CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209511Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA: 209511; SN0043 Resubmission	Submission Date: 02/26/2020
Link to EDR	\\cdsesub1\evsprod\NDA209511\0043
Relevant IND(s):	IND 77127
Submission Type; Code:	505 (b) (2)
Brand Name:	XARACOLL
Generic Name:	Bupivacaine hydrochloride (HCl) collagen-matrix implants
Reference Drug:	MARCAINE (NDA 016964)
Formulation; Strength(s):	Collagen-matrix implants; 300 mg (3x100 mg implants) bupivacaine HCl
Clinical Pharmacology Reviewer:	Suresh B Naraharisetti, Ph.D.
Team Leader:	Yun Xu, Ph.D.
OCP Division:	Division of Neuropsychiatric Products
OND Division:	Division of Anesthesiology, Addiction Medicine, Pain Medicine
Sponsor:	Innocoll Pharmaceuticals
Indication:	Post-surgical analgesia
Dosing Regimen:	XARACOLL is intended for single-dose administration. The recommended dose is 300 mg bupivacaine HCl (equivalent to 266.4 mg bupivacaine) consisting of three bupivacaine HCl collagen-matrix implants, each containing 100 mg bupivacaine HCl

1.0 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Neurology Products (OCP/DNP) has reviewed the Complete Response Resubmission submitted by the applicant on 02/26/2020, for NDA 209511; SN0043.

For this NDA, in the first review cycle, there were no approvability issues from clinical pharmacology perspective. However, the non-clinical team had deficiency #1 listed in the complete response letter (CRL) (dated 11/30/18) related to systemic safety based on bupivacaine exposure. The deficiency #1 is, “you have not provided an adequate characterization of the

systemic safety of bupivacaine exposures via your drug product formulation. Specifically, based on the existing human pharmacokinetic data, your product results in an $AUC_{(0\text{-last})}$ that is twice that of the referenced product. Your existing toxicology data in the rat model do not test exposures that provide coverage for the human exposures via your product".

To address deficiency #1, the applicant utilized nonparametric superposition (NPS) method to bridge the systemic exposure (Cmax, AUC_{inf} and partial AUCs) of XARACOLL obtained from the completed PK study to that of the Listed Drug, MARCAINE dose of 400 mg/day. Specifically, the applicant compared the exposures obtained by PK predictions of MARCAINE at 400 mg dose via NPS to the exposure observed following implantation of a 300-mg dose of XARACOLL (the proposed dose) in the same surgical procedure [Study INN-CB-022: unilateral inguinal hernioplasty (with placement of mesh)].

Note: In the text, bupivacaine HCl or MARCAINE were interchangeably used.

From the clinical pharmacology perspective, this resubmission is acceptable. We have the following comments to the non-clinical team regarding bupivacaine systemic exposure comparison between XARACOLL and the listed drug, MARCAINE, based on the information submitted by the Applicant.

- The rate and extent of bupivacaine absorption, as assessed by Cmax and AUC_{inf} following implantation of 300 mg of XARACOLL were lower by ~25 to 54% and ~ 12%, respectively compared to those predicted for three different 400 mg dosage paradigms of MARCAINE. These results extend the scientific bridge between XARACOLL and MARCAINE, and addresses CRL nonclinical deficiency #1 regarding inadequate characterization of the systemic safety of bupivacaine exposure via XARACOLL.

2. Regulatory Background

For this NDA, Agency issued a CR Letter on 11/30/18 indicating deficiencies related to non-clinical and product-quality teams. A post-action Type A meeting was held with applicant, for which the meeting-minutes were posted to DARRTS on 06/28/2019.

In the original NDA submission, there were no clinical pharmacology related deficiencies and the clinical pharmacology review for this NDA is in DAARTS dated 10/29/2018.

In the CR letter, the non-clinical team had the following deficiency #1 related to systemic safety of bupivacaine exposure from the product. The deficiency #1 is as follows:

> *"You have not provided an adequate characterization of the systemic safety of bupivacaine exposures via your drug product formulation. Specifically, based on the*

existing human pharmacokinetic data, your product results in an AUC(0-last) that is twice that of the referenced product. Your existing toxicology data in the rat model do not test exposures that provide coverage for the human exposures via your product".

To address deficiency #1, the Applicant during a Type A meeting (post NDA action) submitted NPS methods approach to predict MARCAINE exposure. Related to this meeting, the applicant's Q3, agency's responses and discussion to Q3 can be found in meeting minutes (DARRTS, 06/28/2019). Some of the comments provided to Q3 by Agency is shown below.

- *"You may use this pharmacokinetic modeling approach to create a bridge from Xaracoll to MARCAINE; however, the acceptability of this approach will be determined during the NDA review cycle. You also need to provide rationale to justify why you choose this approach instead of conducting a PK study".*
- *"The nonparametric superposition methods you propose appear reasonable to predict the systemic exposure of MARCAINE; however, the acceptability of the resulting prediction(s) will be determined during the NDA review cycle".*

3. Review of Resubmission:

MARCAINE is the listed drug for this NDA. The original NDA for XARACOLL included 2 PK studies comparing XARACOLL to MARCAINE injection in which the Study INN-CB-013 used a developmental formulation, while the Study INN-CB-022 used a final formulation. Both were multicenter, single-blind, randomized, single-dose, PK/bioavailability studies in patients scheduled for unilateral inguinal hernioplasty (with placement of mesh). The details of the studies are as below:

- Study INN-CB-013 compared 2 doses (200 and 300 mg) of a **developmental XARACOLL** formulation with a 150-mg dose of bupivacaine HCl injection (with epinephrine) injected into the surgical site. In Study INN-CB-013 either Sensorcaine® (Fresenius Kabi) or MARCAINE (Hospira) was used as the comparator treatment. The Sensorcaine is therapeutically equivalent to MARCAINE (NDA 016964).
- Study INN-CB-022, the **definitive PK study** (pivotal PK study), compared the same formulation and dose (300 mg) of XARACOLL that was used in the 2 pivotal Phase 3 studies (Study INN-CB-014 and Study INN-CB-016) with a 175-mg dose of MARCAINE injection (without epinephrine).

Comparative Clinical PK Using NPS Methods Approach to Extend the Scientific Bridge Between XARACOLL and MARCAINE (the Listed Drug):

As per MARCAINE (bupivacaine HCl) label, the maximum recommended daily dose is 400 mg.

As mentioned above, the Study INN-CB-022 is the definitive PK/BA study in which final formulation of XARACOLL was used. In this study, the PK of XARACOLL at 300 mg dose

(three 100 mg bupivacaine collagen matrices) was compared with 175 mg dose of MARCAINE. From this study, utilizing 175 mg dose PK data of MARCAINE, the NPS analyses* were conducted to predict bupivacaine systemic exposures for three dosing regimens up to 400 mg total daily dose. The predicted systemic exposures were then compared to systemic exposures of 300 mg XARACOLL. These results were used to extend the scientific bridge between XARACOLL and MARCAINE and permit reliance on the Agency's previous findings of the safety of MARCAINE, the listed drug for this NDA.

*Note: In the NPS analyses, linearity of the PK parameters was assumed for MARCAINE up to 400 mg.

NPS analyses:

For the 400-mg total daily dose of MARCAINE, the NPS method predictions were made for three possible daily dosage regimens (1 single-dose and 2 repeated-dose regimens). The MARCAINE dosage regimens for NPS include:

- a single 400 mg dose
- a 400-mg dosage divided as 3 equal doses of 133.3 mg administered every 3 hours (q3h)
- a 400-mg dosage administered as an initial 175 mg bolus followed by 2 doses of 112.5 mg q3h

With regards to the selected dosage regimens of MARCAINE, at the 28 May 2019 Type A Meeting, the Agency informed applicant to provide adequate justification that each of the selected regimens is clinically relevant. The applicant provided following justification:

- "A single-dose administration of bupivacaine HCl at 400 mg was chosen as one of the dosage regimens because it most closely mimics the one-time placement of XARACOLL at 300 mg during open inguinal hernia repair. Innocoll confirmed that a single administration of Marcaine at 400 mg administered into the surgical site for postoperative pain management is used clinically. In an independent online survey of 56 physicians in the US who utilize bupivacaine HCl infiltration into the surgical site during open inguinal hernia repair, 50% of the survey respondents reported use a 400-mg dose of bupivacaine HCl. Of these respondents, 68% administer the dose as a single dose and 32% administer 400 mg as a divided dose over 24 hours" (b) (4)"
- "Repeated intermittent doses of bupivacaine HCl (delivered via subcutaneous catheter) for postoperative pain management have been used after inguinal hernia repair to overcome the short duration of effect, as noted in the medical literature (Zieren et al 1999[1], Vintar et al 2002[2]) and the (b) (4) survey:
    - A dose of 400 mg divided as 3 equal doses of 133.3 mg administered every 3 hours via subcutaneous catheter for postoperative pain management is consistent with the Marcaine prescribing information directions regarding repeat dosage, which is every 3 hours.
    - Treatment with an initial bolus of Marcaine followed by 2 smaller repeat doses for postoperative pain management is consistent with Marcaine labeling, regarding the choice of initial dose depending whether Marcaine is given with or without epinephrine".

This reviewer has reconducted the NPS analyses of same three 400 mg dosing regimens of MARCAINE as the applicant conducted. The reviewer's results match to applicant's results.

[1] Zieren et al Eur J Surg 1999; 165: 460–464
[2] Vintar et al Can J Anesth 2002 ; 49: 481–486

Comparative Pharmacokinetic Analyses:

In Figure 1a shows the mean bupivacaine plasma concentration versus time profiles for XARACOLL at 300 mg and MARCAINE at 175 mg (observed data from Study INN-CB-022).

In Figure 1b shows the combined mean bupivacaine plasma concentration versus time profiles for XARACOLL at 300 mg and MARCAINE at 175 mg (observed data from Study INN-CB-022) along with three 400 mg MARCAINE dosage regimens (predicted using NPS methods).

Figure 1a

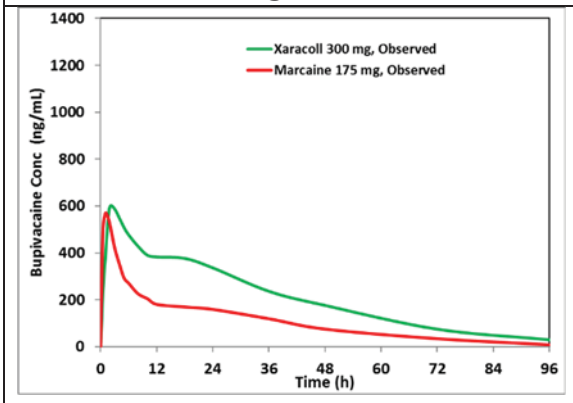
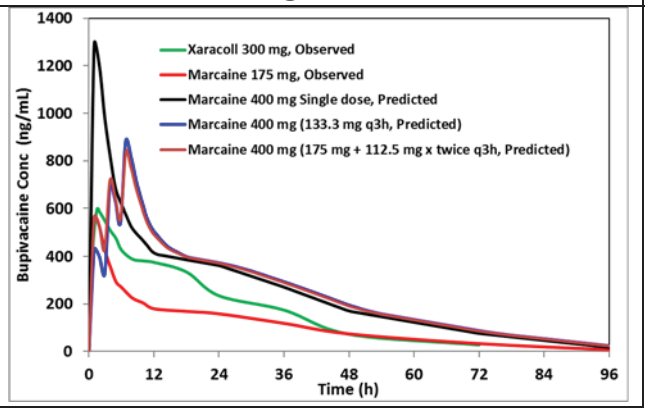


Figure 1b



The mean Cmax and AUCs of XARACOLL at 300 mg and MARCAINE at 175 mg (observed from Study INN-CB-022) and three 400 mg MARCAINE dosage regimens predicted using NPS methods are shown in Table 1.

Table 1:

Treatment	Mean (SD)				
	Cmax (ng/mL)	AUCinf (h•ng/mL)	Partial Areas		
			AUC_{24} (h•ng/mL)	AUC_{48} (h•ng/mL)	AUC_{72} (h•ng/mL)
XARACOLL 300 mg, observed [a]	663 (264)	20368 (7912)	9799 (3505)	15690 (5617)	18683 (7075
MARCAINE 175 mg, observed [b]	641 (262)	9815 (4570)	5742 (1881)	8562 (3180)	9698 (4256)
MARCAINE 400 mg: single dose, predicted [b]	1457 (601)	23032 (10685)	13144 (4289)	19589 (7272)	22190 (9743)
MARCAINE 400 mg (total dose): 133.33 mg q3h, predicted [b]	942 (352)	23061 (10714)	12029 (4049)	19016 (6823)	22010 (9548)
MARCAINE 400 mg (total dose): 175 mg (initial) and 2 doses of 112.5 mg q3h, predicted [b]	889 (327)	23054 (10707)	12203 (4083)	19105 (6892)	22038 (9578)

[a] N=34 subjects

[b] N=16 subjects

The comparison of bupivacaine PK parameters following XARACOLL at 300 mg (test drug, observed data from study INN-CB-022) and three dosage regimens of MARCAINE at 400 mg (reference drug, predicted from NPS analyses) are shown in Table 2. It is to be noted that, for the

three different dosing regimens proposed for 400 mg total dose of MARCAINE, the AUCinf values are comparable.

Table 2:

Treatment	Parameter	Observed (test)	Predicted (reference)	Ratio (XARACOLL observed / MARCAINE predicted)
XARACOLL 300 mg [a] ***versus*** MARCAINE 400 mg: single dose [b]	**Cmax**	663	1457	0.46
	AUC_{inf}	20368	23032	0.88
XARACOLL 300 mg [a] ***versus*** MARCAINE 400 mg (total dose): 133.33 mg q3h [b]	**Cmax**	663	942	0.70
	AUC_{inf}	20368	23061	0.88
XARACOLL 300 mg [a] ***versus*** MARCAINE 400 mg (total dose): 175 mg (initial) and 2 doses of 112.5 mg q3h [b]	**Cmax**	663	889	0.75
	AUC_{inf}	20368	23054	0.88

[a] N=34 subjects
[b] N=16 subjects

Both Cmax and AUCs observed with 300 mg XARACOLL were lower than those predicted for all three MARCAINE 400 mg dosage paradigms (Table 1). Specifically, the Cmax and AUC_{inf} values for 300 mg XARACOLL were lower by 25 to 54% and ~12%, respectively in comparison to three MARCAINE 400 mg predicted dosage paradigms (Table 2).

Conclusions:
From the clinical pharmacology perspective, this resubmission is acceptable. We have the following comments to the non-clinical team regarding the bupivacaine systemic exposure comparison between XARACOLL and the listed drug, MARCAINE, based on the information submitted by the Applicant.

- The rate and extent of bupivacaine absorption, as assessed by C_{max} and AUC_{inf} following implantation of 300 mg of XARACOLL were lower by ~25 to 54% and ~ 12%, respectively compared to those predicted for three different 400 mg of MARCAINE dosage paradigms. These results extend the scientific bridge between XARACOLL and MARCAINE and addresses CRL nonclinical deficiency #1 regarding inadequate characterization of the systemic safety of bupivacaine exposure via XARACOLL.

4. Labelling Comments.

The proposed labeling changes were made during this cycle are shown below. When this review is documented in DARRTS, the labeling negotiation is still ongoing with the Sponsor.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

SURESH B NARAHARISETTI
08/03/2020 11:01:33 AM

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08/03/2020 12:40:39 PM

Office of Clinical Pharmacology Review

NDA or BLA Number	209511 Refusal-to-File Re-submission
Link to EDR	\\CDSESUB1\EVSPROD\NDA209511\0008
Submission Date	2/2/18; 1° review due: 10/24/18; 2° review due: 11/2/18; PDUFA date: 11/30/18
Submission Type	505(b)(2)
Brand Name	Xaracoll
Generic Name	Bupivacaine hydrochloride collagen-matrix implants
Dosage Form and Strength	Collagen-matrix implants; 300 mg (3x100 mg implants) bupivacaine hydrochloride
Route of Administration	Implantation during surgery through placement within multiple layers at the surgical site
Proposed Indication	Post-surgical analgesia
Applicant	Innocoll Pharmaceuticals
Associated IND	77127
OCP Reviewer	David Lee, Ph.D.
OCP Team leader	Yun Xu, Ph.D.

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1. EXECUTIVE SUMMARY

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted in this Refusal-to-File resubmission (submitted on 2/2/18) for Xaracoll, NDA 209511, 300 mg buprenorphine HCl collagen-matrix implants. From a clinical pharmacology perspective, the information submitted in this Refusal-to-File resubmission is acceptable. When the review is documented in Darrts, labeling negotiation is still ongoing with the Sponsor.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The Applicant conducted two Phase 3 studies in the US in adults with a planned unilateral inguinal hernioplasty, a model of soft tissue surgery (INN-CB-014 [n=305] and INN-CB-016 [n=319]). The primary efficacy variable in both Phase 3 studies was the time-weighted sum of pain intensity from Time 0 through 24 hours (SPI24) after implantation. The key secondary efficacy endpoints included Total use of opioid analgesia from Time 0 through 24 hours (TOpA24), Sum of pain intensity from Time 0 to 48 hours (SPI48), Total use of opioid analgesia from Time 0 through 48 hours (TOpA48), Sum of pain intensity from Time 0 to 72 hours (SPI72), and, Total use of opioid analgesia from Time 0 through 72 hours (TOpA72). The Applicant reported that Xaracoll had statistically significantly less pain over 24 hours ($p=0.0004$ and $p<0.0001$, respectively) after local placement of study treatment, as measured by SPI24 (i.e., primary endpoint).
General dosing instructions	Xaracoll is intended for single-dose administration. The recommended dose of Xaracoll is 300 mg bupivacaine HCl (equivalent to 266.4 mg of bupivacaine) consisting of 3 bupivacaine HCl collagen-matrix implants, each containing 100 mg of bupivacaine HCl (equivalent to 88.8 mg of bupivacaine). (b) (4) Xaracoll requires no preparation and

	should not be moistened prior to use. Xaracoll can be cut using sterile technique before placement into the surgical site at the source of pain. The maximum dose of Xaracoll should not exceed 300 mg.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No pediatric data are available for Xaracoll at the time of this NDA submission. However, a study to investigate the PK of INL-001 in pediatric patients ages 2 to <17 years (INN-CB-020) has been initiated and a second study (INN-CB-021) in pediatric patients ages 0 to 2 years will be deferred per the Agreed initial Pediatric Study Plan (iPSP). The Applicant requests to defer *submission* and *initiation* of the following studies, respectively: 1) ongoing pediatric study INN-CB-020 (pediatric population ages 2 to <17 years), and, 2) planned pediatric study INN-CB-021 (pediatric population ages 0 to < 2 years). Safety and efficacy of bupivacaine in pediatric patients have not been established (Marcaine Lebel). No specific studies were conducted to evaluate the bupivacaine pharmacokinetics in special populations such as geriatric patients, hepatic and renal impairments. In general, since bupivacaine is metabolized by the liver, Xaracoll dose should be carefully chosen in patients with hepatic impairment. With respect to renal impairment, bupivacaine is known to be excreted by the kidney. Accordingly, Xaracoll dose should be carefully chosen in patients with renal impairment. With respect to geriatric patients, the Applicant reported that, out of the total number of patients in the Phase 3 studies (N = 411), 60 patients were greater than or equal to 65 years of age and 14 patients were greater than or equal to 75 years of age. The Applicant stated in the submission that no overall differences in efficacy and safety were observed between geriatric patients and younger patients. Clinical studies have noted that, in general, differences in various PK parameters have been observed between geriatric and younger patients. Since hepatic and/or renal functions may be lower in geriatric patients compared to younger patients, bupivacaine exposure may be higher in geriatric patients (bupivacaine is metabolized by the liver and known to be excreted by the kidney). As such, Xaracoll dose should be carefully chosen in geriatric patients, and may be monitor renal function in these patients (Marcaine Label). No dedicated Xaracoll pharmacokinetic studies were conducted to evaluate drug interactions. This is a 505(b)(2)

<table>
<tr><td></td><td>application and the Applicant will rely upon Marcaine Label.
It is noted in the proposed Xaracoll Label that “the clinical data support the use of low dose lidocaine as a local anesthetic administered topically or subcutaneously for intravenous catheter placement or administered intravenously during anesthesia induction prior to surgery and placement of XARACOLL. (b) (4)
(b) (4)</td></tr>
<tr><td>Labeling</td><td>See Section 2.4 for Labeling recommendation.</td></tr>
<tr><td>Bridge between the to-be-marketed and clinical trial formulations</td><td>Final to-be-marketed (or commercial) formulation was used in Pharmacokinetic study INN-CB-022, as well as in Phase 3 studies:

Summary of Manufacturing Changes during Development of INL-001
<table>
<tr><th>Manufacturing Change</th><th>Timing</th><th>Studies Conducted</th></tr>
<tr><td>(b) (4)</td><td>Early development</td><td>Initial PK study (INN-CB-013)
Nonclinical studies</td></tr>
<tr><td></td><td>Completed prior to Phase 3 studies</td><td>Phase 3 studies (INN CB-014 and INN-CB-016)
Repeat PK study (INN-CB-022)
Repeat pivotal nonclinical studies (00134510 [supportive] and 00134509 [56-day])
Biocompatibility studies</td></tr>
</table>
1.11.4 Multiple Module Amendment – Guide for Refuse to File Letter; p.11/39.</td></tr>
<tr><td>Other (specify)</td><td>Not applicable.</td></tr>
</table>

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

Innocoll Pharmaceuticals has re-submitted a New Drug Application (NDA) for Xaracoll® (bupivacaine HCl collagen-matrix implants) as a 505(b)(2) submission. The proposed indication is “for placement into the surgical site to produce postsurgical analgesia following (b) (4) (b) (4) The Applicant’s intent of developing Xaracoll appears to stem from providing extended delivery of bupivacaine to the tissues and avoids the risk of unintended intravascular

injection within the surgical site. It is noted that the Applicant previously submitted this application on 10/31/16. On 12/23/16 the Agency sent a Refusal-to-File (RTF) letter to the Applicant due to formulation issues (see discussion below under the subheading, 'Concerns of Xaracoll formulation used in clinical studies in the original NDA submission').

