CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209511Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	209511
Priority or Standard	Standard
Submit Date(s)	February 2, 2018
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Division/Office	DAAAP/OND
Reviewer Name(s)	Renee Petit-Scott, M.D.
Review Completion Date	November 29, 2018
Established/Proper Name	Bupivacaine HCl collagen matrix-implant
(Proposed) Trade Name	XaraColl®
Applicant	Innocoll, Inc., a wholly owned subsidiary of Innocoll Pharmaceuticals
Dosage Form(s)	Implantation
Applicant Proposed Dosing Regimen(s)	Three collagen matrices, each containing 100 mg of bupivacaine HCl, should be placed (b) (4) at the surgical site (b) (4) and can be cut using aseptic technique before placement into the surgical site
Applicant Proposed Indication(s)/Population(s)	For placement into the surgical site to produce postsurgical analgesia following (b) (4)
Recommendation on Regulatory Action	Approval of XaraColl®
Recommended Indication(s)/Population(s) (if applicable)	For single-dose placement in adults to produce postsurgical local analgesia following open unilateral inguinal hernia repair with mesh Limitations of Use: Safety and efficacy has not been established following other surgical procedures.

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Glossary

AC	advisory committee
ACLS	advanced cardiac life support
AE	adverse event
AR	adverse reaction
ASA	American Society of Anesthesiologists
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CPR	cardiopulmonary resuscitation
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HCl	hydrochloride
ICH	International Council for Harmonization
IHR	inguinal hernia repair
IND	Investigational New Drug Application
INL-001	XaraColl implant
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat

MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PACU	post-anesthesia care unit
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TAH	total abdominal hysterectomy
TEAE	treatment emergent adverse event

1. Executive Summary

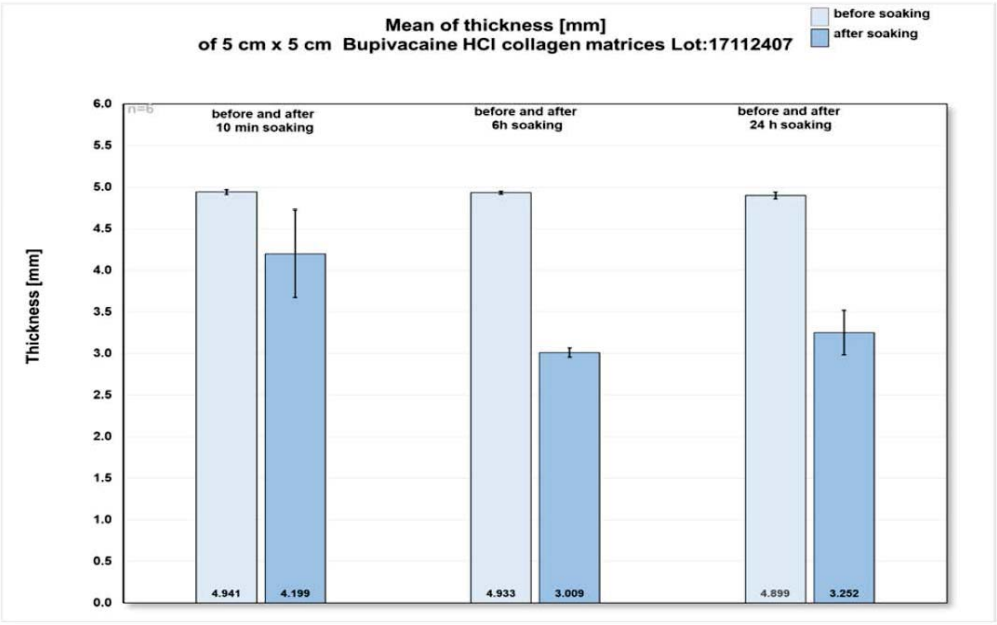
1.1. Product Introduction

The bupivacaine hydrochloride (HCl) collagen-matrix implant, hereinafter referred to as bupivacaine collagen-matrix, INL-001, or XaraColl®, manufactured by Innocoll Technologies, Incorporated, is a combination product containing bupivacaine HCl and purified bovine collagen, which when implanted, releases drug over time. Innocoll Technologies, Inc., has submitted this New Drug Application for marketing approval of their product for the management of postsurgical pain after (b) (4) This product is not marketed anywhere in the world at the time of NDA submission. However, there are pharmaceutical products marketed in Europe which have employed the CollaRX® technology for the delivery of medications, such as the gentamicin-collagen product (Collatamp® G) for the prophylactic management of surgical site infections. Collatamp® G has also been evaluated for the management of diabetic foot ulcers and sternal wound infections. Currently, the bupivacaine HCl collagen-matrix is the only CollaRX® product under evaluation by the Agency. Collagen products such as J-Coll™, Collastat™, Superstat™, and Novacol™ have been used in the U.S. as absorbable hemostatic agents under pre-market approval applications, (b) (4)

The CollaRX® technology is a sterile, resorbable, biodegradable (b) (4) porous matrix comprised of 75 mg of Type I collagen purified from bovine Achilles tendons. The Type I collagen is obtained from (b) (4) closed herds, which have been certified as transmissible bovine spongiform encephalopathy-free (b) (4) (b) (4) (b) (4) The Applicant contends that the collagen does not confer additional therapeutic benefit and its only purpose is to aide delivery of bupivacaine HCl into the surgical wound. The collagen-containing matrices, each of which measure 5 x 5 x 0.5 cm, undergo enzymatic degradation and resorption.

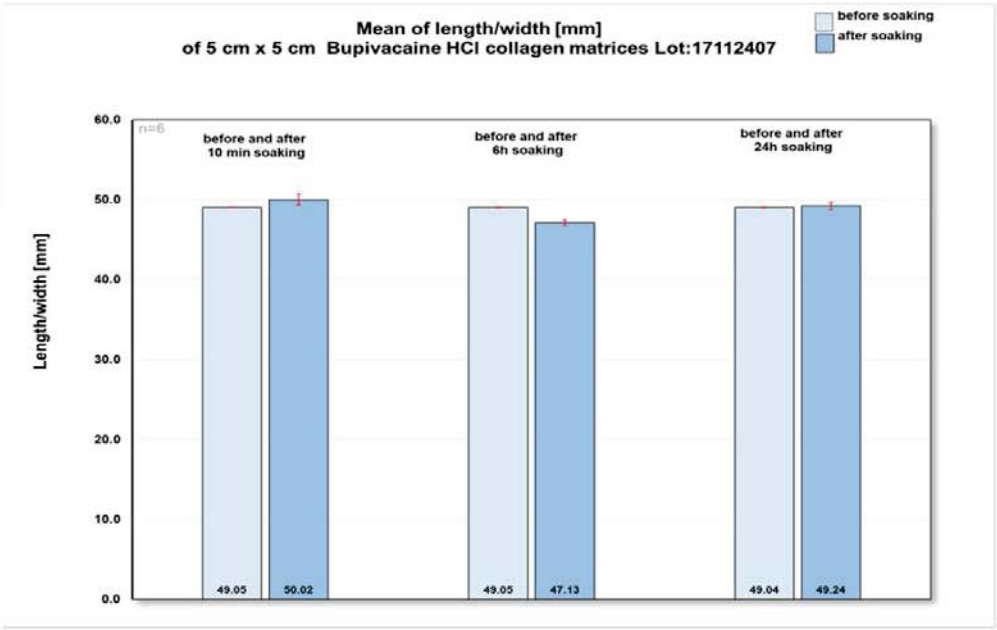
As described in the Description and Composition of the Drug Product of the Applicant's submission, the collagen device component of the product matrix serves as an inert delivery system and releases the bupivacaine HCl through dissolution and diffusion from the porous matrix. Specifically, when the XaraColl® collagen-matrix absorbs surrounding fluid, (b) (4) (b) (4) (b) (4) (b) (4) In response to an Information Request (IR) dated July 27, 2018, the Applicant provided the following figures for clarification on how the matrices likely change during implantation in the body.

Figure 1. Mean Thickness Change of the Bupivacaine Collagen-Matrices After Soaking



Source: Applicant's Response to IR dated July 27, 2018, p. 2 (PDF), Applicant's submission, NDA 209511

Figure 2. Mean Length/Width Changes to the Bupivacaine Collagen-Matrices After Soaking



Source: Applicant's Response to IR dated July 27, 2018, p. 3 (PDF), Applicant's submission, NDA 209511

Bupivacaine, an amide local anesthetic, was first approved by the Food and Drug Administration (FDA) for clinical use in the United States in 1972. It is used primarily for the management of

postsurgical pain, either as infiltration into the surgical site or as a regional nerve block, including neuraxial anesthesia and peripheral nerve blockade. Due to the preferential nerve fiber blockade, to be discussed in further detail in Section 4.5, Clinical Pharmacology, nerve conduction via sensory fibers is more readily inhibited than nerve conduction via motor fibers, resulting in pain relief with some preserved mobility. This makes bupivacaine often the local anesthetic of choice for continuous neuraxial anesthesia as well as peripheral nerve blockade.

Innocoll Technologies, Inc., intends to manufacture and market bupivacaine HCl collagen-matrix under the trade name XaraColl®. The proposed indication is as follows:

> *…for placement into the surgical site to produce postsurgical analgesia following* (b) (4) (b) (4)

The proposed dosing is three bupivacaine HCl collagen-matrices implanted in (b) (4) into the surgical wound. The matrices may be cut prior to insertion, as they were in the Applicant's Phase 3 studies. The total proposed maximum dose of bupivacaine HCl is 300 mg, or three matrices, which provides 266.4 mg of bupivacaine for release.

The Applicant has referred to XaraColl® as INL-001 throughout the drug development program and many tables included in this review have used that same nomenclature.

1.2. Conclusions on the Substantial Evidence of Effectiveness

According to my review of the clinical data presented in the application and review of articles in the published literature, I recommend approval of XaraColl® with revisions to the proposed labeling as outlined in Section 10, Labeling Recommendations. The revisions clarify the recommended surgical population, contraindicated medications, adverse reactions, and the clinical study results. For reasons discussed extensively in Section 7.3, Integrated Assessment of Efficacy, the impact of XaraColl® on post-operative opioid use is likely not clinically relevant (b) (4) (b) (4) particularly because a standard of care active comparator group was not used during the Phase 3 studies.

As described in Section 4.4, Nonclinical Pharmacology/Toxicology, the review team is recommending a Complete Response for this application based on an inadequate assessment of the extractable/leachable components of this drug product.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Bupivacaine HCl was first approved in the United States in 1972 (NDA 016964) and has been widely used in the management of postsurgical pain, as well as other painful conditions, since that time. It is safe and effective for use via wound infiltration, peripheral nerve blockade, and neuraxial anesthesia in a variety of clinical settings and for a range of surgical procedures. Based on the well-known safety profile and demonstrated effectiveness, in combination with the on-going opioid epidemic, there is considerable interest in developing bupivacaine products with extended-release or slow release profiles in an effort to prolong the analgesic effect. Currently, there are no such products marketed. The results of the XaraColl® drug development program support an analgesic benefit over placebo matrices for up to 24 hours post-operatively after open unilateral inguinal hernia repair (IHR or herniorrhaphy) with mesh, however, there are four issues with the reported findings suggesting the clinical significance may be less than the statistical results.

First, an efficacy evaluation with comparison to a placebo treatment is much less meaningful in this clinical circumstance than comparison to the standard of care treatment, which generally includes would infiltration with immediate-release bupivacaine and analgesics as needed. It is unlikely that patients in the United States undergoing this surgical procedure would not be administered a local anesthetic for the management of postsurgical pain. The use of a placebo group in the pivotal Phase 3 studies suggest that those patients may have had their postsurgical pain inadequately treated, resulting in an apparent enhanced clinical benefit of XaraColl®. From a regulatory standpoint, use of a placebo group is acceptable for drug approval; however, results from studies using this comparator are less impressive and less clinically meaningful than the results reported for studies using an active comparator. Second, the observed pain curves for the treatment and placebo groups for each Phase 3 study are less impressive than the reported areas under the curve, or the sum of pain intensity, which was the primary efficacy endpoint. Specifically, the mean pain scores for both groups at the evaluated time points appears to be consistently three or greater and the pain curves converge at 24-hours post-operatively and overlap for the duration of both studies. Because the analgesic effect appears to extend only through 24 hours, any additional clinical benefit over immediate release bupivacaine with opioid analgesic supplementation is unclear.

Third, because the drug development program for XaraColl® extensively evaluated a single surgical model, open inguinal hernia repair with mesh, it can only be approved for use in that patient population. The variability in bupivacaine release from the matrices in this surgical model, as demonstrated in the PK/BA Study INN-CB-022, makes approval for use in other soft tissue surgical models difficult (refer to Section 4.5, Clinical Pharmacology, for additional information). The PK profile in other, more vascular soft tissue locations, such as the breast, vagina, or rectum, is unknown, and while the PK profile does not translate directly with the pharmacodynamic response or efficacy of XaraColl®, the safety of the product when used in such sites is a concern. Additionally, while the Phase 2 studies conducted by the Applicant were not powered to detect a statistically significant difference in efficacy outcomes and the dose of bupivacaine was lower than that evaluated in the

Phase 3 studies, it is concerning that XaraColl® did not reliably demonstrate a clinical benefit over the active comparator or placebo treatments, depending on the study. Lastly, the majority of patients evaluated during the drug development program were male and while it is unlikely that there is a gender influence on the PK profile for bupivacaine release from XaraColl®, there is concern about its release in soft tissue locations unique to female patients, such as the lactating breast or vagina.

In addition to these issues with the reported efficacy pain data, there are also issues with the opioid analgesic use data as reported by the Applicant. The median, not the mean, opioid use data was evaluated and reported as statistically significant. It appears that this median data is more impressive than the mean data, as discussed in detail in Section 7.3, Integrated Assessment of Effectiveness. Specifically, the mean differences in opioid analgesic use between the XaraColl® treatment and placebo groups are consistently smaller than those reported with median data (refer to Table 39 for additional information). Additionally, the timing of the difference in opioid analgesic use between the two groups appears less supportive of clinically meaningful postsurgical pain management with XaraColl® treatment. Specifically, in Study INN-CB-014, the largest differences in opioid use between the two groups appear early in the post-operative period, a time when both intravenous (IV) and oral analgesics were administered. The difference in opioid analgesic use at the later time points was 2.9 mg IV morphine equivalents at 48 hours and 2 mg at 72 hours. These differences correspond to 8.7 mg and 6 mg oral morphine equivalents respectively, less than one 10 mg oral tablet, are clinically insignificant, (b) (4)

The efficacy endpoints that appear the most supportive of XaraColl®'s positive impact on opioid analgesic use include time to first opioid rescue and percentage of patients not using any opioid rescue through 72 hours. There was a statistically significant difference in median time to first rescue between the XaraColl® treatment and placebo groups, with the most impressive results from Study INN-CB-014. There was approximately a 10-hour difference in requesting opioid analgesia between the groups. For Study INN-CB-016, the difference in median time was approximately 5 hours; less impressive but likely still represents a clinically meaningful amount of time for patients. The Applicant reported that approximately 36% of XaraColl®-treated patients and 22% of placebo-treated patients in Study INN-CB-014 did not need opioid rescue analgesia. For Study INN-CB-016, approximately 28% of XaraColl®-treated patients and 12% of placebo-treated patients did not require opioid rescue analgesia. These findings may be clinically meaningful, however, as previously mentioned, the mean amount of opioid analgesia appears similar between the treatment and placebo groups after 24 hours, suggesting that of those that did require opioid rescue after 24 hours, the doses were similar for both groups.

In addition to the reported efficacy findings from the XaraColl® drug development program, another potential clinical benefit involves the treatment of local anesthetic systemic toxicity (LAST) that may occur after administration of XaraColl®. Unlike the treatment modalities for LAST associated with bupivacaine wound infiltration, peripheral nerve blockade, neuraxial anesthesia, or inadvertent intravascular injection,

an available treatment option is removal of the matrices, which was performed for one patient in Study INN-CB-004. While the surgical removal of the matrices is not the ideal treatment for LAST, particularly because the patient would need to have general anesthesia and an additional surgical procedure, and it would only impact additional local anesthetic absorption, it is an option that is not available in the case of toxicity associated with other commonly used routes of administration.

A final clinical benefit of XaraColl® over other routes of bupivacaine administration is the ability to cut the matrices into smaller sizes, allowing implantation into a variety of surgical wounds. Because the safety and efficacy of XaraColl® was primarily evaluated in a single surgical population, the approved indication will be for postsurgical analgesia after open inguinal hernia repair. However, additional safety and efficacy evaluations could permit approval for use in other surgical models, which may require variable matrix size and dosing. Furthermore, the novel route of administration may lend itself to the delivery of other drug products, impacting patient outcomes beyond postsurgical pain management.

The primary safety concerns associated with use of XaraColl® are the development of LAST and the potential adverse impact on wound healing. The proposed maximum dose of bupivacaine in XaraColl® is higher than that recommended in the bupivacaine product label. Specifically, the single maximum recommended dose of bupivacaine is 175 mg without epinephrine and 225 mg with the addition of epinephrine. The dose for each XaraColl® matrix is 100 mg of bupivacaine HCl (88.8 mg of bupivacaine), for a maximum recommended dose of 300 mg (266.4 mg bupivacaine). Additionally, due to the variable and potentially unpredictable release profile for bupivacaine HCl from the XaraColl® matrices, the development of LAST may occur later than is commonly observed after administration of immediate release bupivacaine. Based on the PK data from Study INN-CB-022, the greatest risk for the development of LAST appears to be up to 24 hours after administration, a time when the majority of patients after open IHR would be discharged and no longer in a monitored setting.

The Applicant's drug development program included a total of 612 patients exposed to a dose of XaraColl® and 469 patients received the maximum dose, XaraColl® 300 mg. There was a single patient who has signs and symptoms that may be related to LAST, and required intensive hemodynamic support, including vasopressors, albumin, hydrocortisone, fluid resuscitation, intralipid, and ultimately surgical removal of the matrices. Refer to Section 8.4.2, Serious Adverse Events, for a comprehensive discussion, but briefly the patient was a 57-year-old female, weighing 65 kg, with a moderately benign past medical history who underwent a bladder sling procedure under general anesthesia. There was a discrepancy regarding the total amount of bupivacaine administered, either 150 mg or 200 mg. Post-operatively the patient developed ECG changes and refractory hypotension, requiring removal of the matrices. Over the following 18 hours after removal of the matrices, the patient was weaned off vasopressors and discharged on post-operative day four. There are two prominent concerns regarding this case. First, the dose of bupivacaine administered was low and not expected to cause toxicity in an average-size adult patient. And second, the reported

plasma concentrations should not have resulted in toxicity. The highest reported concentration was 900 ng/mL at 22 hours post-operatively. If this was a case of LAST, it is concerning and highlights the variable and unpredictable PK profile of XaraColl® and further underscores the poorly defined relationship between the pharmacodynamic response and the pharmacokinetic profiles.

It is possible, however, that this was not a case of LAST, but rather another drug reaction/interaction that resulted in profound hemodynamic instability. Such an alternate explanation is supported by the relatively low bupivacaine dose administered, the relatively low bupivacaine plasma levels, the lack of improvement with administration of intralipid, and the continued need for vasopressor support for 18 hours after removal of the matrices. It is difficult to imagine, however, another condition that could result in these clinical findings. A cardiac evaluation, consisting of cardiac enzyme analyses, echocardiography, and repeated ECG analyses, was unremarkable with the exception of QT prolongation. Oxygen saturation on minimal supplemental oxygen was reportedly 100% making pulmonary embolism unlikely. There was no reported rash, urticaria, or angioedema and measured IgE levels were within normal limits, making a drug allergy also unlikely.

In conclusion, pending another explanation, this may be considered a case of bupivacaine toxicity. While this is concerning for the reasons discussed, it is reassuring that it appears to be the only documented case throughout the XaraColl® development program, which consisted of 612 patient exposures. Review of adverse events that are commonly associated with bupivacaine neurotoxicity, such as dysgeusia and tinnitus, occurred with similar frequency in patients treated with XaraColl® and placebo in the Phase 3 studies. Additionally, there were three patients in the placebo group and none in the XaraColl® treatment group in Study INN-CB-016 who experienced dysgeusia and tinnitus, suggesting these neurological findings may be observed after administration of general anesthesia and in the absence of bupivacaine administration. Review of the 24-hour Holter ECG data from both PK/BA studies, INN-CB-013 and INN-CB-022, did not demonstrate cardiotoxicity associated with administration of XaraColl®. Specifically, the Applicant evaluated the Holter data with focus on the time surrounding maximal plasma concentration, T_{max}, and known cardiac adverse events associated with administration bupivacaine. There were reportedly no abnormal ECG findings at T_{max} and no adverse events reported that suggest possible cardiotoxicity. Additionally, there were no ECG changes or cardiac adverse events reported for the patient with the highest reported plasma concentration, 1230 ng/mL, after XaraColl® administration. Table 50 summarizes the Holter findings for both treatment groups in Study INN-CB-022.

The second safety concern associated with administration of XaraColl® is the potential adverse impact on wound healing. While there is support in the published literature for improved rate of wound healing and reduction in wound contracture with the use of collagen, there are also studies which suggest hematoma formation, infection, wound dehiscence, inflammation, edema, adhesions, allergic reactions, foreign body reactions, and subgaleal seroma. In the Clinical Study Report (CSR) for Study INN-CB-010, p. 30 (PDF), the Applicant has stated, "*Adverse reactions reported for the collagen products that have been used for hemostasis include hematoma, potentiation of infection, wound*

dehiscence, inflammation, and edema". The use of collagen in dental extraction sockets has been reported to increase the incidence of alveolalgia (commonly referred to as a dry socket). Migration into the spinal cord of collagen products used in laminectomy patients has resulted in cauda equina syndrome, spinal stenosis, meningitis, arachnoiditis, headaches, paresthesias, pain, bladder and bowel dysfunction, impotency, and paralysis.

The impact on wound healing was extensively reviewed, with an emphasis on surgical procedure performed, amount of implanted collagen per matrix, history of previous ipsilateral hernia repair, safety information from other research INDs, and information from the published literature. Initial review of the adverse events related to wound healing indicated an increased incidence in patients treated with the collagen-matrix when compared to patients treated with a comparator, refer to Table 45. The adverse events that were reported with the highest incidence included incision site swelling and pain. Given the size and composition of the collagen implant, it is not surprising that there would be an increased incidence of these adverse events when compared to bupivacaine wound infiltration, for example. Wound dehiscence and post-procedural discharge, which may indicate a wound infection, are more concerning adverse events and while the incidence was reportedly higher in patients who received a collagen-matrix, the overall numbers were low and appear consistent with reports in the published literature after the same surgical procedure without the implanted collagen matrix. Analysis of wound-related adverse events and surgery type did not indicate an increased incidence in patients undergoing hysterectomy, an initial consideration given selection of a single surgical population for evaluation in the pivotal Phase 3 studies.

Increasing amounts of Type I collagen per matrix did not appear to increase the incidence of wound-related adverse events. The majority of patients, 77%, received three, 75 mg matrices, for a total collagen dose of 225 mg. While the numbers of patients exposed to other amounts of collagen are low, those treated with 280 mg total did not appear to have an increased incidence of wound-related adverse events. History of previous ipsilateral hernia repair with mesh did appear to result in a higher percentage of patients with incision site swelling and pain when compared to patients without this history. This is not surprising, however, given the increased surgical dissection typically required during repeat procedures, resulting in increased swelling and pain. The incidence of more clinically significant wound-related adverse events such as post-procedural discharge and dehiscence was similar for patients with and without a history of previous hernia repair. There have been (b) (4) INDs submitted using products with the CollaRX® technology, and while they were all subsequently withdrawn, it does not appear for reasons related to wound-healing. And finally, review of the information in the published literature suggests that the incidence of wound-related adverse events reported with XaraColl® appears the same or lower compared to reports from studies in IHR in which XaraColl® was not used.

A final consideration regarding the use of XaraColl® during open inguinal hernia repair with mesh is the potential for scar tissue or adhesions to develop at the site of implantation and the impact on future surgical dissection. Specifically, the results of the non-clinical studies have

indicated complete dissolution of the implant at 56-days and did not suggest an increased amount of fibrotic tissue at the time of necropsy on either Day 35 or Day 56. Understandably, the Phase 3 studies did not the evaluate the ease or difficulty of surgical re-exploration after treatment with XaraColl®. With the exception of the single patient who required removal of the matrices on post-operative day 1 secondary to possible LAST, no other patients were reported as having a repeat surgical exploration or dissection after XaraColl® implantation. Evaluation of this potential clinical issue will likely be addressed in the post-market surveillance program.

In conclusion, XaraColl® bupivacaine collagen-matrix has been shown to be a safe and effective short-term, ≤24 hours, treatment for postsurgical pain in patients undergoing open unilateral inguinal hernia repair with mesh. It may not offer additional clinical benefit when compared to standard of care local anesthetic wound infiltration but can be approved for its demonstrated efficacy over placebo collagen-matrices. There should be limited information in the product label or promotional materials regarding a decrease in post-operative opioid use. For reasons stated throughout this review, to suggest or imply that (b) (4) is inaccurate and misleading for practitioners and patients alike and overemphasizes the true clinical benefit of this product.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• As the Applicant has stated, inguinal herniorrhaphy is one of the most common soft tissue surgical procedures performed in the United States. While many of these procedures are performed either laparoscopically or Robot-assisted in an attempt to minimize post-operative pain, decrease recovery time, and improve patient outcome, there are still a large number performed via the open technique. • Surgical reduction of inguinal hernias using the open technique is generally reserved for large, incarcerated or non-reducible hernias, those that are otherwise complicated, or in patients with a history of previous major abdominal surgery. Because the	**While exposure to bupivacaine may be low in the general population, patients undergoing a surgical procedure have a high likelihood of receiving bupivacaine. Due to the disease process and anatomic pathology, the development of an inguinal hernia is more common in male patients, suggesting the post-market exposure to XaraColl® will be primarily in males.** **Inguinal hernias can be bilateral and can recur, potentially resulting in repeat exposure to bupivacaine products, either in the same location or a new location. The impact of XaraColl® on the development of fibrotic or granulation tissue was evaluated in the non-clinical studies, and while the results do**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	open technique involves a larger incision and potentially more extensive surgical dissection, postsurgical pain appears to be increased when compared to smaller, less complicated hernias repaired laparoscopically. • A large number of inguinal herniorrhaphies, both open and laparoscopic, are performed in outpatient ambulatory surgical centers in an attempt to lower health care costs and improve efficiency. The goal of any ambulatory surgical center is to deliver quality care in the most efficient manner, which includes the ability to effectively manage postsurgical pain in a timely fashion. Longer acting local anesthetics could potentially aid these centers in reaching these health care goals. • Efficacious, rapidly-acting, and extended duration of action are the goals of all postsurgical pain management strategies and while there are a number of opioid analgesics that meet these criteria, the large numbers of opioid-related adverse events and deaths are a clear indication that alternate treatment options are needed.	**not indicate increased development of such tissue, the impact of XaraColl® in the clinical setting will likely be addressed in the post-market surveillance program.** **Open inguinal herniorrhaphy is an ideal surgical model to evaluate the safety and efficacy of potentially longer acting local anesthetics for three reasons. First, they do not involve boney or large neuronal structures, thereby eliminating the small but measurable risk of boney penetration with an injection needle and large nerve injury. Second, they are relatively benign surgical procedures and rarely result in life-threatening complications. And lastly, they are very common procedures. Because the open technique is generally performed for more complicated inguinal hernias, the management of postsurgical pain can be challenging and the need for longer-acting analgesics readily apparent.**
Current Treatment Options	• Current treatment options for postsurgical pain include the following: – opioid analgesics – non-opioid analgesics – local anesthetics for wound infiltration, peripheral nerve blockade, or neuraxial	**While there are several marketed, approved bupivacaine products for use in the management of postsurgical pain, none have an extended release profile that reliably prolongs postsurgical analgesia beyond that observed after administration of immediate release bupivacaine.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	anesthesia • For acute postsurgical pain that develops into a chronic or neuropathic condition, antidepressants, gabapentanoids, and anti-seizure medications can also be used. • Non-traditional therapeutic strategies have also been employed, including acupuncture and massage therapy. Physical therapy is a mainstay for treatment of a variety of musculoskeletal disorders as well as other painful conditions, including post-operative neuropathy and disability. • Of the local anesthetics available for postsurgical pain management, lidocaine, ropivacaine, and bupivacaine, with and without epinephrine, are the most commonly used. Ropivacaine and bupivacaine are considered longer-acting than lidocaine and generally provide up to eight hours of postsurgical pain relief when administered via wound infiltration. • There are currently no approved local anesthetics with an extended release or slow release profile that have demonstrated reliable prolonged postsurgical analgesia. A continuous infusion of a dilute concentration of bupivacaine via a peripheral nerve or neuraxial catheter appears to be the only available mechanism to prolong the duration of action of bupivacaine.	**Approval of XaraColl® would provide clinicians an additional, potentially longer-acting bupivacaine product for use in the management of postsurgical pain. The results from the Applicant's Phase 3 studies have demonstrated improved sum of pain intensity over 24 hours after XaraColl® implantation when compared to placebo treatment, and the PK/BA study results suggested a different release profile than the currently marketed bupivacaine products. However, the clinical significance of these findings is less clear and the impact on overall opioid use post-inguinal herniorrhaphy may be negligible.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Bupivacaine has been used for decades in the treatment of post-operative pain when administered for wound infiltration, peripheral nerve blockade, or neuraxial anesthesia/analgesia. It is an effective local anesthetic with a well-established safety profile as documented in premarket clinical studies and in the published literature in the form of clinical studies, case reports, and epidemiological studies. • When used for wound infiltration, the administration of bupivacaine decreases post-operative pain for a finite period of time. When administered for peripheral nerve blockade, the duration of anesthesia and analgesia is a function of the peripheral nerve blocked, the dose of bupivacaine administered, and whether the block is via a single injection or continuous peripheral nerve catheter. Peripheral nerve blockade generally has a much longer duration of action than wound infiltration. • When bupivacaine is administered in either the intrathecal or epidural space, the duration of the anesthetic and analgesic effects depends on the dose administered, the spinal level injected, and whether a single injection or continuous catheter is used. • Well-controlled post-operative pain results in the following: – Improved patient outcomes, including	**Approval of the bupivacaine collagen-matrix would offer clinicians an additional bupivacaine product to administer for postsurgical pain management after a commonly performed surgical procedure, inguinal herniorrhaphy. It may provide longer postsurgical analgesia than currently approved products, however, the comparison to placebo treatment makes definitive conclusions about improved efficacy beyond standard of care treatments challenging.** **Additional benefits of XaraColl® include the following:** **• Bupivacaine is a widely-used local anesthetic with a long history of clinical use and a large safety database spanning decades** **• Variable matrix size, due to cutting, will permit implant into a variety of surgical wounds** **• In the event of LAST, the matrices can be surgically removed, which is not a treatment option after wound infiltration, peripheral nerve blockade, or neuraxial block** **• The Phase 3 studies did demonstrate a clinically meaningful difference in time to first opioid rescue analgesia between the XaraColl® and placebo groups; e.g., 10 hours in Study INN-CB-014** **The totality of the impact of adequate postsurgical pain management on health care outcomes is likely immeasurable and the benefits are likely to extend beyond individual patient outcomes, potentially impacting overall cost and societal burden of poorly managed pain.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	decrease length of hospital stay – Improved patient satisfaction, which may translate into reimbursement assurances – Less time lost from work and school – Ability to perform procedures on an out-patient basis – Improved mobility and ambulation, and less time for return to baseline function, depending on the procedure performed – Potential decreased health care cost and burden due to short-term disability	
Risk and Risk Management	• The two safety issues of greatest concern with administration of XaraColl® include the development of LAST and potential adverse effects on wound healing. LAST • Factors influencing the development of LAST include the site of administration and total dose administered. The proposed maximum dose of bupivacaine in XaraColl®, 266.4 mg, is higher than the recommend dose in the bupivacaine product label, 175 mg without epinephrine. Use of a higher than currently recommended dose may lead to increased incidence of LAST depending on the surgical location, specifically the vascularity of the surrounding tissue. • Because the PK profile of XaraColl® appeared	**Despite the bupivacaine dose in XaraColl® being greater than the maximum recommended dose in the bupivacaine product label, there were no reported cases of LAST in the Applicant's Phase 3 studies. The only case of presumed LAST was reported for a 57-year-old female patient who received either 150 mg or 200 mg during bladder sling surgery. While this case is concerning and emphasizes the variable PK profile of XaraColl® when used in different surgical locations, it is reassuring that no other patient experienced bupivacaine toxicity, even with the highest doses administered.** **Review of the neurological assessment data and the 24-hour ECG data captured via Holter monitoring did not identify other cases of bupivacaine toxicity. Specifically, the incidence of neurological adverse events that could be related to bupivacaine toxicity, including dysgeusia and tinnitus, appeared to occur with similar frequency in both treatment**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	variable in the single surgical population evaluated, use of the product in other surgical models or for other painful conditions is not recommended. While bupivacaine has a long history of clinical use and the safety profile is well-established, it is highly cardiotoxic due to its strong affinity for cardiac Na^+ channels and the high degree of protein binding. Systemic exposure to increased amounts of bupivacaine poses the greatest risk for the development of toxicity and XaraColl® implantation into highly vascular sites is likely to increase the risk above what has been characterized in the Applicant's Phase 3 clinical studies evaluating inguinal herniorrhaphy. • An additional concern regarding the variable PK profile of XaraColl® is the likelihood of patients being in an unmonitored setting around C_{max}, a time when the risk of toxicity is the highest. This can potentially be mitigated by adequate and comprehensive patient education regarding the signs and symptoms associated with bupivacaine toxicity. <u>Wound Healing</u> • While the published literature contains contradictory information regarding the impact of exogenously administered collagen on wound healing, the data from the Applicant's development program appears adequate to address wound healing after open	**and placebo groups during the Phase 3 studies. Furthermore, in Study INN-CB-016 there were three patients treated with placebo matrices who experienced both dysgeusia and tinnitus, compared to no patients treated with INL-001. Additionally, the Applicant reported that review of the 24-hour continuous Holter data, from Study INN-CB-013 and Study INN-CB-022, did not reveal clinically concerning ECG changes or other clinical findings that may indicate cardiotoxicity.** **Risk mitigation strategies for the development of LAST after treatment with XaraColl® include the following:** • **Limited surgical use – the product label should recommend use of XaraColl® only in the surgical population for which the safety and efficacy were thoroughly evaluated. Because the PK profile was variable when used in a single surgical model, it is likely there would be variability among different surgical sites, with bupivacaine absorption from more vascular sites presenting a possible safety issue.** • **Available resuscitative medications and equipment – as with all local anesthetics, administration of XaraColl® should occur only those clinical settings that have immediate access to resuscitative equipment and medications, including lipid emulsion therapy, in the event of LAST. As previously mentioned, an additional treatment strategy for LAST that is not an option for other routes of bupivacaine administration is surgical removal of the implants. Removal of the matrices will not treat toxicity associated with already absorbed**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	inguinal herniorrhaphy. Specifically, 816 patients who underwent inguinal herniorrhaphy received the collagen-matrix, either as component of XaraColl® or the placebo matrix. • There was initial concern regarding the increased number of wound-related adverse events in patients who received the collagen matrix when compared to patients who received a comparator treatment without the matrix. Closer evaluation, however, revealed that the adverse events with the greatest increased incidence, incision site pain and swelling, may have been anticipated given the size and composition of XaraColl®. • Adverse events that are likely considered more serious, such as wound dehiscence and discharge, appear to have occurred with a similar frequency as that reported in the published literature.	**bupivacaine, but will prevent further release, thereby limiting on-going exposure.** • **Patient education – because a large number of patients may be in an unmonitored setting around the time of maximal plasma concentration, there should be adequate patient education prior to discharge regarding signs and symptoms that may be related to early LAST.** **The potential adverse impact of XaraColl® on wound healing was of initial concern, particularly when comparing the incidence of wound-related adverse events in XaraColl®-treated and comparator-treated patients. Review of the totality of the data presented, including the Applicant's clinical development program of 892 patients treated with a dose of collagen-matrix, however, appears to support the safe use of XaraColl® in the surgical population evaluated, inguinal herniorrhaphy. Specifically, it appears that the most commonly reported wound-related adverse events, incision site pain and swelling, may be anticipated due to the size and composition of XaraColl®, an implantable matrix versus local anesthetic wound infiltration, and not likely to result in the development of more severe or serious adverse events. Information from the published literature, including clinical studies, case reports, and epidemiological studies, have indicated that the frequency of more clinically significant wound-related adverse events, such as dehiscence and discharge, as reported in the Applicant's Phase 3 studies is consistent with the rate of wound complications after inguinal**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		herniorrhaphy. **The single outstanding issue is the impact of XaraColl® administration on the ease of future surgical dissection. The results from the nonclinical studies did not demonstrate an increased production of fibrotic or granulation tissue after treatment with XaraColl® at the time of necropsy, Days 35 or 56. This is reassuring, however, it is not known if these results are completely applicable to the clinical setting and if the findings are the same at Days >56. Any increase in scar tissue or adhesions would likely increase the difficulty of surgical dissection in the case of future surgical procedures. This is an issue that can be addressed with post-market surveillance and does not rise to the level of an approvability concern.** **In conclusion, I recommend approval of XaraColl® bupivacaine collagen-matrix for use in the management of postsurgical pain after open inguinal hernia repair with mesh.**

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

As reported by the Applicant, inguinal hernia repair (IHR), referred to either as inguinal herniorrhaphy or hernioplasty, is a common surgical procedure in the United States. In 2006, the Centers for Disease Control National Statistics Report indicates there were 515,000 patients

who underwent this procedure. This includes both patients who had either the open or the laparoscopic procedure. The open procedure is still performed most commonly for patients with larger, complicated hernias, however, the trend is toward laparoscopic-assisted surgery in an attempt to decrease post-operative complications, including acute pain and opioid use.

