%, while for bupivacaine HCl the values are higher and range between 65 to 81%.

Table A: Comparison of AUC_{0-24} to overall AUC (AUC_{inf}) for HTX-011 in different surgical procedures:

Surgical Procedure	**Dose (Bup/Mel)**	**N**	**AUC_{0-24} (h·ng/mL)**	**AUC_{inf} (h·ng/mL)**	**Mean Ratio % (AUC_{0-24}/AUC_{inf})**
Bunionectomy (Study 208)	60 mg/1.8 mg	17	883 ± 538	1718 ± 1211	51%
Herniorrhaphy (Study 202)	300 mg/9 mg	16	4712 ± 2144	15524 ± 8921	30%
Total Knee Arthroplasty (Study 209)	400 mg/12 mg	53 (without ropivacaine) [a]	11223 ± 6142	38173 ± 29400 (n=50)	29%
Complete Abdominoplasty (Study 203)		17 (Part C)	5327 ± 1590	18247 ± 7069	29%
Augmentation Mammoplasty (Study 211)		49	11758 ± 3990	31072 ± 17998	38%

PK parameters values are arithmetic mean ± standard deviation

[a] In TKA study, HTX-011 was instilled with or without ropivacaine (0.5%, 50 mg). PK parameters of only HTX-011 without ropivacaine (N=53) are reported

Table B: Comparison of AUC_{0-24} to overall AUC (AUC_{inf}) for bupivacaine HCl in different surgical procedures:

Surgical Procedure	**Dose (strength)**	**N**	**AUC_{0-24} (h·ng/mL)**	**AUC_{inf} (h·ng/mL)**	**Mean Ratio % (AUC_{0-24}/AUC_{inf})**
Bunionectomy (Study 208)	50 mg (0.5%)	25	2169 ± 903	2745 ± 1357	79%
Herniorrhaphy (Study 202)	75 mg (0.25%)	17	1697 ± 363	2349 ± 564	72%
Total Knee Arthroplasty (Study 209)	125 mg (0.25%)	65	4646 ± 2082	7097 ± 3898	65%
Complete Abdominoplasty (Study 203)	100 mg (0.25%)	17 (Part C)	4069 ± 1622	5509 ± 2340	74%
Augmentation Mammoplasty	50 mg (0.25%) (Study 211)	41	2482 ± 779	3120 ± 1302	80%
	150 mg (Study BUPI 502*)	30	7500	9280 + 4550	81%

PK parameters values are arithmetic mean ± standard deviation

*In study BUPI-502, AUC values are average of instillation (n=15) and injection (n=15) methods of administration

Applicant extrapolated the AUC_{0-24} of bupivacaine HCl for up to 400 mg as a single-dose as shown in Table 11 above. Whether or not the extrapolation of PK parameters for bupivacaine HCl to 400 mg as a single-dose is an appropriate approach, and the dose-linearity assessment of bupivacaine for perioperative products are discussed below in 3.4b.

Conclusion on comparison of bupivacaine AUC_{0-24} between HTX-011 and Marcaine:
Based on observed lower bupivacaine AUC_{0-24} / AUC_{inf} ratio-values of HTX-011 (Table A) compared to bupivacaine HCl (Table B), it is a reasonable estimation that the bupivacaine AUC_{0-24} of HTX-011 at 400 mg/12 mg dose will be lower than that of bupivacaine HCl when given 400 mg /day.

3.4 Comparison of bupivacaine AUC_{inf} between HTX-011 and Marcaine:

3.4a. Applicant's provided data/ information on AUC_{inf}:

Per Applicant,

- *Bupivacaine is released from HTX-011 for approximately 3 days. To enable comparison of AUCinf to HTX-011 400 mg/12 mg, bupivacaine mean AUCinf data for bupivacaine HCl from Study BUPI-501 was extrapolated to 400 mg/day dosing for approximately 3 days (60 hours). Extrapolation of bupivacaine AUCinf data is supported by regulatory precedence and dose proportionality.*
- *The highest observed bupivacaine AUCinf exposure for HTX-011 at the proposed maximum recommended dose (which is released for approximately 3 days) was 33,300 h·ng/mL (Study 209) and is less than that for bupivacaine HCl extrapolated to 400 mg/day dosing. In Study BUPI-501 where bupivacaine was continuously infused for 60 hours and then extrapolated to the maximum approved dose (400 mg dose per 24 hours), the AUCinf was 54,300 h·ng/mL (Table 12).*
- *It is noted that a higher bupivacaine mean AUCinf was observed for Study 209 compared to Study 211. This can be attributed to the 4 subjects from Study 209 (Subjects* (b) (6) (b) (6) *) who are considered statistical outliers. These outliers were detected by statistical testing to identify individual AUCinf values above the third quartile plus 1.5 times the interquartile range. The bupivacaine mean AUCinf for HTX-011-56 400 mg/12 mg for Study 209 excluding these outliers is 29,100 h·ng/mL, which is consistent with the mean AUCinf (27,000 h·ng/mL) observed for Study 211. The poor metabolizer status of these 4 subjects was confirmed in the 1 subject who received ropivacaine concomitantly and showed similarly higher exposures of ropivacaine compared to other subjects within the same treatment group.*

Table 12: Clinical PK Bridge Established With Bupivacaine Mean AUC_{inf} for HTX-011-56 and Bupivacaine HCl From Heron Clinical Studies

Heron Study	Product and Administration	Bupivacaine Dose	n[a]	Bupivacaine Mean AUC_{inf} (h·ng/mL)
209	HTX-011-56 instillation	Observed from 400 mg	65	33,300
211	HTX-011-56 instillation	Observed from 400 mg	39	27,000
BUPI-501	Bupivacaine HCl continuous infusion via elastomeric pump	Observed from 300 mg total over 60 hours	14	16,300
		Extrapolated to up to 400 mg/day (1,000 mg total over 60 hours)[b]		*54,300*

Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from Time 0 extrapolated to infinity; PK, pharmacokinetic(s); TKA, total knee arthroplasty.
[a] n presents the number of subjects who exhibited a terminal log-linear phase.
[b] Estimated bupivacaine HCl AUC_{inf} data are extrapolated based on the bupivacaine HCl mean data in dose levels administered in the clinical studies.

- *As mentioned before, there is regulatory precedence for comparison of extrapolated bupivacaine AUCinf for bupivacaine HCl to the bupivacaine AUCinf of EXPAREL, an extended-release bupivacaine product. The observed AUCinf for 300 mg EXPAREL (16,758 h·ng/mL) was approximately 29% higher than the extrapolated AUCinf for 300 mg bupivacaine HCl (~13,000 h·ng/mL), and these AUCinf values were considered comparable by the FDA reviewer. Similarly, the observed mean bupivacaine AUCinf values for bupivacaine HCl from the Heron Phase 2 and 4 clinical studies were extrapolated to 400 mg bupivacaine HCl. The AUCinf for HTX-011 400 mg/12 mg was comparable to the extrapolated AUCinf for 400 mg bupivacaine HCl from the Phase 2 and 4 studies (difference ranging from 10.2% to 29.3%; Table 13)*

Table 13: Clinical PK Bridge Supported by Regulatory Precedence and Comparable Bupivacaine Mean AUC_{inf} Values for HTX-011-56 and Bupivacaine HCl

Comparison	Study/Source	Product and Administration	Bupivacaine Dose	Bupivacaine Mean AUC_{inf} (h·ng/mL)	% Difference
Regulatory Precedence					
1	EXPAREL FDA Review	Bupivacaine HCl injection	Observed from 100 mg	4,374	--
			Extrapolated to 300 mg	*~13,000*	28.9
		EXPAREL injection	Observed from 300 mg	16,758	
Heron Study Data					
2	Study 211	Bupivacaine HCl via nerve block	Observed from 50 mg	3,060	--
			Extrapolated to 400 mg	*24,500*[a]	10.2
		HTX-011-56 instillation	Observed from 400 mg	27,000	
3	Study 209	Bupivacaine HCl injection	Observed from 125 mg	7,020	--
			Extrapolated to 400 mg	*22,500*[a]	29.3
		HTX-011-56 instillation (outliers excluded)[b]	Calculated for 400 mg	29,100	
4	BUPI-502	Bupivacaine HCl injection or instillation (pooled)	Observed from 150 mg	9,280	--
			Extrapolated to 400 mg	*24,700*[a]	17.8
	Study 209	HTX-011-56 instillation (outliers excluded)[b]	Calculated for 400 mg	29,100	

Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from Time 0 extrapolated to infinity; NDA, New Drug Application; PK, pharmacokinetic(s).
[a] Estimated bupivacaine HCl AUC_{inf} data are extrapolated based on dose linearity and the bupivacaine HCl mean data in dose levels administered in the clinical studies
[b] Four subjects were considered statistical outliers and were not included in the mean AUC_{inf} calculated value.

- *In addition, PK and safety data for bupivacaine HCl at doses greater than 400 mg administered for longer than 24 hours have been reported in the literature and are provided to support the safety of bupivacaine in HTX-011-56 at the proposed maximum recommended dose (Table 14). These data demonstrate that the mean bupivacaine AUC_{inf} values estimated from the literature for doses of bupivacaine HCl up to 720 mg administered for more than 24 hours were higher than the highest mean bupivacaine AUC_{inf} observed for HTX-011-56 [>70,000 h·ng/mL (Kastrissios 1991) and >120,000 h·ng/mL (Denson 1983) vs 33,300 h·ng/mL in Study 209].*

Table 14: Bupivacaine Mean AUC_{inf} for Bupivacaine HCl from Published Literature in Support of the Proposed Maximum Recommended Dose of HTX-011-56 400 mg/12 mg

Literature Study Data						
Treatment	**Procedure**	**Study**	**Bupivacaine Dose**	**n**	**Bupivacaine Mean AUC_{inf} (h·ng/mL)**	**Safety Findings**
Bupivacaine HCl	Cholecystectomy	(Kastrissios 1991)	Interpleural infusion of 8 mL/h 0.25% bupivacaine + 20 mL bolus of 0.5% bupivacaine HCl (100 mg) with epinephrine at start and repeated 5 hours later. Total of 680 mg on first day. 480 mg Day 2/3.	12	>70,000[a]	No CNS toxicities or significant cardiovascular changes. No patients suffered drug-related. complications
	Chronic Pain	(Denson 1983)	Epidural, brachial plexus, or lumbar sympathetic chain block and continuous infusion of 0.125%, 0.25%, or 0.5% bupivacaine HCl 5-30 mg/h. Up to 720 mg/day.	50	>120,000[b]	No systemic toxicity at 30 mg/h even when clearance is reduced by 60%. Minor toxicity was observed in patients with renal and hepatic disease at 30 mg/h (details not provided).

Abbreviations: AUC_{0-24}, area under the plasma concentration-time curve from Time 0 to 24 hours postdose; AUC_{inf}, area under the plasma concentration-time curve from Time 0 extrapolated to infinity; CNS, central nervous system; C_{ss}, concentration at steady state; LAST, local anesthetic systemic toxicity; NA, not applicable; TEAEs, treatment-emergent adverse events; TKA, total knee arthroplasty.

[a] Estimated AUC_{0-24} of approximately 24,000 h·ng/mL and AUC_{inf} of >70,000 h·ng/mL were calculated based on concentrations observed over time in Figure 1 in Kastrissios 1991. Steady plasma concentration of at least approximately 1,000 ng/mL was observed through 24 hours and up to approximately 70 hours.

[b] Estimated C_{max} was calculated as Infusion rate/Clearance. Estimated AUC_{0-24} of approximately 24,000 h·ng/mL was calculated based on the C_{ss} of approximately 1,000 ng/mL over 24 hours. Estimated AUC_{inf} of >120,000 h·ng/mL was calculated based on the C_{ss} of approximately 1,000 ng/mL over 120 hours.

3.4b. Reviewer's comments on dose-linearity for perioperative products, extrapolation of PK parameters for bupivacaine HCl and AUC_{inf} comparison between HTX011 and Bupivacaine HCl:

A. Dose-proportionality / linearity for perioperative products (HTX-011 and Bupivacaine HCl):

In the NDA submission in first cycle, applicant attempted to assess PK dose-linearity of bupivacaine from HTX-011 using PK data from different procedures in which different modes of administration (injection, nerve block, combination of instillation and injection) were used. From the assessment, Applicant concluded that "mean Cmax and AUC for bupivacaine and meloxicam increased linearly with dose at HTX-011 doses ranging from 60 mg/1.8 mg to 400 mg/12 mg regardless of the anatomic space, vascularity of the surgical site, or administration technique". However, in our analyses, it was identified that bupivacaine and meloxicam PK parameters are significantly different between surgical procedures. For example, for the same nominal dose of HTX-011 400 mg/12 mg, the bupivacaine and meloxicam PK parameters are significantly different between surgical procedures (Clinical pharmacology review, DAARTS 04/10/2019). The similar information can be noted in Marcaine label, which states that, "the rate of systemic absorption of local anesthetics is dependent upon the total dose and concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic solution".

In the PK dose linearity assessment of HTX-011, since the surgical procedure-differences is a confounding factor, the dose-linearity assessment of HTX-011between different procedures is not appropriate. Hence, the PK linearity within-procedure between different HTX-011 doses was assessed. For this assessment, the data was available in herniorrhaphy procedure for two HTX-011 doses, 200 mg/6mg and 400 mg/12 mg; and in bunionectomy for two HTX-011 doses, 60

mg/1.8 mg and 120 mg/3.6 mg. The data from both procedures showed within-procedure dose-linearity for both Cmax and AUC for both bupivacaine and meloxicam of HTX-011(Clinical pharmacology review, DAARTS 04/10/2019). Based on the data submitted in this review cycle, for bupivacaine HCl also, within procedure dose-linearity was also observed for both Cmax and AUC in augmentation mammoplasty between 50 and 150 mg (Table B and 11, above).

Overall, based on the data available so far from the NDA clinical trials, the 'within procedure' PK dose-linearity for bupivacaine was observed up to 400 mg dose for HTX-011 in two procedures, while for bupivacaine HCl up to 150 mg in one procedure.

B. Whether or not the extrapolation of AUC (AUC_{0-24} and AUC_{inf}) of Bupivacaine HCl is acceptable? If acceptable, on what basis?

- Per Marcaine label, the maximum dosage limit for bupivacaine HCl is a 'single-dose' up to 175 mg without epinephrine and a 225 mg with epinephrine, or a MRHD of 400 mg/day. The 400 mg bupivacaine HCl is not given as single-dose, but is given in separate doses over 24 h duration.
- Since there was no PK data for 400 mg/day dosage for bupivacaine HCl, Applicant has extrapolated the AUC_{0-24} and AUC_{inf} values for bupivacaine HCl up to 400 mg as a 'single-dose' in each surgical procedure from their conducted studies (shown in Tables 11 and 13, respectively above). This extrapolation of AUC of bupivacaine HCl for up to 400 mg as a 'single-dose' may be questionable, since the 400 mg is labeled to be given over 24 h duration as separate doses. However, as noted above, since within-procedure dose proportionality was observed for HTX-011 up to 400 mg, this data may be used to support the dose proportionality of reference bupivacaine HCl.
- In addition to their own studies, applicant 'estimated' the AUC_{0-24} and AUC_{inf} values for bupivacaine HCl based on literature studies in which doses higher than the recommended dosage of 400 mg/day were used (shown in Tables 11 and 14, respectively above). As per the discussion with clinical team, the usage of doses higher than 400 mg/day for bupivacaine HCl is not an accepted approach, since it is higher than the current approved Marcaine dose. In addition, the literature studies lack bioanalytical information, discussed in section 3.5 below. Therefore, this approach to use literature data is not acceptable.

C. Study BUPI-501, Bupivacaine HCl AUC_{inf} value:

- Study BUPI-501 was a randomized Phase 4 study to assess the efficacy, duration of analgesia and PK following either liposomal bupivacaine administered via injection or bupivacaine HCl administered by continuous infusion via an elastomeric pump into surgical wound following unilateral open inguinal herniorrhaphy. The observed AUC_{inf} value for bupivacaine HCl infusion into surgical wound from a total 300 mg dose over 60 hours was16300 h.ng/mL (Table 12 above). Based on this value, the applicant extrapolated AUC_{inf} value for up to 400 mg/day over 60 hours (1000 mg total dose over 60 hours), assuming dose-proportionality for bupivacaine HCl, and reported a calculated

AUC_{inf} value of 54300 h.ng/mL. As per discussion with clinical team, the continuous usage of 400 mg/day over 60 hours, with a total dose of 1000 mg, for bupivacaine HCl may not be a clinically accepted approach. The reviewer's calculation of AUC_{inf} for study BUPI-501 is in Table C below in 'section D'.

D. Comparison of bupivacaine AUC_{inf} value for systemic exposure comparison [(400 mg Bupivacaine HCl (calculated) versus 400 mg HTX-011 (observed)] across procedures (Source: applicant's studies).

- As shown above, since within-procedure dose proportionality was observed for HTX-011 up to 400 mg, this data may be used to support the dose proportionality of reference bupivacaine HCl. The AUC_{inf} values for bupivacaine HCl were calculated for 400 mg dose for studies BUP1-501 and 209 (TKA). These two studies were selected because of their highest observed AUC_{inf} values for bupivacaine HCl compared to the other studies. The obtained values are used to compare HTX-011 bupivacaine AUC_{inf} value across procedures those used 400 mg dose (Table C).
    - Study BUPI-501: The observed bupivacaine HCl AUC_{inf} value from 300 mg infusion into surgical wound of over 60 hours was 16300 h.ng/mL. Based on this, the calculated AUC_{inf} value for 400 mg dose over 60 hours (not as 400 mg/day for 60 hours as Applicant calculated) is 21733 h.ng/mL.
    - Study 209: The observed AUC_{inf} value from 125 mg dose of bupivacaine HCl was 7097 h.ng/mL. Based on this, the calculated AUC_{inf} value for 400 mg dose is 22710 h.ng/mL.

Table C: Comparison of bupivacaine AUC_{inf} obtained in applicant's studies for systemic exposure comparison [(HTX-011 (observed) versus bupivacaine HCl (calculated)].

Surgical Procedure	**Bupivacaine AUC_{inf} (h.ng/mL)**		**Fold ratio (HTX011 / Bupi. HCl)**	
	Bupivacaine HCl 400 mg (Calculated)	**HTX-011 400 mg** (Observed)	**Based on study BUPI-501**	**Based on study TKA 209**
BUPI 501 (Hernia repair)	*21733*			
Study 209 (TKA)	*22710*	38173	1.76 (76% higher for HTX)	1.68 (68% higher for HTX)
Study 211 (Aug. mammoplasty)		31072	1.43 (43% higher for HTX)	1.37 (37% higher for HTX)
Study 203 (Abdominoplasty)		18247	0.84 (16% lower for HTX)	0.80 (20% lower for HTX)

Based on the above Table C, for 400 mg dose, compared to the calculated bupivacaine HCl AUC_{inf} values, the observed HTX-011 AUC_{inf} value is lower by ~18% for abdominoplasty (Study 203); while it is higher by ~40% and ~72%, respectively for augmentation mammoplasty

(Study 211) and TKA (Study 209). However, it is to be noted that the non-clinical team informed in the team meeting held on 03/10/2020 that the applicant has submitted new animal data that provides systemic safety coverage up to 400 mg of HTX-011.

Conclusions on comparison of bupivacaine AUC_{inf} between HTX-011 and Marcaine:
In comparison to the calculated 400 mg bupivacaine HCl AUC_{inf} values, the observed HTX-011 AUC_{inf} value is lower by ~18% for abdominoplasty (Study 203); while it is higher by ~40% and ~72%, respectively for augmentation mammoplasty (Study 211) and TKA (Study 209). However, in the team meeting held on 03/10/2020, the non-clinical team informed the team that the applicant has submitted new data that provides systemic safety coverage up to 400 mg of HTX-011. In such case, this newly submitted animal data may be adequate to address the non-clinical comment in the complete response letter mentioned above, regardless whether the Sponsor has provided adequate PK information to address the systemic exposure of HTX-011 at 400 mg dose. Hence, we defer to non-clinical team on systemic safety coverage up to 400 mg of HTX-011 based on totality of the data.

3.4c. Other AUC_{inf} review aspects based on applicant's resubmission:

1) In TKA Study 209 (HTX-011 400 mg), the applicant excluded 4 subjects with higher AUCinf values, claiming that these subjects were statistical outliers, and reported a mean value of 29,100 h.ng/mL (Table 13 above). The justification of "statistical outliers" provided by applicant on the exclusion of these 4 subjects is not valid and hence we cannot agree on the exclusion of subjects. For this study, the mean AUC_{inf} value based on 50 subjects was 38173 h.ng/mL (Clinical pharmacology review, DAARTS 04/10/2019).

2) AUC_{inf} comparison for 300 mg dose between HTX-011 and bupivacaine HCl in hernia repair (cross-study comparison in same surgical procedure):
    - The mean AUC_{inf} value of bupivacaine HCl 300 mg dose administered by infusion into surgical wound over 60 hours in hernia repair (study BUPI-501) was 16300 h.ng/mL. In comparison, the AUC_{inf} value of HTX-011 300 mg in hernia repair procedure (Study 202) was lower by ~5% of 15524 h.ng/mL.

3.5. Bioanalytical information provided by Applicant for literature articles:
We communicated to the Applicant during pre-NDA meetings and the post-action meeting regarding need of bioanalytical supportive information for the literature articles. Applicant provided the following information.

"To support the bupivacaine PK findings reported in the literature, a review of available bioanalytical methodology information was conducted. While supportive bioanalytical methodology, such as sample extraction and quantitation information, is available in separate referenced literature, there is limited information reported on precision, accuracy,

stability, and incurred sample reanalysis (ISR) for the bioanalytical methods (Table 15). The published literature for bupivacaine HCl used to support the scientific bridge predates the release of the first FDA Guidance for Industry: Bioanalytical Method Validation in 2001. In addition, proposals to incorporate incurred sample ISR for PK samples occurred in 2007 with the publication of the white paper: Quantitative Bioanalytical Methods Validation and Implementation: Best Practices for Chromatographic and Ligand Binding Assay; therefore, ISR information is not available for studies conducted prior to 2007".

Table 15: Bioanalytical Method Validation Information in Literature for Bupivacaine HCl

PK Literature	Supportive BA Methodology Literature	Stability	Accuracy	Precision
(Kastrissios 1991)	(Wiegand 1984)	NR	0.06-6.9%	5.9%
(Emanuelsson 1995)	(Bjork 1990)	Plasma samples were stored at -20°C. Duration of stability not specified.	QC samples: 100%-108%	QC samples: 4.6%-11.7%
(Tuominen 1987)	NR[a]	NR	NR	NR
(Tuominen 1989)	NR[a]	NR	NR	NR
(Denson 1983)	(Mather 1974)	NR	NR	NR
(Kopacz 1994)	(Bjork 1990)	Plasma samples were stored at -20°C. Duration of stability not specified.	QC samples: 100%-108%	QC samples: 4.6%-11.7%
(Reynolds 1971)	(Reynolds 1968; Reynolds 1970)	NR	NR	NR
(Wildsmith 1977)	(Mather 1974)	Plasma samples were stored at 4°C. Duration of stability not specified.	NR	NR
(Fletcher 1992)	(Reynolds 1989)	Plasma samples were stored at -10°C. Duration of stability not specified.	NR	NR

Abbreviations: BA, bioanalytical; NR, not reported; PK, pharmacokinetic(s); QC, quality control.
[a] Tuominen 1987 and Tuominen 1989 reference the literature Tuominen 1983. Tuominen 1983 used gas chromatography method described by Mather et al (Mather 1974).

With regards to the bioanalytical information for literature articles, we communicated following information request (IR) to applicant on 11/27/2019.

> Provide your response by 12/06/19:
> *As noted in Table 15 of Section 2.7.1, for most of the literature articles, the bioanalytical information is lacking. For three literature articles, Kastriossios 1991, Kopacz 1994 and Emanuelsson 1995, the bioanalytical accuracy and precision information provided does not seem to belong to methods used for in-study PK samples; instead, they appear to belong supportive bioanalytical methodology of the original method validation articles (Wiegand 1984 and Bjork 1990). The precision and accuracy information for bioanalytical method of original articles will not be applicable to in-study methods used in Kastriossios 1991, Kopacz 1994 and Emanuelsson 1995. Provide the bioanalytical method information, if available for the methods used in-study. If you contact the authors but cannot obtain the information, also indicate it in your response.*

Applicant responded to the IR on 12/05/2019 as below.

In-Study Precision and Accuracy for Bioanalytical Methods

The in-study precision information for the bioanalytical methods is available in the PK publications for Kastrissios 1991, Emanuelsson 1995, and Kopacz 1994, and is presented in Table 1. The reported in-study precision ranged from approximately 5% to 8%, which is consistent with the precision reported in the original bioanalytical method validation publications. The in-study precision is within the ±15% acceptance criteria as required by the *FDA Guidance for Industry: Bioanalytical Method Validation Guidance (May 2018)*.