Xaracoll is a single-use, drug-matrix combination surgical implant product consisting of an active moiety, bupivacaine, and a drug-delivery component consisting of purified Type I bovine collagen. The proposed dosing regimen is *three* 100 mg bupivacaine collagen matrices (each collagen matrix contains 100 mg of (b) (4) bupivacaine HCl; a total of dose of 300 mg bupivacaine HCl, equivalent to 266.4 mg bupivacaine; per matrix size: 5cm x 5cm x 0.5cm) implanted at different layers within the surgical site. The Applicant stated that Xaracoll is designed to provide rapid drug release via dissolution and diffusion from the porous collagen matrix.

Xaracoll utilizes COLLARX® technology, a proprietary collagen matrix technology, which produces a (b) (4) porous matrix comprised of 75 mg of type 1 collagen purified from bovine Achilles tendons. The Applicant stated that the collagen matrix is biocompatible, biodegradable, and bio-resorbable.

Xaracoll was developed under IND 77127. It is noted that throughout the drug development process, designation "INL-001" was also used for Xaracoll.

Original Submission

In the original submission, the Applicant stated that Xaracoll has been evaluated in 10 clinical studies (see Table 1-reproduced from the original filing review), including two identical Phase 3 double-blind, placebo-controlled studies (INN-CB-014 and -016) to support Xaracoll as (b) (4) for the management of postoperative pain. Both studies assessed 300 mg bupivacaine. Overall, 578 subjects were treated with INL-001; 435 of these subjects were treated at the proposed commercial dose of 300 mg (3 x 100 mg bupivacaine HCl matrices).

Table 1: Clinical studies submitted in the original submission

Study ID	Study Title
INN-CB-001	A Phase I, Single Dose, Open-Label, Prospective Study to Investigate the Pharmacokinetic Profile, Safety and Tolerability of Collatamp® B in Patients Following Hysterectomy
INN-CB-002	A Phase II, Single-Dose, Blinded, Prospective Study to Investigate the Efficacy and Safety of the CollaRx® Bupivacaine Implant in Women following Abdominal Hysterectomy or other Nonlaparoscopic Benign Gynecological Procedure
INN-CB-003	A Phase II, Randomized, Single-dose, Double-blind, Placebo-controlled Study to Investigate the Efficacy, Safety and Pharmacokinetic Profile of the CollaRx® Bupivacaine Implant in Men After Open Mesh Herniorrhaphy
INN-CB-004	A Phase II, Randomized Single-dose, Double-blind, Placebocontrolled Study to Investigate the Efficacy, Safety and Pharmacokinetic Profile of the of the CollaRx® Bupivacaine Implant in Patients After Gastrointestinal Surgery
INN-CB-005	A Phase II, Randomized, Single-dose, Unblinded Study to Compare the Efficacy and Safety of the CollaRx® Bupivacaine Implant With the ON-Q® PainBuster® Post-op Pain Relief System in Women Following Abdominal Hysterectomy
INN-CB-010	A Phase II, Randomized, Single-dose, Double-blind, Placebo-controlled Study to Investigate the Efficacy and Safety Profile of the CollaRx® Bupivacaine Implant (200 mg Bupivacaine Hydrochloride) in Men After Open Laparotomy Herniorrhaphy
INN-CB-011	A Phase II, Single-dose, Open-label Study to Investigate the Feasibility and Efficacy of the CollaRx® Bupivacaine Implant (200 mg Bupivacaine Hydrochloride) in Men After Laparoscopic Inguinal or Umbilical Herniorrhaphy
INN-CB-013	A Randomized, Blinded, Inpatient Study to Investigate the Pharmacokinetics, Relative Bioavailability and Safety of 2 Doses of the XaraColl® Bupivacaine Collagen Implant (200 and 300 mg Bupivacaine Hydrochloride) Compared to Bupivacaine Hydrochloride Infiltration (150 mg) After Open Laparotomy Hernioplasty
INN-CB-014	A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy and Safety of the XaraColl® Bupivacaine Implant (300 mg Bupivacaine Hydrochloride) After Open Laparotomy Hernioplasty
INN-CB-016	A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy and Safety of the XaraColl® Bupivacaine Implant (300 mg Bupivacaine Hydrochloride) After Open Laparotomy Hernioplasty

With respect to clinical pharmacology information submitted in the original NDA submission, it is noted that the Studies INN-CB-001 and -002 were conducted in hysterectomy patients, not the targeted patient population for this submission, and not considered critical for the NDA submission.

Study INN-CB-003 was a Phase 2 single dose, double-blind, placebo-controlled study in men undergoing unilateral inguinal hernioplasty (with placement of mesh). This study assessed use of two 50 mg implants (total bupivacaine HCl 100 mg) or matching placebo implanted into hernioplasty wound during surgery. Study INN-CB-013 was a multicenter, blinded, randomized, single dose pharmacokinetic study in subjects (mostly men) undergoing unilateral inguinal hernioplasty (with placement of mesh). This study assessed a) 2x100 mg Xaracoll implants (total bupivacaine HCl 200 mg), b) threex100 mg Xaracoll implants (total bupivacaine HCl 300 mg), and c) a local infiltration of 150 mg bupivacaine HCl (60 mL of 0.25% solution with epinephrine).

As discussed below (subheading, *Concerns of Xaracoll formulation used in clinical studies in the original NDA submission*) the formulation/product utilized in -003 and 0-13 studies were "substantially" different from the to-be-marketed (TBM) formulation/product, as well as formulation/product utilized in Phase 3 trials. Therefore, Studies INN-CB-003 (conducted period 3/2008-1/2009) and Study INN-CB-013 (conducted period 10/2014-3/2015) will *not* be reviewed. Noted that the formulations used in hysterectomy studies, Studies INN-CB-001 (conducted period 1/2007-7/2007) and INN-CB-002 (conducted period 12/2007-5/2008) were considered also substantially different from the TBM formulation/product, due to the fact that these studies were the first of pharmacokinetic studies conducted. Therefore, Studies INN-CB-001, and, INN-CB-002 will *not* be reviewed.

Concerns of Xaracoll formulation used in clinical studies in the original NDA submission:

During the original NDA submission filing period, a discussion (CMC/Biopharmaceutics) occurred related to formulations used in the clinical studies. It was noted that multiple formulation modifications (b) (4) (b) (4) were made to Xaracoll formulation, which the Applicant deemed not critically important. However, a further discussion revealed that modifications made may be "substantial enough," that, further information may be needed.

This impact of "substantial formulation changes" with respect to clinical pharmacology was that Xaracoll formulation(s) used in clinical pharmacology studies were not considered to be the final commercial formulation. During the discussion, CMC/Biopharmaceutics group stated that the Applicant did not provide adequate linkage between formulation used in the PK study and commercial formulation. It was also mentioned that such change cannot be bridged by in vitro data.

Therefore, the information obtained from Study INN-CB-013, in particular, was considered not acceptable from the clinical pharmacology perspective. To rectify the situation, the Applicant needed to provide additional bupivacaine exposure information from the commercial Xaracoll formulation for the proposed surgical procedure in the labeling (i.e., patients undergoing hernia repair), or, to provide justification/rationale that such submitted information in Study INN-CB-013 is appropriate. Therefore, the following Refused to File (RTF) comment was conveyed to the Applicant:

> "It appears that multiple formulation modifications (b) (4) (b) (4) were made to Xaracoll formulation during the development. The changes are considered substantial, so the PK data obtained with the pre-change formulation cannot be applied to the commercial formulation. You need to conduct an additional PK study similar to Study INN-CB-013 to evaluate bupivacaine exposure using your commercial Xaracoll formulation under proposed surgical procedure in your label, i.e., patients undergoing hernia repair. In your

relative bioavailability study, you need to carefully specify the treatments with all pertinent information, e.g., lot number, expiration date, NDA or ANDA numbers, etc."

Current re-submission:

In this current re-submission, to address the deficiency stated in the RTF letter, the Applicant has submitted a new study, Study INN-CB-022, entitled "A Randomized, Single Blind Study to Investigate the Pharmacokinetics, Relative Bioavailability, and Safety of INL-001 Bupivacaine Hydrochloride (HCl) Collagen-Matrix Implant 300 mg Compared to Marcaine 0.25% (Bupivacaine HCl) 175 mg Infiltration After Open Hernioplasty." This study compared Xaracoll 300 mg with Marcaine 0.25% in subjects scheduled for unilateral inguinal hernioplasty and mesh placement.

As stated in the protocol title, this study provides a relative bioavailability linkage between Xaracoll and Marcaine, the reference product. As such, Study INN-CB-022 will be reviewed in detail. Of note, however, this study will not considered be considered as a pivotal study for the approval of Xaracoll, as there were two Phase 3 trials (randomized, multi-center, double-blind, placebo-controlled) in patients undergoing hernioplasty.

Again, Studies INN-CB-003 and INN-CB-013, studies submitted in the original submission, will not be reviewed, per the discussion above, due to formulation changes occurring during the drug development.

Discussion on 505(b)(2) linkage:

In the original NDA submission, the Applicant listed the following applications as references: Marcaine (NDA 16964) and (b) (4) In the re-submission, however, the Applicant listed only Marcaine as a listed drug.

Clinical pharmacology findings

Xaracoll is intended to be locally active. Systemic bupivacaine plasma concentration-effect relationships are not considered for the efficacy, but, from an overall systemic safety perspective.

Single dose relative bioavailability

Study INN-CB-022 assessed the relative bioavailability of Xaracoll (300 mg bupivacaine HCl) compared to Marcaine 0.25% (175 mg bupivacaine), the reference product, in patients undergoing open hernioplasty surgery. Bupivacaine concentrations were observed at the first-time point measured (0.5 hours) for all subjects treated with Xaracoll and Marcaine 0.25%. Bupivacaine concentrations were detectable through 96 hours in both treatment groups. Bupivacaine concentrations were lower during the initial 1.5 hours in the Xaracoll treatment group, and, was higher after that time period in comparison with the Marcaine 0.25% treatment group. See Figure 2 and Table 6 in the review for PK profiles and PK parameters, respectively.

Observed bupivacaine Cmax values were similar (663.41 ng/mL vs. 641.00 ng/mL, Xaracoll and Marcaine 0.25%, respectively) between Xaracoll and Marcaine 0.25%. Observed AUC0-inf values were approximately 2-fold higher (20368.4 h*ng/mL vs. 9814.8 h*ng/mL, Xaracoll and Marcaine 0.25%, respectively) for Xaracoll compared Marcaine 0.25%.

Exposure-Response Relationship

There is no exposure-response relationship for Xaracoll, since the systemic bupivacaine measured do not reflect the concentrations in the local surgical site(s).

Pediatrics

With respect to pediatric development plan, the Applicant requests to defer *submission* and *initiation* of the following studies, respectively: 1) ongoing pediatric study INN-CB-020[1] (pediatric population ages 2 to < 17 years), and, 2) planned pediatric study INN-CB-021[2] (pediatric population ages 0 to < 2 years). The Applicant states that the deferral request is in accordance with an Agreed initial Pediatric Study Plan (iPSP), which was received from the Agency on 9/23/16.

In the current re-submission, the Applicant states that Study INN-CB-020 is not scheduled to be completed prior to approval of the current submission in adults, and, additional safety data are needed from Study INN-CB-020 to identify a safe dosing range for neonates and infants before INN-CB-021 can be initiated. Therefore, the initiation of Study INL-CB-021 will be deferred until information from INL-CB-020 is available so that a safe estimation of dose can be determined. The Applicant states that submission of a protocol for study INN-CB-021 is estimated to be in November 2018, with study initiation in January 2019.

Special population

No specific studies were conducted to evaluate the bupivacaine pharmacokinetics in special populations such as geriatric patients, hepatic and renal impairments. In general, since bupivacaine is metabolized by the liver, Xaracoll dose should be carefully chosen in patients with hepatic impairment.

With respect to renal impairment, bupivacaine is known to be excreted by the kidney. Accordingly, Xaracoll dose should be carefully chosen in patients with renal impairment.

With respect to geriatric patients, the Applicant reported that, out of the total number of patients in the Phase 3 studies (N = 411), 60 patients were greater than or equal to 65 years of age and 14

patients were greater than or equal to 75 years of age. The Applicant stated in the submission that no overall differences in efficacy and safety were observed between geriatric patients and younger patients. Clinical studies have noted that, in general, differences in various PK parameters have been observed between geriatric and younger patients.
Since hepatic and/or renal functions may be lower in geriatric patients compared to younger patients, bupivacaine exposure may be higher in geriatric patients (bupivacaine is metabolized by the liver and known to be excreted by the kidney). As such, Xaracoll dose should be carefully chosen in geriatric patients, and may be monitor renal function in these patients (Marcaine Label).

Drug interactions

No drug interaction studies were submitted. This is a 505(b)(2) application and the Applicant will rely upon Marcaine Label.

2.1 Pharmacology and Clinical Pharmacokinetics

2.1.1. What is the proposed indication for Xaracoll?

The proposed indication for Xaracoll use is "placement into the surgical site to produce post-surgical analgesia following (b) (4)

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing for Xaracoll

Xaracoll is intended for single-dose administration. The recommended dose is 300 mg bupivacaine HCl (equivalent to 266.4 mg of bupivacaine) consisting of *three* bupivacaine HCl collagen-matrix implants, each containing 100 mg of bupivacaine HCl (equivalent to 88.8 mg of bupivacaine). The collagen matrices are implanted during the surgery at multiple layers in the soft tissue and in the layers below the skin closure.

Per the package insert:

(b) (4)

Because bupivacaine is evenly dispersed in the matrix, Xaracoll can be cut as needed to accommodate surgical and individual patient factors. The Applicant states that collagen matrix has been shown to be biocompatible with surgical materials such as mesh and suture. The

collagen matrix degrades by slow chemical and enzymatic hydrolysis, to soluble peptides and amino acids; the proteins are absorbed into surrounding tissues. Subsequently, the quantity of matrix material decreases over time in the wound, and, the Applicant states that, based on animal studies, is no longer present by 56 days.

2.2.2 Therapeutic individualization

2.2.2.1 Pediatric development iPSP

With respect to pediatric development plan, the Applicant requests to defer *submission* and *initiation* of the following studies, respectively: 1) ongoing pediatric study INN-CB-020[1] (pediatric population ages 2 to < 17 years), and, 2) planned pediatric study INN-CB-021[2] (pediatric population ages 0 to < 2 years).

The Applicant states that the deferral request is in accordance with an Agreed initial Pediatric Study Plan (iPSP), which was received from the Agency on 9/23/16. In that Agreed iPSP, the final report projected timeline for INN-CB-020 was listed as December 2018. In the current re-submission, the Applicant states that Study INN-CB-020 is not scheduled to be completed prior to approval of the current submission in adults, and, additional safety data are needed from Study INN-CB-020 to identify a safe dosing range for neonates and infants before INN-CB-021 can be initiated. Therefore, the initiation of Study INL-CB-021 will be deferred until information from INL-CB-020 is available so that a safe estimation of dose can be determined. The Applicant states that submission of a protocol for study INN-CB-021 is estimated to be in November 2018, with study initiation in January 2019.

Briefly, in Study INN-CB-020, after considering the appropriate doses (the concept is to achieve similar bupivacaine exposure in all age groups), pediatric patients in the 12 to <17-year cohort will receive Xaracoll at the selected dose to evaluate the safety and efficacy of Xaracoll. The process used in the 12 to <17-year cohort will continue in a step-wise fashion until adequate doses are established for the subsequent age cohorts, 6 to <12 years and 2 to <6 years. Additionally, to confirm Xaracoll doses in children, modeling and simulations will be conducted to estimate systemic exposures based on the proposed dose regimens for the age cohorts. If deemed necessary, Xaracoll doses may be adjusted based on the findings (e.g., organ immaturity and/or differential toxicity).

[1]Study INN-CB-020: a multicenter, randomized controlled study to evaluate the pharmacokinetics, safety, and efficacy of Xaracoll for postoperative analgesia in children 2 to <17 years of age who are undergoing open inguinal hernia repair surgery.
[2]Study INN-CB-021; a multicenter, single-dose, randomized, blinded study; the study design is similar to INN-CB-020 in 0 to <2 years of age who are scheduled for open inguinal hernia repair surgery.

2.3 Outstanding Issues

There are no outstanding issues at this time.

2.4 Summary of Labeling Recommendations

The labeling review and the labeling changes for this product were conducted. The following recommendations are proposed for Xaracoll (Table 2).

Table 2 Labeling comparison and recommendation

Marcaine	Proposed Xaracoll	Labeling Comments
--------PRECAUTIONS---------- PRECAUTIONS General: *The safety and effectiveness of local anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use.* (See WARNINGS, ADVERSE REACTIONS, and OVERDOSAGE.) During major regional nerve blocks, the patient should have IV fluids running via an indwelling catheter to assure a functioning intravenous pathway. The lowest dosage of local anesthetic that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should be used when feasible. Epidural Anesthesia: During epidural administration of MARCAINE, 0.5% and 0.75% solutions should be administered in incremental doses of 3 mL to 5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Injections should be made slowly, with frequent aspirations before and during the injection to avoid intravascular injection. Syringe aspirations should also be performed before and during each supplemental injection in continuous (intermittent) catheter techniques. An intravascular injection is still possible even if aspirations for blood are negative. During the administration of epidural anesthesia, it is recommended that a test dose be administered initially and the effects monitored before the full dose is given. When using a "continuous" catheter technique, test doses should be given prior to both the original and all reinforcing doses, because plastic tubing in the epidural space can migrate into a blood vessel or through the dura. When clinical conditions permit, the test dose should contain epinephrine (10 mcg to 15 mcg has been suggested) to serve as a warning of unintended intravascular injection. If injected into a blood vessel, this amount of epinephrine is likely to produce a transient "epinephrine response" within 45 seconds, consisting of an increase in heart rate and/or systolic blood pressure, circumoral pallor, palpitations, and nervousness in the unsedated patient. The sedated patient may exhibit only a	**----WARNINGS AND PRECAUTION--------** 5 WARNINGS AND PRECAUTIONS 5.1 Warnings and Precautions for Bupivacaine Containing Products (b) (4)	-No issues – Marcaine Label: Precautions Marcaine Label: Adverse Reactions; Central Nervous System Reactions Cardiovascular System Reactions Allergic

pulse rate increase of 20 or more beats per minute for 15 or more seconds. Therefore, following the test dose, the heart rate should be monitored for a heart rate increase. Patients on beta-blockers may not manifest changes in heart rate, but blood pressure monitoring can detect a transient rise in systolic blood pressure. The test dose should also contain 10 mg to 15 mg of MARCAINE or an equivalent amount of another local anesthetic to detect an unintended intrathecal administration. This will be evidenced within a few minutes by signs of spinal block (e.g., decreased sensation of the buttocks, paresis of the legs, or, in the sedated patient, absent knee jerk). The Test Dose formulation of MARCAINE contains 15 mg of bupivacaine and 15 mcg of epinephrine in a volume of 3 mL. An intravascular or subarachnoid injection is still possible even if results of the test dose are negative. The test dose itself may produce a systemic toxic reaction, high spinal or epinephrine-induced cardiovascular effects. Injection of repeated doses of local anesthetics may cause significant increases in plasma levels with each repeated dose due to slow accumulation of the drug or its metabolites, or to slow metabolic degradation. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with their age and physical status. Local anesthetics should also be used with caution in patients with hypotension or heartblock.		
Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be performed after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.	Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be performed after administration of bupivacaine [redacted (b) (4)]. Restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.	
Local anesthetic solutions containing a vasoconstrictor should be used cautiously and in carefully restricted quantities in areas of the body supplied by end arteries or having otherwise compromised blood supply such as digits, nose, external ear, or penis. Patients with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response. Ischemic injury or necrosis may result.		
Because amide-local anesthetics such as MARCAINE are metabolized by the liver, these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations. Local anesthetics should also be used with caution in patients with impaired cardiovascular function because they	Because amide-local anesthetics such as bupivacaine are metabolized by the liver, [redacted (b) (4)] patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the	

may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by these drugs. Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of potent inhalation anesthetics. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account. Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Because it is not known whether amide-type local anesthetics may trigger this reaction and because the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for management should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and prompt institution of treatment, including oxygen therapy, indicated supportive measures and dantrolene. (Consult dantrolene sodium intravenous package insert before using.)	prolongation of AV conduction produced by (b) (4) (b) (4) Nervous System (b) (4) (b) (4) reactions are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors (b) (4) convulsions. (b) (4) (b) (4) High plasma levels may lead to depression of the myocardium, decreased cardiac output, heartblock, hypotension, bradycardia, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, and cardiac arrest. (b) (4) Allergic-type reactions (b) (4) occur as a result of sensitivity to (b) (4) or to other formulation ingredients. These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and (b) (4) severe hypotension). Cross-sensitivity among members of the amide-type local anesthetic group has been reported. (b) (4) (b) (4) (b) (4)	- Marcaine Label: Warnings Section 2.5.1.4 Defer to clinical