Given the current opioid crisis facing the United States, postsurgical pain management has become a rapidly advancing field. The goal is to decrease opioid prescriptions and use post-operatively via a multimodal peri-operative approach, including use of local anesthetics for wound infiltration, peripheral nerve blocks, and neuraxial blocks. A variety of soft tissue surgical procedures are amenable to local anesthetic administration and, depending on the location, patient comorbid conditions, concomitant medications, and contraindications, is considered standard of care. The local anesthetics currently approved for use in the management of post-operative pain are considered immediate release and there are no approved products labeled for extended release.

The Applicant has described XaraColl® as *"…an extended-release product…"* (Clinical Overview, p. 20, PDF, Applicant's submission, NDA 209511) based on the pharmacokinetic profile (to be discussed in detail in Section 4.5, Clinical Pharmacology). The extended bupivacaine release from XaraColl® is expected to prolong the post-operative analgesia observed after administration of immediate release products. While the data from Study INN-CB-022, the PK/BA study, is supportive of prolonged bupivacaine release when compared to Marcaine™, clinically we know that the pharmacokinetics of local anesthetics do not translate into efficacy, or in this case prolonged analgesia. More simply stated, the PK profile does not correlate to the pharmacodynamic (PD) responses. Furthermore, the bupivacaine release profile for XaraColl® may ultimately have an adverse impact on the safety of the drug product. As will be discussed throughout this review, the determination of safety and efficacy of local anesthetic products developed to extend the analgesic benefit of immediate release products is complicated. While the opioid epidemic in the U.S. is an overwhelming challenge facing practitioners, researchers, and pharmaceutical companies alike, product development that is unsafe or no more efficacious than currently available standard of care products is not helpful and may ultimately result in other adverse outcomes.

2.2. Analysis of Current Treatment Options

The management of post-operative pain involves a multimodal approach utilizing local anesthetics, non-opioid analgesics, and opioid analgesics. Anti-depressants and anti-seizure medications are also commonly added depending on the comorbid medical conditions of the patient and the procedure performed. Until the extent of the opioid epidemic was understood, opioid analgesics were the mainstay for the management of not only acute pain conditions, including post-operative pain, but also chronic pain conditions. Currently, however, the focus has shifted from opioid-based pain management to alternative treatment strategies, including local anesthetic wound infiltration, peripheral nerve blockade, and neuraxial anesthesia. This

shift has resulted in an increasing interest to develop products that can prolong the efficacy of immediate release local anesthetics, such as XaraColl®. As previously mentioned, however, there is no approved extended-release local anesthetic product that has reliably extended the duration of analgesia observed after administration of immediate-release local anesthetics.

Soft tissue procedures, such as open inguinal herniorrhaphy with mesh, are excellent models for local anesthetic wound infiltration for three reasons. First, soft tissue surgical procedures do not commonly involve boney or neuronal structures, thereby eliminating the small but measurable risks of boney penetration with an injection needle and large nerve injury. Second, most soft tissue procedures are relatively benign and do not routinely result in life-threatening complications. And third, they are very common procedures and are performed in many areas of the body, across a wide range of ages, and for a variety of surgical diseases.

Table 1 summarizes the local anesthetics most commonly used in the peri-operative period for analgesia.

Table 1. Summary of FDA-Approved Local Anesthetics for Postsurgical Analgesia After Open Unilateral Inguinal Hernia Repair

Product Name NDA #	Relevant Indication	Route of Administration	Efficacy Information	Important Safety and Tolerability Issues
Exparel (022496)	For single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia	Local infiltration	Liposomal bupivacaine HCl used for postsurgical analgesia. No clear efficacy benefit demonstrated when compared to bupivacaine HCl.	The safety issue with all local anesthetics involves systemic and local toxicities. LAST presents as central nervous system excitation and/or depression and cardiotoxicity. As documented in the Adverse Reactions section of the bupivacaine labeling, but applicable to all local anesthetics, the following LAST reactions are described by system: <u>Central nervous system</u> Excitation and/or depression; restlessness, anxiety, dizziness, tinnitus, blurred vision, tremors, convulsions <u>Cardiovascular system</u> High doses or inadvertent intravascular injection
Bupivacaine HCl (016964)	Production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures	Local infiltration	First approved in 1972. Many approved bupivacaine products are widely used for postsurgical analgesia, either as wound infiltrate or nerve block. Considered a long-acting local anesthetic with a duration of action ranging from 4 to 18 hours, depending on the route and site of administration.	
Ropivacaine HCl (20533)	Production of local or regional anesthesia for surgery and for	Local infiltration	Similar efficacy benefits as bupivacaine HCl but with more favorable	

Product Name NDA #	Relevant Indication	Route of Administration	Efficacy Information	Important Safety and Tolerability Issues
	acute pain management		cardiotoxicity profile. Considered a long-acting local anesthetic with a duration of action ranging from 4 to 18 hours.	may result in myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmias, cardiac arrest. Bupivacaine HCl is considered the most cardiotoxic local anesthetic due to its potency in blocking nerve conduction and depressing cardiac contractility. Local reactions can include persistent anesthesia, paresthesia, weakness, or paralysis
Mepivacaine HCl (12250)	Production of local or regional analgesia and anesthesia by local infiltration, peripheral nerve block techniques, and central neural techniques	Local infiltration	Considered an intermediate-acting local anesthetic with a duration of action ranging from 90 to 180 minutes.	
Lidocaine HCl (006488)	Production of local or regional anesthesia by infiltration techniques and intravenous regional anesthesia, by peripheral nerve block techniques, and by central neural techniques, when the accepted procedures for the techniques as described in standard textbooks are observed.	Local infiltration	First approved in 1948 as Xylocaine® 2% injectable solution. Considered an intermediate-acting local anesthetic with a duration of action ranging from 90 to 180 minutes.	

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The bupivacaine HCl collagen-matrix has not been marketed anywhere in the world. As previously mentioned, there have been (b) (4) investigative products, aside from the current NDA premarketing program, using collagen as part of a therapeutic combination product. The following table summarizes the previous INDs and Pre-INDs which have incorporated collagen into the final drug product:

Table 2. Therapeutic Products with Collagen

IND#, Pre-IND#	Drug Product	Proposed Indication	Status
(b) (4)	(b) (4)		(b) (4)
	Collagen + gentamicin	External application for treatment of diabetic foot ulcers	
	(b) (4)		
IND 77127 (current NDA)	Collagen + bupivacaine	Postsurgical analgesia	NDA submitted

Source: Reviewer's analysis

While there is support in the published literature for improved rate of wound healing and reduction in wound contracture with the use of collagen, there are also studies which suggest hematoma formation, infection, wound dehiscence, inflammation, edema, adhesions, allergic reactions, foreign body reactions, and subgaleal seroma. The use of collagen in dental extraction sockets has been reported to increase the incidence of alveolalgia. Collagen products used in laminectomy patients have resulted in cauda equina syndrome, spinal stenosis, meningitis, arachnoiditis, headaches, paresthesia, pain, bladder and bowel dysfunction, and impotency. Collagen migration into the spinal cord has also resulted in paralysis.

3.2. Summary of Presubmission/Submission Regulatory Activity

Innocoll Technologies, Inc. opened IND 77127 in March 2007, for evaluation of the bupivacaine

collagen-matrix in surgical patients. The following table is a high level summary of the key interactions between Innocoll and the Agency regarding the clinical development program.

Table 3. Summary of Pre-Submission and Submission Regulatory Activities

Meeting/Communication/Date	Event/Key Clinical Issues
IND 77127 opened/March 2007	
End of Phase 2 Meeting/December 5, 2011	• Phase 3 study constructs reasonable, 200 mg and 300 mg proposed doses • Primary endpoint of integrated assessment of pain- (b) (4) • PK/BA study reasonable but should be concluded prior to Phase 3 studies (cardiotoxicity and neurotoxicity should be fully evaluated prior to Phase 3 study initiation) • Post-operative analgesic indication may be too broad • Wound healing and effects of (b) (4) on suture and mesh needs to be evaluated
Type C Meeting/WRO/July 6, 2015	• Xaracoll® 300 mg bupivacaine collagen-matrix acceptable • Safety database needs to contain at least 500 exposed subjects • Primary endpoint should be SPID24 • Hierarchical testing acceptable for multiple endpoints • Standard acetaminophen dosing post-operatively acceptable
Initial Pediatric Study Plan (iPSP) Received/January 27, 2016	Written feedback in the form of a tracked-changes document was sent to the Sponsor.
Type C Meeting/WRO/April 20, 2016	• Pooling of data in the ISS and ISE is acceptable • Primary and secondary efficacy endpoints should be expressed as SPI versus SPID • Screening laboratory values need to be included • CRFs and patient narratives should be submitted for all subjects who experienced an SAE, discontinued due to an adverse event, or died
Agreed iPSP/June 17, 2016	No additional advice provided.
NDA 209511 Submission/October 31, 2016	NDA received.
Refuse to File NDA 209511/December 23,	There no refuse to file clinical issues identified. The

Meeting/Communication/Date	Event/Key Clinical Issues
2016	refuse to file issues included the following: • Reliance on which bupivacaine product needed clarification • PK/BA study was not conducted with the to-be-marketed formulation • There were a variety of sterilization and packaging issues described by the CMC review team • The nonclinical review team had several issues including inadequate nonclinical data to qualify the safety of the to-be-marketed formulation and inadequate extractable/leachable evaluation • Xaracoll® is a drug-device combination product and there was no biocompatibility information included in the NDA submission
NDA 209511 Resubmission/February 2, 2018	NDA received.
NDA 209511 Filed/April 17, 2018	Potential clinical review issues include the following: • The incidence of wound-related issues is higher in subjects treated with collagen matrix compared to subjects treated with comparators (no collagen matrix) • Adequacy of cardiotoxicity evaluation • Phase 3 studies were identical in design and surgical population, therefore the results less strongly support a broad postsurgical analgesic indication • DRUG INTERACTIONS section of the label needs to included comprehensive information regarding the use of additional local anesthetics

3.3. Foreign Regulatory Actions and Marketing History

XaraColl® bupivacaine-collagen matrix is not marketed anywhere in the world. As previously discussed, the CollaRX® technology has been used in other drug products in Europe.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Applicant has indicated that the following four clinical studies were evaluated and pertinent to the claimed indication:

- Phase 2 Studies
  - Study INN-CB-003
  - Study INN-CB-010
- Phase 3 studies
  - Study INN-CB-014
  - Study INN-CB-016

Because the Phase 2 studies failed to demonstrate efficacy on the primary endpoint, only the efficacy findings of the Phase 3 studies will support the labeling indication. Therefore, only the clinical sites involved with conducting these studies were considered for inspection.

There were a total of 39 clinical sites involved in the Phase 3 studies, 20 for Study INN-CB-014 and 19 for Study INN-CB-016. None of the sites overlapped with enrollment between the two Phase 3 studies. The following table highlights the relevant information regarding the clinical Phase 3 study sites.

Table 4. Clinical Phase 3 Study Sites

Study	Investigator	Site ID	Number of enrolled subjects	CSR-Reportable Protocol Deviations	Treatment effect, SPI24	Reported adverse events
INN-CB-014	Fadi Saba	417	50	193	33	380
	Jose Suarez[#]	420[+]	39	146	9	11
	James Cain	407	20	62	14	64
	Paul Rider	408	17	29	5	25
	Carlos Suarez	409	15	44	17	13
	Abel Murillo	410	15	25	44	21
	Tim Melson	402	13	15	-32	4
	Raj Rajan	426	13	44	65	15
	Charles St. Hill	418	9	20		34
	Vic Velanovich	419	8	53	41	49
	Ryan Ramos	412	8	51	8	9
	Jon Fuller	411	7	20	33	11
	Kasia Osadzinska	413	7	34	4	5
	Julio Paez	416	7	45	-50	3
	Angel Moralex	423	5	15	-34	12

(b) (6)

Study	Investigator	Site ID	Number of enrolled subjects	CSR-Reportable Protocol Deviations	Treatment effect, SPI24	Reported adverse events
	Emanuele LoMenzo	404	5	31	180	13
	Tarik Wasfie	421	4	8		4
	Michael Zadeh	424	2	6		1
	Stefan Chock	406	1	3		0
INN-CB-016	Kenneth Deck	603+	45	130	46	54
	Kurt Stockamp	608	40	100	20	202
						(b) (6)
	Derek Muse	607	30	43	40	52
	Michael DeMicco	605	28	66	32	22
	Steven Hopson	619	24	86	1	9
	Jim Garaz	627	24	59	21	26
	Sonia Singla	628	21	25	30	18
	Craig Iwamoto	604	20	36	22	36
	Edmund Molnar	610	11	57	70	35
	Sergio Bergese	618	10	27	72	43
	Almena Free	601	9	25	39	1
	Orestes Pablos	621	9	16	61	3
	Maury Jayson	615	5	22	72	3
	Albert Lai	616	3	6		3
	Ajita Prabhu	609	2	10	68	7
	Ignacio Badiola	622	2	6		1
	Timothy Miller	611	1	12		5
	Paul Montero	626	1	14		3

+Clinical sites recommended for inspection

*Principle investigators undergoing inspection for another marketing application

#Previously inspected due to large number of protocol deviations, but no action indicated upon inspection results

Source: Reviewer's analysis, with input from Dr. Ren, statistical reviewer

The clinical sites, 417, 420, and 603, were chosen for inspection based on the number of enrolled and treated subjects, as well as the efficacy and safety data reported for each site. The following is an excerpt from Dr. Roy Blay, reviewer in the Division of Clinical Compliance Evaluation, Office of Scientific Investigations:

> *The clinical sites of Drs. Saba, Suarez, and Deck were inspected in support of this NDA. Based on the results of these inspections, the studies (Protocols INN-CB-014 and INN-CB-016) appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. The final compliance classification of the inspections of Drs. Saba, Suarez, and Deck was No Action Indicated (NAI).*

Detailed analyses of the safety data will be presented in Section 8, Review of Safety and the large number of protocol deviations for certain investigative sites will be discussed for each

study in Sections 6.1.2, Study Results.

4.2. Product Quality

The Type I collagen in INL-001 is purified from bovine Achilles tendons obtained exclusively from (b) (4) closed herd cows that have been certified as transmissible spongiform encephalopathy-free, (b) (4) The purpose of the collagen component of INL-001 is to provide a biocompatible matrix to allow placement into the surgical wound for local delivery of bupivacaine. The Applicant states that the collagen matrix is not intended to have a beneficial or detrimental effect on the surgical wound or impact wound healing. For additional information, refer to the CMC review completed by Valerie Amspacher.

4.3. Clinical Microbiology

Xaracoll® is not an antimicrobial agent, therefore, clinical microbiology information was not submitted in the NDA.

4.4. Nonclinical Pharmacology/Toxicology

The pharmacology-toxicology review team is recommending a Complete Response Letter for this marketing application based on the following deficiencies (paraphrased from Dr. Gary Bond's review):

- An adequate characterization of the systemic safety of bupivacaine exposures via the drug product formulation was not provided. Specifically, based on the existing human pharmacokinetic data, the product results in an $AUC_{(0\text{-last})}$ that is twice that of the referenced product. The existing toxicology data in the rat model do not test exposures that provide coverage for the human exposures via this drug product.
- A valid in vivo micronucleus assay for bupivacaine was not provided. Specifically, the high dose selected for the assay did not result in frank toxicity.
- An adequate extractables/leachables evaluation to support the safety of the proposed container closure system was not provided.
- An adequate justification for the proposed specification for (b) (4) in the drug product formulation was not provided.

For a more comprehensive discussion of the pharmacology-toxicology concerns, refer to the review completed by Dr. Gary Bond.

The following is a high-level discussion of the nonclinical wound healing data, which will help guide the clinical expectations after use of this product.

The Applicant conducted two nonclinical 56-day bupivacaine collagen implant toxicology studies in rats. Study (b) (4)-134502 was conducted using an earlier collagen development

product, therefore, the results were considered inadequate to address possible concerns associated with use of the to-be-marketed [redacted] (b) (4) collagen-containing drug product. In response to the Refuse to File (RTF) letter issued on December 23, 2016, the Applicant conducted a repeat nonclinical 56-day bupivacaine collagen implant toxicology study in rats, Study 00134509, using the final to-be-marketed formulation of XaraColl®. The collective results from these studies as reported by the Applicant are as follows:

> *"There was no impact on overall wound healing for either INL-001 test article (i.e., developmental and Phase 3/final commercial formulation lots) compared to the saline control in the two 56-day studies conducted in rats. The quantity of collagen implant material progressively decreased with increasing time as part of the healing process. In the initial study, no collagen-matrix material was observed microscopically by Day 28 and in the second study, the attrition rate was 95% by Day 28 and 100% at the external site (attrition) and ≥ 98% at the internal site by Day 35. By Day 56, no collagen matrix was observed microscopically. Although the complete absence of collagen matrix cannot be definitely ascertained, the biological attrition/incorporation of the extrinsic collagen by Day 56 is sufficient such that any remaining non-native collagen has been incorporated and/or undergone biological degradation with no overt cellular response and cannot be distinguished from native collagen."* (Source: Nonclinical Overview, p, 43 (PDF), Applicant's submission, NDA 209511)

The Applicant then states,

> *"A number of findings, often associated with the repair process, were observed across all dose groups including the saline controls in one or both of the 56-day rat studies. Findings of necrosis, chronic inflammation or mononuclear cell infiltrate, and/or fibroplasia while observed in control rats, tended to be greater in incidence, severity, and/or persistence in rats implanted with the bupivacaine collagen-matrix implant".* (Source: Nonclinical Overview, p, 43 (PDF), Applicant's submission, NDA 209511)

And finally concludes by stating,

> *"… no adverse impact on wound healing for animals administered the bupivacaine collagen-matrix implant compared to animals administered saline".* (Source: Nonclinical Overview, p, 43 (PDF), Applicant's submission, NDA 209511)

In general, the collective results from both nonclinical 56-day toxicology studies in rats appear supportive of wound healing after administration of XaraColl®, however, it is difficult to conclude that the development of fibrotic or scar tissue or adhesions will not have an adverse impact on future surgical dissection or re-exploration in the same surgical location, in the case of mesh removal or repeat ipsilateral inguinal hernia repair.

4.5. Clinical Pharmacology

4.5.1. Mechanism of Action

Nerve cells maintain a resting membrane potential (RMP) at -70 millivolts (mV) using an active Na^+-K^+ pump, which transports Na^+ out of the cell and K^+ into the cell. This pump results in a concentration gradient favoring intracellular Na^+ flux and extracellular K^+ flux via ion specific channels. Because the cell membrane is more permeable to K^+, there is greater efflux of K^+ versus influx of Na^+, which results in the negative RMP. During an electrical impulse, Na^+ channels are activated resulting in a sudden and fast influx of Na^+. The nerve membrane depolarizes and if it reaches the threshold level of -55 mV, the impulse is propagated as an action potential. As a result of this substantial influx of Na^+, the membrane potential rises to +35 mV, the Na^+ channels inactivate, and the membrane potential returns to -70 mV, the RMP.

Bupivacaine is an amide local anesthetic, which binds Na^+ channels in the inactive state, thereby preventing subsequent neuronal cell depolarization to the threshold level. Because the impulse is not properly conducted, sensation and motor function are impaired, depending on nerve fiber diameter, myelin composition, and conduction velocity. In general, small, unmyelinated fibers that mediate pain and temperature sensations are more readily blocked than larger, unmyelinated fibers. Bupivacaine is a potent local anesthetic due to its high lipid solubility and has a longer duration of action than lidocaine due to its high degree of protein binding.

4.5.2. Pharmacokinetics

Bupivacaine is primarily metabolized in the liver via conjugation with glucuronic acid. Pipecoloxylidine is the major inactive metabolite of bupivacaine and is excreted in the urine with any unconjugated parent compound. Renal excretion of bupivacaine and the metabolites is dependent on urine pH and renal perfusion.

The Applicant conducted two PK/BA studies, INN-CB-013 and INN-CB-022. It was determined that Study INN-CB-013 did not establish an adequate scientific bridge to another bupivacaine product for two reasons. First, the to-be-marketed formulation of INL-001 was not used in the study, which would likely impact the reported PK profile. Second, it was unclear which listed drug (LD) was used being used for the bridge. The problems with Study INN-CB-013, along with other issues, were the basis for support for the Refuse to File letter issued on December 23, 2016. In response to the RTF letter, the Applicant conducted a second PK/BA study, INN-CB-022, which will be briefly discussed here. For a complete evaluation of the clinical pharmacology assessment of XaraColl® and the results of the PK studies, refer to Dr. David Lee's review.

Study INN-CB-022

This was a randomized, single blind study to evaluate the PK, relative bioavailability, and safety of INL-001 compared to Marcaine™ 0.25%, 175 mg, wound infiltration, after open herniorrhaphy. Subjects were randomized 2:1 to receive XaraColl®, 300 mg total dose (3 x 100 mg), or Marcaine™ 0.25% wound infiltration intraoperatively. Subjects were transferred to the PACU post-operatively and treated with parenteral morphine as needed for pain and once tolerating oral medication, were started on a standard acetaminophen regimen of 650 mg three times daily. Immediate release morphine 15 mg was prescribed for breakthrough pain. Subjects remained in the clinic through the 72-hour PK blood sample collection and were instructed to return for the 96-hour blood sample collection. Follow-up assessments occurred on Days 7, 15, and 30. Safety assessments included frequent vital sign measurement through 72-hours, continuous ECG monitoring for at least 24-hours post-operatively, wound assessments, and adverse event reporting, with an emphasis on central nervous system (CNS) or cardiovascular toxicity. Refer to the following table for a complete listing of all study assessments:

Table 5. Schedule of Assessments for Study INN-CB-022

	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.

[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.
Source: CSR INN-CB-022, p. 34 (PDF), Applicant's submission, NDA 209511

The following PK parameters were assessed:

- Maximum plasma concentration, C_{max}
- Time to maximum plasma concentration, T_{max}
- Lag-time, t_{lag}
- Terminal half-life, $t_{1/2}$
- Terminal phase rate constant, λ_Z
- Area under the curve (AUC) from Time 0 to last time of last quantifiable plasma concentration, $AUC_{0\text{-last}}$
- AUC from Time 0 to infinity, $AUC_{0\text{-}\infty}$
- Percentage extrapolation, $AUC_{extrap\%}$

Calculated parameters included apparent plasma clearance, apparent volume of distribution, and relative bioavailability.

A total of 52 subjects were randomized and 50 completed the study. There was a single subject in each treatment group who was randomized but not enrolled.

PK results

The following PK results were reported:

- There was a quantifiable bupivacaine concentration for all subjects in both groups at 0.5 hours and through 96 hours.
- For the INL-001 group, the mean C_{max} was 663.4 ng/mL (274 ng/mL to 1230 ng/mL) and the median T_{max} was 3 hours. The geometric mean for $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ were 18186.9 h*ng/mL and 19012.5 h*ng/mL, respectively. The mean $t_{1/2}$ was approximately 19 hours.
- For the Marcaine™ group, the mean C_{max} was 641 ng/mL (275 ng/mL to 1140 ng/mL) and the median T_{max} was 1 hour. The geometric mean for $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ were 8836.9 h*ng/mL and 8920.1 h*ng/mL, respectively. The mean $t_{1/2}$ was 9 hours.
- The dose-normalized relative bioavailability for the INL-001 treatment group over the Marcaine™ treatment group for C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$ with a 90% confidence interval was 60.3% (48.8%, 74.6%), 120% (98%, 147%), and 124.3% (101.6%, 152.2%), respectively.

Based on these results, the Applicant has concluded that treatment with INL-001 results in a prolonged rate of absorption and clearance for bupivacaine when compared to treatment with Marcaine™. It is interesting, however, that both treatment groups had bupivacaine levels measurable at 0.5 and 96 hours, suggesting that both products can be detected in plasma for extended periods of time, regardless of any observed clinical effect. The reported dose-

normalized relative bioavailability demonstrated a lower C_{max} with comparable exposure for the INL-001 treatment group.

Safety Results

Greater than 90% of subjects in both treatment groups experienced at least one treatment-emergent adverse event (TEAE), with a slightly larger percentage in the INL-001 group (97% versus 94%). Somnolence was the most common TEAE reported in both groups with a similar incidence. There were no TEAEs that led to discontinuation and all TEAEs were mild or moderate in severity. There were no reported serious adverse events (SAE).

Approximately 18% of subjects in the INL-001 treatment group and 13% of subjects in the Marcaine™ treatment group experienced a drug-related TEAE, which included tremor, dysgeusia, and somnolence. For the nervous system SOC (system organ class), subjects treated with Marcaine™ wound infiltration had a consistently higher incidence of TEAE than subjects treated with INL-001, headache being the exception. Refer to the following table for a summary of TEAE by SOC and preferred term.

Table 6. Summary of TEAE (≥5% Overall) by System Organ Class and Preferred Term

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)

Source: CSR INN-CB-022, p. 57 (PDF), Applicant's submission, NDA 209511

There were no subjects in either treatment group who appeared to experience any of the known signs and symptoms of bupivacaine toxicity. The 24-hour continuous ECG data was evaluated and those results are discussed in Section 8.4.8, Electrocardiograms. Briefly, it did not appear that any subject in either group experienced cardiotoxicity due to bupivacaine administration, with particular focus on changes around T_{max}.

With respect to wound healing, subjects in the Marcaine™ wound infiltration treatment group had a higher incidence of adverse events early in the study and subjects in the INL-001 treatment group had a higher incidence later in the study. Specifically, approximately 13% of subjects treated with Marcaine™ experienced a wound-related adverse event on Day 1 compared to no subjects treated with INL-001. On Day 5, there were approximately 24% of subjects treated with INL-001 and 13% of subjects treated with Marcaine™ who experienced a wound-related adverse event. On Day 7, the incidence of wound related adverse events is similar, but on Days 15 and 30, there is a higher incidence of these adverse events reported for subjects treated with INL-001 compared to those treated with Marcaine™. Refer to the following table for a summary of wound-related adverse events on study Days 15 and 30.

Table 7. Wound-Related Adverse Events on Days 15 and 30

Visit Category	INL-001 (N= 34) n (%)	Marcaine (N= 16) n (%)
Day 15	2 (5.9)	0 (0.0)
Admitted to a hospital with an infection of the surgical wound	0 (0.0)	0 (0.0)
Any wound pain or soreness	0 (0.0)	0 (0.0)
Discharge or leakage of fluid	0 (0.0)	0 (0.0)
Prescribed antibiotics for an infection in the wound	0 (0.0)	0 (0.0)
Problems with hernia repair surgery	1 (2.9)	0 (0.0)
Redness or inflammation spreading from the edges	1 (2.9)	0 (0.0)
See a health care provider about the wound	1 (2.9)	0 (0.0)
Separation of the edges of any part of the wound	0 (0.0)	0 (0.0)
Swelling in the area around the wound	1 (2.9)	0 (0.0)
Warmth in the area around the wound	1 (2.9)	0 (0.0)
Day 30	3 (8.8)	0 (0.0)
Admitted to a hospital with an infection of the surgical wound	0 (0.0)	0 (0.0)
Any wound pain or soreness	1 (2.9)	0 (0.0)
Discharge or leakage of fluid	0 (0.0)	0 (0.0)
Prescribed antibiotics for an infection in the wound	0 (0.0)	0 (0.0)
Problems with hernia repair surgery	0 (0.0)	0 (0.0)
Redness or inflammation spreading from the edges	1 (2.9)	0 (0.0)
See a health care provider about the wound	0 (0.0)	0 (0.0)
Separation of the edges of any part of the wound	0 (0.0)	0 (0.0)
Swelling in the area around the wound	2 (5.9)	0 (0.0)
Warmth in the area around the wound	1 (2.9)	0 (0.0)

Source: CSR INN-CB-022, p. 252 (PDF), Applicant's submission, NDA 209511

It is reassuring that the late-appearing wound-related adverse events did not result in hospital admission, antibiotic treatment, or leakage of fluid or discharge. However, the impact of INL-001 on wound healing was extensively evaluated during the course of this NDA review and final conclusions are discussed in Section 8.4.5, Treatment Emergent Adverse Events and Adverse Reactions.

In conclusion, the PK profile of XaraColl®, when compared to Marcaine™ wound infiltration, suggests higher overall bupivacaine exposure with a later mean T_{max}. The release profile for bupivacaine from the XaraColl® matrices may be less consistent than that observed after wound infiltration, as demonstrated by a reported T_{max} of 24 hours for one subject in the INL-001 treatment group, and a total of three subjects with T_{max} greater than 23 hours. The latest T_{max} for the Marcaine™ treatment group was approximately 4 hours. Furthermore, there were 21% of subjects treated with INL-001 who had C_{max} levels >900 ng/mL, compared to 13% of subjects in the Marcaine™ treatment group.