Table 1: In-Study Bioanalytical Method Precision Information Reported in Literature for Bupivacaine

PK Literature	Reported In-Study Precision in PK Publication	Original Method Validation Precision
(Kastrissios 1991)	Approximately 8% at plasma concentration of 400 ng/mL[a]	5.9% (n=12) (Wiegand 1984)
(Emanuelsson 1995)	Approximately 5% at plasma concentration of 300 ng/mL[b]	QC samples: 4.6% - 11.7% (n=7 to 8) (Bjork 1990)
(Kopacz 1994)	Approximately 5% at plasma concentration of 300 ng/mL[c]	QC samples: 4.6% - 11.7% (n=7 to 8) (Bjork 1990)

Abbreviations: PK, pharmacokinetic(s); QC, quality control.
[a] Precision (intra- and inter-day assay coefficients of variation) information is found in Methods, *Data Collection* section on page 252 of Kastrissios 1991.
[b] Precision (coefficient of variation) information is found in Methods section on page 1164 of Emanuelsson 1995.
[c] Precision (coefficient of variation) information is found in Methods, *Drug Concentration and Pharmacokinetic Analysis* section on page 1140 of Kopacz 1994.

The in-study accuracy information of the bioanalytical method was not reported in the PK publications. Heron reached out to the corresponding authors for these 3 publications to obtain additional information. (b) (6) (b) (4) the primary author, Dr. Helen Kastrissios, was contacted. Dr. Kastrissios provided additional information on the in-study intra-assay accuracy and precision and inter-assay precision (Table 2). At the bupivacaine concentration of 2,000 ng/mL, the intra-assay accuracy and precision were 2.0% and 3.6%, respectively, and the inter-assay precision was 2.8%, which are within the 15% acceptance criteria for in-study accuracy and precision mentioned in the guidance.

Table 2: In-Study Bioanalytical Method Accuracy and Precision Information for Bupivacaine in Kastrissios 1991 Publication

Bupivacaine Concentration (ng/mL)	Intra-Assay		Inter-Assay
	Accuracy (%)	Precision (%) (n=8)	Precision (%) (n=10)
200	5.0	7.2	15.2
400	0.0	5.9[a]	7.0[a]
800	3.8	5.0	NA
1,000	NA	NA	5.1
1,600	0.6	5.3	1.4
2,000	2.0	3.6	2.8

Abbreviations: NA, not applicable
[a] The in-study accuracy and precision data for the bioanalytical method in this table was provided by Dr. Helen Kastrissios, the primary author of the PK publication (Kastrissios 1991). The author noted that data in this table used in her doctoral thesis is slightly different from the published precision data, which may have been an earlier cut of the dataset.

Dr. Dan Kopacz responded to Heron's request, but indicated that he was not able to provide any additional information on the bioanalytical methods from these studies and suggested that Heron contact the second author, Britt-Marie Emanuelsson. Dr. Britt-Marie Emanuelsson (b) (6) was contacted for both publications, Emanuelsson 1995 and Kopacz 1994. (b) (6) (b) (6) Dr. Emanuelsson confirmed that the in-study sample analysis was performed using the bioanalytical method outlined in Bjork 1990; however, she was not able to provide any additional in-study data.

Reviewers comments on Applicant's response dated 12/05/2019 with regards to bioanalytical information for literature articles:

- For two articles (Emanuleson 1995 and Kopacz 1994), applicant did not provide in-study bioanalytical information, but referred to information from another article (Bjork et al 1990). Hence these two articles are not acceptable.
- For Kastriossos 1991 article, the precision and accuracy data provided for only one concentration, 400 ng/mL. For this concentration, the accuracy number reported in the literature article is 8% (Table 1 above), however this value differs from what was provided by the first author from her thesis of 5.9% (Table 2 above). Hence it is not reliable and acceptable.

Overall for literature articles bioanalytical information, for two articles the data was not provided and for one article, there is discrepancy and is not reliable.

Conclusions on bioanalytical information of literature articles:

- The bioanalytical information provided by applicant is not sufficient or reliable to rely on the PK information of bupivacaine HCl from literature articles. Hence for PK information of bupivacaine HCl, the applicant can only rely on their own clinical studies.

4. Labelling Comments.

The labeling changes that were made during this cycle in Section 12.3 are shown below.

(b) (4)

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Office of Clinical Pharmacology Review

NDA: 211988	Submission Date: 10/30/2018
Link to EDR	\\cdsesub1\evsprod\nda211988
Relevant IND(s):	IND 125927
Submission Type; Code:	505 (b) (2)
Priority Classification	Priority
Brand Name:	Zynrelef™
Generic Name:	Bupivacaine (2.5% bupivacaine base) and Meloxicam (0.075%)
Reference Drugs:	MARCAINE (NDA 016964) and MOBIC (NDA 020938)
Formulation; Strength(s):	ER solution; bupivacaine (2.5% bupivacaine base) and meloxicam (0.075%)
Clinical Pharmacology Reviewer:	Suresh B Naraharisetti, Ph.D.
Team Leader:	Yun Xu, Ph.D.
Pharmacometrics Reviewer:	Michael Bewernitz, Ph.D.
Pharmacometrics Team Leader:	Kevin Krudys, Ph.D.
OCP Division:	Division of Clinical Pharmacology II
OND Division:	Division of Anesthesia and Analgesia Products
Sponsor:	Heron Therapeutics, Inc.
Indication:	(b) (4)
Dosage Regimen:	Single dose by instillation

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1.0 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted in current application, NDA 211988, for bupivacaine and meloxicam extended release (ER) solution (b) (4) From a clinical pharmacology perspective, the information submitted in the NDA is acceptable and no further communication is necessary with the Applicant. Based on the discussion in the wrap-up meeting, there were approvability issues with other disciplines in this review cycle. Hence, the NDA is not being approved in this cycle.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

Heron Therapeutics, Inc. (Heron) submitted HTX-011 (Trade name, ZYNRELEF), bupivacaine (2.5% bupivacaine base) and meloxicam (0.075%) ER solution (b) (4) HTX-011 is intended for single-dose administration and is applied by instillation without a needle into the surgical site following final irrigation and suction and prior to suturing. For this 505(b)(2) new drug application, the referenced drugs for relying on the Agency's previous findings of safety and efficacy are MARCAINE (NDA 016964, bupivacaine immediate release (IR) injection) for bupivacaine component and MOBIC (NDA 020938, meloxicam IR tablets) for meloxicam component, with additional published literature to support its use.

The recommended dose of HTX-011based on size of the surgical site, volume required to cover the tissues within the surgical site is as follows:

	Procedure	Dose
For small surgical sites:	Bunionectomy	60 mg/1.8 mg (up to 2.3 mL)
For medium surgical sites:	Open inguinal herniorrhaphy	300 mg/9 mg (up to 10.5 mL)
For large surgical sites:	Total knee arthroplasty	400 mg/12 mg (up to 14 mL)
	Augmentation mammoplasty	400 mg/12 mg (200 mg/6 mg up to 7 mL per side)

During NDA review, it was determined that ZYNRELEF 60 mg/1.8 mg for bunionectomy and 300 mg/9 mg for open inguinal hernia repair may be approved, if there are no approvability issues from other disciplines in the review team.

The clinical program for HTX-011 consisted of Phase 2 and Phase 3 clinical studies in surgical procedures, with PK sampling and is shown in Table 1.3. In all clinical studies, reference drug, bupivacaine HCl was administered as a separate treatment arm. For Phase 2 studies, for both HTX-011 and bupivacaine HCl, full PK sampling from 0 to 120 h, except for study 209, where it was 0 to 240 h, was conducted. For Phase 3 studies, HTX-011 and bupivacaine HCl had population-PK sampling with 4 samples collected from each subject.

For HTX-011, Applicant has evaluated other modes of administration in some clinical studies, in addition to the instillation. Since the final proposed mode of administration for HTX-011 is 'instillation', the PK parameters of instillation mode of administration is only reported in this review. From Phase 2 studies, the PK parameters of final to be marketed formulation, HTX-011-56 were reported in this review. The dose and number of subjects for each study are shown in Table 1.3.

For bupivacaine HCl, strength, dose, and administration procedure in each surgical procedure are shown in Table 1.3.

Table 1.3: Clinical studies of HTX-011 in surgical procedures.

Study (Phase)	**Surgical Procedure**	**Dose (N) and administration procedure**		**Type and duration of PK sampling**
		HTX-011 (bupivacaine/meloxicam)	**Bupivacaine HCl**	
Study 202 (P2)	Herniorrhaphy	300 mg/ 9 mg (N=16); Instillation plus, fentanyl 50 mcg IV	75 mg (0.25%) (N=17); Infiltration injection plus, fentanyl 50 mcg IV	Full PK, 120 h
Study 208 (P2)	Bunionectomy	60 mg/ 1.8 mg (N=17); Instillation	50 mg (0.5%) (N=25); Infiltration injection (with or without using Mayo block)	Full PK, 120 h
Study 211 (P2)	Augmentation Mammoplasty	400 mg/ 12 mg (N=49); Instillation	50 mg (0.25%) (N=41); Nerve block	Full PK, 120 h
Study 209 (P2)	Total Knee Arthroplasty	400 mg/ 12 mg (N=53); Instillation	125 mg (0.25%) (N=65); Injection	Full PK, 240 h
Study 203 (P2)	Complete Abdominoplasty	400 mg/ 12 mg (N=17); Instillation	100 mg (0.25%); (N=17, Part C) Infiltration injection	Full PK, 120 h
Study 302 (P3)	Herniorrhaphy	300 mg/ 9 mg (N=161); Instillation	75 mg (0.25%); Injection	Population-PK * (4 samples)
Study 301 (P3)	Bunionectomy	60 mg/ 1.8 mg (N=157); Instillation	50 mg (0.5%); Injection	Population-PK * (4 samples)

* Population PK sampling was conducted for HTX-011 and bupivacaine HCl.

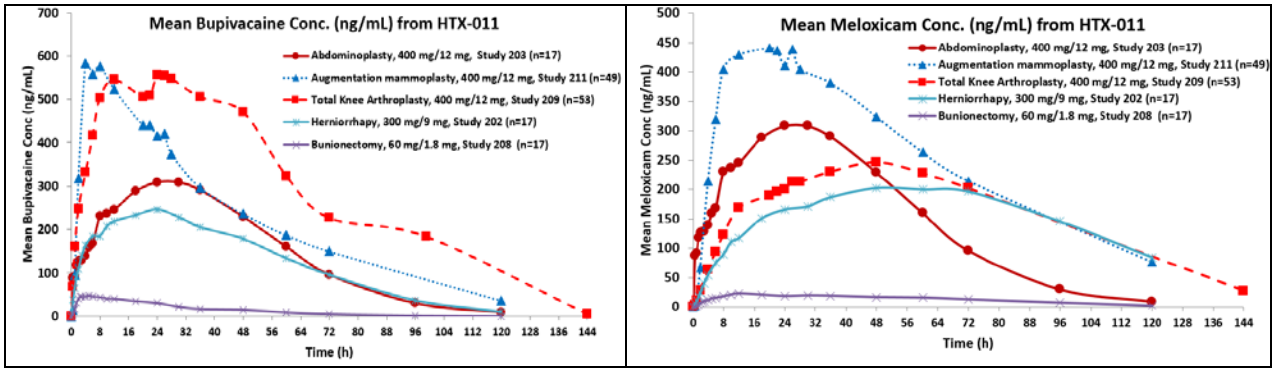
1.3.1. PK of bupivacaine and meloxicam from HTX-011 administered by instillation in HTX-011 clinical trials:

The PK of bupivacaine and meloxicam following single dose of HTX-011 with full PK sampling was evaluated in five Phase 2 procedures, bunionectomy (Study 208, n=16), herniorrhaphy (Study 202, n=16), augmentation mammoplasty (Study 211, n=49), complete abdominoplasty (Study 203, n=17), and total knee arthroplasty (Study 209, n=53) (Table 1.3). The number of subjects in these studies were adequate from PK evaluation perspective.

Two procedures that were further evaluated in adequate and well controlled Phase 3 trials were bunionectomy (Study 301) and herniorrhaphy (Study 302). In these studies, pop-PK sampling was utilized with 4 samples collected from each subject (4, 18, 24, and 48 hours post-dose) in 157 and 161 subjects in bunionectomy and herniorrhaphy, respectively. Applicant calculated PK parameters using pop-PK modelling in these two studies. Due to the variability factors associated with peri-operative products, PK parameters obtained from pop PK is not as reliable as that of full PK sampling (in phase 2 trials). Hence, only the PK parameters obtained from Phase 2 studies with full PK sampling were reported in this review.

The PK profiles and PK parameters of bupivacaine and meloxicam following single dose HTX-011 (bupivacaine/meloxicam) administered by instillation in each surgical procedure are shown in Figure 1.3.1, Table 1.3.1a and Table 1.3.1b, respectively.

Figure 1.3.1: Mean bupivacaine and meloxicam concentration profiles following single dose HTX-011 administered by instillation in surgical procedures.



Notes: The PK sampling was 0 to 120 h post-dose, except for total knee arthroplasty, where it is 240 h post dose (profile up till 144 h is shown)

Table 1.3.1a: PK parameters of bupivacaine following single dose HTX-011 (bupivacaine/meloxicam) administered by instillation in surgical procedures (Phase 2 studies with full PK sampling).

Surgical Procedure	**Bunionectomy (Study 208)**	**Herniorrhaphy (Study 202)**	**Total Knee Arthroplasty (Study 209)**	**Augmentation Mammoplasty (Study 211)**	**Complete Abdominoplasty (Study 203)**
Dose (Volume)	**60 mg/1.8 mg (2.1 mL)**	**300 mg/9 mg (10.3 mL) plus, fentanyl 50 mcg IV**	**400 mg/12 mg (13.7 mL)**		
N	17	16	53 (without ropivacaine) [a]	49	17 (Part C)
C_{max} (ng/mL)	54 ± 33	271 ± 147	695 ± 411	710 ± 246	366 ± 127
AUC_{0-24} (h·ng/mL)	883 ± 538	4712 ± 2144	11223 ± 6142	11758 ± 3990	5327 ± 1590
AUC_{0-48} (h·ng/mL)	1371 ± 910	9740 ± 5021	23580 ± 14035	19042 ± 6692	12090 ± 3939
AUC_{0-72} (h·ng/mL)	1595 ± 1085	12980 ± 6687	30807 ± 20122 (n=50)	23563 ± 8192	16051 ± 16051
AUC_{0-t} [b] (h·ng/mL)	1681 ± 1154	15174 ± 8545	35890 ± 28400	27363 ± 9227	18040 ± 6943
AUC_{inf} (h·ng/mL)	1718 ± 1211	15524 ± 8921	38173 ± 29400 (n=50)	31072 ± 17998	18247 ± 7069
Tmax	3 [1.55, 24]	18 [3, 30]	21 [4, 59]	4 [1, 35]	25 [9, 38]
Clast (120 h) (ng/mL)	0.18 ± 0.14	10 ± 15	5 ± 20 [C]	35 ± 71	9 ± 8
Half-life (h)	15 ± 8	16 ± 9	17 ± 7 (n=50)	25 ± 20	14 ± 3

PK parameters values are arithmetic mean ± standard deviation, except for Tmax for which it is median (minimum, maximum)
Notes:

[a] In TKA study, HTX-011 was instilled with or without ropivacaine (0.5%, 50 mg). PK parameters of only HTX-011 without ropivacaine (N=53) are reported

[b] AUC_{0-t} is 0 to 120 h post-dose for all studies, expect for Study 209, where it is 240h post dose

[C] Conc at 144 h

Table 1.3.1b: PK parameters of meloxicam following single dose HTX-011 (bupivacaine/ meloxicam) administered by instillation in surgical procedures (Phase 2 studies with full PK sampling).

Surgical Procedure	**Bunionectomy (Study 208)**	**Herniorrhaphy (Study 202)**	**Total Knee Arthroplasty (Study 209)**	**Augmentation Mammoplasty (Study 211)**	**Complete Abdominoplasty (Study 203)**
Dose (Volume)	**60 mg/1.8 mg (2.1 mL)**	**300 mg/9 mg (10.3 mL) plus, fentanyl 50 mcg IV**	**400 mg/12 mg (13.7 mL)**		
N	16	16	53 (without ropivacaine) [a]	49	17 (Part C)
C_{max} (ng/mL)	26 ± 14	225 ± 96	275 ± 134	527 ± 149	142 ± 72
AUC_{0-24} (h·ng/mL)	437 ± 250	2569 ± 855	3350 ± 1442	9034 ± 1924	2016 ± 631
AUC_{0-48} (h·ng/mL)	904 ± 516	6996 ± 2685	8926 ± 4102	17995 ± 4245	4541 ± 1492
AUC_{0-72} (h·ng/mL)	1285 ± 745	11973 ± 4592	13483 ± 6625	24331 ± 6332	6969 ± 2820
AUC_{0-t} [b] (h·ng/mL)	1621 ± 927	18721 ± 7923	19525 ± 12259	30499 ± 9460	9997 ± 6045
AUC_{inf} (h·ng/mL)	2079 ± 1631	NC	25673 ± 17666 (n=35)	41808 ± 38413	10069 ± 4123 (n=16)
Tmax	18 [8.13, 60]	54 [24, 96]	36 [12, 72]	20 [6, 49]	24 [9, 97]
Clast (120 h) (ng/mL)	3 ± 3	85 ± 53	4 ± 10 [C]	76 ± 86	39 ± 73
Half-life (h)	33 ± 36	NC	42 ± 37 (n=35)	42 ± 70	30 ± 23 (n=16)

PK parameters values are arithmetic mean ± standard deviation, except for Tmax for which it is median (minimum, maximum)
Notes:

[a] In TKA study, HTX-011 was instilled with or without ropivacaine (0.5%, 50 mg). PK parameters of HTX-011 without ropivacaine (N=53) are reported

[b] AUC_{0-t} is 0 to 120 h post-dose for all studies, expect for Study 209, where it is 240h post dose

[C] Conc at 240 h

NC：Not calculated, because terminal elimination phase was not captured in sufficient number of patients

Highest observed Cmax, AUC, and individual concentrations of bupivacaine and meloxicam across HTX-011 clinical studies:

Across HTX-011 clinical studies, the highest observed Cmax and AUC, and individual concentrations of bupivacaine and meloxicam following single dose HTX-011 by instillation, are shown below in Table 1.3.1c and Table 1.3.1d, respectively.

Across HTX-011 clinical studies:

- the highest bupivacaine Cmax was in augmentation mammoplasty, and AUC and individual concentration (1830 ng/mL) were in total knee arthroplasty.
- the highest meloxicam Cmax and AUC and individual concentration (1220 ng/mL) were in augmentation mammoplasty.

Table 1.3.1c: Highest observed AUC and Cmax of bupivacaine and meloxicam following single dose of HTX-011administered by instillation across surgical procedures.

PK parameter	HTX-011 Clinical trials			
	Bupivacaine from HTX-011		Meloxicam from HTX-011	
	Maximum value	Procedure (dose)	Maximum value	Procedure (dose)
Cmax (ng/mL)	710 ± 246	augmentation mammoplasty (400/12 mg)	527 ± 149	augmentation mammoplasty (400/12 mg)
AUCt (h·ng/mL)	35890 ± 28400	total knee arthroplasty (400/12 mg)	30499 ± 9460	
AUCinf (h·ng/mL)	38173 ± 29400		41808 ± 38413	

Table 1.3.1d: Highest observed individual concentrations of bupivacaine and meloxicam following single dose of HTX-011administered by instillation in each surgical procedure.

Procedure (dose; number of subjects)	Bupivacaine		Meloxicam	
	Conc. (ng/mL)	Time point (h)	Conc. (ng/mL)	Time point (h)
Phase 2 Bunionectomy (60 mg/1.8 mg; n=16)	119	3	52	18
Phase 3 Bunionectomy (60 mg/1.8 mg; n=157)[$]	314	4	317	24
Phase 2 Herniorrhaphy (300 mg/9 mg; n=16)	591	30	391	48
Phase 3 Herniorrhaphy (300 mg/9 mg; n=161)[$]	1290	24	410	24
Phase 2 Total knee arthroplasty (400 mg/12 mg; n= 53)	1830	28	557	72
Phase 2 Augmentation mammoplasty (400 mg/12 mg; n= 49)	1550	6	1220	26
Phase 2 Complete abdominoplasty (400 mg/12 mg; n= 17)	630	8	350	96

[$] Phase 3 trials utilized pop-PK sampling with 4 samples (4, 18, 24, and 48 hours post-dose) collected from each subject. Hence, the value is not from full PK sampling.

1.3.2. PK of bupivacaine from bupivacaine HCl products (listed drug) across HTX-011 clinical trials:

In Phase 2 clinical studies, reference drug, bupivacaine HCl was administered as a separate treatment arm. The strength, dose, and administration procedure, and PK parameters of bupivacaine HCL in each surgical procedure are shown in Table 1.3.2a.

The mean bupivacaine profiles from bupivacaine HCl in surgical procedures are shown in Figure 1.3.2. The highest observed bupivacaine concentrations from bupivacaine HCl in each surgical procedure are shown in Table 1.3.2b.

Figure 1.3.2.: Mean bupivacaine profiles from bupivacaine HCl in surgical procedures. The 0-12 h profile is represented as the smaller graph within the figure.

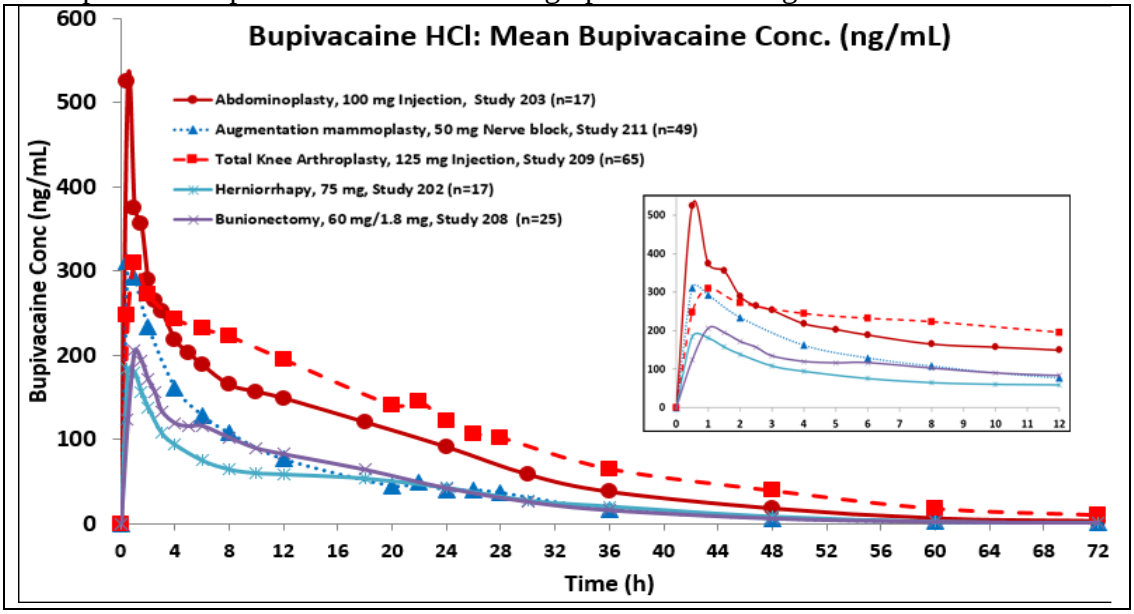


Table 1.3.2a.: PK parameters of bupivacaine following administration of bupivacaine HCl injection in surgical procedures (Phase 2 studies with full PK sampling).

Surgical Procedure	Bunionectomy (Study 208)	Herniorrhaphy (Study 202)	Total Knee Arthroplasty (Study 209)	Augmentation Mammoplasty (Study 211)	Complete Abdominoplasty (Study 203)
Strength	**0.5%**	**0.25%**	**0.25%**	**0.25%**	**0.25%**
Dose	**50 mg**	**75 mg**	**125 mg**	**50 mg**	**100 mg**
Mode of administration	**Infiltration injection (with or without using Mayo block)**	**Infiltration injection plus, fentanyl 50 mcg IV**	**injection**	**Nerve block**	**Infiltration injection**
N	25	17	65	41	17 (Part C)
C_{max} (ng/mL)	228 ± 89	196 ± 97	399 ± 171	341 ± 136	479 ± 234
AUC_{0-24} (h·ng/mL)	2169 ± 903	1697 ± 363	4646 ± 2082	2482 ± 779	4069 ± 1622
AUC_{0-48} (h·ng/mL)	2640 ± 1240	2243 ± 501	6359 ± 3193	3027 ± 1169	5217 ± 2204
AUC_{0-72} (h·ng/mL)	2717 ± 1327	2336 ± 553	6870 ± 3623	3105 ± 1282	5445 ± 2328
AUC_{0-t} [b] (h·ng/mL)	2735 ± 1356	2345 ± 563	6862 ± 3618	3107 ± 1283	5505 ± 2340
AUC_{inf} (h·ng/mL)	2745 ± 1357	2349 ± 564	7097 ± 3898	3120 ± 1302	5509 ± 2340
Tmax	1.32 [0.55, 8.1]	0.5 [0.75, 24]	1.0 [0.4, 21]	0.55 [0.4, 2.05]	1.6 [0.48, 19]
Clast (120 h) (ng/mL)	0.3 ± 1.4	BLOD	11 ± 14 [C]	BLOD	0.2 ± 0.2
Half-life (h)	8 ± 2	6 ± 2	12 ± 4	6 ± 3	12 ± 5

PK parameters values are arithmetic mean ± standard deviation, except for Tmax for which it is median (minimum, maximum);
BLOD, below limit of detection;
[C] 72 h

Table 1.3.2b: Highest observed individual bupivacaine concentrations following administration of bupivacaine HCl in each surgical procedure.