	(b) (4) [redacted]	
7 DRUG INTERACTIONS	7 DRUG INTERACTIONS (b) (4) [redacted] (b) (4) [redacted] Since lidocaine and bupivacaine are both amide anesthetics, an additive effect may be seen when used concomitantly so caution should be used. Monitor for neurologic and cardiovascular effects related to toxicity.	The toxic effects of local anesthetics are additive and their co-administration should be used with caution including monitoring for neurologic and cardiovascular effects related to local anesthetic systemic toxicity [*See Dosage and Administration (2.2) , Warnings and Precautions (5.1) and Overdosage (10)*]. Avoid additional use of local anesthetics within 96 hours following administration of Xaracoll. <u>Bupivacaine:</u> Bupivacaine HCl administered together with Xaracoll may impact the overall exposure of bupivacaine. <u>Non-Bupivacaine Local Anesthetics:</u> (b) (4) [redacted] (b) (4) [redacted] Since lidocaine and bupivacaine are both amide anesthetics, an additive effect may be seen when used concomitantly so caution should be used. Monitor for neurologic and cardiovascular effects related to toxicity.
8.4 Pediatric Use	8.4 Pediatric Use Safety and effectiveness in pediatric patients have not been established.	Section 2.7.2.5.2 No issues – Keep wording
8.5 Geriatric Use	8.5 Geriatric Use	Section 2.7.2.5.2

	Of the total number of patients in the Phase 3 XARACOLL studies (N=411), 60 patients were greater than or equal to 65 years of age and 14 patients were greater than or equal to 75 years of age. No overall differences in efficacy and safety were observed between these patients and younger patients. Clinical experience with XARACOLL has not identified differences in efficacy or safety between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In clinical studies, differences in various pharmacokinetic parameters have been observed between elderly and younger patients. Because elderly patients are more likely to have decreased renal function, (b) (4) it may be useful to monitor renal function. The effects of age (elderly versus younger) on the pharmacokinetics of XARACOLL have not been studied.	No issue from clinical pharmacology perspective Marcaine Label: Precautions; Geriatric Use No issues-
8.6 Hepatic Impairment	8.6 Hepatic Impairment (b) (4) amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, (b) (4) Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations.	Section 2.5.3.1.8 Section 2.7.2.5.2 Marcaine Label: Precautions Marcaine Label: Clinical Pharmacology (b) (4) Amide-type local anesthetics, such as bupivacaine, are metabolized by the liver. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations, and potentially local anesthetic systemic toxicity. Therefore, consider increased monitoring for local anesthetic systemic toxicity in subjects with moderate to severe hepatic disease.
8.7 Renal Impairment	8.7 Renal Impairment Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.	Section 2.5.3.1.8 Section 2.7.2.5.2 Marcaine Label: Precautions; Geriatric Use (b) (4) Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Consider increased monitoring for

		local anesthetic systemic toxicity in subjects with renal disease.
CLINICAL PHARMACOLOGY Local anesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone. Systemic absorption of local anesthetics produces effects on the cardiovascular and central nervous systems (CNS). At blood concentrations achieved with normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure. Recent clinical reports and animal research suggest that these cardiovascular changes are more likely to occur after unintended intravascular injection of bupivacaine. Therefore, incremental dosing is necessary. Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression, or both. Apparent central stimulation is manifested as restlessness, tremors and shivering progressing to convulsions, followed by depression and coma progressing ultimately to respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited state.	**12 CLINICAL PHARMACOLOGY** **12.1 Mechanism of Action** (b) (4) bupivacaine block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. Clinically, the order of loss of nerve function is (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone. **12.2 Pharmacodynamics** Systemic absorption of (b) (4) bupivacaine, produces effects on the cardiovascular and central nervous system. At blood concentrations achieved with normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conduction and excitability that may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure. (b) (4) these cardiovascular changes are more likely to occur after unintended intravascular injection of liquid formulations of bupivacaine. Following systemic absorption, (b) (4) can produce central nervous system stimulation, depression, or both. Central (b) (4) stimulation is manifested as restlessness, tremors, and shivering progressing to convulsions, followed by depression and coma progressing ultimately to respiratory arrest. (b) (4) bupivacaine have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited state.	Overall, no issues– however, **See the proposed table below, and, a revision to the heading under *Elimination* subheading**
Pharmacokinetics	**12.3 Pharmacokinetics** Local placement of XARACOLL within the surgical site during (b) (4) resulted in detectable plasma levels of bupivacaine at the first measured time point (0.5 hours) and throughout the 96-hour observation period [see Warnings and Precautions (5.2)]. (b) (4)	Section 2.7.2.3.1 Marcaine Label: Clinical Pharmacology; Pharmacokinetics Delete the following: (b) (4)

The rate of systemic absorption of local anesthetics *is dependent upon the total dose* and concentration of drug administered, the route of administration, *the vascularity of the administration site*, and the presence or absence of epinephrine in the anesthetic solution. A dilute concentration of epinephrine (1:200,000 or 5 mcg/mL) usually reduces the rate of absorption and peak plasma concentration of MARCAINE, permitting the use of moderately larger total doses and sometimes prolonging the duration of action.

The onset of action with MARCAINE is rapid and anesthesia is long lasting. The duration of anesthesia is significantly longer with MARCAINE than with any other commonly used local anesthetic. It has also been noted that there is a period of analgesia that persists after the return of sensation, during which time the need for strong analgesics is reduced.

The onset of action following dental injections is usually 2 to 10 minutes and anesthesia may last two or three times longer than lidocaine and mepivacaine for dental use, in many patients up to 7 hours. The duration of anesthetic effect is prolonged by the addition of epinephrine 1:200,000.

Local anesthetics are bound to plasma proteins in varying degrees. Generally, the lower the plasma concentration of drug the higher the percentage of drug bound to plasma proteins.

Local anesthetics appear to cross the placenta by passive diffusion. The rate and degree of diffusion is governed by (1) the degree of plasma protein binding, (2) the degree of ionization, and (3) the degree of lipid solubility. Fetal/ maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding, because only the free, unbound drug is available for placental transfer.

MARCAINE with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4). The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid soluble, nonionized drugs readily enter the fetal blood from the maternal circulation.

Absorption

The rate of systemic absorption of bupivacaine is dependent on the total dose administered and the vascularity of the administration site.

Pharmacokinetic parameters for XARACOLL following placement in the surgical site during hernioplasty are presented in Table 2.

Table 2: Pharmacokinetic Parameters for Bupivacaine After Placement of XARACOLL

Parameter	XARACOLL 300 mg
	N=34
Cmax (ng/mL)1,2	663 (264)
Tmax (hour)3	3 (b) (4)
AUC0-last (ng/mL·h)4	(b) (4)
AUC0-∞ (ng/mL·h)4	
t1/2 (hours)1	19 (6)

(b) (4)

3Median (minimum – maximum)

(b) (4)

Distribution

After bupivacaine is released from XARACOLL it is absorbed systemically. Local anesthetics including bupivacaine are distributed to some extent to all body tissues, with higher concentrations found in highly perfused organs such as the liver, lungs, heart, and brain.

Local anesthetics including bupivacaine appear to cross the placenta by passive diffusion. The rate and degree of diffusion is governed by (1) the degree of plasma protein binding, (2) the degree of ionization, and (3) the degree of lipid solubility. Fetal/maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding, because only the free, unbound drug is available for placental transfer.

Bupivacaine with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4). The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid soluble, non-ionized drugs such as bupivacaine readily enter the fetal blood from the maternal circulation.

Section 2.7.2.5.1 Marcaine Label: Clinical Pharmacology; Pharmacokinetics

Section 2.7.2.5.1, Table 12

Replace with this table:

Parameter	XARACOLL 300 mg Mean (SD)
	N=34
Cmax (ng/mL)	663 (264)
Tmax (hour)#	3 (1.5, 24)
AUC0-last (ng.h/mL)	19493 (7564)
AUC0-∞ (ng h/mL)	20368 (7912)
t1/2 (hours)	19 (6)

#Median (minimum, maximum)

Section 2.7.2.5.1

Marcaine Label: Clinical Pharmacology; Pharmacokinetics

Depending upon the route of administration, *local anesthetics are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain.*		Revise heading to **Elimination** with subheadings, *Metabolism* and *Excretion*
Pharmacokinetic studies on the plasma profile of MARCAINE after direct intravenous injection suggest a three-compartment open model. The first compartment is represented by the rapid intravascular distribution of the drug. The second compartment represents the equilibration of the drug throughout the highly perfused organs such as the brain, myocardium, lungs, kidneys, and liver. The third compartment represents an equilibration of the drug with poorly perfused tissues, such as muscle and fat. The elimination of drug from tissue distribution depends largely upon the ability of binding sites in the circulation to carry it to the liver where it is metabolized. After injection of MARCAINE for caudal, epidural, or peripheral nerve block in man, peak levels of bupivacaine in the blood are reached in 30 to 45 minutes, followed by a decline to insignificant levels during the next three to six hours. Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of hepatic or renal disease, addition of epinephrine, factors affecting urinary pH, renal blood flow, the route of drug administration, and the age of the patient. The half-life of MARCAINE in adults is 2.7 hours and in neonates 8.1 hours.	***Metabolism*** Amide-type local anesthetics such as bupivacaine are metabolized primarily in the liver via conjugation with glucuronic acid. (b) (4) [redacted] Pipecoloxylidine is the major metabolite of bupivacaine. ***Excretion*** After bupivacaine has been released from XARACOLL and is absorbed systemically, bupivacaine excretion is expected to be the same as for other bupivacaine formulations. The kidney is the main excretory organ for most local anesthetics and their metabolites. Only 6% of bupivacaine is excreted unchanged in the urine. (b) (4) [redacted]	Section 2.7.2.5.1 Marcaine Label: Clinical Pharmacology; Pharmacokinetics Section 2.7.2.5.1 Marcaine Label: Clinical Pharmacology; Pharmacokinetics

In clinical studies, elderly patients reached the maximal spread of analgesia and maximal motor blockade more rapidly than younger patients. Elderly patients also exhibited higher peak plasma concentrations following administration of this product. The total plasma clearance was decreased in these patients.	**Specific Populations**	Section 2.5.3.1.8 Section 2.7.2.5.2
Amide-type local anesthetics such as MARCAINE are metabolized primarily in the liver via conjugation with glucuronic acid. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics. Pipecoloxylidine is the major metabolite of MARCAINE.	*Hepatic Impairment* (b) (4) Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics.	Marcaine Label: Clinical Pharmacology; Pharmacokinetics
The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Only 6% of bupivacaine is excreted unchanged in the urine.	*Renal Impairment* (b) (4) affecting urinary pH. Only 6% of bupivacaine is excreted unchanged in the urine [see Geriatric Use (8.5)].	
When administered in recommended doses and concentrations, MARCAINE does not ordinarily produce irritation or tissue damage and does not cause methemoglobinemia.	*Age* Various pharmacokinetic parameters of the local anesthetics such as bupivacaine can be significantly altered by the age of the patient.	Marcaine Label: Precautions; Geriatric Use

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

3.1.1 What is Xaracoll and what is the proposed route of Xaracoll administration?

Xaracoll is a combination product consisting of one active moiety, bupivacaine, and a drug delivery component consisting solely of purified Type I collagen. It is a surgical implant composed of three (b) (4) purified, resorbable Type I bovine collagen matrices. Each matrix (5 × 5 × 0.5 cm) contains 100.0 mg of uniformly distributed bupivacaine HCl (equivalent to 88.8 mg bupivacaine as the free base) and is designed to provide extended drug release of bupivacaine

from the wound site via the dissolution and diffusion of bupivacaine from the porous (b) (4) collagen matrix.

The purpose of the collagen is to provide a biocompatible matrix to allow placement of Xaracoll for the local delivery of bupivacaine in a surgical wound. As such, the collagen is not intended to have a beneficial effect. The drug release mechanism from the matrix involves via diffusion and dissolution of the porous collagen matrix, which bupivacaine is imbedded. The released bupivacaine is absorbed from the wound site for the reduction of postsurgical pain.

The collagen matrix in INL-001 is manufactured using Innocoll's proprietary COLLARX® technology, which results in a (b) (4) purified, porous, biocompatible, biodegradable, and bioresorbable collagen matrix that releases the locally acting bupivacaine over time in the surgical wound. [The Applicant stated that the collagen is extracted from bovine Achilles tendons (obtained exclusively from (b) (4) closed herds that have been certified as transmissible spongiform encephalopathy free and negligible for the risk of bovine spongiform encephalopathy; (b) (4) Collagen implants are (b) (4) (b) (4) (b) (4) devices in the United States and other parts of the world to aid in the management of wound healing, for cosmetic reconstruction and as absorbable hemostatic agents.

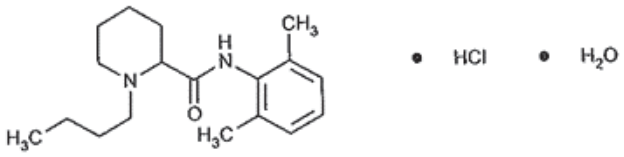
Physical characteristics of bupivacaine:

Bupivacaine HCl (Figure 1) is a white crystalline powder. Bupivacaine HCl is freely soluble in 95 % ethanol, soluble in water, and slightly soluble in acetone. (b) (4) (b) (4) The melting range of bupivacaine is 250 °C–260 °C.

Chemical name
(±)-1-butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide, monohydrochloride, monohydrate

Empirical formula
$C_{18}H_{28}N_2O.HCl\ H_2O$, 324.90 g/mol

Figure 1 Bupivacaine structural formula



3.1.2 Xaracoll development and formulation

During Xaracoll development, a 50 mg bupivacaine HCl matrix implant was initially developed and used in nonclinical and early phase clinical investigations. Subsequently, a 100 mg matrix implant was developed, due to (b) (4) based on the outcome of the initial clinical studies. Table 3 provides the batches used in clinical studies. The 100 mg implant used in the pharmacokinetic study (INN-CB-022) and the Phase 3 studies (INN-CB-014 and INN-CB-016) is the intended commercial formulation (i.e., same formulation and manufacturing process).

Table 3 Xaracoll batches used in clinical studies

Study Number	Clinical Phase	INL-001 Dosage Strength (mg of bupivacaine HCl per implant)	Total Bupivacaine HCl Dose (number of implants/subject)	Bupivacaine HCl Implant Lot Number
INN-CB-001	1	50	150 mg (3)	DEV-0206-002
INN-CB-002	2	50	150 mg (3)	DEV-0807-013
INN-CB-003	2	50	100 mg (2)	DEV-0807-013
INN-CB-004	2	50	150-200 mg (3 or 4)	DEV-0807-013
INN-CB-005	2	50	150 mg (3)	DEV-0807-013
INN-CB-010	2	100	200 mg (2)	10001706
INN-CB-011	2	50	200 mg (4)	DEV-0807-013
INN-CB-013	2	100	200-300 mg (2 or 3)	14021606
INN-CB-014	3	100	300 mg (3)	15012801
INN-CB-016	3	100	300 mg (3)	15012801
INN-CB-022	1	100	300 mg (3)	15041002

Data sources: INN-CB-001, INN-CB-002, INN-CB-003, INN-CB-004, INN-CB-005, INN-CB-010, INN-CB-011, INN-CB-013, INN-CB-014, INN-CB-016, and INN-CB-022 CSRs
Note: m2/27-summary-biopharm.pdf, p.9/28

The list of all Xaracoll components, quality standards, and function in the drug product are provided in Table 4. The Applicant stated that the collagen matrix serves as an inert delivery system and releases the bupivacaine HCl through wetting, dissolution and diffusion from the porous matrix. The mechanisms of bupivacaine release from the collagen matrix undergo the following steps: when hydrated, the sponge-like matrix fills with fluid, the entrapped air in the matrix escapes, bupivacaine HCl solubilizes, and, finally, the solubilized bupivacaine delivers to the wound site.

Table 4 Composition of Xaracoll

Component	**Quality standard**	**Quantity per matrix**	**Function**
Bovine type I collagen, purified	(b) (4)	75 mg	Excipient
Bupivacaine HCl	USP	100 mg	Drug substance
(b) (4)	USP	[1]	(b) (4)
	USP	[2]	
(b) (4)			

3.2 General Pharmacology and Pharmacokinetic Characteristics

3.2.1 What are the proposed mechanism(s) of actions and known clinical pharmacology information for bupivacaine?

The following Clinical Pharmacology information was obtained from Marcaine Label:

> CLINICAL PHARMACOLOGY
> Local anesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.
> Systemic absorption of local anesthetics produces effects on the cardiovascular and central nervous systems (CNS). At blood concentrations achieved with normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure. (b) (4) these cardiovascular changes are more likely to occur after unintended intravascular injection of bupivacaine. (b) (4)
> Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression, or both. Apparent central stimulation is manifested as restlessness, tremors and shivering progressing to convulsions, followed by depression and coma progressing ultimately to respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited state.
>
> Pharmacokinetics:
> (Distribution) The rate of systemic absorption of local anesthetics is dependent upon the total dose and concentration of drug administered the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic solution. A dilute concentration of epinephrine (1:200,000 (b) (4)) usually reduces the rate of absorption and peak plasma concentration of MARCAINE, permitting the use of moderately larger total doses and sometimes prolonging the duration of action.
> (b) (4) The duration of anesthesia is significantly longer with MARCAINE than with any other commonly used local anesthetic. It has also been noted that there is a period of analgesia that persists after the return of sensation, during which time the need for strong analgesics

is reduced. The onset of action following dental injections is usually 2 to 10 minutes and anesthesia may last two or three times longer than lidocaine and mepivacaine for dental use, in many patients up to 7 hours. The duration of anesthetic effect is prolonged by the addition of epinephrine 1:200,000.

Local anesthetics are bound to plasma proteins in varying degrees. Generally, the lower the plasma concentration of drug the higher the percentage of drug bound to plasma proteins.

Local anesthetics appear to cross the placenta by passive diffusion. The rate and degree of diffusion is governed by (1) the degree of plasma protein binding, (2) the degree of ionization, and (3) the degree of lipid solubility. Fetal/ maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding, because only the free, unbound drug is available for placental transfer. MARCAINE with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4). The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid soluble, nonionized drugs readily enter the fetal blood from the maternal circulation. Depending upon the route of administration, local anesthetics are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain.

Pharmacokinetic studies on the plasma profile of MARCAINE after direct intravenous injection suggest a three-compartment open model. The first compartment is represented by the rapid intravascular distribution of the drug. The second compartment represents the equilibration of the drug throughout the highly perfused organs such as the brain, myocardium, lungs, kidneys, and liver. The third compartment represents an equilibration of the drug with poorly perfused tissues, such as muscle and fat. The elimination of drug from tissue distribution depends largely upon the ability of binding sites in the circulation to carry it to the liver where it is metabolized.

After injection of MARCAINE for caudal, epidural, or peripheral nerve block in man, peak levels of bupivacaine in the blood are reached in 30 to 45 minutes, followed by a decline to insignificant levels during the next three to six hours.

(b) (4)

The half-life of MARCAINE in adults is 2.7 hours (b) (4)

(b) (4)

Elderly patients also exhibited higher peak plasma concentrations following administration of this product. The total plasma clearance was decreased in these patients.

Amide-type local anesthetics such as MARCAINE are metabolized primarily in the liver via conjugation with glucuronic acid. Patients with hepatic disease, especially those with

severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics. Pipecoloxylidine is the major metabolite of MARCAINE.

The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Only 6% of bupivacaine is excreted unchanged in the urine.

(b) (4)

Additionally, the literature information (Clinical Pharmacology Online) indicates that:

- Bupivacaine is excreted renally; approximately 6% is excreted as unchanged drug
- Bupivacaine half-life is 3.5 +/- 2 hours in adults
- Metabolism is primarily in the liver via conjugation
  - Formation of major metabolite pipecolylxylidine appears to be mediated by the CYP3A subfamily (N-dealkylation) - a cDNA expressed form of human CYP3A4 catalyzed the biotransformation of bupivacaine into pipecolylxylidine; however, formation of pipecolylxylidine by N-dealkylation of bupivacaine does not appear to account for a large percentage of the drug's metabolism, and the clinical significance of concurrent use of CYP3A4 inhibitors and bupivacaine is unknown.
  - CYP2C19 and CYP2D6 may also metabolized bupivacaine into pipecolylxylidine slightly
  - Major metabolite pipecoloxylidine is hydroxylated followed by glucuronidation.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical and clinical pharmacology information, e.g., dose-systemic exposure relationships, provide pivotal or supportive evidence of effectiveness?