The results from this study do support the safe use of XaraColl® during open inguinal hernia repair with mesh. Because XaraColl® has not been extensively studied in other surgical populations and given the wide range of some measured PK parameters in this study, which consisted of a single surgical population in almost all male patients, it is challenging to predict the PK profile of XaraColl® when used in different surgical models. Therefore, the results from this study can only support an indication for use during open inguinal hernia repair.

4.6. Devices and Companion Diagnostic Issues

Under 21 Code of Federal Regulations 3.2(e), the bupivacaine collagen-matrix is considered a drug/device combination product comprised of bupivacaine, the drug, and the collagen matrix, the device. Reviewers from CDRH and Office of Combination Products will address the potential issues surrounding the combination product classification in consultation responses, including whether XaraColl® is considered an implant in permanent contact with tissue and/or bone.

As discussed more thoroughly in Section 1.1, Product Introduction, the apparent mechanism of bupivacaine release is absorption of liquid from surrounding tissue into the collagen matrix, resulting in diffusion of bupivacaine and dissolution of collagen over time. The release of bupivacaine is not immediate, with approximately 57% released in the first hour, 81% released by eight hours, and 99% released by 24 hours, as determined in nonclinical studies. The Applicant has stated that this release profile is the same regardless of the surgical site. The collagen implant is degraded via slow chemical and enzymatic hydrolysis to soluble peptides and amino acids, which are subsequently absorbed into surrounding tissues. The nonclinical studies suggest that the implant is entirely degraded and absorbed by 56-days post-implantation, supporting the Applicant's claim that this is likely not a permanent implant.

As will be described in the final product label, the bupivacaine collagen-matrix can be cut into smaller pieces and inserted at various layers throughout the soft tissue surgical wound. INL-001 is compatible with surgical materials such as mesh and suture. The matrices do not need to be secured in place, either via suturing or stapling.

5. Sources of Clinical Data and Review Strategy

5.1. Tables of Clinical Studies

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Table 8. Clinical Trials Supporting NDA 209511

Study Identity	NCT no.	Study Design	Regimen and Route	Primary Study Objective(s)	Study Population	No. of patients enrolled	No. and location of centers
Controlled Studies to Support Efficacy and Safety							
INN-CB-003	NCT00626886	Phase 2, multi-center, randomized, single-dose, double-blind, placebo-controlled	Surgical implantation of the following: INL-001 – two 50 mg bupivacaine implants (total dose 100 mg) Pbo – two placebo collagen implants Each matrix contained 70 mg bovine Type I collagen (total dose 140 mg)	To compare the total use of opioid rescue analgesia over 24 hours after hernioplasty by treatment group	Adult males scheduled to undergo an open unilateral inguinal herniorrhaphy, performed according to standard surgical technique	INL-001: 24 enrolled and completed pbo-collagen: 29 enrolled and completed	8 investigative sites within the U.S. randomized subjects
INN-CB-010	NCT01220024	Phase 2, multi-center, randomized, single-dose, double-blind, placebo-controlled	Surgical implantation of the following: INL-001 – two 100 mg bupivacaine implants (total dose 200 mg) Pbo – two placebo collagen implants Each matrix contained 75 mg bovine Type I collagen (total dose 225 mg)	To compare the sum of pain intensity after aggravated movement over the first 72 hours after hernioplasty by treatment group	Adult males scheduled to undergo an open unilateral inguinal herniorrhaphy, performed according to standard surgical technique	50 male patients enrolled, 48 completed	5 investigative sites within the U.S. randomized subjects
INN-CB-014	NCT02523599	Phase 3, multi-center, randomized, double-blind, placebo-	Surgical implantation of the following: INL-001 – three 100 mg bupivacaine implants (total dose	To compare the analgesic effect of INL-001 to the placebo-collagen implant for the management of	Adult males and females scheduled to undergo an open unilateral inguinal herniorrhaphy,	INL-001: 204 enrolled, 196 completed pbo-collagen: 101	20 investigative sites within the U.S. randomized subjects

Study Identity	NCT no.	Study Design	Regimen and Route	Primary Study Objective(s)	Study Population	No. of patients enrolled	No. and location of centers
		controlled	300 mg) Pbo – three placebo collagen implants Each matrix contained 75 mg bovine Type I collagen (total dose 225 mg)	acute post-operative pain after open laparotomy inguinal hernioplasty	performed according to standard surgical technique	enrolled, 100 completed	
INN-CB-016	NCT02525133	Phase 3, multi-center, randomized, double-blind, placebo-controlled	Surgical implantation of the following: INL-001 – three 100 mg bupivacaine implants (total dose 300 mg) Pbo – three placebo collagen implants Each matrix contained 75 mg bovine Type I collagen (total dose 225 mg)	To compare the analgesic effect of INL-001 to the placebo-collagen implant for the management of acute post-operative pain after open laparotomy inguinal hernioplasty	Adult males and females scheduled to undergo an open unilateral inguinal herniorrhaphy, performed according to standard surgical technique	INL-001: 213 enrolled, 203 completed pbo-collagen: 106 enrolled, 103 completed	19 investigative sites within the U.S. randomized subjects
Clinical Pharmacology Studies							
INN-CB-013	NCT02232178	Phase 2, randomized, single-dose, double-blind, active control	Surgical implantation of the following: INL-001 – two 100 mg bupivacaine implants (total dose 200 mg) INL-001 – three 100 mg bupivacaine implants (total dose 300 mg)	To estimate the pharmacokinetic profile of two doses of INL-001 after open laparotomy hernioplasty To estimate the relative bioavailability of INL-001 compared	Adult males and females scheduled to undergo an open unilateral inguinal herniorrhaphy, performed according to standard surgical technique	2 INL-001: 26 enrolled, 25 completed 3 INL-001: 25 enrolled, 24 completed Bupivacaine infiltration: 13 enrolled, 12 completed	5 investigative sites within the U.S. randomized subjects

Study Identity	NCT no.	Study Design	Regimen and Route	Primary Study Objective(s)	Study Population	No. of patients enrolled	No. and location of centers
			Bupivacaine infiltration – 60 mL of 0.25% bupivacaine with epinephrine Each matrix contained 75 mg bovine Type I collagen (total dose 225 mg)	to local bupivacaine infiltration			
INN-CB-022	NCT03234374	Phase 1, randomized, single-dose, double-blind, active control	Surgical implantation of three 100 mg bupivacaine implants (total dose 300 mg) Bupivacaine infiltration – 70 mL of 0.25% Marcaine™ Each matrix contained 75 mg bovine Type I collagen (total dose 225 mg)	To estimate the PK profile of INL-001 during and after open hernioplasty To estimate the relative bioavailability of INL-001 compared with local bupivacaine infiltration	Adult males and females scheduled to undergo an open unilateral inguinal herniorrhaphy, performed according to standard surgical technique	3 INL-001: 34 enrolled and completed Bupivacaine infiltration: 16 enrolled and completed	5 investigative sites within the U.S. randomized subjects

Source: Adapted from *Tabular Listing of All Clinical Studies*, Applicant's submission, NDA 209511

In addition to the studies used to support the claimed indication, described in the table above, the Applicant also conducted one Phase 1 and four Phase 2 studies. These studies evaluated different doses of INL-001 in different surgical populations, and while the efficacy data does not entirely support the claimed indication for this drug product, the safety information was evaluated during the clinical review of this NDA. The additional studies are briefly summarized in the table below.

Table 9. Additional Phase 1 and Phase 2 Clinical Studies Conducted by the Applicant

Study number	Study design	Regimen and route	Study population	Number of patients
INN-CB-001	Phase 1, single-dose, open-label, PK, safety	Surgical implantation of three 50 mg bupivacaine implants (total dose 150 mg) Each matrix contained 75 mg bovine Type I collagen (total dose 225 mg)	Adult females scheduled for hysterectomy for reasons other than known or suspected malignancy	13 enrolled 12 completed
INN-CB-002	Phase 2, randomized, single-dose, double-blind, placebo controlled	Surgical implantation of the following: INL-001 – three 50 mg bupivacaine implants (total dose 150 mg) Pbo – three placebo collagen implants Each matrix contained 70 mg bovine Type I collagen (total dose 210 mg) Standard of care – same treatment as active and pbo groups but not implanted matrices	Adult females scheduled for hysterectomy or other non-laparoscopic benign gynecological procedure for reasons other than known or suspected malignancy	INL-001: 28 enrolled, 27 completed pbo-collagen: 15 enrolled and completed standard care: 11 enrolled, 10 completed
INN-CB-004	Phase 2, randomized, single-dose, double-blind, placebo controlled	Surgical implantation of the following: INL-001 – three 50 mg bupivacaine implants (total dose 150 mg) or four 50 mg bupivacaine implants (total dose 200 mg) Pbo – three or four placebo collagen implants Each matrix contained 70 mg bovine Type I collagen (total dose 210 mg or 280 mg)	Adult males and females scheduled for elective surgery that required a vertical or transverse abdominal incision	3 INL-001: 2 enrolled, 1 completed 4 INL-001: 2 enrolled and completed 3 pbo-collagen: 1 enrolled and completed 4 pbo-collagen: 2 enrolled, 1 completed

Study number	Study design	Regimen and route	Study population	Number of patients
INN-CB-005	Phase 2, randomized, single-dose, unblinded	Surgical implantation of three 50 mg bupivacaine implants (total dose 150 mg) Each matrix contained 70 mg bovine Type I collagen (total dose 210 mg or 280 mg) ON-Q PainBuster® bupivacaine HCl infused at 5 mL (12.5 mg)/hour for 72 hours (total dose 900 mg)	Adult females scheduled for hysterectomy or other non-laparoscopic benign gynecological procedure for reasons other than known or suspected malignancy	INL-001: 14 enrolled, 13 completed ON-Q: 13 enrolled and completed
INN-CB-011	Phase 2, single-dose, open-label	Surgical implantation of four 50 mg bupivacaine implants (total dose 200 mg) Each matrix contained 70 mg bovine Type I collagen (total dose 280 mg)	Adult males scheduled to undergo an open or laparoscopic unilateral inguinal herniorrhaphy or laparoscopic umbilical hernioplasty, performed according to standard surgical technique	10 enrolled and completed

Source: Adapted from *Tabular Listing of All Clinical Studies*, Applicant's submission, NDA 209511

5.2. Review Strategy

The following sources of information were included in the review of this 505(b)(2) marketing application:

Studies performed by Innocoll Inc.

The Applicant has conducted two clinical pharmacology, PK/BA, studies, two Phase 2 clinical studies, and two Phase 3 clinical studies. A brief overview of these supportive studies is included in Table 8, above. Additional information was provided from the Phase 1 and Phase 2 clinical studies conducted by the Applicant and briefly described in Table 9.

Listed drug referenced in this NDA

The Applicant is relying on the Agency's previous findings of safety and effectiveness for Marcaine™ 0.25% (NDA 016964). The scientific rationale for such reliance is based on the results of the PK/BA study, INN-CB-022, conducted by the Applicant. While some of the PK parameters would be expected to be different between the immediate release bupivacaine and the slower release XaraColl®, such as T_{max} and AUC values for all time periods, the C_{max} values were similar, 641 ng/mL versus 663 ng/mL respectively. Additionally, the peak C_{max} values were also similar for both groups, 1140 ng/mL versus 1230 ng/mL respectively. Because bupivacaine toxicity is primarily dependent on the peak systemic exposure and not overall exposure, the Applicant states that the risk of toxicity after administration of XaraColl® is comparable to that

observed after administration of Marcaine™.
As will be discussed in Section 8.10, Integrated Assessment of Safety, the peak systemic exposure impacts the safety profile of all local anesthetics and is historically the PK parameter that defines toxicity. There are three concerns, however, regarding safety claims for XaraColl® based solely on C_{max} values. First, the definitive peak concentration at which toxicity can be observed is variable and depends on underlying individual comorbid medical conditions and concomitant medication administration. Additionally, the reported systemic concentration likely to lead to toxicity is different for each local anesthetic. Second, the release profile for bupivacaine from XaraColl® is variable and somewhat unpredictable, as demonstrated in Study INN-CB-022. And third, a single surgical population was evaluated in the Phase 3 studies, making broad generalizations about the PK profile of XaraColl® for all soft tissue surgeries unreliable and challenging.

The sections of the Marcaine™ label specifically relied upon include the following:

- Section 2 – DOSAGE AND ADMINISTRATION
  - 2.2 – Compatibility Considerations
- Section 5 – WARNINGS AND PRECAUTIONS
  - 5.1 – Warnings and Precautions for Bupivacaine Containing Products, CNS Reactions, CVS Reactions, Allergic Reactions
  - 5.2 – Warnings and Precautions Specific for XaraColl®
- Section 6 – ADVERSE REACTIONS
  - 6.1 – Bupivacaine Adverse Reactions
- Section 8 – USE IN SPECIAL POPULATIONS
  - 8.1 – Pregnancy
  - 8.2 – Lactation
  - 8.5 – Geriatric Use
  - 8.6 – Hepatic Impairment
  - 8.7 – Renal Impairment
- Section 10 – OVERDOSAGE
- Section 12 – CLINICAL PHARMACOLOBY
  - 12.1 – Mechanism of Action
  - 12.2 – Pharmacodynamics
  - 12.3 – Pharmacokinetics
- Section 13 – NONCLINICAL TOXICOLOGY
  - Section 13.1 – Carcinogenesis, Mutagenesis, Impairment of Fertility
- Section 17 – PATIENT COUNSELING INFORMATION

There are no outstanding patents or exclusivity periods, as indicated in the Approved Drug Products with Therapeutic Equivalence Evaluations publication, commonly referred to as the Orange Book.

Information from the published literature

The Applicant is relying on information in the published literature to support the safety and efficacy of XaraColl®, including information regarding its use during pregnancy and lactation. The literature searches were conducted in Medline, Embase, and the Cochrane Library with a cutoff date of December 2017. The search terms included "bupivacaine", "Marcaine", and relevant soft tissue surgeries, including herniorrhaphy, hysterectomy, and cholecystectomy. The reliance on the published literature information is summarized below for efficacy and safety. The information relied upon for use of XaraColl® during pregnancy and lactation is discussed in Section 8.8.3, Pregnancy and Lactation.

Efficacy information

The database searches yielded 82 clinical studies, which were summarized in the Applicant's submission, to support the claimed efficacy of bupivacaine. Both placebo-controlled and active-controlled studies were reviewed. The active-controls included levobupivacaine, lidocaine, lignocaine, ropivacaine, opioid analgesics, and non-opioid analgesics. In general, the findings of these studies support the Applicant's claim that bupivacaine wound infiltration provides post-operative analgesia following soft tissue surgical procedures. The degree and duration of the analgesic effect can vary between soft tissue surgical sites, the dose administered, and infiltration techniques employed.

Safety information

The Applicant relied on safety information for bupivacaine from 40 clinical studies described in the published literature. The studies reviewed included a range of administered bupivacaine doses; from 25 mg to 660 mg for single administrations and 1.2 mg to 12.5 mg per hour for continuous infusions. The adverse events discussed in the reviewed clinical studies are consistent with those described in the Marcaine™ product label and include constipation, dizziness, sedation, nausea, and vomiting. These adverse events were reported for all surgery types. Other adverse events reported in the published literature include the following:

- Arrhythmia, bradycardia, tachycardia
- Chest infection, respiratory infections, fever, shivering, tachypnea, lactic acidosis
- Constipation, ileus
- Dysgeusia, metallic taste, numbness
- Paresthesia, somnolence, tinnitus
- Wound infection, seroma, hydrocele, hematomas
- Pruritus, headache
- Urinary retention

In the bupivacaine treatment groups, there were no serious adverse events or deaths reported in the clinical studies reviewed by the Applicant. In the study by Kushner *et al* (2005), serious adverse events including myocardial infarction, cerebrovascular accident, pulmonary emboli, and allergic reaction (to presumed paclitaxel) were all reported for subjects in the placebo group.

Information in the published literature did not frequently include vital sign or physical examination findings, unless there was a clinical concern or relevant observation. Vijayakumar *et al* (2016) reported that patients in the bupivacaine treatment group had better immediate post-operative blood pressure and heart rate relative to those in the placebo group. Raetzell *et al* (1995) reported a decrease in respiratory function after laparoscopic cholecystectomy in all groups, with the greatest decrease and more hypoxic periods observed in the bupivacaine treatment group.

The review of the safety information from the published literature submitted by the Applicant appears to support the safe use of bupivacaine as the drug component of XaraColl®. No new safety signals were identified during the literature review.

6. Review of Relevant Individual Trials Used to Support Efficacy

The controlled clinical studies used to support the proposed indication are two Phase 2 studies, INN-CB-003 and INN-CB-010, and two Phase 3 studies, INN-CB-014 and INN-CB-016. The Phase 2 studies were randomized, double-blind, placebo-controlled studies in subjects undergoing IHR with mesh, however, they do not fully support the proposed indication for to-be-marketed product for the following reasons and will not be discussed in detail in this review:

- Study INN-CB-003 failed on the primary efficacy endpoint of total opioid rescue analgesia over 0 to 24 hours. The total dose of bupivacaine in the collagen-matrices was 100 mg, which may explain the lack of efficacy.
- Study INN-CB-010 also failed on the primary efficacy endpoint of sum of pain intensity with cough (aggravated movement) over 1 to 72 hours. The total dose of bupivacaine in the collagen-matrices was 200 mg, lower than the proposed 300 mg in the to-be-marketed product.

6.1. 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-014)

6.1.1. Study Design

Overview and Objective

Study INN-CB-014, a Phase 3 study, was conducted by Innocoll Pharmaceuticals to evaluate the safety and efficacy of XaraColl® for postsurgical analgesia following open inguinal hernia repair with mesh. The objectives of the study were as follows:

- Primary objective (verbatim): to compare the analgesic effect of the INL-001 implant to

that with the placebo implant for the management of acute postsurgical pain using the surgical model of open laparotomy inguinal hernioplasty

- Secondary objective (verbatim): to assess the safety and tolerability of INL-001 after its implantation into surgical wounds during hernioplasty surgery

Trial Design

This study was a Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled study in adults who were scheduled for unilateral inguinal hernioplasty via open laparotomy (tension-free technique using mesh) under general anesthesia. Patients were stratified by gender and history of previous ipsilateral hernia repair. A total of 305 subjects were randomized in a 2:1 ratio to receive three INL-001, 100 mg collagen-matrices (for a total dose of 300 mg of bupivacaine) or three placebo collagen-matrices. Both matrices measured 5 x 5 x 0.5 cm and were off-white to white. A total of 304 subjects were treated.

The INL-001 or placebo collagen-matrices were implanted at multiple layers in the soft tissue between the fascia/muscle closure and in the layers below the skin closure. Specifically, each of the three matrices was cut in half, resulting in six half matrices each measuring approximately 2.5 x 2.5 x 0.5 cm. Three half matrices were implanted below the mesh, on the abdominal wall repair, and the remaining three half matrices were implanted between the fascial closure and the skin incision. Following surgery, subjects were transferred to the post-anesthesia care unit (PACU) for a minimum observation period of 3 hours. Analgesia was provided initially via parenteral morphine as needed. Once subjects were tolerating oral medication, they received a standard acetaminophen regimen (650 mg three times daily) and were offered immediate-release morphine, 15 mg, for breakthrough pain if needed. Pain intensity was reported using an 11-point numerical rating scale (NRS), 0 to 10, at the following time points:

- prior to taking analgesic medication from Time 0 through 72 hours post-operatively (Time 0 defined as time of first implant of test article)
- at pre-defined time points from 1 hour through 72 hours post-operatively
- prior to the standard acetaminophen doses beginning the morning after surgery through 72 hours post-operatively

Subjects were discharged from the PACU after the 3-hour vital sign and pain intensity assessments were completed. Follow-up phone calls occurred approximately 6, 24, and 48 hours after study drug implantation. Subjects returned to the clinic 72 hours post-operatively to perform final pain intensity and safety assessments. Subjects recorded any new or ongoing AEs through Day 7. Final follow-up assessments were performed on post-operative day 7 (telephone call), and Days 15 and 30 (clinic visits). The schedule of assessments during this study is summarized in Table 10.

Table 10. Study Assessments

	Screening	Immediate Preoperative Period	Intra-operative Period	Post Implantation Period										Follow-up		
Day	**-30 to -1**	**0**		**0**							**1**	**2**	**3 ET**	**7**	**15**	**30**
Time (hours)			**0**	**1 ±15 min**	**2 ±15 min**	**3 ±15 min**	**5 ±15 min**	**6 ±1 hr**	**8 ±1 hr**	**12 ±2 hr**	**24 ±3 hr**	**48 ±3 hr**	**72 ±4 hr**	**±1 day**	**±2 days**	**±3 days**
Written informed consent	X															
Inclusion/exclusion criteria	X	X														
Obtain screening number	X															
Medical history	X	X[a]														
Demographics	X															
Electrocardiogram	X															
Physical examination, weight, and height	X															
Clinical laboratory tests[b]	X															
Urine for pregnancy test (female subjects)		X[c]														
Vital signs	X	X		X	X	X	X[d]		X[d]				X			
Adverse events[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Enrollment/randomization		X														
Surgery/implantation			X													
Provide eDiary				X												
Pain intensity rating (NRS)			X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]			
Record use of analgesic medication			X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]			
Provide acetaminophen and prescription for oral morphine							X[h]									
Confirm eDiary use								X			X	X				
Subject general evaluation													X			
Collect eDiary and acetaminophen													X			
Telephone call								X			X	X		X		
Clinic visit													X		X[i]	X[i]

ET = early termination

[a]Updated medical history since screening.

[b]Included hematology, chemistry, urinalysis, and urine for drugs of abuse or misuse, including cannabinoids. A blood sample for pregnancy testing was obtained from female subjects.

[c]Results must have been available before implantation.

[d]Assessments were not performed in subjects who discharged prior to the designated time point.

[e]Adverse events were collected from the time of implantation through Day 30.

[f]beginning at Time 0 (when first test article was implanted) and continuing through the 72-hour time point (Day 3), PI was assessed by the subject using the 11-point NRS immediately before the administration of any parenteral or oral rescue opioid analgesia for breakthrough pain. While in the PACU, PI before administration of opioid analgesia was recorded on the CRF by the site coordinator. Pain intensity was also assessed by the subject at all protocol-defined time points (1, 2, 3, 5 [each had a ±15 minutes window], and at 8±1, 12±2, 24±3, 48±3, and 72±4 hours after Time 0) and recorded in the eDiary. Additionally, beginning the morning after surgery, subjects recorded PI in their diary immediately before taking scheduled acetaminophen 3 times daily until the 72-hour visit.

[g]Subjects took acetaminophen 650 mg 3 times daily and recorded in their diary until the 72-hour time point. Rescue opioid analgesia for breakthrough pain starting at Time 0 through the 72-hour time point was also recorded in the CRF (i.e., unscheduled time points between Time 0 and Hour 3) and/or eDiary.

[h]At time of discharge (any time after 3 hours), instructed subject on use of analgesia medications (acetaminophen and oral morphine) and eDiary use.

[i]Visit to assess surgical site and adequacy of hernia repair.

Source: CSR INN-CB-014, p. 25-26 (PDF), Applicant's submission, NDA 209511. Of note, the study protocol does not indicate a pain score was recorded at the 6-hour post-operative time point. This appears to be checked in error in this table.

Study Population

Eligibility criteria

Pertinent inclusion criteria included the following:

- adult patient
- planned, non-emergent unilateral inguinal hernia repair under general anesthesia
- non-pregnant female
- willing to use opioid analgesia

Pertinent exclusion criteria included the following:

- hypersensitivity to amide local anesthetics, morphine, acetaminophen, or bovine products
- planned bilateral inguinal hernioplasty or other significant concomitant surgical procedure(s)
- major surgical procedure in the preceding three months or planned laparotomy within 30 days
- any analgesic use, aside from acetaminophen, within 24 hours
- aspirin, aspirin-containing products within seven days; aspirin ≤325 mg was permitted for cardiovascular prophylaxis if the dose had been stable for ≥30 days before screening
- use of systemic steroids, anticonvulsants, antiepileptics, or antidepressants for the management of chronic pain, or monoamine oxidase inhibitors on a regular basis within ten days of surgery
- use of any opioid analgesic for an extended daily basis (30 - 60 mg oral morphine equivalent per day for three or more days a week) within four weeks before surgery; subjects who, in the investigator's opinion, may have been developing opioid tolerance were also excluded
- any chronic painful condition (e.g., fibromyalgia) or routinely used pain medication other than acetaminophen (including nonsteroidal anti-inflammatory drugs)
- showed evidence of tolerance or physical dependency on opioid analgesics or sedative-hypnotic medications
- positive urine drug screen
- liver function tests >three times the upper limit of normal or history of cirrhosis
- any clinically significant unstable cardiac disease (e.g., uncontrolled hypertension, clinically significant arrhythmia at baseline, or an implantable cardioverter-defibrillator)
- any clinically significant unstable neurological, immunological, renal, or hematological disease (e.g., uncontrolled diabetes or significantly abnormal laboratory findings)
- open workmans' compensation claim
- participated in clinical trial within 30 days of surgery

Study Endpoints

Primary efficacy endpoint

The primary efficacy endpoint was the time-weighted sum of pain intensity from Time 0 to 24 hours (SPI24) and was compared once using a 2-sided 0.05 level of significance. No multiplicity adjustments were necessary for the primary efficacy analysis.

Key secondary efficacy endpoints

The key secondary efficacy endpoints are as follows:

- Total use of opioid analgesia from Time 0 through 24 hours (TOpA24)
- Time-weighted sum of pain intensity from Time 0 to 48 hours (SPI48)
- Total use of opioid analgesia from Time 0 through 48 hours (TOpA48)
- Time-weighted sum of pain intensity from Time 0 to 72 hours (SPI72)
- Total use of opioid analgesia from Time 0 through 72 hours (TOpA72)

These endpoints were tested sequentially in a fixed order at the 0.05 significance level to control the Type-I error rate. Each secondary endpoint was tested in a hierarchical manner, such that the subsequent endpoint was evaluated only if the preceding ones were statistically significant.

Other secondary efficacy endpoints

- Continuous secondary efficacy endpoints included the following:
  - sum of pain intensity (SPI) at predefined time points through 12 hours
  - numeric rating scale (NRS) of PI at scheduled time points
  - total use of parenteral opioid analgesia (POpA) from 0 through 24 hours
  - TOpA at scheduled time points through 12 hours
  - TOpA from Time 0 to prior to discharge
- Categorical secondary efficacy endpoints included the following:
  - percentage of patients who used any oral rescue opioid analgesia after leaving the PACU at scheduled time points through 72 hours
  - percentage of patients who did not use opioid rescue analgesia
  - patient general evaluation of pain through 72 hours on a 5-point verbal rating scale
  - patient overall evaluation of pain through 72 hours compared with expectation on a 5-point categorical scale
  - patient overall evaluation of pain interference on activity through 72 hours on an 11-point NRS
- Time to event secondary efficacy endpoints included the following:
  - time to first use of rescue opioid analgesia (FOpA)
  - time to first use of oral rescue opioid analgesia (FOpA oral)

Exploratory efficacy endpoint

Integrated sum of pain intensity and total use of opioid analgesia (using the Silverman method of summated percentage differences from mean rank) from Time 0 to 24, 48, and 72 hours.

Intravenous Morphine Equivalents

The Applicant used the opioid conversion table as described by Gordon *et al* (1999), included below. All opioid analgesics were converted to IV morphine equivalents and calculated on a cumulative basis through 72 hours.

Table 11. Opioid Conversion Table

TABLE 1. EQUIANALGESIC TABLE

Drug	*Parenteral*	*PO*	*Parenteral:PO ratio*	*Duration of action (hr)*
Morphine	10	30	1:3	3–4
Hydromorphone (Dilaudid)	1.5	7.5	1:5	3–4
Oxymorphone (Numorphone)	1	10	1:10	3–4
Oxycodone° (Roxicodone, Roxicet, Percocet)	Not available in U.S.	20–30	—	3–4
Codeine	130	200 NA	1:1.5	3–4
Hydrocodone°° (Vicodin, Vicoprofen, Lortab, Lorcet)	—	30 NA	—	3–4
Propoxyphene (Wygesic, Darvocet)	—	NA*	—	4–6
Meperidine (Demerol)	75	300**	1:4	3–4
Levorphanol (Levo-Dromoran)	2	4	1:2	3–4
Methadone (Dolophine)	10	3–5***	—	4–12
Fentanyl (Sublimaze) (Duragesic^)	0.1^	—	—	1–3^^

Adapted from Cherny NI. Drugs 1996[43]; 51:713–737; Pasero C, Portenoy R, McCaffery M. *Pain: Clinical Manual*. St. *Louis, Mosby* 1999[14]; UW Health Pain Reference Card 4th ED, UW Board of Regents, 1998.

Source: Gordon DB, Stevenson KK, Griffie J, Muchka S, Rapp C, Ford-Roberts K. Opioid equianalgesic calculations. *J Palliat Med*. 1999;2(2):209-218.

Statistical Analysis Plan

Summary statistics were presented by treatment group. For continuous variables, the number of available observations, mean, standard deviation, median, and range were provided unless otherwise stated. For categorical variables, the frequency and percentage in each category was displayed. All statistical tests were given with two-sided p-values. For descriptive purposes, two-sided 95% confidence intervals were provided.

The intent-to-treat population consisted of all randomized patients who may or may not have received any dose of XaraColl® or placebo. This population was used for disposition count purposes and no statistical evaluations were performed using this population.

The efficacy assessments were performed using the modified intent-to-treat population, which consisted of all subjects who were randomized and received any dose of XaraColl® or placebo and had at least one pain intensity score prior to hospital discharge. The subjects were analyzed according to the assigned treatment at randomization.

The per protocol population was all mITT subjects who had non-significant protocol violations and had at least three pain intensity assessments, of which at least one was prior to hospital discharge and at least one corresponded to a pain intensity assessment at 24 hours or later.

Refer to Dr. Yi Ren's statistical review for additional information regarding the SAP.

Protocol Amendments

There was one amendment to the original protocol that was implemented prior to the enrollment of any study subjects. The key changes to the original protocol in this amendment were as follows:

- Updated sections and the synopsis to:
  - clarify the primary objective and patient stratification for consistency
  - state that nausea, vomiting, and constipation were collected and reported as adverse events
  - correct the fentanyl dose to 100 mcg
  - correct the time when the NRS was used to assess PI
  - clarify the definition of the ITT and mITT analysis populations
  - add details to the intraoperative procedure technique
  - revise the sample size
  - update primary efficacy endpoint from integrated sum of pain intensity and total use of opioid analgesia from Time 0 to 24 hours (I-SPI-TOpA24) to sum of pain intensity difference from Time 0 through 24 hours (SPID24)
  - change primary and secondary efficacy variables
  - add exploratory efficacy variables
- Increased patient enrollment to 300
- Patients with evidence of tolerance or physical dependence to opioid analgesics or sedative-hypnotic medications
- Clarified the size of the INL-001 and placebo implant
- Added sections 11.2.1.2 Rescue Opioid Analgesia for Breakthrough Pain and 11.2.1.3 Scheduled Acetaminophen Analgesia
- Clarified the pre-rescue or pre-acetaminophen pain intensity assessment
- Correct the sum of pain intensity time points
- Clarified timing of laboratory, ECG, and physical examination assessments and analyses
- Clarified that compliance of INL-001 would not be evaluated by compliance of other medications would be
- Urine pregnancy testing on Day 3 omitted

Handling of Missing Data (per SAP)

<u>Missing pain intensity (PI) assessments</u> (verbatim)

- PI at scheduled time point: if no observed PI assessment fell within the time window of a scheduled time point, the PI value at that time point was considered as missing
- Pre-rescue PI in the PACU: if a subject received a rescue medication in the PACU but there was no PI assessment recorded on the CRF that immediately preceded the administration of the rescue medication within 30 minutes, the "pre-rescue" PI score for this rescue medication was considered as missing
- Pre-rescue PI after discharge from PACU: if a subject recorded a rescue medication in the eDiary but there was no associated PI assessment recorded in the eDiary, the "pre-rescue" PI score for this rescue medication was considered as missing
- Pre-acetaminophen PI after Day 0: if a subject recorded an acetaminophen administration in the eDiary but there was no associated PI assessment recorded in the eDiary, the "pre-acetaminophen" PI score for this acetaminophen dose was considered as missing.

Imputation for missing PI assessments

Missing PI values before the first observed PI value were imputed using the worst observed PI for that patient. Missing PI values between two observed PI values, or intermittent missing, were imputed using linear interpolation. Missing PI values after the last observed PI value, or monotone missing, were imputed using last observation carried forward (LOCF), except under the following situations:

- If a patient was terminated early and surgical removal of the matrices was performed, worst observation carried forward (WOCF) method was applied from the time of termination through 72h
- If a patient was terminated early and had taken opioid rescue less than four hours before, the last observed pre-rescue PI value was carried forward through 72h.

Several sensitivity analyses were performed to demonstrate that the above imputation rules were adequate to describe the pain intensity profile for each patient.

6.1.2. Study Results

The study results presented by the Applicant are discussed in this section. The reviewer's analyses and interpretation of efficacy results are discussed in Section 7, Integrated Review of Effectiveness.