Procedure (Strength, dose; number of subjects)	**Mode of administration**	**Bupivacaine**	
		Conc. (ng/mL)	**Time point (h)**
Phase 2 Bunionectomy (0.5%, 50 mg; n=25)	Infiltration injection (with or without using Mayo block)	485	1
Phase 3 Bunionectomy (0.5%, 50 mg; n=154) [$]	Injection into surgical site	314	4
Phase 2 Herniorrhaphy (0.25% 75 mg; n=17)	Infiltration injection plus, fentanyl 50 mcg IV	434	0.5
Phase 3 Herniorrhaphy (0.25% 75 mg; n=172) [$]	Infiltration injection plus, fentanyl 50 mcg IV	588	unscheduled
Phase 2 Total knee arthroplasty (0.25% 125 mg; n= 65)	Injection	950	0.5
Phase 2 Augmentation mammoplasty (0.25%, 50 mg; n= 41)	Nerve block	705	0.5
Phase 2 Complete abdominoplasty (0.25%, 100 mg; n= 17)	Infiltration injection	951	1

[$] Phase 3 trials utilized pop-PK sampling with 4 samples (4, 18, 24, and 48 hours post-dose) collected from each subject. Hence, the value is not from full PK sampling.

Across clinical studies, from bupivacaine HCl, the highest bupivacaine Cmax and individual concertation was observed in complete abdominoplasty of 479 ± 234 ng/ ml (mean ± SD) and 951 ng/mL, respectively. The highest AUCt and AUCinf were observed in total knee arthroplasty of 6862 ± 3618 and 7097 ± 3898 h·ng/mL (mean ± SD), respectively.

1.3.3. Bupivacaine HCl products used in HTX-011 clinical trials:

In the HTX-011 clinical trials, in addition to listed drug MARCAINE (NDA 016964), Applicant also used other IR bupivacaine HCl NDA and ANDA products. Since NDA 016964 was only listed for bupivacaine in form 356h, we have sent an information request (IR) (dated 10/30/2018) to Applicant to state the reason for their usage of other bupivacaine HCl NDAs or ANDAs, in addition to MARCAINE and to provide the NDA and ANDAs numbers of those products.

In response (dated 12/21/2018), Applicant mentioned that they had to use other products due to limited supply and drug shortage of branded product MARCAINE. Applicant also added that the bupivacaine HCl drug products used in HTX-011 clinical trials were assigned a therapeutic equivalence code of "AP" to the reference listed drug MARCAINE per Orange Book (Table 1). Applicant provided the following reason:

"For the Phase 3 studies of HTX-011 (Studies HTX-011-301 and HTX-011-302, Heron provided the bupivacaine hydrochloride injection, USP to the clinical sites due to the difficulty in sourcing MARCAINE for clinical trial use. Beginning in March 2017, the branded product MARCAINE (bupivacaine hydrochloride injection, USP) without epinephrine was in limited supply due to a severe drug shortage as noted by the American Society of Health System Pharmacists (ASHP) drug shortage listings as presented in the NDA in Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods and in the Response to Clinical Pharmacology IR

submitted to NDA 211988 in SN0006 on November 26, 2018. Based on the information provided by Pfizer (the parent company of Hospira, Inc.) to customers and included in the FDA Drug Shortages website, the drug shortage for MARCAINE and bupivacaine hydrochloride injection, USP manufactured by Pfizer is due to issues at the manufacturing site. Based on a December 17, 2018 update by ASHP, Pfizer currently has all MARCAINE vials on back order and the company estimates a release date of 1st quarter 2020.

For the Phase 2 studies of HTX-011 (Studies HTX-011-202, HTX-011-203, HTX-011-208, HTX-011-209 and HTX-011-211), the protocols indicated that the study sites should source MARCAINE or bupivacaine HCl for the study. With the exception of 36 subjects who received MARCAINE in Study HTX-011-211 (NDC 0409-1559-30), the other sites used the therapeutically equivalent generic products of bupivacaine hydrochloride injection, USP.

As described in the Response to Clinical Pharmacology IR (SN0006, November 26, 2018), the bupivacaine HCl drug products used in these studies were assigned a therapeutic equivalence (TE) code of "AP" per the FDA publication Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the "Orange Book," 38th edition). This designation confirms that the approved injectable aqueous solutions of bupivacaine hydrochloride are therapeutically equivalent to each other and to the Reference Listed Drug (RLD), MARCAINE (bupivacaine hydrochloride injection, USP). Therefore, all are equivalent substitutes for MARCAINE and serve as appropriate reference standard in the evaluation of efficacy and safety in HTX-011 clinical studies.

In addition, the MARCAINE USPI that is referenced in the HTX-011 NDA (MARCAINE USPI 2015) lists the product name as MARCAINE (bupivacaine hydrochloride injection, USP); therefore, it is a compendial product".

There is only one NDA listed as the Reference Listed Drug (RLD) for bupivacaine hydrochloride injection, USP (without epinephrine). It is NDA 016964 for MARCAINETM (bupivacaine hydrochloride injection, USP) manufactured by Hospira Inc. All bupivacaine hydrochloride injection products listed in Table 1 are shown to be therapeutically equivalent TE to each other and to the RLD with an "AP" TE code…".

Table 1: ANDA and NDA numbers of bupivacaine HCl used in Phase 2 and Phase 3 studies.

Clinical Study Phase	Bupivacaine hydrochloride injection, USP Manufacturer	NDC #	NDA# or ANDA#
Phase 3	Hospira Inc.	0409-1162-01[a]	018053 [b]
	Hospira Inc.	0409-1159-02[a]	018053 [b]
Phase 2	Hospira Inc.	0409-1159-02	018053 [b]
	Hospira Inc.	0409-1159-19	018053 [b]
	Hospira Inc.	0409-1160-01	018053 [b]
	Hospira Inc.	0409-1160-18	018053 [b]
	Hospira Inc.	0409-1162-19	018053 [b]
	Hospira Inc.	0409-1559-30	016964 [b] (RLD)
	Hospira Inc.	0409-1160-10	Not Located
	Hospira Inc.	0409-1749-29	016964 (RLD) [b, c]
	Auromedics (Aurobindo)	55150-0168-30	203895 [d]
	Auromedics (Aurobindo)	55150-0169-10	203895 [d]
	APP, Fresenius Kabi USA, LLC	63323-0465-57	018304 [d]

[a] Corresponds to List Numbers 11620486 for Study HTX-011-301 and 1159-04-87 for Study HTX-011-302 presented in SN0006.
[b] Listed as an NDA number on the Drugs@FDA Website.
[c] NDC number is for bupivacaine hydrochloride with epinephrine.
[d] Listed as an ANDA number on the Drugs@FDA Website.

Reviewer's comments on usage of other bupivacaine HCl NDA and ANDA products in addition to Marcaine in HTX-011 clinical trials:

Since the bupivacaine HCl drug products used were assigned a therapeutic equivalence code of "AP" to reference listed drug MARCAINE per Orange Book, these products are expected to have similar PK, thereby same clinical effect and safety profile as that of MARCAINE. Overall, from a scientific/clinical perspective, the outcome/data from the studies is unlikely to be impacted by different marketed products.

On further discussion, the (b) (2) regulatory team provided the following:

"The committee agreed that the use of the various bupivacaine products (NDA and ANDA) in the P2 and P3 studies will be a scientific issue. However, Heron needs to update their 356h to also cite reliance on NDA 018053 and NDA 018304 and needs to provide patent certification (which should not be a problem since there are no patents or exclusivity to worry about). ANDA 203895 appears to have been an expedited review due to the drug shortage and the RLD was NDA 016964, which they have already cited as a LD.

Your review should provide scientific justification on the use of the various bupivacaine products in the P2 and P3 studies and you should also note the concentration of the bupivacaine products used in the studies (they provided the NDC # in the Dec 2018 and Nov 2018 IR response).

Suggested language for an IR to applicant:

Please provide a revised Form FDA 356h specifying reliance on NDA 018053 for bupivacaine hydrochloride and NDA 018304 for Sensorcaine (bupivacaine hydrochloride) as additional listed drugs that are the basis of your 505(b)(2) application. We note that you currently have only cited reliance on NDA 016964 (Marcaine) and NDA 020938 (Mobic). Please also provide an appropriate patent certification or statement with respect to any relevant patents that claim the listed drug, NDA 018053 and NDA 018304."

Applicant's Response to above IR (dated 01/30/2019, sequence 022):

Applicant has added bupivacaine HCL NDA products, 018053 and 018304 to form 356 h, additionally to 016964 (MARCAINE) and 020938 (MOBIC).

1.3.4. Comparison of systemic exposure of bupivacaine and meloxicam following single dose administration of HTX-011 to listed drugs (MARCAINE and MOBIC) for clinical bridge:

HTX-011 is a local acting drug product. The systemic levels of bupivacaine or meloxicam from HTX-011 have implications for systemic safety, hence their systemic exposure is evaluated from systemic safety point of view.

For clinical bridge, the systemic exposure (Cmax and AUC) of bupivacaine and meloxicam from HTX-011 was compared to systemic exposure of listed drugs.

For bupivacaine, the PK parameters of bupivacaine from HTX-011 were compared to the PK parameters of bupivacaine HCL treatment arm in HTX-011 clinical trials.

For meloxicam, the PK parameters of meloxicam from HTX-011 were compared to the PK parameters listed in the MOBIC label.

Note: MARCAINE label has no PK parameters data of bupivacaine for comparison.

1.3.4.1. Bupivacaine (for clinical bridge):

The bupivacaine PK parameters of HTX-011 and bupivacaine HCl from five surgical procedures are shown above in Tables 1.3.1a and Table 1.3.2, respectively. The maximum total dose for bupivacaine in HTX-011 product was 400 mg, and the maximum dose of bupivacaine HCl studied in HTX-011 clinical trials was 125 mg.

During NDA review, it was determined that Zynrelef 60 mg/1.8 mg for bunionectomy and 300 mg/9 mg for open inguinal hernia repair would be approved. Hence, for systemic safety comparison based on systemic levels of bupivacaine, the following two comparisons were made across studies and are shown in Table 1.3.4.1a.

- Comparison of bupivacaine Cmax and AUC of HTX-011, for to be approved herniorrhaphy (300 mg dose) to Cmax and AUC of bupivacaine HCl from all surgical procedures. This comparison shows that Cmax is lower, while AUC is higher for HTX-011 in herniorrhaphy compared to bupivacaine HCl (column 1 Vs. column 3).
- Comparison of bupivacaine Cmax and AUC values of HTX-011 to Cmax and AUC of bupivacaine HCl, across all 5 studies. This comparison shows that both Cmax and AUC values of HTX-011 are higher compared to Cmax and AUC values of bupivacaine HCl (column 2 vs. column 3).

Table 1.3.4.1a: Highest bupivacaine Cmax and AUC values of HTX-011 and bupivacaine HCl in surgical procedures:

PK parameter *	**HTX-011 Clinical trials**		
	Highest bupivacaine values of HTX-011		**Highest bupivacaine values from Bupivacaine HCl across five surgical procedures**
	Herniorrhaphy (300/9 mg, study 202)	**Highest value across five surgical procedures**	
Cmax (ng/mL)	271 ± 147	710 ± 246 augmentation mammoplasty (400/12 mg, study 211)	479 ± 234 complete abdominoplasty (100 mg, study 203)
AUCt (h·ng/mL)	15174 ± 8545	35890 ± 28400 total knee arthroplasty (400/12 mg, study 209)	6862 ± 3618 total knee arthroplasty (125 mg, study 209)
AUCinf (h·ng/mL)	15524 ± 8921	38173 ± 29400 total knee arthroplasty (400/12 mg, study 209)	7097 ± 3898 total knee arthroplasty (125 mg, study 209)

*PK parameters values are arithmetic mean ± standard deviation

Overall, across five Phase 2 PK studies, when the highest observed bupivacaine exposure was compared between HTX-011 and reference drug, bupivacaine HCl, both Cmax and AUC values of bupivacaine from HTX-011 are higher compared to bupivacaine HCl. For the to be approved herniorrhaphy procedure with 300 mg/9 mg dose, the Cmax is lower, while AUC is higher for HTX-011 compared to bupivacaine HCl.

Bupivacaine Cmax and AUC ratio (HTX-011/ bupivacaine HCl) from individual study:
The ratio of means of bupivacaine Cmax and AUCinf (HTX-011 / bupivacaine HCl) in each study are shown in Table 1.3.4.1b below.

Table 1.3.4.1b: Bupivacaine mean Cmax and AUCinf ratio (HTX-011 / bupivacaine HCl) in each study

Surgical Procedure	Bupivacaine Cmax ratio (HTX-011/ Bupivacaine HCl)	Bupivacaine AUC ratio (HTX-011/ Bupivacaine HCl)
Herniorrhaphy, Study 202	1.38	6.61
Bunionectomy, Study 208	0.24	0.63
Complete Abdominoplasty, Study 203	0.76	3.31
Total Knee Arthroplasty, Study 209	1.74	5.38
Augmentation Mammoplasty, Study 211	2.08	9.96

- When individual studies were compared, the bupivacaine Cmax of HTX-011 is lower in bunionectomy and complete abdominoplasty, whilst higher in other three studies; the bupivacaine AUCinf of HTX-011 is lower in bunionectomy, whilst higher in other four studies in comparison to bupivacaine HCL.

Applicant proposed comparison of bupivacaine PK to listed drugs for scientific bridge in the NDA submission:
For scientific bridge comparison, Applicant provided a literature article (Wildsmith 1977) [1] which reports a bupivacaine Cmax of 2160 ng/mL at a dose of 150 mg for bupivacaine HCl. This article has no AUC information. When compared, the Cmax of bupivacaine from HTX-011is lower than the reported Cmax value from this article. However, the validity of the reported Cmax value is questionable, because 1) literature article does not report the bioanalytical method validation information (e.g., precision, accuracy etc.) for quantifying bupivacaine, and 2) literature article lacks the tradename for bupivacaine HCl used. In addition, the sample size of bupivacaine is not mentioned in the study. Therefore, even if there are no reported adverse events in this study, it cannot be concluded that a buprenorphine concentration of 2160 ng/mL is safe.

Bupivacaine Toxic Concentrations as per literature
Knudsen and co-workers (*British Journal of Anaesthesia* 1997; 78: 507–514) who studied central nervous and cardiovascular effect of ropivacaine, bupivacaine and placebo in healthy volunteers, with a sample size from 11 to 14 subjects reports that the mean maximum tolerated

[1] Wildsmith, J. A., G. T. Tucker, S. Cooper, D. B. Scott and B. G. Covino Plasma concentrations of local anaesthetics after interscalene brachial plexus block. Br J Anaesth (1977). 49(5): 461-466

venous plasma concentration of bupivacaine was 2,100 ng/mL, with a minimum value of as low as 800 ng/mL. The Table copied is from article is shown below.

Table 2 Maximum tolerated plasma concentrations of ropivacaine and bupivacaine at the end of i.v. infusion of 10 mg min^{-1} (mean SD) (min.–max.) Crossover study in 12 volunteers. ***$P<0.001$ (ropivacaine *vs* bupivacaine)

	Plasma concentration (mg $litre^{-1}$)	
Sampling/drug	Total	Unbound
Arterial		
Ropivacaine	4.3 (0.6)	0.56 (0.14)***
	(3.4–5.3)	(0.34–0.85)
Bupivacaine	4.0 (1.4)	0.30 (0.11)
	(1.1–6.2)	(0.13–0.51)
Venous		
Ropivacaine	2.2 (0.8)	0.15 (0.08)
	(0.5–3.2)	(0.01–0.24)
Bupivacaine	2.1 (1.2)	0.11 (0.10)
	(0.8–4.5)	(0.01–0.38)

Reviewer comments on Applicant's comparison of HTX-011 Cmax to literature: Based on the minimum value of 800 ng/mL for bupivacaine tolerated plasma concentration, as reported in Knudsen and co-worker's literature article mentioned above, the adequate justification to support the safety of Cmax observed in studies with HTX-011 was not provided.

In the NDA submission, for scientific bridge, since Applicant compared only bupivacaine Cmax of HTX-011 to reference IR bupivacaine (from literature) and did not attempt to compare AUC. Applicant mentioned that HTX-011 being is an ER product, the AUC values would be higher than an IR bupivacaine product. However, since we use both Cmax and AUC for comparison between test and reference drugs, we sent an IR to Applicant on 11/19/2018.

In response (dated 12/26/2018), Applicant provided the following rationale:

> *"Because HTX-011 is an extended-release product, it was expected and confirmed that the bupivacaine AUC exposures are greater than those from bupivacaine HCl, an immediate release solution of bupivacaine (NDA Table 7). The dose of bupivacaine, the disease active ingredient, included in HTX-011 is higher than a single dose of bupivacaine HCl since an effective dose of bupivacaine is needed for each of the 3 days it is released from the polymer. Bupivacaine from HTX-011 is absorbed over the first 3 days with approximately 50% of the exposure on Day 1, whereas approximately 70% of the exposure to bupivacaine from bupivacaine HCl occurs within the first 24 hours; therefore, a more relevant comparison of bupivacaine AUC values for bupivacaine HCl and HTX-011 is for the first 24 hours only. For this comparison, the AUC values for bupivacaine HCl were extrapolated based on the bupivacaine HCl data at the same HTX- 011 bupivacaine dose levels studied in the HTX-011 Phase 2 studies that are also the proposed recommended doses for each surgical procedure (Table 1). For each*

surgical procedure, the actual bupivacaine AUC0-24 values following HTX-011 administration are lower than the estimated bupivacaine AUC0-24 values for bupivacaine HCl. The maximum dosage limit for MARCAINE administered via local infiltration is a single dose up to 175 mg without epinephrine, or a daily MRHD of 400 mg/day (MARCAINE USPI, 2011). Based on the bupivacaine HCl AUC data at dose levels administered in the HTX-011 Phase 2 studies, a 400 mg dose of bupivacaine HCl is estimated to yield a higher AUC0-24 than any 24-hour interval bupivacaine AUC for HTX-011 at the proposed maximum recommended dose of HTX-011 of 400 mg/12 mg (Table 1).”

Table 1: Bupivacaine AUC Following a Single Injection of Bupivacaine HCl or Instillation of HTX-011-56 in Various Surgical Procedures (PK Population)

Parameter	Bunionectomy (Study 208)			Herniorrhaphy (Study 202)			Total Knee Arthroplasty (Study 209)			Augmentation Mammoplasty (Study 211)		
	BPV HCl		HTX-011	BPV HCl		HTX-011	BPV HCl		HTX-011	BPV HCl[c]		HTX-011
	50 mg	60 mg (Estimated)[a]	60 mg	75 mg	300 mg (Estimated)[a]	300 mg	125 mg	400 mg (Estimated)[a]	400 mg[b]	50 mg	400 mg (Estimated)[a]	400 mg
Mean AUC_{0-24}, h·ng/mL	2,150	2,580	880	1,880	7,520	4,740	4,610	14,752	10,900	2,440	19,520	11,700
Mean AUC_{24-48}, h·ng/mL	--	--	480	--	--	5,010	--	--	11,800	--	--	7,200
Mean AUC_{48-72}, h·ng/mL	--	--	210	--	--	3,250	--	--	7,300	--	--	4,500
Mean AUC_{inf}, h·ng/mL	2,710	3,252	1,680	2,650	10,600	15,300	7,020	22,464	33,300	3,060	24,480	27,000

Reviewer’s comments on Applicant’s response:

- The maximum dose of MARCAINE administered as a single dose is up to 175 mg without epinephrine, or a daily MRHD of 400 mg/day (MARCAINE USPI, 2011). It is to be noted that, the total daily dose 400 mg is given in split doses in 24 h time-period, but not as a single dose. In the conducted clinical trials, for bupivacaine HCl, there are differences in 1) the mode drug adminsiatrion between trials, 2) surgical procedures and, 3) anatomical site. These factors could result in differences in the PK.
- In HTX-011 clinical trials, the maximum dose of bupivacaine HCl administered was 125 mg. In each study, since an equivalent / matching dose of bupivacaine HCl to HTX-011 dose was not used, applicant extrapolated the PK parameters (AUC_{0-24} and AUC_{inf} values) of bupivacaine HCL dose to match HTX-011 dose (Table 1 above). This extrapolation of PK parameters may not be an acceptable approach, because for bupivacaine HCL, the PK dose-linearity between different doses, by a specific mode of drug-administration, in a specific surgical procedure is lacking. Overall, the applicant’s extrapolation of PK parameters, AUC_{0-24} and AUC_{inf} values of bupivacaine HCL may not be appropriate.

Overall, across five Phase 2 PK studies, when the highest observed bupivacaine exposure was compared between HTX-011 and reference drug, bupivacaine HCl, both Cmax and AUC values of bupivacaine from HTX-011 are higher compared to bupivacaine HCl. For the to be approved

herniorrhaphy procedure with 300 mg/9 mg dose, the Cmax is lower, while AUC is higher for HTX-011 compared to bupivacaine HCl.

1.3.4.2. Meloxicam (for clinical bridge):

Meloxicam systemic exposure from HTX-011

The meloxicam PK parameters of HTX-011 are shown above in Table 1.3.1b. The HTX-011 contains maximum meloxicam dose of 12 mg. However, during the NDA review, it was determined that the highest recommended HTX-011 dose would be 300 mg/9 mg (bupivacaine /meloxicam), evaluated in herniorrhaphy (Study 202).

- Across all clinical studies, from HTX-011, the highest meloxicam Cmax, $AUC_{t,\ 0\text{-}120h}$ and AUCinf (mean ± SD) were 527 ± 149 ng/mL, 30499 ± 9460 h·ng/mL and 41808 ± 38413 h·ng/mL, respectively, observed in augmentation mammoplasty.
- For to be approved herniorrhaphy, the meloxicam Cmax and $AUC_{t,\ 0\text{-}120h}$ were 225 ± 96 ng/mL and 18721 ± 7923, respectively. [Note: AUC_{inf} in herniorrhaphy was not calculated, because terminal elimination phase was not captured in sufficient number of patients]

Meloxicam systemic exposure from MOBIC label:

- MOBIC label has meloxicam PK information at steady state after oral dose of 7.5 mg in healthy male adults, which reports a mean Cmax of 1050 ng/mL and mean clearance (Cl/F) of 8.8 mL/min. Using clearance values, meloxicam AUC_{tau} for MOBIC was calculated. The calculated mean steady state AUCtau for 15 mg[$] MOBIC based on the clearance value for 7.5 mg MOBIC at steady state was 28,409 h.ng/mL. The equation for calculation of AUC_{tau} is as follows

$$AUC_{tau} = \frac{Dose}{CL/F} = \frac{15\ mg}{8.8\ mL/min} \times \frac{1 \times 10^6\ ng}{1\ mg} \times \frac{1\ hr}{60\ min} = 28{,}409\ hr \cdot ng/mL$$

[$Note: The PK of meloxicam of MOBIC capsules are dose-proportional over the range of 7.5 mg to 15 mg].

Meloxicam systemic exposure comparison:

- For HTX-011, the PK sampling duration was 5 days (120 h). Since MOBIC is dosed once daily, the AUC values were obtained by multiplying with 5 (days) to match HTX-011 PK sampling duration. The resultant calculated oral MOBIC AUC is ~142045 h.ng/mL for 5 days. When compared to 5-day AUC of MOBIC, meloxicam AUC following 9 mg and 12 mg doses of HTX-011are approximately 13% and 29%, respectively. Similarly, for Cmax, meloxicam Cmax following 9 mg and 12 mg doses of HTX-011are approximately 21% and 50%, respectively of that of oral MOBIC Cmax.

Therefore, based on comparison, both Cmax and AUC of meloxicam from HTX-011 are lower than that of MOBIC.

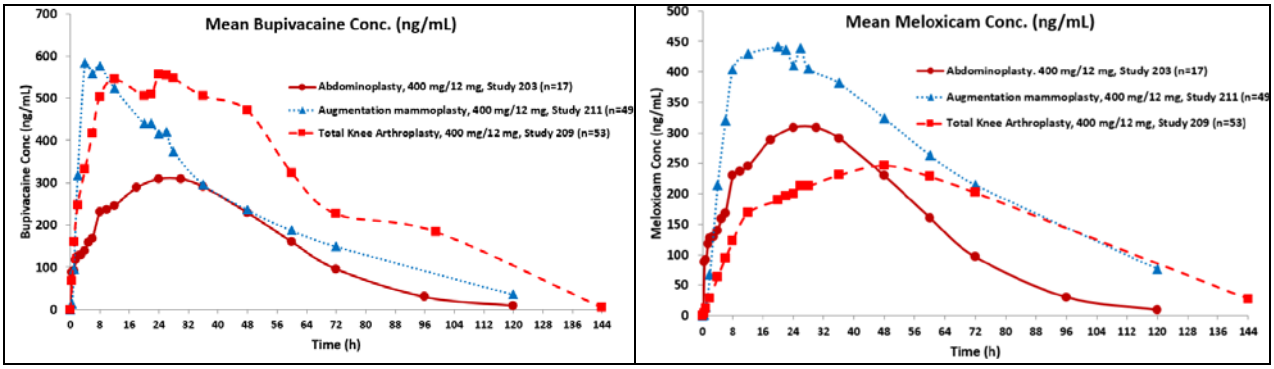
1.3.5 PK comparison of bupivacaine and meloxicam between surgical procedures that used same dose of HTX-011 400 mg/12 mg:

The PK of meloxicam or bupivacaine when compared between three different procedures that used same HTX-011 dose of 400 mg/12 mg, significant differences were observed between the procedures. The following three surgical procedures used same highest dose of HTX-011, 400 mg bupivacaine/ 12 mg meloxicam.