Xaracoll is a locally administered drug and exerts its action locally, thus, bupivacaine systemic exposure cannot be linked to its efficacy directly.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant conducted two Phase 3 studies in the US in adults with a planned unilateral inguinal hernioplasty, a model of soft tissue surgery (INN-CB-014 [n=305] and INN-CB-016 [n=319]). The primary efficacy variable in both Phase 3 studies was the time-weighted sum of pain intensity from Time 0 through 24 hours (SPI24) after implantation. The key secondary efficacy endpoints included Total use of opioid analgesia from Time 0 through 24 hours (TOpA24), Sum of pain intensity from Time 0 to 48 hours (SPI48), Total use of opioid analgesia from Time 0 through 48 hours (TOpA48), Sum of pain intensity from Time 0 to 72 hours (SPI72), and, Total use of opioid analgesia from Time 0 through 72 hours (TOpA72). The

reader is referred to clinical review conducted by Drs. R. Petit-Scott and Y. Ren, medical and statistical reviewers, respectively.

The Applicant reported that Xaracoll had statistically significantly less pain over 24 hours ($p=0.0004$ and $p<0.0001$, respectively) after local placement of study treatment, as measured by SPI24 (i.e., primary endpoint) (Table 5).

Table 5 Sequential Testing Results for the Primary and Key Secondary Efficacy Endpoints in Studies INN-CB-014 and INN-CB-016 Side-by-Side and Combined

		INN-CB-014		INN-CB-016		Combined Analysis[a]	
Endpoint	Order/ Parameter	Observed p-value	Significance Based on the Sequential Testing Algorithm	Observed p-value	Significance Based on the Sequential Testing Algorithm	Observed p-value	Significance Based on the Sequential Testing Algorithm
Primary	SPI24	0.0004	*	<0.0001	*	<0.0001	*
Key secondary	TOpA24	<0.0001	*	<0.0001	*	<0.0001	*
	SPI48	0.0568	NS	0.0270	*	0.0033	*
	TOpA48	0.0248	NS	0.0003	*	<0.0001	*
	SPI72	0.1737	NS	0.1490	NS	0.0441	*
	TOpA72	0.0655	NS	0.0016	NS	0.0004	*

Data source: INN-CB-014 CSR Table 14.2.1.2 and Table 14.2.2.2A; INN-CB-016 CSR Table 14.2.1.2 and Table 14.2.2.2A; ISE Table 14.2.1.2 and Table 14.2.2.2.
a Data from studies INN-CB-014 and INN-CB-016 combined.
SPI: individual study p-values from an ANOVA model with treatment, gender, and history of previous ipsilateral hernia repair as main effects.
SPI: combined p-values from an ANOVA model with treatment, study, gender, and history of previous ipsilateral hernia repair as main effects.
TOpA: p-values from a Wilcoxon Rank sum test.
*=statistical significance based on sequential testing algorithm.

3.3.3 What are the characteristics of the dose-systemic exposure relationships for safety observed in the pharmacokinetic study?

No dose-systemic bupivacaine exposure relationship was analyzed in the pharmacokinetic study INN-CB-022. Based on the safety information provided by the Applicant in study INN-CB-022, the incidences of treatment-emergent adverse events (TEAE) or drug-related adverse events were similar between Xaracoll and the reference product, Marcaine.

Overall, the Applicant reported that 48 (96.0%) subjects had a TEAE, of which 8 (16.0%) subjects had a drug-related TEAE. No subject was discontinued due to a TEAE. In the INL-001 treatment group, 33 (97.1%) subjects had a TEAE, of which 6 (17.6%) subjects had a drug-related TEAE. In the Marcaine 0.25% treatment group, 15 (93.8%) subjects had a TEAE, of which 2 (12.5%) subjects had a drug-related TEAE. The Applicant stated that all TEAEs were considered to be mild or moderate in intensity.

The most common TEAEs that were experienced by >15% of subjects were somnolence (19 [55.9%] subjects), dizziness (12 [35.3%] subjects), constipation (8 [23.5%] subjects), vision blurred (8 [23.5%] subjects), tremor (6 [17.6%] subjects), and restlessness (6 [17.6%] subjects). For the Marcaine treatment group, 15 (93.8%) subjects experienced a TEAE. The most common TEAEs that were experienced by >15% of subjects were somnolence (10 [62.5%] subjects), dizziness (7 [43.8%] subjects), dysgeusia (4 [25.0%] subjects), tremor (3 [18.8%] subjects), and vision blurred (3 [18.8%] subjects).

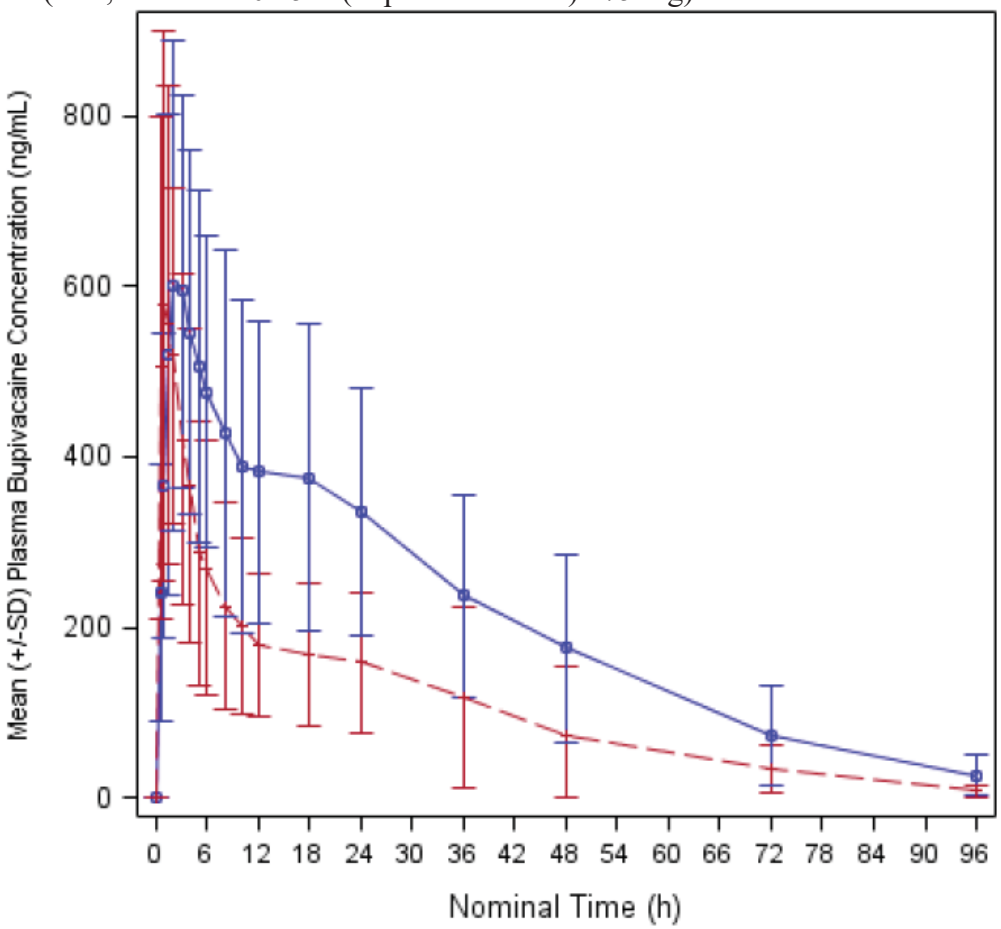
Regard to drug-related adverse events, the Applicant reported that for the INL-001 treatment group, 6 (17.6%) subjects experienced a drug-related TEAE. The drug-related TEAEs included tremor (3 [8.8%] subjects), dysgeusia (2 [5.9%] subjects), and somnolence (2 [5.9%] subjects). Each of the following drug-related TEAE was experienced by 1 subject: dry mouth, hypoaesthesia oral, paresthesia oral, incision site inflammation, dizziness, and restlessness. For the Marcaine treatment group, 2 (12.5%) subjects experienced a drug-related TEAE.

3.3.4 What is the single dose relative bioavailability pharmacokinetic information of Xaracoll?

Study INN-CB-022 was a multicenter, randomized, single-blind, active comparator-controlled study, conducted in patients undergoing open hernioplasty surgery. Prior to surgery on Day 1, subjects were randomized just prior to surgery (open hernioplasty according to standard procedures) in a 2:1 ratio to receive either 3x100 mg INL-001 bupivacaine HCl collagen-matrix implants (total bupivacaine HCl dose 300 mg) or Marcaine 0.25% (bupivacaine HCl) 175 mg infiltration. For INL-001 dosing, three 5 cm x 5 cm x 0.5 cm matrices (100 mg per matrix for a total of 300 mg) were cut in half for a total of 6 half-matrices each measuring approximately 2.5 cm x 5 cm x 0.5 cm in size. After the hernia sac was reduced and the mesh was ready for insertion, 3 half-matrices (150 mg bupivacaine HCl) were placed into the hernia repair site below the site of mesh placement. The mesh placement was completed per the surgeon's typical technique. The muscle/fascial layer was closed and the remaining 3 half-matrices (150 mg bupivacaine HCl) were placed between the fascia/muscle closure and the skin closure. The skin incision was to be closed in the usual fashion. For Marcaine 0.25% infiltration, 70 mL (a total of 175 mg of bupivacaine HCl) was administered according to standard practice or as follows. Approximately 25 mL (62.5 mg) was infiltrated into the muscular planes (transverse abdominis and interior oblique muscles), and, approximately 45 mL (112.5 mg) was infiltrated into the surrounding subcutaneous tissues. Blood samples were collected for bupivacaine analysis at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 36, 48, 72, and 96 h post dosing. Blood samples were analyzed using a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) methods for bupivacaine in human plasma (bupivacaine concentration range: 1.00 - 1000 ng/mL; lower limit of detection (LLOQ): 1.0 ng/mL).

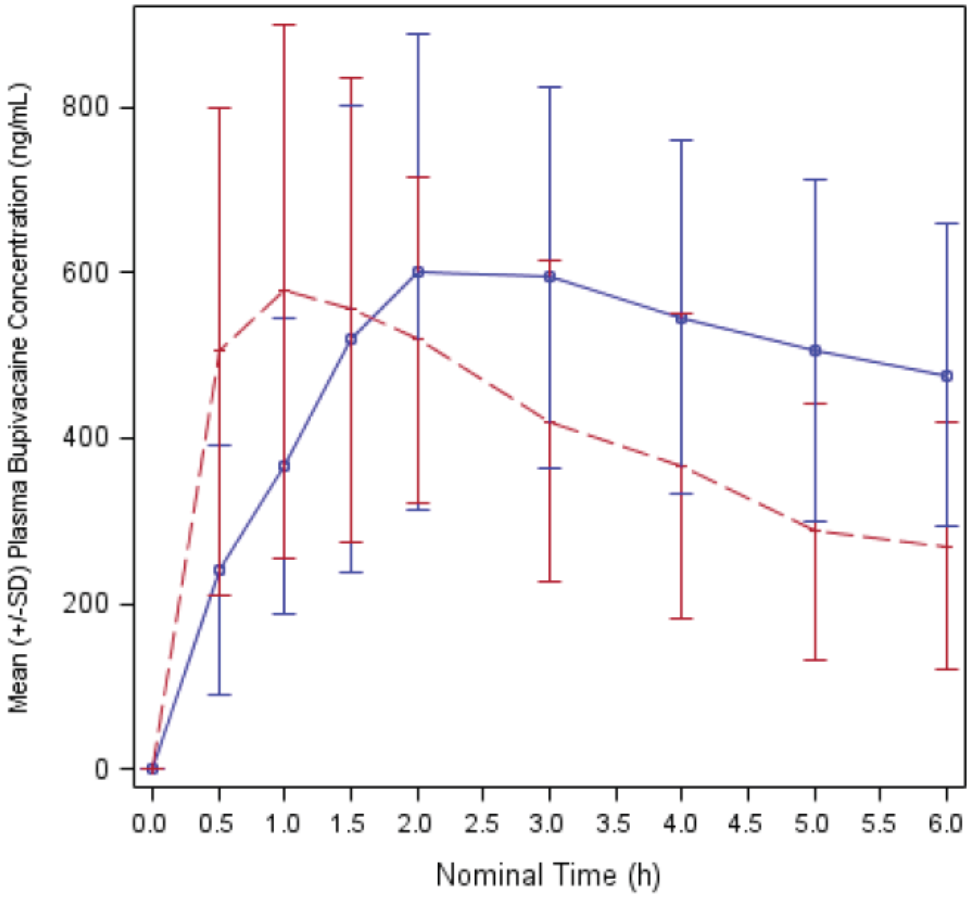
Figure 2 displays the mean ±SD plasma bupivacaine concentrations by treatment on linear scale for the PK Population. Figure 3 displays the mean bupivacaine HCl plasma concentrations for the first 6 h.

Figure 2 Mean (±SD) Plasma Bupivacaine Concentrations by Treatment (linear scale) – PK Population. Treatment A (blue; INL-001 bupivacaine HCl collagen-matrix implant, 300 mg) and Treatment B (Red; Marcaine 0.25% (bupivacaine HCl) 175 mg)



Note: If the actual sampling time (measured from dosing) was outside of the collection window for nominal time points, the corresponding concentration was excluded from concentration vs. time descriptive summaries and plots but was still used in the calculation of PK parameters.
A = INL-001 bupivacaine HCl collagen-matrix implant (300 mg); B = Marcaine 0.25% (bupivacaine HCl) 175 mg.
LLOQ for bupivacaine = 1 ng/mL.
Source: Post-text Figure 14.2.1.1a

Figure 3 Mean (±SD) Plasma Bupivacaine Concentrations by Treatment (linear scale) – PK Population (0-6 hours). Treatment A (blue; INL-001 bupivacaine HCl collagen-matrix implant, 300 mg) and Treatment B (Red; Marcaine 0.25% (bupivacaine HCl) 175 mg)



Note: If the actual sampling time (measured from dosing) was outside of the collection window for nominal time points, the corresponding concentration was excluded from concentration vs. time descriptive summaries and plots but was still used in the calculation of PK parameters.
A = INL-001 bupivacaine HCl collagen-matrix implant (300 mg); B = Marcaine 0.25% (bupivacaine HCl) 175 mg.
LLOQ for bupivacaine = 1 ng/mL.
Source: Post-text Figure 14.2.1.1b

Bupivacaine concentrations were observed at the first-time point measured (0.5 hours) for all subjects treated with INL-001 and Marcaine 0.25%. Bupivacaine concentrations were detectable through 96 hours in both treatment groups. Bupivacaine concentrations were lower during the initial 1.5 hours in the INL-001 (bupivacaine HCl 300 mg) treatment group, and, was higher after that time period in comparison with the Marcaine 0.25% (bupivacaine HCl 175 mg) treatment group.

Table 6 summarizes the plasma bupivacaine PK parameters by treatment for the Per-Protocol PK Population.

Table 6 Summary of Mean (SD) Plasma Bupivacaine PK Parameters by Treatment – Per-Protocol PK Population

PK parameters	n	INL-001 (300 mg)	n	Marcaine 0.25% (175 mg)
Cmax (ng/mL)	34	663.41 (263.83)	16	641.00 (262.68)
Tmax (h)*	34	3.03 (1.48, 24.02)	16	1.01 (0.53, 3.97)
AUC0-last (h*ng/mL)	34	19492.9 (7564.17)	16	9708.2 (4480.36)
AUC0-inf (h*ng/mL)	34	20368.4 (7911.94)	16	9814.8 (4569.74)
AUC extrapolated (h*ng/mL)	34	4.27 (3.59)	16	0.93 (0.743)
CL/F (L/h)	34	16.85 (7.6, 31.4)	16	22.29 (9.7, 34.6)
Vz/F (L)	34	472.28 (282.46)	16	256.08 (116.74)
tlag (h)	34	0.51 (0.13)	16	0.47 (0.13)
λz (1/h)	34	0.04 (0.01)	16	0.09 (0.04)
T1/2(h)	34	18.95 (5.95)	16	9.08 (3.75)

Note: * median (min-max)

Observed bupivacaine Cmax values were similar (663.41 ng/mL vs. 641.00 ng/mL, Treatment A, INL-001 and Treatment B, Marcaine 0.25%, respectively) between Treatment A, INL-001 (bupivacaine HCl 300 mg) compared to Treatment B, Marcaine 0.25% (bupivacaine HCl 175 mg). Observed AUC0-inf values were approximately 2-fold higher (20368.4 h*ng/mL vs. 9814.8 h*ng/mL, Treatment A, INL-001 and Treatment B, Marcaine 0.25%, respectively) for Treatment A, INL-001 (bupivacaine HCl 300 mg) compared to Treatment B, Marcaine 0.25% (bupivacaine HCl 175 mg).

Table 7 summarizes the ANOVA analysis results for the dose-normalized relative bioavailability of bupivacaine between Treatment A, INL-001 (bupivacaine HCl 300 mg) and Treatment B, Marcaine 0.25% (bupivacaine HCl 175 mg).

Table 7 Relative Bioavailability Analysis of dose-normalized Plasma Bupivacaine PK Parameters: ANOVA Model – Per-Protocol PK Population

PK parameters	INL-001 300 mg (A)		Marcaine 0.25% 175 mg (B)		Ratio of Geometric mean (A/B) %	90% CI for Ratio %	Intra-subj. CV %
	n	Geometric mean1	n	Geometric mean1			
C_{max} (ng/[mL*mg])	34	2.0	16	3.4	60.34	48.81, 74.59	43.6
$AUC_{0\text{-last}}$ (h*ng/[mL*mg])	34	60.6	16	50.5	120.05	98.07, 146.97	41.4
$AUC_{0\text{-inf}}$ (h*ng/[mL*mg])	34	63.4	16	51.0	124.33	101.60, 152.16	41.3

Note: Note: An ANOVA model was performed on logarithm-transformed dose-normalized PK parameters.
Time 0 was defined as the time when the first INL-001 bupivacaine HCl collagen matrix was implanted or the time of Marcaine 0.25% infiltration.
1. Geometric LS means were the LS means from the mixed model presented after back transformation to the original scale.
2. The 90% CIs were presented after back transformation to the original scale.
3. Intra-subject CV (%) is calculated as 100*SQRT(EXP(SIGMA2)-1), where SIGMA2 is the residual variance estimate from PROC MIXED.

The dose-normalized point estimates of the INL-001 (bupivacaine HCl 300 mg) treatment group compared to the Marcaine 0.25% (bupivacaine HCl 175 mg) treatment group for Cmax, AUC0-last, and AUC0-∞ with 90% CI were 60.34% (48.81%, 74.59%), 120.05% (98.07%, 146.97%), and 124.33% (101.60%, 152.16%), respectively.

3.3.5 What are alternative dosing regimen and/or management strategy required for subpopulations?

No dedicated Xaracoll pharmacokinetic studies were conducted to evaluate the bupivacaine pharmacokinetics in special populations such as geriatric patients, hepatic and renal impairments. According to the reference product, Marcaine, the following descriptions are provided with respect to hepatic, renal and geriatric populations:

> Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of hepatic or renal disease, addition of epinephrine, factors affecting urinary pH, renal blood flow, the route of drug administration, and the age of the patient.
>
> Geriatric:
> In clinical studies, elderly patients reached the maximal spread of analgesia and maximal motor blockade more rapidly than younger patients. Elderly patients also exhibited higher peak plasma concentrations following administration of this product. The total plasma clearance was decreased in these patients.
>
> Hepatic:
> Amide-type local anesthetics such as MARCAINE are metabolized primarily in the liver via conjugation with glucuronic acid. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics. Pipecoloxylidine is the major metabolite of MARCAINE.
>
> Renal:
> The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Only 6% of bupivacaine is excreted unchanged in the urine.
> When administered in recommended doses and concentrations, MARCAINE does not ordinarily produce irritation or tissue damage and does not cause methemoglobinemia.

3.3.6 Are there any potential drug interactions for Xaracoll with other drugs?

No dedicated Xaracoll pharmacokinetic studies were conducted to evaluate drug interactions.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Pharmacokinetic (PK) samples were analyzed using a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) methods for bupivacaine in human plasma.
The following bupivacaine concentration ranges were used (Report No. RPT17261 for Study No. INN-CB-022): Bupivacaine: 1.00 - 1000 ng/mL [lower limit of detection (LLOQ): 1.0 ng/mL]. Quality control (QC) samples for bupivacaine analyzed on the given specific analyses days were 3.0, 30.0, and 800.0 ng/mL, for Study INN-CB-022. There were 898 primary and 793 backup plasma samples from Study No. INN-CB-022. Overall coefficient of variation (precision) was ≤ 5.8% for bupivacaine low-, mid- and high- QC samples (4.7, 4.5, and 5.8, respectively). The overall Bias% (accuracy) was ≤ 6.0% for bupivacaine for bupivacaine low-, mid- and high- QC samples (5.3, 6.0, and 5.6, respectively). The 10-fold dilution QC samples showed the overall CV of 4.8% and the overall Bias% of 5.8%. The analytical information provided by the Applicant is acceptable and there is no further information needed regarding bioanalytical information.

4.2 Summary of Study INN-CB-022

Title: A Randomized, Single Blind Study to Investigate the Pharmacokinetics, Relative Bioavailability, and Safety of INL-001 Bupivacaine Hydrochloride (HCl) Collagen-Matrix Implant 300 mg Compared to MarcaineTM 0.25% (Bupivacaine HCl) 175 mg Infiltration After Open Hernioplasty

Investigational Product: INL-001 (bupivacaine HCl collagen-matrix implant)
Indication Studied: Postsurgical analgesia following (b) (4)
Initiation Date: 02 June 2017; Completion Date: 15 August 2017

Primary objectives: □ Pharmacokinetic (PK) profile of the INL-001 bupivacaine HCl collagen-matrix implant 300 mg during and after open hernioplasty, and □ Relative bioavailability of the INL-001 bupivacaine HCl collagen-matrix implant 300 mg compared to Marcaine 0.25% (bupivacaine HCl) 175 mg infiltration.