Compliance with Good Clinical Practices

Per the CSR for Study INN-CB-014, p. 11 (PDF), "*This study was conducted in compliance with the Declaration of Helsinki and its amendments, the International Council for Harmonisation (ICH) principles of Good Clinical Practice (GCP; including archiving of essential study documents), all United States (US) Food and Drug Administration regulations, and other applicable local regulations and guidelines.*"

Financial Disclosure

Pepe Carmona, Chief Financial Officer, Innocoll Pharmaceuticals, signed FDA form 3454 on October 4, 2016, certifying that he has not entered into any financial arrangement with any of the listed clinical investigators. He further certified that none of the individual investigators has a proprietary interest in this drug product or a significant equity in the Sponsor per 21 CFR 54.2(b) or received payments in excess of what is permitted per 21 CFR 54.2(f).

Patient Disposition

A total of 305 patients were randomized in Study INN-CB-014; 204 were randomized to the INL-001 treatment group and 101 were randomized to the placebo group. The following table summarizes patient disposition:

Table 12. Patient Disposition

	INL-001	Placebo	Total
Randomized	204	101	305
Completed	196	100	296
Discontinued	8	1	9
– Adverse event	1 (SAE)	0	1
– Lost to f/u	4	1	5
– Other	3 (2 did not complete 30-d eval, 1 not treated)	0	3

Reviewer's summary

The majority of patients completed the study and the most common reason for premature discontinuation from the study was being lost to follow-up.

Protocol Violations/Deviations

The Applicant defined significant protocol deviations as those related to test article implantation, violation of eligibility criteria, use of prohibited medications (with a focus on those that could have impacted pain assessments), and absence of the required number of pain intensity assessments post-implantation. There were 23 subjects with significant protocol deviations, as summarized in the following table. These subjects were excluded from the analysis populations.

Table 13. Subjects Excluded from the Analysis Populations

Subject Number	Population Excluded From:	Reason
INL-001		
(b) (6)	mITT, PP, safety	Did not receive INL-001 or placebo matrix; violation of eligibility criteria[a]
	mITT, PP	Did not have at least 1 NRS PI score prior to hospital discharge, as needed, to compute SPI
	PP	Took prohibited medication
	mITT, PP	Did not have at least 1 NRS PI score prior to hospital discharge, as needed, to compute SPI
	mITT, PP	Did not have at least 1 NRS PI score prior to hospital discharge, as needed, to compute SPI
	PP	Took prohibited medication
	PP	Took prohibited medication
	PP	Violation of eligibility criteria[b]
	PP	Violation of eligibility criteria[c]
	PP	Took prohibited medication
	mITT, PP	Did not have at least 1 NRS PI score prior to hospital discharge, as needed, to compute SPI
	mITT, PP	Did not have at least 1 NRS PI score prior to hospital discharge, as needed, to compute SPI
	PP	Took prohibited medication
	mITT, PP	Did not have at least 1 NRS PI score prior to hospital discharge, as needed, to compute SPI
	PP	Took prohibited medication
	PP	Violation of eligibility criteria[d]
	PP	Violation of eligibility criteria[e]
	PP	Did not have 3 or more PI assessments with at least 1 prior to hospital discharge and at least 1 at 24 hours or later
	PP	Took prohibited medication
	PP	Took prohibited medication
	PP	Violation of eligibility criteria[f]
	PP	Took prohibited medication
	PP	Violation of eligibility criteria[g]

Data source: Appendix 16.2, Listings 16.2.1, 16.2.2, and 16.2.3

[a]Subject (b) (6) did not meet Exclusion Criterion No. 13 (i.e., had any clinically significant unstable cardiac disease); the subject was not implanted with test article.

[b]Subject (b) (6) did not meet Exclusion Criterion No. 7 (i.e., had used any opioid analgesic for an extended daily basis within 4 weeks before surgery; subjects who may have been developing opioid tolerance were also excluded), Exclusion Criterion No. 10 (i.e., showed evidence of tolerance or physical dependency on opioid analgesics or sedative hypnotic medications), and Exclusion Criterion No. 11 (ie, had a urine drug screen that tested positive for drugs of abuse or misuse, including cannabinoids); the subject completed the study.

[c]Subject (b) (6) did not meet Exclusion Criterion No. 4 (i.e., had used any analgesic other than acetaminophen within 24 hours of surgery; acetaminophen may have been used on the day of surgery but was subject to preoperative restrictions for oral intake), Exclusion Criterion No. 8 (i.e., had any chronic painful condition or routinely used pain medication other than acetaminophen that, in the opinion of the investigator, may have confounded the assessment of pain associated with the hernioplasty), Exclusion Criterion No. 9 (i.e., had a physical or mental condition that, in the opinion of the investigator, may have confounded the assessment of post-operative pain after hernioplasty), and Exclusion Criterion No. 14 (ie, had any clinically significant unstable, neurological, immunological, renal, or hematological disease or any

other condition that, in the opinion of the investigator, could have compromised study participation); the subject completed the study.
[d]Subject (b) (6) did not meet Exclusion Criterion No. 12 (i.e., had liver function test results greater than 3× the upper limit of normal or a history of cirrhosis); the subject completed the study.
[e]Subject (b) (6) did not meet Inclusion Criterion No. 2 (i.e., had a planned unilateral inguinal hernioplasty to be performed according to standard surgical technique under general anesthesia; repair of multiple hernias through a single incision was permitted provided only a single mesh was used); the subject completed the study.
[f]Subject (b) (6) did not meet Exclusion Criterion No. 6 (i.e., had used systemic steroids, anticonvulsants, antiepileptics, antidepressants for the management of chronic pain, or monoamine oxidase inhibitors on a regular basis within 10 days of surgery); the subject completed the study.
[g]Subject (b) (6) did not meet Exclusion Criterion No. 6 (i.e., had used systemic steroids, anticonvulsants, antiepileptics, antidepressants for the management of chronic pain, or monoamine oxidase inhibitors on a regular basis within 10 days of surgery); the subject completed the study.
Source: CSR INN-CB-014, p. 44-45 (PDF), Applicant's submission, NDA 209511

The Applicant further defined and summarized all CSR-reportable protocol deviations, which are deviations consistent with the definition of 'important protocol deviations' in Section 10.2 of ICH E3. The main categories and numbers of CSR-reportable protocol deviations are as follows:

- Investigational product violation (444)
- Pain intensity assessment violation (329)
- Restricted concomitant medication change (verbatim) (270)
- Informed consent violation (26)
- Exclusion violation (11)
- Excluded medication received (5)
- Inclusion violation (3)

The majority (>98%) of protocol deviations in this study were those involving the investigational product, pain intensity assessments, and restricted concomitant medication changes. The Applicant did not provide a text summary describing more specifically the meaning and interpretation of these deviations. For example, a protocol violation involving the investigational product could have several meanings, including incorrect product or dose administration, which has the potential to impact the interpretation of the study results. A high-level review of the tabular data suggests, however, that a large number of the investigational product violations involved incorrect dosing of acetaminophen, specifically missed scheduled doses, which appeared to be evenly distributed across both the treatment and placebo groups. There was a seemingly large number of deviations reported for study sites 401, 417, and 420 relative to the number of enrolled patients. High-level review of this information suggests that treated patients may not have understood the study protocol and the necessary recording they were expected to have completed. For example, it appears that several of the reported deviations included incorrect or missing eDiary documentation, which included acetaminophen dosing or documentation errors and missing PI scores. It is unclear whether the large numbers of deviations impacted reported study results, however, they did appear to be evenly distributed across both treatment and placebo groups.

Table of Demographic Characteristics

Demographic and other baseline characteristics are presented in in the following table. Briefly, the majority of patients were male (96%), white (91%), and less than 65 years of age (84%). The median age of treated patients was 55 years. Most patients did not have a history of ipsilateral hernia repair with mesh. In general, the demographic characteristics were similar across the treatment and placebo groups.

Table 14. Demographic and Baseline Characteristics (Intent-to-Treat Population)

Parameter[a]	INL-001 (N=204)	Placebo (N=101)	Total (N=305)
Age (years)			
Mean (SD)	53.1 (12.82)	53.3 (14.01)	53.1 (13.20)
Median	55.0	54.0	55.0
Minimum, maximum	19, 83	21, 86	19, 86
Age group (years), n (%)			
<65	174 (85.3)	83 (82.2)	257 (84.3)
≥65	30 (14.7)	18 (17.8)	48 (15.7)
Gender, n (%)			
Male	196 (96.1)	97 (96.0)	293 (96.1)
Female	8 (3.9)	4 (4.0)	12 (3.9)
Ethnicity, n (%)			
Hispanic or Latino	77 (37.7)	38 (37.6)	115 (37.7)
Not Hispanic or Latino	127 (62.3)	62 (61.4)	189 (62.0)
Missing	0 (0.0)	1 (1.0)	1 (0.3)
Race, n (%)			
American Indian or Alaskan Native	1 (0.5)	1 (1.0)	2 (0.7)
Asian	2 (1.0)	2 (2.0)	4 (1.3)
Black or African American	15 (7.4)	7 (6.9)	22 (7.2)
Native Hawaiian or Pacific Islander	1 (0.5)	0 (0.0)	1 (0.3)
White	185 (90.7)	91 (90.1)	276 (90.5)
Body mass index (kg/m^2)	(N=202)	(N=100)	(N=302)
Mean (SD)	27.05 (3.899)	27.26 (4.596)	27.12 (4.136)
Median	26.60	26.49	26.55
Minimum, maximum	18.7, 39.6	19.2, 42.1	18.7, 42.1
Previous ipsilateral hernia repair using mesh, n (%)			
Yes	20 (9.8)	12 (11.9)	32 (10.5)
No	184 (90.2)	89 (88.1)	273 (89.5)
Multiple hernias, n (%)			
Yes	13 (6.4)	4 (4.0)	17 (5.6)
No	190 (93.1)	96 (95.0)	286 (93.8)
Missing	1 (0.5)	1 (1.0)	2 (0.7)
Incision duration (hours)	(N=203)	(N=100)	(N=303)
Mean (SD)	0.80 (0.432)	0.75 (0.379)	0.78 (0.415)
Median	0.72	0.67	0.72
Minimum, maximum	0.2, 3.0	0.2, 1.8	0.2, 3.0

Source: CSR INN-CB-014, p. 47 (PDF), Applicant's submission, NDA 209511

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The surgical population was comprised primarily of subjects with a single hernia (94%) and no previous history of ipsilateral hernia repair with mesh (90%).

With regard to prior analgesic medication, all analgesics except acetaminophen were prohibited within 24 hours of surgery. Acetaminophen may have been used the day of surgery, but the standardized dosing regimen was then adjusted to adhere to the maximum daily recommendations. Prohibited medications and the recommended time for avoidance included the following:

- Aspirin or aspirin-containing products for 7 days, unless necessary for cardiovascular prophylaxis and the dose had been stable for ≥30 days
- Extended-release opioid analgesics for 4 weeks before surgery
- Any investigational drug product within 30 days of surgery
- Other pain medication, including nonsteroidal anti-inflammatory medications), before randomization
- After randomization, all pain medications except those specifically outlined in the protocol
- Centrally acting alpha agents, such as clonidine, neuroleptic agents, and other antipsychotic agents within 2 weeks of surgery
- Antidepressant medications unless the dosing regimen had been stable for ≥30 days prior to screening and no change in dosing was anticipated during the study
- Monoamine oxidase inhibitors within 10 days of surgery
- Systemic corticosteroids within 10 days of surgery; inhaled and topical steroids were permitted
- Any anesthetics, except those used during the administration of general anesthesia

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study drug compliance was 100% for subjects who received the implants. There was no subject in either group who required surgical re-exploration or removal of the implants.

A total dose of fentanyl 100 mcg, IV, was permitted intra-operatively, but dosing was to be avoided within 30 minutes of the anticipated end of the procedure. Other opioid analgesics were not permitted pre- or intra-operatively. A pre-operative dose of an antiemetic for nausea prophylaxis was allowed, but post-operatively was only administered to treat documented nausea.

As discussed in Section 6.1.1, parenteral morphine was used for as needed rescue analgesia during the time the subjects were in the PACU (a minimum of three hours post-operatively). Once subjects were tolerating oral medication, they received a standard acetaminophen regimen (650 mg three times daily) and were offered immediate-release morphine, 15 mg, for breakthrough pain if needed.

Efficacy Results – Primary and Key Secondary Endpoints

Subjects who received the bupivacaine collagen-matrices had statistically significantly less pain over the first 24 hours post-operatively (SPI24) when compared to subjects who were treated with the placebo collagen-matrices. The primary efficacy endpoint results are described in the following table.

Table 15. Primary Efficacy Endpoint: Time-Weighted Sum of Pain Intensity From Time 0 through 24 Hours (SPI24) (mITT Population)

Parameter Statistic	INL-001 (N=197)	Placebo (N=101)
SPI24		
Mean (SD)	85.9 (47.18)	106.8 (48.20)
Median	82.2	107.5
Minimum, maximum	0.0, 224.4	6.6, 230.4
Observed p-value[a]	0.0004	

[a] p-value based on ANOVA model with treatment, gender, and history of previous ipsilateral hernia repair as main effects

Source: CSR INN-CB-104, p. 50 (PDF), Applicant's submission, NDA 209511

The only key secondary efficacy endpoint to reach statistical significance was TOpA24. The Applicant reported that subjects who received the bupivacaine collagen-matrices reported less pain over 48 hours (SPI48), when compared to placebo subjects, however this was not statistically significant. The secondary endpoint TOpA48 had a p-value of 0.0248, however, it was not significant due to the hierarchical testing. Refer to Table 16 for key secondary efficacy endpoint results.

Table 16. Key Secondary Efficacy Endpoints: Analysis of TOpA24, SPI48, TOpA48, SPI72, TOpA72 (mITT Population)

Parameter Statistic	INL-001 (N=197)	Placebo (N=101)
Total use of opioid analgesia through 24 hours (TOpA24)		
Median	5.0	10.0
Minimum, maximum	0.0, 47.0	0.0, 40.0
Observed p-value[a]	<0.0001	
P-value based on sequential testing	*	
Sum of pain intensity through 48 hours (SPI48)		
Mean (SD)	179.3 (94.98)	201.3 (93.84)
Median	165.7	190.1
Minimum, maximum	0.0, 408.9	6.6, 470.4
Observed p-value[b]	0.0568	
P-value based on sequential testing	NS	
Total use of opioid analgesia through 48 hours (TOpA48)		
Median	5.0	14.0
Minimum, maximum	0.0, 82.0	0.0, 65.0
Observed p-value[a]	0.0248	
P-value based on sequential testing	NS	
Sum of pain intensity through 72 hours (SPI72)		
Mean (SD)	257.8 (139.31)	281.1 (139.71)
Median	245.2	263.3
Minimum, maximum	0.0, 594.1	6.6, 710.4
Observed p-value[b]	0.1737	
P-value based on sequential testing	NS	
Total use of opioid analgesia through 72 hours (TOpA72)		
Median	5.0	14.0
Minimum, maximum	0.0, 102.0	0.0, 100.0
Observed p-value[a]	0.0655	
P-value based on sequential testing	NS	

[a] p-value is from Wilcoxon Rank Sum Test; [b] p-value was based on ANOVA model with treatment, gender, and history of previous ipsilateral hernia repair as main effects; *=significant; NS=not significant
Source: CSR INN-CB-014, p. 49 (PDF), Applicant's submission, NDA 209511

It is worth mentioning here, and will be discussed further in Section 7, Integrated Review of Effectiveness, that the median amount of opioid use was used for the statistical analyses, not the mean amount. It appears that comparison of the mean amount of opioid use was less impressive and ultimately, less clinically meaningful.

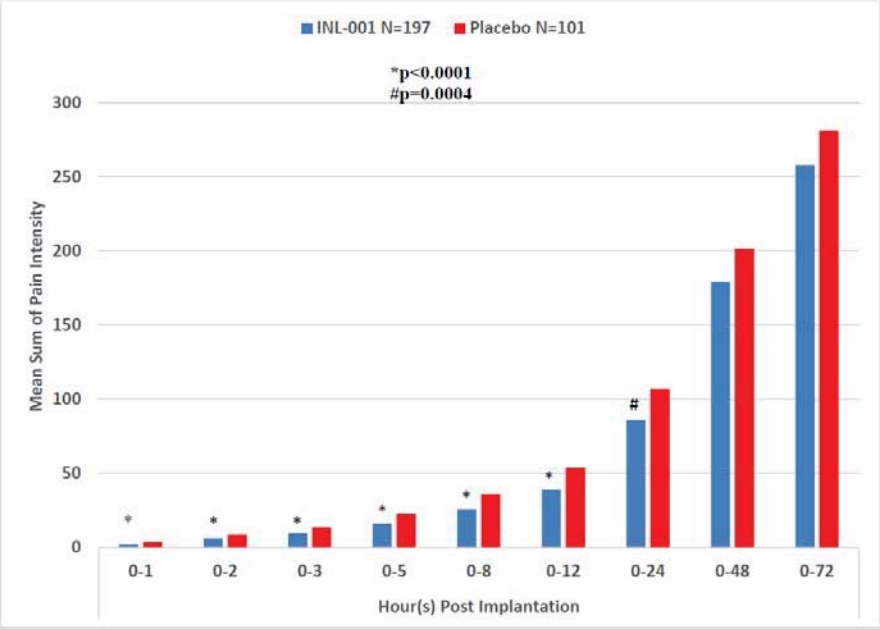
Other Secondary and Exploratory Efficacy Endpoints

Other Secondary Efficacy Endpoints

- SPI cumulative – the Applicant reported that the subjects who received INL-001 had statistically significantly lower mean pain scores cumulative from Time 0 through each

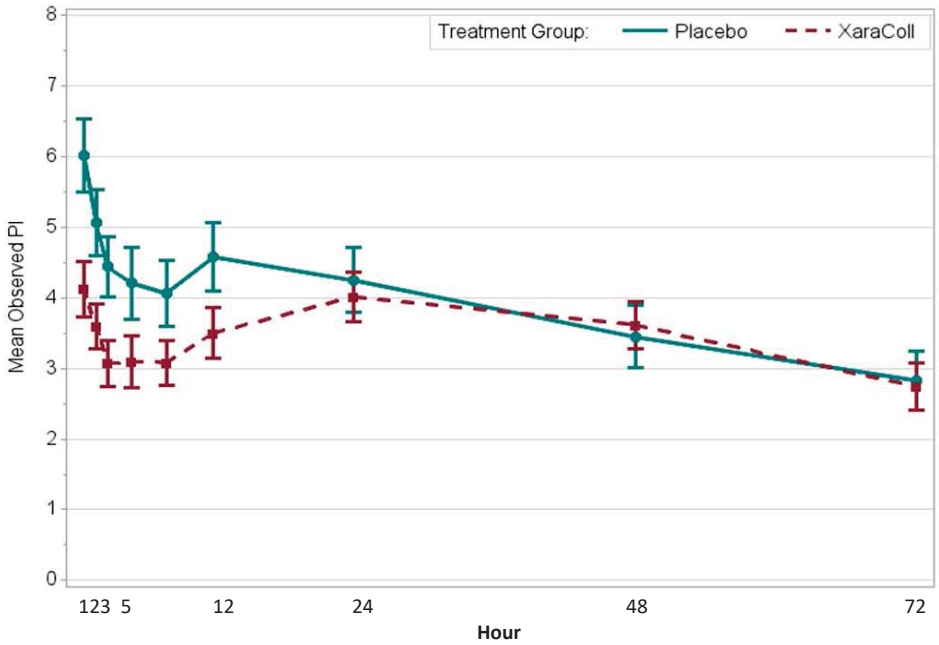
of the predefined time periods until 24 hours when compared with subjects who received the placebo implants. And while the cumulative pain scores at 48 and 72 hours were not statistically significant between the groups, the trend was toward the INL-001 group having lower scores through those time points as well. Refer to Figure 3 for graphical representation of the results for the SPI cumulative efficacy endpoint.
Figure 4 is a graphical representation of the mean pain intensity scores through 72 hours, provided by Dr. Yi Ren, the statistical reviewer for this application. The Applicant provided a similar graph; however, the pain curves were plotted to 24 hours, not 72 hours. As will be discussed in Section 7, Integrated Review of Effectiveness, it appears that at the 24-hour and later time points, there is no difference in pain intensity between the INL-001 treatment and placebo groups, suggesting there is no additional benefit of INL-001 at >24 hours post-operatively. Additionally, it appears that the mean pain intensity scores for subjects in both groups were ≥3 using the NRS through 48 hours.

Figure 3. Time-Weighted Mean Sum of Pain Intensity Cumulative at Predefined Time Periods from Time 0 through 72h (mITT Population)



p-values were from an ANOVA model with treatment, gender, and history of previous ipsilateral hernia repair as main effects
Source: CSR INN-CB-014, p. 53 (PDF), Applicant's submission, NDA 209511

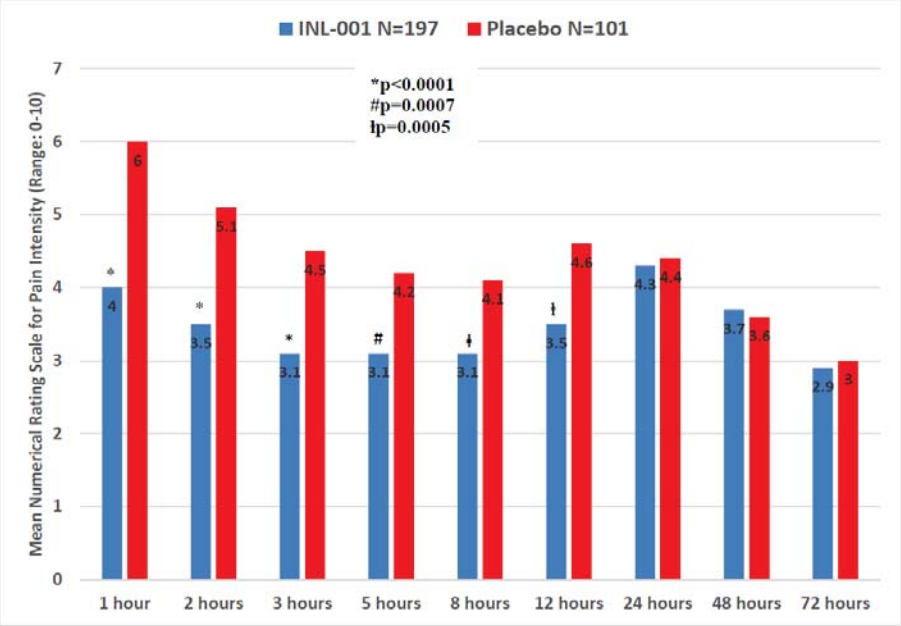
Figure 4. Mean Pain Intensity Scores at Predefined Time Points Through 72 Hours



Source: Dr. Yi Ren's statistical analysis review, internal correspondence

- NRS of PI at predefined time points – pain intensity was measured at predefined time points using the 11-point NRS. Patients who received INL-001 had statistically significantly lower mean PI scores at all time points through 12 hours compared with patients who received the placebo implants. Mean pain scores after 12 hours appeared similar in both groups. Refer to Figure 5 for graphical representation of these efficacy results.

Figure 5. Mean Numerical Rating Scale of Pain Intensity at Predefined Time Points From Time 0 through 72 Hours (mITT Population)



p-values were from an ANOVA model with treatment, gender, and history of previous ipsilateral hernia repair as main effects

Source: CSR INN-CB-014, p. 54 (PDF), Applicant's submission, NDA 209511

- Number of patients who did not use rescue opioid analgesia – the Applicant reported that 36% of patients who received INL-001 did not require any rescue opioid analgesia through 72 hours post-operatively. This is in contrast to 21.8% of patients who received placebo implants. Additionally, almost 60% of patients who received INL-001 did not require opioid analgesia during their PACU admission, compared to almost 30% of patients who received placebo implants, as described in Table 17.

Table 17. Percentage of Patients Who Did Not Use Rescue Opioid Analgesia (mITT Population)

Parameter Statistic	INL-001 (N=197)	Placebo (N=101)
Subjects who did not use rescue opioid analgesia, n (%)		
Time 0 through PACU discharge	115 (58.4)	29 (28.7)
Time 0 through 24 hours	82 (41.6)	22 (21.8)
Time 0 through 48 hours	72 (36.5)	22 (21.8)
Time 0 through 72 hours	71 (36.0)	22 (21.8)

Source: CSR INN-CB-014, p. 55 (PDF), Applicant's submission, NDA 209511

While these reported results are clinically meaningful, they become less so when considering the percentage of patients who used oral opioid rescue after leaving the

PACU. As outlined in Table 18, the overall percentage of subjects who used oral opioid rescue analgesia through 72 hours was similar in the treatment and placebo groups.

Table 18. Number (%) of Patients with Oral Rescue Opioid Analgesia after Leaving the PACU

	XaraColl (N=197)			Placebo (N=101)			P-value
	n	(%)	95% CI [1]	n	(%)	95% CI [1]	[2]
Number of Patients with Any Oral Rescue Opioid Analgesia after Leaving the PACU through (n, %)							
72 HOURS	104	(52.8)	(45.6, 59.9)	60	(59.4)	(49.2, 69.1)	0.2912
48 HOURS	103	(52.3)	(45.1, 59.4)	60	(59.4)	(49.2, 69.1)	0.2549
24 HOURS	87	(44.2)	(37.1, 51.4)	55	(54.5)	(44.2, 64.4)	0.1033
12 HOURS	58	(29.4)	(23.2, 36.3)	46	(45.5)	(35.6, 55.8)	0.0074
8 HOURS	38	(19.3)	(14.0, 25.5)	30	(29.7)	(21.0, 39.6)	0.0543
5 HOURS	8	(4.1)	(1.8, 7.8)	10	(9.9)	(4.9, 17.5)	0.0685

[1] 95% Confidence interval for proportion of patients with any oral rescue opioid analgesia after leaving the PACU is obtained from one-sample binomial distribution; [2] p-value is obtained from the Cochran-Mantel-Haenzel (CMH) test adjusted for gender and history of previous ipsilateral hernia repair.
Source: CSR INN-CB-014, p. 194 (PDF), Applicant's submission

- Time to first use of rescue opioid analgesia (FOpA) – patients who received INL-001 had a statistically significantly longer time to FOpA compared to patients who received placebo implants, median times were 10.7 hours versus 1 hours, respectively. Refer to Table 19 for the FOpA efficacy results.

Table 19. Time to First Use of Rescue Opioid Analgesia (FOpA) (mITT Population)

Parameter Statistic	INL-001 (N=197)	Placebo (N=101)
Subjects who used rescue opioid from Time 0 through 72 hours, n (%)	126 (64.0)	79 (78.2)
Time to FOpA (hours)		
Median (95% CI)[a]	10.7 (5.2, 17.8)	1.0 (0.9, 1.1)
Hazard ratio (95% CI)[b]	0.52 (0.39, 0.70)	
Log rank p-value[c]	<0.0001	

[a]The 95% CI for median was computed using the Brookmeyer-Crowley method.
[b]The hazard ratio and 95% CI were based on a Cox proportional hazards regression model with treatment, gender, and history of previous ipsilateral hernia repair as exploratory variables.
[c]p-value (2-sided) was obtained using stratified log rank test based on stratification factors of gender and history of previous ipsilateral hernia repair.
Source: CSR INN-CB-014, p. 55 (PDF), Applicant's submission, NDA 209511

The opioids most commonly administered to patients in both groups for post-operative analgesia included IV and oral morphine. A few patients received IV hydromorphone, ketorolac, or pethidine, or oral oxycocet, oxycodone, or tramadol.

- POpA at predefined time periods from Time 0 – patients who received INL-001 required statistically significantly less median parenteral opioid analgesia at all predefined time periods through 24 hours compared to patients who received placebo.

- TOpA at predefined time periods from Time 0 – the Applicant reported that patients who received INL-001 required statistically significantly less median opioid analgesia at all time periods through 48 hours compared with patients who received placebo. However, because the secondary endpoints were tested using a hierarchical analysis, the TOpA after 24 hours is not considered statistically significant.

- TOpA from Time 0 through prior to discharge – patients who received INL-001 required statistically significantly less median opioid analgesia from Time 0 through prior to discharge compared to patients who received placebo, 0 mg IV morphine equivalents versus 4 mg IV morphine equivalents.

- Subject evaluation of pain through 72 hours – using a 5-point verbal rating scale, there was no statistically significant difference observed between the INL-001 treatment and placebo group on subject general evaluation of pain through 72 hours.

- Subject overall evaluation of pain through 72 hours compared with expectation – using a 5-point categorical scale, there was no significant difference between the INL-001 and placebo groups regarding the pain experienced and the expected pain. It appears the majority of patients in both groups rated the pain as about the same, less, or a lot less than what they expected.

- Subject evaluation of pain interference on activity through 72 hours – using an 11-point NRS there was no significant difference between the INL-001 and placebo groups regarding the pain interference on activity. The majority of patients in both groups rated the interference on activity as what would appear to be mild or slight interference.

<u>Exploratory efficacy endpoint</u>

- The Applicant evaluated the integrated sum of pain intensity and total use of opioid analgesia (using the Silverman method of summated percentage differences from mean rank) in an attempt to better characterize the true effect of the study drug. The results for this exploratory efficacy endpoint are presented in Table 20.

Table 20. Integrated Sum of Pain Intensity and Total Use of Opioid Analgesia

Parameter	INL-001	Placebo	Difference (95% CI)	p-value
SPITOpA24	-49.5	2.1	-51.5 (-74.9, -28.2)	<0.001
SPITOpA48	-43.4	-15.8	-27.6 (-51.5, -3.7)	0.024
SPITOpA72	-39.5	-18.7	-20.8 (-44.7, 3.1)	0.088

Confidence intervals (CI) around the treatment difference; 95% CI and p-value are from an ANOVA model with treatment, gender, and history of previous ipsilateral hernia repair as main effects.
Silverman method used (Silverman DG, O'Connor TZ, Brull SJ. Integrated assessment of pain scores and rescue morphine use during studies of analgesic efficacy. *Anesth Analg*. 1993;77(1):168–170.)
Source: Adapted from Table 14.2.6.2, CSR INN-CB-014, p. 202 (PDF), Applicant's submission, NDA 209511

- Time to discharge from PACU – the time to discharge from PACU was evaluated by the Applicant as an exploratory endpoint. The results demonstrate no significant difference in the time to discharge between the INL-001 and placebo groups, however, there was a trend toward earlier discharge in the treatment group. The median time of discharge for patients in both groups was three hours post-operatively.

Missing Data

There appears to be missing pain score data for all recorded time points through 72 hours. Specifically, per Dr. Yi Ren's statistical analyses, the following table summarizes the number and percentage of missing pain scores for each time point (rounded to the nearest whole number).

Table 21. Number and Percentage of Missing Data at Each Analysis Time Point

	Number (%) of Missing Data by Analysis Time Point								
Hour	**1**	**2**	**3**	**5**	**8**	**12**	**24**	**48**	**72**
XaraColl (N=187)	27 (14%)	16 (8%)	13 (7%)	41 (21%)	18 (9%)	11 (6%)	6 (3%)	11 (6%)	35 (18%)
Placebo (N=101)	10 (10%)	7 (7%)	8 (8%)	25 (25%)	8 (8%)	9 (9%)	3 (3%)	8 (8%)	16 (16%)

Source: Dr. Yi Ren's statistical analysis review, internal correspondence

It is not surprising that there are missing data at each time point and some may be explained by the clinical scenario. Specifically, the five-hour time point is likely during patient discharge or transit home, times when pain scores may not have been captured. Additionally, the large percentage of missing data for the 72-hour time point may be explained by study fatigue or subject forgetfulness. The relatively high percentage of missing data at the one-hour time point, however, cannot be readily explained. It would seem that the majority of patients only one hour post-operative would still be in phase 1 of the PACU, closely monitored. It is also interesting that the largest number and percentage of captured pain score data was for the 24-hour time point, the primary efficacy endpoint.

It does not appear that the missing data impacted the Applicant's reported results. For additional information on the missing data and reported results, refer to Dr. Yi Ren's statistical review.

Data Quality and Integrity

The preliminary report from an audit conducted by OSI, Division of Clinical Compliance Evaluation, has indicated that the reviewed data, including informed consent procedures, drug accountability records, and information related to study blinding and electronic source data, were reliable for Study INN-CB-014 and recommended accepting the clinical portion of the studies for further FDA review.

Dose/Dose Response

There was a single dose of the bupivacaine collagen-matrix, 100 mg, evaluated in this study. Each subject received three matrices for a total bupivacaine dose of 300 mg. The collagen composition of the matrices was 75 mg each, for a total dose of 225 mg. The Applicant did evaluate different doses of both bupivacaine, ranging from 100 to 300 mg total dose, and collagen, ranging from 140 to 280 mg total dose, in the Phase 1 and Phase 2 studies. Although the number of subjects who received different doses was low and the studies were not powered for efficacy, it did appear that the lower doses of bupivacaine were less efficacious and when compared to active comparators, the INL-001 implant lost on the primary efficacy endpoints.

Durability of Response

As discussed under Efficacy Results of this section, the bupivacaine collagen-matrices did result in less pain and less opioid rescue analgesia for 24 hours when compared to the placebo matrices. The Applicant suggests that the bupivacaine collagen-matrices may result in less opioid rescue analgesia through 48 hours, however, those results were not statistically significant due to the hierarchical testing and the failure to demonstrate statistical significance for the secondary efficacy endpoint of SPI48.