Type of Model and Anatomical space	Surgical Procedure
Soft tissue, large anatomical space	Augmentation mammoplasty (N=49) Complete abdominoplasty (N=17)
Bony tissue, large anatomical space	Total knee arthroplasty (TKA) (N=53)

The comparison was done between PK profiles, individual concentrations at each time point, and PK parameters. The mean bupivacaine and meloxicam concentration profiles of HTX-011 400 mg/12 mg dose is shown in Figure 1.3.5a. As can be noted, for 400 mg/12 mg dose of HTX-011, between different surgical procedures, the PK profiles of bupivacaine or meloxicam are different. For example, between soft tissues procedures, the bupivacaine Tmax is earlier and Cmax is higher in augmentation mammoplasty (blue triangles profile), compared to complete abdominoplasty (brown circles profile). The resulting systemic exposure (AUC and Cmax) for both bupivacaine and meloxicam are different between two procedures.

Figure 1.3.5a: Mean bupivacaine and meloxicam concentration profiles of HTX-011 in surgical procedures that used HTX-011 400 mg/12 mg dose.

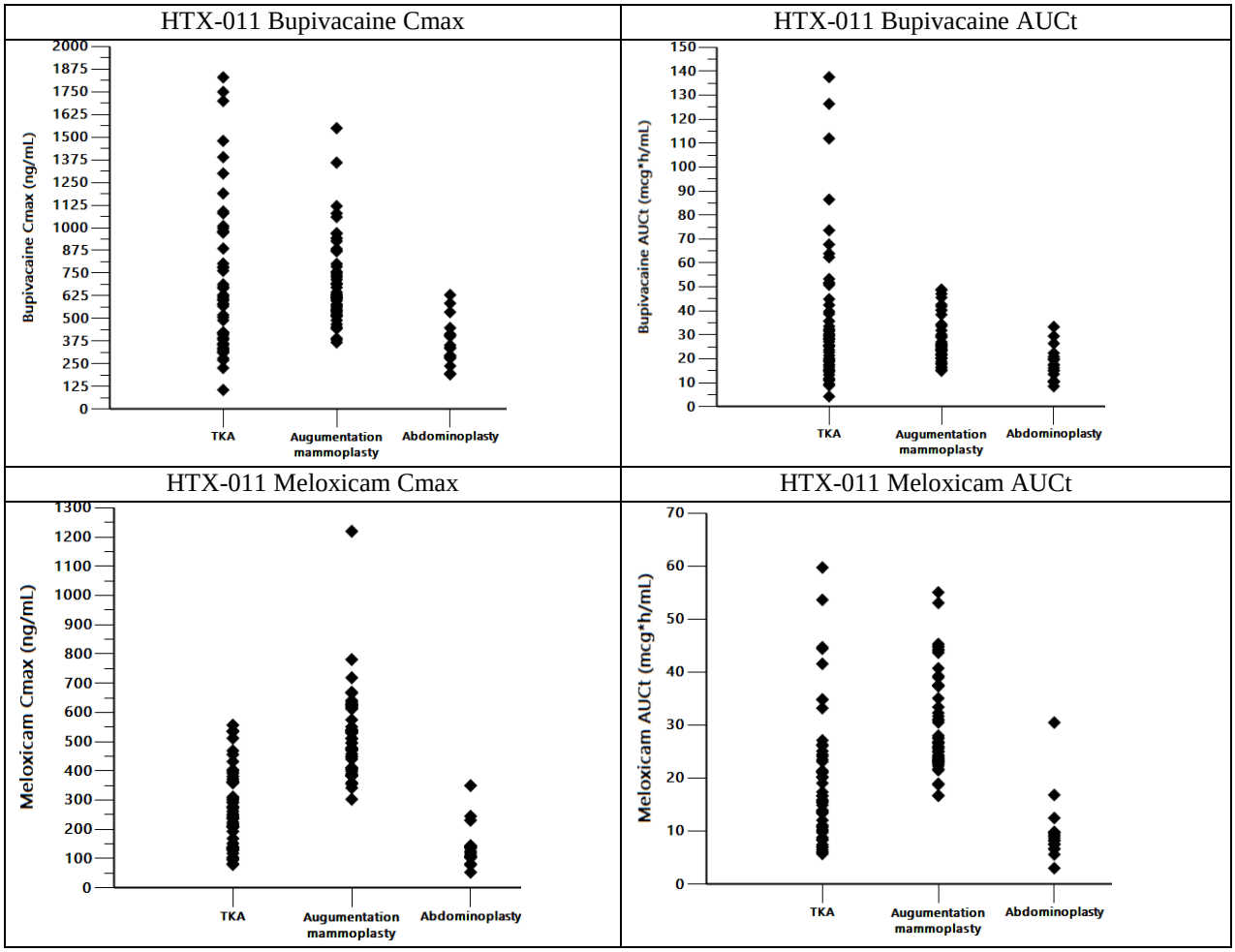


Notes: The PK sampling was 0 to 120 h post-dose for augmentation mammoplasty and complete abdominoplasty, while 240h post dose for total knee arthroplasty (till 144 h profile was shown)

The PK parameters of meloxicam and bupivacaine were shown above in Section 1.3.1, Tables 1.3.1a and 1.3.1b, respectively. The scatter plot of individual bupivacaine and meloxicam Cmax

and AUCt from HTX 400 mg/12 mg dose between different surgical procedures is shown in Figure 1.3.5b:

Figure 1.3.5b: Scatter plot of individual bupivacaine and meloxicam Cmax and AUCt from HTX 400 mg/12 mg dose between different surgical procedures.



Some example PK parameters differences between procedures that used same dose in are presented as below:

- **Comparison between soft tissue procedures (abdominoplasty vs. mammoplasty):**
  - Mean bupivacaine Cmax and AUCt were ~49% and 34%, and while meloxicam was ~73 and 67%, respectively lower for abdominoplasty compared to mammoplasty
- **Comparison between soft tissue vs. bony tissue (TKA vs. abdominoplasty or mammoplasty):**
  - Mean bupivacaine Cmax and AUCt were ~90% and 100% higher, respectively for TKA compared to abdominoplasty
  - Mean bupivacaine Cmax was approximately equal, while AUCt is 31% higher for TKA compared to mammoplasty
  - Mean meloxicam Cmax and AUCt were ~94% and 95% higher, respectively for TKA compared to abdominoplasty
  - Mean meloxicam Cmax and AUCt were ~48% and 36% lower, respectively for TKA compared to mammoplasty

Conclusions of PK comparison between procedures that used HTX-011400 mg/12 mg:

- The comparison shows that, between surgical procedures that used same dose of HTX-011 400 mg/12 mg, the systemic exposure is different. Based on this, it can be concluded that the systemic absorption of bupivacaine or meloxicam of HTX-011 is dependent upon surgical site, surgical procedure and vascularity of the administration site.

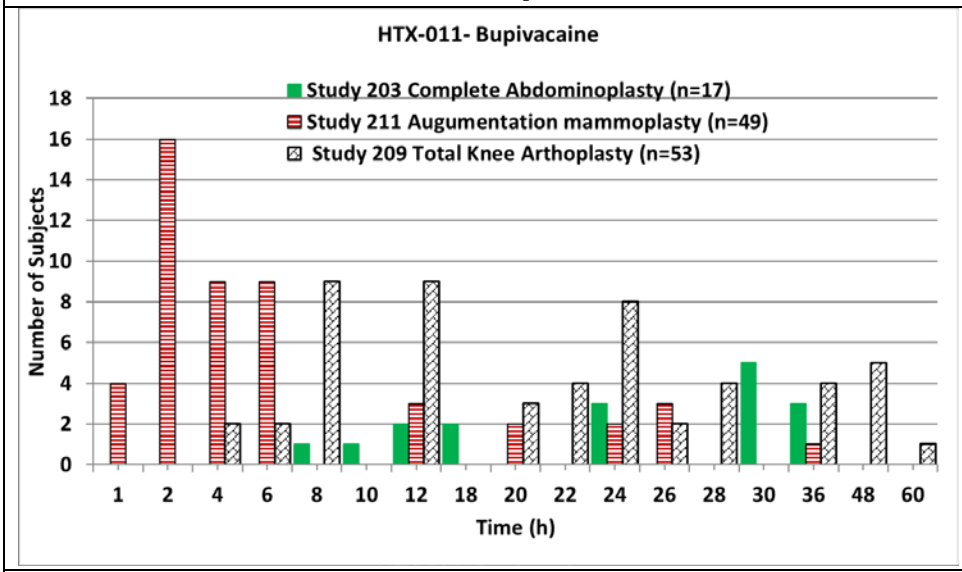
Tmax comparison of bupivacaine and meloxicam from HTX 400 mg/12 mg dose between different surgical procedures:

Tmax comparison for bupivacaine and meloxicam from HTX 400 mg/12 mg dose between different surgical procedures is shown in Figure 1.3.5c. The median (min, max) of bupivacaine and meloxicam is as below:

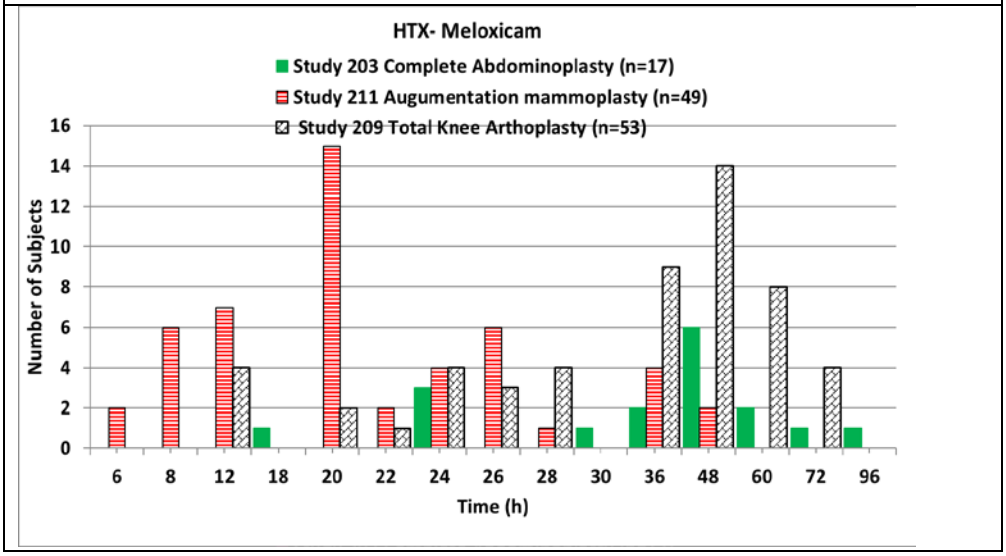
Moiety	**Tmax: Median (min, max)**		
	Complete abdominoplasty	**Augmentation mammoplasty**	**Total Knee Arthroplasty**
Bupivacaine	25 [9, 38]	04 [1, 35]	21 [4, 59]
Meloxicam	24 [9, 96]	20 [6, 49]	36 [12, 72]

Figure 1.3.5c: Tmax comparison of bupivacaine and meloxicam from HTX 400 mg/12 mg dose between different surgical procedures

HTX-011 Bupivacaine



HTX-011 Meloxicam



Tmax Conclusions:

- For HTX-011 400 mg/12 mg, between different procedures, Tmax of bupivacaine ranges between 1h and 59 h, while Tmax of meloxicam ranges between 6h and 96 h.
- When two moieties released for HTX-011 were compared, the median Tmax of bupivacaine was quicker for augmentation mammoplasty compared to other two procedures, while median Tmax of meloxicam occurred beyond 20 h for all procedures and did not appear to differ much between procedures. It is to note that for augmentation mammoplasty, the dose was divided, 200 mg/6 mg per side and is separated in time (sided procedures performed sequentially, not simultaneously).
- Overall differences in Tmax for bupivacaine or meloxicam from HTX-011 between procedures can be attributed to anatomical site, surgical site, surgical procedure and way the HTX-011 dose was instilled.

Reviewer's comments for HTX-011 (b) (4)

- (b) (4)

1.3.6. PK dose linearity assessment of HTX-011

1.3.6.1 Applicant's PK dose linearity assessment of HTX-011 between different doses and different procedures:

In the NDA submission, applicant attempted the PK dose-linearity assessment of bupivacaine and meloxicam of HTX-011. The dose-linearity assessment was done between different procedures with different modes of administration, such as injection, nerve block, combination of instillation and injection. In conclusion, applicant mentioned that "mean Cmax and AUC for bupivacaine and meloxicam increased linearly with dose at HTX-011 doses ranging from 60 mg/1.8 mg to 400 mg/12 mg regardless of the anatomic space, vascularity of the surgical site, or administration technique".

In applicant's dose-linearity analyses, different modes of HTX-011 administration, between different procedures were included, which is scientifically inappropriate. In addition, since the PK profiles of HTX-011 are different from procedures for the same dose, the PK linearity should be compared within a procedure. This will eliminate the confounding factor of differences between procedures. Hence, the PK dose linearity of within procedure that used

instillation mode of administration was compared (final proposed mode of HTX-011 administration).

1.3.6.2 Reviewer's within procedure PK dose linearity assessment of HTX-011 by instillation mode of administration:

Out of all procedures, bunionectomy and herniorrhaphy studied two doses, administered by instillation. It is to be noted that, in general to evaluate dose-linearity, at least three doses are recommended. Since only two doses are available, the PK parameter ratios of two doses in bunionectomy and herniorrhaphy are evaluated.

Purpose: HTX-011 is a single dose peri-operative ER solution product. The proposed maximum dose-volume in bunionectomy and herniorrhaphy are up to 2.3 mL (60 mg/1.8 mg) and up to 10.5 mL (300 mg/9 mg), respectively. Since it is "up to", it is not a fixed volume of drug for every subject, however the maximum limit was set to 2.3 mL and 10.5 mL, respectively in bunionectomy and herniorrhaphy. Hence, there is a chance that some-patients may require a lower volume of drug (a lower dose) than the maximum set limit. The purpose of dose-linearity evaluation of HTX-011 of within-procedure is to understand PK behavior of this peri-operative product after different doses.

Dose- linearity assessment in Bunionectomy:

In bunionectomy (Study 208), two doses of HTX-011 by instillation were studied in three treatments, as follows:

- 60 mg/1.8 mg instillation 'with' cone-shaped applicator (n=17)
- 120 mg/3.6 mg instillation 'with' cone-shaped applicator (n-18)
- 120 mg/3.6 mg instillation 'without' cone-shaped applicator (n=19)

(b) (4)

(b) (4) cone-shaped applicator

Note: Of the two doses above, for bunionectomy, up to 2.3 mL (60 mg/1.8 mg) by instillation is the proposed labeled dose.

PK parameters of bupivacaine and meloxicam from two doses of HTX-011 administered by instillation in bunionectomy are shown in Table 1.3.6.2a and Table 1.3.6.2b, respectively. The higher dose, 120 mg/ 3.6 mg instilled as two separate treatments, one with cone-shaped applicator and another without cone-shaped applicator.

Table 1.3.6.2a: PK parameters of bupivacaine from two doses of HTX-011 administered by instillation in bunionectomy (Study 208). The higher dose, HTX 011 120 mg/ 3.6 mg instilled as two separate treatments, with cone and without cone-shaped applicator.

Surgical Procedure	**Bupivacaine from HTX-011 (Bunionectomy, Study 208)**			**Ratio**	
	60 mg/1.8 mg instillation 'with' cone-shaped applicator	**120 mg/3.6 mg instillation 'with' cone-shaped applicator**	**120 mg/3.6 mg instillation 'without' cone-shaped applicator**	**Treatment B/A**	**Treatment B/C**
Treatment	Treatment A	Treatment B	Treatment C		
N	17	18	19		
Cmax (ng/mL)	54 ± 33 (61)	114 ± 113 (99)	80 ± 101 (127)	2.1	1.4
AUC_{0-t} (h·ng/mL)	1681 ± 1154 (69)	3739 ± 3049 (82)	2817 ± 3635 (129)	2.2	1.3
AUC_{inf} (h·ng/mL)	1718 ± 1211 (70)	3690 ± 3010 (82)	2844 ± 3676 (129)	2.2	1.3
Tmax (h)	13 [1.55, 24]	6 [1.4, 24]	8 [2, 30]		
Half-life (h)	15 ± 8	15 ± 5	13 ± 3		

PK parameters values are arithmetic mean ± standard deviation (% CV)

Table 1.3.6.2b: PK parameters of meloxicam from two doses of HTX-011 administered by instillation in bunionectomy (Study 208). The higher dose, HTX 011 120 mg/ 3.6 mg instilled as two separate treatments, one with cone and another without cone-shaped applicator

Surgical Procedure	**Meloxicam from HTX-011 in Bunionectomy**			**Ratio**	
	60 mg/1.8 mg instillation 'with' cone-shaped applicator	**120 mg/3.6 mg instillation 'with' cone-shaped applicator**	**120 mg/3.6 mg instillation 'without' cone-shaped applicator**	**Treatment B/A**	**Treatment B/C**
Treatment	Treatment A	Treatment B	Treatment C		
N	16	18	19		
Cmax (ng/mL)	26 ± 14 (54)	47 ± 30 (65)	35 ± 44 (125)	1.8	1.3
AUC_{0-t} (h·ng/mL)	1621 ± 927 (57)	3104 ± 1827 (59)	2262 ± 2643 (117)	1.9	1.4
AUC_{inf} (h·ng/mL)	2079 ± 1631 (78)	3661 ± 2391 (65)	2414 ± 2944 (122)	1.8	1.5
Tmax (h)	18 [8.1, 60]	18 [5, 48]	18 [8.1, 72]		
Half-life (h)	33 ± 36	32 ± 14	23 ± 7		

PK parameters values are arithmetic mean ± standard deviation (% CV)

Based on observed PK parameters in bunionectomy, the following conclusions are made:

- Two doses of HTX-011, 60/1.8 mg and 120/3.6 mg instilled with cone-shaped applicator exhibited dose-linear PK for both meloxicam and bupivacaine, based on mean Cmax and AUC ratios (Column 5, in Tables 1.3.6.2a and 1.3.6.2b.)

- Instillation of HTX-011 with cone-shaped applicator results in 40% and 30% higher Cmax and AUC0-t for bupivacaine, respectively; and 30% and 40% higher Cmax and AUC0-t of meloxicam, respectively compared to without cone-shaped applicator (Column 6, in Tables 1.3.5.2a and 1.3.5.2b.).
- Instillation of HTX-011 results in lower coefficient of variation in bupivacaine and meloxicam Cmax and AUC0-t, when instilled with cone-shaped applicator (% CV range, 59 to 99%) compared to without cone-shaped applicator (% CV range,117 to 129%).

Dose-linearity assessment in Herniorrhaphy:
In herniorrhaphy (Study 202), three doses of HTX-011 by instillation were studied in three treatments, as follows:

- 200 mg/6 mg by instillation (n=16)
- 300 mg/9 mg by instillation plus fentanyl 50 mcg IV (n=16)
- 400 mg/12 mg by instillation (n=16)
- 400 mg/12 mg by instillation plus fentanyl 50 mcg IV (n=5)

Note: Of the doses above, for herniorrhaphy, up to 10.5 mL (300 mg/9 mg) by instillation plus fentanyl 50 mcg IV is the proposed labeled dose.

PK parameters of bupivacaine and meloxicam from three doses of HTX-011 administered by instillation in herniorrhaphy are shown in Table 1.3.5.2c and Table 1.3.5.2d, respectively.

Table 1.3. 6.2c: PK parameters of bupivacaine from three doses of HTX-011 administered by instillation in herniorrhaphy (Study 202).

Surgical Procedure	**Bupivacaine from HTX-011 (Herniorrhaphy, Study 202)**				**Ratio**
	200 mg/6 mg by instillation	**300 mg/9 mg by instillation plus fentanyl 50 mcg IV**	**400 mg/12 mg by instillation**	**400 mg/12 mg by instillation plus fentanyl 50 mcg IV**	**Treatment C/A**
Treatment	Treatment A	Treatment B	Treatment C	Treatment D	
N	16	16	16	5	
Cmax (ng/mL)	279 ± 105 (38)	271 ± 147 (54)	553 ± 238 (43)	693 ± 800 (115)	1.98
AUC_{0-t} (h·ng/mL)	13447 ± 5232 (39)	15174 ± 8545 (56)	28015 ± 14726 (53)	37818 ± 39606 (105)	2.08
AUC_{inf} (h·ng/mL)	13470 ± 5228 (39)	15524 ± 8922 (57)	28236 ± 14771 (52)	37970 ± 39568 (104)	2.09
Tmax (h)	24 [3.9, 48]	18 [3.1, 30.3]	18 [6.2, 60.1]	18 [3.1, 48.1]	
Half-life (h)	9 ± 3	16 ± 9	13 ± 4	11 ± 4	

PK parameters values are arithmetic mean ± standard deviation (% CV)

Table 1.3.6.2d: PK parameters of meloxicam from three doses of HTX-011 administered by instillation in herniorrhaphy (Study 202).

Surgical Procedure	**Meloxicam from HTX-011 (Herniorrhaphy, Study 202)**				**Ratio**
	200 mg/6 mg by instillation	**300 mg/9 mg by instillation plus fentanyl 50 mcg IV**	**400 mg/12 mg by instillation**	**400 mg/12 mg by instillation plus fentanyl 50 mcg IV**	**Treatment C/A**
Treatment	Treatment A	Treatment B	Treatment C	Treatment D	
N	16	16	16	5	
C_{max} (ng/mL)	164 ± 48 (29)	225 ± 96 (43)	330 ± 69 (21)	298 ± 103 (35)	2.06
AUC_{0-t} (h·ng/mL)	12028 ± 3227 (27)	18721 ± 7923 (42)	25293 ± 5669 (22)	25203 ± 7614 (30)	2.10
AUC_{inf} (h·ng/mL)	13318 ± 3959 (30) (n=14)	NC	27959 ± 7030 (25) (n=15)	NC	2.09
Tmax (h)	60[30, 72]	54 [24, 96]	48 [12, 72]	72 [18, 97]	
Half-life (h)	23 ± 7	NC	26 ± 7	NC	

PK parameters values are arithmetic mean ± standard deviation (% CV)
NC: Not calculated, because terminal elimination phase was not captured in a sufficient number of patients

In this study, the following comparisons were attempted:

- dose-linearity assessment
  - 400 mg /12 mg plus fentanyl 50 mcg IV (n=5) Versus 300 mg /12 mg by instillation plus fentanyl 50 mcg IV (n=16)
  - 400 mg /12 mg by instillation (n=16) Versus 200 mg /6 mg by instillation (n=16)

- instillation with and without fentanyl assessment
  - 400 mg /12 mg plus fentanyl 50 mcg IV (n=5) Versus 400 mg /12 mg by instillation (n=16)

From the obtained PK parameters in herniorrhaphy, the following conclusions are made:

- Two doses of HTX-011, 200 mg /6 mg and 400 mg /12 mg administered by instillation exhibited dose-linear PK for both meloxicam and bupivacaine, based on the mean Cmax and AUC ratios (Column 6, in Tables 1.3.5.2c and 1.3.5.2d.)
- No comparisons involving '400 mg /12 mg plus fentanyl 50 mcg IV treatment arm was made. It is because 1) in '400 mg /12 mg plus fentanyl 50 mcg IV treatment arm, there were only 5 subjects. In contrast, other treatment arms had adequate number of subjects, n=16, and 2) PK parameters of '400 mg /12 mg plus fentanyl 50 mcg IV treatment arm showed high variability, based on % CV, ranging from 104 to 115% compared to the other treatment arms, ranging from 38 to 56%.

1.3.7. QT review

QT Interdisciplinary Review Team evaluated the effect of ZYNRELEF on cardiac repolarization as assessed by the QTc interval following a single administration in patients undergoing surgical procedures. As their review, ZYNRELEF, at single doses up to the maximum recommended dose, did not demonstrate an effect on the QTc interval. The review can be found in DARRTS dated 02/01/2019.

1.3.8. Population Pharmacokinetic Analyses

Applicant proposes to add the following statement to section 12.3 Specific Populations: "Based on the population pharmacokinetic analysis, age, sex, race, and ethnicity do not have a clinically meaningful effect on the pharmacokinetics of bupivacaine and meloxicam in ZYNRELEF".

