

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211988Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 125927

MEETING MINUTES

Heron Therapeutics, Inc.
4242 Campus Point Court, Suite 200
San Diego, CA 92121

Attention: Lynley Thinnes
Executive Director, Regulatory Affairs

Dear Ms. Thinnes:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for HTX-011 (bupivacaine and meloxicam extended-release solution) 2.5%/0.075%.

We also refer to the meeting between representatives of your firm and the FDA on June 20, 2018. The purpose of the meeting was to obtain feedback and guidance on the proposed content and format of the planned New Drug Application.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 240-402-2476.

Sincerely,

{See appended electronic signature page}

Eva Yuan, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: June 20, 2018 at 3:00 p.m. to 4:00 p.m. EDT
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1313
Silver Spring, MD 20903

Application Number: IND 125927
Product Name: HTX-011 (bupivacaine and meloxicam extended-release solution)

Indication: Post-operative pain management
Sponsor/Applicant Name: Heron Therapeutics, Inc.

Meeting Chair: Rigoberto Roca, MD, Deputy Division Director, DAAAP
Meeting Recorder: Sandy Truong, PharmD, Regulatory Project Manager, DAAAP

FDA ATTENDEES

Sharon Hertz, MD	Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Rigoberto Roca, MD	Deputy Director, DAAAP
Yun Xu, PhD	Clinical Pharmacology Supervisor, Division of Clinical Pharmacology (DCP2)
Suresh Naraharisetti, PhD	Clinical Pharmacology Reviewer, DCP2
Martha Van Clief, MD	Clinical Team Leader, DAAAP
Alla Bazini, MD	Clinical Reviewer, DAAAP
Daniel Mellon, PhD	Nonclinical Supervisor, DAAAP
Jay Chang, PhD	Nonclinical Team Lead, DAAAP
Jaime D'Agostino, PhD	Nonclinical Reviewer, DAAAP
Julia Pinto, PhD	Branch Chief, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Ciby Abraham, PhD	CMC Acting Team Lead, ONDP, OPQ
David Petullo, MS	Biometrics Team Lead, Division of Biometrics II (DBII)
Yi Ren, PhD	Biometrics Reviewer, DBII
Cameron Johnson, PharmD	Division of Medication Error Prevention and Analysis (DMEPA) Reviewer, Office of Surveillance and Epidemiology (OSE)

Otto L. Townsend, PharmD	DMEPA Team Lead, OSE
Keith Marin	Device Reviewer
Eva Yuan, PharmD	Regulatory Project Manager, DAAAP
Sandy Truong, PharmD	Regulatory Project Manager, DAAAP
Matthew Sullivan, MS	Supervisory Regulatory Project Manager, DAAAP
Kelly Kitchens, PhD	Biopharmaceutics Quality Assessment Lead
Hansong Chen, PharmD, PhD	Biopharmaceutics Reviewer
Bindi Nikhar, MD	Associate Clinical Director, Office of Combination Products (OCP)

SPONSOR ATTENDEES

Barry Quart, PharmD	Chief Executive Officer
Kimberly Manhard	Executive Vice President, Drug Development
Paul Blake, MD	Chief Medical Officer
Thomas Ottoboni, PhD	Senior Vice President, Pharmaceutical and Translational Sciences
Kenneth Schupp	Sr. Director, Quality Control
Erol Onel, MD	Vice President, Clinical Research
Matt Cravets, MA, MBA	Vice President, Biometrics
Clynn Wilker, DVM, PhD, DACT	Vice President, Translational Sciences
Lynley Thinnies	Executive Director, Regulatory Affairs
Stacy MacDonald, MS, MBA	Sr. Manager, Regulatory Affairs, CMC
Amy Yamamoto	Scientist II, Translational Sciences
(b) (4)	Device Consultant, (b) (4)
Mary Rose Keller	Vice President, Clinical Operations

BACKGROUND

Heron Therapeutics, Inc. is developing an extended-release solution that contains a fixed-ratio combination of bupivacaine as the disease-active ingredient and low-dose meloxicam to enhance the effects of bupivacaine. This product is indicated for single-dose, (b) (4). The purpose of the meeting is to obtain feedback and guidance on the proposed content and format of the planned New Drug Application.

The questions from the May 18, 2018, meeting package are shown in *italic font*, the Division's preliminary responses are shown in **bold font**, the Sponsor's pre-meeting comments received on June 21, 2018, are shown in arial font, and the meeting discussion is shown in normal font.

FDA sent preliminary comments to Heron Therapeutics, Inc. on June 18, 2018.

DISCUSSION

Multidisciplinary

*Question 1: Does the FDA agree with the proposed established name for HTX-011?
[Trademark (bupivacaine and meloxicam) extended-release solution]*

FDA Response:

The final evaluation of the product title, including the established name, will be determined during the labeling review of the NDA. You may refer to draft guidance for industry: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products – Content and Format*, available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM592850.pdf>, for additional information.

Heron's Pre-meeting Comments:

Heron understands that the final evaluation of the product title, including the established name, will be determined during the labeling review of the NDA.

Discussion: No further discussion.

Product Quality

Question 2: Does the FDA agree to the approach to support the shelf life for the 60 mg/1.8 mg drug product using stability data from lots manufactured [REDACTED] (b) (4)?

FDA Response:

No, we do not agree. [REDACTED] (b) (4)

You will need to provide at least 12 months of data for 2 stability lots of the 60 mg/1.8 mg products [REDACTED] (b) (4). Further, the batches selected should include AP135 polymer from both suppliers.

Heron's Pre-meeting comments:

Since the time of the submission of the briefing materials, Heron has additional stability data from the 60 mg/1.8 mg configuration [REDACTED] (b) (4)

[REDACTED] The 12-month data will be included in the NDA.

In addition, a 60 mg/1.8 mg lot was manufactured

(b) (4)

The NDA will include 3 months of long-term (25°C/60% RH) and accelerated (40°C/75% RH) stability data for all 3 of these lots. For all presentations, future lots will be manufactured

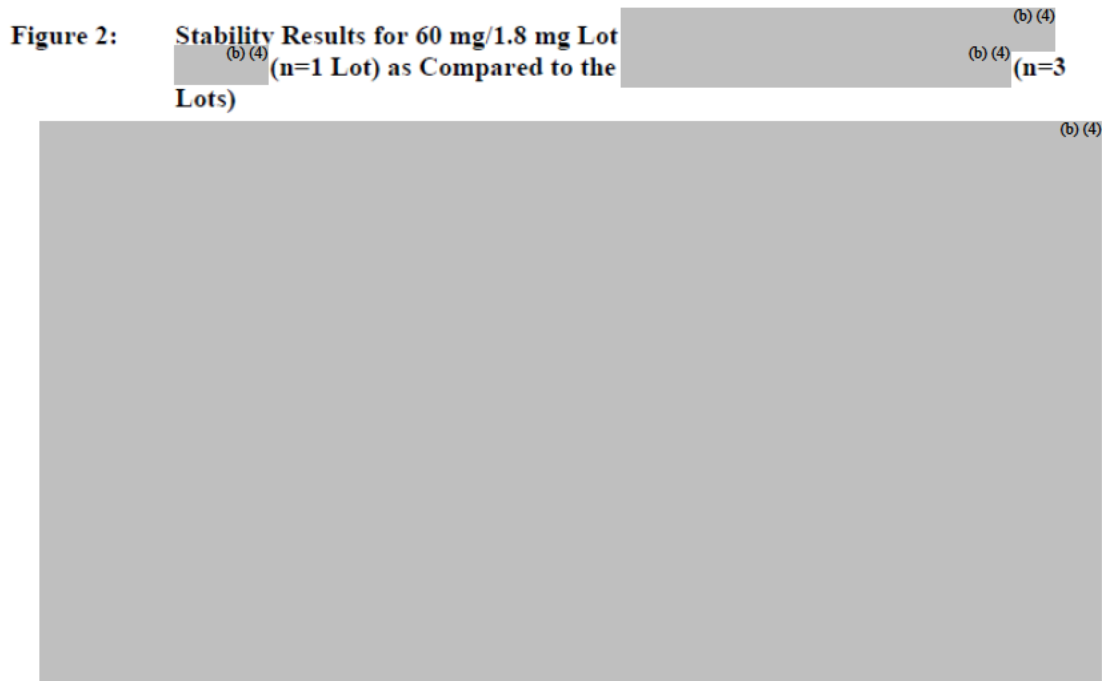
(b) (4)

Figure 1: Stability Results for 60 mg/1.8 mg Lots

(b) (4)

(b) (4)

(b) (4)



Heron has received Fast Track and Breakthrough Therapy designations for HTX-011. The Guidance “Expedited Programs for Serious Conditions – Drugs and Biologics” (2014) indicates that “FDA may exercise some flexibility on the type and extent of manufacturing information that is expected at the time of submission and approval for certain components (e.g., stability updates, validation strategies, inspection planning, manufacturing scale-up).” HTX-011 shelf life will be based on the 12-month data for the drug product manufactured (b) (4)

Based on those designations and the Guidance, Heron requests that FDA allow Heron to submit 6-month data under long-term and accelerated storage conditions for the 3 lots (b) (4) during the NDA review to support the proposed shelf life.

Discussion:

The Sponsor proposed to submit 6 months of stability data under long-term and accelerated storage conditions for the 3 lots (b) (4) in which the initial 3-month stability data will be submitted at the time of NDA submission, and the remainder 3 months will be submitted 3 months following initial NDA submission. The Division emphasized that 3 months of data at the time of NDA submission does not permit identification of any trends. If the Sponsor is granted Priority Review, submitting any additional stability data 3 months into a 6-month review timeline may lead to either inadequate time for review of the data at all or an extension of the review timeclock.

The Division further clarified that the molecular weight distribution profiles and associated viscosity data, for the polymer from both suppliers, should be included in the NDA.

Post Meeting Note: Changes in viscosity over the course of your proposed shelf-life may impact product performance. Your NDA must include justification that the proposed acceptable viscosity specification will not adversely impact performance (e.g., safety, efficacy) at either end of the range.

The Division also stated that the Sponsor should determine whether the (b) (4) (b) (4) will affect extractability and leachability safety profile as this may have significant implications. The Sponsor understood and agreed.

Question 3: Does the FDA agree that it is acceptable for Heron to submit stability data for 13 lots in the NDA submission and submit additional stability data for the 2 lots manufactured with AP135 from a secondary supplier for inclusion in the NDA within 1 month following the final complete application of the NDA to allow for an earlier NDA submission?

FDA Response:

No, we do not agree. The application must be complete at the time of submission and should include all data to qualify the second supplier of AP135, as was agreed to at the CMC-only Pre-NDA meeting on May 17, 2018.

Heron's Pre-meeting comments:

Heron understands that the application must be complete at the time of submission and will include all data to qualify the second supplier of AP135 as was agreed to at the CMC-only Pre-NDA meeting on May 17, 2018. For the qualification of (b) (4) AP135 in HTX-011, Heron will submit 3-month stability data at 25°C/60% RH and 40°C/75% RH on 2 lots of drug product in the NDA as agreed to at the CMC-only Pre-NDA meeting. Heron understands that FDA does not agree with submitting the 3-month stability data 1 month after the final complete submission of the NDA. The 6-month data will be available at the end of November 2018 during the review.

Discussion: No further discussion.

Question 4: Does the FDA agree that it is acceptable to commercialize 2 presentations of the 10 mL vial (60 mg/1.8 mg fill and 200 mg/6 mg fill) and 1 presentation of the 20 mL vial (400 mg/12 mg fill) to deliver doses that cover a variety of surgical procedures?

FDA Response:

From the CMC perspective, sufficient stability data is needed to support all commercialized presentations, at the time of the NDA submission.

Heron's Pre-meeting comments:

Heron will provide sufficient stability data to support all commercialized presentations at the time of the NDA submission.

Discussion: No further discussion.

Question 5: Is the proposed evaluation of extractables and leachables for HTX-011 adequate?

FDA Response:

Your proposed evaluations of extractables and leachables appear reasonable. Extractable/leachable studies should be conducted according to USP Chapter 1663/1664. Conditions used should be vigorous enough such that the extraction study can identify all potential leachables from the container closure system in order to demonstrate a good correlation with the leachable assessment. Further, determination of leachables should be included as part of the stability protocol for each presentation.

Heron's Pre-meeting comments:

The extractable/leachable studies are being conducted according to USP <1663> and <1664>. The conditions used are intended to be vigorous enough so that the extraction study can identify all potential leachables from the container closure system to demonstrate a good correlation with the leachable assessment. The determination of leachables will be assessed as part of the stability for the 60 mg/1.8 mg, 200 mg/6 mg, and 400 mg/12 mg presentations.

Discussion: No further discussion.

Question 6: Does the Agency agree that the proposed validated method to monitor the IVR of bupivacaine and meloxicam from HTX-011 drug product is acceptable?

FDA Response:

You have not submitted adequate information to determine the acceptability of your proposed IVR method. We remind you that the full IVR method development and validation report needs to be reviewed by the Agency to determine the acceptability of your proposed IVR method. Refer to the (CMC-only) End-Of-Phase 2 meeting preliminary comments dated May 8, 2017. We also have the following comments regarding your proposed IVR method:

- 1. We recommend that you include additional time points between 6 and 24 hours to establish a complete in vitro release profile.**
- 2. You have not adequately demonstrated the discriminating ability of your proposed IVR method. Drug products manufactured with different viscosities had similar IVR profiles per f2 calculations when using 60 rpm (b) (4) therefore no conclusions can be made regarding the IVR method's ability to discriminate for different viscosity using this rotational speed. In addition, you did not provide the complete IVR data for Figure 4, therefore no conclusions can be made regarding the**

IVR method's ability to discriminate for altered drug product formulations. We remind you that to demonstrate the discriminating ability of the selected IVR method, you should compare the IVR profiles of the reference (target) drug product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical material attributes, critical formulation variables, and critical process parameters (e.g., $\pm 10\text{-}20\%$ change to the specified values or ranges for these variables).

- 3. Provide the complete IVR data (i.e., individual, mean, SD, %RSD and profiles) for all IVR studies conducted as part of your method development process.**

Heron's Pre-meeting comments:

For additional method development, Heron will add a timepoint between 6 and 24 hours to further characterize the IVR profile, and include these data in the development report. These data will support the final choice of timepoints for the QC method.

We have established (b) (4)

The development report will contain more examples of the discriminatory power of the validated (b) (4) rpm method. (b) (4)

This information will be provided in the NDA.

Furthermore, the IVR method captures (b) (4)

(Figure 3). The changes in % released at each timepoint, for each viscosity, are tabulated in Table 1 and Table 2.

Figure 3: IVR Profiles for HTX-011 as a Function of Viscosity for the (b) (4) rpm Method (Top: Bupivacaine; Bottom: Meloxicam)



Table 1: Change in % Released (Bupivacaine) Relative to

(b) (4)

(b) (4)

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Table 2: Change in % Released (Meloxicam) Relative to

(b) (4)

(b) (4)

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(b) (4)

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The individual dissolution data for Figure 4 in the briefing material is given in Table 3 and [Table 4](#).

Table 3: IVR Results for HTX-011-49, Research Lot 0414182

(b) (4)



Table 4: IVR Results for HTX-011, Research Lot 0414183

(b) (4)



Heron will provide complete IVR data (ie, individual, mean, SD, % RSD and profiles) for all IVR studies conducted as part of method development.

Discussion:

The Sponsor agreed to include additional time points between 6 and 24 hours to establish a complete in vitro release profile. The Sponsor proposed (b) (4)
(b) (4) The Division stated that an adequate justification of their proposed methodologies will be needed, (b) (4)
(b) (4) The Division reminded the Sponsor that in order to demonstrate discriminating ability of the selected IVR method, the Sponsor should look at meaningful changes for the most relevant critical material attributes, critical formulation variables, and critical process parameters (± 10 -20% change to the specified values or ranges for these variables). The Division also advised the Sponsor to submit a full in-vitro in-vivo-correlation (IVIVC) report for the Division to review if they want to rely on their IVIVC. In addition, the Division recommended the Sponsor investigate the correlation between the proposed drug product (b) (4)
(b) (4) The Sponsor agreed to provide these requested data.

Post Meeting Note:

The Sponsor should fully validate the proposed IVR method and submit the validation report to the Division for review. The provided data show that the proposed IVR method might not be sensitive enough to discriminate the meaningful changes in viscosity (± 10 -20% change to the specified viscosity ranges). It is crucial for the Sponsor to set acceptable ranges for the polymer degradation. When such a range is established, the Sponsor should explore if the proposed IVR method is able to discriminate the meaningful changes (b) (4)

Nonclinical

Question 7: *Does the FDA agree that the polymer, AP135, in the intended commercial formulation of HTX-011 is adequately qualified?*

FDA Response:

As discussed during a teleconference on April 3, 2018, AP135 is considered a novel excipient that must be adequately qualified for safety consistent with the FDA Guidance for Industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf>. It was also discussed that adequate qualification must include the fate of the polymer via detailed discussion of the histopathology at the injection site over time and/or leveraging knowledge of the metabolic fate of the polymer to provide an estimate of total tissue residence time. The approach of using the new 28-day studies described in your briefing package with the to-be-marketed formulation (HTX-011-056) and the reproductive and genetic toxicity studies conducted with APF18A to qualify this excipient appear to be adequate to support filing an NDA. However, final determination of the adequacy of your assessment will be determined upon review of your collective data at the time of the NDA review.

Heron's Pre-meeting comments:

Heron appreciates FDA confirmation that the approach described for the 28-day studies and the use of APF18A for reproductive and genetic toxicity appears to be adequate to support the NDA filing for qualification of AP135.

Heron understands that adequate qualification must include the fate of the polymer. Preliminary results from the 28-day repeat-dose toxicity study in dogs with HTX-011-56, with dosing every 48 hours, demonstrated by histopathology that test material was present in the injection sites and was observed in most of the animals in the HTX-024 (vehicle control) and HTX-011-56 treated groups at terminal necropsy 16 days after the last of 14 total doses. These findings were no longer noted in these groups at the 14-day recovery necropsy, except for 2 vehicle control females. At the recovery necropsy, no other dermal injection sites findings were noted, indicating a reversal of all the adverse effects following cessation of dosing and complete elimination of AP135 from the injection site. Similarly findings were observed in the 28-day repeat dose toxicity in rats with HTX-011-56 demonstrating complete elimination of AP135 by the end of the 14-day recovery period.

Discussion: No further discussion.

Question 8: Does the FDA agree that the (b) (4) excipients in the intended commercial formulation of HTX-011 are adequately qualified?

FDA Response:

We cannot agree at this time that the (b) (4) excipients in the intended clinical formulation are adequately qualified. The new 28-day nonclinical studies utilizing the clinical formulation described in your briefing package have not been submitted and are key studies for evaluating the excipients. Final determination of the adequacy of your assessment will be determined upon review of your collective data at the time of the NDA.

Heron's Pre-meeting comments:

The data from the recent 28-day repeat-dose toxicity studies utilizing the to-be-marketed formulation, HTX-011-56, will be included in the NDA to support the qualification of the (b) (4) excipients. Results from the high dose of HTX-011-56 administered in the recently completed 28-day repeat-dose toxicity study in dogs will provide qualification of all (b) (4) excipients. In addition, as noted in the Briefing Document, all 3 (b) (4) excipients are listed in the FDA's Inactive Ingredients for Approved Drug Products database and are categorized to have low acute toxicity via many routes of exposure with approval for use in cosmetics and/or in human food. Triacetin is also on the Generally Recognized as Safe list.

Discussion: No further discussion.

Question 9: *Does the FDA agree that the impurities in the drug substances bupivacaine and meloxicam used in the manufacture of HTX-011 are adequately qualified, and that the process for qualification of degradation products is acceptable?*

FDA Response:

Impurity and degradation products should be assessed as described in ICH Q3A(R2), ICH Q3B(R2), and ICH M7. Based on the data submitted in your briefing package, your proposed specifications appear to be within the appropriate thresholds outlined in these guidances. However, final determination of the adequacy of your assessment will be determined upon review of your collective data at the time of the NDA.

Heron's Pre-meeting comments:

As noted by FDA, all current specifications for impurities and degradation products for HTX-011 drug substances and drug product are within the relevant thresholds that are outlined in ICH Q3A(R2), ICH Q3B(R2), and ICH M7.

Discussion: No further discussion.

Clinical Pharmacology

Question 10: *Does the FDA agree with the described approach for establishing a scientific bridge between HTX-011 and MARCAINE using PK data from HTX-011 clinical studies?*

FDA Response:

No, we do not agree. As indicated in our March 30, 2018, Type C meeting responses, your product is locally acting, so systemic exposure will provide information on systemic safety, but not local efficacy and safety.

The rate of systemic absorption and PK profile for peri-operative products irrespective of the type of formulation will depend upon vascularity of the administration site, the surgical procedure, the total dose of drug administered, the route of administration, etc. As such, PK parameters from one dose, administration site or route of administration cannot be extrapolated to another dose, administration site or route of administration. Therefore, for MARCAINE, your assumption of dose proportionality between different surgical procedures and to a dose outside your tested dose range is not appropriate.

In addition, when we assessed the dose-proportionality among different doses of HTX-011, in different surgical procedures using the mean AUC_{inf} and C_{max} values provided in the meeting package, we note that HTX-011 does not exhibit dose-proportionality for bupivacaine or meloxicam. See our response to Question 12.

For systemic exposure comparison, we will use the observed C_{max} and AUC values, not the (b) (4) ratio as you proposed.

Based on your clinical studies, the systemic exposure of bupivacaine from your product is higher than the exposure from Marcaine. For establishing the scientific bridge between HTX-011 and MARCAINE, if your product results in higher systemic exposure than the listed product, you may need to provide additional justification to support the systemic safety of your product.

Additional Comments:

In addition, to establish the necessary scientific bridge between HTX-001 and MARCAINE, ensure that:

- 1. MARCAINE was administered as per dosing regimen recommended in the product labeling.**
- 2. HTX-001 is administered using the dosing regimen and route of administration for which you are seeking approval.**
- 3. The final to be marketed formulation of HTX-001 was used in clinical studies.**

You have not provided any details regarding the PK comparison of your product to MOBIC in the pre-NDA meeting package. Therefore, we recommend that you follow the advice provided in March 30, 2018, Type C meeting responses to establish the necessary scientific bridge.

Heron's Pre-meeting comments:

PK/PD: Heron understands that for a long-acting local anesthetic product, systemic exposure generally does not provide information on local efficacy. Rather than using the systemic plasma concentrations as the basis of the PK/PD analysis, the HTX-011 PK/PD correlation presented in the Briefing Document used the in vivo release rate of bupivacaine (disease active ingredient), calculated from deconvolution of the plasma concentrations, correlated to analgesia provided by HTX-011. The release rate of bupivacaine represents the exposure of bupivacaine at the local site following application of HTX-011. In addition, Heron is developing (b) (4)

C_{max} vs AUC: The C_{max} vs AUC plot is not intended to address local and systemic safety, but is useful for understanding the consistency of absorption across multiple surgical sites. Thus, the analysis is primarily intended to inform dosing considerations across surgical procedures with varying anatomic spaces and vascularity.

Overall systemic exposures of peri-operative products are affected by 3 variables: rate of absorption affecting C_{max} , dose affecting C_{max} and AUC, and the rate of clearance affecting C_{max} and AUC.

The size of the surgical incision and vascularity can only have an effect on the rate of absorption; dose is an independent variable and clearance will be unaffected. Therefore, to isolate the effect of surgical size and vascularity, the rate of absorption from the site of administration must be understood. One way this can be accomplished is by evaluating the relationship between $C_{\max}$ and AUC. In a plot of $C_{\max}$ vs AUC, the effects of dose and clearance rate are cancelled out and we are left only with the rate of absorption that is proportional to the slope of the line formed by the data points. If the rate of absorption is consistent, then the data points for all subjects will form a single line indicating they all have the same rate of absorption. The greater the scatter (ie, the more the data points deviate from the regression line), the greater the variability in absorption. As can be seen in the plot of $C_{\max}$ vs AUC for bupivacaine HCl (Figure 4), there is a large scatter in the data points around the line of regression indicating high variability in the rate of absorption of bupivacaine HCl. This is consistent with historical clinical experience. In contrast, there is much less scatter about the regression line for the same plot with HTX-011 (Figure 5). For example, the results from bunionectomy, with a small dose in a small surgical site, fall on the same regression line as the results for TKA and herniorrhaphy, which have much higher doses, larger surgical sites and higher vascularity. This indicates that the rate of absorption of bupivacaine from HTX-011 is relatively independent of surgical size and vascularity. Absorption of bupivacaine into the surrounding tissues, once released from bupivacaine HCl, is very rapid compared to the rate of release of bupivacaine from HTX-011; thus, the rate of release of bupivacaine from HTX-011 is the rate-controlling step in systemic absorption.