6.2. 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)

6.2.1. Study Design

Overview and Objective

Study INN-CB-016, a Phase 3 study, was conducted by Innocoll Pharmaceuticals to evaluate the safety and efficacy of XaraColl® for postsurgical analgesia following open inguinal hernia repair

with mesh. The objectives of the study were as follows:

- Primary objective (verbatim): to compare the analgesic effect of the INL-001 implant to that of the placebo implant for the management of acute postsurgical pain using the surgical model of open laparotomy inguinal hernioplasty
- Secondary objective (verbatim): to assess the safety and tolerability of INL-001 after its implantation into surgical wounds during hernioplasty surgery

Trial Design

This study was a Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled study in adults who were scheduled for unilateral inguinal hernioplasty via open laparotomy (tension-free technique using mesh) under general anesthesia. Patients were stratified by gender and history of previous ipsilateral hernia repair. A total of 319 subjects were randomized in a 2:1 ratio to receive three INL-001 100 mg collagen-matrices (for a total dose of 300 mg of bupivacaine) or three placebo collagen-matrices. Both matrices measured 5 x 5 x 0.5 cm and were off-white to white. A total of 315 subjects were treated.

The INL-001 or placebo collagen-matrices were implanted at multiple layers in the soft tissue between the fascia/muscle closure and in the layers below the skin closure. Specifically, each of the three matrices was cut in half, resulting in six half matrices each measuring approximately 2.5 x 2.5 x 0.5 cm. Three half matrices were implanted below the mesh, on the abdominal wall repair, and the remaining three half matrices were implanted between the fascial closure and the skin incision. Following surgery, subjects were transferred to the post-anesthesia care unit (PACU) for a minimum observation period of 3 hours. Analgesia was provided initially via parenteral morphine as needed. Once subjects were tolerating oral medication, they received a standard acetaminophen regimen (650 mg three times daily) and were offered immediate-release morphine, 15 mg, for breakthrough pain if needed. Pain intensity was reported using an 11-point numerical rating scale (NRS), 0 to 10, at the following time points:

- prior to taking analgesic medication from Time 0 through 72 hours post-operatively (Time 0 defined as time of first implant of test article)
- at pre-defined time points from 1 hour through 72 hours post-operatively
- prior to the standard acetaminophen doses beginning the morning after surgery through 72 hours post-operatively

Subjects were discharged from the PACU after the 3-hour vital sign and pain intensity assessments were completed. Follow-up phone calls occurred approximately 6, 24, and 48 hours after study drug implantation. Subjects returned to the clinic 72 hours post-operatively to perform final pain intensity and safety assessments. Subjects recorded any new or ongoing AEs through Day 7. Final follow-up assessments were performed on post-operative day 7 (telephone call), and Days 15 and 30 (clinic visits). The schedule of assessments during this study is summarized in Table 22.

Table 22. Study Assessments

	Screening	Immediate Preoperative Period	Intra-operative Period	Post Implantation Period										Follow-up		
Day	**-30 to -1**	**0**		**0**							**1**	**2**	**3 ET**	**7**	**15**	**30**
Time (hours)			**0**	**1 hr ±15 min**	**2 hr ±15 min**	**3 hr ±15 min**	**5 hr ±15 min**	**6 ±1 hr**	**8 ±1 hr**	**12 ±2 hr**	**24 ±3 hr**	**48 ±3 hr**	**72 ±4 hr**	**±1 day**	**±2 days**	**±3 days**
Written informed consent	X															
Inclusion/exclusion criteria	X	X														
Obtain screening number	X															
Medical history	X	X[a]														
Demographics	X															
Electrocardiogram	X															
Physical examination, weight, and height	X															
Clinical laboratory tests[b]	X															
Urine for pregnancy test (female subjects)		X[c]														
Vital signs	X	X		X	X	X	X[d]		X[d]				X			
Adverse events[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Enrollment/randomization		X														
Surgery/implantation			X													
Provide eDiary				X												
Pain intensity rating (NRS)			X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]			
Record use of analgesic medication			X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]			
Provide acetaminophen and prescription for oral morphine				X[h]												
Confirm eDiary use								X			X	X				
Subject general evaluation													X			
Collect eDiary and acetaminophen													X			
Telephone call								X			X	X		X		
Clinic visit													X		X[i]	X[i]

ET = early termination

[a]Updated medical history since screening.

[b]Included hematology, chemistry, urinalysis, and urine for drugs of abuse or misuse, including cannabinoids. A blood sample for pregnancy testing was obtained from female subjects.

[c]Results must have been available before implantation.

[d]Assessments were not performed in subjects who discharged prior to the designated time point.

[e]Adverse events were collected from the time of implantation through Day 30.

[f]Beginning at Time 0 (when first test article was implanted) and continuing through the 72-hour time point (Day 3), PI was assessed by the subject using the 11-point NRS immediately before the administration of any parenteral or oral rescue opioid analgesia for breakthrough pain. While in the PACU, PI before administration of opioid analgesia was recorded on the CRF by the site coordinator. Pain intensity was also assessed by the subject at all protocol-defined time points (1, 2, 3, 5 [each had a ±15 minutes window], and at 8±1, 12±2, 24±3, 48±3, and 72±4 hours after Time 0) and recorded in the eDiary. Additionally, beginning the morning after surgery, subjects recorded PI in their diary immediately before taking scheduled acetaminophen 3 times daily until the 72-hour visit.

[g]Subjects took acetaminophen 650 mg 3 times daily and recorded in their diary until the 72-hour time point. Rescue opioid analgesia for breakthrough pain starting at Time 0 through the 72-hour time point was also recorded in the CRF (ie, unscheduled time points between Time 0 and Hour 3) and/or eDiary.

[h]At time of discharge (any time after 3 hours), instructed subject on use of analgesia medications (acetaminophen and oral morphine) and eDiary use.

[i]Visit to assess surgical site and adequacy of hernia repair.

Source: CSR INN-CB-019, p. 24-25 (PDF), Applicant's submission, NDA 209511. Of note, the study protocol does not indicate a pain score was recorded at the 6-hour post-operative time point. This appears to be checked in error in this table.

Study Population

Eligibility criteria

Pertinent inclusion criteria included the following:

- adult patient
- planned, non-emergent unilateral inguinal hernia repair under general anesthesia
- non-pregnant female
- willing to use opioid analgesia

Pertinent exclusion criteria included the following:

- hypersensitivity to amide local anesthetics, morphine, acetaminophen, or bovine products
- planned bilateral inguinal hernioplasty or other significant concomitant surgical procedure(s)
- major surgical procedure in the preceding three months or planned laparotomy within 30 days
- any analgesic use, aside from acetaminophen, within 24 hours
- aspirin, aspirin-containing products within seven days; aspirin ≤325 mg was permitted for cardiovascular prophylaxis if the dose had been stable for ≥30 days before screening
- use of systemic steroids, anticonvulsants, antiepileptics, or antidepressants for the management of chronic pain, or monoamine oxidase inhibitors on a regular basis within ten days of surgery
- use of any opioid analgesic for an extended daily basis (30 - 60 mg oral morphine equivalent per day for three or more days a week) within four weeks before surgery; subjects who, in the investigator's opinion, may have been developing opioid tolerance were also excluded
- any chronic painful condition (e.g., fibromyalgia) or routinely used pain medication other than acetaminophen (including nonsteroidal anti-inflammatory drugs)
- showed evidence of tolerance or physical dependency on opioid analgesics or sedative-hypnotic medications
- positive urine drug screen
- liver function tests >three times the upper limit of normal or history of cirrhosis
- any clinically significant unstable cardiac disease (e.g., uncontrolled hypertension, clinically significant arrhythmia at baseline, or an implantable cardioverter-defibrillator)
- any clinically significant unstable neurological, immunological, renal, or hematological disease (e.g., uncontrolled diabetes or significantly abnormal laboratory findings)
- open workmans' compensation claim
- participated in clinical trial within 30 days of surgery

Study Endpoints

Primary efficacy endpoint

The primary efficacy variable was the time-weighted sum of pain intensity from Time 0 to 24 hours (SPI24) and was compared once using a 2-sided 0.05 level of significance. No multiplicity adjustments were necessary for the primary efficacy analysis.

Key secondary efficacy endpoints

The following were the key secondary endpoints:

- Total use of opioid analgesia from Time 0 through 24 hours (TOpA24)
- Time-weighted sum of pain intensity from Time 0 to 48 hours (SPI48)
- Total use of opioid analgesia from Time 0 through 48 hours (TOpA48)
- Time-weighted sum of pain intensity from Time 0 to 72 hours (SPI72)
- Total use of opioid analgesia from Time 0 through 72 hours (TOpA72)

These endpoints were tested sequentially in a fixed order at the 0.05 significance level to control the Type-I error rate. Each secondary endpoint was tested in a hierarchical manner, such that the subsequent endpoint was evaluated only if the preceding ones were statistically significant.

Other secondary efficacy endpoints

- Continuous secondary efficacy endpoints included the following:
  - sum of pain intensity (SPI) at predefined time points through 12 hours
  - numeric rating scale (NRS) of PI at scheduled time points
  - total use of parenteral opioid analgesia (POpA) from 0 through 24 hours
  - TOpA at scheduled time points through 12 hours
  - TOpA from Time 0 to prior to discharge
- Categorical secondary efficacy endpoints included the following:
  - percentage of patients who used any oral rescue opioid analgesia after leaving the PACU at scheduled time points through 72 hours
  - percentage of patients who did not use opioid rescue analgesia
  - patient general evaluation of pain through 72 hours on a 5-point verbal rating scale
  - patient overall evaluation of pain through 72 hours compared with expectation on a 5-point categorical scale
  - patient overall evaluation of pain interference on activity through 72 hours on an 11-point NRS
- Time to event secondary efficacy endpoints included the following:
  - time to first use of rescue opioid analgesia (FOpA)
  - time to first use of oral rescue opioid analgesia (FOpA oral)

Exploratory efficacy endpoint

Integrated sum of pain intensity and total use of opioid analgesia (using the Silverman method of summated percentage differences from mean rank) from Time 0 to 24, 48, and 72 hours.

Intravenous Morphine Equivalents

The Applicant used the opioid conversion table as described by Gordon *et al* (1999), pictured in Table 11. All opioid analgesics were converted to IV morphine equivalents and calculated on a cumulative basis through 72 hours.

Statistical Analysis Plan

Summary statistics were presented by treatment group. For continuous variables, the number of available observations, mean, standard deviation, median, and range were provided unless otherwise stated. For categorical variables, the frequency and percentage in each category was displayed. All statistical tests were given with two-sided p-values. For descriptive purposed, two-sided 95% confidence intervals were provided.

The intent-to-treat population consisted of all randomized patients who may or may not have received any dose of XaraColl® or placebo. This population was used for disposition count purposes and no statistical evaluations were performed using this population.

The efficacy assessments were performed using the modified intent-to-treat population, which consisted of all subjects who were randomized and received any dose of XaraColl® or placebo and had at least one pain intensity score prior to hospital discharge. The subjects were analyzed according to the assigned treatment at randomization.

The per protocol population was all mITT subjects who had non-significant protocol violations and had at least three pain intensity assessments, of which at least one was prior to hospital discharge and at least corresponded to a pain intensity assessment at 24 hours or later.

Refer to Dr. Yi Ren's statistical review for additional information regarding the SAP.

Protocol Amendments

There was one amendment to the original protocol that was implemented prior to the enrollment of any study subjects. The key changes to the original protocol in this amendment were as follows:

- Updated sections and the synopsis to:
  - clarify the primary objective and patient stratification for consistency
  - state that nausea, vomiting, and constipation were collected and reported as adverse events
  - correct the fentanyl dose to 100 mcg
  - correct the time when the NRS was used to assess PI
  - clarify the definition of the ITT and mITT analysis populations
  - add details to the intraoperative procedure technique
  - revise the sample size

  - update primary efficacy endpoint from integrated sum of pain intensity and total use of opioid analgesia from Time 0 to 24 hours (I-SPI-TOpA24) to sum of pain intensity difference from Time 0 through 24 hours (SPID24)
  - change primary and secondary efficacy variables
  - add exploratory efficacy variables
- Increased patient enrollment to 300
- Patients with evidence of tolerance or physical dependence to opioid analgesics or sedative-hypnotic medications
- Clarified the size of the INL-001 and placebo implant
- Added sections 11.2.1.2 Rescue Opioid Analgesia for Breakthrough Pain and 11.2.1.3 Scheduled Acetaminophen Analgesia
- Clarified the pre-rescue or pre-acetaminophen pain intensity assessment
- Correct the sum of pain intensity time points
- Clarified timing of laboratory, ECG, and physical examination assessments and analyses
- Clarified that compliance of INL-001 would not be evaluated by compliance of other medications would be
- Urine pregnancy testing on Day 3 omitted

Handling of Missing Data (per SAP)

Missing pain intensity (PI) assessments (verbatim)

- PI at scheduled time point: if no observed PI assessment fell within the time window of a scheduled time point, the PI value at that time point was considered as missing
- Pre-rescue PI in the PACU: if a subject received a rescue medication in the PACU but there was no PI assessment recorded on the CRF that immediately preceded the administration of the rescue medication within 30 minutes, the “pre-rescue” PI score for this rescue medication was considered as missing
- Pre-rescue PI after discharge from PACU: if a subject recorded a rescue medication in the eDiary but there was no associated PI assessment recorded in the eDiary, the “pre-rescue” PI score for this rescue medication was considered as missing
- Pre-acetaminophen PI after Day 0: if a subject recorded an acetaminophen administration in the eDiary but there was no associated PI assessment recorded in the eDiary, the “pre-acetaminophen” PI score for this acetaminophen dose was considered as missing.

Imputation for missing PI assessments

Missing PI values before the first observed PI value were imputed using the worst observed PI for that patient. Missing PI values between two observed PI values, or intermittent missing, were imputed using linear interpolation. Missing PI values after the last observed PI value, or monotone missing, were imputed using last observation carried forward (LOCF), except under the following situations:

- If a patient was terminated early and surgical removal of the matrices was performed, worst observation carried forward (WOCF) method was applied from the time of termination through 72h
- If a patient was terminated early and had taken opioid rescue less than four hours before, the last observed pre-rescue PI value was carried forward through 72h.

Several sensitivity analyses were performed to demonstrate that the above imputation rules were adequate to describe the pain intensity profile for each patient.

6.2.2. Study Results

The study results presented by the Applicant are discussed in this section. The reviewer's analyses and interpretation of efficacy results are discussed in Section 7, Integrated Review of Effectiveness.

Compliance with Good Clinical Practices

Per the CSR for Study INN-CB-016, p. 10 (PDF), *"This study was conducted in compliance with the Declaration of Helsinki and its amendments, the International Council for Harmonisation (ICH) principles of Good Clinical Practice (GCP; including archiving of essential study documents), all United States (US) Food and Drug Administration regulations, and other applicable local regulations and guidelines."*

Financial Disclosure

Pepe Carmona, Chief Financial Officer, Innocoll Pharmaceuticals, signed FDA form 3454 on October 4, 2016, certifying that he has not entered into any financial arrangement with any of the listed clinical investigators. He further certified that none of the individual investigators has a proprietary interest in this drug product or a significant equity in the Sponsor per 21 CFR 54.2(b) or received payments in excess of what is permitted per 21 CFR 54.2(f).

Patient Disposition

A total of 319 patients were randomized in Study INN-CB-016; 213 were randomized to the INL-001 treatment group and 106 were randomized to the placebo group. The following table summarizes patient disposition:

Table 23. Patient Disposition

	INL-001	Placebo	Total
Randomized	213	106	319
Completed	203	103	306
Discontinued	10	3	13
– Adverse event	0	1 (abd. Pain)	1
– Lost to f/u	5	1	6
– Other	5 (1 did not meet random. criteria, 1 withdrew, 3 not enrolled)	1 (death)	6

Reviewer's summary

The majority of patients completed the study and the most common reason for premature discontinuation from the study was being lost to follow-up.

Protocol Violations/Deviations

Similar to the protocol deviations discussed for Study INN-CB-014, the Applicant defined significant protocol deviations as those related to the test article implantation, violation of eligibility criteria, use of prohibited medications (with a focus on those that could have impacted pain assessments), and absence of the required number of pain intensity assessments post-implantation. There were 19 subjects with significant protocol deviations, as summarized in Table 24. These subjects were excluded from the analysis populations.

Table 24. Subjects Excluded from the Analysis Populations

Subject Number	Population Excluded From:	Reason
INL-001		
(b) (6)	PP	Took prohibited medication
	PP	Did not have 3 or more PI assessments with at least 1 prior to hospital discharge and at least 1 at 24 hours or later
	mITT, PP, safety	Failed to meet randomization criteria
	PP	Took prohibited medication
	PP	Took prohibited medication
	mITT, PP, safety	Did not receive INL-001 or placebo matrix
	mITT, PP, safety	Randomized, not enrolled
	PP	Took prohibited medication
	mITT, PP	Did not have at least 1 NRS PI score prior to hospital discharge, as needed, to compute SPI; took prohibited medication
	mITT, PP	Did not have at least 1 NRS PI score prior to hospital discharge, as needed, to compute SPI; took prohibited medication
	mITT, PP, safety	Did not receive INL-001 or placebo matrix; violation of eligibility criteria[a]
	PP	Took prohibited medication
	PP	Took prohibited medication
	PP	Took prohibited medication
	PP	Took prohibited medication
	mITT, PP	Did not have at least 1 NRS PI score prior to hospital discharge, as needed, to compute SPI
	PP	Did not have 3 or more PI assessments with at least 1 prior to hospital discharge and at least 1 at 24 hours or later
	PP	Took prohibited medication
	PP	Did not have 3 or more PI assessments with at least 1 prior to hospital discharge and at least 1 at 24 hours or later

Data source: Appendix 16.2, Listings 16.2.1, 16.2.2 and 16.2.3

[a] Subject (b) (6) did not meet Exclusion Criterion No. 14 (ie, had any clinically significant unstable, neurological, immunological, renal, or hematological disease or any other condition that, in the option of the investigator, could have compromised study participation); the subject was randomized to the INL-001 group but not enrolled.

Source: CSR INN-CB-016, p. 44 (PDF), Applicant's submission, NDA 209511

The Applicant further defined and summarized all CSR-reportable protocol deviations, which are deviations consistent with the definition of 'important protocol deviations' in Section 10.2 of ICH E3. The main categories and numbers of CSR-reportable protocol deviations are as follows:

- Investigational product violation (375)
- Restricted concomitant medication change (verbatim) (261)
- Pain intensity assessment violation (227)
- Excluded medication received (8)
- Exclusion violation (4)
- Wrong treatment or incorrect dose received (1)

The majority (>98%) of protocol deviations in this study were those involving the investigational product, restricted concomitant medication changes, and pain intensity assessments. As discussed in Section 6.1.2, for Study INN-CB-014, the Applicant did not provide a text summary describing more specifically the meaning and interpretation of these deviations. A high-level review of the tabular data suggests, however, that a large number of the investigational product violations involved incorrect dosing of acetaminophen, specifically missed scheduled doses, which appeared to be evenly distributed across both the treatment and placebo groups. There was a seemingly large number of deviations reported for study sites 603, 602, and 608 relative to the number of enrolled patients. High-level review of this information suggests that treated patients may not have understood the study protocol and the necessary recording they were expected to have completed. For example, it appears that several of the reported deviations included incorrect or missing eDiary documentation, which included acetaminophen dosing or documentation errors and missing PI scores. It is unclear whether the large numbers of deviations impacted reported study results, however, they did appear to be evenly distributed across both treatment and placebo groups.

Table of Demographic Characteristics

Demographic and other baseline characteristics are presented in Table 25. Briefly, the majority of subjects were male (98%), white (85%), and less than 65 years of age (85%). There were no statistically significant differences in baseline or demographic characteristics between the treatment and placebo groups.

Table 25. Demographic and Baseline Characteristics (Intent-to-Treat Population)

Parameter[a]	INL-001 (N=213)	Placebo (N=106)	Total (N=319)
Age (years)			
Mean (SD)	50.7 (13.69)	48.5 (13.94)	50.0 (13.79)
Median	52.0	50.0	51.0
Minimum, maximum	18, 85	19, 75	18, 85
Age group (years), n (%)			
<65	180 (84.5)	92 (86.8)	272 (85.3)
≥65	33 (15.5)	14 (13.2)	47 (14.7)
Gender, n (%)			
Male	208 (97.7)	103 (97.2)	311 (97.5)
Female	5 (2.3)	3 (2.8)	8 (2.5)
Ethnicity, n (%)			
Hispanic or Latino	44 (20.7)	23 (21.7)	67 (21.0)
Not Hispanic or Latino	169 (79.3)	83 (78.3)	252 (79.0)
Race, n (%)			
American Indian or Alaskan Native	2 (0.9)	1 (0.9)	3 (0.9)
Asian	4 (1.9)	3 (2.8)	7 (2.2)
Black or African American	23 (10.8)	12 (11.3)	35 (11.0)
Native Hawaiian or Pacific Islander	1 (0.5)	0 (0.0)	1 (0.3)
White	182 (85.4)	90 (84.9)	272 (85.3)
Missing	1 (0.5)	0 (0.0)	1 (0.3)
Body mass index (kg/m^2)	(N=209)	(N=106)	(N=315)
Mean (SD)	26.84 (4.025)	27.22 (5.062)	26.97 (4.397)
Median	26.66	26.64	26.65
Minimum, maximum	17.8, 40.8	17.4, 45.9	17.4, 45.9
Previous ipsilateral hernia repair using mesh, n (%)			
Yes	22 (10.3)	10 (9.4)	32 (10.0)
No	189 (88.7)	96 (90.6)	285 (89.3)
Missing	2 (0.9)	0 (0.0)	2 (0.6)
Multiple hernias, n (%)			
Yes	5 (2.3)	4 (3.8)	9 (2.8)
No	204 (95.8)	102 (96.2)	306 (95.9)
Missing	4 (1.9)	0 (0.0)	4 (1.3)
Incision duration (hours)	(N=209)	(N=106)	(N=315)
Mean (SD)	0.80 (0.327)	0.84 (0.352)	0.81 (0.335)
Median	0.75	0.77	0.75
Minimum, maximum	0.2, 2.1	0.2, 2.5	0.2, 2.5

Source: CSR INN-CB-016, p. 45 (PDF), Applicant's submission, NDA 209511

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The population was comprised primarily of subjects with a single hernia (96%) and no history of previous ipsilateral hernia repair with mesh (89%).

With regard to prior analgesic medication, all analgesics except acetaminophen were prohibited within 24 hours of surgery. Acetaminophen may have been used the day of surgery, but the standardized dosing regimen was then adjusted to adhere to the maximum daily recommendations. Prohibited medications and the recommended time for avoidance included the following:

- Aspirin or aspirin-containing products for 7 days, unless necessary for cardiovascular prophylaxis and the dose had been stable for ≥30 days
- Extended-release opioid analgesics for 4 weeks before surgery
- Any investigational drug product within 30 days of surgery
- Other pain medication, including nonsteroidal anti-inflammatory medications, before randomization
- After randomization, all pain medications except those specifically outlined in the protocol
- Centrally acting alpha agents, such as clonidine, neuroleptic agents, and other antipsychotic agents within 2 weeks of surgery
- Antidepressant medications unless the dosing regimen had been stable for ≥30 days prior to screening and no change in dosing was anticipated during the study
- Monoamine oxidase inhibitors within 10 days of surgery
- Systemic corticosteroids within 10 days of surgery; inhaled and topical steroids were permitted
- Any anesthetics, except those used during the administration of general anesthesia

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study drug compliance was 100% for subjects who received the implant. Similar to the findings in Study INN-CB-014, there were no subjects in either group who required surgical re-exploration and removal of the implants.

A total dose of fentanyl 100 mcg, IV, was permitted intra-operatively, but dosing was to be avoided within 30 minutes of the anticipated end of the procedure. Other opioid analgesics were not permitted pre- or intra-operatively. A pre-operative dose of an antiemetic for nausea prophylaxis was allowed, but post-operatively was only administered to treat documented nausea.

As discussed in Section 6.1.1, parenteral morphine was used as needed for rescue analgesia during the time the subjects were in the PACU (a minimum of three hours post-operatively). Once subjects were tolerating oral medication, they received a standard acetaminophen regimen (650 mg three times daily) and were offered immediate-release morphine, 15 mg, for breakthrough pain if needed.

Efficacy Results – Primary and Key Secondary Endpoints

Subjects who received the bupivacaine collagen-matrices had statistically significantly less pain over the first 24 hours post-operatively (SPI24) when compared to subjects who were treated with the placebo collagen-matrices. The Applicant reported that subjects who received the bupivacaine collagen-matrices had approximately 24% less pain over the first 24 hours post-operatively when compared to subjects treated with placebo. Additionally, subjects who received the bupivacaine collagen-matrices used statistically significantly less opioid analgesia

during the first 24 hours (TOpA24) and 48 hours (TOpA48) and reported statistically significantly less pain over the first 48 hours post-operatively (SPI48) when compared to subjects treated with placebo matrices. The primary and key secondary efficacy endpoint results are described in the following tables.

Table 26. Primary Efficacy Endpoint: Time-Weighted Sum of Pain Intensity From Time 0 Through 24 Hours (SPI24) (mITT Population)

Parameter Statistic	INL-001 (N=207)	Placebo (N=105)
SPI24		
Mean (SD)	88.3 (47.01)	116.2 (44.04)
Median	84.4	119.3
Minimum, maximum	0.0, 219.8	23.5, 213.3
Observed p-value[a]	<0.0001	

[a] p-value based on ANOVA model with treatment, gender, and history of previous ipsilateral hernia repair as main effects

Source: CSR INN-CB-016, p. 47 (PDF), Applicant's submission, NDA 209511

Table 27. Sequential Testing Results for the Primary and Key Secondary Efficacy Endpoints (mITT Population)

Endpoint	Parameter	Observed p-value	Significance Based on the Sequential Testing Algorithm
Primary	Sum of pain intensity Time 0 through 24 hours (SPI24)	<0.0001	*
Key secondary	Total opioid analgesia Time 0 through 24 hours (TOpA24)	<0.0001	*
	Sum of pain intensity Time 0 through 48 hours (SPI48)	0.0270	*
	Total opioid analgesia Time 0 through 48 hours (TOpA48)	0.0003	*
	Sum of pain intensity Time 0 through 72 hours (SPI72)	0.1490	NS
	Total opioid analgesia Time 0 through 72 hours (TOpA72)	0.0016	NS

*=significant (based on sequential testing algorithm).
NS=not significant (based on sequential testing algorithm).

Source: CSR INN-CB-016, p. 47 (PDF), Applicant's submission, NDA 209511

Table 28 further summarizes the key secondary efficacy endpoints and provides additional details regarding the pain score and total opioid use data.

Table 28. Key Secondary Efficacy Endpoints: Analysis of TOpA24, SPI48, TOpA48, SPI72, TOpA72 (mITT Population)

Parameter Statistic	INL-001 (N=207)	Placebo (N=105)
Total use of opioid analgesia through 24 hours (TOpA24)		
Median	5.0	14.0
Minimum, maximum	0.0, 70.0	0.0, 53.0
Observed p-value[a]	<0.0001	
P-value based on sequential testing algorithm	*	
Sum of pain intensity through 48 hours (SPI48)		
Mean (SD)	192.6 (91.90)	216.8 (90.95)
Median	188.1	214.9
Minimum, maximum	0.0, 435.8	47.5, 429.3
Observed p-value[b]	0.0270	
P-value based on sequential testing algorithm	*	
Total use of opioid analgesia through 48 hours (TOpA48)		
Median	10.0	20.0
Minimum, maximum	0.0, 90.0	0.0, 73.0
Observed p-value[a]	0.0003	
P-value based on sequential testing algorithm	*	
Sum of pain intensity through 72 hours (SPI72)		
Mean (SD)	277.6 (137.94)	301.2 (134.51)
Median	264.5	299.7
Minimum, maximum	0.0, 651.7	62.8, 645.3
Observed p-value[b]	0.1490	
P-value based on sequential testing algorithm	NS	
Total use of opioid analgesia through 72 hours (TOpA72)		
Median	10.0	20.0
Minimum, maximum	0.0, 107.0	0.0, 110.0
Observed p-value[a]	0.0016	
P-value based on sequential testing algorithm	NS	

[a] p-value is from Wilcoxon Rank Sum Test; [b] p-value was based on ANOVA model with treatment, gender, and history of previous ipsilateral hernia repair as main effects; *=significant; NS=not significant
Source: CSR INN-CB-016, p. 50 (PDF), Applicant's submission, NDA 209511

Similar to the findings in Study INN-CB-014, the median amount of opioid rescue was used for the statistical analyses, not the mean amount. It appears that comparison of the mean amount of opioid use was less impressive and ultimately, less clinically meaningful. This will be discussed further in Section 7, Integrated Review of Effectiveness.

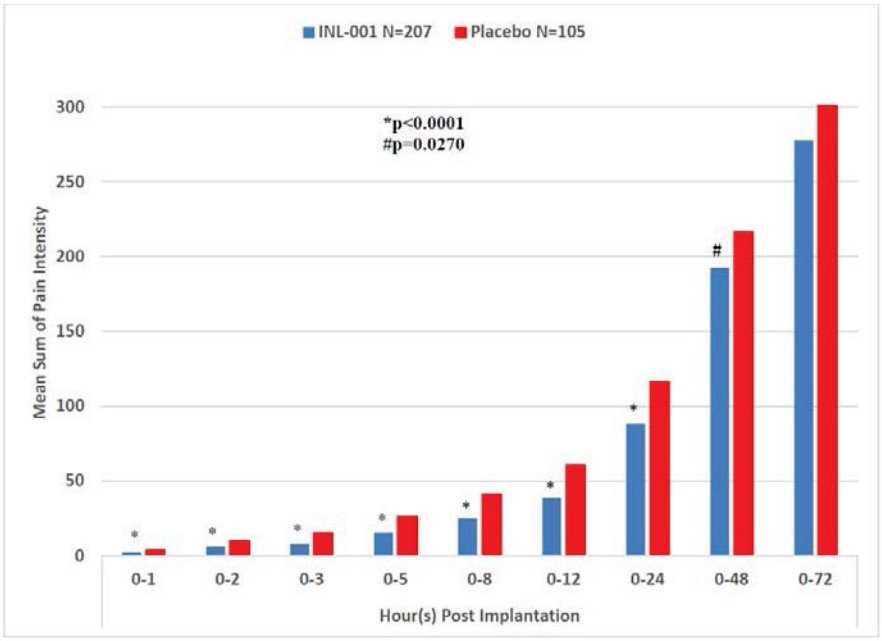
Other Secondary and Exploratory Efficacy Endpoints

Other Secondary Efficacy Endpoints

- SPI cumulative – the Applicant reported that the subjects who received INL-001 had statistically significantly lower mean pain scores cumulative from Time 0 through each of the predefined time points until 48 hours when compared with subjects who received

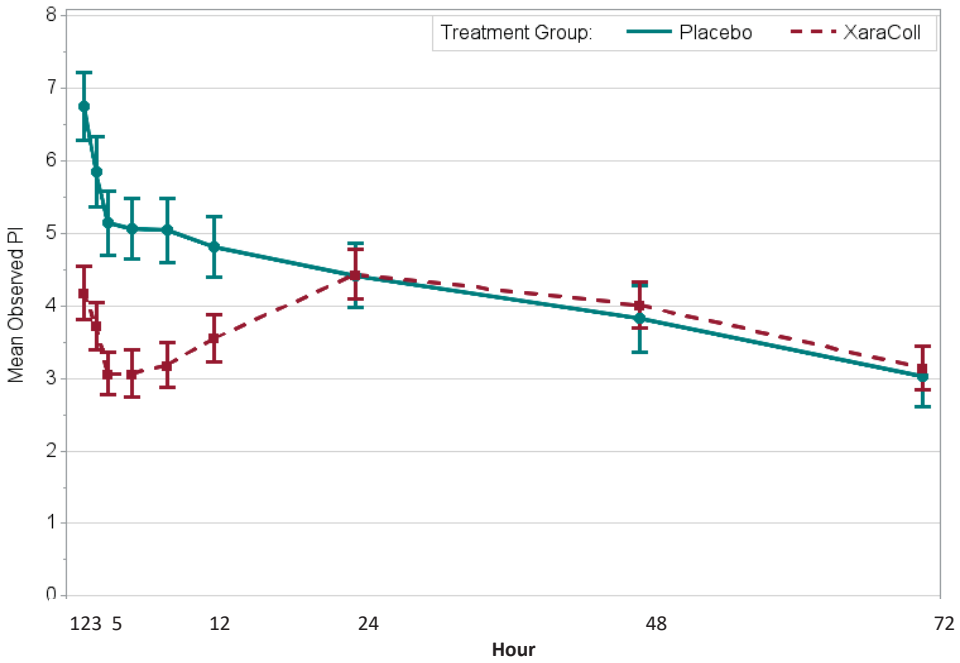
the placebo implants. While the cumulative pain scores at 72 hours were not statistically significantly different between the two groups, they were lower for subjects in the the INL-001 treatment group. Refer to Figure 6 for graphical representation of the results for the SPI cumulative efficacy endpoint reported by the Applicant.
Figure 7 is a graphical representation of the mean pain intensity scores through 72 hours, provided by Dr. Yi Ren, the statistical reviewer for this application. The Applicant provided a similar graph; however, the pain curves were plotted to 24 hours, not 72 hours. As will be discussed in Section 7, Integrated Review of Effectiveness, it appears that at the 24-hour and later time points, there is no difference in pain intensity between the INL-001 treatment and placebo groups, suggesting there is no additional benefit of INL-001 at 24 hours post-operatively and later. Additionally, the mean pain intensity scores for subjects in both groups were reported as ≥3 using the NRS through the 48 hour time point.