Based on Pharmacometrics team review, the above statement is acceptable. Their review is included in Section 5 of this review

Summary of findings:

- Clinical bridge:
    - Across five PK studies, when the highest observed bupivacaine exposure was compared between HTX-011 and reference drug, bupivacaine HCl, both Cmax and AUC values of bupivacaine from HTX-011 are higher compared to bupivacaine HCl. For the to be approved herniorrhaphy procedure with 300 mg/9 mg dose, the Cmax is lower, while AUC is higher for HTX-011 compared to bupivacaine HCl.
    - When the Cmax and AUC of meloxicam of HTX-011 is compared to the PK parameters of MOBIC, both Cmax and AUC of meloxicam from HTX-011 are lower than that of MOBIC.
- Among the three surgical procedures (i.e. augmentation mammoplasty, complete abdominoplasty, total knee arthroplasty) that used same dose of HTX-011 400 mg/12 mg, the systemic exposure in terms of Cmax and AUC is different. Systemic absorption of bupivacaine or meloxicam from HTX-011 is dependent upon surgical site, surgical procedure and the vascularity of the administration site.
- Within procedure administration of HTX-011 by instillation exhibits dose-linear PK for both meloxicam and bupivacaine (based on two doses in bunionectomy and herniorrhaphy)
- Instillation of HTX-011 with cone-shaped applicator results in higher exposure (Cmax and AUC) and lower coefficient of variation for both bupivacaine and meloxicam compared to without cone-shaped applicator.

- Based on QT Interdisciplinary Review Team review, ZYNRELEF, at single doses up to the maximum recommended dose, did not demonstrate an effect on the QTc interval.
- Based on Pharmacometrics team review on the population pharmacokinetic analysis, the age, sex, race, and ethnicity do not have a clinically meaningful effect on the pharmacokinetics of bupivacaine and meloxicam in ZYNRELEF
- (b) (4)

2.0 Question Based Review

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the formulation of the drug product?

Drug product (Source Module 3.2.P.1)
HTX-011 is an extended-release solution containing a fixed-dose combination of bupivacaine and meloxicam that is intended for single-dose local administration by instillation into the surgical site. HTX-011 is filled in a 10 mL or 20 mL vial. The HTX-011 vials are supplied in a co-packaged combination product kit with device components for preparation and administration. The composition of HTX-011 is shown in Table 2.1.1a. The unit composition of filled into vials is described in Table 2.1.1b.

Table 2.1.1a: Composition of HTX-011 Extended-Release Solution

Component	Concentration (% w/w)	Concentration (mg/g)	Concentration (mg/mL)	Function	Reference to Quality Standard
Bupivacaine base	2.50	25.0	29.25	Active ingredient	Manufacturer
Meloxicam	0.075	0.75	0.88	Active ingredient	USP, Ph Eur
AP135	62.375	623.75	729.788	Release-controlling polymeric excipient	Manufacturer
Dimethyl sulfoxide	10.00	100	117	(b) (4)	USP, Ph Eur
Triacetin	25.00	250	292.5		USP, Ph Eur
Maleic acid	0.05	0.5	0.585		NF, Ph Eur
Totals	**100.00**	**1000.0**	**1170**		

Abbreviations: AP135, tri(ethylene glycol) poly(orthoester); USP, United States Pharmacopeia; Ph Eur, European Pharmacopoeia; NF, National Formulary

Table 2.1.1b: Unit Composition for HTX-011 Extended-Release Solution

Bupivacaine (mg)	Meloxicam (mg)	Vial Size (mL)	Maximum Intended Dose Volume (mL)
60	1.8	10	2.0
200	6		6.7
400	12	20	13.5

2.1.2 What are the proposed mechanism of action and therapeutic indication(s)?

HTX-011 contains bupivacaine and meloxicam (b) (4)

- **Bupivacaine:** Local anesthetics such as bupivacaine block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential.
- **Meloxicam:** The mechanism of action of meloxicam, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

2.1.3 What are the proposed dosage and route of administration?

Applicant proposed a maximum dose of 400 mg/ 12 mg (bupivacaine /meloxicam). This dose was evaluated in Phase 2 trials in three surgical procedures with limited number of subjects with PK sampling, in augmentation mammoplasty (N=49), complete abdominoplasty (N=17) and total knee arthroplasty (TKA) (N=53). The Phase 3 studies was conducted for two surgical procedures, bunionectomy (60 mg/1.8 mg; n=157) and herniorrhaphy (300 mg/9 mg; n=161).

These two studies utilized pop-PK sampling with 4 samples (4, 18, 24, and 48 hours post-dose) collected from each subject.

The proposed route of administration of HTX-011 is application by instillation without a needle into the surgical site following final irrigation and suction and prior to suturing into surgical wound.

2.1.4 What are the core studies submitted in this NDA?

The clinical program for HTX-011 consisted of Phase 2 and Phase 3 clinical studies in surgical procedures, with PK sampling and is shown in Table 2.14. In all clinical studies, reference drug, bupivacaine HCl was administered as a separate treatment arm. For Phase 2 studies, for both HTX-011 and bupivacaine HCl, full PK sampling from 0 to 120 h, except for study 209, where it was 0 to 240 h, was conducted. For Phase 3 studies, HTX-011 and bupivacaine HCl had population-PK sampling with 4 samples collected from each subject.

For HTX-011, Applicant has evaluated other modes of administration in some clinical studies, in addition to the instillation. Since the final proposed mode of administration for HTX-011 is 'instillation', the PK parameters of instillation mode of administration is only reported in this review. From Phase 2 studies, the PK parameters of final to be marketed formulation, HTX-011-56 were reported in this review. The dose and number of subjects for each study are shown in Table 2.1.4.

For bupivacaine HCl, strength, dose, and administration procedure in each surgical procedure are shown in Table 2.1.4.

Table 2.1.4: Clinical studies of HTX-011 in surgical procedures.

Study (Phase)	Surgical Procedure	Dose (N) and administration procedure		Type and duration of PK sampling
		HTX-011 (bupivacaine/meloxicam)	Bupivacaine HCl	
Study 202 (P2)	Herniorrhaphy	300 mg/ 9 mg (N=16); Instillation plus, fentanyl 50 mcg IV	75 mg (0.25%) (N=17); Infiltration injection plus, fentanyl 50 mcg IV	Full PK, 120 h
Study 208 (P2)	Bunionectomy	60 mg/ 1.8 mg (N=17); Instillation	50 mg (0.5%) (N=25); Infiltration injection (with or without using Mayo block)	Full PK, 120 h
Study 211 (P2)	Augmentation Mammoplasty	400 mg/ 12 mg (N=49); Instillation	50 mg (0.25%) (N=41); Nerve block	Full PK, 120 h
Study 209 (P2)	Total Knee Arthroplasty	400 mg/ 12 mg (N=53); Instillation	125 mg (0.25%) (N=65); Injection	Full PK, 240 h
Study 203 (P2)	Complete Abdominoplasty	400 mg/ 12 mg (N=17); Instillation	100 mg (0.25%); (N=17, Part C) Infiltration injection	Full PK, 120 h
Study 302 (P3)	Herniorrhaphy	300 mg/ 9 mg (N=161); Instillation	75 mg (0.25%); Injection	Population-PK * (4 samples)
Study 301 (P3)	Bunionectomy	60 mg/ 1.8 mg (N=157); Instillation	50 mg (0.5%); Injection	Population-PK * (4 samples)

* Population PK sampling was conducted for HTX-011 and bupivacaine HCl.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Table 2.1.4 above shows the clinical studies conducted for this application. In all these studies, a single dose of HTX-011 is administered by instillation without a needle into the surgical site following final irrigation and suction and prior to suturing into surgical wound.

2.2.2. What are the characteristics of drug absorption? Is the PK of HTX-011 similar between surgical procedures that used same dose?

HTX-011 have been investigated in soft tissue (herniorrhaphy, augmentation mammoplasty) and bony (bunionectomy, TKA) surgical models covering different sizes and vascularity as shown in Table 2.2.2a. The rate of systemic absorption of bupivacaine or meloxicam of HTX-011 is dependent upon total dose of drug administered, the route of administration, and vascularity of the administration site. Hence the absorption of bupivacaine and meloxicam from

HTX-011 in different surgical procedures will result different exposures, even if it is the same dose.

Table 2.2.2: Surgical procedures in the HTX-011

Study or Studies	Surgical Procedure	Type of Model	Anatomic Space
301, 208	Bunionectomy	Bony	Small
302, 202	Herniorrhaphy (open)	Soft tissue	Medium
211	Augmentation mammoplasty	Soft tissue	Large
209	Total knee arthroplasty	Bony	Large
203	Abdominoplasty	Soft tissue	Large

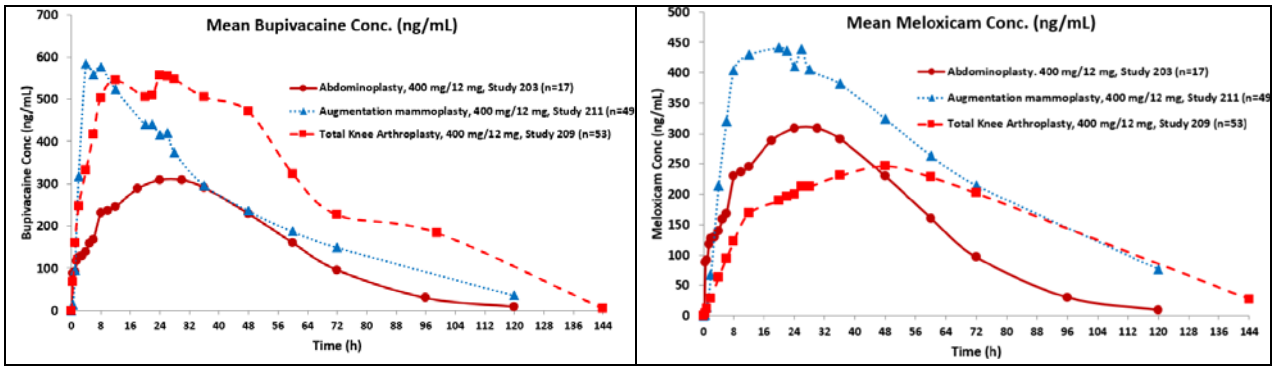
A comparison of bupivacaine and meloxicam pharmacokinetics of HTX-011 that used same dose was done to see the differences between procedures.

The following three surgical procedures used same highest dose of HTX-011, 400 mg bupivacaine/ 12 mg meloxicam.

Type of Model and Anatomical space	Surgical Procedure
Soft tissue, large anatomical space	Augmentation mammoplasty (N=49) Complete abdominoplasty (N=17)
Bony tissue, large anatomical space	Total knee arthroplasty (TKA) (N=53)

The comparison was done between PK profiles, individual concentrations at each time point, and PK parameters between three procedures. The mean bupivacaine and meloxicam concentration profiles of HTX-011 in surgical procedures that used HTX-011 400 mg/12 mg dose is shown in Figure 2.2.2a. As can be noted, for 400 mg/12 mg dose of HTX-011, between different surgical procedures, the PK profiles of bupivacaine or meloxicam are different. For example, between soft tissues procedures, the bupivacaine Tmax is earlier and Cmax is higher in augmentation mammoplasty (blue triangles profile), compared to complete abdominoplasty (brown circles profile). The resulting systemic exposure (AUC and Cmax) for both bupivacaine and meloxicam are different between two procedures.

Figure 2.2.2a: Mean bupivacaine and meloxicam concentration profiles of HTX-011 in surgical procedures that used HTX-011 400 mg/12 mg dose.



Notes: The PK sampling was 0 to 120 h post-dose for augmentation mammoplasty and complete abdominoplasty, while 240h post dose for total knee arthroplasty (till 144 h profile was shown)

The PK parameters of meloxicam and bupivacaine are shown above in Tables 1.3.1a and 1.3.1b, respectively. The scatter-plot of bupivacaine and meloxicam concentrations at each time point in individual subjects in surgical procedures that used HTX-011 400 mg/12 mg dose is shown in figures 2.2.2b and 2.2.2c, respectively.

Figure 2.2.2b: Scatter-plot of bupivacaine concentrations at each time point in individual subjects in surgical procedures that used HTX-011 400 mg/12 mg dose

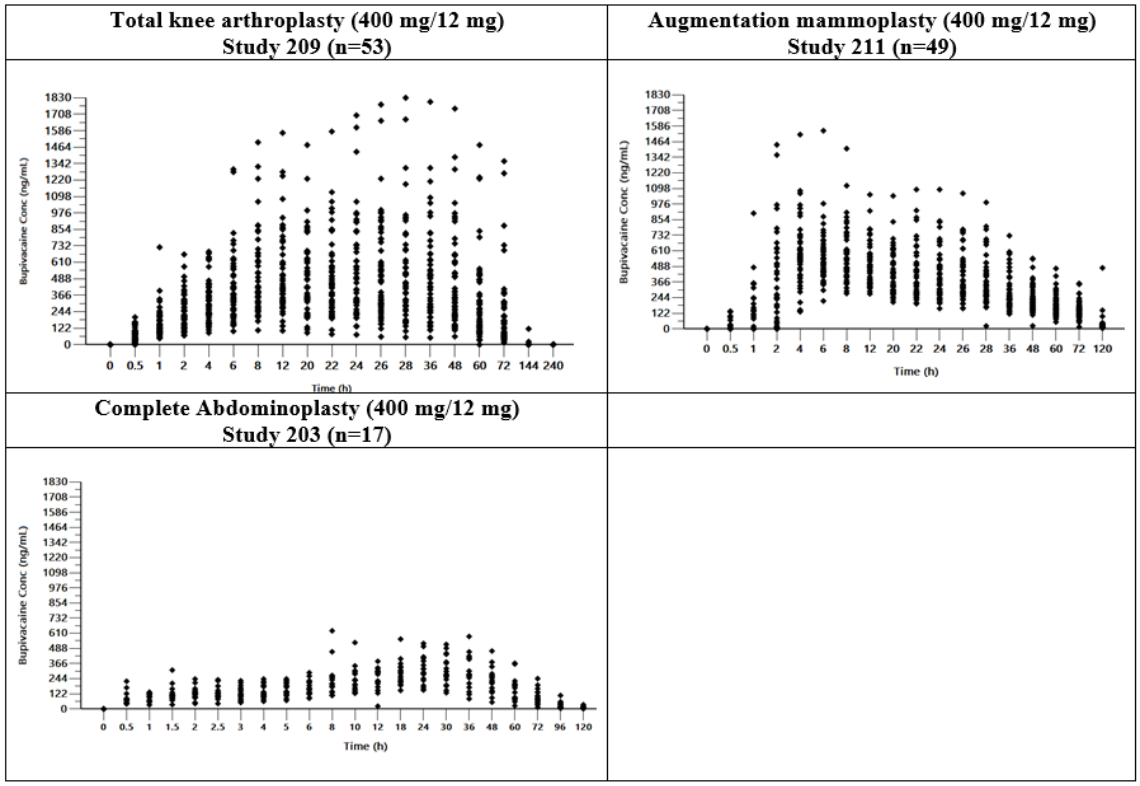
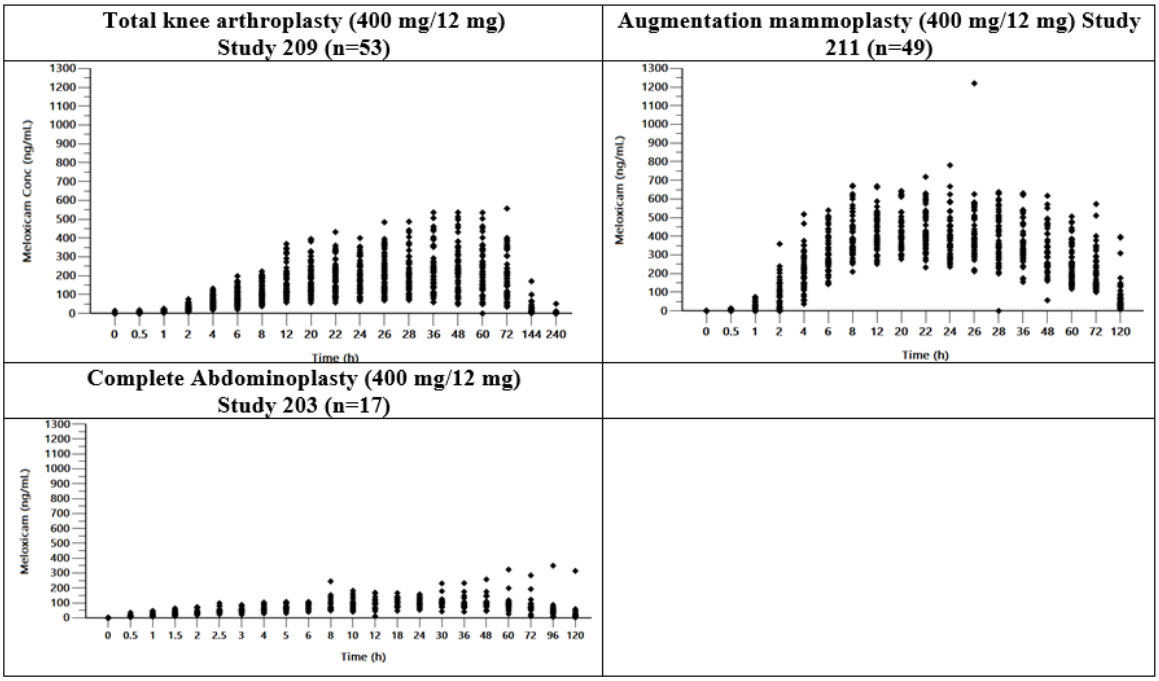


Figure 2.2.2c: Scatter-plot of meloxicam concentrations at each time point in individual subjects in surgical procedures that used HTX-011 400 mg/12 mg dose



Some example PK parameters differences between procedures that used same dose in are presented as below:

- **Comparison between soft tissue procedures (abdominoplasty vs. mammoplasty):**
  - Mean bupivacaine Cmax and AUCt were ~49% and 34%, and while meloxicam was ~73 and 67%, respectively lower for abdominoplasty compared to mammoplasty
- **Comparison between soft tissue vs. bony tissue (TKA vs. abdominoplasty or mammoplasty):**
  - Mean bupivacaine Cmax and AUCt were ~90% and 100% higher, respectively for TKA compared to abdominoplasty
  - Mean bupivacaine Cmax was approximately equal, while AUCt is 31% higher for TKA compared to mammoplasty
  - Mean meloxicam Cmax and AUCt were ~94% and 95% higher, respectively for TKA compared to abdominoplasty
  - Mean meloxicam Cmax and AUCt were ~48% and 36% lower, respectively for TKA compared to mammoplasty

Conclusions of PK comparison between procedures that used HTX-011400 mg/12 mg:

- The comparison shows that, between surgical procedures that used same dose of HTX-011 400 mg/12 mg, the systemic exposure is different. Based on this, it can be concluded that the systemic absorption of bupivacaine or meloxicam of HTX-011 is dependent

upon type of surgical procedure, surgical site and the vascularity of the administration site.

Tmax comparison of bupivacaine and meloxicam from HTX 400 mg/12 mg dose between different surgical procedures:

Tmax comparison for bupivacaine and meloxicam from HTX 400 mg/12 mg dose between different surgical procedures is shown is as below:

Moiety	**Tmax: Median (min, max)**		
	Complete abdominoplasty	**Augmentation mammoplasty**	**Total Knee Arthroplasty**
Bupivacaine	25 [9, 38]	04 [1, 35]	21 [4, 59]
Meloxicam	24 [9, 96]	20 [6, 49]	36 [12, 72]

Tmax Conclusions:

- For HTX-011 400 mg/12 mg, between different procedures, Tmax of bupivacaine ranges between 1h and 59 h, while Tmax of meloxicam ranges between 6h and 96 h.
- When two moieties released for HTX-011 were compared, the median Tmax of bupivacaine was quicker for augmentation mammoplasty compared to other two procedures, while the median Tmax of meloxicam occurred beyond 20 h for all procedures and did not appear to differ much between procedures. It is to note that for augmentation mammoplasty, the dose was divided, 200 mg/6 mg per side and is separated in time (sided procedures performed sequentially, not simultaneously).
- Overall differences in Tmax for bupivacaine or meloxicam from HTX-011 between procedures can be attributed to anatomical site, surgical procedure and way the HTX-011 dose was instilled.

2.2.3 What are the general PK characteristics of the drug?

For the general PK characteristics with respect to bupivacaine and meloxicam, the information from MARCAINE and MOBIC labels may be referred.

2.2.4 What are the single dose and multiple dose PK parameters?

The HTX-011 is for single dose administration only. The PK after single dose in different surgical procedures is described in 2.4.1

2.4 General Biopharmaceutics

2.4.1. What is the relative bioavailability of bupivacaine and meloxicam from HTX-011 compared to the listed drugs, MARCAINE and MOBIC?

Applicant has conducted 5 clinical studies in surgical procedures for HTX-011, which included reference drug, bupivacaine HCl as a treatment arm. These 5 clinical studies have full PK

sampling. The dose, mode of administration for HTX-011 and bupivacaine HCl is shown in Table 2.4.1.

Table 2.4.1a: Clinical studies of HTX-011 (bupivacaine/meloxicam) and bupivacaine HCl in surgical procedures with PK sampling.

Study (Phase)	**Surgical Procedure**	**HTX-011 dose (bupivacaine/meloxicam) by instillation**	**Bupivacaine HCl**	
			Strength	**Dose, mode of administration)**
Study 202 (P2)	Herniorrhaphy	300 mg/ 9 mg	0.25%	75 mg, Infiltration injection plus, fentanyl 50 mcg IV
Study 208 (P2)	Bunionectomy	60 mg/ 1.8 mg	0.5%	50 mg, Infiltration injection (with or without using Mayo block)
Study 203 (P2)	Complete Abdominoplasty	400 mg/ 12 mg	0.25%	100 mg, Infiltration injection
Study 209 (P2)	Total Knee Arthroplasty	400 mg/ 12 mg	0.25%	125 mg, Injection
Study 211 (P2)	Augmentation Mammoplasty	400 mg/ 12 mg	0.25%	50 mg, Nerve block

The ratio of means of bupivacaine Cmax and AUCinf (HTX-011 / bupivacaine HCl) in each study are shown in Table 2.4.1 below.

Table 2.4.1b: Cmax and AUCinf comparison between bupivacaine from HTX-011 and bupivacaine HCl in each study

Surgical Procedure	**Bupivacaine Cmax ratio (HTX-011/ Bupivacaine HCl)**	**Bupivacaine AUC ratio (HTX-011/ Bupivacaine HCl)**
Herniorrhaphy, Study 202	1.38	6.61
Bunionectomy, Study 208	0.24	0.63
Complete Abdominoplasty, Study 203	0.76	3.31
Total Knee Arthroplasty, Study 209	1.74	5.38
Augmentation Mammoplasty, Study 211	2.08	9.96

Overall, bupivacaine Cmax of HTX-011 in comparison to bupivacaine HCL is lower in bunionectomy and complete abdominoplasty whilst higher in all other three studies. The bupivacaine AUCinf of HTX-011 in comparison to bupivacaine HCL is lower in bunionectomy whilst higher in all other four studies.

The PK profiles, PK parameters in each individual study is presented below in subsections.

2.4.1.1. Phase 2 Study 202: Herniorrhaphy

The PK parameters of bupivacaine and meloxicam from HTX-011 (300 mg/9 mg) and bupivacaine from bupivacaine HCl (75 mg) in herniorrhaphy (Study 202) is shown in Table 2.4.1.1. The PK profiles and Tmax comparison is shown in Figure 2.4.1.1a. and 2.4.1.1b, respectively.

Both Cmax and AUC of bupivacaine from HTX-011 is higher than bupivacaine of bupivacaine HCl in herniorrhaphy.

Table 2.4.1.1: PK parameters of bupivacaine and meloxicam from HTX-011 and bupivacaine from bupivacaine HCl in herniorrhaphy (Study 202).