Secondary objectives: To assess the safety and tolerability of the INL-001 bupivacaine HCl collagen-matrix implant after placement in the surgical site during open hernioplasty, with particular emphasis on signs and symptoms of bupivacaine toxicity.

Methodology:
Study INN-CB-022 was a multicenter, randomized, single-blind, active comparator-controlled study. Prior to surgery on Day 1, subjects were randomized just prior to surgery (open hernioplasty according to standard procedures) in a 2:1 ratio to receive either 3x100 mg INL-001 bupivacaine HCl collagen-matrix implants (total bupivacaine HCl dose 300 mg) or Marcaine 0.25% (bupivacaine HCl) 175 mg infiltration.

For INL-001 dosing, three 5 cm x 5 cm x 0.5 cm matrices (100 mg per matrix for a total of 300 mg) were cut in half for a total of 6 half-matrices each measuring approximately 2.5 cm x 5 cm x 0.5 cm in size. After the hernia sac was reduced and the mesh was ready for insertion, 3 half-matrices (150 mg bupivacaine HCl) were placed into the hernia repair site below the site of mesh placement. The mesh placement was completed per the surgeon's typical technique. The muscle/fascial layer was closed and the remaining 3 half-matrices (150 mg bupivacaine HCl) were placed between the fascia/muscle closure and the skin closure. The skin incision was to be closed in the usual fashion.

For Marcaine 0.25% infiltration, 70 mL (a total of 175 mg of bupivacaine HCl) was administered according to standard practice or as follows. Approximately 25 mL (62.5 mg) was infiltrated into the muscular planes (transverse abdominis and interior oblique muscles), and, approximately 45 mL (112.5 mg) was infiltrated into the surrounding subcutaneous tissues.

Following surgery, subjects (in a post-anesthesia care unit (PACU)) may receive as needed rescue medication, parenteral morphine (15 mg), for breakthrough pain. Subjects were switched over to acetaminophen 650 mg TID (if they can tolerate oral medication) for as long as clinically required, and, were administered morphine.

Subjects remained in the clinic until at least after the PK 72-h blood sample (Day 4). Subjects returned to the clinic for the PK 96-h sample (Day 5). Follow-up safety assessments included clinic visits on Day 7, Day 15, and Day 30.

Pharmacokinetic blood samples were collected at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 36, 48, 72, and 96 h post dosing. Safety assessments included vital signs through 72 h, continuous ECG monitoring for at least 24 h, oxygen saturation levels, and adverse events reporting with emphasis on the signs and symptoms of potential CNS and cardiovascular bupivacaine toxicity. The surgical wound was assessed for signs and symptoms associated with altered wound healing.

<u>Restricted or prohibited medications before and during surgery</u>
Treatment with the following medications before study entry or during surgery was restricted or prohibited as follows: All analgesics except acetaminophen were prohibited within 24 h of surgery. Acetaminophen may have been used the day of surgery but was subject to preoperative restrictions for oral intake; A preoperative dose of an antiemetic for nausea prophylaxis was allowed, but antiemetic medications were only to be given postoperatively to treat actual reports of nausea; Aspirin or aspirin-containing products were prohibited within 7 days of surgery. Aspirin at a dose of ≤325 mg was allowed for cardiovascular prophylaxis if the subject had been on a stable dose regimen for at least 21 days before Day 1; The use of any investigational product within 30 days of surgery was prohibited; Any anesthetics (except for propofol, midazolam, and short acting agents), including epidural or local infiltrations, were prohibited. Subjects who required the use of other anesthetics intraoperatively, including any local intravenous anesthetic to reduce the burning effect of the propofol infusion, were prohibited from receiving the test article; Doses of up to 100 mcg of fentanyl may have been utilized

intraoperatively. Other opioid analgesics were to be avoided pre- or intraoperatively; and Epidural anesthesia and local anesthetic infiltration were prohibited.

Table of assessments

	Screening	Inpatient				Outpatient			
	Day -21 to Day -1	Day 1 Surgical Procedure	Day 2 (24 h)	Day 3 (48 h)	Day 4 (72 h)	Day 5 (96 h)	Day 7 (± 1 day)	Day 15 (± 3 days)	Day 30 (± 3 days) EOS/Early Termination
Written informed consent	X								
Inclusion/exclusion	X	X[a]							
Medical history	X	X[a]							
Prior/concomitant medications/procedures	X	X	X	X	X	X	X	X	X
Physical examination including body weight and height	X								
Vital signs[b]	X	X	X	X	X	X	X	X	X
12-lead ECG	X								
Clinical laboratory testing	X								
Serum pregnancy testing	X								
Urine pregnancy testing		X[c]							
Study drug administration		X							
Continuous 12-lead ECG monitoring[d]	X[h]	X	X						
Oxygen saturation levels[e]		X							
Pharmacokinetic sampling[f]		X	X	X	X	X			
Bupivacaine toxicity assessment[g]		X	X	X	X				
Surgical wound assessment		X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X

NOTE: Time 0 = the time when the first INL-001 bupivacaine HCl collagen-matrix was implanted or the time of Marcaine 0.25% infiltration. Time 0 was required to be recorded on the eCRF for all treated subjects.

a. Updated before surgery.
b. Blood pressure (systolic/diastolic), respiratory rate, heart rate, and body temperature were assessed. For detailed procedures, refer to Appendix 16.1.1 (Protocol, Section 5.12.7).
c. Testing was performed before surgery; surgery proceeded only if testing results were negative.
d. From the time of surgery through 24 hours or longer if indicated.
e. Before and for at least 12 hours after Time 0.
f. Before Time 0 and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 36, 48, 72, and 96 hours after Time 0.
g. At 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15, 18, 24, 36, 48, and 72 hours after Time 0, or more frequently if clinically indicated.
h. 24 hour baseline to be obtained prior to surgery and after the subject confirmed eligible within the Screening window.

ECG = electrocardiogram; eCRF = electronic case report form; EOS = end of study; HCl = hydrochloride.

Completed: 50 subjects

Inclusion Criteria:

1. Man or woman ≥18 years of age; 2. Was eligible for unilateral inguinal hernioplasty with mesh (open laparotomy, tension-free technique) performed according to standard surgical technique under general anesthesia. Repair of multiple hernias through a single incision was permitted; 3. Female subjects of childbearing potential must have had a negative pregnancy test at Screening and before randomization on Day 1, AND have been using an effective contraception method (i.e., abstinence, intrauterine device, hormonal [estrogen/progestin] contraceptives, or barrier control) for at least 1 menstrual cycle prior to study enrollment and for the duration of the study, OR have been surgically sterile, OR have been a postmenopausal female (no menses for at least 1 year or hysterectomy); 4. Had the ability and willingness to comply with the study procedures; 5. Was willing to use only permitted medications throughout the study; 6. Was willing to use opioid analgesia; and 7. Was able to fluently speak and understand either English or Spanish and was able to provide meaningful written informed consent for the study.

Exclusion Criteria:
1. Had a known hypersensitivity to amide local anesthetics, morphine, acetaminophen, or bovine products; 2. Was scheduled for bilateral inguinal hernioplasty or other significant concomitant surgical procedure; 3. Had undergone major surgery within 3 months of the scheduled hernioplasty or planned to undergo another laparotomy procedure within the 30-day postoperative period; 4. Had known or suspected history of alcohol or drug abuse or misuse within 3 years of Screening or evidence of tolerance or physical dependency on opioid analgesics or sedative-hypnotic medications;
5. Had any clinically significant unstable cardiac, neurological, immunological, renal, hepatic or hematological disease or any other condition that, in the opinion of the Investigator, could have compromised the subject's welfare, ability to communicate with the study staff, or otherwise contraindicate study participation;
6. Had venous access difficulties that may have precluded the frequent PK sampling requirements of the study; or 7. Had participated in a clinical trial (investigational or marketed product) within 30 days of surgery.

Treatments:

Study drug	Administration	Lot number
INL-001 bupivacaine HCl collagen-matrix implant[1]	Implantation	15041002
Marcaine 0.25% (bupivacaine HCl) infiltration[2]	Infiltration	73355DD and 68375DD

[1]Approx. 5 cm × 5 cm × 0.5 cm off-white to white, porous matrix that contains 100 mg of bupivacaine HCl in a (b) (4) matrix of Type I collagen
[2]Marcaine 0.25% contains 2.5 mg of bupivacaine HCl/mL

PK parameters assessed: Cmax, Tmax, tlag, t1/2, λz, AUC0-last, AUC0-∞ and AUCextrap%, apparent plasma clearance, and apparent volume of distribution.

Safety endpoints: Clinical laboratory assessments (Screening only); ECG (Screening and continuous ECG monitoring for at least 24 hours pre-surgery during the Screening period and 24 hours post-administration of study drug); Oxygen saturation levels; Vital signs (blood pressure, heart rate, respiratory rate, and body temperature); Adverse events; and Special signs and symptoms associated with potential bupivacaine toxicity and wound healing [(as applicable) at the following time points after Time 0 (or more frequently if needed): 0.5, 1 , 2 , 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 hours ±15 minutes and then 15, 18, 24, 36, 48, and 72 hours (±1 hour)].

Statistical Methods:
No formal sample size calculations were performed for this study. However, it was expected that 48 subjects (32 in the INL-001 group and 16 in the Marcaine 0.25% group) were sufficient to evaluate PK, estimate relative bioavailability, and adequately assess safety with respect to bupivacaine plasma concentrations.

Pharmacokinetics

PK parameters were obtained using non-compartmental analysis with Phoenix WinNonlin version 6.4. The linear trapezoidal method was used in the computation of AUC. The relative bioavailability (AUC0-last, AUC0-∞, and Cmax) of the INL-001 bupivacaine collagen-matrix implant (300 mg) was calculated with respect to the Marcaine 0.25% (175 mg) infiltration using an analysis of variance (ANOVA) model with a term for treatment. The ANOVA model was run on the dose-normalized natural logarithm transformed values. The least-squares means and the standard error values from the analyses were used to construct the 90% confidence intervals (CIs) for the relative bioavailability evaluations.

Analysis

All concentrations below the lower limit of quantification (LLOQ) were set to 0 for the purpose of calculating descriptive statistics. For the purpose of determining λz and calculating AUC and AUC-related PK parameters (apparent plasma clearance [CL/F] and apparent volume of distribution [Vz/F]), when 2 consecutive plasma concentrations below the LLOQ were encountered after Tmax, all subsequent values were excluded from the analysis. When embedded missing values occurred, they were excluded from the analysis. Quantifiable concentrations at pre-dose (>LLOQ), if any, were set to 0.

Summary of Results:

Table 4 summarizes demographic and baseline characteristics by treatment for the Safety Population.

Table 4. Demographic and Baseline Characteristics by Treatment – Safety Population

Demographic/Baseline Characteristic Category/Statistic	INL-001 (300 mg) n (%)	Marcaine 0.25% (175 mg) n (%)	Overall (N = 50)
Age at informed consent (years)			
n	34	16	50
Mean (SD)	45.6 (14.84)	41.6 (12.18)	44.3 (14.04)
Gender (n, %)			
Male	33 (97.1)	16 (100.0)	49 (98.0)
Female	1 (2.9)	0 (0.0)	1 (2.0)
Race (n, %)			
White	31 (91.2)	15 (93.8)	46 (92.0)
Black or African American	3 (8.8)	0 (0.0)	3 (6.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (6.3)	1 (2.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity (n, %)			
Hispanic or Latino	7 (20.6)	3 (18.8)	10 (20.0)
Not Hispanic or Latino	27 (79.4)	13 (81.3)	40 (80.0)
Height at Screening (cm)			
n	34	16	50
Mean (SD)	176.4 (8.62)	177.8 (7.29)	176.8 (8.17)
Body weight at Screening (kg)			
n	34	16	50
Mean (SD)	85.31 (16.375)	87.86 (16.227)	86.13 (16.206)
Baseline BMI (kg/m2)			
n	34	16	50
Mean (SD)	27.44 (5.008)	27.79 (4.859)	27.55 (4.914)

Note: Percentages were calculated using the number of subjects in the column heading as the denominator. Baseline was defined as the measurement at Screening.
BMI = body mass index; SD = standard deviation.
Source: Post-text Table 14.1.2.1

Concomitant Medications

In the INL-001 treatment group, all 34 (100.0%) subjects used concomitant medications during the study. The most commonly used concomitant medications (taken by >10% of subjects) by Anatomical Therapeutic Chemical (ATC) class and Preferred term (PT) were paracetamol (34 [100.0%] subjects), morphine (18 [52.9%] subjects), tramadol (9 [26.5%] subjects), ibuprofen (7 [20.6%] subjects), vicodin (5 [14.7%] subjects), and multivitamins plain (4 [11.8%] subjects).
In the Marcaine 0.25% treatment group, all 16 (100.0%) subjects used concomitant medications during the study. The most commonly used concomitant medications (taken by >10% of subjects) by ATC class and PT were paracetamol (16 [100.0%] subjects), morphine (9 [56.3%] subjects), ibuprofen (3 [18.8%] subjects), tramadol (2 [12.5%] subjects), and lisinopril (2 [12.5%] subjects).

Prior Medical Procedures/Non-drug Therapies

No subjects had any prior medical procedures/non-drug therapies.

Concomitant Medical Procedures/Non-Drug Therapies

In the INL-001 treatment group, 4 (11.8%) subjects received at least 1 concomitant medical procedure/non-drug therapy during the study. In the Marcaine 0.25% treatment group, 3 (18.8%) subjects received at least 1 concomitant medical procedure/non-drug therapy during the study.

Table 5. Number of Subjects with Concomitant Medical Procedures/Non-Drug Therapies by System Organ Class and Preferred Term – Safety Population

System Organ Class Preferred Term	INN-001 (300 mg) N = 34 n (%)	Marcaine (175 mg) N = 16 n (%)
Subjects with any concomitant medical procedure/non-drug therapies	4 (11.8)	3 (18.8)
Investigations	3 (8.8)	1 (6.3)
Body temperature	0 (0.0)	1 (6.3)
Chest x-ray	1 (2.9)	0 (0.0)
Electrocardiogram	2 (5.9)	1 (6.3)
Surgical and medical procedures	2 (5.9)	2 (12.5)
Bladder catheterization	1 (2.9)	0 (0.0)
Hydrotherapy	1 (2.9)	0 (0.0)
Localized cooling therapy	1 (2.9)	2 (12.5)
Nutritional supplementation	1 (2.9)	0 (0.0)

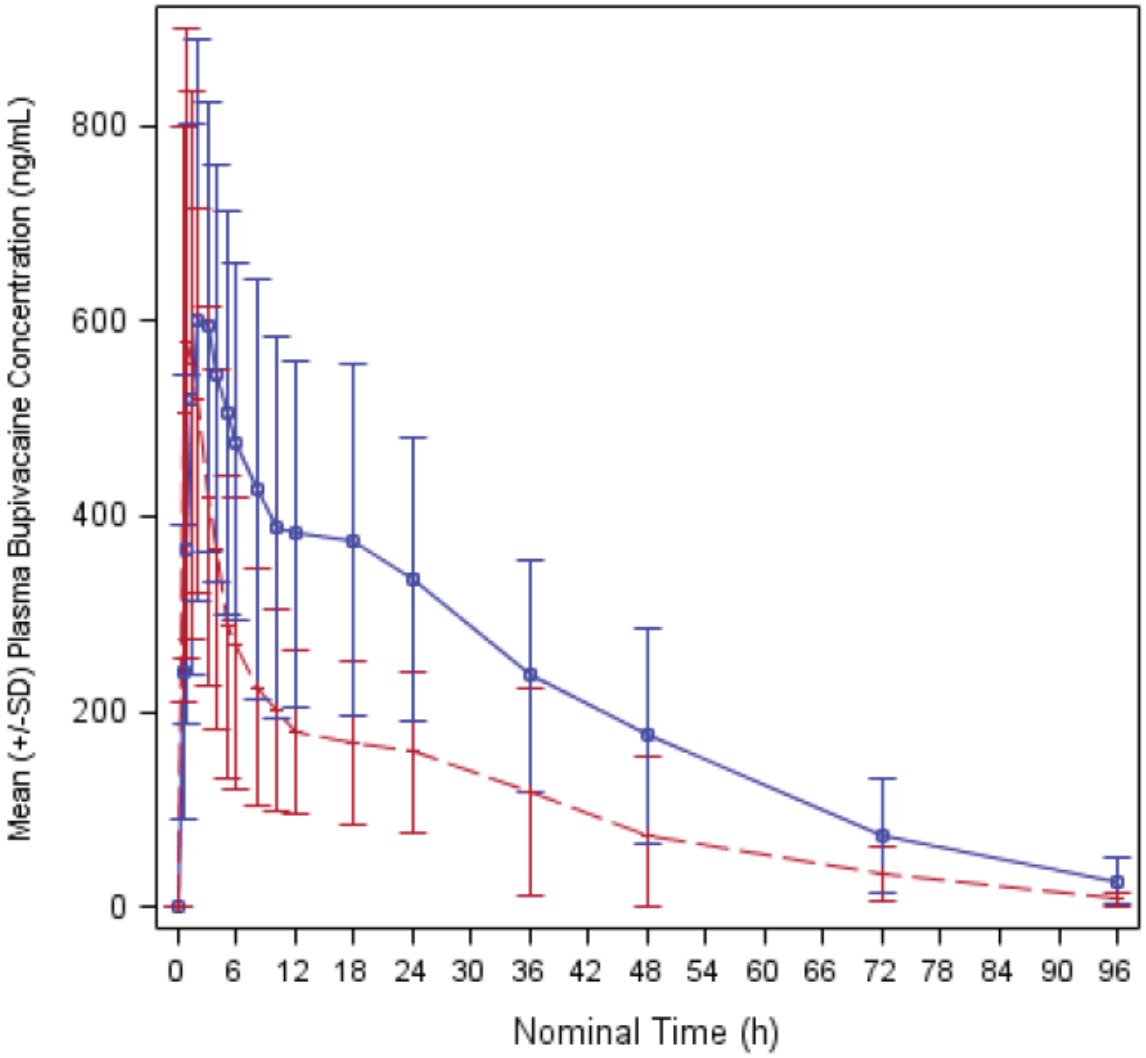
Note: Concomitant medical procedure/non-drug therapies were coded using the MedDRA 18.0.
MedDRA = Medical Dictionary for Regulatory Activities.
Source: Post-text Table 14.1.3.4

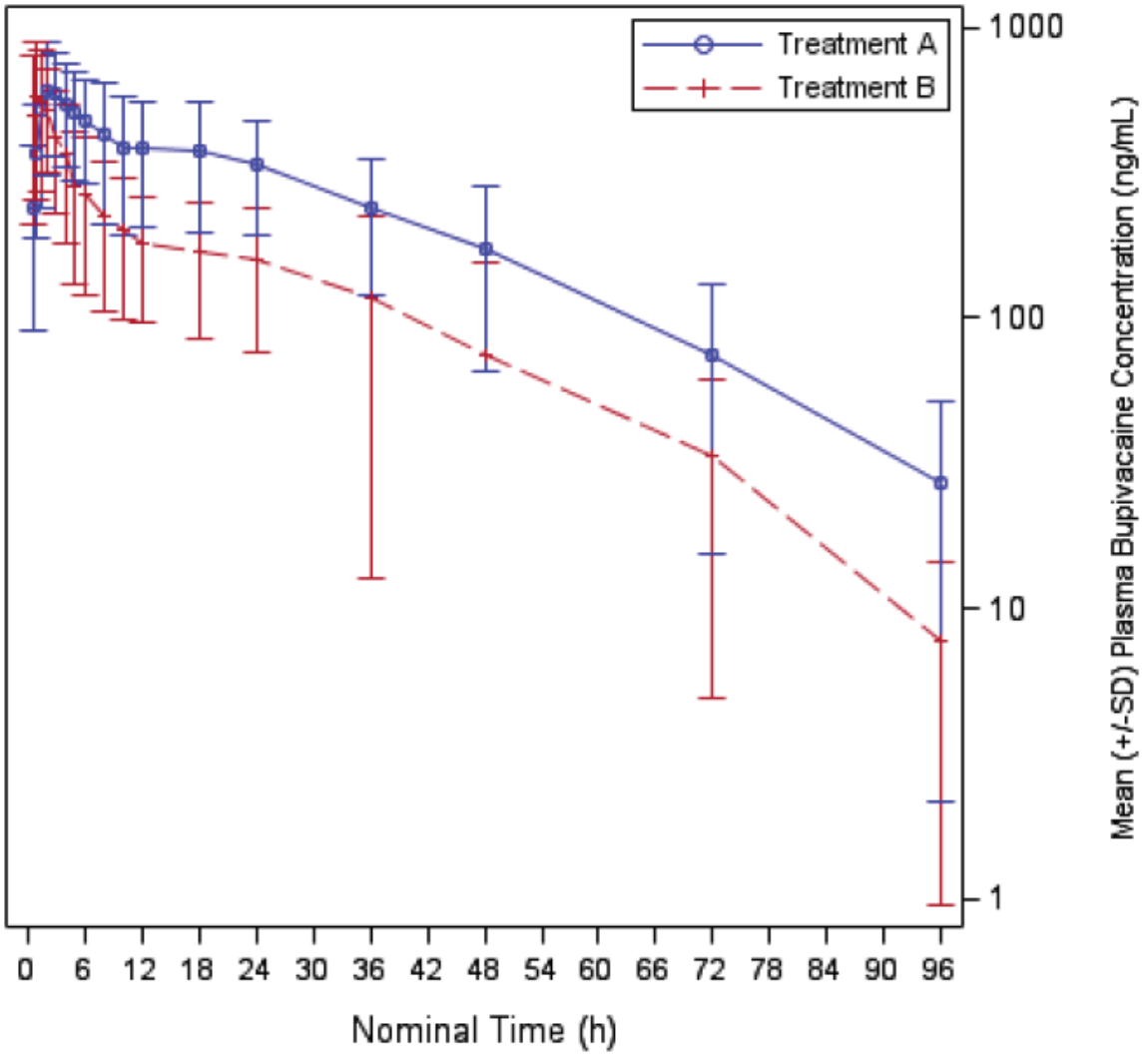
Pharmacokinetics

Figure 1 displays the mean ±SD plasma bupivacaine concentrations by treatment on linear and semi-logarithmic scale for the PK Population. Figure 2 displays that the mean bupivacaine HCl plasma concentrations were lower during the initial 1.5 hours in the INL-001 (bupivacaine HCl 300 mg) treatment group, and was higher after that time period in comparison with the Marcaine 0.25% (bupivacaine HCl 175 mg) treatment group.