Figure 6. Time-Weighted Mean Sum of Pain Intensity Cumulative at Predefined Time Periods from Time 0 through 72 Hours (mITT Population)



p-values were from an ANOVA model with treatment, gender, and history of previous ipsilateral hernia repair as main effects
Source: CSR Study INN-CB-016, p. 51 (PDF), Applicant's submission, NDA 209511

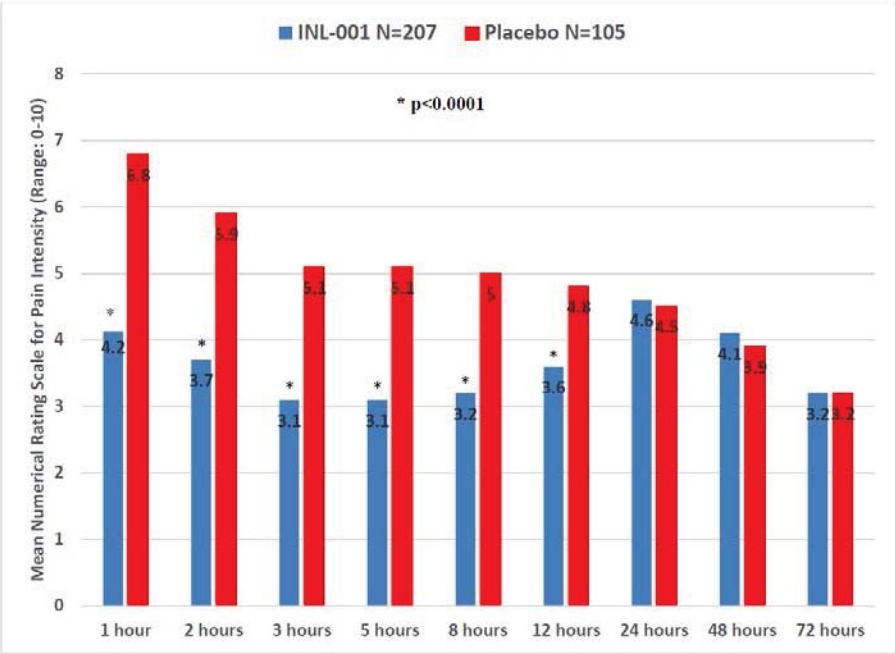
Figure 7. Mean Pain Intensity Scores at Predefined Time Points Through 72 Hours



Source: Dr. Yi Ren's statistical analysis review, internal correspondence

- NRS of PI at predefined time points – pain intensity was measured at predefined time points using the 11-point NRS. Patients who received INL-001 had statistically significantly lower mean PI scores at all time points through 12 hours compared with patients who received the placebo implants. Mean pain scores after 12 hours appeared similar in both groups. Refer to Figure 8 for graphical representation of these efficacy results.

Figure 8. Mean Numerical Rating Scale of Pain Intensity at Predefined Time Points From Time 0 through 72 Hours (mITT Population)



p-values were from an ANOVA model with treatment, gender, and history of previous ipsilateral hernia repair as main effects

Source: CSR Study INN-CB-014, p. 54 (PDF), Applicant's submission, NDA 209511

- Subjects who did not use any rescue opioid analgesia – the Applicant reported that approximately 28% of patients treated with INL-001 did not use opioid rescue through the 72 hour post-operative period, compared to 12% of patients in the placebo group. Refer to Table 29 for a summary of this data.

Table 29. Percentage of Patients Who Did Not Use Rescue Opioid Analgesia (mITT population)

Parameter Statistic	INL-001 (N=207)	Placebo (N=105)
Subjects who did not use rescue opioid analgesia, n (%)		
Time 0 through PACU discharge	110 (53.1)	18 (17.1)
Time 0 through 24 hours	74 (35.7)	13 (12.4)
Time 0 through 48 hours	59 (28.5)	13 (12.4)
Time 0 through 72 hours	57 (27.5)	13 (12.4)

Source: CSR INN-CB-016, p. 53 (PDF), Applicant's submission, NDA 209511

While these reported results are clinically meaningful, they become less so when considering the percentage of patients who used oral opioid rescue after leaving the PACU. As outlined in Table 30, the overall percentage of subjects who used oral opioid rescue analgesia through 72 hours was similar in the treatment and placebo groups.

Table 30. Number (%) of Patients with Oral Rescue Opioid Analgesia after Leaving the PACU

	XaraColl (N=207)		Placebo (N=105)		P-value
	n (%)	95% CI [1]	n (%)	95% CI [1]	[2]
Number of Patients with Any Oral Rescue Opioid Analgesia after Leaving the PACU through (n, %)					
72 Hours	137 (66.2)	(59.3, 72.6)	68 (64.8)	(54.8, 73.8)	0.7713
48 Hours	132 (63.8)	(56.8, 70.3)	66 (62.9)	(52.9, 72.1)	0.8414
24 Hours	108 (52.2)	(45.1, 59.1)	63 (60.0)	(50.0, 69.4)	0.2075
12 Hours	75 (36.2)	(29.7, 43.2)	59 (56.2)	(46.2, 65.9)	0.0010
8 Hours	42 (20.3)	(15.0, 26.4)	41 (39.0)	(29.7, 49.1)	0.0005
5 Hours	19 (9.2)	(5.6, 14.0)	12 (11.4)	(6.0, 19.1)	0.5482

[1] 95% Confidence interval for proportion of patients with any oral rescue opioid analgesia after leaving the PACU is obtained from one-sample binomial distribution; [2] p-value is obtained from the Cochran-Mantel-Haenzel (CMH) test adjusted for gender and history of previous ipsilateral hernia repair.
Source: CSR INN-CB-016, p. 192 (PDF), Applicant's submission

- Time to first use of rescue opioid analgesia (FOpA) – patients who received INL-001 had a statistically significantly longer time to FOpA compared to patients who received placebo implants, median times were 6.2 hours versus 0.9 hours, respectively. Refer to Table 31 for the FOpA efficacy results.

Table 31. Time to First Use of Rescue Opioid Analgesia (FOpA) (mITT Population)

Parameter Statistic	INL-001 (N=207)	Placebo (N=105)
Subjects who used rescue opioid from Time 0 through 72 hours, n (%)	150 (72.5)	92 (87.6)
Time to FOpA (hours)		
Median (95% CI)[a]	6.2 (2.0, 12.0)	0.9 (0.8, 1.0)
Hazard ratio (95% CI)[b]	0.43 (0.33, 0.56)	
Log rank p-value[c]	<0.0001	

[a]The 95% CI for median was computed using the Brookmeyer-Crowley method.
[b]The hazard ratio and 95% CI were based on a Cox proportional hazards regression model with treatment, gender, and history of previous ipsilateral hernia repair as exploratory variables.
[c]p-value (2-sided) was obtained using stratified log rank test based on stratification factors of gender and history of previous ipsilateral hernia repair.
Source: CSR INN-CB-016, p. 53 (PDF), Applicant's submission, NDA 209511

The opioids most commonly administered to patients in both groups for post-operative analgesia included IV fentanyl and morphine, as well as oral morphine once they were tolerating oral intake.

- POpA at predefined time periods from Time 0 – patients who received INL-001 required statistically significantly less median parenteral opioid analgesia at all predefined time periods through 24 hours compared to patients who received placebo.

- TOpA at predefined time periods from Time 0 – the Applicant reported that patients who received INL-001 required statistically significantly less median opioid analgesia at all time periods through 72 hours compared with patients who received placebo.

- TOpA from Time 0 through prior to discharge – patients who received INL-001 required statistically significantly less median opioid analgesia from Time 0 through prior to discharge compared to patients who received placebo, 0 mg IV morphine equivalents versus 6 mg IV morphine equivalents.

- Subject evaluation of pain through 72 hours – using a 5-point verbal rating scale, there was no statistically significant difference observed between the INL-001 treatment and placebo group on subject general evaluation of pain through 72 hours.

- Subject overall evaluation of pain through 72 hours compared with expectation – using a 5-point categorical scale, there was a statistically significant difference between the INL-001 and placebo groups regarding the pain experienced and the expected pain. It appears the majority of patients in both groups rated the pain as about the same, less, or a lot less than what they expected.

- Subject evaluation of pain interference on activity through 72 hours – using an 11-point NRS there was no significant difference between the INL-001 and placebo groups regarding the pain interference on activity. The majority of patients in both groups rated the interference on activity as what would appear to be mild or slight interference. There was, however, a larger percentage of patients treated with placebo who reported higher scores, more interference, when compared to patients treated with INL-001.

<u>Exploratory efficacy endpoint</u>

- The Applicant evaluated the integrated sum of pain intensity and total use of opioid analgesia (using the Silverman method of summated percentage differences from mean rank) in an attempt to better characterize the true effect of the study drug. They argue that some subjects will tolerate more or less pain and some subjects will chose more or less opioid rescue medication, therefore the true effect of treatment should incorporate both assessments. The results indicate that there was a statistically significant treatment effect for INL-001 compared to placebo at the 0 through 24-hour, 0 through 48-hour, and 0 through 72-hour time periods.

Table 32. Integrated Sum of Pain Intensity and Total Use of Opioid Analgesia

Parameter	INL-001	Placebo	Difference (95% CI)	p-value
SPITOpA24	-51.0	18.6	-69.6 (-92, -47.2)	<0.001
SPITOpA48	-42.6	-2.1	-40.5 (-63.8, -17.3)	0.0007
SPITOpA72	-40.3	-8.1	-32.2 (-55.7, -8.7)	0.0075

Confidence intervals (CI) around the treatment difference; 95% CI and p-value are from an ANOVA model with treatment, gender, and history of previous ipsilateral hernia repair as main effects.
Silverman method used (Silverman DG, O'Connor TZ, Brull SJ. Integrated assessment of pain scores and rescue morphine use during studies of analgesic efficacy. *Anesth Analg*. 1993;77(1):168–170.)
Source: Adapted from Table 14.2.6.2, CSR INN-CB-016, p. 200 (PDF), Applicant's submission, NDA 209511

Data Quality and Integrity

The Applicant reported a randomization issue that occurred at site 603. On treatment day, patient (b) (6) was not randomized due the IVRS blocking randomization due to limited study drug availability. The Applicant instructed the study site to use any study drug kit available. The patient was treated with kit 2090 on (b) (6) and subsequently randomized on (b) (6) to receive kit 1196. Both kits were placebo collagen matrices. It appears, however, that randomization on treatment day would have been to the INL-001 treatment group, given there were placebo kits but not INL-001 treatment kits available. The Applicant has conducted post-hoc sensitivity analyses, which suggests no change in reported study conclusions based on this error. Additionally, the Applicant has indicated that no other patients were affected.

It is reassuring that this did not impact study conclusions and appears to involve only a single patient, however, the Applicant's instruction to over-ride the randomization system and treat regardless of the block assignment, is concerning. This study site has been selected for inspection so any additional irregularities should be captured by the clinical site inspectors.

Missing Data

Similar to the reported results for Study INN-CB-014, there appears to be missing pain score data for all recorded time points through 72 hours for this study as well. Specifically, per Dr. Yi Ren's statistical analyses, the following table summarizes the number and percentage of missing pain scores for each time point (rounded to the nearest whole number).

Table 33. Number and Percentage of Missing Data at Each Analysis Time Point

	Number (%) of Missing Data by Analysis Time Point								
Hour	**1**	**2**	**3**	**5**	**8**	**12**	**24**	**48**	**72**
XaraColl (N=207)	9 (4%)	6 (3%)	8 (4%)	45 (22%)	7 (3%)	9 (4%)	4 (2%)	7 (3%)	23 (11%)
Placebo (N=105)	3 (3%)	7 (7%)	10 (10%)	22 (21%)	11 (11%)	8 (8%)	3 (3%)	7 (7%)	13 (12%)

Source: Dr. Yi Ren's statistical analysis review, internal correspondence

It is not surprising that there are missing data at each time point and some may be explained by the clinical scenario. Specifically, the five-hour time point is likely during patient discharge or transit home, times when pain scores may not have been captured. Additionally, the large percentage of missing data for the 72-hour time point may be explained by study fatigue or subject forgetfulness. It is, however, interesting that the largest number and percentage of captured pain score data was for the 24-hour time point, the primary efficacy endpoint.

It does not appear that the missing data impacted the Applicant's reported results. For additional information on the missing data and reported results, refer to Dr. Yi Ren's statistical review.

Dose/Dose Response

There was a single dose of the bupivacaine collagen-matrix, 100 mg, evaluated in this study. Each subject received three matrices for a total bupivacaine dose of 300 mg. The collagen composition of the matrices was 75 mg each, for a total dose of 225 mg. The Applicant did evaluate different doses of both bupivacaine, ranging from 100 to 300 mg total dose, and collagen, ranging from 140 to 280 mg total dose, in the Phase 1 and Phase 2 studies. Although the number of subjects who received different doses was low and the studies were not powered for efficacy, it did not appear that the lower doses of bupivacaine were efficacious and when compared to active comparators, the INL-001 implant lost on the primary endpoints.

Durability of Response

As discussed under Efficacy Results of this section, the bupivacaine collagen-matrices did result in statistically significantly less pain and less median opioid rescue analgesia for 48 hours when compared to the placebo matrices. However, as will be discussed in the following section, Integrated Review of Effectiveness, analysis of the pain intensity scores, pain curves, and the mean opioid use between the treatment and placebo groups appears less impressive. Additionally, the clinical significance of these differences, most notably observed early in the post-operative period, may be negligible.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

A detailed evaluation and discussion of the efficacy across the Applicant's drug development program is provided in Section 7.3, Integrated Assessment of Effectiveness. A high-level summary of the reported combined efficacy results from the Phase 3 studies will be presented here for the primary, key secondary, and the most relevant exploratory efficacy endpoints. While the label indication must be supported by the individual efficacy results from the Phase 3 studies, because the studies were identical in design, a combined analysis of the study results may provide additional information regarding analgesic trends and opioid use.

7.1.1. Primary Endpoints

The results from the combined analysis of the primary endpoint of time-weighted mean SPI24 for the Phase 3 studies was statistically significantly different for the XaraColl® treatment group compared to the placebo group. Specifically, there appeared to be approximately a 22% reduction in SPI24 in patients treated with XaraColl® compared to those treated with placebo. The combined analysis results are presented in the following table.

Table 34. Combined Analysis (Phase 3 Studies) for the Primary Endpoint, Time-Weighted Sum of Pain Intensity from Time 0 Through 24 Hours (mITT population)

Parameter Statistic	INL-001 N=404	Placebo Collagen Matrix Implants N=206
SPI24		
Mean (SD)	87.1 (47.05)	111.6 (46.25)
Median	82.5	112.3
Minimum, maximum	0, 224.4	6.6, 230.4
Observed p-value[a]	<0.0001	-

[a] p-value from an ANOVA model with treatment, study, gender, and history of previous ipsilateral hernia repair as main effects. Source: Summary of Clinical Efficacy, p. 57 (PDF), Applicant's submission, NDA 209511

As discussed in detail in Section 7.3, Integrated Assessment of Efficacy, the results from the Phase 3 studies are supportive of the revised indication and were statistically significant, however, they may not be clinically significant for the following reasons:

- the comparator group was a placebo, not a meaningful standard of care treatment
- the observed pain curves for the treatment and placebo groups for the Phase 3 studies were less impressive than the SPI24
- a single surgical population was evaluated, making extrapolation of the results to other soft tissue surgical procedures difficult

Because the Phase 2 studies (b) (4) (Study INN-CB-003 and Study INN-CB-010) did not demonstrate a statistically significant difference between the treatment and placebo groups on the primary efficacy endpoint, they will not be discussed further.

7.1.2. Key Secondary and Exploratory Endpoints

In evaluating the combined results from the Phase 3 studies, it appears they are more supportive of an extended duration of analgesic action for XaraColl® than the individual results for each study. Specifically, the combined data demonstrated a statistically significant difference in all key secondary efficacy endpoints between the treatment and placebo groups, including SPI72 and TOpA72 (refer to Table 35 for a summary of results).

Table 35. Combined Analysis for Key Secondary Endpoints (mITT population)

Parameter Statistic	INL-001 N=404	Placebo Collagen-Matrix Implants N=206
TOpA24, mg IV morphine equivalent		
Median	5.0	12.3
Minimum, maximum	0.0, 70.0	0.0, 53.0
Observed p-value[a]	<0.0001	-
p-value based on sequential testing algorithm	*	-
SPI48		
Mean (SD)	186.1 (93.53)	209.2 (92.48)
Median	180.5	208.8
Minimum, maximum	0.0, 435.8	6.6, 470.4
Observed p-value[b]	0.0033	
p-value based on sequential testing algorithm	*	
TOpA48 mg IV morphine equivalent		
Median	7.0	15.0
Minimum, maximum	0.0, 90.0	0.0, 73.0
Observed p-value[a]	<0.0001	-
p-value based on sequential testing algorithm	*	-
SPI72		
Mean (SD)	268.0 (138.79)	291.3 (137.12)
Median	253.0	274.9
Minimum, maximum	0.0, 651.7	6.6, 710.4
Observed p-value[b]	0.0441	
p-value based on sequential testing algorithm	*	
TOpA72 mg IV morphine equivalent		
Median	9.0	17.0
Minimum, maximum	0.0, 107.0	0.0, 110.0
Observed p-value[a]	0.0004	-
p-value based on sequential testing algorithm	*	-

[a] p-value from the Wilcoxon rank sum test.

[b] p-value from an ANOVA model with treatment, study, gender, and history of previous ipsilateral hernia repair as main effects.

*Represents statistical significance based on the sequential testing algorithm

Source: Summary of Clinical Efficacy, p. 59 (PDF), Applicant's submission, NDA 209511

These results may guide clinical expectations, however, as discussed in Section 7.3, Integrated Assessment of Effectiveness, an overestimation of the true clinical benefit of XaraColl® may also result in provider and patient dissatisfaction. Furthermore, demonstration of a decrease in postsurgical opioid use appears to be a common objective for the clinical development program for many local anesthetic products. However, a decrease in opioid use of less than one 10 mg morphine tablet, as calculated for Study INN-CB-014, is clinically meaningless (b) (4) Furthermore, when evaluating the overall opioid use for the specific time points, the mean difference between treatment and placebo groups is smaller than the reported median differences and the reported maximum opioid use for TOpA24 and TOpA48 was higher for the INL-001 group when compared to the placebo group. Refer to the table below for TOpA24, TOpA48, and TOpA72 data for each group.

Table 36. Combined Total Opioid Use for the Phase 3 Studies (mITT)

Parameter Statistic	XaraColl (N=404)	Placebo (N=206)
TOpA24		
N	404	206
Mean	8.5	14.5
Standard Deviation	10.92	12.42
CV%	128.2	85.7
Median	5.0	12.3
Q1, Q3	0.0, 13.0	4.0, 23.0
Min, Max	0.0, 70.0	0.0, 53.0
TOpA48		
N	404	206
Mean	14.6	19.8
Standard Deviation	17.98	18.22
CV%	123.3	92.1
Median	7.0	15.0
Q1, Q3	0.0, 24.5	4.0, 33.0
Min, Max	0.0, 90.0	0.0, 73.0
TOpA72		
N	404	206
Mean	18.2	23.1
Standard Deviation	23.22	23.20
CV%	127.7	100.6
Median	9.0	17.0
Q1, Q3	0.0, 27.5	4.0, 38.3
Min, Max	0.0, 107.0	0.0, 110.0

Source: ISE, p. 21 (PDF), Applicant's submission, NDA 209511

A reduction in opioid-related adverse events may be more supportive of a clinically relevant decrease opioid usage, however, the results from the Phase 3 studies with XaraColl® are not impressive. Refer to Table 37 for the incidence of opioid-related adverse events in the treatment and placebo groups. Arguably, there does appear to be a trend toward lower incidence of these adverse events, however, the differences between groups are small and not likely to represent meaningful improvement in patient satisfaction or outcomes.

Table 37. Incidence of Opioid-Related Adverse Events, Phase 3 Studies

Treatment-Emergent Adverse Event	INL-001 300 mg Group (N=411) n, %	Placebo Group (N=208) n, %
Somnolence	69 (17%)	39 (19%)
Nausea	39 (10%)	34 (16%)
Constipation	35 (9%)	31 (15%)
Vomiting	9 (2%)	10 (5%)

Source: Adapted from Summary of Clinical Safety, p. 53 (PDF), Applicant's submission, NDA 209511

The exploratory efficacy endpoints of time to first opioid rescue and percentage of subjects needing no rescue through 72 hours appear to be more clinically meaningful than a difference in mean or median opioid usage between the treatment and placebo groups. Refer to Section 6, Review of Relevant Individual Trials Used to Support Efficacy, and Section 7.3, Integrated Assessment of Effectiveness, for additional discussion regarding these exploratory endpoints.

7.1.3. Subpopulations

The efficacy results from the Phase 3 studies for SPI24 and TOpA24 endpoints were evaluated to identify potential differences in treatment effect across the following subgroups:

- Gender
- Age (<55, ≥55 to <65, ≥65 to <75, or ≥75 years)
- Race (black or non-black)
- Baseline body mass index (<30 or ≥30 kg/m^2)
- History of previous ipsilateral hernia repair
- History of multiple hernias

Analysis of SPI24 by subgroups was performed using ANOVA model with treatment and study as the main effects. Analysis of TOpA24 by subgroups was performed using Wilcoxon rank sum test.

Gender did appear to have an impact on the reported efficacy findings in the Phase 3 studies. Specifically, there was a statistically significant difference for SPI24 between the treatment and placebo groups for male patients, p<0.0001, but not for female patients, p=0.3389. This may be concerning, however, there was a total of only 20 female patients treated in these studies, potentially too small a number to demonstrate a clinical benefit. Furthermore, as previously mentioned, it is unlikely that the efficacy of bupivacaine is influenced by patient gender, and because the label indication will be revised to describe use only in open inguinal hernia repair with mesh, an almost exclusively male surgical population, these findings are not likely to have a significant post-market impact on clinical outcomes. Additional supportive data for a possible benefit of XaraColl® in female patients is that there was statistically significantly less opioid use during the first 24 hours for both male and female patients when treated with INL-001 compared to placebo.

For the primary efficacy endpoint SPI24, patients in all evaluated age subgroups who received INL-001 reported statistically significantly less pain than patients treated with placebo. It appeared that while the number of patients in the older age groups, ≥65 to <75 and ≥75 years, was small, the differences in reported pain between the treatment and placebo groups were the largest. For TOpA24, there was a statistically significant difference between the treatment and placebo groups for all ages except ≥75-year-old patients (p=0.0681).

Race, as defined in this study as black and non-black, did not appear to impact the efficacy results reported for SPI24 or TOpA24. Specifically, statistical significance for SPI24 and TOpA24 was reached in patients treated with INL-001 for both racial subgroups. The number of black patients treated in the Phase 3 studies, however, was low compared to non-black patients (56 versus 553). Body mass index, defined as <30 and ≥30 kg/m^2, and history of previous ipsilateral hernia repair also did not appear to impact the reported efficacy results for SPI24 and TOpA24.

A history of multiple hernias did appear to impact the results reported for SPI24 and TOpA24.

Specifically, there was no statistically significant difference between the treatment and placebo groups in reported pain or total opioid use over 24 hours in patients with a history of multiple hernias. As mentioned for other subgroup analyses, however, the number of patients with this history was low, 26 in total.

In summary, there were some statistical differences in efficacy for some of the subgroup analyses, however, the number of treated patients was generally low in these subgroups and the trends did suggest a measurable treatment effect after XaraColl® administration.

7.1.4. Dose and Dose-Response

There were several doses of INL-001, ranging from 100 mg to 300 mg, evaluated for efficacy in the Applicant's drug development program, and while the majority of participating patients underwent an open inguinal herniorrhaphy, there were female patients who had other surgical procedures including abdominal hysterectomy and bladder sling. The two Phase 2 studies which evaluated the safety and efficacy of INL-001, 150 mg in patients undergoing abdominal hysterectomy did not demonstrate a statistically significant difference in SPI or opioid use endpoints between the treatment and placebo groups.

Of the four clinical studies that were considered pertinent to the claimed indication, the two Phase 2 studies evaluated doses of 100 mg and 200 mg compared to placebo matrices in patients undergoing open inguinal hernia repair. There were trends toward improved pain and reduced opioid use post-operatively, but neither study demonstrated a statistically significant difference in the primary efficacy endpoint between treatment and placebo groups.

The results from the Phase 3 studies, as previously discussed, did demonstrate a statistically significant improvement in the sum of pain intensity through 24 hours, the primary efficacy endpoint, as well as other key secondary endpoints including the use of opioid rescue analgesia. While these efficacy findings may not translate into improved patient outcomes for a variety of reasons, as discussed at length in Section 7.3, Integrated Assessment of Effectiveness, they are supportive of a dose-response for INL-001.

The proposed labeling dose is 300 mg total, the dose evaluated in the Phase 3 studies. There is no therapeutic indication for either a higher or lower dose or repeat administration.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

XaraColl® is intended to provide reliable postsurgical analgesia after open inguinal hernia repair with mesh. Based on the reported efficacy results for the Phase 3 studies, specifically the SPIs at early time points, it appears that the onset of analgesic action for XaraColl® is within one hour of implantation. While the combined results from the Phase 3 studies suggest the duration of analgesic benefit may extend through 72 hours, the individual study results do not support such a prolonged duration of action. Because this is intended for a single

administration for patients undergoing the indicated procedure, there is little clinical concern for the development of tolerance or withdrawal effects.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

There are currently no FDA-approved bupivacaine products that are labeled for extended-release and while it seems unlikely that XaraColl® will be labeled as such, it is an additional bupivacaine product administered via a novel route that clearly has some clinical benefit. Approval of this product would offer clinicians an additional treatment option for managing acute postsurgical pain after open inguinal hernia repair, a relatively common surgical procedure, with the potential to have a positive impact on a large number of patient outcomes.

(b) (4)

7.3. Integrated Assessment of Effectiveness

The Phase 3 studies conducted by the Applicant demonstrated a statistically significant difference between the treatment and placebo groups on the primary efficacy endpoint. Additionally, there were key secondary efficacy endpoints that reached statistical significance, including TOpA24 for both Phase 3 studies, and SPI48 and TOpA48 for Study INN-CB-016. These data are supportive of the revised labeling indication, however, there are several issues which impact the clinical significance of the findings.

First, the comparator group was patients treated with placebo collagen-matrices, not an active treatment. While use of a placebo comparator is regulatorily acceptable, it is much less informative and clinically useful than an active comparator, particularly for soft tissue surgical procedures where local anesthetic wound infiltration is considered the standard of care and universally performed unless there is a contraindication to do so. A comparison of patient-reported pain and opioid use between XaraColl® and wound infiltration with immediate release bupivacaine, or another local anesthetic, would have likely been more informative in characterizing the true clinical benefit of XaraColl® over existing standard of care treatment options. It is highly unlikely that patients undergoing an open inguinal hernia repair with mesh would not receive any supplemental local anesthesia to proactively treat post-operative pain, suggesting that the efficacy comparison(s) to patients treated with placebo matrices did not represent a relevant or realistic comparison and, in fact, those patients may have been inadequately treated. This would seemingly lead to an overestimation of the analgesic benefit reported for XaraColl® bupivacaine collagen-matrices.

Second, the observed pain curves for the treatment and placebo groups for each Phase 3 study are less impressive than the reported areas under the curve, particularly for Study INN-CB-014

(refer to Figures 4 and 7 for pain curve data for each Phase 3 study). Specifically, the mean pain scores for both the treatment and placebo groups appear to be consistently three or greater for each time point. Additionally, the pain curves converge at 24 hours post-operatively for both studies and overlap for the duration of the studies, suggesting loss of efficacy at precisely the 24-hour time point. Based on this data, there does not appear to be any additional efficacy benefit beyond 24 hours post-operatively and while the Applicant is not making that claim, relatively short-term post-operative pain management questions the true clinical benefit of XaraColl® over immediate release bupivacaine products with opioid analgesic supplementation. Furthermore, decreased post-operative opioid use for 24 hours is unlikely to have a long-term or meaningful impact on overall post-operative use, as demonstrated by the 72-hour opioid data.

Third, a single surgical population and single dose of XaraColl® was evaluated in the two identical Phase 3 studies. The Applicant did evaluate the efficacy of varying doses of XaraColl® in several Phase 2 studies, (b) (4) in a variety of surgical populations, as noted below:

- total abdominal hysterectomy alone or with bilateral salpingo-oophorectomy
- myomectomy
- exploratory laparotomy with removal of dermoid cyst
- cystoscopy
- ovarian cystectomy
- pubovaginal sling, bladder sling
- ventral hernia repair
- laparoscopic inguinal and umbilical herniorrhaphy

While not all Phase 2 studies were powered to detect a statistically significant difference in efficacy outcomes and the dose of bupivacaine was lower than that evaluated in the Phase 3 studies, it is concerning that XaraColl® did not consistently demonstrate a clinical benefit over an active comparator or placebo, depending on the study. It is not clear why the Applicant did not evaluate other surgical procedures in the pivotal Phase 3 studies, and while it may not be necessary to demonstrate the efficacy of XaraColl® in every soft tissue surgical model, the demonstration of effectiveness in more than one population would be supportive of the broad "…postsurgical analgesia following (b) (4) indication that has been proposed.

With respect to secondary and other efficacy endpoints, the Phase 3 study results that appear to be the most clinically relevant include the time to first opioid use and percentage of patients not using any opioid rescue through 72 hours (refer to Table 38 for a summary of these results). There was a statistically significant difference in median time to first rescue between the XaraColl® treatment and placebo groups, with the most impressive results coming from Study INN-CB-014. There was approximately a 10-hour difference in requesting opioid analgesia between the treatment and placebo groups in this study. For Study INN-CB-016, the difference in median time to first opioid analgesia rescue was reported as approximately 5 hours between the treatment and placebo groups, and while less impressive than the time delay reported for

Study INN-CB-014, the results represent a clinically meaningful amount of time.

There appeared to be a larger percentage of patients treated with XaraColl® who did not require any opioid rescue analgesia, both IV and oral, through 72 hours compared to patients treated with placebo. Approximately 36% of XaraColl®-treated patients and 22% of placebo-treated patients did not need opioid rescue analgesia in Study INN-CB-014. For Study INN-CB-016, approximately 28% of XaraColl®-treated patients and 12% of placebo-treated patients did not require opioid rescue analgesia. These results are potentially supportive of the efficacy of XaraColl® after open inguinal hernia surgery with mesh, however, the clinical significance of the opioid use data is not entirely clear.

Table 38. Clinically Meaningful Exploratory Efficacy Endpoints

Study Treatment Group	Median Time to First Opioid Rescue (CI)	Percentage of Subjects Needing No Opioid Rescue Through 72 Hours
INN-CB-014		
• XaraColl (N=197)	10.7h (5.2, 17.8)+	36%
• Placebo (N=101)	1h (0.9, 1.1)*	22%
INN-CB-016		
• XaraColl (N=207)	6.2h (2, 12)+	28%
• Placebo (N=105)	0.9h (0.8, 1)*	12%

* Log rank p<0.0001; + 95% CI for median was computed using the Brookmeyer-Crowley method
Source: Adapted from tables in CSRs INN-CB-014 (p. 55, PDF) and INN-CB-016 (p. 53, PDF), Applicant's submission, NDA 209511

As previously discussed, the median opioid analgesic data was analyzed and appears to be more impressive than the mean data. Table 39 summarizes these findings. In Study INN-CB-014, the TOpA24 was reported as statistically significant with a median value of 5 mg for the XaraColl® treatment group compared to 10 mg for the placebo group, a difference of 5 mg. However, the mean TOpA24 data demonstrated a smaller difference of 4.7 mg between the groups (7.6 mg in the XaraColl® group and 12.3 mg in the placebo group). For the secondary endpoint of TOpA48, the median opioid difference was reported as 9 mg (5 mg in the XaraColl® group and 14 mg in the placebo group) and the mean difference was 2.9 mg (13.5 mg in the XaraColl® group and 16.4 mg in the placebo group). For TOpA72, the median difference of 9 mg is more impressive than the mean difference of 2 mg between the treatment and placebo groups. Similar results were observed for Study INN-CB-106. It is clear that the differences in mean opioid use between the two groups are consistently smaller than those reported with median data, and while a case could be made that any reduction in opioid use is clinically relevant given the current opioid epidemic, the reported results represent an over-estimation of XaraColl's analgesic benefit.

Table 39. Median Versus Mean Opioid Analgesic Use During the Phase 3 Studies

Efficacy Variable	INN-CB-014			INN-CB-016		
	XaraColl Group (mg)	Placebo Group (mg)	mg change	XaraColl Group (mg)	Placebo Group (mg)	mg change
TOpA24						
• median	5	10	5*	5	14	9*
• mean	7.6	12.3	4.7	9.4	16.6	7.2
TOpA48						
• median	5	14	9	10	20	10*
• mean	13.5	16.4	2.9	15.6	23	7.4
TOpA72						
• median	5	14	9	10	20	10[+]
• mean	16.6	18.6	2	19.7	27.4	7.7

*p<0.0001; [+]significant p value, 0.0016, but due to sequential testing, reported as not significant
Source: Reviewer's analysis

In addition to the reported differences in opioid use, the timing of these observed differences between the XaraColl® and placebo groups is an important consideration and appears less supportive of clinically meaningful post-operative pain management with XaraColl® treatment, as summarized in Table 40. Specifically, for Study INN-CB-014, the largest differences (increases) in opioid use in the placebo group appear to be early in the post-operative period, when both IV and oral analgesia was administered. There appears to be a minimal difference between opioid use in the XaraColl® and placebo groups after 24 hours; 2.9 mg at 48 hours and 2 mg at 72 hours. This finding supports the conclusions made based on the pain curve data that XaraColl® is unlikely to offer additional clinical benefit beyond 24 hours when compared to other standard of care post-operative analgesic treatments. Furthermore, the finding that fewer XaraColl®-treated patients needed opioid rescue is less meaningful when considering that of those who used opioid rescue, the mean amount was similar for both groups after 24 hours.