Figure 4: Updated Briefing Document Figure 9: Bupivacaine C_{max} Versus AUC_{inf} Following a Single Injection of Bupivacaine HCl in Various Surgical Models (includes additional cohorts from Phase2b Studies 209 and 211)

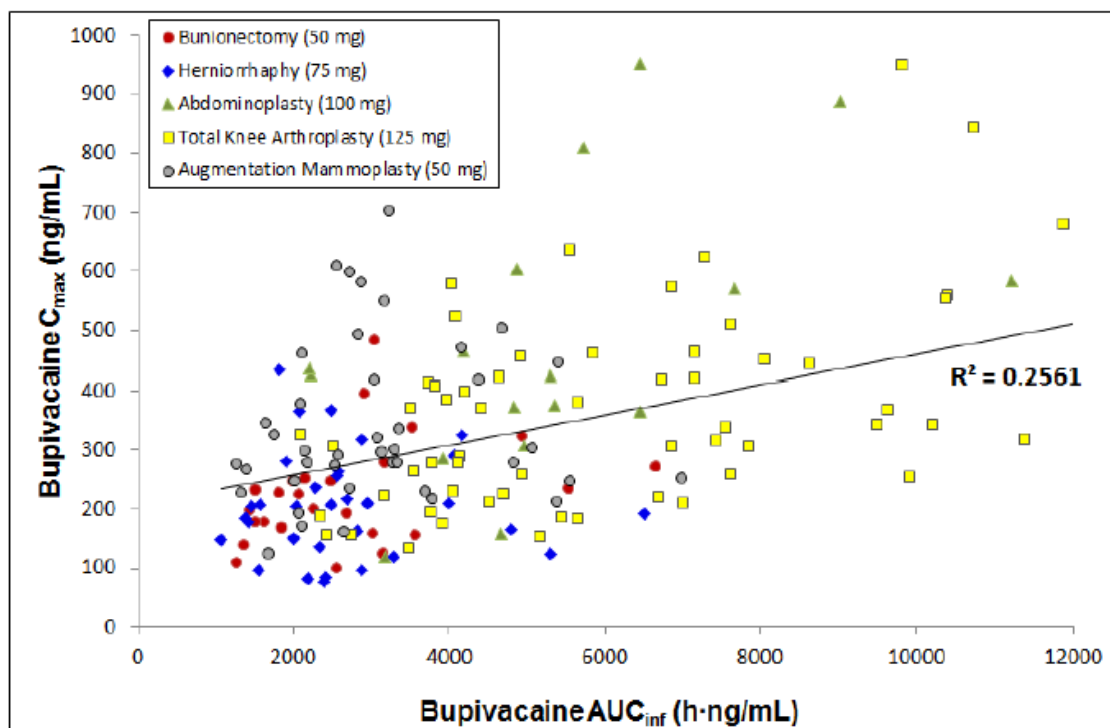
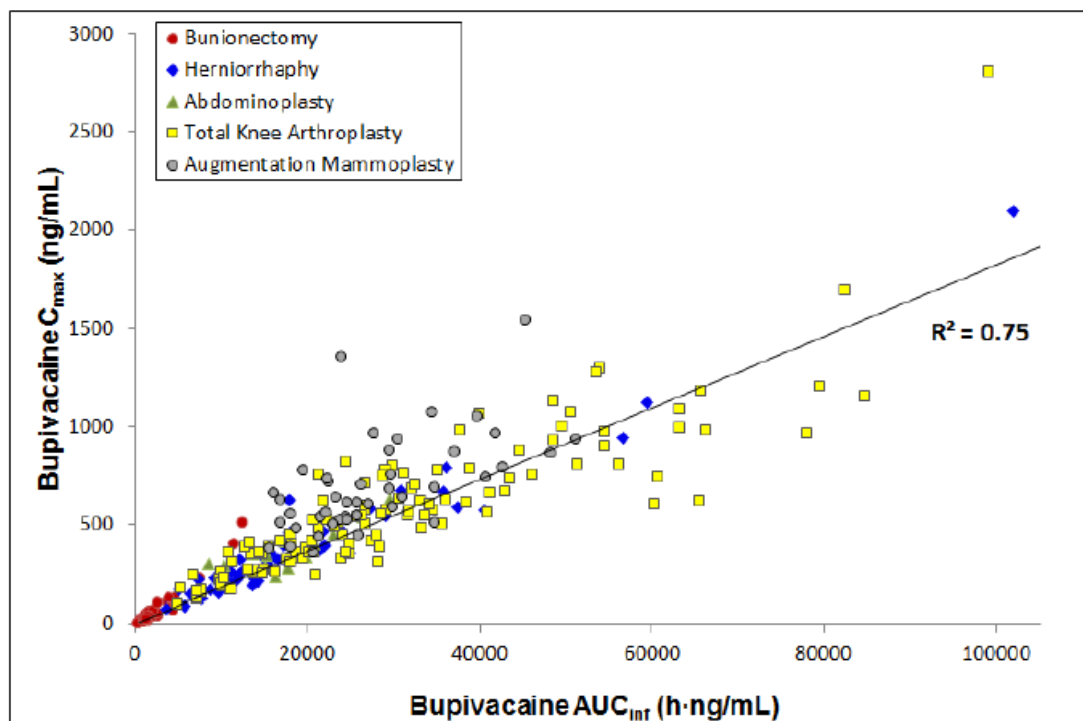


Figure 5: Updated Briefing Book Figure 11: Bupivacaine C_{max} vs AUC_{0-inf} Following Administration of HTX-011 by Instillation Only (includes Phase2b Studies 209 and 211 HTX-011 400 mg/12 mg given by instillation)



Dose proportionality: As mentioned on page 91 of the Briefing Document, the exposure of bupivacaine and meloxicam administered via instillation in abdominoplasty was unexpectedly low. In this study, the procedures involving drain placement, irrigation, and suction were not specified by the protocol and therefore could be highly variable. It is possible that some quantity of drug was lost due to draining, irrigation, and suction. This may explain the decreased efficacy and reduced bupivacaine plasma C_{max} and AUC exposures observed with the HTX-011 400 mg/12 mg instillation cohort, the only cohort in the study that received the product by instillation. To mitigate this risk, Heron intends to include appropriate recommendations in labeling to administer following irrigation and suction and to consider location of drain placement. Therefore, the PK parameters obtained for instillation administration in abdominoplasty cannot be compared with other surgeries. When this abdominoplasty group is removed from the dose-linearity figure, a proportional increase in C_{max} and AUC with dose across surgical procedures becomes more apparent (Figure 6 and Figure 7). This trend suggests that systemic exposure for HTX-011 is consistent across surgical procedures.

Data in the Briefing Document presented preliminary analysis for Study 209 PK analyses that included all available data for all subjects in Cohort 1. In Cohort 1 (HTX-011 200 mg/6 mg), plasma sampling was limited to collection up to 72 hours postdose. As a result there was insufficient plasma concentration data in some subjects to be able

to accurately calculate AUC_{inf} . When those subject are excluded as set forth in the PK analysis plan that is consistent with all studies, the preliminary result for mean AUC_{inf} for HTX-011 200 mg/6 mg by instillation is 16,663 ng·h/mL rather than the cited 23,200 ng·h/mL in the Briefing Document, which compares well to the mean AUC_{inf} of 13,200 ng·h/mL for HTX-011 200 mg/6 mg given by instillation for herniorrhaphy (Study 202). The preliminary PK data is now available for Cohort 2 of Study 209 and the preliminary result for mean AUC_{inf} for HTX-011 400 mg/12 mg by instillation is ~38,000 ng·h/mL (without ropivacaine) and ~33,600 ng·h/mL when given with low dose ropivacaine. This compares well to the mean AUC_{inf} of 29,700 ng·h/mL for HTX-011 400 mg/12 mg given by instillation for herniorrhaphy (Study 202).

For a parenterally-administered product, one expects that there is 100% bioavailability. Therefore, AUC should be linear with dose if there is a sufficient sample size. This is the case with both HTX-011 and bupivacaine HCl; we in fact see that AUC is quite linear over a very wide range of doses even when including both bupivacaine HCl and HTX-011. The higher AUC values for HTX-011 simply reflect the higher overall mass of bupivacaine administered over the 3-day period.

Figure 6: Updated Briefing Book Figure 8: Bupivacaine Dose Versus Systemic Exposure (C_{max}) Following Single Administration of HTX-011 via Instillation in Various Surgical Models (Study 203 data removed; includes Phase 2b Studies 209 [400 mg dose cohort] and 211 [all instillation cohort] and Phase 3 Studies 301 and 302 [all data])

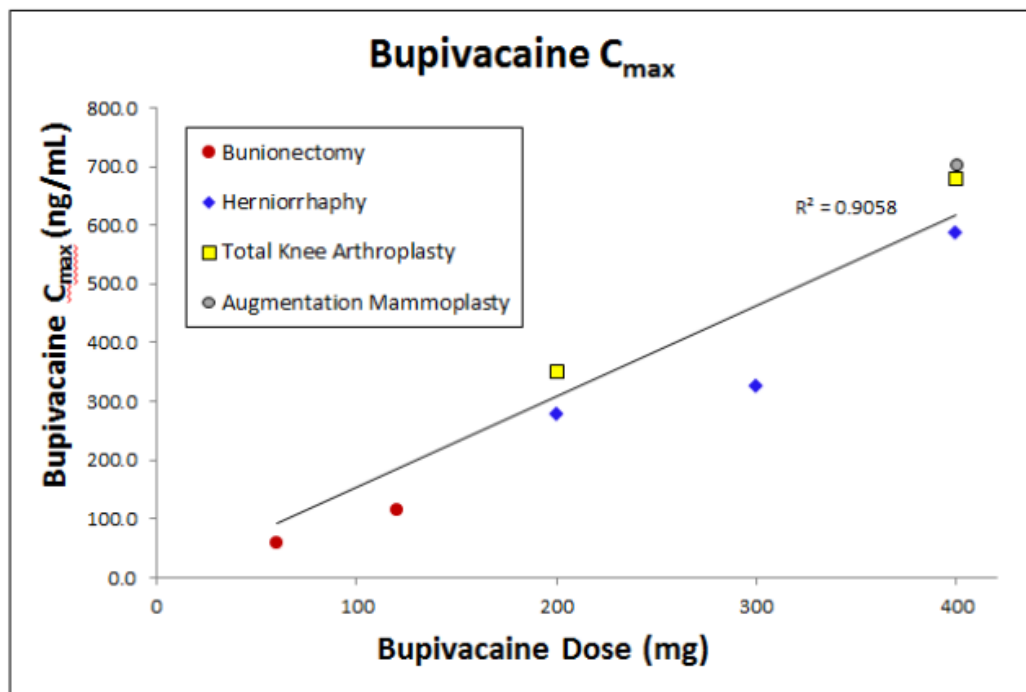
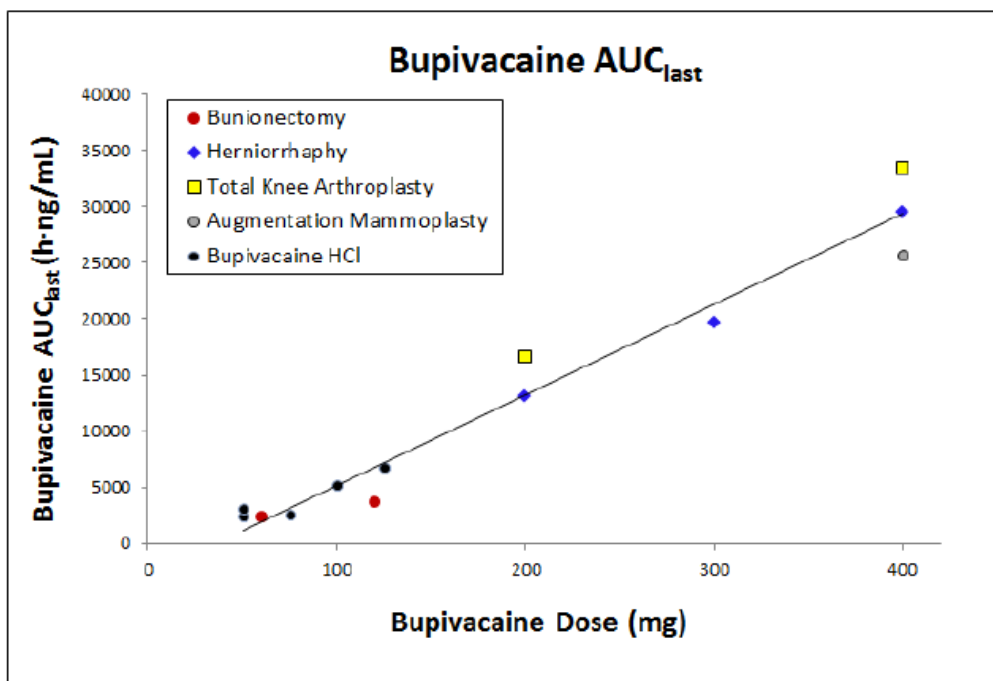


Figure 7: Bupivacaine Dose Versus Systemic Exposure (AUC_{last}) Following Single Administration of HTX-011 via Instillation in Various Surgical Models (all available data)



Note: Bupivacaine doses are as follows:

- Bunionectomy: HTX-011 60 mg (instillation with a Luer-lock applicator, Study 208 and 301 pooled), HTX-011 120 mg (instillation with and without a Luer-lock applicator, Study 208).
- Herniorrhaphy: HTX-011 200 mg (instillation, Study 202), HTX-011 300 mg (instillation with fentanyl, Study 202 and 302 pooled), and HTX-011 400 mg (instillation with and without fentanyl, Study 202).
- Total Knee Arthroplasty (preliminary data): HTX-011 200 mg (instillation, Study 209, AUC_{inf} is shown), HTX-011 400 mg (instillation with and without ropivacaine, Study 209).
- Augmentation mammoplasty (preliminary data): HTX-011 400 mg (instillation, Study 211).
- Bupivacaine HCl: bupivacaine HCl 75 mg (injection with and without fentanyl, Study 202), bupivacaine HCl 100 mg (injection, Study 203), bupivacaine HCl 50 mg (injection with and without a Mayo block, Study 208), bupivacaine HCl 125 mg (injection, Study 209, preliminary data), bupivacaine HCl 50 mg (injection by nerve block, Study 211, preliminary data).

PK Bridge to MARCAINE: In establishing a scientific bridge between HTX-011 and MARCAINE, Heron acknowledges that the systemic exposure (C_{max} and AUC) of bupivacaine from HTX-011 is higher than the exposure from MARCAINE in certain surgical procedures with higher bupivacaine doses of HTX-011. When bupivacaine doses are similar (as seen in bunionectomy with bupivacaine HCl 50 mg and HTX-011 60 mg/1.8 mg), C_{max} and AUC for HTX-011 is considerably lower than MARCAINE. The systemic safety of HTX-011 observed with higher doses (eg, HTX-011 400 mg/12 mg) should be supported by the clinical safety data established in the Phase 2 and 3 clinical studies.

Discussion:

The Sponsor clarified that the C_{max} and AUC plots only addresses the rate of absorption at different locations in the body, and is not intended to be used for understanding local or systemic safety. The Division stated that when the Sponsor conduct PK/PD modeling, they should make it clear as to what the purpose and intention is for each model. The Division also recommended

the Sponsor to submit PK graphs with different dosages and procedures on the same graph to show how the PK profiles are different. The Division informed the Sponsor to plot individual data to show variability as well as mean data. The Sponsor agreed and will look at release rate at the site over time as well as variability over surgical procedures.

Post Meeting Note:

The Sponsor is encouraged to check the clinical pharmacology backgrounder and slides for the Exparel AC meeting held on February 14 and 15, 2018, and follow the PK data analysis plan for this NDA submission.

(<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm591101.htm>)

Clinical

Question 11: Does the Agency agree that TKA is an appropriate surgical model to represent high vascularity and a large anatomic space?

FDA Response:

No, we do not agree. A knee may arguably be considered a large anatomical space, however, this anatomical compartment is not a highly vascular compartment. Surgical models involving the thoracic cavity (intercostal space), head and neck procedures, as well as large spine procedures would be more appropriate examples of highly vascular, as well as, potentially large anatomical spaces, because higher level of systemic drug absorption would be expected in these anatomical sites. Although blood loss in a TKA may be substantial, it is typically associated with surgical skill or technique, tourniquet time, and possibly patient-related factors. Since the incision for TKA is not near a major vascular plexus and blood loss would be well-controlled at the time of HTX-011 application, this anatomic compartment does not adequately represent a highly vascular space.

Heron's Pre-meeting comments:

Heron would like to seek clarification on the examples of highly vascular surgical procedures provided by the FDA (thoracic cavity [intercostal space], head and neck procedures, and large spine procedures) that would be appropriate for infiltration rather than nerve block.

Discussion:

The Sponsor asked the Division for clarification on examples of highly vascular surgical procedures that would be appropriate for infiltration rather than nerve block. The Division stated appropriate examples of highly vascular procedures as well as large anatomical spaces include: spinal, intrathoracic cavity procedures involving a sternotomy, and head and neck procedures (i.e., large neck dissection). The Division also stated that since breast procedures are extrathoracic, these would also not represent a highly vascular space.

Question 12: Given the totality of the data to be included in the NDA, does the FDA believe that an Advisory Committee Meeting will be required for the HTX-011 NDA?

FDA Response:

Determination of whether an Advisory Committee Meeting will be necessary will be made upon preliminary review of your NDA. An Advisory Committee may be necessary to discuss the totality of the data and the appropriateness of the surgical models in your development program for a generalized indication.

Further, we do not agree with your statement that “HTX-011 demonstrated a consistent, predictable PK profile in several Phase 2 surgical models representing a range of anatomic spaces and vascularities.” As mentioned in our response to Question 10, HTX-011 does not exhibit dose proportional PK for bupivacaine or meloxicam between different procedures, thereby does not exhibit predictable PK. For example:



Note that for your conducted correlations (Figures 9, 10, and 11 in meeting package), the correlation between C_{max} and AUC for HTX compared with MARCAINE appears to be driven by the higher AUC values for HTX on the x-axis.

As indicated in our March 30, 2018, Type C meeting responses, as your product is locally acting, the systemic exposure will provide information on systemic safety, but not local efficacy and safety. Hence, we do not agree that the PK or PK/PD analysis you proposed can be used to support local efficacy and local safety. Note (b) (4)

and we do not think this approach is informative to support systemic safety of your product.

As mentioned in our response to Question 10, for systemic exposure comparison, we will use the observed C_{max} and AUC values not the (b) (4) **as you proposed.**

Heron's Pre-meeting comments:

Heron understands that the determination of whether an Advisory Committee is necessary will be made upon the preliminary review of the NDA and will be communicated to Heron by Day 60 with the determination of Priority Review or with the

Day 74 Letter. See Question 10 for Heron's response as it pertains to the predictable PK profile.

Discussion:

See our response to Question 10.

Question 13: Does the Agency agree that the advice given related to the combination product at the EOP2 meeting on 15 June 2017 has been addressed with the proposed HF Validation protocol, and that there are no additional requirements regarding the combination products for filing the NDA?

FDA Response:

From a human factors perspective, the proposed HF Validation protocol addresses the advice given related to the combination product at the June 15, 2017, End-Of-Phase 2 Meeting. The protocol is currently under review and we will notify you if we determine that there are deficiencies.

From a CDRH perspective, in our previous comments to you on May 24, 2017, we recommended that you describe the final configuration of the administration kit and include the necessary data to ensure safe and effective administration. In addition to demonstrating compatibility of the drug and device, we asked that you address device failure risk such as piston seal blowback, leakage at luer adapter/syringe connection, syringe barrel fracture, and extractable volume in your future marketing submission. Within this meeting package, you have stated that the device components will be 510(k) cleared. In your future marketing submission, please ensure that you include the Letter of Authorization (LOA) for the 510(k) within the NDA so the performance testing can be reviewed. As you intend to provide a convenience kit with the drug product, your marketing application should identify who will perform the co-packaging and other manufacturing steps to produce the final finished product for marketing. Furthermore, your marketing submission should include compatibility testing of all the components in the kit, as well as ensure that their use is within the cleared 510(k) indications. The 510(k) submissions may not contain all of the data necessary to support use of the device in the context of use for the NDA product and we recommend that you work with the 510(k) holders to assure that the 510(k) submission includes the necessary information. Where 510(k) submissions are not referenced for kit components, we recommend that you provide the device safety and effectiveness data in the NDA, or work with the device suppliers to submit a device master file to FDA.

Heron's Pre-meeting comments:

Heron received FDA comments on the HF Validation protocol on June 18, 2018. FDA listed several areas of concern with the protocol.

Protocol

Heron appreciates FDA's comments on the human factors validation study protocol and

Instructions for Use. Heron proposes to incorporate the recommended revisions with the following exceptions, for which we would appreciate FDA feedback:

Human Factors Validation Protocol Comment A4.

After a new product is added to a formulary, its use in a surgical procedure is the decision of the surgeon, based upon at least basic information about the product and its use. In the second formative study, which included 6 surgeons, Heron asked the question, "What would you do when you first learned about a new product like this one...?" to learn what kind of information would be needed by the surgeon prior to product use. In this study, surgeons consistently expressed the need for basic information similar to the information contained in the IFU. Accordingly, the co-package kit containing the IFU was available in the simulated operating room in recent exploratory studies conducted at 2 additional sites to evaluate 2 additional locations for the planned HF validation study. (b) (4)

(b) (4) In light of FDA's comments, Heron recognizes that this question was a holdover from the second formative protocol that was inadvertently included in the proposed HF validation protocol and will be accordingly removed from the protocol. We apologize for any confusion this statement may have caused. Heron proposes to revise the Moderator Guide to provide at least basic information about the product and its use (b) (4)

Proposed revisions to the language in the Moderator Guide appended to the draft HF Validation protocol are as follows (with strikethrough to denote deleted text and underlining to denote new text):

(b) (4)

(b) (4)



Please provide comments on our proposed changes to the Moderator Guide and availability of IFU to the surgeon participants.

Human Factors Validation Protocol Comment A1.

FDA has recommended

(b) (4)



Please confirm whether FDA agrees with this approach.

User Interface Comments B1

FDA recommended

(b) (4)

the IFU

(b) (4)



(b) (4)

Please confirm FDA agreement

(b) (4)

Other comments related to Question 13

(b) (4)

Discussion:

The Sponsor proposed revisions to their HF Validation protocol in their pre-meeting comments. The Division was not able to provide responses to the revised HF Validation Protocol during the meeting, but they can expect feedback within 30 days. The Sponsor should officially submit the revised HF Validation protocol to the IND for review. The Division clarified that resubmission of the entire protocol is not required, and the Sponsor can submit a letter asking for clarification of the protocol instead. The Division also noted

(b) (4)

from the HF Validation protocol, they need to reconcile their response from Question 10 in their May 18, 2018, briefing package, in which the Sponsor stated that in order to mitigate the risk of reduced bupivacaine and meloxicam exposure in abdominoplasty procedures, the Sponsor intends to include appropriate recommendations in labeling to administer following irrigation and suction and to consider location of drain placement. The Sponsor stated they plan to conduct knowledge-based testing versus user-testing. The Division reiterated that the adequacy of the proposed plan and rationale will be reviewed at the time of the resubmission.

Labeling

Question 14: Does the FDA agree that it is appropriate to include the bupivacaine text in PLLR format?

(b) (4)

FDA Response:

No, we do not agree. As previously discussed at the Type C meeting on April 3, 2018, in order to reference any information (b) (4)

you will need to submit appropriate reference and certifications as per the requirements for a 505(b)(2) application. See the '505(b)(2) Regulatory Pathway' information below for more details regarding submissions under 505(b)(2). You may also refer to the following guidances for additional information on PLR and PLLR content and format:

- **Guidance for Industry *Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements***, available at <https://www.fda.gov/downloads/drugs/guidances/ucm075082.pdf>
- **Draft Guidance for Industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format***, available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>

Heron's Pre-meeting comments:

As a clarification, Heron does not intend (b) (4) for our 505(b)(2) application. The intent was to use PLLR-formatted, bupivacaine-related text agreed to by FDA in the proposed HTX-011 prescribing information (PI). However, Heron will use the content from the current approved PIs for the reference listed drugs, MARCAINE (bupivacaine HCl Injection) and MOBIC (meloxicam) to draft the HTX-011 labeling according to the PLR and PLLR.

Discussion: No further discussion.

Question 15: Does the Agency agree with the proposed approach (b) (4) in Prescribing information (b) (4) (see the Target Product Profile in Appendix B) based on the novel characteristics of HTX-011?

FDA Response:

We cannot comment on the appropriateness of the proposed draft Prescribing Information at this time. Your NDA should include a robust justification, supported by clinical PK data, to support using the proposed (b) (4). Additionally, information (b) (4) is not appropriate for the label. Appropriate language for labeling will be determined during the review of your NDA, if the totality of data support approval.

Heron's Pre-meeting comments:

Heron intends to provide a robust justification supporting the (b) (4) in the NDA.

Discussion: No further discussion.

Question 16: Does the agency agree with the proposed content in Dosage and Administration Section 2 in the draft proposed Prescribing Information (see the Target Product Profile in [Appendix B](#))?

FDA Response:

We cannot comment on the appropriateness of the draft Prescribing Information at this time. Appropriate language for labeling will be determined during the review of your NDA, if the totality of data support approval. You may refer to Guidance for Industry, *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*, available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075066.pdf>, for additional information.

Heron's Pre-meeting comments:

Heron intends to propose content for the Dosage and Administration section of the draft PI in the NDA written according to the guidance.

Discussion: No further discussion.

Question 17: Based on the market research project report, does the FDA have any comments on the use of (b) (4) in the indication statement and labeling instead of (b) (4)

FDA Response:

As previously discussed at the Type C Meeting on April 3, 2018, your NDA must contain a complete analysis of your market research and your justification for the proposed indication language. In addition, results of the Human Factor Validation studies will be considered during the final determination of the appropriateness of the proposed indication language, if your NDA data support approval.