Local placement of INL-001 within the surgical site resulted in detectable plasma levels of bupivacaine at the first measured time point (0.5 hours) and throughout the 96-hour observation period.

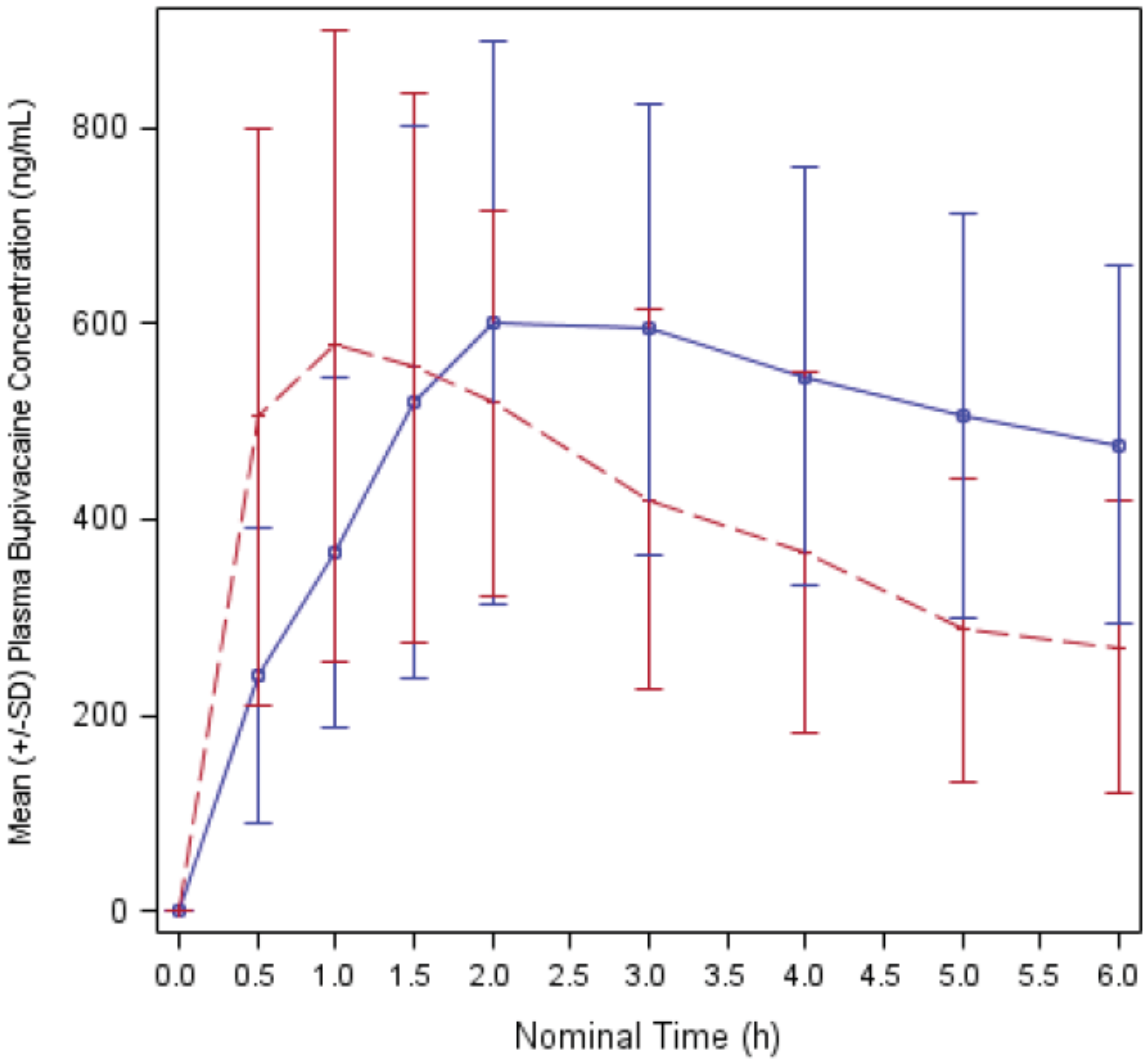
Figure 1. Mean (±SD) Plasma Bupivacaine Concentrations by Treatment on Linear Scale and Semi-Logarithmic Scale – PK Population

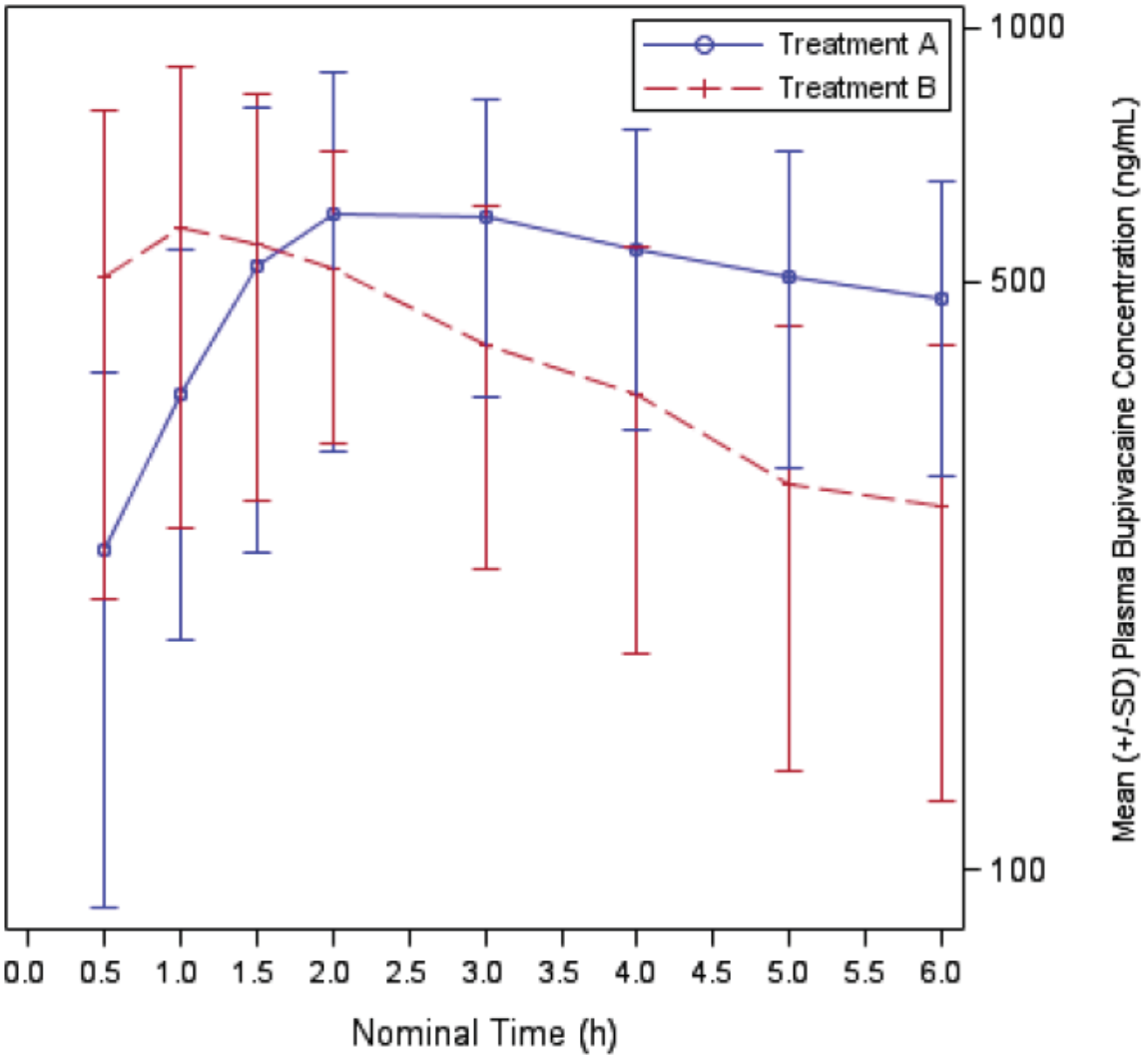




Note: If the actual sampling time (measured from dosing) was outside of the collection window for nominal time points, the corresponding concentration was excluded from concentration vs. time descriptive summaries and plots but was still used in the calculation of PK parameters.
A = INL-001 bupivacaine HCl collagen-matrix implant (300 mg); B = Marcaine 0.25% (bupivacaine HCl) 175 mg.
LLOQ for bupivacaine = 1 ng/mL.
Source: Post-text Figure 14.2.1.1a

Figure 2. Mean (±SD) Plasma Bupivacaine Concentrations by Treatment on Linear Scale and Semi-Logarithmic Scale – PK Population (0-6 hours)





Note: If the actual sampling time (measured from dosing) was outside of the collection window for nominal time points, the corresponding concentration was excluded from concentration vs. time descriptive summaries and plots but was still used in the calculation of PK parameters.
A = INL-001 bupivacaine HCl collagen-matrix implant (300 mg); B = Marcaine 0.25% (bupivacaine HCl) 175 mg.
LLOQ for bupivacaine = 1 ng/mL.
Source: Post-text Figure 14.2.1.1b

Table 6 summarizes the plasma bupivacaine PK parameters by treatment for the Per-Protocol PK Population.

Table 6. Summary of Mean (SD) Plasma Bupivacaine PK Parameters by Treatment – Per-Protocol PK Population

PK parameters	n	INL-001 (300 mg)	n	Marcaine 0.25% (175 mg)
Cmax (ng/mL)	34	663.412 (263.826)	16	641.000 (262.684)
Tmax (h)*	34	3.03 (1.48, 24.02)	16	1.01 (0.53, 3.97)
tlag (h)	34	0.51 (0.13)	16	0.47 (0.13)

λz (1/h)	34	0.04 (0.01)	16	0.09 (0.04)
T1/2(h)	34	18.95 (5.95)	16	9.08 (3.75)
AUC0-last (h*ng/mL)	34	19492.9 (7564.17)	16	9708.2 (4480.36)
AUC0-inf (h*ng/mL)	34	20368.4 (7911.94)	16	9814.8 (4569.74)
AUC extrapolated (h*ng/mL)	34	4.27 (3.59)	16	0.93 (0.743)
CL/F (L/h)	34	16.85 (7.6, 31.4)	16	22.29 (9.7, 34.6)
Vz/F (L)	34	472.28 (282.463)	16	256.08 (116.739)

Note: * median (min-max)

Table 8. Pharmacokinetic Parameters and Relative Bioavailability of INL-001 versus Marcaine 0.25% Infiltration in Subjects Undergoing Hernioplasty (Study INN-CB-022)

Parameter	INL-001 (bupivacaine HCl 300 mg)	Marcaine 0.25% Infiltration (bupivacaine HCl 175 mg)
C_{max} (ng/mL)		
N	34	16
Mean (SD)	663.412 (263.826)	641.000 (262.684)
Geometric mean (CV%)	611.893 (43.5)	591.562 (43.8)
Median	679.500	574.00
Min, Max	274.00, 1230.00	275.000, 1140.00
Relative BA (90% CI)	60.34% (48.81, 74.59)	NA
$AUC_{0\text{-last}}$ (h·ng/mL)		
N	34	16
Mean (SD)	19492.9 (7564.17)	9708.2 (4480.36)
Geometric mean (CV%)	18186.9 (39.0)	8836.9 (46.3)
Median	17961.0	7857.7
Min, Max	8548, 38110	5034, 17884
Relative BA (90% CI)	120.05% (98.07, 146.97)	NA
$AUC_{0\text{-}\infty}$ (h·ng/mL)		
N	34	16
Mean (SD)	20368.4 (7911.94)	9814.8 (4569.74)
Geometric mean (CV%)	19012.5 (38.7)	8920.1 (46.7)
Median	18250.6	7915.1
Min, Max	9547, 39335	5052, 18089
Relative BA (90% CI)	124.33% (101.60, 152.16)	NA
T_{max} (h)		
N	34	16
Mean (SD)	5.91 (6.46)	1.53 (0.90)
Median	3.03	1.01
Min, Max	1.48, 24.02	0.53, 3.97
$T_{1/2}$ (h)		
N	34	16
Mean (SD)	18.95 (5.95)	9.08 (3.75)
Median	18.40	8.23
Min, Max	8.81, 37.67	4.14, 14.52

Note: m2/27-summary-biopharm.pdf, p.23/28

Note: Subject (b) (6) had the highest Cmax value of 1230.00 ng/mL at 2 hours post-surgery, for plasma bupivacaine in the INL-001 treatment group. Subject (b) (6) had the highest Cmax value of 1140.00 ng/mL at 1-h post-surgery, for plasma bupivacaine in the Marcaine 0.25% treatment group.

There was immediate release and absorption of bupivacaine as evidenced by quantifiable bupivacaine concentrations at the first-time point measured (0.5 hours) for all subjects treated with INL-001 and Marcaine 0.25%. Bupivacaine concentrations were detectable through 96 hours in both treatment groups.

Simple table: Mean (SD) Cmax and AUCs

PK parameters	n	INL-001 (300 mg)	n	Marcaine 0.25% (175 mg)
Cmax (ng/mL)	34	663.41 (263.83)	16	641.00 (262.68)
Tmax (h)#	34	3.03 (1.48, 24.02)	16	1.01 (0.53, 3.97)
AUC0-last (h*ng/mL)	34	19492.9 (7564.17)	16	9708.2 (4480.36)
AUC0-inf (h*ng/mL)	34	20368.4 (7911.94)	16	9814.8 (4569.74)
T1/2(h)	34	18.95 (5.95)	16	9.08 (3.75)

#Tmax: Median (min, max)

Table 7 summarizes the ANOVA analysis results for the dose-normalized relative bioavailability of plasma bupivacaine for the Per-Protocol PK Population.

Table 7. Relative Bioavailability Analysis of dose-normalized Plasma Bupivacaine PK Parameters: ANOVA Model – Per-Protocol PK Population

PK parameters	INL-001 300 mg (A)		Marcaine 0.25% 175 mg (B)		Ratio of Geometric mean (A/B) %	90% CI for Ratio %	Intra-subj. CV %
	n	Geometric mean1	n	Geometric mean1			
C_{max} (ng/[mL*mg])	34	2.0	16	3.4	60.34	48.81, 74.59	43.6
$AUC_{0\text{-last}}$ (h*ng/[mL*mg])	34	60.6	16	50.5	120.05	98.07, 146.97	41.4
$AUC_{0\text{-}\square}$ (h*ng/[mL*mg])	34	63.4	16	51.0	124.33	101.60, 152.16	41.3

Note: Note: An ANOVA model was performed on logarithm-transformed dose-normalized PK parameters.
Time 0 was defined as the time when the first INL-001 bupivacaine HCl collagen matrix was implanted or the time of Marcaine 0.25% infiltration.
1. Geometric LS means were the LS means from the mixed model presented after back transformation to the original scale.
2. The 90% CIs were presented after back transformation to the original scale.

3. Intra-subject CV (%) is calculated as 100*SQRT(EXP(SIGMA2)-1), where SIGMA2 is the residual variance estimate from PROC MIXED.

The dose-normalized relative bioavailability of the INL-001 (bupivacaine HCl 300 mg) treatment group over the Marcaine 0.25% (bupivacaine HCl 175 mg) treatment group for Cmax, AUC0-last, and AUC0-∞ with 90% CI was 60.34% (48.81%, 74.59%), 120.05% (98.07%, 146.97%), and 124.33% (101.60%, 152.16%), respectively.

Safety

Overall, the Applicant reported that 48 (96.0%) subjects had a treatment-emergent adverse events (TEAE), of which 8 (16.0%) subjects had a drug-related TEAE. No subject was discontinued due to a TEAE. In the INL-001 treatment group, 33 (97.1%) subjects had a TEAE, of which 6 (17.6%) subjects had a drug-related TEAE. In the Marcaine 0.25% treatment group, 15 (93.8%) subjects had a TEAE, of which 2 (12.5%) subjects had a drug-related TEAE. All TEAEs were considered to be mild or moderate in intensity. Table 8 and 9 provides an overview of TEAEs by treatment for the Safety Population.

Table 8. Overview of Treatment-Emergent Adverse Events – Safety Population

Category	INL-001 (300 mg) (N = 34) n (%)	Marcaine 0.25% (175 mg) (N = 16) n (%)	Overall (N = 50) n (%)
Subjects with any TEAE	33 (97.1)	15 (93.8)	48 (96.0)
Subjects with any TEAE by maximum severity			
Mild	26 (76.5)	11 (68.8)	37 (74.0)
Moderate	7 (20.6)	4 (25.0)	11 (22.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with any drug-related TEAE	6 (17.6)	2 (12.5)	8 (16.0)
Subjects with any drug-related TEAE by severity			
Mild	5 (14.7)	2 (12.5)	7 (14.0)
Moderate	1 (2.9)	0 (0.0)	1 (2.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with any SAE	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with any adverse events leading to withdrawal of study drug	0 (0.0)	0 (0.0)	0 (0.0)

Note: TEAEs were defined as any adverse event that occurred after implantation/infiltration. Adverse events were coded using the MedDRA (version 18.0).
MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: Post-text Table 14.3.1.1

The most common TEAEs that were experienced by >15% of subjects were somnolence (19 [55.9%] subjects), dizziness (12 [35.3%] subjects), constipation (8 [23.5%] subjects), vision

blurred (8 [23.5%] subjects), tremor (6 [17.6%] subjects), and restlessness (6 [17.6%] subjects). For the Marcaine treatment group, 15 (93.8%) subjects experienced a TEAE. The most common TEAEs that were experienced by >15% of subjects were somnolence (10 [62.5%] subjects), dizziness (7 [43.8%] subjects), dysgeusia (4 [25.0%] subjects), tremor (3 [18.8%] subjects), and vision blurred (3 [18.8%] subjects). Table 9 summarizes the TEAEs by treatment and by system organ class (SOC) and preferred term (PT) for the Safety Population.

Table 9. Summary of Treatment-Emergent Adverse Events (□5% Overall) by System Organ Class and Preferred Term − Safety Population

System Organ Class Preferred Term	INL-001 (300 mg) (N = 34) n (%)	Marcaine 0.25% (175 mg) (N = 16) n (%)	Overall (N = 50) n (%)
Subjects with any TEAE	33 (97.1)	15 (93.8)	48 (96.0)
Nervous system disorders	26 (76.5)	13 (81.3)	39 (78.0)
Somnolence	19 (55.9)	10 (62.5)	29 (58.0)
Dizziness	12 (35.3)	7 (43.8)	19 (38.0)
Tremor	6 (17.6)	3 (18.8)	9 (18.0)
Dysgeusia	4 (11.8)	4 (25.0)	8 (16.0)
Headache	4 (11.8)	1 (6.3)	5 (10.0)
Gastrointestinal disorders	12 (35.3)	4 (25.0)	16 (32.0)
Constipation	8 (23.5)	1 (6.3)	9 (18.0)
Hypoaesthesia oral	3 (8.8)	2 (12.5)	5 (10.0)
Nausea	3 (8.8)	2 (12.5)	5 (10.0)
Paraesthesia oral	3 (8.8)	2 (12.5)	5 (10.0)
Eye disorders	10 (29.4)	3 (18.8)	13 (26.0)
Vision blurred	8 (23.5)	3 (18.8)	11 (22.0)
Psychiatric disorders	7 (20.6)	4 (25.0)	11 (22.0)
Restlessness	6 (17.6)	2 (12.5)	8 (16.0)
Anxiety	2 (5.9)	1 (6.3)	3 (6.0)
Injury, poisoning, and procedural complications	6 (17.6)	1 (6.3)	7 (14.0)
Incision site complication	3 (8.8)	0 (0.0)	3 (6.0)
Ear and labyrinth disorders	3 (8.8)	1 (6.3)	4 (8.0)
Tinnitus	3 (8.8)	1 (6.3)	4 (8.0)
Cardiac disorders	2 (5.9)	2 (12.5)	4 (8.0)
Bradycardia	2 (5.9)	1 (6.3)	3 (6.0)

Note: TEAEs were defined as any adverse event that occurred after implantation/infiltration. Adverse events were coded using the MedDRA (version 18.0).
MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Source: Post-Text Table 14.3.1.2

Regard to drug-related adverse events, the Applicant reported that for the INL-001 treatment group, 6 (17.6%) subjects experienced a drug-related TEAE. The drug-related TEAEs included tremor (3 [8.8%] subjects), dysgeusia (2 [5.9%] subjects), and somnolence (2 [5.9%] subjects). Each of the following drug-related TEAE was experienced by 1 subject: dry mouth, hypoaesthesia oral, paresthesia oral, incision site inflammation, dizziness, and restlessness. For the Marcaine treatment group, 2 (12.5%) subjects experienced a drug-related TEAE. No drug-related TEAE was experienced by more than 1 subject. Each of the following drug-related TEAE

was experienced by 1 subject: tremor, dysgeusia, and somnolence. Table 10 summarizes drug-related TEAEs by treatment and by SOC and PT for the Safety Population.