Table 40. Mean Total Opioid Analgesia and Percent Change/Increase Between the XaraColl® Treatment and Placebo Groups

Efficacy Variable	INN-CB-014			INN-CB-016		
	XaraColl Group (mg)	Placebo Group (mg)	% change	XaraColl Group (mg)	Placebo Group (mg)	% change
TOpA1	0.7	1.8	61%	0.7	2.1	67%
POpA1	0.6	1.7	65%	0.6	2.0	70%
TOpA2	1.8	4.1	56%	2.3	5.6	59%
POpA2	1.7	3.8	55%	1.8	5.3	66%
TOpA3	2.1	4.8	56%	2.6	6.3	59%
POpA3	1.9	4.3	56%	2.0	5.8	66%

Efficacy Variable	INN-CB-014			INN-CB-016		
	XaraColl Group (mg)	Placebo Group (mg)	% change	XaraColl Group (mg)	Placebo Group (mg)	% change
TOpA5	2.6	5.7	54%	3.4	7.2	53%
POpA5*	1.9	4.4	57%	2.0	5.9	66%
TOpA8	3.6	7.1	46%	4.1	9.0	54%
TOpA12	4.6	8.9	48%	5.9	12	51%
TOpA24	7.6	12.3	38%	9.4	16.6	43%
TOpA48	13.5	16.4	18%	15.6	23	32%
TOpA72	16.6	18.6	11%	19.7	27.4	28%

TOpA: total opioid analgesia in mg (IV and oral); POpA: parenteral opioid analgesia in mg; * represents the last time point for a recorded change in POpA (IV analgesia no longer administered after this time point)
Source: Reviewer's analysis

An additional consideration for the clinical significance of the reported post-operative analgesic effect of XaraColl® was the number of patients in each group who used any oral opioid rescue analgesia after leaving the PACU. In Study INN-CB-014, a similar percentage of patients in both groups used oral rescue opioid analgesia through 72 hours after PACU discharge; approximately 53% of XaraColl®-treated patients and 59% of placebo-treated patients (refer to Table 18). In Study INN-CB-016, there was a slightly higher percentage of patients (66%) treated with XaraColl® who required oral opioid rescue analgesia compared to the percentage of patients treated with placebo (65%), refer to Table 30. These results further support my conclusions that XaraColl® may not offer additional benefit above the current standard of care local anesthetic wound infiltration.

The remaining outstanding issue that may impact the overall clinical usefulness of XaraColl® bupivacaine collagen-matrices is the patient demographic evaluated during the drug development program. Specifically, approximately 88% of patients treated with XaraColl® were male. While it is unlikely that the efficacy or clinical pharmacology of bupivacaine would be affected by gender, it is reasonable to consider how the efficacy of XaraColl® would be impacted when used for procedures solely, or more commonly, performed in female patients. The Applicant did evaluate the safety and efficacy of lower doses of bupivacaine in XaraColl® in hysterectomy and other gynecological surgeries and while those Phase 2 studies were not *"…sufficiently powered to show a [treatment] difference…"* (Applicant Responses to FDA Filing Issues, May 23, 2018), the results did not support a clinically meaningful analgesic benefit of XaraColl® treatment. Approval of a broad postsurgical analgesic indication is difficult under these circumstances.

In summary, the Phase 3 studies conducted by the Applicant did demonstrate a statistically significant difference between XaraColl® and placebo matrices on the primary efficacy endpoint and some key secondary efficacy endpoints. For reasons discussed extensively in this review, the effect of XaraColl® on post-operative opioid use is likely not clinically relevant (b) (4) (b) (4) particularly

because standard of care wound infiltration was not the comparator group.

The reported results do support approval of this marketing application, with revisions to the product label, as discussed in Section 10, Labeling Recommendations.

8. Review of Safety

8.1. Safety Review Approach

This application is a 505(b)(2), thus the Applicant is relying on the Agency's previous findings of safety and efficacy for Marcaine™ 0.25%, approved under NDA 016964, and is the listed drug referenced in this application. The Applicant is also relying on nonclinical and clinical information in the published literature to support the safety and efficacy of bupivacaine HCl when used to achieve post-operative analgesia for soft tissue surgeries (refer to Section 5.2, Review Strategy, for a detailed discussion regarding the data relied upon in support of this 505(b)(2) application).

The evaluation of the safety profile for XaraColl® involved a comprehensive review of adverse events suspected to be related to bupivacaine and those suspected to be related to the collagen-matrix. The safety issue of greatest concern with administration of bupivacaine is LAST. Like all local anesthetics, bupivacaine binds the Na^+ channel in the inactivated state slowing the rate of neuronal depolarization. Electrophysiological studies, however, suggest that bupivacaine results in more profound depolarization changes, which in combination with its high degree of protein binding, leads to the marked toxicity observed with inadvertent intravascular injection or overdose (Morgan *et al*, 2002). Refer to Section 8.8.4, Overdose, for additional information regarding symptomatology associated with LAST.

While the potential safety concerns with bovine Type I collagen in the matrix include wound healing, immunological responses, and spongiform encephalopathies, the latter two have been adequately addressed by the Applicant and described in the Summary of Clinical Safety, Section 1, Exposure to the Drug (p. 10-11, PDF). The Applicant has also discussed wound healing in the same document and in subsequent correspondence during this NDA review cycle. Because there is limited clinical experience with collagen implantation into surgical wounds and the potential widespread use of this product for postsurgical analgesia after soft tissue surgeries, the concern of poor or impaired wound healing was thoroughly evaluated, as described in this clinical review.

The safety review will consist of evaluation and analysis of the clinical studies conducted by the Applicant and inclusion of information from the published literature as relevant.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The Applicant is seeking approval of XaraColl® for placement into the surgical site for postsurgical analgesia following (b) (4) In the drug development program, the safety database included patients from one Phase 1 study, six Phase 2 studies, two PK/BA studies, and two Phase 3 studies, as outlined in Tables 8 and 9 in Section 5.1, Tables of Clinical Studies. A total of 944 subjects were enrolled in the clinical studies; 892 subjects received the collagen-matrix implant, 612 received INL-001 and 280 received the placebo implant, and 52 subjects received a comparator treatment. Of the 892 subjects who received a collagen-matrix implant, 816 underwent inguinal hernia repair, 69 subjects underwent hysterectomy, and 7 subjects underwent other types of soft tissue surgeries including benign gynecological procedures. The bupivacaine doses administered via the INL-001 matrices ranged from 100 mg to 300 mg. Of the 52 subjects who received a comparator treatment, 12 subjects received bupivacaine 150 mg with epinephrine wound infiltration, 16 subjects received bupivacaine 175 mg wound infiltration, 13 subjects received the ON-Q® PainBuster System (900 mg bupivacaine infused over 72 hours), and 11 subjects received standard of care which did not include bupivacaine administration. The following table summarizes the treatments administered.

Table 41. All Study Subjects - Phase 1, 2, and 3 Studies

	INL-001						
	100 mg n (%)	150 mg n (%)	200 mg n (%)	300 mg n (%)	All INL-001 n (%)	Comparator Treatment[a] n (%)	Placebo Collagen-Matrix Implants n (%)
Number of subjects who received any study treatment	24	56	63	469	612	52	280

[a] includes standard of care (INN-CB-002), bupivacaine HCl 150 mg with epinephrine infiltrate (INN-CB-013), bupivacaine HCl 175 mg (INN-CB-002), and ON-Q PainBuster® (INN-CB-005)
Source: Summary of Clinical Safety, p. 40 (PDF), Applicant's submission, NDA 209511

The amount of bovine Type I collagen also varied throughout the XaraColl® drug development program. The evaluated matrices contained either 70 mg or 75 mg of bovine Type I collagen, with the total amount ranging from 140 mg to 280 mg depending on the number of matrices implanted. The amount of collagen in each matrix was the same for the INL-001 treatment group and the placebo group for each study.

8.2.2. Relevant characteristics of the safety population:

The majority of patients in the safety population and in the literature reviewed included adult patients undergoing open inguinal hernia repair with mesh insertion. Because this disease process affects males more than females, over 90% of treated patients were males. The

population included patients with ASA physical status classification I to III and the majority were Caucasian, not Hispanic or Latino. All clinical studies were conducted in the United States.

8.2.3. Adequacy of the safety database:

The totality of the safety database is adequate for the revised indication as described in Section 10, Labeling Recommendations. The Applicant evaluated a single surgical population in the Phase 3 clinical studies, which not only limits the proposed indication based on the efficacy results, but also limits the clinical utility due to a limited safety database. XaraColl® exposure in a single surgical population, which was greater than 90% male, will not support the broad proposed indication of *'postsurgical analgesia* (b) (4)

The Phase 2 studies that were included to support the efficacy and safety of the proposed indication, Study INN-CB-003 and Study INN-CB-010, were conducted in patients undergoing open inguinal hernia repair with mesh, and used a lower dose of XaraColl® (100mg and 200mg, respectively). They, therefore, do not provide additional safety information to support use of the to-be-marketed product in other surgical populations. The Phase 1 and Phase 2 clinical studies conducted in other surgical populations, including patients undergoing hysterectomy, are not informative regarding the safety profile of XaraColl® based on low numbers of treated patients and lower doses of bupivacaine administered (150 mg to 200 mg).

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no issues regarding the data integrity or the overall quality of the submission. The information provided was organized and easy to locate; however, the Integrated Summaries of Effectiveness and Safety were primarily presentations of the data, including large numbers of tables, and not the integrated and detailed assessment that is expected in these documents. In response to an IR dated May 31, 2018, the Applicant stated that a "split approach" was used for the components of the integrated summaries, such that the data and supportive tables were provided in the ISE and ISS and that the comprehensive text summaries and discussions were included in the Summary of Clinical Efficacy and Summary of Clinical Safety. The Applicant further stated that this was done based on the small size of the NDA and permitted according to the guidance for industry *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*. The relative size of the NDA is debatable, however, the review team determined that while this approach was not ideal, the submitted data and consequent conclusions could be adequately reviewed.

The Applicant stated that the data were frequently reviewed for accuracy and completeness during and after on-site monitoring visits by the CRO. Study monitors conducted site visits, which included an assessment of the clinical supplies dispensing and storage area and study documentation.

8.3.2. Categorization of Adverse Events

The clinical study reports (CSR) did provide definitions for adverse events (AE), FDA-defined serious adverse events (SAE), and treatment emergent adverse events (TEAE). The Applicant specified, however, that a hospital admission based on a complication of a pre-existing condition or an admission for a diagnostic evaluation of an adverse event would not qualify the adverse event as an SAE. The adverse events were categorized by severity and causality relationships were documented. The AEs determined not to be related to the study drug were evaluated for a relationship to the surgical procedure, opioid analgesic use, or something else. The following safety information was provided in the CSRs for the two Phase 3 studies, INN-CB-014 and INN-CB-016, and the PK/BA study using the to-be-marketed formulation, INN-CB-022:

Study INN-CB-022 (summarized in Table 5)
The safety endpoints for this PK/BA study included the following:

- Clinical laboratory assessments during the screening visit
- 12-lead ECG at screening
  - Continuous Holter monitoring beginning at least 24 hours prior to surgery and for 24 hours post-study drug administration
- Vital signs, including heart rate, respiratory rate, blood pressure, and body temperature, at regularly scheduled intervals
- The occurrence of adverse events were assessed throughout the study and reported in detail in the CRF and patient's chart. All adverse events were followed until resolution.
  - Patients were regularly assessed for the occurrence of AEs that could be related to bupivacaine toxicity. AEs of interest included respiratory difficulty, change in level of consciousness, restlessness, anxiety, tremors, drowsiness, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, and depression.
  - Patients were assessed regularly while in-patients for complications related to wound healing. Specifically, the wound was inspected for the presence of discharge or leakage of fluid, redness or inflammation, warmth in the area around the wound, and separation of the edges of the wound.
  - Outpatient wound assessments were conducted during the follow-up visits on Days 5, 7, 15, and 30 and included a list of specific questions regarding general wound problems, fluid leakage, pain, redness, inflammation, warmth, or wound separation. Additionally, they were asked about visits to a provider because of wound issues, antibiotic prescriptions for wound infection, and hospital admission due to wound issues.

Study INN-CB-014 (summarized in Table 10) and Study INN-CB-016 (summarized in Table 22)
The safety assessments conducted during the Phase 3 studies was identical and included the following:

- Physical examination at screening
- Vital signs, including heart rate, respiratory rate, blood pressure, and body temperature,

were measured at screening, preoperatively, and approximately 1, 2, 3, 5, and 8 hours after Time 0 (defined as time of matrix collagen implantation). The vital sign assessments at 5 and 8 hours were only performed if the subject was still in the PACU.

- Blood samples were collected at screening and evaluated for routine chemistry, including liver function markers, hematology, and pregnancy testing in female patients of child-bearing potential. Additional blood samples were collected as needed in patients experiencing an AE or when otherwise clinically indicated.
- Urine samples were collected at screening and evaluated for the presence of routine substances, such as nitrite and ketones, and for drugs of abuse, including cannabinoids. Female patients of child-bearing potential also had urine pregnancy testing on the day of the surgery.
- 12-lead ECG was performed at screening
- The occurrence of adverse events were assessed throughout the study and reported in detail in the CRF and patient's chart. All adverse events were followed until resolution.
  - Patients were regularly assessed for the occurrence of AEs that could be related to bupivacaine toxicity. AEs of interest included respiratory difficulty, change in level of consciousness, restlessness, anxiety, difficult speaking or being understood, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, changes in vision, tremors, depression, and/or drowsiness.
    - Assessments for bupivacaine toxicity were completed by study personnel at predefined time points while subjects were in the PACU, by the patient during follow-up telephone interviews, and by the investigator during the follow-up clinic visit(s).
  - AEs related to wound healing were frequently assessed during the follow-up telephone interviews and on Days 7 and 30 during clinic visits. Patients were specifically questioned about discharge or fluid leakage, pain or soreness, redness or inflammation, warmth, separation of the edges of the wound, had been assessed by a healthcare provider, had been prescribed antibiotics, or had been admitted to the hospital for a wound-related infection.

8.3.3. Routine Clinical Tests

Aside from the efficacy and safety assessments previously described, there were no other routine clinical tests or assessments that were performed during the Phase 3 studies.

8.4. Safety Results

8.4.1. Deaths

There was one patient death reported across the drug development program. The patient was a 42-year-old male with a past medical history significant for hypercholesterolemia, hypertension, and nonspecific ECG findings, who was enrolled and treated for a right inguinal hernia during Study INN-CB-016. Vital signs at the screening visit included a blood pressure of

175/90 mmHg and a heart rate of 68 beats per minute (bpm). He was randomized to the placebo group and had three collagen matrices implanted. Intraoperatively, the patient developed hypertension (peak 200/120 mmHg) and ST elevation was observed on the ECG. His heart rate was 110 bpm. He was treated with esmolol (total dose 80 mg) and hydralazine (5 mg) IV, with partial resolution of the hypertension and complete resolution of the ECG changes. While in PACU, the patient was asymptomatic but still hypertensive (163/102 mmHg) with a heart rate of 100 bpm. At the 6-hour post-operative follow-up phone call, the patient reported nausea but no other symptoms. On the morning of post-operative day 1 (POD), the patient was found "gasping for air" and Emergency Medical Services (EMS) was called. CPR was performed by family until EMS arrived. Cardiac monitoring by EMS revealed ventricular fibrillation. He was electrically defibrillated with return to spontaneous circulation and respiration but remained unresponsive.

The patient was diagnosed with an anterolateral myocardial infarction with elevated cardiac enzymes. Cardiac catheterization revealed 100% ostial stenosis of the left anterior descending (LAD) artery, 80% stenosis of the posterior descending artery and a ventricular branch of the right coronary artery, and an ejection fraction of 30%. The ostial lesion in the LAD was successfully stented with a drug-eluting stent and the patient was transported to the coronary care unit. Electroencephalograms revealed severe anoxic encephalopathy and care was withdrawn. The patient died on study day 20.

The investigator considered the event of ST elevation myocardial infarction as not related to study treatment.

8.4.2. Serious Adverse Events

The SAEs reported across the Applicant's drug development program will be discussed by the phase and identification number of the study.

Phase 3 Studies

There were seven SAEs documented in the Applicant's Phase 3 studies. Two occurred in Study INN-CB-014 and five occurred in Study INN-CB-016. Each SAE, by study, will be discussed in detail.

- INN-CB-014

  300 mg bupivacaine treatment group
  - Patient (b) (6) is a 59-year-old male who experienced urinary retention on post-operative day 2. The urinary obstruction was felt to be related to scrotal and/or penile edema and required an additional hospital visit. He also experienced scrotal cellulitis and epididymitis. This SAE was reported as resolved.
  - Patient (b) (6) is 53-year-old male who experienced bowel injury due to a large hernia and difficult surgical dissection, resulting in recognized serosal tears and a mesenteric rent. These injuries resulted in ischemic colitis. The patient was transferred to another facility for higher level of care and subsequently underwent a

bowel resection. He developed feculent peritonitis and sepsis. Other associated illnesses during hospitalization included a peritoneal abscess, small bowel obstruction, acute bronchitis, and hyponatremia. He was discontinued from the study and his clinical issues were reported as ongoing or resolved.

- INN-CB-016

  300 mg bupivacaine treatment group
  - Patient (b) (6) is a 23-year-old male who experienced appendicitis on post-operative day 8, underwent an uneventful laparoscopic appendectomy and did well. The SAE was reported as resolved.
  - Patient (b) (6) is a 61-year-old male who experienced a non-ST elevation myocardial infarction in the PACU. He was treated with sublingual nitroglycerin and transferred to another hospital for a higher level of care. He underwent cardiac catheterization, which revealed clinically significant stenosis, 80%, of the left circumflex coronary artery and he received a drug-eluting stent. He was discharged on post-operative day 2 and the SAE was reported as resolved.
  - Patient (b) (6) is a 42-year-old male who experienced rate-controlled atrial fibrillation in the PACU. He was admitted to the hospital for observation, spontaneously converted to NSR and was discharged home on post-operative day 1. The SAE was reported as resolved.

  Placebo treatment group
  - Patient (b) (6) is a 75-year-old male who experienced uncontrolled groin pain and hypertension. He was treated with opioid analgesics and acetaminophen and was discharged home on post-operative day 1. The SAE was reported as resolved.
  - Patient (b) (6) is a 38-year-old male who experienced serious abdominal pain and nausea. An abdominal CT scan was within normal limits for post-operative changes. He was treated with opioid analgesics, discharged home on post-operative day 2, and discontinued from the study per his request. The SAE was reported as resolved.

Phase 1 and Phase 2 Studies

- INN-CB-004

  There was a single subject across the entire drug development program who experienced presumed LAST and required removal of the bupivacaine HCl collagen-matrices. The patient is a 57-year-old female with a past medical history, per the MedWatch form, significant for hypothyroidism, urinary incontinence, lumbar vertebral fracture, multiple fractures, and Meniere's disease, who presented for a bladder sling procedure. Preoperative ECG and vital signs were within normal limits. There is a discrepancy on whether the patient received three of four bupivacaine HCl collagen-matrices (50 mg each), with a resulting total bupivacaine HCl dose of either 150 mg or 200 mg.

  The procedure was completed without complications and approximately four hours post-operatively, she developed chest pain and notable QT prolongation on ECG monitoring (QTc

520 msec). She was reportedly hypotensive (not all values provided) and treated with IV fluids, dopamine, albumin, and potassium replacement. She required increasing doses of dopamine and the addition of norepinephrine to maintain adequate blood pressure. Her lowest blood pressure, 69/34 mmHg, was recorded 12 hours post-operatively. Bupivacaine toxicity was suspected, and the patient was treated with intralipid. Eight bupivacaine HCl levels were measured during the first 6 hours after onset of symptoms and ranged from 54 to 143 ng/mL. An additional level drawn 22 hours post-operatively was 900 ng/mL, about the same time the patient returned to the operating room for removal of the matrices. Her condition improved, and she was discharged in stable condition on POD 4.

There is documentation to suggest that during the initial presentation of symptoms, the patient was treated with a "GI cocktail", which included lidocaine, for possible gastroesophageal reflux. The administration of additional local anesthetic may have contributed to the overall symptomatology, however, her clinical symptoms developed prior to administration of the GI cocktail.

The Applicant has suggested that the hypotension and cardiac findings were possibly due to an allergic drug reaction caused by administration of other medications including beta-lactam antibiotics or neuromuscular blockers. While this is possible, it is unlikely for three reasons. First, there were no other signs or symptoms of allergic drug reaction reported, such as wheezing, skin rash, or angioedema. Second, measured IgE levels were reported as normal during the hypotensive episode. And third, the patient's clinical status improved after removal of the implants. Based on the totality of the data, this is a case of presumed LAST until additional data is provided to support an alternate diagnosis.

- Other Phase 1 and Phase 2 Studies

  There were a total of eight SAEs documented in the Phase 1 and Phase 2 studies, including the presumed LAST SAE. The remaining seven SAEs will be briefly discussed here. While they are clinically relevant, it is important to note that the dose of bupivacaine HCl and the size of the collagen-matrix varied throughout the drug development program and patients in the Phase 3 studies were treated with the largest dose of bupivacaine HCl (300 mg) and each matrix included the largest amount of collagen (75 mg). The following table summarizes the SAEs for the Phase 1 and Phase 2 studies.

Table 42. SAE for Phase 1 and Phase 2 Studies

Study	SAE	Treatment/Resolution
Bupivacaine HCl Collagen-Matrix Treatment Groups		
INN-CB-001	Wound dehiscence and infection	Hospital readmission on POD 16, IV antibiotics, discharged on POD 25
INN-CB-002	Seroma of the surgical site	Serosanguinous drainage from superior aspect of incision noted on POD 3, reapproximated with staples
INN-CB-002	Bowel obstruction	Noted on POD 3, re-exploration and lysis of adhesions, discharged on POD 14
INN-CB-003	Hypotension	In PACU, patient developed symptomatic bradycardia and hypotension, IV glycopyrrolate administered, serum bupivacaine HCl levels ranged from 58.9 ng/mL to 86.6 ng/mL
INN-CB-011	OSA	Undiagnosed OSA resulted in hypoxemia and overnight admission
Placebo Collagen Treatment Groups		
INN-CB-003	Hiccups	Hospital readmission on POD 8 due to intractable hiccups, IV chlorpromazine administered
Active Comparator/Standard of Care Treatment Groups		
INN-CB-002	Abdominal abscess	Hospital readmission on POD 8, IV antibiotics

Source: Reviewer's summary from text descriptions of SAEs; POD = post-operative day; PACU = post-anesthesia care unit

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

As discussed above, in section 8.4.2, Serious Adverse Events, a single patient experienced apparent LAST, underwent removal of the matrices, and was removed from the study.
In the Phase 3 studies, INN-CB-014 and INN-CB-016, there were a total of two adverse events, one per study as described above, that resulted in the patients being removed from the study. The Applicant, however, has strictly defined an adverse event discontinuation as an adverse event that resulted in surgical removal of the matrices. Therefore, the two subject discontinuations from the Phase 3 studies have not been described as such. Because the evaluated treatment is surgically implanted, the typical adverse event discontinuation criteria, including no further treatment exposure, does not apply in this circumstance. A more logical definition, including no further efficacy data captured, could apply regardless of the status of the bupivacaine collagen-matrices, suggesting the above patients from the Phase 3 studies would accurately be described as adverse event discontinuations. However, because the overall number of adverse event discontinuations is low, the Applicant's definition and categorization does not impact the interpretation of their reported safety conclusions.

8.4.4. Significant Adverse Events

As previously mentioned, a main safety concern with XaraColl® is the risk of LAST. The challenge with extended or delayed release bupivacaine products is that the local efficacy is unrelated to the systemic concentration, such that C_{max} may be high in the absence of observed efficacy. In other words, a patient may be at risk to develop LAST despite continued postsurgical pain.

It is reassuring that there appears to be only a single patient in the XaraColl® drug development program who developed LAST requiring surgical removal of the matrices. It is also reassuring that analysis of the safety data from the Phase 3 studies demonstrated that the treatment and placebo groups had similar rates of adverse events that could be possibly related to LAST. Additionally, the occurrence of adverse events such as dysgeusia and dizziness could be associated with the development of LAST, however, they may also be due to the residual effects of general anesthesia.

In Study INN-CB-014, the dictionary coded AE terms that were included as possibly related to LAST included the following (similar terms grouped together):

- Altered state of consciousness, anxiety, dizziness, dizziness postural, anxiety, procedural anxiety, tremor, restlessness
- Tinnitus
- Chills, cold sweat
- Non-cardiac chest pain
- Dysgeusia, hypoesthesia and paresthesia oral
- Hypotension
- Vision blurred, visual impairment

There were 59 patients (29%) in the INL-001 group and 22 patients (22%) in the placebo group who experienced signs and/or symptoms that *could* be considered part of the constellation of LAST. While there appears to be a slight increased incidence of these AEs in the INL-001 treatment group, it is likely not clinically relevant. Well-documented AEs that are strong predictors of LAST, such as tinnitus and dysgeusia (metallic taste), appear to have occurred with similar frequency between the INL-001 treatment and placebo groups. Additionally, there was one patient in the placebo group that reported both tinnitus and dysgeusia, which were unlikely related to implantation of the placebo matrices.

In Study INN-CB-016, the dictionary coded AE terms that were included as possibly related to LAST included the following (similar terms grouped together):

- Anxiety, restlessness, dizziness, tremor
- Tinnitus
- Chest discomfort
- Dysgeusia, hypoesthesia and paresthesia oral
- Hypotension and procedural hypotension

- Vision blurred, vision impairment

There were 57 patients (27%) in the INL-001 group and 41 patients (39%) in the placebo group who experienced signs and/or symptoms that *could* be considered part of the constellation of LAST. Because the placebo matrices did not contain bupivacaine, the increased incidence of related AEs is supportive of the safety of the INL-001 matrices. Additionally, there were three patients in the placebo group that reported both tinnitus and dysgeusia, which were unlikely related to implantation of the placebo matrices.

Across the Applicant's drug development program, the overwhelming majority of treated patients were male. There was concern regarding the risk of LAST with administration of XaraColl® in surgical procedures unique to female patients, such as hysterectomy. Table 43 summarizes the incidence of the most relevant AEs associated with LAST by surgical procedure. It does not appear that there is an increased risk of LAST in patients undergoing TAH compared to those undergoing IHR.

Table 43. LAST-Related Adverse Events for Inguinal Hernia Repair and Total Abdominal Hysterectomy

Preferred Terms for LAST	All INL-001 Groups (N=608), n (%)		Comparator Treatment (N=52), n (%)		Placebo Collagen (N=277), n (%)	
	IHR (N=554)	TAH (N=54)	IHR (N=28)	TAH (N=24)	IHR (N=262)	TAH (N=15)
Dizziness	81 (15%)	1 (2%)	8 (29%)	0 (0)	39 (15%)	0 (0)
Vision blurred	23 (4%)	0 (0)	3 (11%)	0 (0)	6 (2%)	0 (0)
Anxiety	17 (3%)	0 (0)	2 (7%)	0 (0)	11 (4%)	0 (0)
Dysgeusia	36 (7%)	0 (0)	4 (14%)	0 (0)	13 (5%)	0 (0)
Tinnitus	11 (2%)	0 (0)	1 (4%)	0 (0)	9 (3%)	0 (0)

Source: Adapted from Applicant's Summary of Clinical Safety, p. 97 (PDF), NDA 209511 submission

For additional discussion regarding LAST, refer to Section 8.8.4, Overdose.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Opioid-Related Adverse Events

The Applicant suggests that because there appears to be a small, but measurable decrease in opioid consumption in each Phase 3 study through 24 hours, and through 72 hours when the analyzed study results are combined, there may also be a corresponding decrease in opioid-related AEs. The following table includes opioid-related AEs for all subjects across the drug development program, including those evaluated in the Phase 1 and Phase 2 studies.

Table 44. Incidence of Potential Opioid-Related Adverse Events

Preferred Term	All INL-001, N=612, n (%)	Comparator Treatment, N=52, n (%)	Placebo Collagen, N=280, n (%)
Somnolence	94 (15%)	11 (21%)	39 (14%)
Nausea	72 (12%)	9 (17%)	56 (20%)
Constipation	67 (11%)	5 (10%)	44 (16%)
Vomiting	18 (3%)	3 (6%)	15 (5%)
Vision blurred	23 (4%)	3 (6%)	6 (2%)

Source: Adapted from Applicant's Summary of Clinical Safety, p. 55 (PDF), NDA 209511 submission
Comparator treatment included bupivacaine HCl 150 mg wound infiltration, bupivacaine HCl 175 mg wound infiltration, and ON-Q PainBuster pump.

It does appear that the incidence of nausea was higher in the placebo collagen group compared to the INL-001 group, which is supportive of the Applicant's conclusion. My interpretation of the data, however, does not support the Applicant's conclusion for the following two reasons. First, the incidence of vomiting in the INL-001 treatment group and the placebo collagen group was similar. And second, comparing the frequency of AEs to a placebo treatment is not clinically relevant in this circumstance, considering the overwhelming majority of patients undergoing soft tissue surgical procedures are likely to receive some type of local anesthetic for post-operative pain management.

Incision Site Issues

As indicated by the Applicant in the CSR for Study INN-CB-010 (p. 30 of the PDF version), "*Adverse reactions reported for the collagen products that have been used for hemostasis include hematoma, potentiation of infection, wound dehiscence, inflammation, and edema*". During review of the wound/incision site adverse events across the entire XaraColl® drug development, it appeared there was a measurable adverse impact of the collagen-matrix on the surgical wound, which was not detected in the Phase 3 safety results because both treatment and placebo groups received the collagen-implants. A thorough evaluation and analysis of all available information was conducted and included the following, to be discussed in detail individually:

- High-level evaluation of wound/incision site issues for all Phase 1, 2, and 3 studies
- Comparison of wound/incision site AEs for IHR and total abdominal hysterectomy (TAH)
- Evaluation of AEs by amount of Type I collagen implanted
- Comparison of wound/incision site AEs for patients with a history of ipsilateral IHR with mesh and patients with no history
- Review of previous INDs with CollaRX® technology
- Review of information in the published literature
  - incidence of AEs for IHR
  - incidence of AEs associated with collagen implants
- Applicant's response to Information Request

Wound/incision site AEs for all Phase 1, 2, and 3 studies

In reviewing the pooled safety results from the Applicant's Phase 1, 2, and 3 studies, as presented in Table 45, it appears there may be an increased incidence of incision site AEs in patients who received the collagen-matrix when compared to patients who received a comparator treatment, which included bupivacaine wound infiltration, ON-Q Painbuster® pump, and standard of care. While pooled safety analyses may be subject to Simpson's paradox (b) (4) it is worth mentioning that this high-level interpretation of the safety data is maintained during review of each clinical study. As indicated in the table, the AEs with the highest incidence were incision site swelling and pain. These AEs may be related, and on some level expected for two reasons. First, it is not surprising that that insertion of three 5 x 5 x 0.5 cm implants, or six half implants, into a small incision, typically less than 10 cm, may result in apparent swelling. The size alone may lead to swelling or the resulting tissue inflammation caused by the surgical wound dissection required to accommodate insertion of the matrix may also contribute to wound swelling. Second, areas of swelling may lead to increased reported pain.

The incision site AEs of most clinical concern and significance are wound dehiscence and post-procedural discharge, which could be an indication of a wound infection. These AEs could result in re-exploration of the wound, re-approximation the wound, removal of the mesh, or administration of IV or oral antibiotics, all of which could increase the morbidity of the involved patient(s). While the incidence of these AEs appears to be increased in patients who received a collagen-matrix compared to the comparator group, the numbers are low and seem consistent with what is reported in the published literature, as discussed below.

Table 45. Incision Site Issues for All Clinical Studies

Preferred Term	All INL-001, N=612, n (%)	Placebo Collagen-Matrix, N=280, n (%)	Comparator Treatment, N=52, n (%)
Swelling	61 (10%)	30 (11%)	0 (0)
Pain	57 (9%)	32 (11%)	0 (0)
Other complication	26 (4%)	16 (6%)	0 (0)
Erythema	15 (3%)	11 (4%)	0 (0)
Post-procedural discharge	20 (3%)	10 (4%)	1 (2%)
Dehiscence	12 (2%)	5 (2%)	0 (0)
Inflammation	9 (2%)	6 (2%)	0 (0)
Infection	7 (1%)	2 (1%)	0 (0)
Hematoma	5 (1%)	1 (0.4%)	0 (0)

Source: Adapted from Applicant's Summary of Clinical Safety, p. 55 (PDF), NDA 209511
Comparator treatment included bupivacaine HCl 150 mg with epinephrine wound infiltration, bupivacaine HCl 175 mg wound infiltration, ON-Q Painbuster® pump, and standard of care.