Heron's Pre-meeting comments:

The market research report justifying the use of (b) (4) was included within Pre-NDA briefing materials. This report includes a complete analysis of the market research. It will be provided in the NDA with a justification for the proposed indication language, taking into account the Human Factor Validation study results.

Discussion: No further discussion.

Question 18: Does the Agency agree that the CV boxed warning included in the MOBIC USPI is not required for HTX-011 and the CV warnings can be addressed in Section 5 Warnings and Precautions as proposed in the Target Product Profile in [Appendix B](#)?

FDA Response:

We cannot comment on the applicability of the CV boxed warning for HTX-011 until all pertinent safety data from your development program have been reviewed. Your NDA should include a robust justification, supported by data from your development program, on why you believe the boxed warning in the MOBIC package insert is not applicable to your drug.

Heron's Pre-meeting comments:

Heron will provide a robust justification of why the CV boxed warning in the MOBIC package insert is not applicable to HTX-011 in the NDA.

Discussion: No further discussion.

Question 19: Does the Agency agree that the GI boxed warning from MOBIC is not required for HTX-011 and the GI warnings can be addressed in Section 5 Warnings and Precautions of the prescribing information in [Appendix B](#)?

FDA Response:

Refer to response to Question 18.

Heron's Pre-meeting comments:

Heron will provide a robust justification of why the GI boxed warning in the MOBIC package insert is not applicable to HTX-011 in the NDA.

Discussion: No further discussion.

Question 20: Does the Agency agree with the proposed approach for Section 12.1, Mechanism of Action in the Prescribing Information for HTX-011?

FDA Response:

We cannot comment on the appropriateness of the proposed draft Prescribing Information at this time. However, note that newly proposed labeling language that is not from the referenced products must be adequately supported by data and be clinically meaningful to be included in labeling. Appropriate language for labeling will be determined during the review of your NDA, if the totality of data support approval.

Heron's Pre-meeting comments:

Heron intends to propose language in the draft PI describing the mechanism of action of the HTX-011 fixed-combination product that is clinically meaningful and adequately supported by data.

Discussion: No further discussion.

Question 21: Does the Agency agree

(b) (4)

FDA Response:

We cannot comment

(b) (4)

until we have reviewed all the relevant data from your development program. However, your NDA must include a robust justification on how you have determined the safety of additional postoperative NSAID use, which is based on data from your development program and literature data, if appropriate.

Heron's Pre-meeting comments:

Heron intends to include in the NDA a robust justification

(b) (4)

Discussion: No further discussion.

Question 22: Does the agency agree that a Medication Guide is not required for HTX-011?

FDA Response:

We concur that a Medication Guide is not necessary since HTX-011 is administered by health care professionals in an inpatient setting.

Heron's Pre-meeting comments:

Thank you for your response. A Medication Guide will not be included in the NDA.

Discussion: No further discussion.

Administrative

Question 23: Does the FDA agree to the proposed approach to submission of portions of the HTX-011 NDA for rolling review?

FDA Response:

The preliminary Phase 3 data in your meeting package appear to demonstrate efficacy of your product. Due to this and your Fast Track designation, your NDA qualifies for a rolling review. You may refer to Guidance for Industry *Expedited Programs for Serious Conditions – Drugs and Biologics*, available at <https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf> for additional

information on portions of the application eligible for early submission. However, as the guidance notes, “If FDA accepts a portion of an application, this does not necessarily mean that review will commence or proceed before the complete application is submitted. Actual commencement and scheduling of review depends on many factors, including staffing, workload, competing priorities, timeline for completing the application, and the perceived efficiency of commencing review before receipt of the complete submission. The review clock will not begin until the applicant informs the Agency that a complete NDA was submitted. After the Agency is notified of the complete application, we will make a filing determination within the usual time frame.”

Heron's Pre-meeting comments:

Heron appreciates the FDA's agreement to a rolling review of the HTX-011 NDA. We understand that the review clock will not begin until the complete NDA is submitted with a filing determination to be made within the usual timeframe.

Discussion: No further discussion.

Question 24: Does the FDA agree that, based on the results of the Phase 3 studies, HTX-011 provides a significant improvement in safety and/or effectiveness for postsurgical analgesia compared with available therapies, and that the NDA will likely qualify for Priority Review?

FDA Response:

The determination of whether your NDA qualifies for Priority Review will be made at the time of NDA filing. We note your synopsis of Phase 3 safety data submitted in your meeting package demonstrate a greater incidence of adverse events related to skin and wound healing in the HTX-011 group in Study 301, which are concerning (e.g., incision site erythema, impaired healing, incision site edema, wound dehiscence). Therefore, your justification for Priority Review should include a thorough assessment of all wound healing data in your development program.

Heron's Pre-meeting response:

Heron will include in the justification for Priority Review a thorough assessment of all wound healing data in the HTX-011 development program.

When considering adverse events, a thorough understanding of the background rate is critical. In a recent review of wound healing complications following hallux valgus bunionectomy surgery ([Kromuszczynska 2018](#)), 19.4% of subjects had complications, including partial dehiscence in 8.4% and infection in 3.8%. The authors cited other studies that showed infection rates ranging from 1.4% to 11%, and wound dehiscence rates consistent with their observed rate. HTX-011-treated subjects in Study 301 had rates consistent with the publication for infection (2.5% incision site infection and 0.6% postoperative wound infection) and wound dehiscence (4.5%).

A very broad, comprehensive, custom list of Preferred Terms (PTs) related to local

inflammation was prespecified for surveying adverse events in the HTX-011 program; these PTs do not necessarily reflect issues with abnormal wound healing. The overall incidence of local inflammatory treatment-emergent adverse events (TEAEs) in Study 301 (bunionectomy) was 28.7% in the HTX-011 group vs 22.1% for bupivacaine HCl and 19.8% for saline placebo. Bupivacaine is a known vasodilator (Newton 2005) and the increase in local inflammatory TEAEs with HTX-011 in Study 301 may be due to the extended release of bupivacaine from the formulation over approximately 3 days, combined with the small anatomic space and relatively superficial placement of study drug in this surgical procedure, leading to vasodilation potentially being interpreted as erythema. Confirming that the list of PTs is not necessarily reflective of abnormal wound healing, the Wound Healing Assessment prespecified by the FDA for this study following the EOP2 meeting, did not show an increase in wound healing issues with HTX-011. The rate was lowest in the HTX-011 group and similar to the saline placebo group (80.9% and 81.9%, respectively), and was highest in the bupivacaine HCl group (84.4%). The most common Wound Healing Assessment symptoms were edema, bruising, and erythema. Most symptoms resolved by the Day 42 Safety Follow-Up Visit. Edema was the most common symptom ongoing at the Day 42 Visit and was highest in the saline placebo group (33.0%) compared with HTX-011 (27.3%) and bupivacaine HCl (25.8%). Of note, none of the HTX-011 subjects had a severe or serious local inflammatory TEAE.

As would be expected, the overall incidence of local inflammatory treatment-emergent adverse events (TEAEs) in Study 301 (bunionectomy) was higher than in Study 302 (herniorrhaphy) as shown in Table 10 of the Briefing Document. Despite the 5-fold higher dose of HTX-011 in Study 302 (300 mg/9 mg), the incidence of local inflammatory TEAEs was 3.7% in the HTX-011 group. The recently-completed Phase 2b studies (Study 209 [TKA], and Study 211 [augmentation mammoplasty]) show a consistent low rate despite the even higher dose of 400 mg/12 mg.

Discussion:

The Sponsor stated that they will include a thorough assessment of all wound healing data in their justification for Priority Review. The Sponsor was advised that if they planned to utilize the Kromuszczynska article as supporting information, they would need to explain how the data from the study, which was done in Poland, is applicable to the US patient population.

Question 25: Does the FDA agree that the proposed NDA Table of Contents for HTX-011 represents a complete submission?

FDA Response:

The NDA Table of Contents for HTX-011 appears reasonable, however, the final determination whether the NDA submission is complete will be determined during the NDA filing period.

Refer to the eCTD guidance that includes information on location of combination product information in Section 5:

<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>.

Heron's Pre-meeting comments:

Thank you for your response.

Discussion: No further discussion.

Question 26: Does the FDA agree to the proposal for inclusion of Reviewer's Guides in the NDA?

FDA Response:

The proposal for inclusion of Reviewer's Guides is acceptable.

Heron's Pre-meeting comments:

Thank you for your response.

Discussion: No further discussion.

Question 27: Does the FDA agree with the proposed plan to provide summary-level clinical site (BIMO) data for pivotal Studies 301 and 302?

FDA Response:

Provide the clinical study-level information, the subject-level data line listings by clinical site, and the summary-level clinical site dataset for pivotal Studies 301 and 302, as described in the two guidance documents: Draft Guidance for Industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*. See the links to the two guidance documents below, under the section labeled "Office of Scientific Investigations (OSI) Requests."

Heron's Pre-meeting comments:

Heron intends to submit the clinical study-level information, the subject-level data line listings by clinical site, and the summary-level clinical site dataset for pivotal studies 301 and 302.

Discussion: No further discussion.

Question 28: Does the FDA agree that the datasets for these early-phase studies that did not include the intended commercial formulation, HTX-011, are not required?

FDA Response:

We concur that the datasets for studies performed with a formulation other than the to-be-marketed formulation are not required.

Heron's Pre-meeting comments:

Thank you for your response. Datasets for studies performed with a formulation other than the to-be-marketed formulation will not be included in the NDA.

Discussion: No further discussion.

Question 29: Does the FDA agree that digital ECG data from the HTX-011 clinical development program are not required to be submitted to the ECG warehouse?

FDA Response:

No, we do not agree. As previously discussed at Type C meeting held on April 3, 2018, in order to adequately evaluate ECG data from all applicable clinical studies, all available digital ECG data should be submitted to the ECG Warehouse at the time of NDA submission.

Heron's Pre-meeting comments:

Heron intends to provide all available digital ECG data in the NDA as requested by FDA. Digital ECG data are available from Phase 2b Studies 209 and 211, and Phase 3 Studies 301 and 302. These data will be submitted to the ECG Warehouse by the time of the NDA submission and will be available for the Rolling Review.

ECG data from Phase 2a Studies 202, 203, and 208 are not available in digitized format; therefore, ECG data from these studies cannot be submitted to the ECG warehouse. Analysis was performed based on information from local-paper ECGs as interpreted by a central reader (Studies 202 and 203) or by a local reader (Study 208). Detailed expert ECG reports are appended to each Clinical Study Report and were submitted as part of the Type C Meeting Briefing Document, Clinical Pharmacology and Clinical Disciplines, Appendix B, TQT Study Waiver Request.

Discussion: No further discussion.

Question 30: Does the FDA agree with the plans outlined for providing the 4MSU?

FDA Response:

No, we do not agree. All adverse events from ongoing clinical studies need to be submitted, not just serious adverse events. In addition to any new clinical trial safety data, the 120-day safety update must also contain the same kind of information (from clinical studies, animal studies, or other data sources such as new literature) as the integrated summary of safety. Refer to 21 CFR 314.50 (5)(vi)(b) for additional information regarding the appropriate content of the 120-day safety update.

Heron's Pre-meeting comments:

Heron intends to provide the 4MSU according to 21 CFR 314.50 (5)(vi)(b).

The NDA cutoff date for clinical trial data for the planned NDA for HTX-011 is 30 June 2018, with an NDA submission date of 30 September 2018. Currently, there are no ongoing studies of HTX-011. If a clinical trial is initiated within the window from the NDA cutoff date until 3 months following NDA submission, Heron will provide a 4MSU.

Discussion: No further discussion.

ADDITIONAL COMMENTS:

Office of Combination Products

The proposed co-package that is to contain the HTX-011 drug product in a vial as well as the Vented Vial Spike, (b) (4) Norm-Ject Luer Lock syringe, Luer Lock adaptor (s), and syringe tip caps is a combination product that is subject to 21 CFR Part 4 "Current Good Manufacturing Practice Requirements for Combination Products" accessible at: <https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>. Related final guidance, "Current Good Manufacturing Practice Requirements for Combination Products, January 2017" is accessible at: <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf>.

As such, current good manufacturing practices (CGMP) requirements are applicable to each constituent part (drug, device, biological product) of the combination product. However, as reflected in the final rule on CGMPs for combination products (21 CFR Part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR Parts 210, 211) and with the device quality system (QS) regulation (21 CFR Part 820) through a streamlined approach. If utilizing a streamlined approach, you must demonstrate compliance with either the drug CGMPs or the QS regulation in its entirety and also with those provisions specified in Part 4 from the other of these two sets of requirements. Alternatively, you may demonstrate compliance with both the drug CGMPs and QS regulation in their entirety (non-streamlined approach).

Heron's Pre-meeting comments:

Heron will demonstrate compliance with the drug CGMP regulations in its entirety (21 CFR Parts 210, 211) and also with the provisions specified in Part 4 from the device quality system (QS) regulation (21CFR Part 820) through the drug based streamlined approach.

Information to include in NDA Form 356h:

List the manufacturing facilities for the combination product and its constituent parts and identify what activities occur at each site (e.g., assembly, filling, sterilization, packaging other) involving which constituents' parts (e.g., drug only, device only, both drug and

device). For facilities that have manufacturing activities for both drug and device constituent parts, you should identify which CGMP operating system is being used at the site for the combination product (streamlined or non-streamlined) and if it is a streamlined system, whether it is a drug-CGMP-based or QS-regulation-based system.

Heron's Pre-meeting comments:

Heron intends to provide in the NDA the list of manufacturing facilities with the site activity, and the CGMP operating system for the combination product and its constituent parts. In addition to 21 CFR 210 and 21 CFR 211, Heron will provide information related to 21 CFR 820 requirements.

Information to include in your NDA application:

If you are using a drug-CGMP-based system, you must demonstrate compliance with the following provisions from the QS regulation. Please provide the following information in your marketing application with respect to these requirements. You are not required to provide this information, but we encourage you to do so. Its review will enable the agency to determine whether inspection is needed with respect to these requirements and, if so, to enhance the efficiency of this inspection. Using the eCTD format, this information should be provided in Section 3.2. P.3.

- **Management Responsibility (21 CFR 820.20)**

Provide a summary of how your firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4). Also, provide a description of the functions and responsibility of each facility involved in the manufacturing of the combination product and its constituent parts.

Heron's Pre-meeting comments:

Heron will provide a summary on the procedures and processes related to Management Responsibility in the NDA to ensure the combination product is manufactured in compliance with all applicable CGMP requirements.

- **Design Control, General (21 CFR 820.30)**

Explain how you utilized the design control process to develop the combination product under review and provide a description of your design control procedures. The description must include how requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file are fulfilled. Provide a copy or a summary of the plan used to design the combination product.

Heron's Pre-meeting comments:

Heron will provide a summary of the design control procedures and the process used in the development of the combination product in the NDA.

- **Purchasing Controls (21 CFR 820.50)**

Provide a summary of the procedure(s) for purchasing controls. The summary should:

- a. Describe your supplier evaluation process and describe how it will determine type and extent of control you will exercise over suppliers.**
- b. Define how you maintain records of acceptable suppliers and how you address the purchasing data approval process.**
- c. Explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.**

Explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Provide a description of how you apply the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement).

Heron's Pre-meeting comments:

Heron will provide a summary of the purchasing control, supplier management and change management procedures in the NDA.

- **Corrective and Preventive Action (21 CFR 820.100)**

Summarize the procedure(s) for your Corrective and Preventive Action (CAPA) System. The CAPA system should require:

- a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;**
- b. Investigation of nonconformities and their causes;**
- c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and**
- d. Verification or validation of the actions taken.**

Heron's Pre-meeting comments:

Heron will provide a summary of Corrective and Preventive Action System for nonconformance investigation and corrective and preventive action implementation systems in the NDA.

- **Installation (21 CFR 820.170) and Servicing (21 CFR 820.200)**

If installation and service requirements apply based on the type of device constituent part included in your combination product, the following information should be provided:

***Installation:* If applicable for the combination product, provide a summary of how your firm has established installation, inspection instructions, and test procedures for the installation of the combination product.**

Servicing: Where servicing is a specified requirement for the combination product, provide a summary of how your firm has established and maintained instructions and procedures for performing and verifying that servicing of the combination product meets the specified requirements.

Heron's Pre-meeting comments:

Installation and Servicing requirements of 21 CFR 820.170 and 21 CFR 820.200 are not applicable to this product.

Nonclinical

- 1. We note that you conducted a study in patients undergoing augmentation mammoplasty. Note that if you plan on conducting further studies or seek an indication for this surgery, additional data or justification will be needed to demonstrate that your drug product will not adversely impact the prosthesis.**

Heron's Pre-meeting comments:

An evaluation of the compatibility of HTX-011-56 with the shells of breast implants was conducted using the silicone membranes typically used to fabricate the implants. There were no changes to the visual appearance of silicone sheet exposed to HTX-011 for 4 days at 37°C. There were no significant changes in weight or tensile properties. No leachables were observed from either sheets or implants. The presence of HTX-011 on the surface of silicone sheets or an implant did not extract more silicone polymers (as silicon) than phosphate-buffered saline (PBS) alone. The results of this study were included in Study Report RPT-0241, which was submitted to the IND for FDA for review prior to the conduct of Study 211, the concluded augmentation mammoplasty study.

A list of the key compatibility studies previously submitted to the IND in support of clinical studies (also presented in the End-of-Phase 2 Briefing Document) are provided in Table 5. Additional compatibility studies have been conducted to support the NDA. All compatibility studies will be summarized in the NDA.

Table 5: Key Nonclinical Compatibility Studies of HTX-011		
Type of Material	Study Number	IND Submission
Silicone membranes used for breast implants	RPT-0241	17JAN2017 (SN0056)
Bone cement	RPT-0184	16DEC2016 (SN0054)
Metal alloys used in surgical implants	RPT-0242	17JAN2017 (SN0056)
Drug delivery and transfer components	RPT-0231	17JAN2017 (SN0056)

- 2. For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2), ICH Q3B(R2) or be demonstrated to be within the specifications of the referenced drug**

used for approval through the 505(b)(2) pathway. In order to provide adequate qualification:

- a. You must complete a minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
- b. In addition, you must conduct a toxicology study of appropriate duration to support the proposed indication. The study must address both local and systemic safety.

Refer to Guidance for Industry Q3A(R2) *Impurities in New Drug Substances*, available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf> and Guidance for Industry Q3B(R2) *Impurities in New Drug Products*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf>

- c. Alternatively, you may be able to justify the safety of a drug product degradant via comparative analytical studies that demonstrate that the levels of the degradant in your drug product are equal to or below the levels found in the referenced drug product. If you elect to pursue this approach, refer to the FDA Guidance for Industry ANDAs: *Impurities in Drug Products*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072861.pdf>. However, local tissue safety must also be addressed.
3. Genotoxic impurities, carcinogenic impurities, or impurities that contain a structural alert for genotoxicity must be adequately controlled during drug development. Drug substance manufacturing often creates the potential for introduction of compounds with structural alerts for genotoxicity through use of reagents, catalysts and other processing aids or the interaction of these with starting materials or intermediates during the stages of chemical synthesis. Refer to the ICH guidance document titled: *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* for the appropriate framework for identifying, categorizing, qualifying, or controlling these impurities. This guidance is available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf>. Briefly, actual and potential impurities likely to arise during synthesis and storage of a new drug substance and manufacture and storage of a new drug product should be identified for assessment. A hazard assessment should be undertaken to categorize these impurities with respect to mutagenic and

carcinogenic potential and risk characterization applied to derive acceptable intakes during clinical development. Finally, a control strategy should be proposed and enacted where this is determined to be necessary to ensure levels are within the accepted limits established for the stage of drug development to mitigate risk.

- 4. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICH Q3A(R2) and ICH Q3B(R2) qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds must be adequately justified for safety from a toxicological perspective.**

Heron's Pre-meeting comments:

As acknowledged by FDA in the Response to Question 9, all specifications for impurities and degradation products for HTX-011 drug substances and drug product are within the relevant thresholds that are outlined in ICH Q3A(R2), ICH Q3B(R2), and ICH M7.

- 5. The NDA submission must contain adequate information on potential leachables and extractables from the drug container closure system and/or drug product formulation, unless specifically waived by the Division. The evaluation of extractables and leachables from the drug container closure system or device should include specific assessments for residual monomers, solvents, polymerizers, etc. Provide justification for the choice of solvents and conditions for the extraction studies (time, temperature, etc). The results of the extraction studies should be used to assure that you are adequately monitoring the drug product stability samples for potential leachables from the primary or secondary container closure systems and from your analysis of data from any upstream manufacturing processes that suggest the potential for additional leachable compounds in the final drug product formulation. Your analytical evaluation threshold (AET) must be established to be able to detect, identify, and quantitate levels of compounds based on these thresholds or you must provide adequate justification that these thresholds are not possible to be met by current analytical methodology. If you cannot meet these thresholds, safety evaluations will be based on the limits of quantitation (LOQ). Your submission must include a detailed discussion of how you established your AET as well as justification for the limits of detection (LOD) and LOQ for the analytical methods used.**

Evaluate at least three batches of your to-be-marketed drug product for leachables and include assessments at multiple timepoints over the course of your stability studies in order to identify trends in leachable levels over time. The materials tested should include any secondary container closure systems, if present, and be subjected to the same sterilization methods, as appropriate. These data are essential to determine the appropriate shelf life of your product.

For all drug products, establish your AET to be able to detect potentially carcinogenic or genotoxic compounds as per ICH M7 qualification thresholds (e.g., not more than 1.5 mcg/day or up to 120 mcg/day pending during of treatment). However, from a general toxicology perspective, for parenteral products, the AET must be able to detect and identify any leachable that is present in the product at 5 mcg/day and higher, unless justified otherwise, to permit an adequate toxicological risk assessment.

For additional guidance on extractables and leachables testing, refer to the following documents:

- **USP <1663>: Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems**
- **USP <1664>: Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems**
- **FDA Guidance for Industry *Container Closure Systems for Packaging Human Drugs and Biologics*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf>**

In your assessment, include a table listing all compounds, including the concentration in ppm, the experimental conditions, and the maximum daily exposure to these compounds based on the maximum daily dose of the product. The extractable/leachable data must be accompanied by an adequate toxicological risk assessment. Although a toxicological risk assessment based on the results of the extraction studies may be adequate to support the safety assessment during development, evaluate at least three batches of your drug product that have been tested at multiple timepoints over the course of your stability studies, as discussed above, and base the final safety assessment on the maximum predicted levels of leachables identified to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified. Include copies of all referenced studies upon which a safety assessment is based.

- **If you employ a Permissible Daily Exposure (PDE) assessment as described in ICH Q3C, provide justification for all safety factors employed.**

- **Published literature to support the safety of any compound rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, (e.g., BIBRA, CIR, HERA), although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports must be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study must be discussed and justification must be provided to support your assertion that these data are adequate to support the safety of your container closure system.**
- **Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your leachable/extractable. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the extractable/leachable compound.**

Heron's Pre-meeting comments:

Heron designed the assessments of leachables and extractables for HTX-011 based on the same comments as provided in Additional Nonclinical Comment 5 that were included in the End-of-Phase 2 Meeting minutes. As acknowledged by FDA in the Response to Question 5, the evaluations of extractables and leachables proposed by Heron appear reasonable.

6. **NOTE: We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity or degradant that exceeds the ICH qualification thresholds, safety justification for a new or novel excipient, or safety characterization of extractables and leachables.**

Heron's Pre-meeting comments:

As acknowledged by FDA in the responses to Questions 5 and 9, all specifications for impurities and degradation products for HTX-011 drug substances and drug product are within the relevant thresholds outlined in the guidances and the evaluations of extractables and leachables proposed by Heron appear reasonable. Heron will include a safety justification in the NDA for the polymeric excipient AP135, considered a new or novel excipient for safety evaluation, as presented in the Heron response to Question 7.

7. **The nonclinical information in your proposed drug product labeling must include relevant exposure margins with adequate justification for how these margins were obtained. As you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional**

pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product labeling.

Heron's Pre-meeting comments:

Heron designed the assessments of leachables and extractables for HTX-011 based on the same comments as provided in Additional Nonclinical Comment 5 that were included in the End of Phase 2 meeting minutes. As acknowledged by FDA in the Response to Question 5, the evaluations of extractables and leachables proposed by Heron appear reasonable.

8. **We note that all NDA applications filed after June 30, 2015 must submit labeling consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). In order to prepare for this new labeling format, conduct a thorough review and integrated analysis of the existing clinical and nonclinical literature for each drug substance in your drug product and propose a risk summary statement and text for Section 8 of the labeling. Information on the final rule and links to the FDA draft guidance document are available at, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>.**
9. **Your NDA submission should include a detailed discussion of the nonclinical information in the published literature and should specifically address how the information within the published domain impacts the safety assessment of your drug product. This discussion should be included in Module 2 of the submission. Copies of all referenced citations should be included in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.**

Heron's Pre-meeting comments:

Heron agrees to perform a thorough review and integrated analysis of the existing clinical and nonclinical literature for each drug substance in HTX-011 to propose a risk summary statement and text for Section 8 of the labeling and will include in Module 2 a detailed discussion of the nonclinical information in the published literature that specifically addresses how the information within the published domain impacts the safety assessment of HTX-011.

ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

ACTION ITEMS

1. The Sponsor will determine whether the (b) (4) will affect extractability and leachability safety profile.
2. The Sponsor will include additional time points between 6 and 24 hours in their IVR method. The Sponsor will also include justification (b) (4) as well as look at meaningful variations in order to demonstrate

discriminating ability. The Sponsor will submit a full report based on the in-vitro and in-vivo correlation (b) (4)

3. The Sponsor will submit a detailed PK profile and look at both variability and mean data.
4. The Sponsor will submit a letter for clarification regarding the revisions to their HF Validation Protocol.
5. The Sponsor will provide a thorough assessment of all wound healing data in their justification for Priority Review.

ATTACHMENTS AND HANDOUTS

Appendix 1 (PowerPoint presentation)

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

In addition, your iPSP should specifically provide your justification why you believe that nonclinical juvenile animal studies are or are not needed to support your pediatric drug development taking into consideration the specific age ranges to be studied. The justification should be based on a comprehensive literature search focusing on the specific toxicological concerns related to the drug substance and each individual excipient in your drug product and any data you have generated suggesting a unique vulnerability to toxicological insult for the proposed age range to be tested. This risk assessment should take into consideration the expected maximum daily dose of the drug product for the intended patient population and include rationale for your proposed maximum daily dose. In addition, your risk assessment should address how the drug substance and excipients are absorbed, distributed, metabolized, and excreted by the ages of the children you will be studying. You must include copies of all referenced citations. If you conclude that a juvenile animal study is necessary, provide a detailed outline of the specific study you propose to conduct, including what toxicological endpoints you

will include in the study design to address any specific questions, and justification for your selection of species and the age of the animal to be tested. We recommend that you refer to the FDA guidance to industry: *Nonclinical Safety Evaluation of Pediatric Drug Products*, available at,

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079247.pdf>.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format.

Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's

finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)

1. Example: Published literature	Nonclinical toxicology
2. Example: NDA XXXXXX “TRADENAME”	Previous finding of effectiveness for indication A
3. Example: NDA YYYYYY “TRADENAME”	Previous finding of safety for Carcinogenicity, labeling section B
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

29 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EVA L YUAN
07/10/2018

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	125927
Request Receipt Date	April 25, 2018
Product	HTX-110 (bupivacaine and meloxicam)
Indication	HTX-110 is indicated for [REDACTED] (b) (4)
Drug Class/Mechanism of Action	Combination product with local anesthetic (bupivacaine) and low-dose meloxicam in an extended-release formulation
Applicant	Heron Therapeutics, Inc.
ODE/Division	ODEII/Division of Anesthesia, Analgesia, and Addiction Products
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	6/24/2018

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes, and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter): The Applicant is proposing that HTX-110 is indicated for [REDACTED] (b) (4)

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?

☐ YES ☒ NO

3. Was the BTDR submitted to a PIND?

☐ YES ☒ NO

If "Yes" do not review the BTDR. The Applicant must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. Consideration of Breakthrough Therapy Criteria:

- a. Is the condition serious/life-threatening¹?

☒ YES ☐ NO

If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

¹ For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- ☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
- ☐ Undetermined
- ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):
- i. Only animal/nonclinical data submitted as evidence ☐
 - ii. Insufficient clinical data provided to evaluate the BTDR
(e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
 - iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
 - iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
 - v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history.

The Applicant proposes that HTX-110 is indicated for

The Applicant describes HTX-011

² For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

Bupivacaine, the disease-active ingredient of HTX-110, is a local anesthetic. Local anesthetics reduce pain by blocking the generation and the conduction of nerve impulses, 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.

Bupivacaine is a well-known immediate-release anesthetic used for analgesia to reduce postoperative pain. However, the mean duration for bupivacaine analgesia administered via infiltration into the surgical wound is approximately 10 hours. Another drug product, liposomal bupivacaine is an extended-release formulation of bupivacaine. The package insert states that in bunionectomy liposomal bupivacaine reduced pain intensity compared to placebo for 24 hours. A second study of liposomal bupivacaine in hemorrhoidectomy also demonstrated a treatment effect compared to placebo, however, the treatment effect did not persist over the 72-hours efficacy period. In this study, the median time to rescue analgesia use was 15 hours for the patients treated with liposomal bupivacaine and one hour for patients treated with placebo.

It is reported that approximately 70% of patients have moderate to severe pain after surgery. Opioids have been the mainstay for postoperative pain management. However, use of opioids in the postoperative setting is associated with serious sequelae, such as, postoperative nausea and vomiting, pruritus, sedation, delirium, urinary retention, constipation, and the potential for development of opioid use disorder. In response to these concerns multimodal analgesic therapy has evolved specifically to decrease the requirements for opioids postoperatively. Multimodal therapy often incorporates local anesthetics, however, the impact of local anesthetic analgesia has been limited due to the short duration of immediate-release local anesthetics. The development of extended-release local anesthetic for postoperative analgesia is highly desirable.

8. Information related to endpoints used in the available clinical data:

- a. Describe the endpoints considered by the Applicant as supporting the BTDR and any other endpoints the Applicant plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

Primary Efficacy Endpoint

Mean area under the curve (AUC) of the Numeric Rating Scale of pain intensity scores with activity (NRS-A) through 72 hours (AUC0-72) for HTX-011 compared with saline placebo.

Key Secondary Efficacy Endpoints (Hierarchical Testing)

1. Mean AUC0-72 of the NRS-A pain intensity scores for HTX-011 compared with bupivacaine HCl.
2. Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with saline placebo.
3. Proportion of subjects who are opioid-free through 72 hours for HTX-011 compared with bupivacaine HCl.
4. Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with bupivacaine HCl.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease.

The Division accepts the mean area under the curve (AUC) of the Numeric Rating Scale of pain intensity scores at rest (NRS-R) and with activity (NRS-A), as appropriate clinical endpoint as measure of postoperative pain, for a prespecified time period.

In addition, the Division is willing to consider the mean total postoperative opioid consumption (in morphine equivalents) through a designated time period as an endpoint for postoperative opioid utilization. However, the Division will determine at the time of NDA review if the reduction in opioid utilization is clinical meaningful.

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

There are numerous opioids analgesics, non-steroidal anti-inflammatory drugs, and acetaminophen approved for acute pain management that are utilized in the treatment of postoperative pain.

In addition, local anesthetics are used for postoperative pain management. Bupivacaine is the most commonly used local anesthetic for local administration into the surgical site. Bupivacaine and ropivacaine are the most commonly used local anesthetics for nerve block procedures for postoperative pain management. The following table provides information about local anesthetics use for postoperative pain management. Exparel is the most recent local anesthetic formulation approved for single- dose infiltration into the surgical site to produce postsurgical analgesia.

	Indication	Endpoint	Results	Population
Exparel (NDA-022496, approved October 28, 2011)	EXPAREL is a liposome injection of bupivacaine, an amide local anesthetic, indicated for single-dose infiltration into the surgical site to produce postsurgical analgesia	Mean area under the curve (AUC) of the numeric rating scale (NRS) of pain intensity through various durations as compared to placebo and bupivacaine	Exparel was superior to placebo in 2 trials (hemorrhoidectomy, bunionectomy) ¹ Exparel was not superior to bupivacaine in 3 trials (total knee arthroplasty, hemorrhoidectomy, breast augmentation) ¹	Postoperative surgical patients via infiltration into the soft tissue
MARCAINE (Bupivacaine HCl), NDA-016964, approved October 3, 1972	MARCAINE is indicated for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures.			Patients undergoing surgery, dental, oral surgery, diagnostic and therapeutic procedures, and obstetrical procedures.
NAROPIN (Ropivacaine HCl), NDA-020533, approved September 24, 1996	NAROPIN is indicated for the production of local or regional anesthesia for surgery and for acute pain management. Acute pain management: epidural continuous infusion (postoperative or labor) or intermittent bolus (local infiltration)		With infiltration of 100mg to 200mg, the time to first request for analgesic was 2 to 6 hours. ² Clinical studies demonstrated that epidural infusion provided adequate analgesia in cases of moderate to severe postoperative pain. Clinical experience supports the use of Naropin epidural infusions for up to 72 hours. ²	Surgical patients and acute pain management in postoperative patients.

¹From the Exparel label ²From the Naropin label

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

Oliceridine (TRV130) IND-113537 is a small molecule mu-opioid receptor modulator. The indication is an intravenous agent for moderate to severe pain and the Applicant is using postsurgical pain for their pain model.

10. Information related to the preliminary clinical evidence:

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

³ Biweekly reports of all BTDRs, including the Applicant, drug, and indication, are generated and sent to all CPMSs.

⁴ Trial design should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

Study	Design	Treatment Groups	# of Subjects	Endpoints	Results
HTX-011-301 Phase 3 Unilateral Bunionectomy	Randomized, double-blind, saline placebo- and active- controlled, multicenter	HTX-011 60 mg/1.8 mg via instillation PBO via instillation BPV 0.5% 50 mg via injection	HTX = 157 PBO = 100 BPV = 155 Total = 412	<u>Primary Endpoint:</u> - Mean AUC of the NRS of pain intensity scores with activity (NRS-A) through 72 hrs (AUC_{0-72}) for HTX-011 compared with PBO <u>Secondary Endpoints:</u> - Mean AUC_{0-72} of the NRS-A pain intensity scores for HTX-011 compared with BPV - Mean total postoperative opioid consumption (MEQ) through 72 hrs for HTX-011 compared with PBO - Proportion of subjects who are opioid-free through 72 hrs for HTX-011 compared with BPV - Mean total postoperative opioid consumption (MEQ) through 72 hrs for HTX-011 compared with BPV	- Results for the primary and all 4 key secondary endpoints were statistically significant in favor of HTX-011 - HTX-011 demonstrated superior, sustained pain reduction and significantly reduced opioid consumption for 72 hrs after study drug administration compared with PBO and BPV - BPV provided superior pain relief compared with PBO over the first 12 hrs after study drug administration in both studies (demonstrating that the dose of active control was effective)
HTX-011-302 Phase 3 Unilateral Open Inguinal Herniorrhaphy	Randomized, double-blind, saline placebo- and active- controlled, multicenter	HTX-011 300 mg/9 mg via instillation BPO via instillation BPV 0.25% 75 mg via injection	HTX = 164 BPO = 82 BPV = 172 Total = 418	<u>Primary Endpoint:</u> - Mean AUC of the NRS of pain intensity scores with activity (NRS-A) through 72 hrs (AUC_{0-72}) for HTX-011 compared with PBO <u>Secondary Endpoints:</u> - Mean AUC_{0-72} of the NRS-A pain intensity scores for HTX-011 compared with BPV - Mean total postoperative opioid consumption (MEQ) through 72 hrs for HTX-011 compared with PBO - Proportion of subjects who are opioid-free through 72 hrs for HTX-011 compared with BPV - Mean total postoperative opioid consumption (MEQ) through 72 hrs for HTX-011 compared with BPV	- Results for the primary and all 4 key secondary endpoints were statistically significant in favor of HTX-011 - HTX-011 demonstrated superior, sustained pain reduction and significantly reduced opioid consumption for 72 hrs after study drug administration compared with PBO and BPV - BPV provided superior pain relief compared with PBO over the first 12 hrs after study drug administration in both studies (demonstrating that the dose of active control was effective)

AUC = Area Under the Curve; BPV = Bupivacaine HCl; MEQ = Morphine Equivalents; NRS = Numerical Rating Scale; PBO = Saline Placebo

- b. Include any additional relevant information.

EFFICACY RESULTS: Study 301 and Study 302

Pain Intensity Assessment and Opioid Use

Per the Applicant, HTX-011 demonstrated superior, sustained pain reduction and significantly reduced opioid consumption for 72 hours after study drug administration compared with both placebo and bupivacaine HCl in both, the bony and the soft tissue, surgical models of postoperative pain.

Table 1 Summary of Results for the Primary and Key Secondary Endpoints for the HTX-011-301 Bunionectomy Study (ITT Population, Preliminary Data)

Study 301	HTX-011 60 mg/1.8 mg (2.1 mL) (N=157)	Saline Placebo (2.1 mL) (N=100)	BPV HCl 50 mg (10 mL) (N=155)
AUC ₀₋₇₂ of the NRS-A Pain Intensity Scores ^a			
Mean (SD)	323.3 (182.64)	445.3 (155.79)	393.5 (153.76)
Primary endpoint: p-value ^b vs. Saline Placebo	<0.0001		
1 st Key secondary endpoint: p-value ^b vs. BPV HCl	0.0002		
Opioid consumption through 72 hours (MME)			
Mean (SD)	18.8 (19.80)	30.1 (21.02)	25.1 (21.55)
Median (Min, Max)	12.5 (0.0, 83.0)	25.0 (0.0, 80.0)	17.5 (0.0, 92.5)
2 nd Key secondary endpoint: p-value ^c vs. Saline Placebo	<0.0001		
4 th Key secondary endpoint: p-value ^c vs. BPV HCl	0.0022		
Opioid-Free through 72 hours			
n (%)	45 (28.7%)	2 (2.0%)	17 (11.0%)
p-value ^c vs. Saline Placebo	<0.0001		
3 rd Key secondary endpoint: p-value ^d vs. BPV HCl	0.0001		

Abbreviations: AUC₀₋₇₂, area under the curve through 72 hours; BPV, bupivacaine; ITT, Intent-to Treat; MME, morphine milligram equivalent; NRS-A, Numeric Rating Scale of the pain intensity score with activity; wWOCF, windowed worst observation carried forward.

Notes: Opioid-Free through 72 hours is defined as subjects who had total MME opioid dose =0 through 0-72 hours. All doses of opioid rescue medication are expressed as intravenous MME. HTX-011 (also referred to as HTX-011-56) is the Phase 3 and intended commercial formulation.

^a Analyzed using wWOCF.

^b p-values reflect results of an analysis of variance (ANOVA) with randomized treatment as the main effect.

^c p-values were obtained using the Wilcoxon rank sum test.

^d p-values from Fisher's exact test.

(Source: Applicant's Request for Breakthrough Therapy Designation, Page 11)

The preliminary results of Study 301 (bunionectomy) indicate that the HTX-011 group had a statistically significant decrease in the mean AUC₀₋₇₂ of NRS-A pain intensity scores compared to placebo and bupivacaine HCl controls. The HTX-011 study group also had a statistically significant reduction in 72-hour opioid consumption compared to both control arms, with a mean of 18.8 morphine equivalents consumed versus 25.1 morphine equivalents in the bupivacaine HCl group and

30.1 morphine equivalents in the placebo group. However, a difference in 6.3 morphine equivalents (HTX-011 versus bupivacaine HCl) is unlikely to have meaningful clinical significance.

A statistically significant number of subjects remained opioid-free through 72 hours in the HTX-011 group (28.7%) versus the bupivacaine HCl group (11%) or the placebo group (2%). Such large differences could potentially translate into clinically meaningful differences because theoretically, if more patients are able to stay opioid-free for the first 72 hours after surgery, there is greater chance that they will remain opioid-free long-term. However, additional data would need to be collected on opioid consumption beyond 72 hours to verify that this is a valid assumption. It should also be noted that the majority of subjects still required opioids in the first 72 hours in the HTX-011 group. Lastly, the differences in the AUC₀₋₇₂ and 72-hour opioid consumption between the placebo and the bupivacaine HCl groups were not as remarkable, although still statistically significant during the first 12 hours, per the Applicant's assessment. On the contrary, the difference in the number of subjects who remained opioid-free in the bupivacaine HCl group (17%) compared to the placebo group (2%) is remarkable. This data suggest that the dose of bupivacaine HCl was appropriate.

Table 2 Summary of Results for the Primary and Key Secondary Endpoints for the HTX-011-302 Herniorrhaphy Study (ITT Population, Preliminary Data)

Study 302	HTX-011 300 mg/9 mg (10.3 mL) (N=164)	Saline Placebo (10.3 mL) (N=82)	BPV HCl 75 mg (30 mL) (N=172)
AUC ₀₋₇₂ of the NRS-A Pain Intensity Scores ^a			
Mean (SD)	269.4 (173.72)	350.8 (171.22)	341.9 (158.30)
<u>Primary endpoint</u> : p-value ^b vs. Saline Placebo	0.0004		
<u>1st Key secondary endpoint</u> : p-value ^b vs. BPV HCl	<0.0001		
Opioid consumption through 72 hours (MME)			
Mean (SD)	10.9 (17.06)	17.5 (18.91)	14.5 (18.19)
Median (Min, Max)	0.0 (0.0, 103.0)	11.3 (0.0, 73.5)	7.3 (0.0, 87.5)
<u>2nd Key secondary endpoint</u> : p-value ^c vs. Saline Placebo	0.0001		
<u>4th Key secondary endpoint</u> : p-value ^c vs. BPV HCl	0.0240		
Opioid-Free through 72 hours			
n (%)	84 (51.2%)	18 (22.0%)	69 (40.1%)
p-value ^c vs. Saline Placebo	<0.0001		
<u>3rd Key secondary endpoint</u> : p-value ^d vs. BPV HCl	0.0486		

Abbreviations: AUC₀₋₇₂, area under the curve through 72 hours; BPV, bupivacaine; ITT, Intent-to Treat; MME, morphine milligram equivalent; NRS-A, Numeric Rating Scale of the pain intensity score with activity; wWOCF, windowed worst observation carried forward.

Notes: Opioid-Free through 72 hours is defined as subjects who had total MME opioid dose =0 through 0-72 hours. All doses of opioid rescue medication are expressed as intravenous MME. HTX-011 (also referred to as HTX-011-56) is the Phase 3 and intended commercial formulation.

^a Analyzed using wWOCF.

^b p-values reflect results of an analysis of variance (ANOVA) with randomized treatment as the main effect.

^c p-values were obtained using the Wilcoxon rank sum test.

^d p-values from Fisher's exact test.

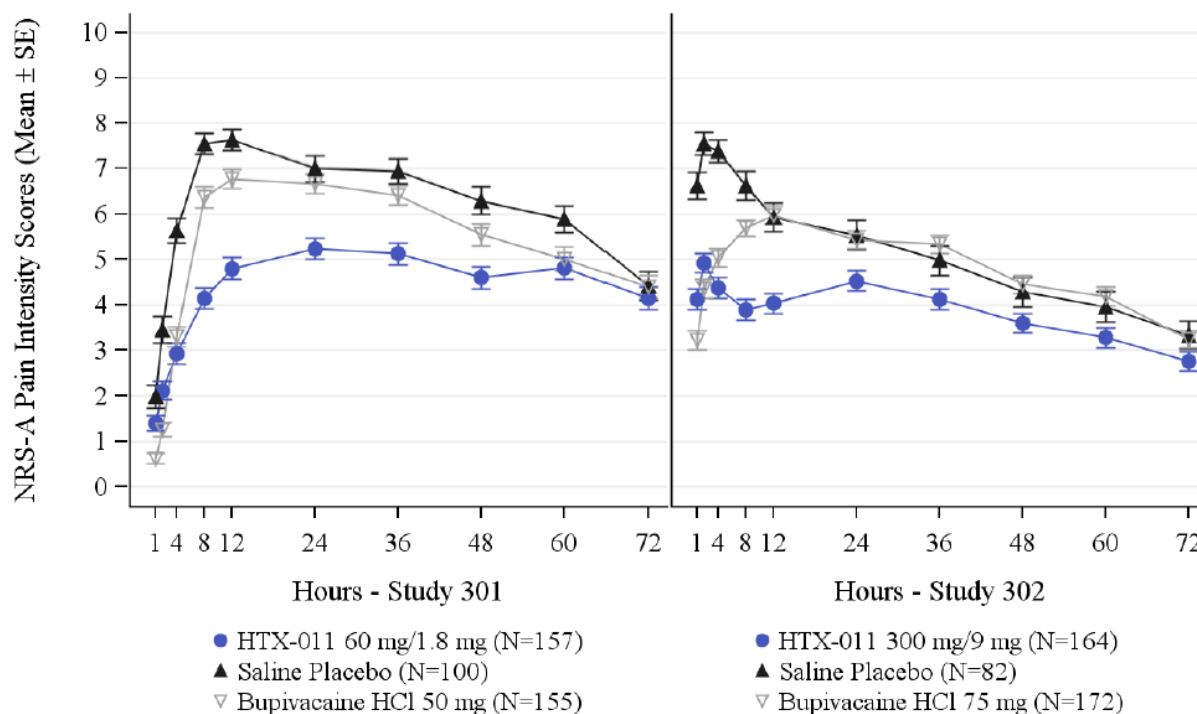
(Source: Applicant's Request for Breakthrough Therapy Designation, Page 12)

Similarly to Study 301 results, the preliminary results of Study 302 (herniorrhaphy) indicate that the HTX-011 group had a statistically significant decrease in the mean AUC_{0-72} of NRS-A pain intensity scores compared to placebo and bupivacaine HCl controls. The HTX-011 study group also had a statistically significant reduction in 72-hour opioid consumption compared to both control arms, with a mean of 10.9 morphine equivalents consumed versus 14.5 morphine equivalents in the bupivacaine HCl group and 17.5 morphine equivalents in the placebo group. The differences in total opioid consumption between study groups are smaller than in Study 301, with a difference of only 3.6 mg morphine equivalents between the HTX-011 and bupivacaine HCl groups. Such differences are unlikely to have clinical significance.

A statistically significant number of subjects remained opioid-free through 72 hours in the HTX-011 group (51.2%) versus the bupivacaine HCl group (40.1%) or the placebo group (22%). Although the difference in opioid-free subjects is smaller between the HTX-011 group and the bupivacaine HCl control group in this study compared to Study 301, this difference could still potentially translate into clinically meaningful results of long-term opioid-free subjects. As with Study 301, additional data would need to be collected on opioid consumption beyond 72 hours to verify that this is a valid assumption. It should also be noted that almost 50% of subjects still required opioids in the first 72 hours in the HTX-011 group. Lastly, the differences in the AUC_{0-72} and 72-hour opioid consumption between the placebo and the bupivacaine HCl groups were not as remarkable, but remained statistically significant for the first 12 hours per the Applicant's assessment. On the contrary, the difference in the number of subjects who remained opioid-free in the bupivacaine HCl group (40.1%) compared to the placebo group (22%) is remarkable. This data suggest that the dose of bupivacaine HCl was appropriate.

The mean pain intensity scores are plotted over time for both studies in Figure 1.

Figure 1 Mean (SE) NRS-A Pain Intensity Scores in Studies 301 and 302 Using wWOCF (ITT Population)



(Source: Applicant's Request for Breakthrough Therapy Designation, Page 13)

Both plots in Figure 1 demonstrate separation of the pain curves for the initial 60 hours. However, in both studies, the differences in pain scores become much less pronounced around 60 hours. In Study 301, at 60 hours, the bupivacaine HCl and the HTX-011 confidence intervals appear to overlap, and

by 72 hours all three groups converge. In addition, separation between the placebo and the bupivacaine HCl groups is apparent in the first 12 hours. In Study 302, the confidence intervals in the HTX-011 and bupivacaine HCl group approach each other at 60 hours, and appear to overlap by 72 hours. Similarly to Study 301, the bupivacaine HCl and placebo group curves demonstrate distinct separation for the first 12 hours, as expected, and converge thereafter. In summary, Figure 1 demonstrates that although there is a statically significant difference in the mean AUC₀₋₇₂ of HTX-011 group controlled to the control groups in both studies, the statistically significant differences are clearly present in the first 48 hours, with smaller differences noted in the 48-72 hour period. The p-values for each appropriate time period is presented in Table 3:

Table 3 P-Values for All Mean AUC Pain Intensity Scores in Studies 301 and 302 (ITT Population)

Treatment Group Comparisons	Study 301				Study 302			
	AUC ₀₋₂₄	AUC ₂₄₋₄₈	AUC ₄₈₋₇₂	AUC ₀₋₇₂	AUC ₀₋₂₄	AUC ₂₄₋₄₈	AUC ₄₈₋₇₂	AUC ₀₋₇₂
HTX-011 vs saline placebo	p<0.0001	p<0.0001	p=0.0083	p<0.0001	p<0.0001	p=0.0170	p=0.0593	p=0.0004
HTX-011 vs bupivacaine HCl	p<0.0001	p<0.0001	p=0.2634	p=0.0002	p<0.0001	p=0.0003	p=0.0044	p<0.0001

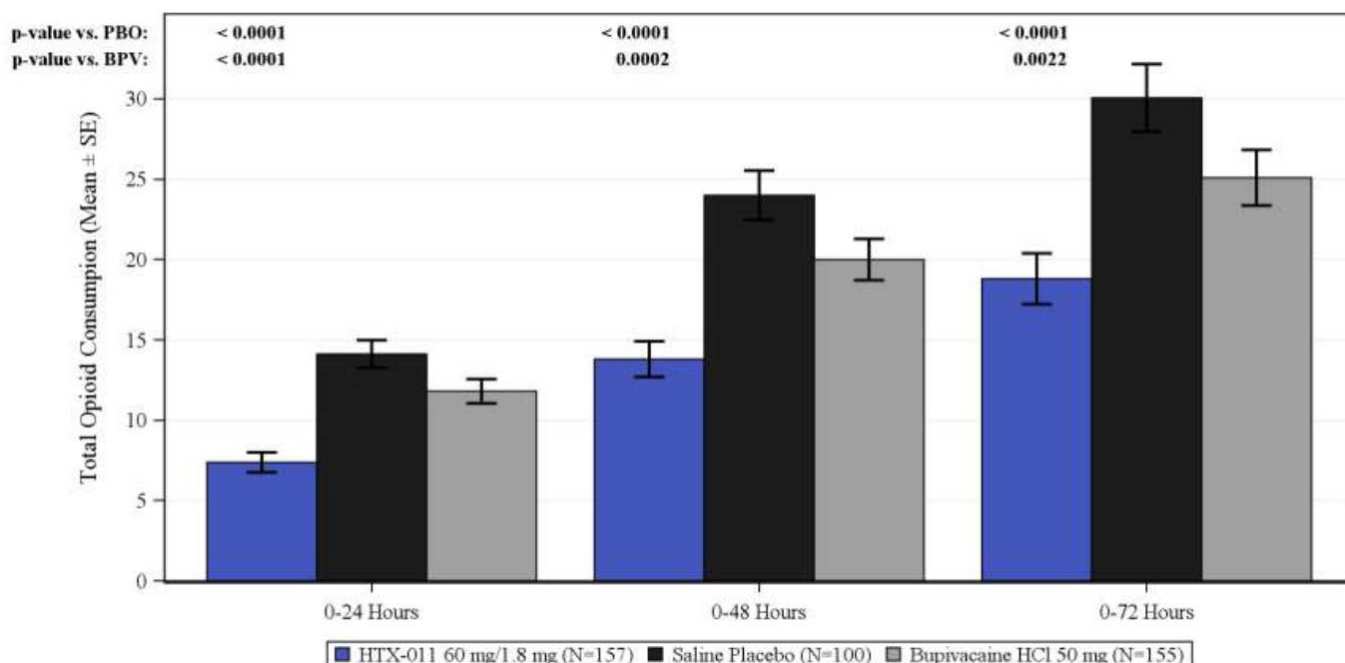
Abbreviations: AUC₀₋₂₄, area under the curve through 24 hours; AUC₂₄₋₄₈, area under the curve from 24 through 48 hours; AUC₄₈₋₇₂, area under the curve from 48 through 72 hours; AUC₀₋₇₂, area under the curve through 72 hours; ITT, Intent-to-Treat; NRS-A, Numeric Rating Scale score with activity; wWOCF, windowed worst observation carried forward.