Study 202: Herniorrhaphy			
Parameter **Athematic Mean ± SD**	**HTX-011** **300 mg/9 mg in 10.3 mL**		**Bupivacaine HCl** **75 mg (0.25%)**
How administered	**Instillation** **plus, fentanyl 50 mcg IV**		**Infiltration injection** **plus, fentanyl 50 mcg IV**
Analyte	**Bupivacaine (n=16)**	**Meloxicam (n=16)**	**Bupivacaine (n=17)**
PK sampling duration (h)	120	120	120
Cmax (ng/mL)	271 ± 147	225 ± 96	196 ± 97
AUC0-24 (ng/mL*h)	4712 ± 2144	2569 ± 855	1697 ± 363
AUC0-48 (ng/mL*h)	9740 ± 5021	6996 ± 2685	2243 ± 501
AUC0-72 (ng/mL*h)	12980 ± 6687	11973 ± 4592	2336 ± 553
AUC0-t (ng/mL*h)	15174 ± 8545	18721 ± 7923	2345 ± 563
AUC (inf) (ng/mL*h)	15524 ± 8921	NC	2349 ± 564
t½ (h)	16 ± 9	NC	6 ± 2
Tmax (h)	18 [3, 30]	54 [24, 96]	0.5 [0.75, 24]

PK parameters values are arithmetic mean ± standard deviation, except for Tmax for which it is median (minimum, maximum)
NC: Not calculated, because terminal elimination phase was not captured in a sufficient number of patients

Figure 2.4.1.1a: PK profile of bupivacaine and meloxicam from HTX-011 and bupivacaine from bupivacaine HCl in herniorrhaphy (Study 202)

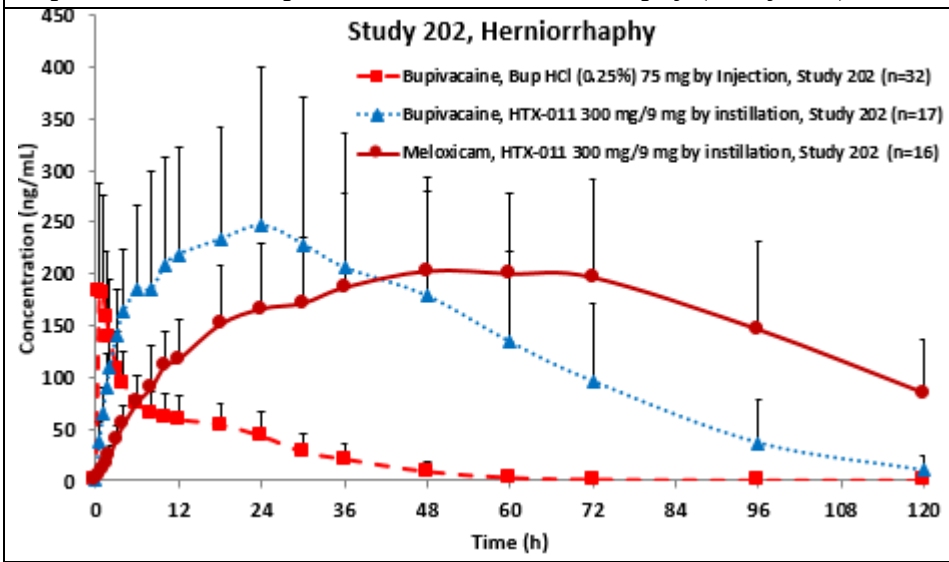
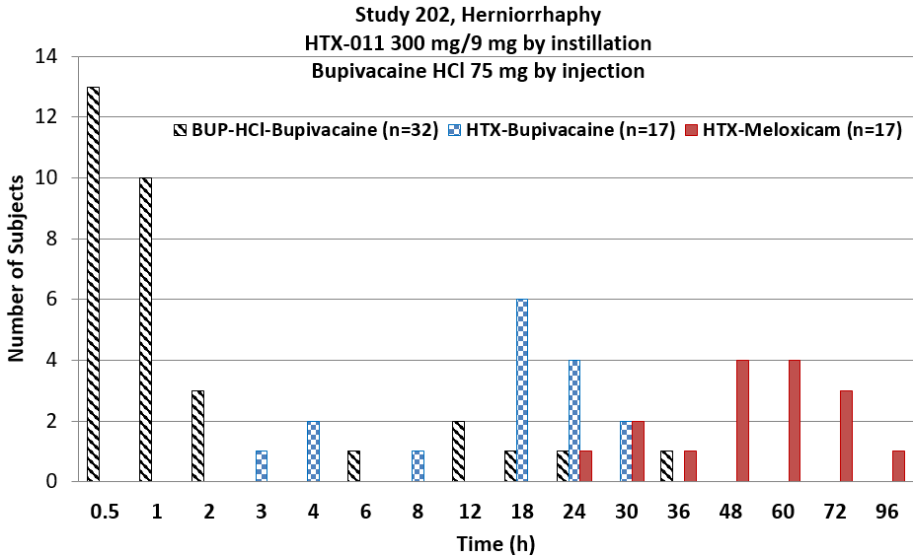


Figure 2.4.1.1b: Tmax of bupivacaine and meloxicam from HTX-011 and bupivacaine from bupivacaine HCl in herniorrhaphy (Study 202)



2.4.1.2. Phase 2 Study 208: Bunionectomy

The PK parameters of bupivacaine and meloxicam from HTX-011 (60 mg/1.8 mg) and bupivacaine from bupivacaine HCl (50 mg) in bunionectomy (Study 208) is shown in Table 2.4.1.2. The PK profiles and Tmax comparison is shown in Figure 2.4.1.2a. and 2.4.1.2b, respectively.

Both bupivacaine Cmax and AUC of HTX-011 is lower compared to bupivacaine HCl in bunionectomy.

Table 2.4.1.2: PK parameters of bupivacaine and meloxicam from HTX-011 and bupivacaine from bupivacaine HCl in bunionectomy (Study 208).

Study 208: Bunionectomy			
Parameter Athematic Mean ± SD	**HTX-011 60 mg/1.8 mg in 2.1 mL**		**Bupivacaine HCl 50 mg (0.5%)**
How administered	**Instillation**		**Infiltration injection**
Analyte	**Bupivacaine (n=17)**	**Meloxicam (n=16)**	**Bupivacaine (n=25)**
PK sampling duration (h)	120	120	120
Cmax (ng/mL)	54 ± 33	26 ± 14	228 ± 89
AUC0-24 (ng/mL*h)	883 ± 538	437 ± 250	2169 ± 903
AUC0-48 (ng/mL*h)	1371 ± 910	904 ± 516	2640 ± 1240
AUC0-72 (ng/mL*h)	1595 ± 1085	1285 ± 745	2717 ± 1327
AUC0-t (ng/mL*h)	1681 ± 1154	1621 ± 927	2735 ± 1356
AUC (inf) (ng/mL*h)	1718 ± 1211	2079 ± 1631	2745 ± 1357
t½ (h)	15 ± 8	33 ± 36	8 ± 2
Tmax (h)	3 [1.55, 24]	18 [8.13, 60]	1.32 [0.55, 8.1]

PK parameters values are arithmetic mean ± standard deviation, except for Tmax for which it is median (minimum, maximum)

Figure 2.4.1.2a: PK profile of bupivacaine and meloxicam from HTX-011 and bupivacaine from bupivacaine HCl in bunionectomy (Study 208)

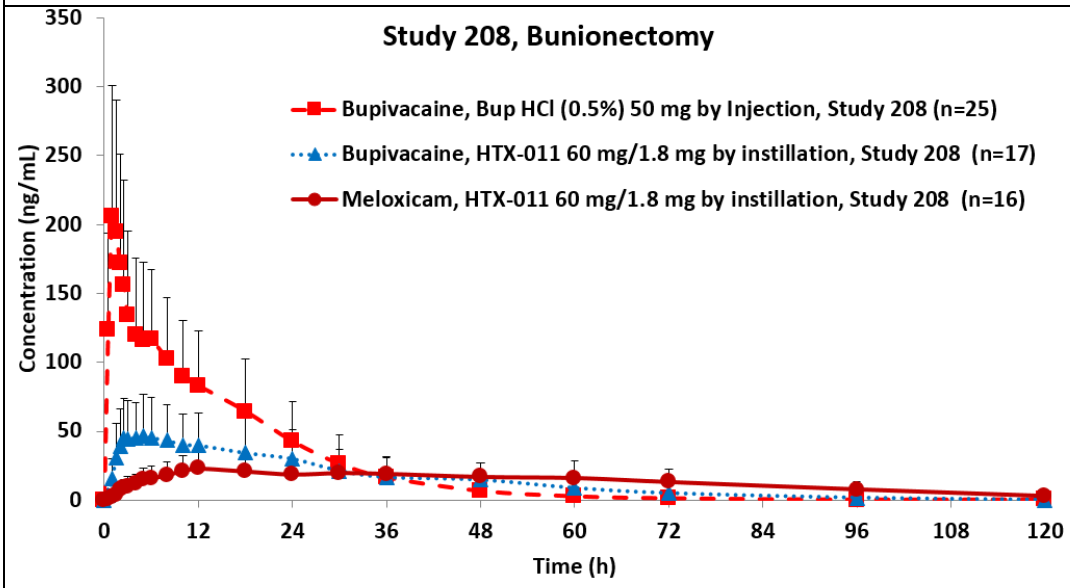
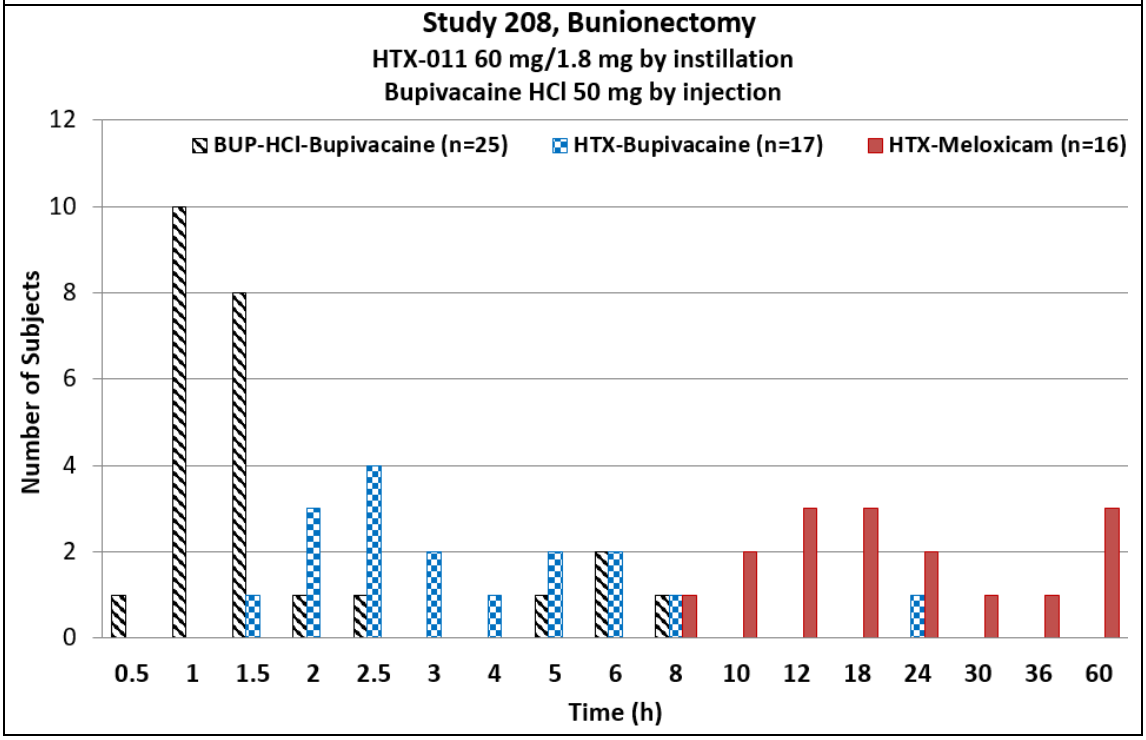


Figure 2.4.1.2b: Tmax of bupivacaine and meloxicam from HTX-011 and bupivacaine from bupivacaine HCl in bunionectomy (Study 208)



2.4.1.3. Phase 2 Study 203: Complete Abdominoplasty

The PK parameters of bupivacaine and meloxicam from HTX-011 and bupivacaine from bupivacaine HCl in complete abdominoplasty (Study 203) is shown in Table 2.4.1.3. The PK profiles and Tmax comparison is shown in Figure 2.4.1.3a. and 2.4.1.3b, respectively.

The bupivacaine Cmax is lower whilst AUC of HTX-011 is higher compared to bupivacaine HCl in complete abdominoplasty.

Table 2.4.1.3: PK parameters of bupivacaine and meloxicam from HTX-011 and bupivacaine from bupivacaine HCl in complete abdominoplasty (Study 203).

Study 203: Complete Abdominoplasty			
Parameter Athematic Mean ± SD	**HTX-011 400 mg/12 mg in 13.7 mL**		**Bupivacaine HCl, 100 mg (0.25%)**
How administered	**Intra-operatively by instillation**		**Infiltration injection**
Analyte	**Bupivacaine (n=17)**	**Meloxicam (n=17)**	**Bupivacaine (n=17)**
PK sampling duration (h)	120	120	120
Cmax (ng/mL)	366 ± 127	142 ± 72	479 ± 234
AUC0-24 (ng/mL*h)	5327 ± 1590	2016 ± 631	4069 ± 1622
AUC0-48 (ng/mL*h)	12090 ± 3939	4541 ± 1492	5217 ± 2204
AUC0-72 (ng/mL*h)	16051 ± 16051	6969 ± 2820	5445 ± 2328
AUC0-t (ng/mL*h)	18040 ± 6943	9997 ± 6045	5505 ± 2340
AUC (inf) (ng/mL*h)	18247 ± 7069	10069 ± 4123 (n=16)	5509 ± 2340
t½ (h)	14 ± 3	30 ± 23 (n=16)	12 ± 5
Tmax (h)	25 [9, 38]	24 [9, 97]	1.6 [0.48, 19]

PK parameters values are arithmetic mean ± standard deviation, except for Tmax for which it is median (minimum, maximum)

Figure 2.4.1.3a: PK profile of bupivacaine and meloxicam from HTX-011 and bupivacaine from bupivacaine HCl in complete abdominoplasty (Study 203)

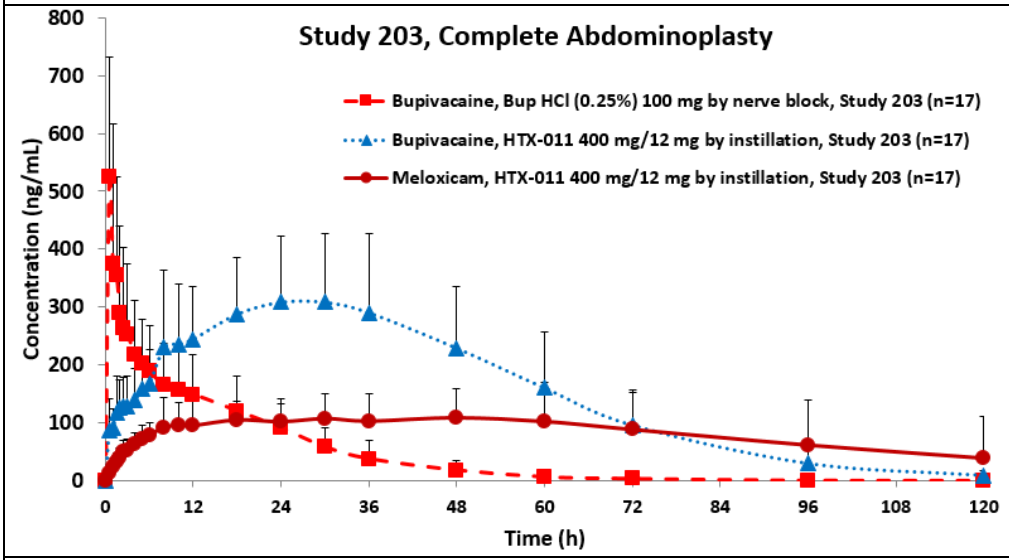
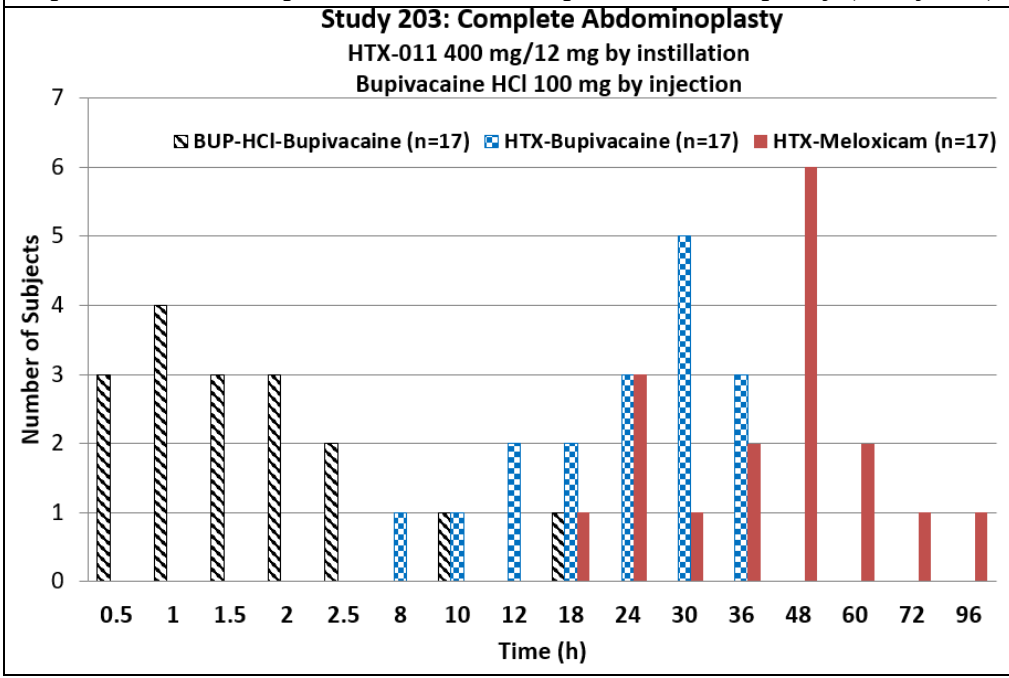


Figure 2.4.1.3b: Tmax of bupivacaine and meloxicam from HTX-011 and bupivacaine from bupivacaine HCl in complete abdominoplasty (Study 203)



2.4.1.4. Phase 2 Study 209: Total Knee Arthroplasty

The PK parameters of bupivacaine and meloxicam from HTX-011 and bupivacaine from bupivacaine HCl in total knee arthroplasty (Study 209) is shown in Table 2.4.1.4. The PK profiles and Tmax comparison is shown in Figure 2.4.1.4a. and 2.4.1.4b, respectively.

Both Cmax and AUC of bupivacaine from HTX-011 is higher than bupivacaine from bupivacaine HCl in total knee arthroplasty.

Table 2.4.1.4: PK parameters of bupivacaine and meloxicam from HTX-011 and bupivacaine from bupivacaine HCl in Total Knee Arthroplasty (Study 209).

Study 209: Total Knee Arthroplasty			
Parameter Athematic Mean ± SD	**HTX-011 400 mg/12 mg in 13.7 mL (without ropivacaine) [a]**		**Bupivacaine HCl, 125 mg (0.25%)**
How administered	**Instillation**		**Injection**
Analyte	**Bupivacaine (n=53)**	**Meloxicam (n=53)**	**Bupivacaine (n=65)**
PK sampling duration (h)	240 (144 and 240 h in 33 subjects)		120
Cmax (ng/mL)	695 ± 411	275 ± 134	399 ± 171
AUC0-24 (ng/mL*h)	11223 ± 6142	3350 ± 1442	4646 ± 2082
AUC0-48 (ng/mL*h)	23580 ± 14035	8926 ± 4102	6359 ± 3193
AUC0-72 (ng/mL*h)	30807 ± 20122 (n=50)	13483 ± 6625	6870 ± 3623
AUC0-t (ng/mL*h)	35890 ± 28400	19525 ± 12259	6862 ± 3618
AUC (inf) (ng/mL*h)	38173 ± 29400 (n=50)	25673 ± 17666 (n=35)	7097 ± 3898
t½ (h)	17 ± 7 (n=50)	42 ± 37 (n=35)	12 ± 4
Tmax (h)	21 [4, 59]	36 [12, 72]	1.0 [0.4, 21]

PK parameters values are arithmetic mean ± standard deviation, except for Tmax for which it is median (minimum, maximum)

[a] HTX-011 was instilled with or without ropivacaine (0.5%, 50 mg). The PK parameters of only HTX-011 without ropivacaine (N=53) are reported

Figure 2.4.1.4a: PK profile of bupivacaine and meloxicam from HTX-011 and bupivacaine from bupivacaine HCl in total knee arthroplasty (Study 209)

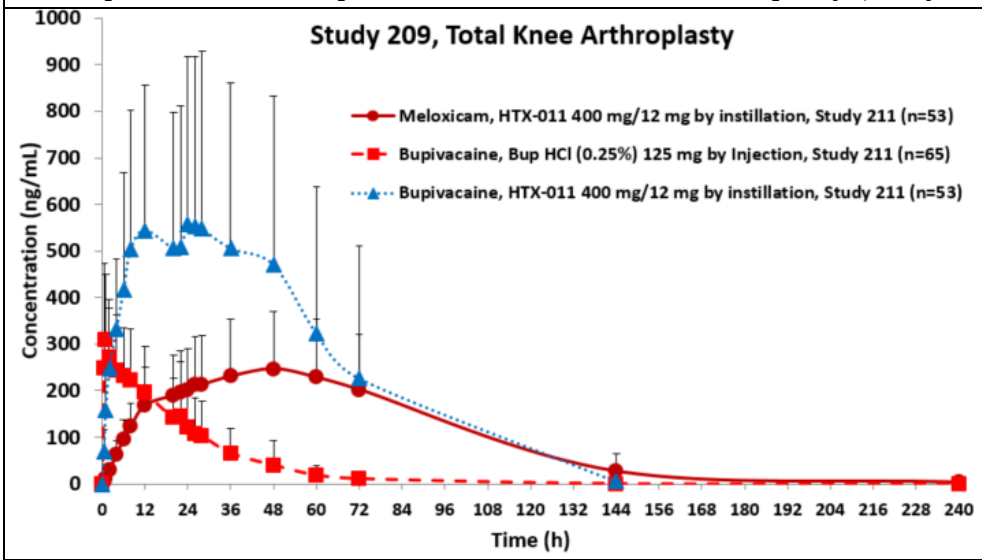
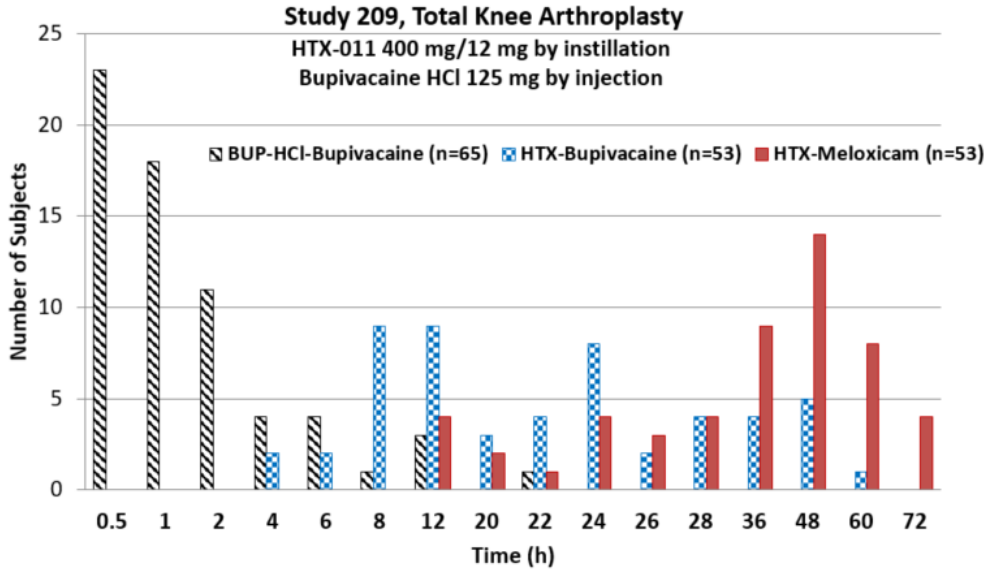


Figure 2.4.1.4b: Tmax of bupivacaine and meloxicam from HTX-011 and bupivacaine from bupivacaine HCl in total knee arthroplasty (Study 209)



2.4.1.5. Phase 2 Study 211: Augmentation Mammoplasty

The PK parameters of bupivacaine and meloxicam from HTX-011 and bupivacaine from bupivacaine HCl in augmentation mammoplasty (Study 211) is shown in Table 2.4.1.5. The PK profiles and Tmax comparison is shown in Figure 2.4.1.5a. and 2.4.1.5b, respectively.

Both Cmax and AUC of bupivacaine of HTX-011 is higher than bupivacaine HCl in augmentation mammoplasty.

Table 2.4.1.5: PK parameters of bupivacaine and meloxicam from HTX-011 and bupivacaine from bupivacaine HCl in augmentation mammoplasty (Study 211).