Table 10. Summary of Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term − Safety Population

System Organ Class Preferred Term	INL-001 (300 mg) (N = 34) n (%)	Marcaine 0.25% (175 mg) (N = 16) n (%)	Overall (N = 50) n (%)
Subjects with any drug-related TEAE	6 (17.6)	2 (12.5)	8 (16.0)
Nervous system disorders	4 (11.8)	2 (12.5)	6 (12.0)
Tremor	3 (8.8)	1 (6.3)	4 (8.0)
Dysgeusia	2 (5.9)	1 (6.3)	3 (6.0)
Somnolence	2 (5.9)	1 (6.3)	3 (6.0)
Dizziness	1 (2.9)	0 (0.0)	1 (2.0)
Gastrointestinal disorders	2 (5.9)	0 (0.0)	2 (4.0)
Dry mouth	1 (2.9)	0 (0.0)	1 (2.0)
Hypoaesthesia oral	1 (2.9)	0 (0.0)	1 (2.0)
Paraesthesia oral	1 (2.9)	0 (0.0)	1 (2.0)
Injury, poisoning, and procedural complications	1 (2.9)	0 (0.0)	1 (2.0)
Incision site inflammation	1 (2.9)	0 (0.0)	1 (2.0)
Psychiatric disorders	1 (2.9)	0 (0.0)	1 (2.0)
Restlessness	1 (2.9)	0 (0.0)	1 (2.0)

Note: TEAEs were defined as any adverse event that occurred after implantation/infiltration. Adverse events were coded using the MedDRA (version 18.0).
MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Source: Post-Text Table 14.3.1.3

Appendix

1. Original table presented in the main body

PK parameters	n	INL-001 (300 mg)	n	Marcaine 0.25% (175 mg)
Cmax (ng/mL) [1]	34	663.412 (263.826)	16	641.000 (262.684)
Tmax (h) [2]	34	3.03 (1.48, 24.02)	16	1.01 (0.53, 3.97)
tlag (h) [1]	34	0.51 (0.13)	16	0.47 (0.13)
λz (1/h) [1]	34	0.04 (0.01)	16	0.09 (0.04)
T1/2(h) [1]	34	18.95 (5.95)	16	9.08 (3.75)
AUC0-last (h*ng/mL) [3]	34	18,186.9 (39.0)	16	8836.9 (46.3)
AUC0-inf (h*ng/mL) [3]	34	19,012.5 (38.7)	16	8920.1 (46.7)
AUC extrapolated (h*ng/mL) [3]	34	2.96 (120.9)	16	0.65 (122.5)
CL/F (L/h) [2]	34	16.44 (7.6, 31.4)	16	22.29 (9.7, 34.6)
Vz/F (L) [1]	34	472.28 (282.463)	16	256.08 (116.739)

Note: Geometric CV% = 100*(exp(SD2)-1)0.5, where SD was the standard deviation of the log-transformed data. Time 0 was defined as the time when the first INL-001 bupivacaine HCl collagen matrix was implanted or the time of Marcaine 0.25% infiltration.
1. Mean (SD).
2. Median (minimum – maximum).
3. Geometric mean (geometric CV%).
Source: Post-text Table 14.2.2.1

2. Table 14.2.2.2 Summary of Plasma Bupivacaine Pharmacokinetic Parameters Per Protocol PK Population

Table 14.2.2.1
Summary of Plasma Bupivacaine Pharmacokinetic Parameters
Per Protocol PK Population

Treatment Subject ID Statistic	Cmax (ng/mL)	Tmax (h)	Tlag (h)	Lambda Z (1/h)	T1/2 (h)	AUC (0-last) (h*ng/mL)	AUC (0-inf) (h*ng/mL)	AUC Extra (%)	CL/F (L/h)	Vz/F (L)
INL-001 (b) (6)	991.00	2.92	0.58	0.04	18.46	18130	18407	1.5	16.3	434.2
	390.00	23.85	0.58	0.03	21.21	22571	24193	6.7	12.4	379.4
	513.00	4.00	0.53	0.07	10.06	22476	22613	0.6	13.3	192.6
	709.00	3.03	0.50	0.03	24.32	15848	17167	7.7	17.5	613.1
	940.00	5.07	0.43	0.05	13.92	34810	35402	1.7	8.5	170.1
	363.00	4.07	0.48	0.03	22.94	15173	16318	7.0	18.4	608.4
	459.00	10.02	0.50	0.03	20.08	18503	19525	5.2	15.4	445.0
	833.00	9.98	0.45	0.05	13.54	31052	31503	1.4	9.5	186.0
	565.00	23.98	0.60	0.03	20.48	33953	36745	7.6	8.2	241.2
	764.00	3.03	0.50	0.04	16.30	16382	16697	1.9	18.0	422.6
	752.00	2.07	0.50	0.05	13.15	23316	23577	1.1	12.7	241.4
	1230.00	2.03	0.57	0.04	16.70	17804	18112	1.7	16.6	399.1
	471.00	8.12	0.47	0.03	25.23	28383	31804	10.8	9.4	343.3
	749.00	2.03	0.00	0.04	18.02	16118	16466	2.1	18.2	473.6
	660.00	24.02	0.55	0.04	15.61	38110	39335	3.1	7.6	171.8
	510.00	1.93	1.07	0.02	37.67	8548	10009	14.6	30.0	1628.8
	430.00	4.00	0.47	0.04	17.00	13492	13973	3.4	21.5	526.5
	778.00	4.03	0.57	0.04	18.34	25518	26354	3.2	11.4	301.2
	387.00	12.10	0.58	0.03	21.08	17050	18200	6.3	16.5	501.4
	742.00	8.02	0.55	0.02	29.66	21996	23382	5.9	12.8	549.0
	363.00	4.00	0.52	0.02	28.55	20171	23540	14.3	12.7	524.9
	872.00	2.00	0.52	0.04	17.01	30820	31804	3.1	9.4	231.4
	395.00	2.00	0.50	0.04	18.78	20325	21379	4.9	14.0	380.2
	323.00	2.02	0.52	0.03	22.22	8985	9547	5.9	31.4	1007.5
	489.00	1.48	0.50	0.05	13.16	11725	11834	0.9	25.4	481.3
	953.00	2.05	0.47	0.03	24.83	12157	12676	4.1	23.7	847.7
	769.00	1.55	0.43	0.08	8.81	14123	14151	0.2	21.2	269.5
	602.00	2.05	0.47	0.04	18.73	11561	12144	4.8	24.7	667.3
	311.00	1.97	0.47	0.05	14.78	14042	14426	2.7	20.8	443.4
	1140.00	2.03	0.52	0.03	23.28	14484	15096	4.0	19.9	667.3

Geometric CV% = 100*(exp(SD^2)-1)^0.5, where SD is the standard deviation of the log-transformed data.

Source Data: ADPP
Program Name: pk_summary.sas Run Date: 18OCT2017 14:22 Data Last Modified: 02OCT2017 10:53

Table 14.2.2.1
Summary of Plasma Bupivacaine Pharmacokinetic Parameters
Per Protocol PK Population

Treatment Subject ID Statistic	Cmax (ng/mL)	Tmax (h)	Tlag (h)	Lambda Z (1/h)	T1/2 (h)	AUC (0-last) (h*ng/mL)	AUC (0-inf) (h*ng/mL)	AUC Extra (%)	CL/F (L/h)	Vz/F (L)
INL-001										
(b) (6)	1130.00	1.57	0.47	0.03	20.50	12400	12787	3.0	23.5	693.9
	699.00	6.00	0.50	0.06	11.74	20973	21136	0.8	14.2	240.4
	274.00	12.05	0.55	0.05	13.48	13642	13920	2.0	21.6	419.1
	1000.00	2.00	0.55	0.05	15.00	18118	18302	1.0	16.4	354.8
n	34	34	34	34	34	34	34	34	34	34
Mean	663.412	5.91	0.51	0.04	18.95	19492.9	20368.4	4.27	16.85	472.28
Standard Deviation	263.826	6.46	0.13	0.01	5.95	7564.17	7911.94	3.587	6.096	282.463
CV%	39.8	109.3	27.1	32.0	31.4	38.8	38.8	83.9	36.2	59.8
Standard Error	45.245	1.10	0.02	0.00	1.02	1297.24	1356.89	0.615	1.046	48.442
Median	679.500	3.03	0.50	0.03	18.40	17961.0	18250.6	3.14	16.44	428.36
Minimum	274.00	1.48	0.00	0.02	8.81	8548	9547	0.2	7.6	170.1
Maximum	1230.00	24.02	1.07	0.08	37.67	38110	39335	14.6	31.4	1628.8
Geometric Mean	611.893	3.94	0.52	0.03	18.10	18186.9	19012.5	2.96	15.78	412.12
Geometric CV%	43.5	102.2	15.7	31.7	31.7	39.0	38.7	120.9	38.7	55.5

Geometric CV% = 100*(exp(SD^2)-1)^0.5, where SD is the standard deviation of the log-transformed data.

Source Data: ADPP
Program Name: pk_summary.sas Run Date: 18OCT2017 14:22 Data Last Modified: 02OCT2017 10:53

Table 14.2.2.1
Summary of Plasma Bupivacaine Pharmacokinetic Parameters
Per Protocol PK Population

Treatment Subject ID Statistic	Cmax (ng/mL)	Tmax (h)	Tlag (h)	Lambda Z (1/h)	T1/2 (h)	AUC (0-last) (h*ng/mL)	AUC (0-inf) (h*ng/mL)	AUC Extra (%)	CL/F (L/h)	Vz/F (L)
Marcaine										
(b) (6)	824.00	3.97	0.50	0.16	4.20	10161	10184	0.2	17.2	104.1
	275.00	2.00	0.42	0.08	8.62	7192	7207	0.2	24.3	301.9
	334.00	1.95	0.50	0.05	14.17	17378	17781	2.3	9.8	201.2
	466.00	0.98	0.50	0.07	10.56	15145	15245	0.7	11.5	174.9
	891.00	1.02	0.50	0.11	6.30	6457	6491	0.5	27.0	244.9
	468.00	1.57	0.58	0.05	13.10	14224	14407	1.3	12.1	229.6
	728.00	2.08	0.50	0.15	4.61	6077	6087	0.2	28.8	191.2
	354.00	0.98	0.52	0.05	14.52	6218	6377	2.5	27.4	574.8
	648.00	1.57	0.52	0.17	4.14	5874	5880	0.1	29.8	177.6
	554.00	3.02	0.00	0.10	6.87	9182	9280	1.1	18.9	186.9
	481.00	0.53	0.53	0.09	7.85	5226	5263	0.7	33.3	376.7
	594.00	0.97	0.48	0.05	12.65	8523	8623	1.2	20.3	370.5
	1140.00	0.97	0.53	0.13	5.45	6929	6976	0.7	25.1	197.4
	1110.00	1.00	0.47	0.06	11.32	17884	18098	1.2	9.7	157.9
	536.00	1.00	0.47	0.05	13.70	13826	14087	1.9	12.4	245.5
	853.00	0.97	0.52	0.10	7.25	5034	5052	0.4	34.6	362.2
n	16	16	16	16	16	16	16	16	16	16
Mean	641.000	1.53	0.47	0.09	9.08	9708.2	9814.8	0.93	21.38	256.08
Standard Deviation	262.684	0.90	0.13	0.04	3.75	4480.36	4569.74	0.743	8.526	116.739
CV%	41.0	58.8	27.7	45.7	41.4	46.2	46.6	79.9	39.9	45.6
Standard Error	65.671	0.22	0.03	0.01	0.93	1120.09	1142.43	0.186	2.131	29.185
Median	574.000	1.01	0.50	0.08	8.23	7857.7	7915.1	0.69	22.29	215.40
Minimum	275.00	0.53	0.00	0.05	4.14	5034	5052	0.1	9.7	104.1
Maximum	1140.00	3.97	0.58	0.17	14.52	17884	18098	2.5	34.6	574.8
Geometric Mean	591.562	1.34	0.50	0.08	8.31	8836.9	8920.1	0.65	19.62	235.21
Geometric CV%	43.8	55.3	7.2	47.0	47.0	46.3	46.7	122.5	46.7	43.7

Geometric CV% = 100*(exp(SD^2)-1)^0.5, where SD is the standard deviation of the log-transformed data.

Source Data: ADPP
Program Name: pk_summary.sas Run Date: 18OCT2017 14:22 Data Last Modified: 02OCT2017 10:53

Summary of Plasma Bupivacaine Pharmacokinetic Parameters Per Protocol PK Population (Exclusion Samples) - note

Table 14.2.2.2
Summary of Plasma Bupivacaine Pharmacokinetic Parameters
Per Protocol PK Population (Exclusion Samples)

Treatment Subject ID Statistic	Cmax (ng/mL)	Tmax (h)	Tlag (h)	Lambda Z (1/h)	T1/2 (h)	AUC (0-last) (h*ng/mL)	AUC (0-inf) (h*ng/mL)	AUC Extra (%)	CL/F (L/h)	Vz/F (L)
INL-001										
(b) (6)	991.00	2.92	0.58	0.04	18.46	18130	18407	1.5	16.3	434.2
	390.00	23.85	0.58	0.03	21.21	22571	24193	6.7	12.4	379.4
	513.00	4.00	0.53	0.07	10.06	22476	22613	0.6	13.3	192.6
	709.00	3.03	0.50	0.03	24.32	15848	17167	7.7	17.5	613.1
	940.00	5.07	0.43	0.05	13.92	34810	35402	1.7	8.5	170.1
	363.00	4.07	0.48	0.03	22.94	15173	16318	7.0	18.4	608.4
	459.00	10.02	0.50	0.03	20.08	18503	19525	5.2	15.4	445.0
	833.00	9.98	0.45	0.05	13.54	31052	31503	1.4	9.5	186.0
	565.00	23.98	0.60	0.03	20.48	33953	36745	7.6	8.2	241.2
	764.00	3.03	0.50	0.04	16.30	16382	16697	1.9	18.0	422.6
	752.00	2.07	0.50	0.05	13.15	23316	23577	1.1	12.7	241.4
	1230.00	2.03	0.57	0.04	16.70	17804	18112	1.7	16.6	399.1
	471.00	8.12	0.47	0.03	25.23	28383	31804	10.8	9.4	343.3
	749.00	2.03	0.00	0.04	18.02	16118	16466	2.1	18.2	473.6
	660.00	24.02	0.55	0.04	15.61	38110	39335	3.1	7.6	171.8
	510.00	1.93	1.07	0.02	37.67	8548	10009	14.6	30.0	1628.8
	430.00	4.00	0.47	0.04	17.00	13492	13973	3.4	21.5	526.5
	778.00	4.03	0.57	0.04	18.34	25518	26354	3.2	11.4	301.2
	387.00	12.10	0.58	0.03	21.08	17050	18200	6.3	16.5	501.4
	742.00	8.02	0.55	0.02	29.66	21996	23382	5.9	12.8	549.0
	363.00	4.00	0.52	0.02	28.55	20171	23540	14.3	12.7	524.9
	872.00	2.00	0.52	0.04	17.01	30820	31804	3.1	9.4	231.4
	395.00	2.00	0.50	0.04	18.78	20325	21379	4.9	14.0	380.2
	323.00	2.02	0.52	0.03	22.22	8985	9547	5.9	31.4	1007.5
	489.00	1.48	0.50	0.05	13.16	11725	11834	0.9	25.4	481.3
	953.00	2.05	0.47	0.03	24.83	12157	12676	4.1	23.7	847.7
	769.00	1.55	0.43	0.08	8.81	14123	14151	0.2	21.2	269.5
	602.00	2.05	0.47	0.04	18.73	12197	12780	4.6	23.5	634.1

Geometric CV% = 100*(exp(SD^2)-1)^0.5, where SD is the standard deviation of the log-transformed data.
* The concentration values with imputed analysis time points will be excluded for the concentration summary.

Source Data: ADPP
Program Name: pk_summary.sas Run Date: 18OCT2017 14:22 Data Last Modified: 02OCT2017 10:53

Table 14.2.2.2
Summary of Plasma Bupivacaine Pharmacokinetic Parameters
Per Protocol PK Population (Exclusion Samples)

Treatment Subject ID Statistic	Cmax (ng/mL)	Tmax (h)	Tlag (h)	Lambda Z (1/h)	T1/2 (h)	AUC (0-last) (h*ng/mL)	AUC (0-inf) (h*ng/mL)	AUC Extra (%)	CL/F (L/h)	Vz/F (L)
INL-001										
(b) (6)	311.00	1.97	0.47	0.05	14.78	14042	14426	2.7	20.8	443.4
	1140.00	2.03	0.52	0.03	23.28	14484	15096	4.0	19.9	667.3
	1130.00	1.57	0.47	0.03	20.50	12400	12787	3.0	23.5	693.9
	699.00	6.00	0.50	0.06	11.74	20973	21136	0.8	14.2	240.4
	274.00	12.05	0.55	0.05	13.48	13642	13920	2.0	21.6	419.1
	1000.00	2.00	0.55	0.05	15.00	18118	18302	1.0	16.4	354.8
n	34	34	34	34	34	34	34	34	34	34
Mean	663.412	5.91	0.51	0.04	18.95	19511.6	20387.1	4.27	16.81	471.30
Standard Deviation	263.826	6.46	0.13	0.01	5.95	7544.73	7892.65	3.586	6.052	281.826
CV%	39.8	109.3	27.1	32.0	31.4	38.7	38.7	84.0	36.0	59.8
Standard Error	45.245	1.10	0.02	0.00	1.02	1293.91	1353.58	0.615	1.038	48.333
Median	679.500	3.03	0.50	0.03	18.40	17961.0	18250.6	3.14	16.44	428.36
Minimum	274.00	1.48	0.00	0.02	8.81	8548	9547	0.2	7.6	170.1
Maximum	1230.00	24.02	1.07	0.08	37.67	38110	39335	14.6	31.4	1628.8
Geometric Mean	611.893	3.94	0.52	0.03	18.10	18215.6	19041.1	2.96	15.76	411.50
Geometric CV%	43.5	102.2	15.7	31.7	31.7	38.8	38.5	120.8	38.5	55.3

Geometric CV% = 100*(exp(SD^2)-1)^0.5, where SD is the standard deviation of the log-transformed data.
* The concentration values with imputed analysis time points will be excluded for the concentration summary.

Source Data: ADPP
Program Name: pk_summary.sas Run Date: 18OCT2017 14:22 Data Last Modified: 02OCT2017 10:53

Table 14.2.2.2
Summary of Plasma Bupivacaine Pharmacokinetic Parameters
Per Protocol PK Population (Exclusion Samples)

Treatment Subject ID Statistic	Cmax (ng/mL)	Tmax (h)	Tlag (h)	Lambda Z (1/h)	T1/2 (h)	AUC (0-last) (h*ng/mL)	AUC (0-inf) (h*ng/mL)	AUC Extra (%)	CL/F (L/h)	Vz/F (L)
Marcaine										
(b) (6)	824.00	3.97	0.50	0.16	4.20	10161	10184	0.2	17.2	104.1
	275.00	2.00	0.42	0.08	8.62	7192	7207	0.2	24.3	301.9
	334.00	1.95	0.50	0.05	14.17	17378	17781	2.3	9.8	201.2
	466.00	0.98	0.50	0.07	10.56	15145	15245	0.7	11.5	174.9
	891.00	1.02	0.50	0.11	6.30	6457	6491	0.5	27.0	244.9
	468.00	1.57	0.58	0.05	13.10	14224	14407	1.3	12.1	229.6
	728.00	2.08	0.50	0.15	4.61	6077	6087	0.2	28.8	191.2
	354.00	0.98	0.52	0.05	14.52	6218	6377	2.5	27.4	574.8
	648.00	1.57	0.52	0.17	4.14	5874	5880	0.1	29.8	177.6
	554.00	3.02	0.00	0.10	6.87	9182	9280	1.1	18.9	186.9
	481.00	0.53	0.53	0.09	7.85	5226	5263	0.7	33.3	376.7
	594.00	0.97	0.48	0.05	12.65	8523	8623	1.2	20.3	370.5
	1140.00	0.97	0.53	0.13	5.45	6929	6976	0.7	25.1	197.4
	1110.00	1.00	0.47	0.06	11.32	18011	18225	1.2	9.6	156.8
	536.00	1.00	0.47	0.05	13.70	13766	14027	1.9	12.5	246.5
	853.00	0.97	0.52	0.10	7.25	5034	5052	0.4	34.6	362.2
n	16	16	16	16	16	16	16	16	16	16
Mean	641.000	1.53	0.47	0.09	9.08	9712.4	9819.0	0.93	21.38	256.07
Standard Deviation	262.684	0.90	0.13	0.04	3.75	4492.32	4581.52	0.744	8.528	116.795
CV%	41.0	58.8	27.7	45.7	41.4	46.3	46.7	79.9	39.9	45.6
Standard Error	65.671	0.22	0.03	0.01	0.93	1123.08	1145.38	0.186	2.132	29.199
Median	574.000	1.01	0.50	0.08	8.23	7857.7	7915.1	0.69	22.29	215.40
Minimum	275.00	0.53	0.00	0.05	4.14	5034	5052	0.1	9.6	104.1
Maximum	1140.00	3.97	0.58	0.17	14.52	18011	18225	2.5	34.6	574.8
Geometric Mean	591.562	1.34	0.50	0.08	8.31	8838.4	8921.7	0.65	19.62	235.17
Geometric CV%	43.8	55.3	7.2	47.0	47.0	46.4	46.8	122.5	46.8	43.7

Geometric CV% = 100*(exp(SD^2)-1)^0.5, where SD is the standard deviation of the log-transformed data.
* The concentration values with imputed analysis time points will be excluded for the concentration summary.