Note: p-values reflect results of an analysis of variance (ANOVA) with randomized treatment as the main effect, tested at 24, 48, and 72 hours timepoints (graph) and at 0-24, 0-48, and 0-72 hour intervals. HTX-011 (also referred to as HTX-011-56) is the Phase 3 and intended commercial formulation.

(Source: Applicant's Request for Breakthrough Therapy Designation, Page 13)

Figures 2 and 3 are graphical representations of the differences in total postoperative opioid consumption in Studies 301 and 302, respectively.

Figure 2 Study 301 Mean (SE) Total Postoperative Opioid Consumption (MME); ITT Population

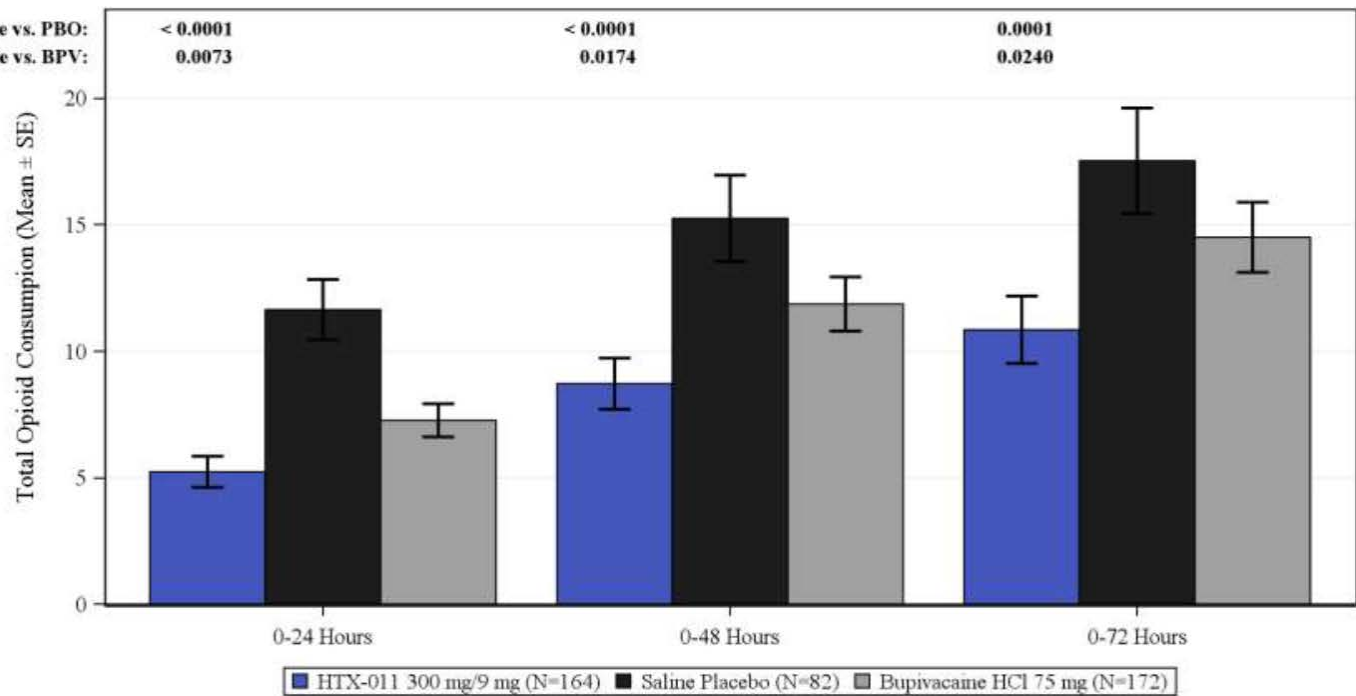


Abbreviations: BPV, bupivacaine HCl; ITT, Intent-to-Treat; MME, morphine milligram equivalents; PBO, saline placebo. P-values from the Wilcoxon rank sum test.

(Source: Summary of Preliminary Phase 3 Study Results received on March 28, 2018; Page 13)

Large differences, which are statistically significant, in total opioid consumption between HTX-011 group and the control groups are evident in each respective time period. It is unclear whether the differences in total opioid consumption are statistically significant between the placebo and bupivacaine HCl groups.

Figure 3 Study 302 Mean (SE) Total Postoperative Opioid Consumption (MME); ITT Population



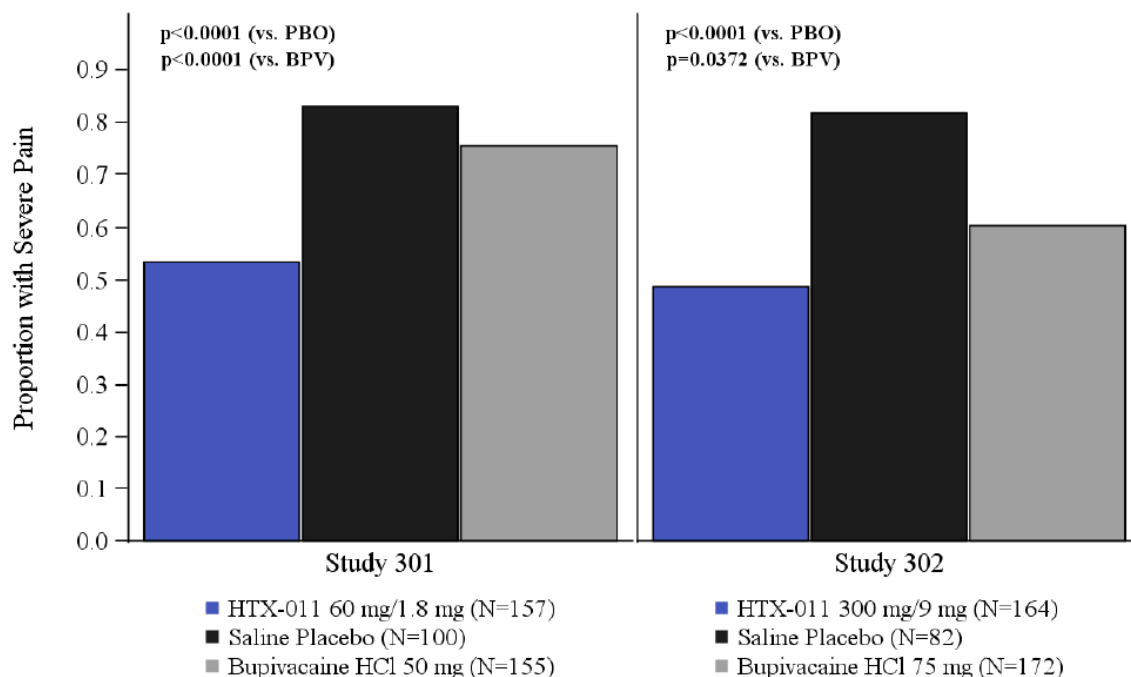
Abbreviations: BPV, bupivacaine HCl; ITT, Intent-to-Treat; MME, morphine milligram equivalents; PBO, saline placebo. P-values from the Wilcoxon rank sum test.

(Source: Summary of Preliminary Phase 3 Study Results received on March 28, 2018; Page 36)

Similarly to Study 301, large differences, which are statistically significant, in total opioid consumption between HTX-011 group and the control groups are seen in each respective time period. It is unclear whether the differences in total opioid consumption are statistically significant between the placebo and bupivacaine HCl groups.

Figure 4 illustrates the proportion of subjects experiencing severe pain during the first 72 hours in each study. Severe pain was defined as pain intensity score greater than or equal to seven on the NRS-A scale.

Figure 4 Proportion of Subject Experiencing Severe Pain at Any Time From 0 to 72 Hours in Studies 301 and 302 (ITT Population)



Abbreviation: BPV, bupivacaine; ITT, Intent-to-Treat; PBO, placebo.

Note: HTX-011 (also referred to as HTX-011-56) is the Phase 3 and intended commercial formulation.

(Source: Applicant's Request for Breakthrough Therapy Designation, Page 14)

In both studies, a relatively small proportion of subjects experienced severe pain regardless of the study group. In Study 301, however, a statistically significant reduction in the number of subjects who experienced severe pain is evident in the HTX-011 group versus the control groups. No significant differences are noted in the incidence of severe pain between the placebo and the bupivacaine HCl groups. In Study 302, a statistically significant reduction in the number of subjects who experienced severe pain is also evident in the HTX-011 group compared to the control groups. Larger differences in the incidence of severe pain are observed between the placebo and the bupivacaine HCl groups as well.

In the denial letter for the original Breakthrough Therapy Designation request, dated July 18, 2017, the Applicant was asked to provide data or rationale on how their product compares to Exparel, an approved long-acting formulation of bupivacaine HCl, which is indicated for treatment of postoperative pain. In the current submission, the Applicant proposes several arguments on why Exparel has not become the "standard-of-care," as well as, properties of Exparel that make it potentially less beneficial than the proposed product, HTX-011. The Applicant references the most recent USPI for Exparel, as well as data presented and discussed during the Anesthetic and Analgesic Drug Products Advisory Committee Meeting for the Exparel NDA that took place on February 14 and 15, 2018. The Applicant's rationale is as follows:

- Exparel is injected, thus creating a possibility of inadvertent intravascular administration, whereas HTX-011 is given via "installation," and therefore, has no risk of intravascular administration.
- In the Exparel bunionectomy and hemorrhoidectomy studies, significant differences in pain reducts were only seen in the first 24 hours after administration. Whereas between 24 and 72 hours after study drug administration, there was minimal to no difference between Exparel and placebo treatments on mean pain intensity.
- Although there were small, but statistically significant differences in the amount of opioid consumption between groups in the Exparel hemorrhoidectomy study, the clinical benefit of

these small differences was not demonstrated. In addition, there were no significant differences in the opioid consumption between groups in the Exparel bunionectomy study.

- Superiority of Exparel over bupivacaine HCl has not been demonstrated in any study in the Exparel development program.

In addition to the rationale above, the Applicant also provides a clinical cross-study comparison of Exparel and HTX-011 in bunionectomy (Table 4 and Figure 5).

Table 4 Mean AUC of Pain Intensity Scores Over Time for HTX-011 and EXPAREL vs. Saline Placebo Following Bunionectomy

Timepoint	HTX-011		EXPAREL	
	60 mg/1.8 mg (N=157)	Placebo (N=100)	120 mg (N=97)	Placebo (N=96)
AUC₀₋₂₄				
Mean (SD)	98.7 (59.5)	155.8 (48.5)	123 (49)	146 (41)
Difference	-57.1		-23	
p-value vs saline placebo	<0.0001		0.0002	
Percent reduction in pain vs. saline placebo	37%		16%	
AUC₀₋₄₈				
Mean (SD)	218.0 (122.3)	317.8 (102.8)	266 (108)	297 (94)
Difference	-99.9		-31	
p-value vs saline placebo	<0.0001		0.03	
Percent reduction in pain vs. saline placebo	31%		10%	
AUC₀₋₇₂				
Mean (SD)	323.3 (182.6)	445.3 (155.8)	398 (171)	429 (153)
Difference	-122.1		-31	
p-value vs saline placebo	<0.0001		0.16	
Percent reduction in pain vs. saline placebo	27%		7%	

Abbreviations: AUC₀₋₂₄, area under the curve through 24 hours; AUC₀₋₄₈, area under the curve through 48 hours; AUC₀₋₇₂, area under the curve through 72 hours.

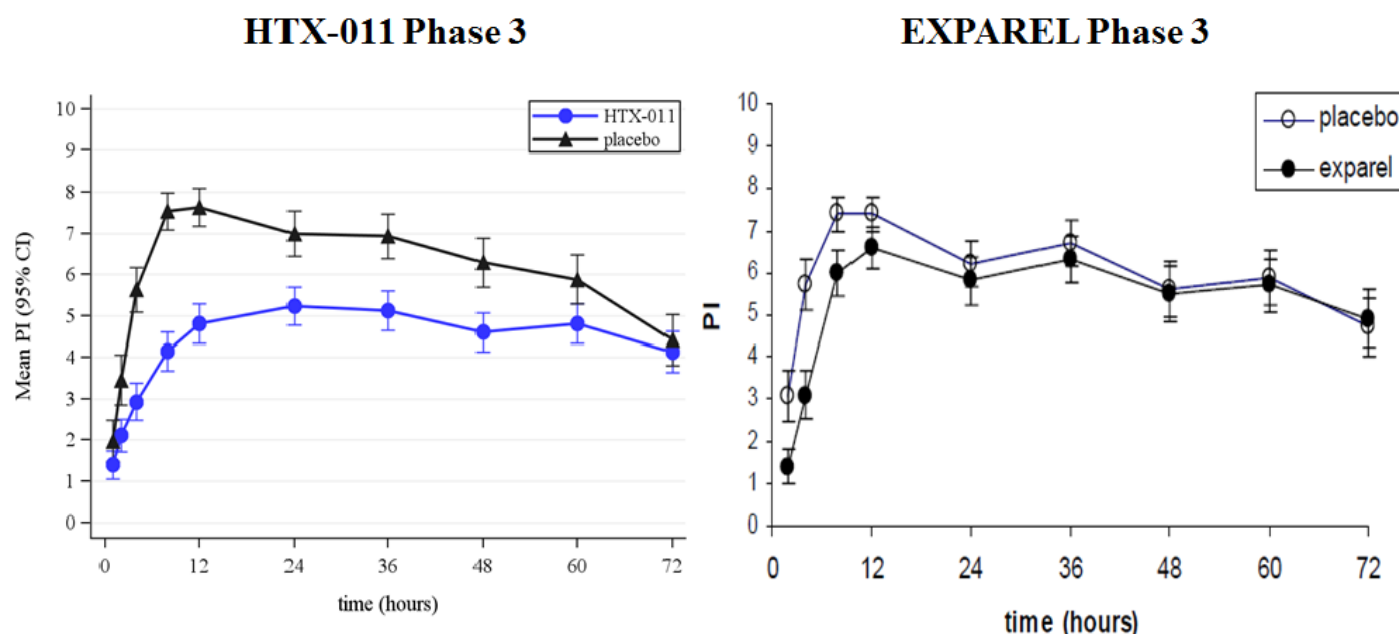
(Source: Applicant's Request for Breakthrough Therapy Designation, Page 20)

The Applicant compared the results of the AUC₀₋₂₄, AUC₀₋₄₈, and AUC₀₋₇₂ of the NRS pain intensity scores for HTX-011 60 mg/1.8 mg to Exparel 120 mg (Exparel Study C-317 (NCT00890682)). Both studies were Phase 3 and performed in subjects undergoing unilateral bunionectomy. In the current submission, the Applicant states, "This comparison was considered relevant due to the excellent reproducibility of bunionectomy studies, evidenced by the very similar results observed in Heron's Phase 2 and Phase 3 studies, and the similar placebo results observed between the HTX-011 and EXPAREL Phase 3 studies." Table 4 demonstrates that there was a statistically significant difference in the AUC of NRS-A pain intensity scores for all listed time periods between HTX-011 and placebo. While the difference of the mean AUC of the NRS at rest (NRS-R) pain intensity scores was statistically significant in favor of Exparel compared with placebo over the 0 to 24-hour and 0 to 48-hour time periods, it was not statistically significant over the 0 to 72-hour time period.

The Applicant also notes that the percent reduction in pain in the study groups versus the placebo groups was higher over the 0 to 24-hour, 0 to 48-hour, and 0 to 72-hour time periods for HTX-011

(37%, 31%, and 27%, respectively) compared with Exparel (16%, 10%, and 7%). However, it is important to consider the differences in the pain assessments in these studies (HTX-011 study utilized NRS-A (with activity) score, whereas the Exparel study utilized the NRS-R (with rest) score). The inherent difference in pain with activity versus pain at rest makes the presented comparison more difficult to interpret.

Figure 5 Mean Pain Intensity Scores at Each Assessed Timepoint Through 72 Hours For HTX-011 and EXPAREL vs. Saline Placebo Following Bunionectomy



(Source: Applicant's Request for Breakthrough Therapy Designation, Page 20)

Another observation presented by the Applicant pertains to the peak pain intensity score differences between HTX-011 and Exparel, in each respective study. The mean NRS-A pain intensity scores in the HTX-011 group peaked at approximately the numerical value of “5,” and remained below the pain intensity values for placebo until 72 hours, with significant differences noted for the 24 to 48-hour and 48 to 72-hour time periods (Figure 1). In contrast, the mean NRS-R pain intensity scores for Exparel peaked at approximately the “7.5” numerical value, 25% higher than HTX-011. In addition, although the NRS-R scores for Exparel were lower than those for placebo for approximately 24 hours after study drug administration, there was no difference beyond 24 hours evident by the overlapping confidence intervals from 24 to 72 hours.

Based on the cross-study comparison, the Applicant concludes that “HTX-011 60 mg/1.8 mg produced greater and longer postoperative analgesia through 72 hours after study drug administration than EXPAREL 120 mg.”

In summary, in the Breakthrough Therapy Designation request received on April 25, 2018, the Applicant presents preliminary data from two Phase 3 clinical studies to support the use of HTX-011 as significant improvement over the current standard-of-care, bupivacaine HCl in both pain intensity scores and duration of pain control. Specifically, the data demonstrate statistically lower mean AUC₀₋₇₂ of NRS-A pain intensity scores, 72-hour opioid consumption, and opioid-free subjects in the first 72 hours after drug administration in the HTX-011 group compared to the placebo and bupivacaine HCl groups. The Applicant does not provide a rationale on whether the magnitude of the differences observed would be clinically meaningful or sustained long-term, particularly with regard to opioid consumption and maintenance of opioid-free subjects. However, the differences in opioid-free subjects in both studies is noteworthy.

Furthermore, the Applicant provides a cross-study comparison between HTX-011 and Exparel in bunionectomy, which is currently the only approved long-acting formulation of bupivacaine on the market. Per the Applicant, the data suggest superiority of HTX-011 over Exparel in postoperative pain relief, particularly beyond 24 hours after administration. This cross-study comparison is intriguing, however, it's interpretation is difficult given some important differences in the data collected between studies (i.e., NRS-A versus NRS-R scores). Since an Exparel comparator arm was not included in Phase 3 clinical studies, no definitive conclusions can be made regarding whether HTX-011 offers significant improvement over Exparel.

The totality of the data do suggest that HTX-011 provides a superior method of postoperative pain relief compared to bupivacaine HCl, and possibly provides superior method of postoperative pain relief compared to Exparel, and thus, a clinically meaningful improvement over currently available therapies.

SAFETY RESULTS: Study 301 and Study 302

Preliminary results demonstrate that the overall incidence of treatment-emergent adverse events (TEAEs) was similar across treatment groups. The incidence of the TEAE of "skin odour abnormal" was higher in the HTX-011 group (8.0%) compared with the placebo (1.2%) and bupivacaine HCl (0.6%) groups. The majority of TEAEs were mild or moderate in severity, and the incidence of TEAEs considered by Investigators to be at least possibly related to study drug was higher in the HTX-011 group (25.2%) compared with the saline placebo and bupivacaine HCl groups (18.3% and 17.9%, respectively).

One death was reported in Study 301 in a subject who received bupivacaine HCl. In both studies, no serious adverse events (SAEs) were considered by the Investigators to be at least possibly related to study drug, and no SAE preferred term was reported in more than 1 subject. In Study 301, 1 subject in the HTX-011 group experienced a TEAE, not considered treatment-related, that led to premature withdrawal from the study.

The incidence of the most common TEAEs in both studies is presented in Table 5.

Table 5 Incidence of the Most Common TEAEs by Treatment (Studies 301 and 302; Safety Populations; Preliminary Data)

Preferred Term n (%)	Study 301 (Bunionectomy)			Study 302 (Herniorrhaphy)		
	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=101)	Bupivacaine HCl 50 mg (N=154)	HTX-011 300 mg/9 mg (N=163)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=173)
Nausea	59 (37.6%)	44 (43.6%)	70 (45.5%)	30 (18.4%)	28 (34.1%)	37 (21.4%)
Dizziness	34 (21.7%)	18 (17.8%)	36 (23.4%)	24 (14.7%)	13 (15.9%)	42 (24.3%)
Constipation	9 (5.7%)	7 (6.9%)	18 (11.7%)	28 (17.2%)	15 (18.3%)	41 (23.7%)
Incision site oedema	27 (17.2%)	13 (12.9%)	22 (14.3%)	0	0	0
Vomiting	23 (14.6%)	19 (18.8%)	33 (21.4%)	7 (4.3%)	4 (4.9%)	12 (6.9%)
Headache	22 (14.0%)	10 (9.9%)	20 (13.0%)	21 (12.9%)	10 (12.2%)	24 (13.9%)
Incision site erythema	20 (12.7%)	8 (7.9%)	18 (11.7%)	0	0	4 (2.3%)
Post procedural contusion	19 (12.1%)	13 (12.9%)	18 (11.7%)	0	0	0
Bradycardia	12 (7.6%)	6 (5.9%)	12 (7.8%)	15 (9.2%)	6 (7.3%)	16 (9.2%)
Dysgeusia	4 (2.5%)	6 (5.9%)	6 (3.9%)	15 (9.2%)	3 (3.7%)	21 (12.1%)
Skin odour abnormal	0	0	0	13 (8.0%)	1 (1.2%)	1 (0.6%)
Impaired healing	10 (6.4%)	1 (1.0%)	6 (3.9%)	0	0	0
Muscle twitching	9 (5.7%)	5 (5.0%)	8 (5.2%)	6 (3.7%)	4 (4.9%)	6 (3.5%)
Pruritus	8 (5.1%)	6 (5.9%)	1 (0.6%)	0	0	3 (1.7%)
Tremor	0	2 (2.0%)	2 (1.3%)	7 (4.3%)	8 (9.8%)	12 (6.9%)
Sinus arrhythmia	6 (3.8%)	6 (5.9%)	10 (6.5%)	3 (1.8%)	0	3 (1.7%)
Gamma- glutamyltransferase increased	5 (3.2%)	1 (1.0%)	5 (3.2%)	2 (1.2%)	6 (7.3%)	5 (2.9%)
Pruritus generalised	4 (2.5%)	4 (4.0%)	8 (5.2%)	2 (1.2%)	1 (1.2%)	1 (0.6%)
Tinnitus	2 (1.3%)	2 (2.0%)	8 (5.2%)	3 (1.8%)	5 (6.1%)	6 (3.5%)
Nasopharyngitis	1 (0.6%)	5 (5.0%)	0	1 (0.6%)	1 (1.2%)	0

Abbreviations: TEAE, treatment-emergent adverse event.

Notes: The most common TEAEs are defined as those that occurred in $\geq 5\%$ of the subjects in any treatment group. TEAEs were coded using the Medical Dictionary for Regulatory Activities MedDRA, Version 19.1. For each Preferred Term (PT), subjects are included only once, even if they experienced multiple events in that PT.