211: Augmentation Mammoplasty			
Parameter **Athematic Mean ± SD**	**HTX-011** **400 mg/12 mg in 13.7 mL**		**Bupivacaine HCl** **50 mg (0.25%)**
How administered	**Instillation**		**Nerve block**
Analyte	**Bupivacaine (n=49)**	**Meloxicam (n=49)**	**Bupivacaine (n=41)**
PK sampling duration (h)	120	120	120
Cmax (ng/mL)	710 ± 246	527 ± 149	341 ± 136
AUC0-24 (ng/mL*h)	11758 ± 3990	9034 ± 1924	2482 ± 779
AUC0-48 (ng/mL*h)	19042 ± 6692	17995 ± 4245	3027 ± 1169
AUC0-72 (ng/mL*h)	23563 ± 8192	24331 ± 6332	3105 ± 1282
AUC0-t (ng/mL*h)	27363 ± 9227	30499 ± 9460	3107 ± 1283
AUC (inf) (ng/mL*h)	31072 ± 17998	41808 ± 38413	3120 ± 1302
t½ (h)	25 ± 20	42 ± 70	6 ± 3
Tmax (h)	4 [1, 35]	20 [6, 49]	0.55 [0.4, 2.05]

PK parameters values are arithmetic mean ± standard deviation, except for Tmax for which it is median (minimum, maximum)

Figure 2.4.1.5a: PK profile of bupivacaine and meloxicam from HTX-011 and bupivacaine from bupivacaine HCl in augmentation mammoplasty (Study 211)

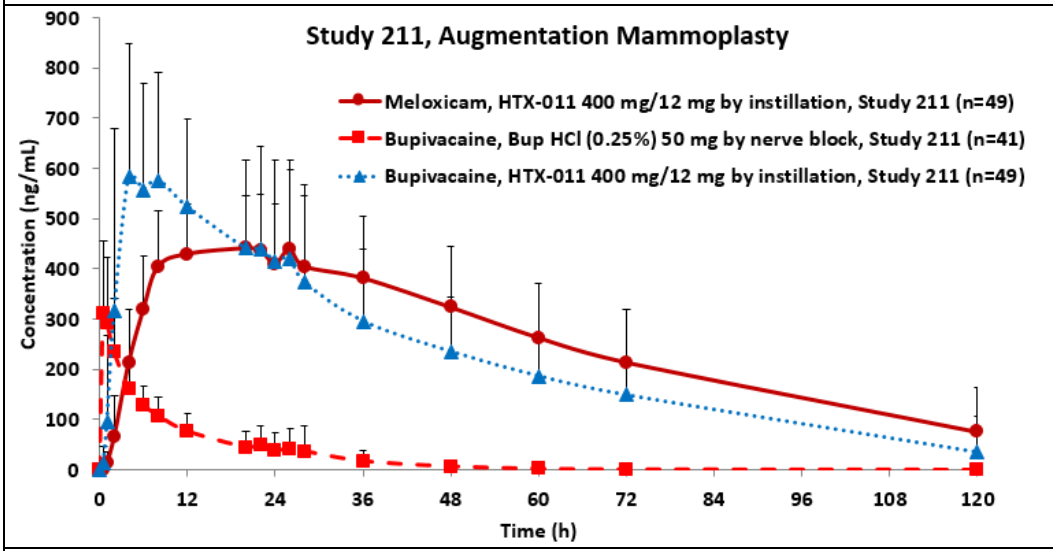
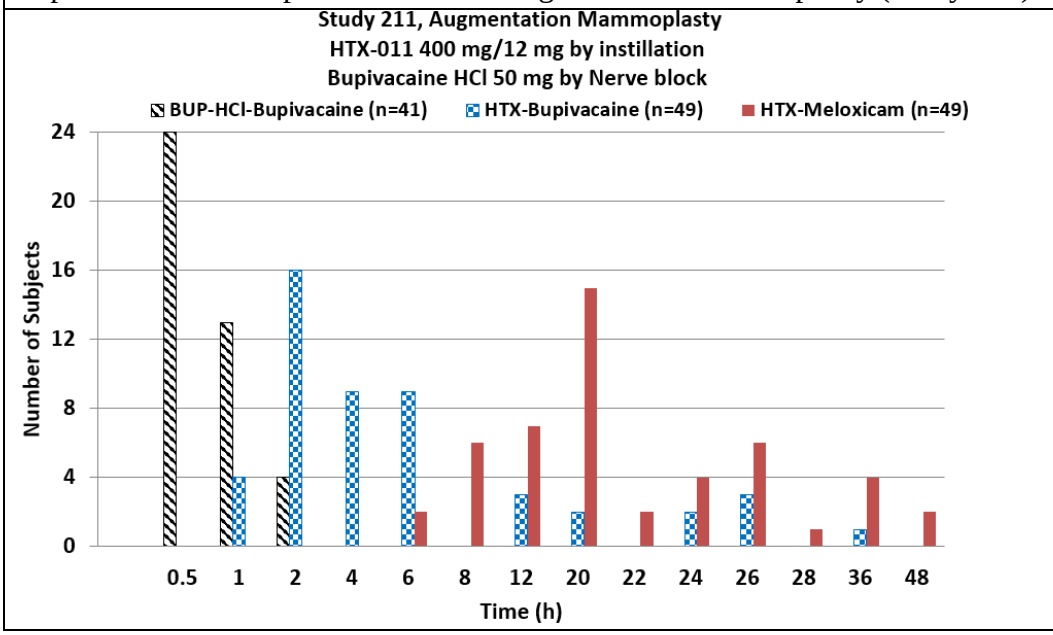


Figure 2.4.1.5b: Tmax of bupivacaine and meloxicam from HTX-011 and bupivacaine from bupivacaine HCl in augmentation mammoplasty (Study 211)



2.6 Analytical Section

2.6.1 Are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method?

The plasma concentrations of bupivacaine and meloxicam were analyzed using validated HPLC-MS/MS.

Clinical facility: Multiple clinical hospital sites
Bio-analytical Facility: (b) (4)

- The range of calibrators and QCs used for studies were:
    - Bupivacaine or Meloxicam Calibrators range:
        - 10 to 5000 ng/mL (high assay range)
        - 0.1-50 ng/mL (low assay range)
    - Bupivacaine or Meloxicam Quality controls range: 0.1 to 4000 ng/mL
- Accuracy and Precision of the range:
    - Accuracy (expressed as % bias): < ± 15%
    - Precision (expressed as % CV): < 15%
- Internal standards:
    - Bupivacaine-$^{2}H_{9}$
    - Meloxicam-$^{13}C_{6}$
- Stability: PK samples were analyzed within established frozen-storage stability for all studies.

3.0 LABELING COMMENTS

There is no labeling negotiation with the sponsor since the submission will receive a complete response. The labelling comments have been made to the following section 12.3 in the Label:

(b) (4)

7 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

4.0 Study Designs:

HTX-011-C2015-202: *A Phase 2, Randomized, Pilot Study to Investigate the Safety, Efficacy, Pharmacokinetics and Bioavailability of HTX-011, HTX-002, or HTX-009 Administered Via Injection and/or Topical Application Following Unilateral Open Inguinal Herniorrhaphy*
\\cdsesub1\evsprod\NDA211988\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\postoperative-pain-management\5351-stud-rep-contr\htx-011-c2015-202\htx-011-202-study-report-body.pdf

HTX-011-C2015-203: *A Phase 2, Randomized, Controlled Evaluation of the Efficacy and Safety of HTX-011 or HTX-002 for Post-Operative Analgesia Following Abdominoplasty Surgery*
\\cdsesub1\evsprod\NDA211988\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\postoperative-pain-management\5351-stud-rep-contr\htx-011-c2015-203\htx-011-203-study-report-body.pdf

HTX-011-C2015-208: *A Phase 2, Randomized, Controlled, Multicenter, Evaluation of the Efficacy and Safety of Locally Administered HTX-011, HTX-002, or HTX-009 for Postoperative Analgesia Following Bunionectomy*
\\cdsesub1\evsprod\NDA211988\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\postoperative-pain-management\5351-stud-rep-contr\htx-011-c2016-208\htx-011-208-study-report-body.pdf

HTX-011-209: *A Phase 2b, Randomized, Double Blind, Saline Placebo- and Active-Controlled, Multicenter Study of HTX-011 via Infiltration for Postoperative Analgesia in Subjects Undergoing Total Knee Arthroplasty*
\\cdsesub1\evsprod\NDA211988\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\postoperative-pain-management\5351-stud-rep-contr\htx-011-209\htx-011-209-study-report-body.pdf

HTX-011-211: *A Phase 2B, Randomized, Controlled Study of HTX-011 Administered Via Pectoral Nerve Block in Subjects Undergoing Upper Extremity Surgery for Augmentation Mammoplasty*
\\cdsesub1\evsprod\NDA211988\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\postoperative-pain-management\5351-stud-rep-contr\htx-011-211\htx-011-211-study-report-body.pdf

Phase 3:

HTX-011-301: *A Phase 3, Randomized, Double-Blind, Saline Placebo- and Active-Controlled, Multicenter Study of HTX-011 via Local Administration for Postoperative Analgesia and Decreased Opioid Use Following Unilateral Simple Bunionectomy*
\\cdsesub1\evsprod\NDA211988\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\postoperative-pain-management\5351-stud-rep-contr\htx-011-301\htx-011-301-study-report-body.pdf

HTX-011-302: *A Phase 3, Randomized, Double-Blind, Saline Placebo- and Active-Controlled, Multicenter Study of HTX-011 via Local Administration for Postoperative Analgesia and Decreased Opioid Use Following Unilateral Open Inguinal Herniorrhaphy*
\\cdsesub1\evsprod\NDA211988\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\postoperative-pain-management\5351-stud-rep-contr\htx-011-302\htx-011-302-study-report-body.pdf

5.0. Population Pharmacokinetic and Exposure Response Analyses

5.1 Population Pharmacokinetic Analyses

The Applicant submitted three reports containing population pharmacokinetic (PPK) analyses.

- Report 34-12.pdf describes analyses of the effect of renal impairment on the PK of the metabolite of the vehicle (b) (4)
- Report 34-16.pdf describes the PPK of bupivacaine and PPK of meloxicam. This report also includes results of exposure-response relationship for efficacy for bupivacaine and meloxicam which will not be reviewed (please refer to section 4.4 for details).
- Report 33-82.pdf describes PK simulations used to inform the effect of hepatic impairment on bupivacaine exposure and meloxicam exposure.

5.1.1 PPK Analysis of Bupivacaine and Meloxicam (Report 34-16)

Report 34-16 is titled "Population Pharmacokinetic and Exposure-Response Analysis for HTX-011". The report describes population PK models to characterize the plasma pharmacokinetics of bupivacaine and meloxicam in adult surgery patients and assess the relationship of PK parameters with covariates.

Summary of PK Data.

A total of 8840 bupivacaine and 8714 meloxicam concentrations from 731 subjects were available for the population PK analysis. The median age was 52 (range 18 to 85 years).

Studies: There were five Phase 2 studies and two Phase 3 trials utilized in the population PK modeling (please refer to **Table 5.1.1** for details).

Table 5.1.1: Studies and Trial included in population PK modeling of bupivacaine and meloxicam

Study	Subjects with PK Data, Surgery Site	Dose, Formulation
HTX-011-C2015-202 Phase 2a, multi-center, single-dose, randomized, study	N=53 adults inguinal herniorrhaphy	HTX-011: 200 mg / 6 mg to 400 mg / 12 mg by instillation only PBO: saline by any route
HTX-011-C2015-203 Phase 2a, randomized, multicenter, observer-blind controlled study	n=123 adults abdominoplasty	HTX-011: 300 mg / 9 mg and 400 mg / 12 mg by instillation, injection, and combination; PBO: saline by any route
HTX-011-C2016-208 Phase 2a, randomized, 9-part, multicenter, controlled study	N=54 adults unilateral simple bunionectomy	HTX-011: 60 mg / 1.8 mg to 120 mg / 3.6 mg by instillation PBO: saline by any route
HTX-011-209 Phase 2b, randomized, double-blind, saline placebo and active-controlled, multicenter study	N=134 adults total knee arthroplasty	HTX-011: 200 mg / 6 mg to 400 mg / 12 mg by instillation PBO: saline by any route
HTX-011-211 Phase 2b, randomized, double-blind, active- and saline placebo-controlled, multicenter study	N=49 adults augmentation mammoplasty	HTX-011: 400 mg / 12 mg by instillation PBO: saline by any route
HTX-011-301 Phase 3, randomized, double-blind, saline placebo and active-controlled, Multicenter study	N=157 adults unilateral simple bunionectomy	HTX-011: 60 mg / 1.8 mg by instillation PBO: saline by any route
HTX-011-302 Phase 3, randomized, double-blind, saline placebo and active-controlled, multicenter study	N=161 adults inguinal herniorrhaphy	HTX-011: 300 mg / 9 mg by instillation PBO: saline by any route

Source: Sequence 0002, module 5335, 34-16.pdf, page 21 and 22 of 771

Applicant utilized PK data from n=608 subjects age 18-85 (median 52) years that received HTX-011 for postoperative pain relief. The subjects underwent unilateral open inguinal herniorrhaphy (studies 202 and 302), abdominoplasty (study 203), unilateral simple bunionectomy (study 208 and 301), total knee arthroplasty (study 209), or upper extremity surgery augmentation mammoplasty (study 211).

5.1.1.1 Bupivacaine Population PK Model

The structural model is a 2-compartment model with parallel absorption pathways. One absorption pathway utilizes a depot from which a first-order absorption model describes uptake into the central compartment. The other absorption pathway utilizes a depot from which a zero-order absorption and absorption lag describes uptake into the central compartment. The zero-order absorption rate varies with dose according to an E_{max} model such that A_{50} is the dose at which dose resulting in half-maximal zero-order absorption.

Allometric Scaling: allometric scaling is applied to V_p/F with weight normalized to 70 kg.
Inter-individual variability: exponential
Residual variability: additive plus proportional error model
Final Covariate Model:

- *Weight*: V_p/F
- *Type of Surgery:*
    - *Inguinal Herniorrphaphy*: ZORATE for 400 mg (versus all other bupivacaine dose levels in this surgery combined)
    - The following surgeries have covariate effects that are presented as change relative to the inguinal herniorrphaphy:
        - *Bunionectomy*: $F_{zero\text{-}order}$, ZORATE, K_a, A_{50}, $ALAG_{zero\text{-}order}$, $F_{60\ mg}$, $F_{120\ mg}$
        - *Breast augmentation mammoplasty*: $F_{zero\text{-}order}$, ZORATE, K_a, A_{50}, $ALAG_{zero\text{-}order}$, Vp/F
        - *Total Knee Arthroplasty*: ZORATE, A_{50}

Final model parameters, sorted by surgery site, are shown in **Table 5.1.1.1a**.

Table 5.1.1.1a: PK Parameters for Bupivacaine Final Population PK Model (B367a) by Surgery Site

Parameter (Unit)	Surgery Type			
	Augmentation Mammoplasty	Bunionectomy	Inguinal Herniorrhaphy	Total Knee Arthroplasty
$F_{zero\text{-}order}$ (fraction)	0.878	0.956	0.978	0.978
ZORATE (mg/hr)	9.95	1.89	6.33[a]	9.95[b]
Vc/F (L)	12.2	12.2	12.2	12.2
CL/F (L/hr)	14.5	14.5	14.5	14.5
Ka (hr^{-1})	0.0546	0.178	0.0315	0.0315
Q/F (L/hr)	101	101	101	101
Vp/F (L)	0.194	29.3	29.3	29.3
A50 (mg)	204	29.4	79.7	95.1
$ALAG_{zero\text{-}order}$ (hr)	0.192	0.716	0.322	0.322
F	1	0.638 for 60 mg 0.290 for 120 mg	1	1

Where ZORATE is the zero-order absorption rate, $ALAG_{zero\text{-}order}$ is the lag before zero-order absorption begins, A_{50} = dose resulting in half-maximal zero-order absorption, $F_{zero\text{-}order}$ is the fraction of the administered dose which undergoes the zero-order absorption pathway, ka is first order absorption rate constant, V_c/F is apparent volume of distribution of central compartment, Cl/F is apparent clearance, Q/F is apparent intercompartmental clearance, V_p/F is apparent peripheral volume of distribution. A) the ZORATE presented for inguinal herniorrhaphy represents the 200 and 300 mg dose levels. B) the ZORATE presented for total knee arthroplasty represents the 400 mg dose level.

Source: Sequence 0002, module 5335, 34-16.pdf, page 72 of 771

Table 5.1.1.1b provides a qualitative description of the effects of surgery site on various PK parameter estimates.

Table 5.1.1.1b: Covariate Effect Description in Bupivacaine Final Population PK Model (B367a)

Surgery Type	Bupivacaine Final Model[a]
All Surgeries	Vp/F~Weight
Inguinal Herniorrhaphy	↑ ZORATE for 400 mg compared to other doses in this surgery
Bunionectomy	↓Fzero-order ↓ ZORATE ↑ Ka ↓ A50 ↑ ALAG F 60 mg=0.638 F 120 mg=0.290
Augmentation Mammoplasty	↓Fzero-order ↑ ZORATE (same as Total Knee Arthroplasty) ↑ Ka ↑ A50 ↓ ALAG ↓ Vp
Total Knee Arthroplasty	↑ ZORATE (same as Augmentation Mammoplasty) ↑ A50 ↓ ZORATE for 200 mg

[a] The ↑ and ↓ are relative to inguinal herniorrhaphy (reference surgery)

Source: Sequence 0002, module 5335, 34-16.pdf, page 89 of 771

The comprehensive table of parameter estimates including precision, inter-individual variability, and Markov Chain Monte Carlo (MCMC) Bayesian Analysis estimates are found in **Table 5.1.1.1c**.

Table 5.1.1.1c: PK Parameters for Bupivacaine Final Population PK Model (B367a)

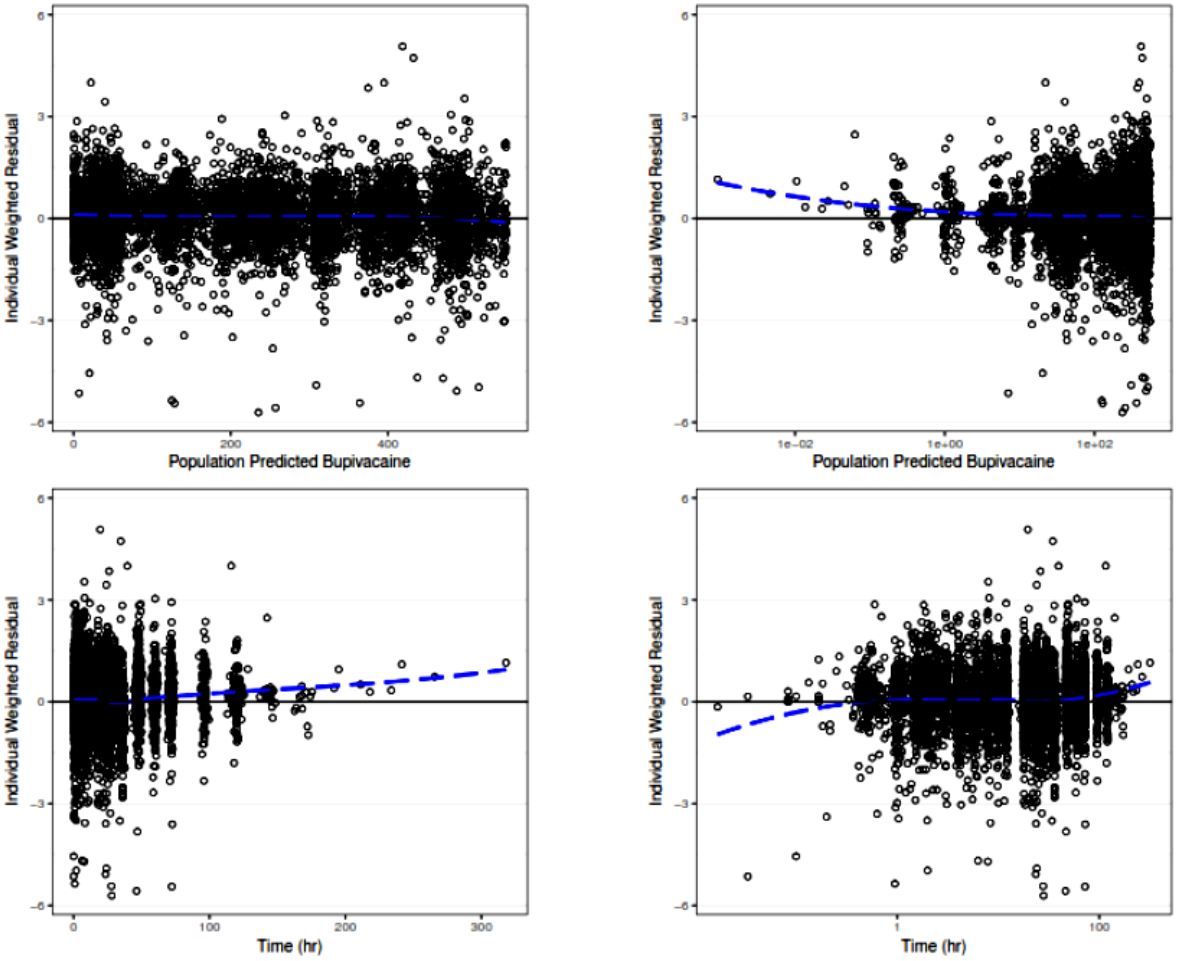
		NONMEM Estimates				MCMC BAYES Estimates[f]
Parameter	**Units**	**Estimate[a]**	**%RSE[b]**	**95% CI[a]**	**IIV[c]**	**Median [95% CI]**
$F_{zero\text{-}order}$ HE & TK	fraction	0.978	0.412	0.968-0.984	189	0.979 [0.972 to 0.986]
ZORATE	mg/hr	6.33	4.00	5.85-6.85	44.5	6.52 [5.96 to 7.14]
Vc/F	L	12.2	8.59	10.3-14.5	116	10.2 [7.18 to 12.9]
CL/F	L/hr	14.5	3.07	13.7-15.4	70.7	14.6 [13.7 to 15.9]
Ka	hr^{-1}	0.0315	12.2	0.0248-0.0400	94.6	0.0323 [0.0231 to 0.0431]
Q/F	L/hr	101	21.5	66.5-155	167	94.3 [66.3 to 135]
Vp/F	L	29.3	8.13	25.0-34.3	111	31.1 [25.3 to 39.9]
A50	mg	79.7	8.07	68.1-93.4	79.8	82.1 [68.5 to 97.9]
$ALAG_{zero\text{-}order}$	hr	0.322	4.46	0.295-0.351	26.4	0.333 [0.308 to 0.355]
F~120 mg	fraction	0.290	9.21	0.238-0.342	--	0.345 [0.296 to 0.393]
$F_{zero\text{-}order}$ BU	fraction	0.956	15.0	0.933-0.971	--	0.963 [0.946 to 0.978]
ZORATE~BU	unitless	0.298	8.76	0.251-0.354	--	0.334 [0.285 to 0.446]
Ka~BU	unitless	5.64	23.8	3.54-8.99	--	5.55 [3.44 to 10.7]
A50~BU	unitless	0.368	14.2	0.279-0.486	--	0.417 [0.314 to 0.626]
$ALAG_{zero\text{-}order}$~BU	unitless	2.23	6.29	1.97-2.52	--	2.28 [2.03 to 2.50]
$F_{zero\text{-}order}$ BA	fraction	0.878	19.0	0.823-0.917	--	0.886 [0.829 to 0.926]
ZORATE~BA & TK	unitless	1.57	5.15	1.42-1.74	--	1.57 [1.41 to 1.73]
Ka~BA	unitless	1.74	18.9	1.20-2.51	--	1.93 [1.28 to 3.03]
Vp/F~BA	unitless	0.00663	68.0	0.00175-0.0251	--	0.0724 [0.00602 to 0.178]
A50~BA	unitless	2.56	10.4	2.09-3.15	--	2.57 [2.05 to 3.21]
$ALAG_{zero\text{-}order}$~BA	unitless	0.596	10.3	0.488-0.729	--	0.613 [0.503 to 0.791]
A50~TK	unitless	1.19	10.7	0.968-1.47	--	1.20 [0.958 to 1.47]
Vp~WT	unitless	1.49	16.2	1.02-1.96	--	1.43 [0.872 to 1.91]
F~60 mg	fraction	0.638	5.53	0.569-0.708	--	0.718 [0.646 to 0.795]
ZORATE~TK 200 mg	unitless	0.676	4.78	0.616-0.742	--	0.671 [0.612 to 0.739]
ZORATE~HE 400 mg	unitless	1.21	4.36	1.11-1.31	--	1.20 [1.11 to 1.30]
σ_{prop}	unitless	0.170	1.22	0.165-0.174	17.0%[d]	0.170 [0.166 to 0.174]
σ_{add}	unitless	0.0947	15.9	0.0652-0.124	0.0947[e]	-0.0780 [-0.123 to 0.121]

HE=unilateral open inguinal herniorrhaphy, BU=bunionectomy, BA= augmentation mammoplasty, TK= total knee arthroplasty. PK parameters for BU, BA, or TK are expressed in relation to a reference population of a 70 kg subject undergoing inguinal herniorrhaphy. Studies 202, 208, 301, 302, 209 and 211 included in the bupivacaine final model (Run B367a) resulting in 6360 concentrations from 608 subjects.

Source: Sequence 0002, module 5335, 34-16.pdf, page 71 of 771

Key model diagnostics are presented in **Figure 5.1.1.1a** and **Figure 5.1.1.1b**.