Source Data: ADPP
Program Name: pk_summary.sas Run Date: 18OCT2017 14:22 Data Last Modified: 02OCT2017 10:53

3. Table 14.2.3.1 Relative Bioavailability Analysis of Plasma Bupivacaine PK Parameters: ANOVA Model Per Protocol PK Population

Table 14.2.3.1
Relative Bioavailability Analysis of Plasma Bupivacaine PK Parameters: ANOVA Model
Per Protocol PK Population

Dose-Normalized PK Parameter	PK Unit	Treatment A n	Treatment A Geom. LS Mean*	Treatment B n	Treatment B Geom. LS Mean*	-- Relative Bioavailability -- Ratio of Geom. LS Mean (A/B) (%)	90% CI for Ratio** (%)	Intra-Subject CV*** (%)
AUC(0-last)	h*ng/(mL*mg)	34	60.6	16	50.5	120.05	(98.07, 146.97)	41.4
AUC(0-inf)	h*ng/(mL*mg)	34	63.4	16	51.0	124.33	(101.60, 152.16)	41.3
Cmax	ng/(mL*mg)	34	2.0	16	3.4	60.34	(48.81, 74.59)	43.6

A = INL-001 bupivacaine HCl collagen-matrix implant (300 mg). B = Marcaine 0.25% (bupivacaine HCl) 175 mg.
An analysis of variance (ANOVA) model is performed on logarithm-transformed dose-normalized PK parameters.
* Geometric LS Means are the least squares means from the mixed model presented after back transformation to the original scale.
** The 90% confidence intervals are presented after back transformation to the original scale.
*** Intra-Subject CV (%) is calculated as 100*SQRT(EXP(SIGMA^2)-1), where SIGMA^2 is the residual variance estimate from PROC MIXED.

Source Data: ADPP
Program Name: pk_analysis.sas Run Date: 18OCT2017 14:25 Data Last Modified: 02OCT2017 10:53

Relative Bioavailability Analysis of Plasma Bupivacaine PK Parameters: ANOVA Model
Per Protocol PK Population (Exclusion Samples) – note

Innocoll Pharmaceuticals
Protocol Number INN-CB-022

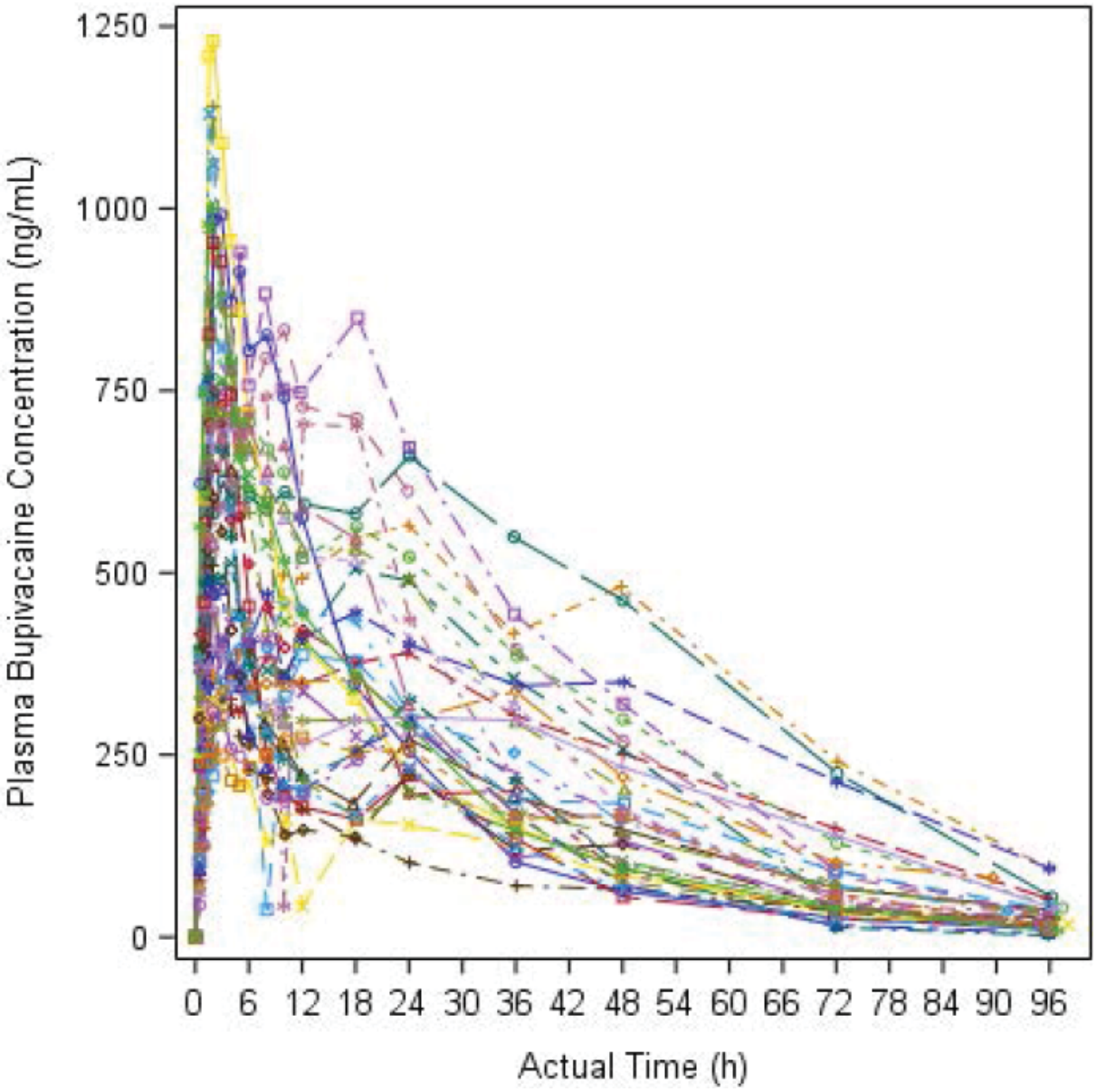
Table 14.2.3.2
Relative Bioavailability Analysis of Plasma Bupivacaine PK Parameters: ANOVA Model
Per Protocol PK Population (Exclusion Samples)

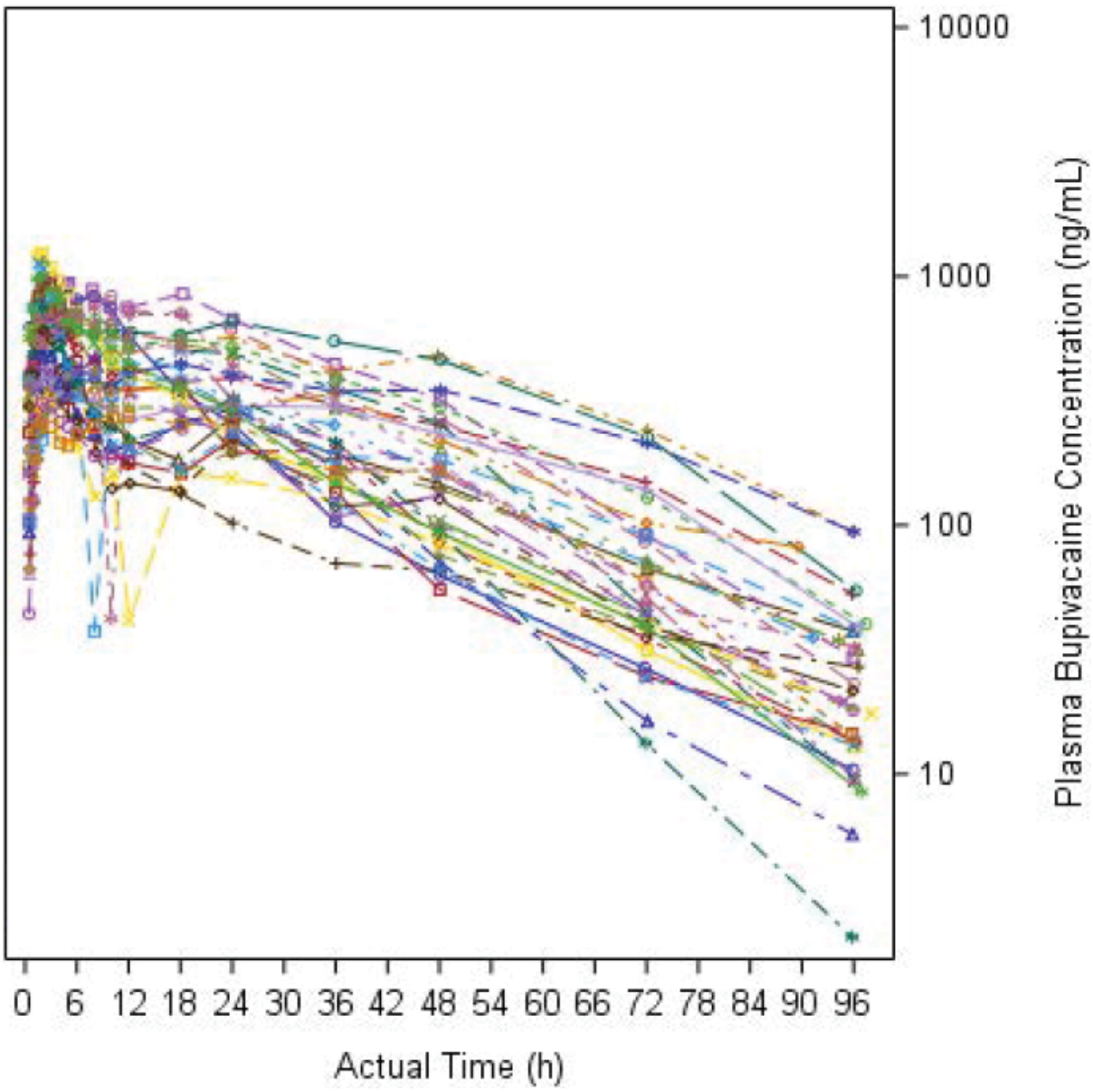
Dose-Normalized PK Parameter	PK Unit	Treatment A n	Treatment A Geom. LS Mean*	Treatment B n	Treatment B Geom. LS Mean*	-- Relative Bioavailability -- Ratio of Geom. LS Mean (A/B) (%)	90% CI for Ratio** (%)	Intra-Subject CV*** (%)
AUC(0-last)	h*ng/(mL*mg)	34	60.7	16	50.5	120.22	(98.26, 147.10)	41.3
AUC(0-inf)	h*ng/(mL*mg)	34	63.5	16	51.0	124.50	(101.78, 152.29)	41.2
Cmax	ng/(mL*mg)	34	2.0	16	3.4	60.34	(48.81, 74.59)	43.6

A = INL-001 bupivacaine HCl collagen-matrix implant (300 mg). B = Marcaine 0.25% (bupivacaine HCl) 175 mg.
An analysis of variance (ANOVA) model is performed on logarithm-transformed dose-normalized PK parameters.
* Geometric LS Means are the least squares means from the mixed model presented after back transformation to the original scale.
** The 90% confidence intervals are presented after back transformation to the original scale.
*** Intra-Subject CV (%) is calculated as 100*SQRT(EXP(SIGMA^2)-1), where SIGMA^2 is the residual variance estimate from PROC MIXED.
Note: The concentration values without actual time points will be excluded for the PK parameter calculation and PK analysis.

Source Data: ADPP
Program Name: pk_analysis.sas Run Date: 18OCT2017 14:25 Data Last Modified: 02OCT2017 10:53

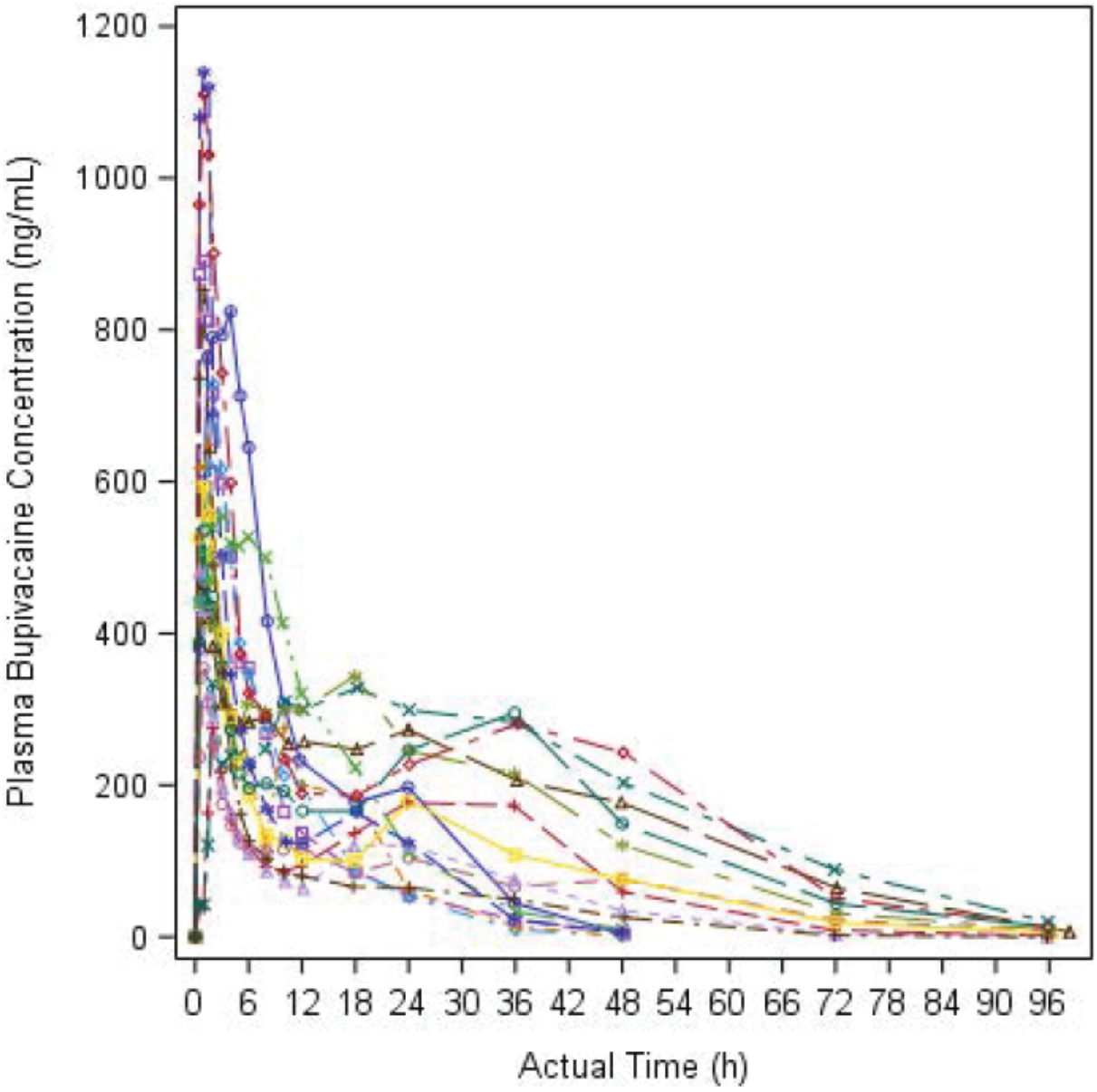
4. Figure 14.2.2.1 Spaghetti Plot of Individual Plasma Bupivacaine Concentrations on Linear and Semi-Log Scale PK Population - INL-001 Bupivacaine HCl Collagen-Matrix Implant (300 mg)

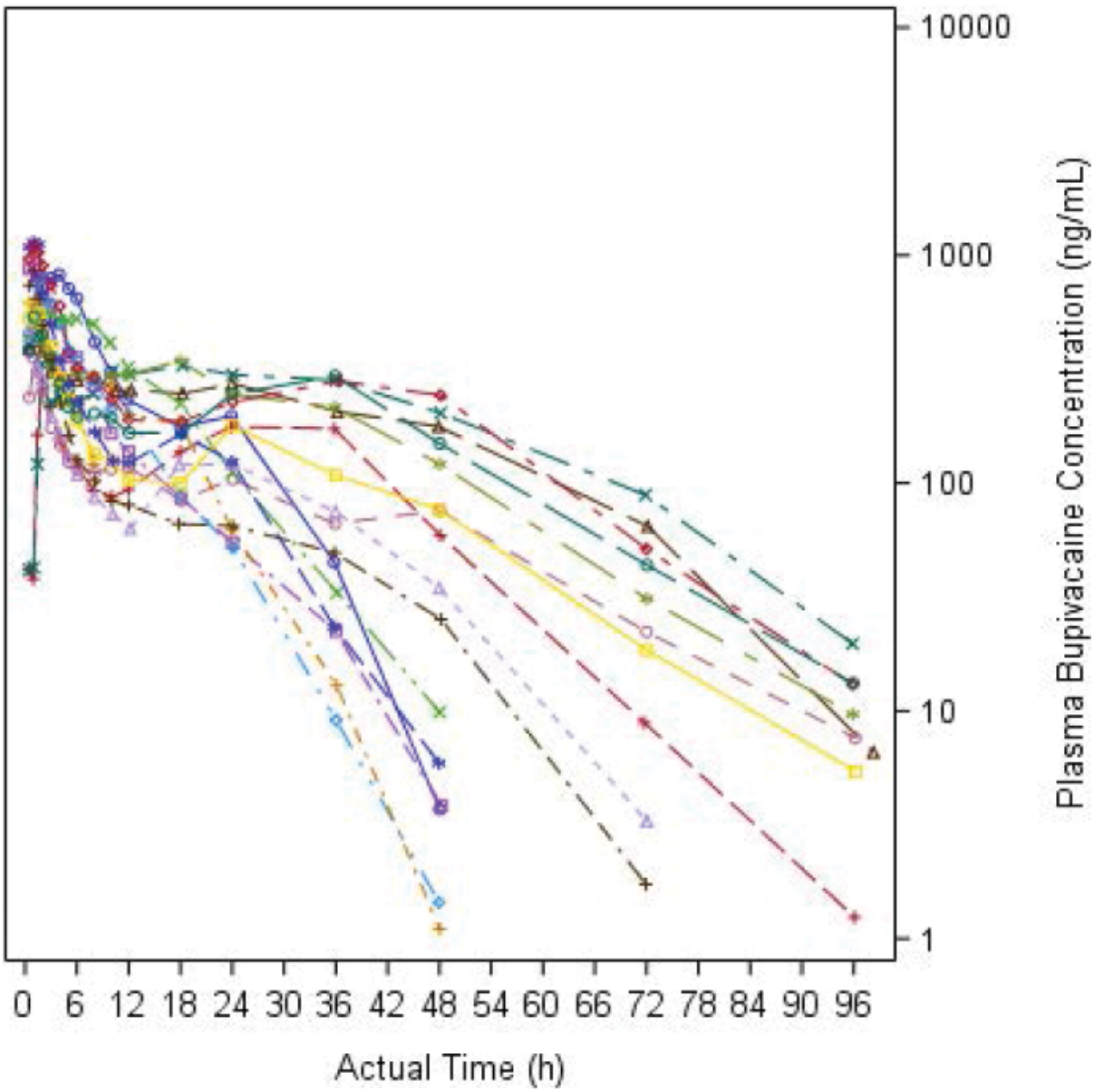




Lower limit of Quantitation (LLOQ) for bupivacaine = 1 ng/mL.
Source Data: T14.2.1.1
Program Name: Figure2.sas Run Date

5. Figure 14.2.2.2 Spaghetti Plot of Individual Plasma Bupivacaine Concentrations on Linear and Semi-Log Scale PK Population - Marcaine 0.25% (bupivacaine HCl) 175 mg





Lower limit of Quantitation (LLOQ) for bupivacaine = 1 ng/mL.

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/s/

DAVID J LEE
10/29/2018

YUN XU
10/29/2018