(Source: Type B Meeting Briefing Package Received on May 18, 2018; Page 30)

Nausea, vomiting, and dizziness were among the most commonly observed TEAEs in all study groups in both studies. No major differences were seen in the incidence of these events between the study groups. In addition, nausea, vomiting, and dizziness are very common postoperative adverse events and are often related to the use of other general anesthetic agents. Of note, however, is the abnormal skin odor events in Study 302 (herniorrhaphy). There were 13 subjects (8%) who had abnormal skin odor in the HTX-011 group compared to only one subject (0.6%) in the bupivacaine HCl group and one subject (1.2%) in the placebo group. Abnormal skin odor is a concerning event because it may indicate an infected wound, which is a serious surgical complication. These events are particularly pertinent because, as indicated by the previous Breakthrough Therapy Designation Determination Review dated July 5, 2017, there were concerns about wound healing and wound-related AEs in the bunionectomy studies early in the drug development program. These studies included earlier formulations of the proposed drug which had different excipients and were more viscous than the to-be-marketed product. The previous Breakthrough Therapy Designation Determination noted, however, that with the introduction of HTX-011-56 formulation (to-be-marketed), “the wound related AEs ceased to be an issue.” It is also noteworthy that there were no

abnormal skin odor adverse events in the Phase 3 bunionectomy study, Study 301. Therefore, although still concerning, it is possible that these events were a random complication of herniorrhaphy, since the procedure often involves incarcerated bowel prone to cause infection, rather than HTX-011.

The incidence of prespecified opioid-related adverse events (ORAEs) for Studies 301 and 302 is presented in Table 6.

Table 6 Incidence of Opioid-Related TEAEs (Studies 301 and 302; Safety Populations; Preliminary Data)

Preferred Term n (%)	Study 301 (Bunionectomy)			Study 302 (Herniorrhaphy)		
	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=101)	Bupivacaine HCl 50 mg (N=154)	HTX-011 300 mg/9 mg (N=163)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=173)
Any ORAE	69 (43.9%)	54 (53.5%)	78 (50.6%)	53 (32.5%)	36 (43.9%)	73 (42.2%)
Nausea	59 (37.6%)	44 (43.6%)	70 (45.5%)	30 (18.4%)	28 (34.1%)	37 (21.4%)
Constipation	9 (5.7%)	7 (6.9%)	18 (11.7%)	28 (17.2%)	15 (18.3%)	41 (23.7%)
Vomiting	23 (14.6%)	19 (18.8%)	33 (21.4%)	7 (4.3%)	4 (4.9%)	12 (6.9%)
Pruritus	8 (5.1%)	6 (5.9%)	1 (0.6%)	0	0	3 (1.7%)
Pruritus generalised	4 (2.5%)	4 (4.0%)	8 (5.2%)	2 (1.2%)	1 (1.2%)	1 (0.6%)
Somnolence	1 (0.6%)	0	1 (0.6%)	0	0	0
Urinary retention	0	0	0	1 (0.6%)	1 (1.2%)	3 (1.7%)

Abbreviations: ORAE, opioid-related adverse event; TEAE, treatment-emergent adverse event.

Notes: TEAEs are events that started during or after study drug administration or those that started before study drug administration but worsened during or after study drug administration. For each Preferred Term (PT), subjects are included only once, even if they experienced multiple events in that PT.

(Source: Type B Meeting Briefing Package Received on May 18, 2018; Page 31)

In both studies, the overall incidence of prespecified opioid-related adverse events is lower in the HTX-011 group than the placebo and the bupivacaine HCl groups, with the exception of generalized pruritis, which has very low incidence and is unlikely to be drug-related. The differences in the incidence of these AEs are possibly the result of decreased opioid consumption seen in the HTX-011 groups compared to the control groups. However, it is difficult to determine whether the overall magnitude of the differences in these specific ORAEs is clinically meaningful. The Applicant did not hypothesize regarding the clinical significance of this data.

The Applicant also provided a table describing the incidence of potential local anesthetic systemic toxicity (LAST) related TEAEs:

Table 7 Incidence of Potential LAST-Related TEAEs (Studies 301 and 302; Safety Populations; Preliminary Data)

Preferred Term n (%)	Study 301 (Bunionectomy)			Study 302 (Herniorrhaphy)		
	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=101)	Bupivacaine HCl 50 mg (N=154)	HTX-011 300 mg/9 mg (N=163)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=173)
Any potential LAST TEAE	55 (35.0%)	34 (33.7%)	64 (41.6%)	54 (33.1%)	28 (34.1%)	71 (41.0%)
Dizziness	34 (21.7%)	18 (17.8%)	36 (23.4%)	24 (14.7%)	13 (15.9%)	42 (24.3%)
Bradycardia	12 (7.6%)	6 (5.9%)	12 (7.8%)	15 (9.2%)	6 (7.3%)	16 (9.2%)
Dysgeusia	4 (2.5%)	6 (5.9%)	6 (3.9%)	15 (9.2%)	3 (3.7%)	21 (12.1%)
Muscle twitching	9 (5.7%)	5 (5.0%)	8 (5.2%)	6 (3.7%)	4 (4.9%)	6 (3.5%)
Hypotension	7 (4.5%)	2 (2.0%)	7 (4.5%)	7 (4.3%)	3 (3.7%)	7 (4.0%)
Tremor	0	2 (2.0%)	2 (1.3%)	7 (4.3%)	8 (9.8%)	12 (6.9%)
Sinus arrhythmia	6 (3.8%)	6 (5.9%)	10 (6.5%)	3 (1.8%)	0	3 (1.7%)
Paraesthesia oral	2 (1.3%)	0	0	4 (2.5%)	0	3 (1.7%)
Paraesthesia	3 (1.9%)	2 (2.0%)	0	1 (0.6%)	0	1 (0.6%)
Tinnitus	2 (1.3%)	2 (2.0%)	8 (5.2%)	3 (1.8%)	5 (6.1%)	6 (3.5%)
Visual impairment	0	0	1 (0.6%)	3 (1.8%)	2 (2.4%)	5 (2.9%)
Sinus bradycardia	0	0	3 (1.9%)	1 (0.6%)	0	0
Vision blurred	0	0	1 (0.6%)	1 (0.6%)	0	1 (0.6%)
Arrhythmia supraventricular	0	0	1 (0.6%)	0	0	0

Abbreviations: LAST, local anesthetic systemic toxicity; ORAE, opioid-related adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Notes: TEAEs are events that started during or after study drug administration or those that started before study drug administration but worsened during or after study drug administration. For each Preferred Term (PT), subjects are included only once, even if they experienced multiple events in that PT.

(Source: Type B Meeting Briefing Package Received on May 18, 2018; Page 32)

In Study 301, lower incidences of total potential local anesthetic systemic toxicity (LAST)-related TEAEs were reported in the HTX-011 group (35.0%) and the placebo group (33.7%) compared with the bupivacaine HCl group (41.6%). The potential LAST-related TEAE preferred terms reported for >5% of subjects in the HTX-011, placebo, or bupivacaine HCl groups were dizziness (21.7%, 17.8%, and 23.4%, respectively), bradycardia (7.6%, 5.9%, and 7.8%), muscle twitching (5.7%, 5.0%, and 5.2%), sinus arrhythmia (3.8%, 5.9%, and 6.5%), dysgeusia (2.5%, 5.9%, and 3.9%), and tinnitus (1.3%, 2.0%, and 5.2%). In Study 302, lower incidences of total potential LAST-related TEAEs were reported in the HTX-011 group (33.1%) and the placebo group (34.1%) compared with the bupivacaine HCl group (41.0%). The potential LAST-related TEAE preferred terms reported for >5% of subjects in the HTX-011, placebo, or bupivacaine HCl groups were dizziness (14.7%, 15.9%, and 24.3%, respectively), dysgeusia (9.2%, 3.7%, and 12.1%), bradycardia (9.2%, 7.3%, and 9.2%), tremor (4.3%, 9.8%, and 6.9%), and tinnitus (1.8%, 6.1%, and 3.5%). Due to multiple confounders related to anesthesia and surgery, it is often difficult to determine whether any one of these prespecified adverse events are due to LAST. However, that data does provide reassurance that the incidence of LAST-related AEs is no greater, and possibly even less, than the incidence of these AEs with bupivacaine HCl.

Table 8 represents the incidence of local inflammatory TEAEs in Studies 301 and 301.

Table 8 Incidence of Local Inflammatory TEAEs Reported for at Least 2 Subjects in a Treatment Group (Studies 301 and 302; Safety Populations; Preliminary Data)

Preferred Term n (%)	Study 301 (Bunionectomy)			Study 302 (Herniorrhaphy)		
	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=101)	Bupivacaine HCl 50 mg (N=154)	HTX-011 300 mg/9 mg (N=163)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=173)
Any local inflammatory TEAE	45 (28.7%)	20 (19.8%)	34 (22.1%)	6 (3.7%)	2 (2.4%)	10 (5.8%)
Incision site oedema	27 (17.2%)	13 (12.9%)	22 (14.3%)	0	0	0
Incision site erythema	20 (12.7%)	8 (7.9%)	18 (11.7%)	0	0	4 (2.3%)
Impaired healing	10 (6.4%)	1 (1.0%)	6 (3.9%)	0	0	0
Incision site cellulitis	7 (4.5%)	1 (1.0%)	2 (1.3%)	0	0	1 (0.6%)
Wound dehiscence	7 (4.5%)	2 (2.0%)	1 (0.6%)	1 (0.6%)	0	0
Incision site infection	4 (2.5%)	0	1 (0.6%)	1 (0.6%)	1 (1.2%)	1 (0.6%)
Erythema	3 (1.9%)	1 (1.0%)	0	0	0	0
Incision site swelling	0	0	0	3 (1.8%)	0	0
Incision site rash	2 (1.3%)	0	0	0	0	1 (0.6%)
Post procedural cellulitis	2 (1.3%)	2 (2.0%)	0	0	0	0
Wound secretion	2 (1.3%)	0	0	1 (0.6%)	0	1 (0.6%)
Incision site haemorrhage	1 (0.6%)	1 (1.0%)	2 (1.3%)	1 (0.6%)	0	0
Blister	0	2 (2.0%)	1 (0.6%)	0	0	0

Abbreviations: TEAE, treatment-emergent adverse event.

Notes: TEAEs are events that started during or after study drug administration or those that started before study drug administration but worsened during or after study drug administration. For each Preferred Term (PT), subjects are included only once, even if they experienced multiple events in that PT.

(Source: Type B Meeting Briefing Package Received on May 18, 2018; Page 33)

In Study 301, the incidence of local inflammatory TEAEs was greater than in Study 302, and highest in the HTX-011 group (28.7%) compared with placebo (19.8%) and bupivacaine HCl (22.1%). The local inflammatory TEAE preferred terms reported for >5% of subjects in the HTX-011, placebo, or bupivacaine HCl groups were incision site oedema (17.2%, 12.9%, and 14.3%, respectively), incision site erythema (12.7%, 7.9%, and 11.7%), and impaired healing (6.4%, 1.0%, and 3.9%). Events of incision site oedema and incision site erythema had the highest incidence, but do not appear to have clinically significant differences in the HTX-011 and the bupivacaine HCl groups. Although the overall incidence is low, there are notably greater number of the following events in the HTX-011 group compared to the bupivacaine HCl group: impaired wound healing (6.4% versus 3.9%), incision site cellulitis (4.5% versus 1.3%), wound dehiscence (4.5% versus 0.6%), and incision site infection (2.5% versus 0.6%). The Applicant does not provide a rationale to explain this higher incidence, which is potentially concerning due to the previously discussed wound healing events noted with earlier drug formulations. However, as noted in the previous Breakthrough Therapy Designation Determination Review dated July 5, 2017, Phase 2 studies, including a bunionectomy study (Study 208), utilizing the to-be-marketed formulation did not appear to have a concerning incidence of local inflammatory TEAEs. In addition, abnormal skin odor adverse event, discussed above, was also not seen in Study 301.

In Study 302, the total incidence of local inflammatory TEAEs was low and similar across the HTX-011, placebo, and bupivacaine HCl groups (3.7%, 2.4%, and 5.8%, respectively). No local

inflammatory TEAEs preferred terms were reported for >5% of subjects in any group. The TEAEs reported in more than 1 subject in the HTX-011, placebo, or bupivacaine HCl groups were incision site swelling (1.8%, 0, and 0, respectively) and incision site erythema (0, 0, and 2.3%).

In summary, although certain TEAEs related to local inflammatory reactions had a greater incidence in the HTX-011 group than in the placebo or bupivacaine HCl groups in Study 301, the overall incidence of these events was still low. In addition, the incidence of these events is not consistent across studies with the to-be-marketed formulation in the development program. Therefore, the totality of the safety data have no impact on the Division decision to grant or deny Breakthrough Therapy Designation.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting:

The Applicant presents preliminary data from two Phase 3 clinical studies to support the use of HTX-011 as significant improvement over the current standard-of-care, bupivacaine HCl in both pain intensity scores and duration of pain control. Specifically, the data demonstrate statistically lower mean AUC0-72 of NRS-A pain intensity scores, 72-hour opioid consumption, and opioid-free subjects in the first 72 hours after drug administration in the HTX-011 group compared to the placebo and bupivacaine HCl groups. The Applicant does not provide a rationale on whether the magnitude of the differences observed would be clinically meaningful or sustained long-term, particularly with regard to opioid consumption and maintenance of opioid-free subjects. However, the differences in opioid-free subjects in both studies is noteworthy.

In addition, the Applicant presents cross-study comparison between HTX-011 and Exparel. The data in this clinical cross-study comparison indicate that there may also be a potential difference in both the intensity of pain control and the duration of pain control in favor of HTX-011, although a properly-conducted prospective comparator study would be needed to confirm these results.

Preliminary totality of safety data from the development program with the to-be-marketed formulation do not reveal any concerning safety signals.

The totality of the data do suggest that HTX-011 provides a superior method of postoperative pain relief compared to bupivacaine HCl, and possibly provides superior method of postoperative pain relief compared to Exparel, and thus, a clinically meaningful improvement over currently available therapies.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

12. Division's next steps and Applicant's plan for future development:

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the Applicant (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Division will be meeting with the Applicant on June 20, 2018, for a Type B, Pre-NDA meeting. The Division will address any questions pertaining to the planned NDA submission during the meeting.

- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the Applicant regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

13. List references, if any:

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☐
NO ☒

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: { See appended electronic signature page }
Team Leader Signature: { See appended electronic signature page }
Division Director Signature: { See appended electronic signature page }

Revised 3/20/18/M. Raggio

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALLA T BAZINI
06/12/2018

MARTHA A VAN CLIEF
06/12/2018

SHARON H HERTZ
06/13/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 125927

MEETING MINUTES

Heron Therapeutics
4242 Campus Point Court
Suite 200
San Diego, CA 92121

Attention: Kimberly Manhard
Executive Vice President, Drug Development

Dear Ms. Manhard:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for HTX-001 (bupivacaine and meloxicam extended-release injection) 2.5%/0.075%.

We also refer to the meeting between representatives of your firm and the FDA on June 15, 2017. The purpose of the meeting was to obtain feedback on the completed nonclinical studies, Phase 2 clinical data supporting the Phase 3 program and the overall clinical plan to support an NDA for HTX-011.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact me, at (240) 402-8807.

Sincerely,

{See appended electronic signature page}

Ogochukwu Ogoegbunam, PharmD
Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: June 15, 2017, 4:00 p.m. – 5:00 p.m.
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room 1315
Silver Spring, Maryland 20903

Application Number: 125927
Product Name: HTX-001 (bupivacaine and meloxicam extended-release injection)
2.5%/0.075%
Indication: reduction of postoperative pain
Sponsor/Applicant Name: Heron Therapeutics, Inc.

Meeting Chair: Rigoberto Roca, MD
Meeting Recorder: Ogochukwu Ogoegbunam, PharmD

FDA ATTENDEES

Sharon Hertz, MD	Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Rigoberto Roca, MD	Deputy Division Director, DAAAP
Martha Van Clief, MD	Medical Officer, DAAAP
Yun Xu, PhD	Clinical Pharmacology Supervisor, Division of Clinical Pharmacology II (DCP2)
Suresh Naraharisetti, PhD	Clinical Pharmacology Reviewer, DCP2
Dan Mellon, PhD	Pharmacology/Toxicology Supervisor, DAAAP
Jay Chang, PhD	Pharmacology/Toxicology Team Leader, DAAAP
Ciby Abraham, PhD	CMC Acting Team Lead, ONDP, OPQ
David Petullo, MS	Biostatistics Team Leader, Division of Biometrics
Katherine Meaker, MS	Biostatistics Reviewer, Division of Biometrics
Bindi Nikhar, MD	Associate Clinical Director, Office of Combination Products
Ogochukwu Ogoegbunam, PharmD	Regulatory Health Project Manager, DAAAP

SPONSOR ATTENDEES

Barry Quart, PharmD	Chief Executive Officer
Kimberly Manhard	Executive Vice President, Drug Development

Erol Onel, MD
Mary Rose Keller
Matt Cravets, MA, MBA
Thomas Ottoboni, PhD

Clynn Wilker, DVM, PhD, DACT
Lynley Thinnies

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BACKGROUND

Heron Therapeutics, Inc. is developing an extended-release solution containing bupivacaine and meloxicam, HTX-011. This product is indicated for (b) (4)

(b) (4) The purpose of the End-of-Phase 2 meeting is to seek feedback from the FDA on the completed nonclinical studies, the Combination Product requirements, the Phase 2 clinical data to support the Phase 3 program, and the overall clinical development plan, including 2 proposed Phase 3 studies, to support an NDA for HTX-011.

FDA sent Preliminary Comments to Heron Therapeutics, Inc. on June 13, 2017.

The questions from the April 14, 2017, briefing package are shown in *italic font*. The Division responses are shown in **bold font** and the meeting discussion is in regular font.

Nonclinical

Question 1:

Does the FDA agree that the completed and planned nonclinical program is sufficient to support the safety of HTX-011-56 for the proposed Phase 3 local administration studies in visceral and non-visceral models and the NDA?

FDA Response to Question 1:

We cannot agree at this time that the nonclinical program is sufficient to support the safety of the planned Phase 3 clinical studies and the NDA. The previously conducted rat bone healing and rabbit hernia studies were not conducted in accordance with good laboratory practices (GLP). We acknowledge that the studies followed laboratory standard operating procedures (SOPs), included signed pathology reports, and that you have provided a justification suggesting that the only deviations from GLP were lack of quality assurance (QA) statements. However, you will need to either provide final

study reports with QA statements or provide a justification for why the studies could not be quality assured and why the results and conclusions are reliable without the appropriate validation.

In addition, it is not clear that the nonclinical program has adequately justified the systemic safety of all of the excipients in the intended clinical formulation. We note that the 28-day repeat-dose subcutaneous rat toxicity study did not test HTX-011-56, but rather different formulations, some of which contained lower levels of the excipient AP135. Moreover, though most of the other excipients were tested at higher concentrations with these formulations compared to the intended formulation, the volumes administered in the 28-day rat study do not appear to be sufficient from a systemic perspective to provide adequate coverage for the levels that will be administered at the highest proposed clinical dose for the planned hernia study and ultimately how the drug product will be labeled for use. Prior to initiating your Phase 3 program, provide a clear justification for how your nonclinical program has qualified the systemic and local safety all of the excipients in the clinical formulation for the proposed clinical use. The adequacy of the data to support the safety of the planned Phase 3 studies and the NDA will be determined after a full review of all of the information submitted.

Refer to the additional nonclinical comments below to determine if any other nonclinical studies will be warranted for your program.

Sponsor follow-up (provided via email on June 15, 2017)

Please refer to the justification that was supplied in Safety Information Amendment to IND 125927 (SN0014; 21 December 2015) for the rabbit hernia study. The non-GLP study (ITR-73119B; Heron Study 33-38) supports the conclusion that the drug product will not adversely affect the surgical mesh to be used in the proposed clinical study. Although the study was performed non-GLP it followed established ITR Laboratory SOPs that are subjected to QA oversight as per general procedures in the facility. The only difference between a GLP and a non-GLP study at ITR is the involvement, or not, of the QA department (see Study ITR-73119B Memo). In addition, the attached letter received from ITR on ITR Study number 73119B "HTX-011: A Hernia Repair Model with Mesh in New Zealand White Rabbit" provides a further justification that the results and conclusion are reliable. This in vivo study is further supported by the findings from the in vitro study performed in response to an FDA request, RPT-PHD-83 "Technical Development Report: Compatibility of Hernia Mesh materials with HTX-011 Solvents", which was submitted to the IND 125927 (SN0007; 11 September 2015).

The rat bone healing study (8330-750; Heron Study 33-39) supports the conclusion that the drug product does not affect bone healing in the cortical bone defect model in the female rat. The attached letter received (b)(4) on Study 8330-750 "Single Subcutaneous Dose Effect of HTX-002-014, HTX-011-49 and HTX-011-56 on Bone Healing in the Cortical Defect Model in Female Sprague Dawley Rats" provides a further justification that the results and conclusion are reliable. In addition, these findings in animals have been confirmed in completed Phase 2 clinical study in bunionectomy, Study HTX-011-208. As

presented in Section 10.3.5.2.1 Study 208 (Bunionectomy) of the Briefing Document, of the 414 subjects with available post-treatment X-ray results, 413 (99.8%) had normal bone healing. The 1 subject with an abnormal bone healing result was reported to have mal-union, which the Investigator considered to be a result of non-compliance with postoperative therapy (not wearing his post-operative boot).

The safety and qualification of all excipients in HTX-011 were either qualified previously and listed on the FDA Inactive Ingredient List or were qualified by the nonclinical studies conducted. In each nonclinical study a saline and vehicle control (HTX-024) were included. The table below presents the dose based on BSA (mg/m^2) of each excipient in the 28-day rat toxicology study for the HTX-011-47 formulation and for the vehicle, HTX-024. The 28-day rat toxicology study was submitted to IND 125927 as an Information Amendment: Pharmacology/Toxicology (SN0011; December 7, 2015). We apologize if the information presented for HTX-024 in Table 10 of the Briefing Document wasn't sufficiently clear. The information was presented for a single dose, rather than the cumulative exposure from 28 days of dosing. Each of the excipients in HTX-011 were qualified based on Body Surface Area (BSA) by the single dose of HTX-011-47 in the rat 28-day repeat dose study and by the twice weekly dose for a total of 8 doses. Animal to human margins ranged from 7- to 28-fold. Special attention was paid to local tolerability for HTX-011 and the vehicle in this study.

Study Description (Study ID)	Formulation	Formulation Dose	Day	Dose Based on BSA (mg/m^2) ^a			
				DMSO	Triacetin	API 35	Maleic Acid
28-Day Rat via SC (33-19)	HTX-024	0.25 mL	1	763	2670	3792	NA
			28	6104	21360	30336	NA
	HTX-011-47	0.25 mL	1	865	3026	4297	12.9
			28	6916	24207	34374	103
Single Dose in Human via Instillation (Study 202)	HTX-011-56	10.3 mL	1	743.	1858	4636	3.75
Animal (HTX-011-47 Day 28)/Human Margins				9	13	7	28

^a The BSA calculation was based on the mg/kg doses for each excipient. The Day 1 mean body weights for females for were used to calculate the mg/kg dose for both Day 1 and 28. The Day 1 mean body weights on Day 1 for both respective formulation groups (Group 2 and Group 5) for, HTX-024 and HTX-011-47, respectively were 230 g. [Note: Footnote added after End of Phase 2 meeting and the API35 dose based on BSA was corrected from 4630 to 4636.]

Furthermore, (b) (4) APF18A, the vehicle for SUSTOL[®] (granisetron) extended-release injection. Studies conducted as part the SUSTOL nonclinical toxicology program included genotoxicity and reproductive toxicity with APF18A. Based on

the results from those studies AP135 was not considered genotoxic or a reproductive toxicant. In addition, 90-day rat and dog studies were conducted with APF18A with daily dosing of animals and submitted to the original HTX-011 IND 125927 (SN0000; May 6, 2015). Although the calculations were not presented in the HTX-011 Briefing Document, at the NOAEL dose the total amount of AP135 administered over those 90 days was 20,815 mg and 83,261 mg for the rat and dog, respectively, compared to a total exposure of 7,517 mg of AP135 in humans following a single dose of 300 mg/9 mg HTX-011-56 as presented in the table that follows. Special attention was paid to local tolerability of the vehicle in this study.

Study Description (Study ID)	Formula tion	Formula tion Dose	Total AP135 Dosed (mg)	Dose Based on BSA (mg/m²)	Animal/Hu man Margins
90-Day Rat via SC (25-07)	AP530	0.25 mL	20815	386660	83.4
90-Day Dog via SC (25-08)	AP530	1.0 mL	83261	187103	40.4
Single Dose in Human via Instillation (Study 202)	HTX- 011-56	10.3 mL	7517	4636	--

^a The BSA calculation was based on the mg/kg doses for AP135. The Day 90 mean body weights for females for AP530 were used to calculate the mg/kg dose. The mean body weights on Day 90 for the rat and dog studies were 323g and 8.9 kg, respectively. [Note: Footnote added after End of Phase 2 meeting and the AP135 dose based on BSA was corrected from 4635 to 4636.]

In summary, we believe that there is sufficient nonclinical safety assessment data to qualify the local and system safety of all the HTX-011 excipients and to support the initiation of Phase 3.

Meeting Discussion:

The Sponsor explained that the data in their rabbit hernia study and rat bone healing study, although non-GLP, were reliable. They have obtained letters from the conducting CROs that attest that the studies were performed in the spirit of GLP, but only lacked quality assurance (QA). They also confirmed that there is no way to retrospectively perform QA. In addition to the bone healing study, the Sponsor noted that the intended clinical product has been administered to 414 patients undergoing bunionectomy in Phase 2 studies and all but one subject had normal bone healing assessed by x-ray. The one subject with abnormal bone recovery did not follow post-op instructions. The Division responded that an internal discussion will take place regarding the adequacy of the non-GLP rat bone healing and rabbit hernia studies and feedback will be provided as a post-meeting note, if possible.