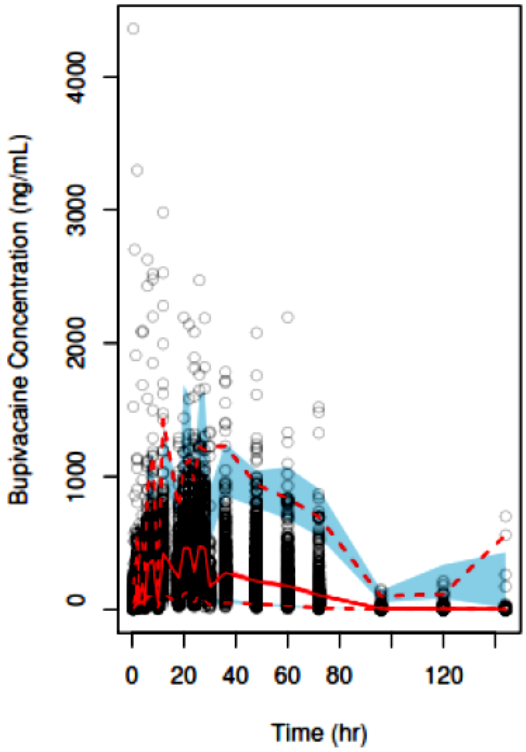
Figure 5.1.1.1a: Diagnostic Plots for the Final Bupivacaine Population PK Model (B367a)



Blue dashed line: Local regression (Loess) smoothing line

Source: Sequence 0002, module 5335, 34-16.pdf, page 74 of 771

Figure 5.1.1.1b: pcVPC for the Final Bupivacaine Population PK Model (B367a)



Source: Sequence 0002, module 5335, 34-16.pdf, page 77 of 771

[*Reviewer comment: The population PK model does not demonstrate systematic bias with respect to concentration (see* ***Figure 5.1.1.1a****). This figure suggests that modest bias is apparent at time < 0.75 hours and time > 100 hours (for which PK samples are sparse). Increased uncertainty in model predictions (i.e. wider blue band) is also apparent in the prediction-corrected visual predictive check (pcVPC) at time > 100 hours (see* ***Figure 5.1.1.1b****) likely due to infrequent PK sampling.*

Each of the 4 surgery types affects a different set of PK parameters (see ***Table 5.1.1.1b****) and each surgery often results in different parameter estimates on the same PK parameter (i.e. ZORATE, K_a, V_p/F, A_{50}, and $ALAG_{zero\text{-}order}$; see* ***Table 5.1.1.1a****). In addition, inter-individual variability estimates are high (e.g. > 30% CV) for all structural PK parameters (44.5% to 189% CV) except for $ALAG_{zero\text{-}order}$ (26.4% CV; see* ***Table 5.1.1.1c****).*

The abrupt upward and downward veering of the mean PK profile over time in the pcVPC (the solid red series in ***Figure 5.1.1.1b****) suggests absorption from the surgical site to systemic circulation is a complex process which may vary with time. Considering the interindividual variability magnitude and the effect of surgical site on absorption into systemic circulation, the bupivacaine plasma PK model for inguinal herniorrhaphy, bunionectomy, augmentation mammoplasty, and total knee arthroplasty are not likely to be generalizable to other surgical sites.* ***Overall, the bupivacaine population PK model appears to capture the central tendency and variability of the bupivacaine PPK dataset. However, this population PK model may not adequately characterize the plasma PK for surgeries other than the 4 procedures included in the population PK dataset.***]

5.1.1.2 Meloxicam Population PK Model

The structural model is a 1-compartment model with parallel absorption pathway. One absorption pathway utilizes a depot from which a first-order absorption model describes uptake into the central compartment. The other absorption pathway utilizes a depot from which a zero-order absorption model with lag describes uptake into the central compartment.

Allometric Scaling: allometric scaling is applied to and CL/F and V_c/F with weight normalized to 70 kg.
Inter-individual variability: exponential
Residual variability: additive plus proportional error model
Final Covariate Model:

- *Weight*: V_c/F
- *Type of Surgery:*
    - *Inguinal Herniorrphaphy*: ZORATE for 12 mg, A_{50} for 12 mg (versus all other meloxicam dose levels in this surgery combined)
    - The following surgeries have covariate effects that are presented as change relative to the inguinal herniorrphaphy:
        - *Bunionectomy*: $F_{zero\text{-}order}$, ZORATE, A_{50}, $ALAG_{zero\text{-}order}$, $F_{1.8\ mg}$, $F_{3.6\ mg}$
        - *Breast augmentation mammoplasty*: ZORATE, K_a, A_{50}, $ALAG_{zero\text{-}order}$, Vc/F, F
        - *Total Knee Arthroplasty*: $F_{zero\text{-}order}$, ZORATE, K_a, A_{50}, $ALAG_{zero\text{-}order}$

Final model parameters are shown in **Table 5.1.1.2a**.

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Table 5.1.1.2a: PK Parameters for Meloxicam Final Population PK Model (M323) by Surgery Site

Parameter (Unit)	Surgery Type			
	Augmentation Mammoplasty	Bunionectomy	Inguinal Herniorrhaphy	Total Knee Arthroplasty
$F_{zero\text{-}order}$ (fraction)	0.962	0.920	0.962	0.850
ZORATE (mg/hr)	0.361	0.0221	0.101[a]	0.147[b]
Vc/F (L)	2.65	6.23	6.23	6.23
CL/F (L/hr)	0.497	0.497	0.497	0.497
Ka (hr^{-1})	0.0807	0.157	0.157	0.0209
A50 (mg)	8.02	0.399	0.962[a]	1.82
$ALAG_{zero\text{-}order}$ (hr)	0.293	0.671	1.19	0.671
F	1.16	0.547 for 60 mg 0.282 for 120 mg	1	1

Where ZORATE is the zero-order absorption rate, $ALAG_{zero\text{-}order}$ is the lag before zero-order absorption begins, A_{50} = dose resulting in half-maximal zero-order absorption, $F_{zero\text{-}order}$ is the fraction of the administered dose which undergoes the zero-order absorption pathway, ka is first order absorption rate constant, V_c/F is apparent volume of distribution of central compartment, Cl/F is apparent clearance, Q/F is apparent intercompartmental clearance, Vp/F is apparent peripheral volume of distribution. A) the ZORATE presented for inguinal herniorrhaphy represents the 200 and 300 mg dose levels. B) the ZORATE presented for total knee arthroplasty represents the 400 mg dose level.

Source: Sequence 0002, module 5335, 34-16.pdf, page 81 to 82 of 771

Table 5.1.1.2b provides a qualitative description of the effects of surgery site on various PK parameter estimates.

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Table 5.1.1.2b: Covariate Effect Description in Meloxicam Final Population PK Model (M323)

Surgery Type	Meloxicam Final Model[a]
All Surgeries	Vc/F~Weight
Inguinal Herniorrhaphy	↑ ZORATE & A50 for 12 mg compared to other doses in this surgery
Bunionectomy	↓Fzero-order ↓ ZORATE ↓ A50 ↓ ALAG (same as Total Knee Arthroplasty) F 1.8 mg=0.547 F 3.6 mg=0.282
Augmentation Mammoplasty	↑ ZORATE ↓ Ka ↑ A50 ↓ ALAG ↓ Vc ↑ F (F=1.16)
Total Knee Arthroplasty	↓Fzero-order ↑ ZORATE ↓ Ka ↑ A50 ↓ ALAG (same as Bunionectomy) ↓ ZORATE for 6 mg

[a] The ↑ and ↓ are relative to inguinal herniorrhaphy (reference surgery).

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The comprehensive table of parameter estimates including precision, inter-individual variability, and Markov Chain Monte Carlo (MCMC) Bayesian Analysis estimates are found in **Table 5.1.1.2c**.

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Table 5.1.1.2c: PK Parameters for Meloxicam Final Population PK Model (M323)

		NONMEM Estimates				MCMC BAYES Estimates[f]
Parameter	**Units**	**Estimate[a]**	**%RSE[b]**	**95% CI[a]**	**IIV[c]**	**Median [95% CI]**
$F_{zero\text{-}order}$ HE & BA	fraction	0.962	0.574	0.950-0.972	80.6	0.961 [0.948 to 0.971]
ZORATE	mg/hr	0.101	5.43	0.0910-0.113	52.9	0.103 [0.0916 to 0.115]
Vc/F	L	6.23	5.25	5.62-6.90	84.6	6.28 [5.67 to 6.98]
CL/F	L/hr	0.497	4.04	0.459-0.538	69.8	0.507 [0.466 to 0.545]
Ka	hr^{-1}	0.157	14.6	0.118-0.209	103	0.150 [0.109 to 0.187]
A50	mg	0.962	13.8	0.734-1.26	94.6	0.977 [0.748 to 1.27]
$ALAG_{zero\text{-}order}$	hr	1.19	6.37	1.05-1.35	30.7	1.15 [1.02 to 1.28]
$F_{zero\text{-}order}$ BU	fraction	0.920	11.4	0.893-0.941	--	0.924 [0.888 to 0.945]
ZORATE~BU	unitless	0.218	11.4	0.174-0.272	--	0.232 [0.196 to 0.276]
A50~BU	unitless	0.415	29.1	0.235-0.733	--	0.449 [0.327 to 0.650]
$ALAG_{zero\text{-}order}$~BU & TK	unitless	0.564	5.99	0.502-0.635	--	0.572 [0.501 to 0.659]
F~3.6 mg	fraction	0.282	14.8	0.201-0.364	--	0.291 [0.241 to 0.352]
ZORATE~BA	unitless	3.57	8.63	3.01-4.23	--	3.61 [3.01 to 4.34]
Ka~BA	unitless	0.514	23.2	0.326-0.810	--	0.439 [0.255 to 0.773]
A50~BA	unitless	8.34	17.1	5.97-11.7	--	8.08 [5.61 to 11.4]
$ALAG_{zero\text{-}order}$~BA	unitless	0.246	10.4	0.201-0.302	--	0.245 [0.198 to 0.317]
$F_{zero\text{-}order}$ TK	fraction	0.850	9.05	0.820-0.876	--	0.865 [0.838 to 0.891]
ZORATE~ TK	unitless	1.46	6.76	1.28-1.66	--	1.53 [1.31 to 1.81]
Ka~TK	unitless	0.133	19.0	0.0918-0.193	--	0.151 [0.110 to 0.220]
A50~TK	unitless	1.90	16.7	1.37-2.63	--	2.07 [1.45 to 2.99]
F~BA	fraction	1.16	4.39	1.06-1.26	--	1.28 [1.02 to 1.45]
Vc/F~BA	unitless	0.426	10.4	0.347-0.522	--	0.408 [0.323 to 0.511]
F~1.8 mg	fraction	0.547	6.61	0.476-0.618	--	0.573 [0.524 to 0.630]
ZORATE~TK 6 mg	unitless	0.723	7.11	0.629-0.831	--	0.712 [0.615 to 0.829]
ZORATE~HE 12 mg	unitless	1.76	9.63	1.46-2.13	--	1.78 [1.45 to 2.16]
A50~HE 12 mg	unitless	2.00	21.8	1.30-3.06	--	2.04 [1.29 to 3.08]
Vc/F	unitless	1 fixed	--	--	--	--
σ_{prop}	unitless	0.171	28.9	0.0743-0.269	17.1%[d]	0.173 [-0.224 to 0.260]
σ_{add}	unitless	0.159	1.24	0.155-0.163	0.159[e]	0.160 [0.156 to 0.164]

HE=unilateral open inguinal herniorrhaphy, BU=bunionectomy, BA= augmentation mammoplasty, TK= total knee arthroplasty. PK parameters for BU, BA, or TK are expressed in relation to a reference population of a 70 kg subject undergoing inguinal herniorrhaphy. Studies 202, 208, 301, 302, 209 and 211 included in the meloxicam final model (Run M323) resulting in 6234 concentrations from 603 subjects.

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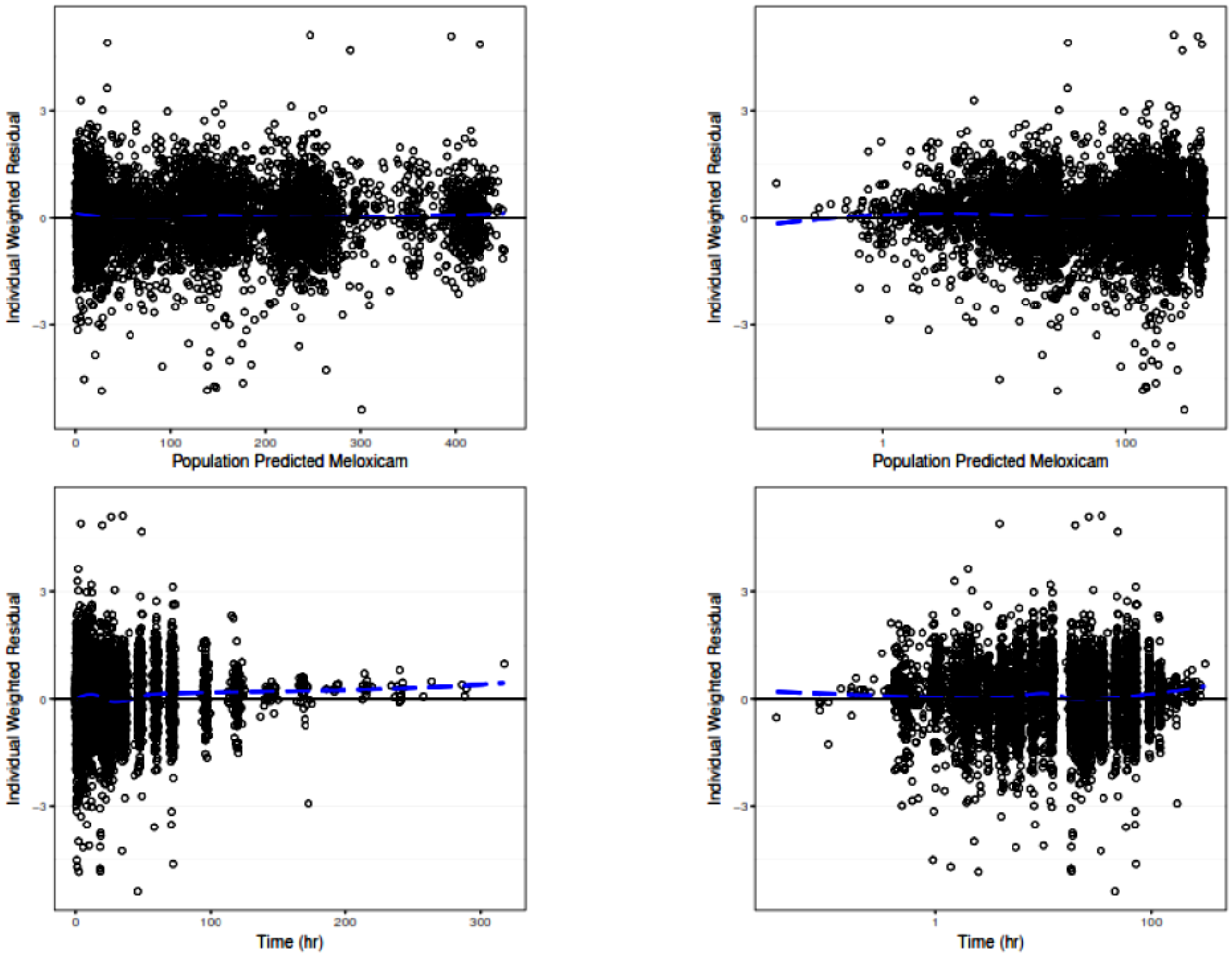
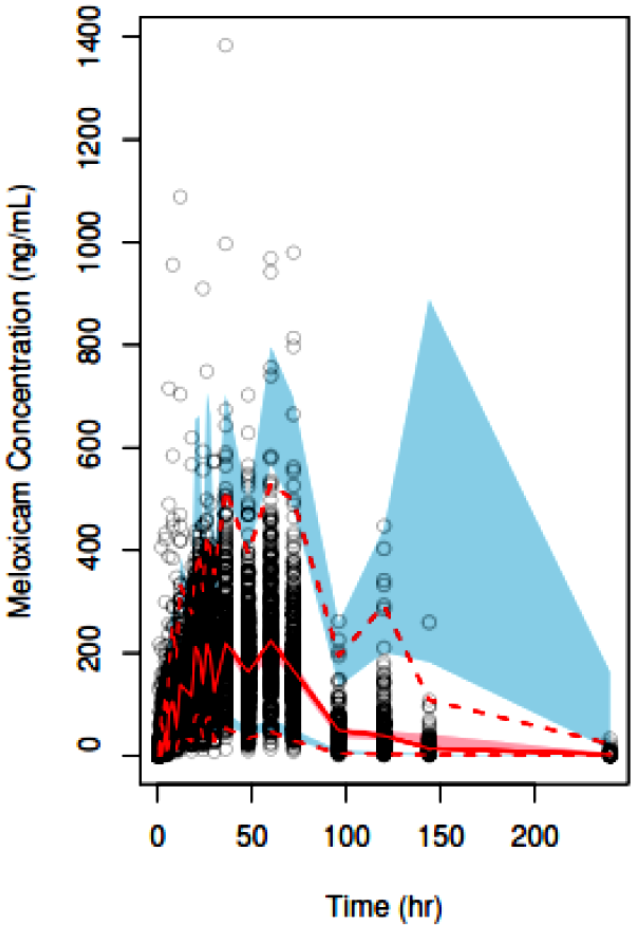
Key model diagnostics are presented in **Figure 5.1.1.2a** and **Figure 5.1.1.2b.**

Figure 5.1.1.2a: Diagnostic Plots for the Final Meloxicam Population PK Model (M323)



Source: Sequence 0002, module 5335, 34-16.pdf, page 84 of 771

Figure 5.1.1.2b: pcVPC for the Final Meloxicam Population PK Model (M323)



Open Circle: Observed Concentrations; Solid Line: Median of Observed Concentrations; Dashed Lines: 2.5th and 97.5th Percentile of Observed Concentrations. Red Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Blue Shaded Regions: 95% Prediction Intervals for the 2.5th and 97.5th Percentiles of Predicted Concentrations

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[*Reviewer comment: The population PK model does not demonstrate systematic bias with respect to concentration (see **Figure 5.1.1.2a**). The pc-PVC (**Figure 5.1.1.2b**) indicates that the model predicts the central tendency well but exhibits modest over-prediction of the higher end of the population exposures, particularly at 50-75 hours and time > 125 hours post-administration. The over-prediction of high exposures as well as reduced certainty in predictions (wider blue band representing the 95% CI of the 97.5th percentile of the predicted concentration) is most pronounced at ~150 hours post-administration. This is likely due to the less frequent PK samples acquired during this time period.*

*As was the case with the bupivacaine PK model, each of the 4 surgery types affects a different set of PK parameters (see **Table 5.1.1.2b**) and each surgery often results in different parameter estimates on the same PK parameter (i.e. $F_{zero\text{-}order}$[fraction], ZORATE, V_c/F, K_a, A_{50}, and*

*$ALAG_{zero\text{-}order}$, and F; see **Table 5.1.1.2a**). In addition, inter-individual variability estimates are high (e.g. > 30% CV) for all structural PK parameters (30.7% to 103% CV; see **Table 5.1.1.2c**).*

*Similar to bupivacaine, the meloxicam mean PK profile presents an abrupt upward and downward veering over time (the solid red series in **Figure 5.1.1.2b**). This suggests a complex, possibly time-varying absorption process is governing uptake from the surgical site into systemic circulation. In addition, as was the case with bupivacaine, the meloxicam plasma PK model for inguinal herniorrhaphy, bunionectomy, augmentation mammoplasty, and total knee arthroplasty are not likely to be generalizable to other surgical sites.* ***Overall, the meloxicam population PK model appears to capture the central tendency and variability of the meloxicam PPK dataset. However, this population PK model may not adequately represent plasma PK for surgeries other than the 4 procedures included in the population PK dataset.***]

5.1.1.3 Label Statements Based on PPK Analyses

The Applicant proposes the following statement for inclusion in Specific Populations, Section 12.3 of the label:

> "*Effect of Age, Sex, Race, and Ethnicity on Pharmacokinetics*
>
> Based on the population pharmacokinetic analysis, age, sex, race, and ethnicity do not have a clinically meaningful effect on the pharmacokinetics of bupivacaine and meloxicam in ZYNRELEF [See Use in Special Populations (8.5)]."

The bupivacaine PK analyses as well as meloxicam PK analyses described in this section suggest that age, sex, race, and ethnicity are not plasma PK covariates for either drug. **As such, this label statement is acceptable**.

[*Reviewer comment: As this drug locally-acting, the plasma PK for either drug is not expected to be associated with efficacy. As such, even if there were a covariate effect on plasma PK, the change in plasma exposures would not be expected to affect efficacy. Any such changes in plasma PK would likely be useful.*]

5.1.2 PPK Analysis [redacted] in Patients with Renal Impairment (Report 34-12.pdf)

Report 34-12.pdf is titled "*Population Modeling Analyses of HTX-011 in Patients with Various Levels of Renal Impairment*". The Applicant conducted population pharmacokinetic modeling analysis [redacted] This report does not address the effects of renal impairment on bupivacaine, meloxicam, nor any of their metabolites.

This report will not be reviewed based on the following rationale:

- The population PK analyses described in report 34-12.pdf are based on [redacted] PK data from n=10 healthy volunteers that received a single dose of 400 mg / 12 mg HTX-011 in Phase 1 study HTX-011-102. As the study was conducted in healthy volunteers, subjects did not have renal impairment. The Applicant made the following assumptions [redacted] (page 12 of 229 of 34-12.pdf):

  [redacted]

  Overall, it is not clear that the assumptions [redacted] are reliable. As such, the analyses may not be reliable.
- The renal impairment effects [redacted] was discussed during the pre-IND meeting. In the meeting minutes for IND 125927 (archived on 04/30/2018), in question 3, the Sponsor asked "*Does the FDA agree that* [redacted] *are sufficiently characterized and no additional studies are required for registration?*". Key excerpts from the FDA response are as follows:
  - "*From a clinical pharmacology perspective, the renal impairment study mainly applies to the active moiety,* [redacted] *So, your question on conducting a renal impairment study* [redacted] *does not seem relevant.*"
  - "*Considering that your product is locally acting,* [redacted] *and it is not for chronic use, renal impairment study is not required.*"
  - "*For bupivacaine and meloxicam, you may rely on relevant information on renal impairment in the listed drugs' label.*"
- The label does not include any statements [redacted]

(b) (4)

- Based on the approved labeling language for bupivacaine and meloxicam products, and since HTX-011 has not been assessed in patients with severe renal impairment, the Sponsor has proposed a statement in section 8.7 that indicates "*The use of ZYNRELEF in patients with severe renal impairment is not recommended*" which is acceptable to OCP. In addition, OCP has provided additional inclusion of cautionary language into section 8.7 from Exparel® label section 8.7 "*…the risk of toxic reactions to these drugs may be greater in patients with impaired renal function. This should be considered when performing dose selection of ZYNRELEF*".
- Since the drug is locally-acting, a dose reduction based on renal impairment effect on plasma exposures would result in reduced local exposures. For both the bunionectomy surgery and open inguinal herniorrhaphy surgery, a single dose was assessed in Phase 3.

(b) (4)

Overall, the proposed label language for renal impairment based on bupivacaine and meloxicam is adequate to cover any concerns which may be raised regarding the effect of renal impairment (b) (4)

5.1.3 PPK Simulation of Bupivacaine PK and Meloxicam PK in Patients with Hepatic (Report 33-82.pdf)

The Applicant conducted PK simulations to predict the effect of hepatic impairment on the pharmacokinetics of bupivacaine. However, this report was not reviewed for the following reasons.

- Mobic® is an oral tablet formulation containing meloxicam, a non-steroidal anti-inflammatory drug. Section 8.6 "Hepatic Impairment" of the Mobic label states: "*No dose adjustment is necessary in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment have not been adequately studied. Since meloxicam is significantly metabolized in the liver and hepatotoxicity may occur, use meloxicam with caution in patients with hepatic impairment*".
- The Applicant did not assess the effect of hepatic impairment on meloxicam.
- Exparel® is a bupivacaine solution for injection that is approved for post-surgical anesthesia (the same indication that is proposed for HTX-011). Section 8.6 "Hepatic Impairment" of the Exparel label states: "*Amide-type local anesthetics, such as bupivacaine, are metabolized by the liver. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations, and potentially local anesthetic systemic*

toxicity. Therefore, consider increased monitoring for local anesthetic systemic toxicity in subjects with moderate to severe hepatic disease." The review team determined that the language from section 8.6 Hepatic Impairment section of the Exparel label is appropriate for both bupivacaine and meloxicam available in HTX-011.

- The Applicant's conclusion from the PK simulations (b) (4) (b) (4) does not provide sufficient support to overturn the existing language from the Exparel label.

As such, the PK simulations to assess the effect of hepatic impairment on bupivacaine PK from report 33-82.pdf were not reviewed.

5.2 Exposure-Response Analyses

Efficacy: The Applicant conducted exposure-response analyses to assess the impact of bupivacaine exposure as well as meloxicam exposure on pain score. The exposure-response analyses for efficacy were included in report 34-16.pdf. However, as the drug is locally-acting, the plasma exposures of either drug are not expected to have a clinically-relevant impact on efficacy. This was communicated to the Sponsor as part of the End of Phase 2 Type B Interaction (see meeting minutes for IND 125927 signed on 07/12/2017, page 17, bullet #3 for details). As such**, exposure-response analyses for efficacy were not reviewed.**

Safety: According to the medical officer, the most common adverse events were wound-related after treatment (i.e. delayed-healing, wound leakage) following HTX-011 administration to patients that underwent bunionectomy. The medical officer and reviewer agree that this type of adverse event is unlikely to be driven by bupivacaine plasma exposure of either drug. Overall, based on discussions with the medical officer, there were no safety issues that warranted exposure-safety analyses by the reviewer. As such, **no exposure-response analyses for safety were conducted by the reviewer**.

There were no exposure-safety analyses conducted by the Sponsor.

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/s/

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