The Sponsor conducted a 28-day rat subcutaneous toxicity study that tested HTX-011 formulations with sufficiently high levels of excipients to qualify the systemic safety of the

intended clinical formulation. They argued that for an extended-release product, (b) (4) should be considered. As such, the Sponsor contended (b) (4)

The Division stated that the safety assessment for excipients should be based on total daily intake in animals (b) (4)

(b) (4) The Division further noted that several of the excipients, including DMSO, are not expected to be released with extended-release properties, but rather, may be exposed immediately after administration. The Sponsor noted they have data that demonstrates all of the excipients, including DMSO, are released at comparable rates as the APIs and will provide this information or indicate where they are located in the IND. The Division noted that they will double check the values to confirm that there is appropriate coverage prior to providing an answer.

The Sponsor also noted that they have provided additional toxicity studies to justify the safety of AP135 that were originally conducted in support of their clinical development of Sustol®, (b) (4) They contended that their previously conducted 90-day rat and dog toxicity studies with Sustol provide large safety margins for this excipient when considering the cumulative exposure over the 90-day study periods. The Division asked if they Sponsor intended to cross reference the data from the Sustol NDA. The Sponsor responded that they have already submitted this data to the HTX-011 IND.

Post-meeting note: We are reviewing your justifications for the validity of the non-GLP rabbit hernia study to determine if this study must be repeated in accordance with GLPs. We note that your rationale for the validity of this study is based, in part, on the fact that the study was conducted in accordance with the laboratory's standard operating procedures (SOPs). However, as we do not have the SOPs from these labs, it is not possible to independently evaluate how these studies may or may not deviate from GLPs. In order to facilitate our review of your justification, submit a copy of the laboratories SOPs to the IND for Agency review.

In terms of the non-GLP rat bone healing study, your justification is also primarily based on the fact that the studies were conducted according to the laboratory's standard operating procedures (SOPs). Submit the SOPs from this organization. Further, you state that although the rat bone healing study was not completed in accordance with GLPs, the existing human data support the conclusion that the drug product does not have an adverse impact on bone healing. We cannot concur with this conclusion until we review the data from the bunionectomy studies.

Question 2:

Does the FDA agree that the excipients in the intended commercial formulation of HTX-011 (HTX-011-56), including the polymer AP135, are adequately qualified and that no additional nonclinical studies of the excipients are required for the NDA?

FDA Response to Question 2:

See response to Question 1.

Meeting Discussion:

See Discussion to Question 1.

Additional Nonclinical Comments:

1. **New excipients must be adequately qualified for safety. Studies must be submitted to the IND in accordance with the guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf>. As noted in the guidance, “the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration.” (emphasis added).**

Sponsor follow-up (provided via email on June 15, 2017)

The safety and qualification of the new excipient, AP135, is provided in Heron’s response to Question 1.

2. **If the drug substance batch(es) proposed for use in your clinical study are not the same batches as those used in your nonclinical toxicology studies, provide a table in your IND submission that compares the impurity profile across batches. Include justification for why the levels of impurities in the pivotal nonclinical toxicology studies provide adequate coverage for the proposed levels in the clinical batches or do not otherwise represent a safety concern.**

Sponsor follow-up (provided via email on June 15, 2017)

The nonclinical toxicology studies used 1 of 2 bupivacaine drug substance batches included in HTX-011 drug product lots proposed for use in the Phase 3 clinical studies. The level of impurities in the 1 bupivacaine drug substance batch planned for Phase 3 studies that was not included in the pivotal nonclinical studies was (b) (4)%. This level of impurities is covered by the pivotal toxicology study (study 33-19), which provides an 8-fold safety margin for the bupivacaine-related impurities based on human dose equivalent calculations.

The nonclinical toxicology studies used none of 2 meloxicam drug substance batches included in HTX-011 drug product lots proposed for use in the Phase 3 clinical studies. The levels of the impurities for the 2 meloxicam drug substance batches planned for Phase 3 studies were the same (nil) or below the levels (b) (4)% vs (b) (4)% in the pivotal nonclinical studies. Therefore, the levels of impurities in the pivotal nonclinical toxicology studies provide adequate coverage for the proposed levels of meloxicam-related impurities in the clinical batches.

A table comparing the impurity profile across nonclinical and clinical batches follows and will be submitted to the IND as requested.

3. For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2), ICH Q3B(R2) or be demonstrated to be within the specifications of the referenced drug used for approval through the 505(b)(2) pathway. In order to provide adequate qualification:
 - a. You must complete a minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
 - b. In addition, you must conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of **14 or 90** days should be completed.

Refer to
Guidance for industry: *Q3A(R2) Impurities in New Drug Substances*, available at,
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf>

and

Guidance for industry: *Q3B(R2) Impurities in New Drug Products*, available at,
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf>

 - c. Alternatively, you may be able to justify the systemic safety of a drug product degradant via comparative analytical studies that demonstrate that the levels of the degradant in your drug product are equal to or below the levels found in the referenced drug product. If you elect to pursue this approach, refer to the FDA guidance for industry: *ANDAs: Impurities in Drug Products*, available at,
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072861.pdf>. However, local tissue safety must also be addressed.
4. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, how these levels compare to ICH Q3A(R2) and ICH Q3B(R2)

qualification thresholds, and if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.

5. Genotoxic impurities, carcinogenic impurities, or impurities that contain a structural alert for genotoxicity must be adequately controlled during drug development. Drug substance manufacturing often creates the potential for introduction of compounds with structural alerts for genotoxicity through use of reagents, catalysts and other processing aids or the interaction of these with starting materials or intermediates during the stages of chemical synthesis. Refer to the ICH guidance document titled: *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* for the appropriate framework for identifying, categorizing, qualifying, or controlling these impurities. This guidance is available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf> . Briefly, actual and potential impurities likely to arise during synthesis and storage of a new drug substance and manufacture and storage of a new drug product should be identified for assessment. A hazard assessment should be undertaken to categorize these impurities with respect to mutagenic and carcinogenic potential and risk characterization applied to derive acceptable intakes during clinical development. Finally, a control strategy should be proposed and enacted where this is determined to be necessary to ensure levels are within the accepted limits established for the stage of drug development in order to mitigate risk.
6. The NDA submission must contain adequate information on potential leachables and extractables from the drug container closure system and/or drug product formulation, unless specifically waived by the Division. The evaluation of extractables and leachables from the drug container closure system or device should include specific assessments for residual monomers, solvents, polymerizers, etc. Provide justification for the choice of solvents and conditions for the extraction studies (time, temperature, etc.). The results of the extraction studies should be used to assure that you are adequately monitoring the drug product stability samples for potential leachables from the primary or secondary container closure systems and from your analysis of data from any upstream manufacturing processes that suggest the potential for additional leachable compounds in the final drug product formulation. Your analytical evaluation threshold (AET) must be established to be able to detect, identify, and quantitate levels of compounds based on these thresholds or you must provide adequate justification that these thresholds are not possible to be met by current analytical methodology. If you cannot meet these thresholds, safety evaluations will be based on the limits of quantitation (LOQ). Your submission must include a detailed discussion of how you established your AET as well as justification for the limits of detection (LOD) and LOQ for the analytical methods used.

Evaluate at least three batches of your to-be-marketed drug product for leachables and include assessments at multiple timepoints over the course of your stability studies in order to identify trends in leachable levels over time. The materials tested should include any secondary container closure systems, if present, and be subjected to the same sterilization methods, as appropriate. These data are essential to determine the appropriate shelf life of your product.

For all drug products, establish your AET to be able to detect potentially carcinogenic or genotoxic compounds as per ICH M7 qualification thresholds (e.g., not more than 1.5 mcg/day or up to 120 mcg/day depending on the duration of treatment). However, from a general toxicology perspective, for parenteral products, the AET must be able to detect and identify any leachable that is present in the product at 5 mcg/day or higher in order, unless justified otherwise, to permit an adequate toxicological risk assessment.

For additional guidance on extractables and leachables testing, refer to the following documents:

- **USP <1663>: Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems**
- **USP <1664>: Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems**
- **FDA guidance for industry: Container Closure Systems for Packaging Human Drugs and Biologics, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf>**

The extractable/leachable data must be accompanied by an adequate toxicological risk assessment. Although a toxicological risk assessment based on the results of the extraction studies may be adequate to support the safety assessment during development, evaluate at least three batches of your drug product that have been tested at multiple timepoints over the course of your stability studies, as discussed above, and base the final safety assessment on the maximum predicted levels of leachables identified to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified. Include copies of all referenced studies upon which a safety assessment is based.

- If you employ a Permissible Daily Exposure (PDE) assessment as described in ICH Q3C, provide justification for all safety factors employed.
 - Published literature to support the safety of any compound rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, (e.g., BIBRA, CIR, HERA), although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports must be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study must be discussed and justification must be provided to support your assertion that these data are adequate to support the safety of your drug product formulation.
 - Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your leachable/extractable. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the novel leachable.
7. **NOTE:** We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity or degradant that exceeds the ICH qualification thresholds, safety justification for a new or novel excipient, or safety characterization of extractables and leachables.
8. The nonclinical information in your proposed drug product labeling must include relevant exposure margins with adequate justification for how these margins were obtained. As you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product labeling.
9. We note that all NDA applications filed after June 30, 2015 must submit labeling consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). In order to prepare for this new labeling format, you should conduct a thorough review of the existing clinical and nonclinical literature for each drug substance in your drug product and propose a risk summary statement and text for Section 8 of the labeling. Information on the final rule and links to the FDA draft guidance document are available at,
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>.

10. Your NDA submission should include a detailed discussion of the nonclinical information in the published literature and should specifically address how the information within the published domain impacts the safety assessment of your drug product. This discussion should be included in Module 2 of the submission. Copies of all referenced citations should be included in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.

Sponsor follow-up (provided via email on June 15, 2017)

Heron acknowledges the Agency's advice provided for Additional Nonclinical Comments #3-10 and will address it in the planned NDA.

Discussion:

The Sponsor provided a table (see attached slides) with the total related impurities in the batches of bupivacaine and meloxicam and stated that the impurities were extremely low and will not pose any safety risk at this time. The Sponsor also noted that the levels of impurities in the clinical batches are covered by the levels in the nonclinical toxicology batches. The Division responded that the information appeared acceptable based on the summary information presented. However, a final determination of the adequacy of the information to support approval of the product will be made during the NDA review.

Clinical Pharmacology

Question 3:

Does the FDA agree that the available hepatic and renal impairment data for bupivacaine and meloxicam are sufficient to support the planned NDA and that hepatic and renal impairment studies as not required?

FDA Response to Question 3:

Yes, we generally agree with your proposal. Note that final labeling instructions for patients with hepatic and renal impairment for your product should reflect the way the Phase 3 clinical trials were conducted in these patient populations. The final determination of label language for hepatic and renal impairment patients for your product will be made during the NDA review.

Sponsor follow-up (provided via email on June 15, 2017)

Heron acknowledges the Agency's response.

Discussion:

No further discussion was needed.

Question 4:

Does the FDA agree that drug-drug interaction (DDI) studies with HTX-011 are not required for the planned NDA?

FDA Response to Question 4:

We generally agree with your proposal. The final determination of label language for DDI for your product will be made during the NDA review.

*Sponsor follow-up (provided via email on June 15, 2017)
Heron acknowledges the Agency's response.*

Meeting Discussion:

No further discussion was needed.

Question 5:

Does the FDA agree with Heron's plan to use population PK data to adequately inform prescribers regarding correlations between PK and intrinsic factors (age, race, ethnicity, and sex) for HTX-011, and that no further studies are necessary?

FDA Response to Question 5:

Yes. You may use population PK data to identify the correlations between PK and intrinsic factors (age, race, ethnicity, and sex) for appropriate dosing of your product. We have the following general comments for submitting the pharmacometric data and models:

- 1. All datasets used for model development and validation should be submitted as a SAS transport files (*.apt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.**
- 2. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).**
- 3. A model development decision tree and/or table which gives an overview of modeling steps should be submitted.**
- 4. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.**
- 5. In terms of where the code and data should be submitted, the following folders can be used as one example for population PK related codes and data. The codes should be submitted under "module5/datasets/PopPK/analysis/programs/" folder (such as run1.ctl.txt, run1.lst.txt, plot1.R.txt) with a define pdf file to**

explain the role of each file, and if necessary a pdf file (e.g., “revieweraid.pdf”) to explain the flow of running the code. The datasets should be submitted under "module5/datasets/PopPK/analysis/datasets/" folder (such as poppk.xpt, pkpd.xpt) with a define pdf file to explain the variables within each data file.

- 6. Please submit all relevant datasets for clinical pharmacology studies containing pharmacokinetic and pharmacodynamic data preferably as SAS transport (xpt) files. Please ensure that the pharmacokinetic (concentration and parameters) and pharmacodynamic data sets include treatment, period, sequence information, as applicable. We also recommend the inclusion of SAS code used to merge datasets used in the final analysis.**

Sponsor follow-up (provided via email on June 15, 2017)

Heron acknowledges the Agency’s advice provided for Question 5: #1-6, and will address it in the planned NDA.

Discussion:

No further discussion was needed.

Question 6:

Does the FDA agree that a thorough QT study is not required prior to conduct of the planned Phase 3 studies of HTX-011?

FDA Response to Question 6:

Yes, we agree that it is not required to conduct the thorough QT study prior to the planned Phase 3 studies.

Sponsor follow-up (provided via email on June 15, 2017)

Heron acknowledges the response that it is not required to conduct a thorough QT study prior to the planned Phase 3 studies.

Discussion:

No further discussion was needed.

Additional Clinical Pharmacology Comments:

- 1. We note that you are planning to use MARCAINE (NDA 016964) and MOBIC (NDA 020938) as listed drugs for your 505(b)(2) application. Also see our general comments below on 505(b)(2) applications.**
- 2. In general, to fulfill the 505(b)(2) regulatory requirements, you must establish a scientific bridge (e.g., via a comparative bioavailability study) between your proposed product and each of listed drug upon which you plan to rely. The listed drug must be administered using its approved dosing regimen in the label in the**

comparative bioavailability study. If the NDA product is discontinued from the market, you may still rely on the safety and efficacy findings of this NDA. In such situations, you can use an ANDA product which is listed as a reference listed drug (RLD) in the Orange Book as the comparator in the relative bioavailability study, and refer to the NDA product in the 505(b)(2) application as the listed drug.

- 3. Considering your product is a perioperative product, the (b) (4) design may not be appropriate for the comparative bioavailability study. You may propose a parallel design instead of (b) (4) design with proper justification. Since your product is local acting, systemic exposure will mainly provide information on systemic safety. Note that you need to demonstrate the systemic exposure of your product is comparable or lower to that of the listed drugs to rely on the systemic safety findings of the listed drug. From the submitted meeting package, it appears you already have PK exposure data for bupivacaine using your proposed Phase 3 product in the procedures of herniorrhaphy (Study 202) and bunionectomy (Study 208). You also have PK data for Marcaine (bupivacaine HCl) in the Studies 202 and 208 for PK comparison. However, it appears that you do not have a PK comparison data in these studies using Mobic. We recommend you to conduct a PK study with Mobic to obtain its PK exposure data. If you plan to use PK data from Mobic label instead of conducting your own study, you need to make a detail proposal on how such “bridge” can be established.**
- 4. As can be noted from your conducted studies, the PK profile for your product at the same dose varies with type of surgical procedure. Multiple factors such as route, vascularity of administered site, method of administration, extend of inflammation in case of the joint administration can alter the PK profile of peri-operative drug products. Hence, you must obtain PK information for your product in every surgical procedure you plan to seek indication for, to adequately describe the entire PK profile covering absorption, distribution, and elimination phases of your product.**
- 5. Note that the final to-be-marketed formulation (including drug device), must be used in all clinical or clinical pharmacology studies intended to support your NDA or you need to provide adequate bridging information or justification as to why the study results using a different formulation apply to your final to-be-marketed product**

Sponsor follow-up (provided via email on June 15, 2017)

Heron acknowledges the Agency’s position for Additional Clinical Pharmacology Comments #1-3 and #5. For #4, please see Heron response for Question 7.

Discussion:

For Comment 4, refer to the Discussion for Question 7.

Clinical

Question 7:

Does the FDA agree that demonstrating efficacy and safety of HTX-011 in the proposed adequate and well controlled Phase 3 studies in a visceral (herniorrhaphy) and nonvisceral (bunionectomy) models are sufficient for the NDA, and support the proposed indication (b) (4)

FDA Response to Question 7:

We understand the question to be referencing the granting (b) (4) for efficacy. The label must reflect the indications that are supported by the data. For a (b) (4) you must demonstrate why the data from the conducted studies support (b) (4). You will need to submit information on PK, PD, and potential factors impacting PK and PD (such as vascularity and available potential anatomic space), to support an argument (b) (4). Furthermore, an Advisory Committee meeting will likely be convened to discuss the proposed (b) (4).

Without an adequate rationale (b) (4) the safety data from your two Phase 3 studies may be supportive, but not sufficient by themselves, (b) (4)

The proposed language (b) (4) cannot be included in the Indications and Usage section of the label. The indication in the label must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition. The statement (b) (4) does not meet this criterion.

Moreover, the term (b) (4) is open to interpretation. The method of administration must be clearly described, particularly because you have utilized different techniques in the drug development program. For example, you have studied the administration of your product via a Mayo block for bunionectomy, which is not the same as administration into the surgical site. The descriptions would be included in the Dosage and Administration section of the label.

Sponsor follow-up (provided via email on June 15, 2017)

(b) (4)
Heron proposed a phase 3 program that encompassed both visceral and non-visceral models. HTX-011 demonstrated, in Phase 2, a generally consistent and predictable PK that was correlated with PD for infiltration into the surgical site by instillation (the method of administration proposed in our Phase 3 studies), and would therefore be expected to be reproducible across further models. To (b) (4) (b) (4) characterize the PK profile of HTX-011 for other surgical sites, Heron proposes a Phase 3, randomized, active-controlled, multicenter safety and PK study in a total of approximately 200 subjects (3:1 randomization) across several surgical models, including non-visceral and visceral of surgeries where the drug would be expected to

be used. Subjects in this study will have safety evaluations and PK sampling to establish the PK profile covering absorption, distribution, and elimination phases of HTX-011. The protocol will be sent at least 60 days prior to initiating of the study.

Discussion:

The Sponsor proposed both visceral and non-visceral Phase 3 models that show a correlation between PK and PD. They also proposed a safety and PK study that included 200 subjects to characterize the PK profile of HTX-011 across multiple surgeries. The Division commented that in principle, the Sponsor's proposal (b) (4)

may be acceptable with proper justification.

The Division commented (b) (4)

The Division will need to look at what surgical procedures the Sponsor plans to study (b) (4)

The Division also stated that without seeing the data and the number of patients in each procedure, it would be difficult to make an agreement. For the Sponsor, they must provide adequate rationale to demonstrate that the surgical procedures chosen are sufficient (b) (4)

The Division stated that both bupivacaine and meloxicam concentrations need to be measured in the study and the Sponsor confirmed their understanding.

Question 8:

Does the FDA agree that (b) (4) is acceptable in the proposed Phase 3 local administration studies to support the proposed indication?

FDA Response to Question 8:

No, we do not agree. (b) (4)

In addition, in order to support a claim (b) (4) you will need to demonstrate that your drug product (b) (4)

Plots of the reduction in pain would need to show separation of the curves over the entire 0-72 hour timeframe.

Sponsor follow-up (provided via email on June 15, 2017)

The proposed Phase 3 protocols

(b) (4)

Given the importance of comparison to the bupivacaine active control arm based on the Agency's comments, we propose to instead implement a hierarchical testing strategy of the primary and key secondary endpoints in the protocol and statistical analysis plan. In this approach the comparison to bupivacaine on postoperative analgesia will be elevated to the first key secondary endpoint in the hierarchy, (b) (4) in order to increase the power of this comparison.

Discussion:

The Sponsor agreed with the importance of comparing their drug product to an active control and stated that they are proposing two control arms; placebo and immediate-release bupivacaine. The Sponsor proposed hierarchical testing of the primary and key secondary endpoints in the protocol and statistical plan. They proposed (b) (4)

The Division stated that with the Hochberg approach for multiplicity, the pain endpoint versus bupivacaine may not get tested. The Division stated that based on the combination rule (CFR 300.50) they will need to demonstrate superiority versus placebo and bupivacaine and that the combination rule applies. The Division explained that the Sponsor would need to demonstrate reproducible results in their studies to claim superiority over the active control.

Question 9:

Does the FDA agree that demonstrating superiority of HTX-011 for the key secondary endpoint of "Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with saline placebo" in the proposed Phase 3 studies would be acceptable to support the proposed indication?

FDA Response to Question 9:

No, we do not agree. Please see the responses for Question 7 and 8.

The synopses of your Phase 3 protocols contain "key" and "other" secondary endpoints. Provide a rationale or criteria for what would be designated as the "key" endpoints.

Be aware that only when "an effect on the primary endpoint is shown, [then] the secondary endpoints can be examined and may contribute important supportive information about the drug's effectiveness."¹

¹ Guidance for Industry, *Multiple Endpoints in Clinical Trials*, available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536750.pdf>

Furthermore, “Study sample size is often determined based only on the amount of information need to adequately assess the primary hypothesis, many studies lack sufficient power to demonstrate effects on secondary endpoints. If success on a secondary endpoint is important, the secondary endpoints should be considered when determining study design (e.g., sample size).”¹

In addition, “It is recommended that the list of secondary endpoints be short, because the chance of demonstrating an effect on any secondary endpoint after appropriate correction for multiplicity becomes increasingly small as the number of endpoints increases. Endpoints intended to serve the purpose of hypothesis generation should not be included in the secondary endpoint family. These should be considered exploratory endpoints.”²

(b) (4)

Sponsor follow-up (provided via email on June 15, 2017)

As specified in the Phase 3 protocols and in accordance with the January 2017 FDA Draft Guidance for Industry on Multiple Endpoints in Clinical Trials, the key secondary endpoints are not formally examined unless an effect on the primary endpoint is shown, and sample sizes for the primary and key secondary endpoints are accounted for in the phase 3 protocols.

Key secondary endpoints are differentiated from “other” secondary endpoints

(b) (4)

The Agency’s comments and feedback regarding opioid sparing endpoints are understood. As such, Heron would like to propose a concept that has significant clinical relevance and is experimentally quantifiable. It is our hypothesis that a greater proportion of subjects administered HTX-011 will remain opioid-free through 72 hours as compared to subjects receiving bupivacaine control. This issue has substantial clinical relevance for multiple reasons: subjects who remain opioid-free after surgery are not at risk for opioid-related

² Guidance for Industry, *Multiple Endpoints in Clinical Trials*, available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536750.pdf>

adverse events, there is a significant percentage of patients who convert from acute opioid use to long-term opioid use (Sun 2016; see Briefing Document), and opioid prescriptions for acute pain lead to the potential for diversion and resultant distribution and proliferation of opioids in the general population.

In the current trial design, all subjects are provided access to opioid rescue medications on an as-needed basis, providing a valid experimental construct to test the hypothesis under consideration. Given that the proportion of subjects who are opioid-free is expected to be clinically meaningful, Heron would like to propose a key secondary endpoint exemplifying this concept: proportion of opioid-free subjects on HTX-011 versus the active control (bupivacaine solution). Thus, based on proposed changes in study design in response to Question 8 and 9, the list of key secondary endpoints remains limited with the number of key secondary endpoints modified to 4 in each study and the hierarchy as follows:

- 1st: Mean AUC of the NRS-A pain intensity scores through 72 hours (AUC_{0-72}) for HTX-011 compared with bupivacaine HCl.*
- 2nd: Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with saline placebo.*
- 3rd: Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with bupivacaine HCl.*
- 4th: Proportion of subjects who are opioid-free through 72 hours for HTX-011 compared with bupivacaine HCl.*

Discussion:

The Sponsor explained that their patients who are administered HTX-011 remain opioid free for over 72 hours so they wanted to confirm its clinical relevance. The Division responded that if the Sponsor can come up with a way to justify a clinically meaning difference in the proportion of patients that are opioid free, it will be considered. The Division stated that it is important to understand what happens after 72 hours, because if subjects continued to remain opioid free throughout their recovery, it would be relevant clinical information.

Question 10:

Does the FDA agree that demonstrating superiority of HTX-011 over bupivacaine HCl solution for the key secondary endpoint of Mean AUC of the NRS-A pain intensity scores through 72 hours (AUC_{0-72}) for HTX-011 compared with bupivacaine HCl in the proposed Phase 3 studies would be acceptable to support a claim for superiority versus bupivacaine HCl with the data included in the Clinical Studies section of the HTX-011 prescribing information?

FDA Response to Question 10:

It is possible that a secondary endpoint may be included in the Clinical Studies section of the label. However, in addition to exhibiting a statistically significant difference, you would also need to demonstrate a substantial, clinically meaningful effect.

See the comments in Question 9 regarding secondary endpoints. The current plan for multiplicity testing does not ensure that the HTX-011 vs. bupivacaine comparison will

be tested. Consider revising the priorities for testing primary and secondary endpoints to address the desired claims.

To claim superiority over an active comparator, you must design your study by selecting an appropriate dose and route of administration for the active comparator that is consistent with current clinical practice. In addition, as stated above, to claim superiority over an active comparator you must demonstrate that your results are reproducible.

Sponsor follow-up (provided via email on June 15, 2017)

Please see Heron's responses to questions 8 and 9 for proposed changes to the study designs with respect to comparisons to bupivacaine. We acknowledge that to claim superiority over an active comparator, we must demonstrate reproducible results in studies 301 and 302.

Discussion:

Refer to the Discussion for Question 8.

Question 11:

Does the FDA agree with the statistical analysis plan approach (including statistical analysis models, (b) (4) imputation methods, and wWOCF adjustment for rescue medication use) for the proposed Phase 3 studies?

FDA Response to Question 11:

The proposed testing plan for the primary and secondary endpoints does not meet the clinical requirements (see responses to Questions 8, 9, and 16). Therefore your sample size calculations should be rechecked when the endpoints have been revised.

It is very important to clearly describe the activity to be performed when assessing the NRS-A pain intensity score with activity. It is essential that this activity be consistent for every patient at every time point across all centers.

The proposed modified Intent-to-Treat (mITT) population for the analyses includes all randomized subjects with at least one post-treatment NRS-A pain intensity score. The preferred population is the ITT population consisting of all randomized subjects. Patients lacking a post-treatment efficacy assessment should not be excluded.

The nonresponder imputation (NRI) for missing data on binary endpoints, and the windowed worst observation carried forward (wWOCF) imputation for use of rescue medication are acceptable. The proposed last observation carried forward (LOCF) approach for other missing pain intensity scores is not acceptable, as it may attribute a good outcome to a patient that discontinues due to a bad outcome, such as adverse events. Propose an alternative approach for these cases, including multiple imputation strategies. You should also fully document all reasons for missing data.

The analysis of variance (ANOVA) model does not specify what terms will be included. This must be prespecified in the protocol. Also provide plots of pain scores over the 0-72 hour timeframe by treatment group.

Sponsor follow-up (provided via email on June 15, 2017)

Please see our responses to questions 8 and 9 regarding our revised proposal to the testing plan for the primary endpoint and key secondary endpoints.

We agree that the activity to be performed when assessing NRS-A pain intensity scores must be clearly described in the phase 3 protocols and standardized at every time point across all centers.

The study drug must be prepared in advance of surgery, so randomization is allowed up to 1 business day prior to the scheduled surgical procedure. Due to the potential time between randomization and the start of surgery, some patients who are randomized may not actually undergo the surgical procedure as a result of extenuating circumstances. Since HTX-011 is designed to reduce post-operative pain, a patient who does not undergo the surgical procedure for reasons unrelated to the study design would not be intended to be treated with HTX-011. We agree with your comment that ITT is the preferred efficacy analysis population. We therefore propose to change the definition of ITT to “randomized and underwent the surgical procedure” and remove

(b) (4)

The primary analysis period is from hours 0-72, a period in which each patient is hospitalized at the study centers after receiving the single (only) dose of study drug. Across our bunion and hernia phase 2 studies, the overall rate of missing pain scores during this 0-72 hour period of hospitalization was $\leq 0.5\%$, and any missing pain scores were sporadic with mostly interval data missing. In addition, there were no dropouts in the HTX-011 groups due to adverse events and the total number of patients who discontinued study prior to 72 hours in our phase 2 bunion and hernia studies was 3 out of a denominator of 893 (0.34%) for a 72-hour completion rate of $> 99.5\%$. As such, LOCF, MI, or any other missing data method to account for this low amount of mostly interval missing data is likely to have little to no impact on the results, so LOCF was chosen for simplicity. However, we recognize your comments that patients who drop out prior to 72 hours and are thus right-censored with respect to pain data may represent a different population than those who complete 72 hours. For the small number of patients expected to discontinue study prior to 72 hours, we propose a conservative approach to impute right-censored missing pain scores with the worst (highest) pain score observed prior to drop out.

The phase 3 protocols and SAPs specify that the ANOVA model will include treatment as the main effect. There are no covariates specified.

Discussion:

The Sponsor agreed to define the primary analysis population (ITT) as “all patients who are randomized and receive study drug.” The Division agreed to the proposed plan for missing data and the ANOVA model.

Question 12:

Does the FDA agree with the doses and method of administration selected for the Phase 3 studies?

FDA Response to Question 12:

Your rationale for selecting the proposed doses is reasonable. However, the preferred method of administration in each procedure is not clear. Please provide information regarding the proposed route of administration for each procedure and the rationale for the chosen route. Additionally, as mentioned above, the dose and route of administration for the active comparator should be consistent with current clinical practice.

Sponsor follow-up (provided via email on June 15, 2017)

Dosing of HTX-011 in the phase 3 studies is by single dose infiltration into the surgical site via instillation, with details provided in Table 44 of the Briefing Book and the Phase 3 protocols. Multiple routes of administration were studied in the predicate phase 2 studies; the route of local infiltration via instillation was chosen based on efficacy, safety, and PK results. Administration of the active control is injected into the surgical site in a manner consistent with current practice, and at doses consistent with current clinical practice (50 mg {10 mL of 0.5%} in the case of bunionectomy, 75 mg {30 mL of 0.25%} in the case of herniorrhaphy).

Discussion:

The Sponsor explained that the drug would be administered by local infiltration via instillation. The Division stated that the word infiltration brings an imagery of “putting into the tissue” and asked the Sponsor to be as clear as possible. The Sponsor responded that it was more of a “squirt and smear” technique. The Division stated that it is important to convey the route of administration in a manner such that all the investigators are using the same approach. The Division stated that the Sponsor should take a more systematic approach by evaluating the planned instruction for administration tested with an appropriate population.

Question 13:

Does the FDA agree that the successful achievement of primary endpoint in the Phase 2b local administration study in total knee arthroplasty with an acceptable safety profile would be acceptable to support the inclusion of data in the Dosing and Administration and the Clinical Studies sections of the HTX-011 prescribing information?

FDA Response to Question 13:

It is possible that the results of a Phase 2b trial may be included in the Clinical Studies section of the label for your drug product. However, in order for a Phase 2b trial to support the claims of effectiveness for your drug product, it must be an adequate and well-controlled study and the results must provide substantial evidence of the effect of your drug product. Based on the protocol and statistical analysis plan submitted, this does not appear to be the case.

Based on the protocol synopsis and statistical analysis plan submitted, (Appendix G of meeting package) this study does not appear to be adequate to support an indication for total knee arthroplasty. Specifically, (b) (4)

The internal review committee (IRC) also has the option of not proceeding to the next cohort of patients. One of the objectives for the IRC is to “guide Phase 3 study design.” We also do not agree (b) (4)

Sponsor follow-up (provided via email on June 15, 2017)

We understand the Agency’s position regarding the present Phase 2b study and analysis design. We plan to amend the protocol so that current cohorts will be considered Part A (an exploratory dose-finding phase). Upon completion of this initial dose-finding phase, Part B will be initiated. Part B will be an adequate and well-controlled, randomized, double-blind phase of the study in which the dosing and administration method for HTX-011 is predetermined based on the findings from Part A, sample sizes for part B are determined from part A, and there are no interim reviews prior to database lock. Additionally, the data from Part A will not be pooled into Part B.

Discussion:

The Sponsor proposed amending the Phase 2b Study 209 to include a Part B. Part B will be a randomized, double-blind, active-and placebo-controlled study and therefore essentially a Phase 3 design. The Division stated that once the protocol is submitted, it will be reviewed.

Question 14:

Does the FDA agree (b) (4)

?

FDA Response to Question 14:

No, we do not agree. (b) (4)

(b) (4)

(b) (4)

Sponsor follow-up (provided via email on June 15, 2017)

Heron acknowledges the agency's position and we will no longer seek a claim

(b) (4)

Discussion:

No further discussion was needed.

Question 15:

Does the FDA agree

(b) (4)

?

FDA Response to Question 15:

No, we do not agree.

(b) (4)

(b) (4)

Sponsor follow-up (provided via email on June 15, 2017)

Heron acknowledges the Agency's position and will modify the endpoint described in Q15 as follows:

- Use NRS-A
- Adjust to 72 hours
- Account for rescue medication utilizing wWOCF

- *Compare HTX-011 to both bupivacaine and saline placebo*

Discussion:

No further discussion was needed.

Question 16:

Does the FDA agree that proposed Phase 3 studies, which are intended to demonstrate superiority of HTX-011 over the disease-active ingredient in HTX-011, bupivacaine solution, are adequate to satisfy the requirements of the Combination Rule and a factorial design study is not necessary?

FDA Response to Question 16:

No. The purpose of a factorial design study is to evaluate whether combining bupivacaine and meloxicam is more effective at treating postoperative pain than the use of bupivacaine or meloxicam alone. We acknowledge that you have concluded, based upon your findings in your Phase 2b study (208) and Phase 2 study (202,) that meloxicam alone is undifferentiated from placebo. Based on this finding, you have concluded that bupivacaine is the active component of HTX-011. Therefore, you are proposing to include an arm in your Phase 3 studies comparing the disease-active-ingredient (bupivacaine) to HTX-011 to satisfy the requirement for a clinical trial comparing the combination drug product to the disease-active ingredient alone to demonstrate the safety and effectiveness of HTX-011 versus the disease-active ingredient. We agree with this plan. However, the comparison to demonstrate superiority of HTX-011 over bupivacaine is a secondary endpoint that may not be tested under your current strategy. Your study design should be revised appropriately (See comment from Questions 9 and 10 regarding secondary endpoints and establishing superiority).

Sponsor follow-up (provided via email on June 15, 2017)

Please refer to Heron responses in Questions 8-10. Per the Agency's comments, Heron has revised the study design to utilize a hierarchical testing strategy of the primary endpoint and key secondary endpoints. In this approach, the comparison to bupivacaine on postoperative analgesia will be elevated to the first key secondary endpoint in the hierarchy.

Discussion:

Refer to the Discussion to Question 8.

Question 17:

Does the FDA agree that the clinical safety database comprising a planned total of approximately 1,000 subjects exposed to HTX-011 is acceptable to support the NDA?

FDA Response to Question 17:

Yes, we agree that 1000 patients exposed to the intended commercial formulation is an adequate clinical safety database to support an NDA.

*Sponsor follow-up (provided via email on June 15, 2017)
Heron acknowledges the Agency's response.*

Discussion:

Refer to the Discussion to Question 8.

Question 18:

Does FDA agree with Heron's proposal to perform a Human Factors validation study with the proposed (b) (4) VVS for commercial use with HTX-011 after the initiation of the proposed Phase 3 studies for submission in the NDA?

FDA Response to Question 18:

If you plan to use an investigational product in your proposed clinical study, we recommend that your product undergoes Human Factors (HF) testing in a simulated use scenario to ensure that the product has been optimized for safety and that the product is ready to be subjected to the conditions of a clinical study. Highly controlled clinical study conditions may not be sufficient to overcome major design flaws in your product or its user interface that could lead to use errors or adverse events during use of the product in a clinical study. Therefore, to minimize confounding the data from your Phase 3 clinical study, we recommend that you conduct HF testing, with at least 15 representative users, prior to starting your Phase 3 clinical study. If the results of such testing indicate that intended users in the study can use the product safely and effectively, then you can proceed with your development program without submission of the HF testing results for prior Agency feedback. This approach carries some risk to you because prospective Agency review is not possible, but this is a business decision for your company. Please note that human factor testing to support the conditions of the clinical study does not replace human factors validation testing to support the commercial product. Please also note that we recommend that you perform the human factors validation testing to support the commercial product at the conclusion of your Phase 3 studies. This will allow you to take into account any necessary modifications to the product user interface as a result of your Phase 3 studies. If you conduct the human factors validation testing in parallel with your Phase 3 studies, it may be possible that additional human factors testing may be necessary to support the commercial product if product modifications are implemented after your Phase 3 studies.

We have the following additional comments as well:

- 1. We recommend you submit your HF validation study protocol (to support the commercial product) for feedback from the Agency before commencing your study. Please note we will need 90 days to review and provide comments on the**

HF validation study protocol. Plan your development program timeline accordingly.

- 2. The following items will facilitate an efficient review of your HF study protocol:**
 - a. A summary of preliminary analyses and evaluations, including formative studies;**
 - i. Include in your summary a discussion of key findings and any changes made to your product or labeling, including how the findings were used to update the user interface and risk analysis**
 - b. An updated risk analysis for your product;**
 - c. Detailed HF validation study protocol to include the following elements:**
 - i. Description of intended product users, uses, use environments, and training (if applicable) for commercial product**
 - ii. Graphical depiction and written description of product user interface**
 - iii. Summary of known use problems with previous models or similar products**
 - iv. User task selection, categorization (e.g., critical) and prioritization**
 - v. Validation testing details**
 - 1. Objective(s)**
 - 2. Type of testing (simulated or actual use)**
 - 3. Test environment and conditions of use**
 - 4. Training provided to participants and rationale for how it corresponds to real-world training (if applicable)**
 - 5. Distinct user groups broken out by number and type of test participants and rationale for how they represent the intended user populations**
 - 6. User tasks and use scenarios that will be studied**
 - 7. Description of data to be collected and methods for documenting observations and interview responses**
 - 8. Methods for root cause analysis of all use errors, difficulties, close calls**
 - 9. Definition of performance success and performance failure**
 - 10. Moderator transcript**
 - d. Intend-to-market labels and labeling (including an editable word version of the IFU if an IFU is proposed) that will be tested in the HF validation study**
 - e. Five intend-to-market samples of product that will be tested in the HF validation study**
- 3. The requested information should be placed in eCTD Ssection 5.3.5.4 – Other Study reports and related information.**
- 4. Guidance on human factors procedures to follow can be found in: Applying Human Factors and Usability Engineering to Medical Devices, available online at:**
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf>

and

Guidance on Safety Considerations for Product Design to Minimize Medication Errors and can be found online at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf>

Note that we recently published two draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development and can be found online at:

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf>

and

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors and can be found online at:

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

Sponsor follow-up (provided via email on June 15, 2017)

Heron acknowledges the Agency's preliminary comments. Based on the Agency's feedback to Question 20 and the acceptable safety and performance of the (b) (4) Luer-lock applicator used in our Phase 2 studies, Heron proposes the use of the (b) (4) Luer-lock applicator in the Phase 3 studies, instead of the (b) (4) Luer-lock applicator as originally described in the briefing package. The (b) (4) Luer-lock applicator was used for drug administration in 56 subjects in our Phase 2 studies and no issues with its use were reported. In addition, Heron has already conducted simulated user evaluations of the other device constituent parts proposed for use in the Phase 3 studies (i.e., the commercially available vented vial spike (b) (4)), which included simulated use evaluations with 20 healthcare professionals. Accordingly, all of the devices proposed for use in Phase 3 have been sufficiently characterized for safety and performance, and we anticipate that the occurrence of device-related use errors or adverse events confounding Phase 3 data will be minimal. We also appreciate FDA's agreement that the human factors validation testing of the commercial devices could be conducted in parallel with (or at the conclusion of) our Phase 3 studies, as originally proposed. We acknowledge that conducting the human factors validation studies in parallel with, rather than at the conclusion of Phase 3 may potentially require additional human factor studies should device modifications subsequently be needed.

Discussion:

No further discussion occurred.

Question 19:

Does FDA agree with Heron's proposal to perform a Human Factors validation study with the commercially available (b) (4) Luer-lock applicator for administration of HTX-011 after the initiation of the proposed Phase 3 studies for submission in the NDA?

FDA Response to Question 19:

See response to Question 18.

Sponsor follow-up (provided via email on June 15, 2017)
Please see Heron's response to Question 18

Discussion:

No further discussion occurred.

Question 20:

Does FDA agree with the strategy for providing data supporting the proposed convenience kit for HTX-011 administration in the NDA?

FDA Response to Question 20:

Your meeting package shows that you are continuing to explore device options for administering HTX-011. You are proposing a variety of kit components, including syringes, (b) (4) and a Luer-lock applicator. Your NDA should describe the final configuration of the administration kit and include the necessary data to ensure safe and effective administration, which needs to include the HF Validation Study and device performance data for the to-be-marketed administration kit. In addition, the performance data should demonstrate compatibility of the drug and device, and demonstrate that device failure risks (i.e., piston seal blowback, leakage at Luer adapter/syringe connection, syringe barrel fracture, extractable volume, etc.) have been adequately mitigated. We also recommend that your pivotal clinical trials be conducted with the to-be-marketed administration kit or a version that is representative of the to-be-marketed device.

With respect to some of the kit options you are proposing, it is noted that you are proposing (b) (4) for use in Phase 3 studies as well as for commercialization to instill drug product onto wound surfaces. Clarify if this (b) (4) will be available in the kit. (b) (4)

(b) (4)

We encourage co-packaging of drug and device products for safe and effective use. Please clarify if the drug product vials are to be co-packaged with the devices. Please also clarify if the devices will be contained in their original packaging with individual labels/Instructions for Use (IFU) or if a separate IFU will be created describing use of these various devices for use with HTX-011. If you intend to develop a convenience kit (also considered a co-package), you should clarify your proposal to develop and label this kit.

We recommend that the (b) (4) be approved under the HTX-011 NDA; alternatively, it could have a 510(k) clearance, in which case the 510(k) clearance should occur concurrently with the NDA.

Sponsor follow-up (provided via email on June 15, 2017)

We acknowledge FDA's comments. The NDA will describe the final configuration of the administration kit and include the necessary data to ensure safe and effective administration, including the HF Validation Study, device performance data for the to-be-marketed administration kit, compatibility of the drug and devices, and demonstration that device failure risks have been adequately mitigated. The pivotal Phase 3 clinical trials will be conducted with the to-be-marketed device constituent parts (b) (4)

As discussed in the briefing package, the (b) (4) version is representative of the to-be-marketed device (i.e., same design principle and use characteristics).

As noted in response to FDA's preliminary feedback for Question 18, based on FDA's feedback to Question 20 and the acceptable safety and performance of the (b) (4) Luer-lock applicator used in the Phase 2 studies, Heron proposes the use of the (b) (4) Luer-lock applicator in the Phase 3 studies, instead of the (b) (4) Luer-lock applicator sourced from the 510(k) cleared (b) (4) as originally described in the briefing package.

Heron plans to co-package the drug vials and device constituent parts into a convenience kit, as FDA recommended. We currently anticipate providing Instructions for Use for the co-packaged combination product. Finally, we acknowledge FDA's response that the (b) (4) (b) (4) can either be approved under the HTX-011 NDA (along with the other device constituent parts included in the co-packaged administration kit) or could have separate 510(k) clearance.

Discussion:

No further discussion occurred.

Additional Clinical Comments:

After a high level review of your protocol synopses, we have the following feedback:

- 1. Include wound assessments through Day 30.**
- 2. Establish adverse event based study stopping criteria and subject stopping criteria.**
- 3. Define adverse events, serious adverse events, and adverse events of special interest.**
- 4. Define the grading scale for classifying the severity of adverse event.**
- 5. Define causality categories for SAEs. Causality assessments should follow the “WHO-UMC system for standardised case causality assessment” found at <https://www.who-umc.org/media/2768/standardised-case-causality-assessment.pdf>.**

Sponsor follow-up (provided via email on June 15, 2017)

The causality assessment categories are provided in Section 8.2.2 of the Phase 3 protocols, which includes a binary assessment approach that is aligned with ICH E2A, 21CFR312.32c, 21CFR312.64b, FDA draft guidance on Safety Reporting Requirements for INDs and BA/BE Studies: Guidance for Industry and Investigators (2012), and Management of Safety information in clinical trials, CIOMS VI Working group (2005).

The “binary” decision choice was the method favored by a majority of the CIOMS VI Working Group members. The CIOMS VI Working Group recommends that the investigator be asked to use a simple binary decision for drug causality (related or not related) for serious adverse events.

Based on the above, Heron has included the following categories of causality assessment in the Phase 3 Protocols.

- **Possibly related:** *The AE is known to occur with the study drug, there is a reasonable possibility that the study drug caused the AE, or there is a temporal relationship between the study drug and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study drug and the AE.*
 - **Unlikely Related:** *There is not a reasonable possibility that the administration of the study drug caused the event, there is no temporal relationship between the study drug and event onset, or an alternate etiology has been established.*

Discussion:

No further discussion occurred.

Combination Product Comments:

- 1. Combination products are subject to 21 CFR Part 4 “Current Good Manufacturing Practice Requirements for Combination Products” accessible at: <https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>**

2. **Related final guidance, “Current Good Manufacturing Practice Requirements for Combination Products, January 2017” is accessible at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf>**

Sponsor follow-up (provided via email on June 15, 2017)
Heron acknowledges the Agency’s comments.

Discussion:
No further discussion occurred.

ACTION ITEMS

1. **The Sponsor will submit a revised clinical protocol according to discussions at this meeting.**

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

In addition, your iPSP should specifically provide your justification why you believe that nonclinical juvenile animal studies are or are not needed to support your pediatric drug development taking into consideration the specific age ranges to be studied. The justification should be based on a comprehensive literature search focusing on the specific toxicological concerns related to the drug substance and each individual excipient in your drug product and any data you have generated suggesting a unique vulnerability to toxicological insult for the proposed age range to be tested. This risk assessment should take into consideration the expected maximum daily dose of the drug product for the intended patient population and include rationale for your proposed maximum daily dose. In addition, your risk assessment should address how the drug substance and excipients are absorbed, distributed, metabolized, and excreted by the ages of the children you will be studying. You must include copies of all

referenced citations. If you conclude that a juvenile animal study is necessary, provide a detailed outline of the specific study you propose to conduct, including what toxicological endpoints you will include in the study design to address any specific questions, and justification for your selection of species and the age of the animal to be tested. We recommend that you refer to the FDA guidance to industry: *Nonclinical Safety Evaluation of Pediatric Drug Products*, available at,

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079247.pdf>.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdet-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>.

NARRATIVE SUMMARIES

Narratives summaries of important adverse events (e.g., deaths, events leading to discontinuation, other serious adverse events) should provide the detail necessary to permit an adequate understanding of the nature of the adverse event experienced by the study subject. Narrative summaries should not merely provide, in text format, the data that are already presented in the case report tabulation/forms, as this adds little value. A valuable narrative summary is written like a discharge summary with a complete synthesis of all available clinical data and an informed discussion of the case, allowing a better understanding of what the patient experienced. The following is a list of components that would be found in a useful narrative summary:

- Patient age and sex
- Signs and symptoms related to the adverse event being discussed
- An assessment of the relationship of exposure duration to the development of the adverse event
- Pertinent medical history
- Concomitant medications with start dates relative to the adverse event
- Pertinent physical exam findings
- Pertinent test results (e.g., lab data, ECG data, biopsy data)
- Discussion of the diagnosis as supported by available clinical data
- For events without a definitive diagnosis, a list of the differential diagnoses

- Treatment provided
- Re-challenge results (if performed)

Outcomes and follow-up information

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017**, the following submission types: **NDA**, **ANDA**, and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to applicants when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), applicants must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., Phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

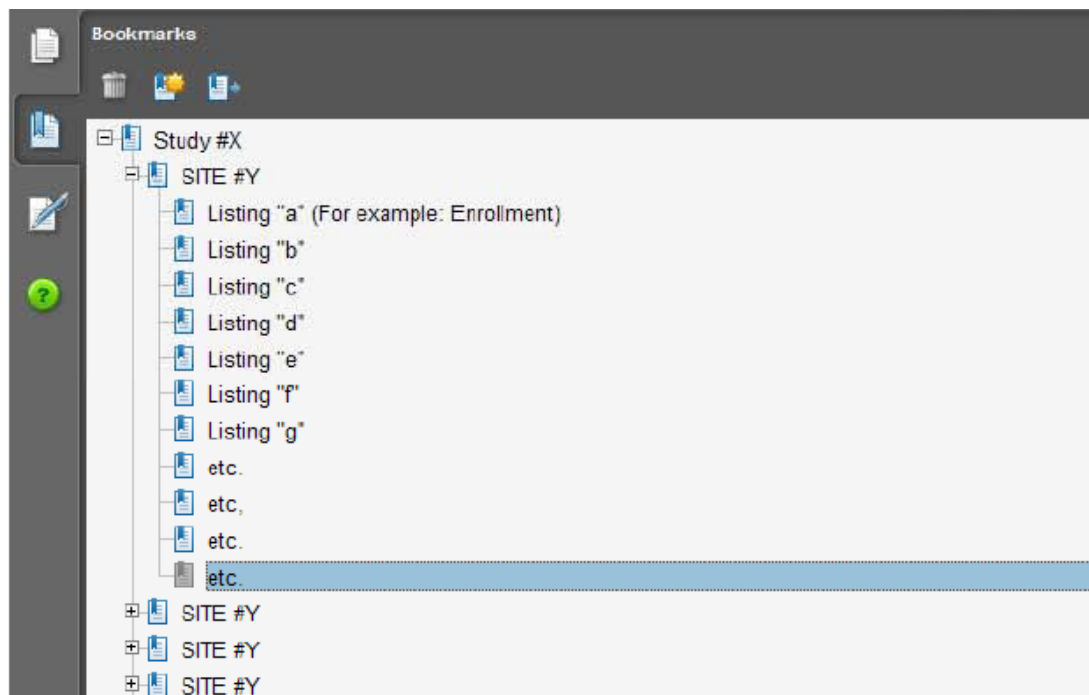
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item³	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

³ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new Phase 2 or Phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

ATTACHMENTS AND HANDOUTS – see below

30 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

OGOCHUKWU U OGOEGBUNAM
07/12/2017