Comparison of wound/incision site AEs for IHR with mesh and TAH

In considering the impact of the collagen-matrix on wound/incision site AEs, the type of surgery may be relevant. The Applicant's Phase 3 studies were conducted in a single surgical

population, and only a small number of patients underwent other surgical procedures including TAH. It is not clear why only IHR with mesh was selected for evaluation in the Phase 3 studies, whether a safety concern, including wound/incision site issues, led to the selection of this surgical population. The following table summarizes the wound/incision site AEs for patients who underwent IHR with mesh or TAH.

Table 46. Wound/Incision Site Adverse Events by Surgical Procedure

Preferred Term	All INL-001 Groups (N=608), n (%)		Comparator Treatment (N=52), n (%)		Placebo Collagen (N=277), n (%)	
	IHR (N=554)	TAH (N=54)	IHR (N=28)	TAH (N=24)	IHR (N=262)	TAH (N=15)
Swelling	61 (11%)	0 (0)	0 (0)	0 (0)	30 (12%)	0 (0)
Pain	57 (10%)	0 (0)	0 (0)	0 (0)	32 (12%)	0 (0)
Other	26 (5%)	0 (0)	0 (0)	0 (0)	16 (6%)	0 (0)
Erythema	15 (3%)	0 (0)	0 (0)	0 (0)	11 (4%)	0 (0)
Dehiscence	11 (2%)	1 (2%)	0 (0)	0 (0)	5 (2%)	0 (0)
Inflammation	9 (2%)	0 (0)	0 (0)	0 (0)	6 (2%)	0 (0)

Source: Reviewer's summary evaluation adapted from Table 34, Clinical Summary of Safety, p. 97 (PDF), Applicant's submission, NDA 209511

While the number of patients who underwent a TAH was low, it does not appear there were safety concerns related to the wound or incision site. Furthermore, the Applicant indicated that the Phase 2 studies were exploratory and not designed to ascertain a comparative safety profile.

Evaluation of amount of Type I collagen

Another consideration of possible wound/incision site AEs is whether the total amount of implanted Type I collagen, in mg, or the amount of Type I collagen per matrix, had an impact. Studies INN-CB-001, INN-CB-002, INN-CB-003, INN-CB-004, INN-CB-005, and INN-CB-011 evaluated collagen-matrices with 70 mg Type I collagen. The remaining studies, INN-CB-010, INN-CB-013, INN-CB-022, INN-CB-014, and INN-CB-016, evaluated collagen-matrices with 75 mg Type I collagen. The amount of Type I collagen per matrix was increased to maintain a similar bupivacaine release profile when the bupivacaine dose was increased from 50 mg to 100 mg per matrix. In evaluating the data at a high-level, as summarized in Table 46, it does not appear that increasing amounts of total implanted collagen or the amount of Type I collagen per matrix had an adverse effect on the wound. Furthermore, patients who received the highest amount of Type I collagen implanted, 280 mg, reportedly had no incision site adverse events and there does not appear to be an increased incidence in AEs when the amount of collagen per matrix increased from 70 mg to 75 mg. Arguably, the number of patients who received an amount other than 225 mg was low.

Table 47. All Incision Site TEAEs by Amount of Implanted Type I Collagen

Preferred Term	Amount of Type I Collagen				
	70 mg (N=92)			75 mg (N=520)	
	140 mg (N=24), n (%)	210 mg (N=56), n (%)	280 mg (N=12), n (%)	150 mg (N=51), n (%)	225 mg (n=469), n (%)
Swelling	0 (0)	0 (0)	0 (0)	0 (0)	61 (13%)
Pain	0 (0)	0 (0)	0 (0)	2 (4%)	55 (12%)
Erythema	0 (0)	0 (0)	0 (0)	0 (0)	15 (3%)
Dehiscence	0 (0)	1 (2%)	0 (0)	1 (2%)	10 (2%)
Inflammation	0 (0)	0 (0)	0 (0)	0 (0)	9 (2%)
Post-procedural discharge	0 (0)	0 (0)	0 (0)	0 (0)	20 (4%)
Seroma	0 (0)	2 (4%)	0 (0)	0 (0)	12 (3%)
Hemorrhage	0 (0)	0 (0)	0 (0)	1 (2%)	5 (1%)
Hematoma	0 (0)	1 (2%)	0 (0)	1 (2%)	3 (1%)
Other complication	0 (0)	0 (0)	0 (0)	0 (0)	26 (6%)

Source: Adapted from ISS, table 5.5.5., p. 807 (PDF), NDA 209511 submission

Evaluation of wound/incision site AEs by history of ipsilateral IHR with mesh

The Applicant evaluated AEs by history of ipsilateral IHR and no history of IHR and those related to the wound/incision site are summarized in the table below. It does appear that a history of prior IHR did result in a higher incidence of swelling and pain. This is not surprising considering the increased amount of surgical dissection that is generally required for repeat procedures due to the development of scar or fibrous tissue. Definitive safety conclusions regarding the impact of the collagen matrix on wound healing in patients with a history of IHR are challenging given the low numbers of treated patients.

Table 48. Wound/Incision Site Adverse Events by History of IHR

Preferred Term	No History of IHR (N=555)		History of Ipsilateral IHR (N=64)	
	INL-001 300 mg (N=369), n (%)	Placebo Collagen (N=186), n (%)	INL-001 300 mg (N=42), n (%)	Placebo Collagen (N=22), n (%)
Swelling	49 (13%)	25 (13%)	11 (26%)	5 (23%)
Pain	43 (12%)	27 (15%)	10 (24%)	5 (23%)
Complication	20 (5%)	16 (9%)	3 (7%)	0 (0)
Post-procedural discharge	18 (5%)	10 (5%)	2 (5%)	0 (0)
Erythema	10 (3%)	9 (5%)	3 (7%)	2 (9%)
Seroma	11 (3%)	3 (2%)	1 (2%)	2 (9%)
Dehiscence	8 (2%)	4 (2%)	0 (0)	1 (5%)
inflammation	6 (2%)	5 (3%)	1 (2%)	1 (5%)

Source: Adapted from Table 33, Summary of Clinical Safety, p. 95 (PDF), Applicant's submission

Previous INDs with CollaRX® technology

As summarized in Table 2, there have been (b) (4) INDs submitted that involved the clinical use of products with the CollaRX® technology. With the exception of the IND under which the clinical studies for this NDA were conducted, the INDs were withdrawn for reasons that do not appear to be related to safety.

Published literature review

- Incidence of wound/incision site adverse events for IHR –
  A review of the published literature supports the Applicant's claim that the incidence of wound/incision site AEs is consistent with information in the published literature regarding IHR. Specifically, articles in the published literature report an incidence of wound related complications ranging from 0% to 35% *without* local anesthetic infiltration. The most common complications reported include seroma, infection, and hematoma. When local bupivacaine infiltration is used, the wound complications range from 0% to 26%, with hematoma and 'other' complications most commonly reported. In a survey of patients (Franneby *et al*, 2008) who have undergone groin hernia repair, the 30-day wound complications range from 0% to 23%, with hematoma, severe pain, infection, and wound rupture the most commonly reported.

  In a retrospective study by Abi-Haidar *et al* (2011), a complication rate of 15% was reported in a study of 1034 elective groin hernia repairs, including femoral and scrotal hernias. The complications included non-wound related issues such as bladder injury, neuralgia, and mesh migration and erosion. The incidence of wound hematoma was reported as 18% and the incidence of surgical site infection was reported as 8%. In a published randomized clinical trial by Fitzgibbons *et al* (2006), the incidence of wound complications after inguinal hernia repair was 6% for wound hematoma, 5% for scrotal hematoma, 2% for infection, and 2% for seroma. The incidence of wound/incision site AEs after IHR with mesh reported by the Applicant appear consistent with reports in the published literature.

- Incidence of wound/incision site adverse events associated with collagen implants –
  Innocoll Pharmaceutical's wholly owned manufacturing facility in Germany, Syntacoll GmbH, has reportedly been manufacturing collagen products for over 30 years. The Applicant has stated that with the worldwide distribution and clinical use of such products, there have been over 800,000 exposures over a 10-year period beginning 2006 through 2016 with no reported safety signals or trends. The domestic experience includes eight collagen-based medical products approved as devices with 510(k) clearance. These products reportedly use the same Type I bovine collagen and the Applicant's review of post-marketing data did not identify any safety signals or concerning trends.

Applicant's response to filing communication

The concerns regarding the wound/incision site AEs were conveyed to the Applicant in the filing communication dated April 17, 2018. The Applicant responded that their data may not adequately characterize the adverse events in the active comparator groups for the following reasons:

- Limited data available due to low numbers of patients in the comparator treatment groups (i.e., N=28 for IHR and N=24 for TAH)
- The studies were not designed to evaluate comparative safety profiles
- The safety assessors for three of the studies were unblinded, which may have resulted in underreporting of AEs in the comparator treatment groups due to familiarity with the treatments compared to the (new) bupivacaine implant
- Information in the published literature with bupivacaine wound infiltration supports a higher incidence of wound-related adverse events than that reported in the Phase 2 studies with the active comparator treatment groups
- Information in the published literature supports an overall complication rate of 15% in patients undergoing elective inguinal hernia repair without the use of a bupivacaine product

The Applicant further states that of the incision site and wound healing issues noted, none were considered serious and only three in the XaraColl® treatment group were considered related to study drug treatment.

In response to an Information Request from July 9, 2018, the Applicant provided the requested information, including a listing of all wound/incision site AEs by study regardless of the incidence. In summary, the Applicant stated that of the 612 patients treated with any dose of XaraColl®, 150 (25%) reported a wound or incision site AE. Additionally, only two AE preferred terms were reported in ≥5% of patients who received XaraColl®, incision site swelling (10%) and incision site pain (9%). Nine preferred terms were reported with incidences between ≥1% to <5%, and included incision site complication, post-procedural discharge, incision site erythema, seroma, wound dehiscence, incision site inflammation, incision site infection, incision site hemorrhage, post-procedural contusion, and wound complication. There were only three SAEs reported in the drug development program related to the wound/incision site. They are individually summarized in Table 42 and include wound dehiscence and infection and seroma in two subjects who received XaraColl® 150 mg, and abscess in one patient who received an active comparator treatment. The Applicant reported all three as not related or unlikely related to study drug and resolved.

In general, the responses and supportive information provided by the Applicant regarding an observed increase in wound/incision site AEs are acceptable and I agree with their explanations and rationale; however, I have the following three comments for consideration. First, while the number of treated subjects in the comparator groups was low compared to the number treated with the collagen-matrices, it is difficult to understand how no patients experienced swelling, pain, erythema, dehiscence, or inflammation, particularly given the incidence of

incision site adverse events reported in the published literature referenced by the Applicant in support of this marketing application. Second, while the Phase 2 clinical studies were not designed to formally evaluate safety outcomes, observational and exploratory analyses can provide a high-level summary of potential adverse events to monitor during larger, Phase 3 studies. And third, bupivacaine is undeniably a widely used local anesthetic and most operating room personnel are familiar with its indications and adverse event profile. This familiarity, however, does not translate into an acceptance and lack of reporting for adverse events, particularly during the course of a known clinical study. It seems unlikely that incision site adverse events would be under-reported simply because the assessor understood the safety profile of bupivacaine. Furthermore, while the Applicant has indicated three of the studies utilized unblinded safety assessors, the CSRs for Studies INN-CB-002, INN-CB-013, and INN-CB-022 indicate they were blinded, leaving only one study, INN-CB-005, that was unblinded. Presumably in the studies described as blinded, the health care provider(s) evaluating the wound post-operatively would not have been aware of subject treatment group, removing the suggested 'observer bias'.

A final consideration regarding the use of XaraColl® during open inguinal hernia repair with mesh is the potential for scar or granulation tissue to develop at the site of implantation and the impact on future surgical dissection. Specifically, the results of the non-clinical studies have indicated complete dissolution of the implant at 56-days and did not suggest an increased amount of fibrotic tissue at the time of necropsy on either Day 35 or Day 56. Understandably, the Phase 3 studies did not the evaluate the ease or difficulty of surgical re-exploration after treatment with XaraColl®. There was the single patient from Study INN-CB-004 who required removal of the matrices secondary to presumed LAST, however, this procedure was performed on post-operative day 1, a time early in the post-operative course when the development of scar tissue would not have been expected. Evaluation of this potential clinical issue will likely be addressed in the post-market surveillance program.

8.4.6. Laboratory Findings

In all Phase 2 and Phase 3 studies, laboratory assessments were performed at the screening visit only, unless indicated as the result of an adverse event or other clinical indication. Screening laboratory data is not included in the clinical summaries or the ISS.

8.4.7. Vital Signs

Vital sign monitoring included heart rate, blood pressure, respiration, pulse oximetry, and body temperature throughout the study, including increased monitoring frequency during surgical implantation.

8.4.8. Electrocardiograms (ECGs)

In the pharmacokinetic studies conducted by the Applicant, Study INN-CB-013 and Study INN-CB-022, a total of 58 patients treated with XaraColl® 300 mg and 16 patients treated with

Marcaine™ 175 mg (the LD) wound infiltration underwent continuous ECG monitoring via Holter for at least 24 hours after study drug treatment. The recording period included the time of maximum serum bupivacaine concentrations in the majority of patients, as reported by the Applicant. Additional treatment groups for Study INN-CB-013 included INL-001 200 mg and bupivacaine 150 mg with epinephrine wound infiltration. Relevant ECG findings from the two studies are as follows:

INN-CB-013

- INL-001 300 mg treatment group

Refer to Table 50 for relevant ECG findings observed in subjects treated with INL-001 300 mg and the corresponding T_{max} and C_{max} values.

Table 49. Relevant ECG Findings for Subjects Treated with INL-001 300 mg

Subject	T_{max} (h)	C_{max} (ng/mL)	Relevant Findings
(b) (6)	36	506	1st degree AV block at 5 to 10 h and at 24 h; LAFB at 24 h
	4	606	Non-specific T wave changes
	3	494	1st degree AV block at 1 h followed by nonspecific T wave changes between 1.5 to 24 h
	24	624	ST between 3 to 10 h
	24	457	1st degree AV block from 1.5 to 4 h; nonspecific T wave changes at 6 to 18 h
	24	775	1st degree AV block at 1.5 h, 10 h, and at 12 h
	24	414	1st degree AV block at 18 h

T_{max}= time of maximum serum concentration; C_{max}=maximum serum concentration; AV=atrioventricular; ST=sinus tachycardia; LAFB=left anterior fascicular block
Source: Adapted from Summary of Clinical Safety, p. 84 (PDF), Applicant's submission, NDA 209511

- INL-001 200 mg treatment group

Four patients developed nonspecific T wave changes, which were not present at baseline, when bupivacaine concentrations were greater than or equal to 400 ng/mL. The Applicant reported that these changes did not persist. A single patient with a history of premature ventricular contractions (PVCs) had mild, intermittent PVCs noted during treatment, which was coded as extrasystole.

- Bupivacaine HCl 150 mg with epinephrine treatment group

The Applicant reported that all patients with a serum concentration of greater than or equal to 400 ng/mL were evaluated for ECG abnormalities at the time their serum concentrations met or exceeded this threshold. A single patient was reported as having sinus tachycardia with a serum bupivacaine concentration of 474 ng/mL at the 4-hour time point. A cardiac adverse event, mild bradycardia, was documented for one additional patient. No other abnormalities were reported for these or other patients treated with bupivacaine 150 mg wound infiltration.

INN-CB-022

The clinically relevant ECG changes observed during Study INN-CB-022 for both treatment groups are included in Table 51.

Table 50. Relevant ECG Findings for Subjects Treated with INL-001 300 mg

Subject	T_{max} (h)	C_{max} (ng/mL)	Relevant Findings
INL-001 300 mg treatment group			
(b) (6)	5	940	Occasional SVT
	10	833	8 beat run of SVT
	8	471	20 beat run of ventricular escape rhythm
	2	510	Rare SVT; single ventricular couplet
	4	430	Rare SVT
	12	387	Frequent ventricular bigeminy
	4	363	Sinus bradycardia; non-sustained ventricular tachycardia
	2	872	Ventricular escape rhythm
	2	395	SVT
	12	274	ST; ventricular ectopy
	2	1000	SB; SVT
Bupivacaine HCl 175 mg			
	1	466	SVT; RBBB
	2	728	Non-sustained ventricular tachycardia
	1	1140	Ventricular ectopy; ventricular couplets

AV=atrioventricular; C_{max}=maximum serum concentration; LAFB=left anterior fascicular block; RBBB=right bundle branch block; SB=sinus bradycardia; ST=sinus tachycardia;; SVT=supraventricular tachycardia; T_{max}= time of maximum serum concentration

Source: Adapted from Summary of Clinical Safety, p. 86 (PDF), Applicant's submission, NDA 209511

In the INL-001 300 mg treatment group, there were four patients who had C_{max} values greater than or equal to 1,000 ng/mL and all four had a measured T_{max} at two hours. Of these four patients, one was hypertensive, 154/96 mmHg, at T_{max}, one experienced the ECG changes noted in Table 51, and all four patients had heart rate measurements at T_{max} ranging from 48 to 60 beats per minute. As reported by the Applicant, no other clinically significant changes in measured hemodynamic parameters were observed for these patients with the highest measured serum bupivacaine concentrations.

These reported ECG results are reassuring, however, there are limitations to use of a Holter monitor for early detection of clinically relevant ECG changes. First, while the Holter can be used to capture continuous ECG data for up to 48 hours, the analysis of the data is retrospective and does not occur in real-time, as is the case with telemetry monitoring. The data does not get transmitted to a manned 24-hour location with immediate notification of clinically relevant ECG changes. Second, there is no mechanism for the patient to manually mark a timepoint during the recording period during symptomatic periods.

An additional limitation to the Holter data captured from the PK studies conducted by the

Applicant is electrical intervals, such as the PR or QT interval, or QRS duration were calculated. The only subject throughout the Applicant's drug development program who was reported to have concerning QT prolongation was the female patient in Study INN-CB-004 who developed apparent LAST, requiring additional ECG monitoring. This is concerning given that early signs of cardiotoxicity associated with local anesthetic administration can be prolongation of the PR and QT intervals, as well as increased duration of the QRS complex. Because the Applicant did not evaluate the QT interval during the clinical studies or conduct a separate QT evaluation, their interpretation of the cardiac safety of XaraColl® may not be totally accurate or reflect the real-time ECG changes potentially occurring after its administration.

During the End of Phase 2 Meeting held on December 5, 2011, the Applicant was informed that if the PK/BA study included continuous ECG monitoring such that there was sufficient data captured to adequately characterize the cardiac risk profile of INL-001, then there may be less need to intensively monitor and conduct prolonged cardiac assessments in the pivotal Phase 3 studies. The Applicant, therefore, did not perform prolonged cardiac assessments during the Phase 3 studies. A single 12-lead ECG was performed at screening and at other times only when clinically indicated. Continuous ECG monitoring is required in patients undergoing general anesthesia according to practice guidelines put forth by the American Society of Anesthesiologists, and while it does not appear there was an in-depth analysis of the captured ECG data as part of the study protocol, there were no reported AEs of clinically significant ECG changes beyond those reported throughout Section 8.4, Safety Results.

8.4.9. QT

The Applicant did not conduct a thorough QT (TQT) evaluation. As discussed in Section 8.4.8, ECGs, retrospective evaluations of the Holter recordings from patients in the PK/BA clinical studies were conducted and the reported results were supportive of the Applicant's claim that use of XaraColl® did not appear to result in clinically meaningful ECG changes or cardiotoxicity. As previously mentioned, however, the evaluation of the data captured during Holter monitoring does not appear to include an assessment of the electrical intervals, including the QT interval, or the QRS morphology after treatment with XaraColl®. Continuous ECG monitoring during the Phase 3 studies included the intra- and immediate post-operative periods only.

While the lack of a TQT evaluation could otherwise be problematic, there are three reasons why it may not be with this marketing application. First, LAST appears to most commonly present with a neurotoxicity prodrome prior to the development of clinically significant cardiac findings. Symptomatic patients will generally describe feeling dizzy or lightheaded, experience a metallic or strange taste, or complain of tinnitus or perioral numbness. In the Phase 3 studies, the reported adverse events that could be related to neurotoxicity were reported with a low frequency and appeared to be evenly distributed across both the INL-001 and placebo groups. Specifically, in Study INN-CB-014, approximately 5% of patients treated with INL-001 and 3% of patients treated with placebo complained of a metallic taste. With respect to tinnitus, in the

same study approximately 1% of patients treated with INL-001 and 2% of patients treated with placebo described experiencing this adverse event. In the PK/BA study, INN-CB-022, there was a larger percentage of subjects in the Marcaine™ infiltration treatment group who complained of dizziness and dysgeusia, compared to the INL-001 treatment group.

Second, of the 411 subjects treated with XaraColl® in the Phase 3 studies, none had signs or symptoms consistent with cardiotoxicity and there were no adverse events reported for the cardiac system organ class (SOC). The most common cardiac adverse event reported during Study INN-CB-022 was bradycardia, with a slightly higher incidence in the Marcaine™ infiltration treatment group compared to the INL-001 treatment group.

And third, immediate-release bupivacaine has a long history of clinical use since its initial U.S. approval in 1972. Not only has it been widely used for more than four decades, but the indications for its use have expanded such that it is routinely used for the management of acute postsurgical pain, via both wound infiltration and peripheral nerve blockade, as well as for neuraxial anesthesia in several surgical patient populations, including a variety of surgical procedures across a wide range of patient ages. The Applicant conducted a relative PK/BA study, INN-CB-022, using the to-be-marketed formulation of XaraColl® and Marcaine™ 175 mg wound infiltration during open inguinal herniorrhaphy. The mean C_{max} values are comparable, 663 ng/mL for the INL-001 group versus 641 ng/mL for the Marcaine™ infiltration group. Additionally, the peak C_{max} was 1230 ng/mL for the INL-001 group and 1140 ng/mL for the Marcaine™ infiltration group. These results support the Applicant's claim that from a clinical pharmacology standpoint, there does not appear to be an increased risk for the development of cardiotoxicity associated with the surgical implantation of INL-001 during open inguinal herniorrhaphy.

For these reasons, I conclude that the Applicant has conducted an adequate cardiotoxicity assessment and agree that there appears to be a low risk of cardiotoxicity associated with the use of this implantable bupivacaine product.

8.4.10. Immunogenicity

The Type I bovine collagen used in the manufacture of XaraColl® has been certified as transmissible bovine spongiform encephalopathy-free (b) (4) It is assumed that the same regulations will be applied to all future XaraColl® manufacturing for commercial sale post-approval.

It does not appear that the collagen component of XaraColl® generates a measurable clinical immunological response.

8.5. Safety Analyses by Demographic Subgroups

Demographic subgroups that were analyzed for safety in this NDA included gender, age (<55 years, 55 to <65 years, 65 to <75, and ≥75 years), and race (white, nonwhite). The safety data for these subgroups was summarized for the Phase 3 studies and all Phase 1, 2, and 3 studies. Additionally, adverse events were summarized by history of prior hernia in the Phase 3 studies and by dose and type of surgery, inguinal hernia repair and hysterectomy, in all Phase 1, 2, and 3 studies.

Gender

For the Phase 3 studies, a slightly higher percentage of male patients experienced ≥1 TEAE; i.e., 63% of male patients and 54% of female patients in the INL-001 treatment groups. As indicated in Table 52, female patients in the INL-001 treatment group tended to have a higher incidence of dizziness, nausea, restlessness, incision site complication and erythema, seroma, pyrexia, dysarthria, and tinnitus. Clinically meaningful conclusions based on this safety data, however, are difficult considering the low number of female patients treated, 20 total for both INL-001 and placebo groups. Most TEAEs reported for both genders were mild or moderate in severity. Severe TEAEs were reported by 2% of males in the INL-001 treatment group and none were considered related to the study treatment. Females treated with INL-001 did not report any severe AEs.

Table 51. Treatment-Emergent Adverse Events by Gender (Phase 3 Studies)

Preferred Term	Males (N=599)		Females (N=20)	
	INL-001 300 mg (N=398) n (%)	Placebo Collagen-Matrix Implant (N=201) n (%)	INL-001 300 mg (N=13) n (%)	Placebo Collagen-Matrix Implant (N=7) n (%)
Subjects with ≥1 TEAE	249 (62.6)	138 (68.7)	7 (53.8)	5 (71.4)
Somnolence	67 (16.8)	39 (19.4)	2 (15.4)	0
Dizziness	62 (15.6)	34 (16.9)	3 (23.1)	0
Incision site swelling	59 (14.8)	30 (14.9)	1 (7.7)	0
Incision site pain	53 (13.3)	31 (15.4)	0	1 (14.3)
Nausea	37 (9.3)	31 (15.4)	2 (15.4)	3 (42.9)
Constipation	35 (8.8)	30 (14.9)	0	1 (14.3)
Dysgeusia	31 (7.8)	13 (6.5)	0	0
Restlessness	28 (7.0)	19 (9.5)	2 (15.4)	0
Incision site complication	21 (5.3)	16 (8.0)	2 (15.4)	0
Post procedural discharge	20 (5.0)	10 (5.0)	0	0
Headache	17 (4.3%)	1 (0.5%)	0	0
Tremor	15 (3.8%)	6 (3.0%)	0	0
Vision blurred	15 (3.8%)	6 (3.0%)	0	0
Incision site erythema	12 (3.0)	11 (5.5)	1 (7.7)	0
Seroma	11 (2.8%)	5 (2.5%)	1 (7.7%)	0
Anxiety	12 (3.0)	11 (5.5)	0	0
Scrotal swelling	12 (3.0%)	2 (1.0%)	0	0
Pyrexia	9 (2.3%)	1 (0.5%)	1 (7.7)	0
Dyspnoea	10 (2.5%)	5 (2.5%)	0	0
Vomiting	9 (2.3)	10 (5.0)	0	0
Hypoaesthesia Oral	9 (2.3%)	4 (2.0%)	0	0
Wound dehiscence	8 (2.0%)	5 (2.5%)	0	0
Dysarthria	7 (1.8%)	5 (2.5%)	1 (7.7%)	0
Tinnitus	5 (1.3%)	9 (4.5%)	2 (15.4%)	0
Incision site inflammation	7 (1.8%)	6 (3.0%)	0	0
Chills	6 (1.5%)	5 (2.5%)	0	0

Source: Summary of Clinical Efficacy, p. 90 (PDF), Applicant's submission, NDA 209511

For all Phase 1, 2, 3 studies, the overall incidence of TEAEs was similar, 66% of male patients and 73% of female patients in the INL-001 treatment groups experienced ≥1 treatment-emergent adverse event and the majority were considered mild to moderate in severity. As in the Phase 3 studies, the overall number of female patients across the XaraColl® development program was low (73 total), making clinically relevant conclusions about the safety data between genders difficult.

Age

For the Phase 3 studies, the overall incidence of TEAEs in the INL-001 treatment group was

slightly higher in the oldest age group, ≥75 years, as indicated in Table 53. The TEAEs with a higher incidence in this age group treated with INL-001 include incision site swelling, constipation, and scrotal swelling when compared to the younger age groups. There does not appear to be other clinically meaningful differences in the incidence of other TEAEs by age group and the majority to TEAEs were reported as mild to moderate in severity.

Table 52. Treatment-Emergent Adverse Events by Age Group - Phase 3 Studies

Age Group	<55 years (N=342)		55 - <65 years (N=185)		65 - <75 years (N=66)		≥75 years (N=26)	
Preferred Term	INL-001 300 mg (N=223) n (%)	Placebo Collagen-Matrix Implant (N=119) n (%)	INL-001 300 mg (N=128) n (%)	Placebo Collagen-Matrix Implant (N=57) n (%)	INL-001 300 mg (N=46) n (%)	Placebo Collagen-Matrix Implant (N=20) n (%)	INL-001 300 mg (N=14) n (%)	Placebo Collagen-Matrix Implant (N=12) n (%)
Subjects with ≥1 TEAE	134 (60.1)	87 (73.1)	85 (66.4)	36 (63.2)	26 (56.5)	11 (55.0)	11 (78.6)	9 (75.0)
Somnolence	40 (17.9)	22 (18.5)	20 (15.6)	13 (22.8)	7 (15.2)	4 (20.0)	2 (14.3)	0
Dizziness	35 (15.7)	19 (16.0)	28 (21.9)	12 (21.1)	2 (4.3)	2 (10.0)	0	1 (8.3)
Incision site swelling	26 (11.7)	13 (10.9)	24 (18.8)	10 (17.5)	6 (13.0)	1 (5.0)	4 (28.6)	6 (50.0)
Incision site pain	32 (14.3)	18 (15.1)	17 (13.3)	10 (17.5)	3 (6.5)	1 (5.0)	1 (7.1)	3 (25.0)
Nausea	25 (11.2)	23 (19.3)	12 (9.4)	8 (14.0)	2 (4.3)	2 (10.0)	0	1 (8.3)
Constipation	17 (7.6)	19 (16.0)	8 (6.3)	7 (12.3)	6 (13.0)	3 (15.0)	4 (28.6)	2 (16.7)
Dysgeusia	16 (7.2)	6 (5.0)	11 (8.6)	6 (10.5)	4 (8.7)	1 (5.0)	0	0
Restlessness	15 (6.7)	8 (6.7)	10 (7.8)	7 (12.3)	4 (8.7)	2 (10.0)	1 (7.1)	2 (16.7)
Incision site complication	11 (4.9)	9 (7.6)	7 (5.5)	4 (7.0)	4 (8.7)	2 (10.0)	1 (7.1)	1 (8.3)
Post procedural discharge	11 (4.9)	8 (6.7)	4 (3.1)	1 (1.8)	4 (8.7)	1 (5.0)	1 (7.1)	0
Headache	7 (3.1)	1 (0.8)	8 (6.3)	0	2 (4.3)	0	0	0
Tremor	6 (2.7)	3 (2.5)	3 (2.3)	3 (5.3)	6 (13.0)	0	0	0
Vision blurred	5 (2.2)	3 (2.5)	8 (6.3)	3 (5.3)	2 (4.3)	0	0	0
Incision site erythema	5 (2.2)	9 (7.6)	6 (4.7)	2 (3.5)	1 (2.2)	0	1 (7.1)	0
Seroma	3 (1.3)	1 (0.8)	5 (3.9)	2 (3.5)	3 (6.5)	2 (10.0)	1 (7.1)	0
Anxiety	7 (3.1)	4 (3.4)	4 (3.1)	4 (7.0)	1 (2.2)	1 (5.0)	0	2 (16.7)
Scrotal swelling	4 (1.8)	0	4 (3.1)	1 (1.8)	2 (4.3)	0	2 (14.3)	1 (8.3)
Pyrexia	8 (3.6)	0	2 (1.6)	1 (1.8)	0	0	0	0
Dyspnoea	5 (2.2)	3 (2.5)	5 (3.9)	1 (1.8)	0	1 (5.0)	0	0
Vomiting	5 (2.2)	5 (4.2)	4 (3.1)	3 (5.3)	0	1 (5.0)	0	1 (8.3)
Hypoaesthesia oral	6 (2.7)	3 (2.5)	3 (2.3)	1 (1.8)	0	0	0	0
Wound dehiscence	4 (1.8)	4 (3.4)	3 (2.3)	1 (1.8)	1 (2.2)	0	0	0
Dysarthria	4 (1.8)	3 (2.5)	3 (2.3)	1 (1.8)	0	1 (5.0)	1 (7.1)	0
Tinnitus	3 (1.3)	7 (5.9)	2 (1.6)	2 (3.5)	1 (2.2)	0	1 (7.1)	0
Incision site inflammation	4 (1.8)	5 (4.2)	3 (2.3)	1 (1.8)	0	0	0	0
Chills	3 (1.3)	1 (0.8)	2 (1.6)	3 (5.3)	1 (2.2)	1 (5.0)	0	0

Source: Summary of Clinical Safety, p. 92 (PDF), Applicant's submission, NDA 209511

For all Phase 1, 2, 3 studies, the overall incidence of TEAEs was similar across all age groups treated with INL-001. Specifically, 65% of patients <55 years of age, 70% of patients 55 to <65 years, 62% of patients 65 to <75 years, and 80% of patients ≥75 years reported at least one TEAE. When evaluating the incidence of TEAEs between the youngest and oldest age groups treated with any dose of INL-001, there does appear to be a higher incidence of TEAEs in the injury, poisoning, and procedural complications SOC. Specifically, the incidence of TEAEs in this SOC was 47% in patients aged ≥75 years and 24% in patients aged <55 years. As previously mentioned, however, the number of patients ≥75 years of age treated with INL-001 was low, 15 total, making meaningful conclusions about these results difficult. The majority of TEAEs for all age groups were reported as mild to moderate in severity.

Race

During the Phase 3 studies, nonwhite patients in the INL-001 treatment group experienced a higher incidence of several TEAEs including somnolence, dizziness, headache, vision blurred, and dysgeusia when compared to white patients in the same treatment group. As with the other subgroup analyses, however, these results may not be supportive of clinical conclusions given the low number of nonwhite patients treated. The majority of TEAEs were reported as mild to moderate in severity. The highest percentage of severe TEAEs were reported for nonwhite patients in the placebo group, a group which included only 27 patients.

Across all Phase 1, 2, 3 studies, a slightly higher percentage of nonwhite patients treated with any dose of INL-001 reported ≥1 TEAE. Specifically, 72% of nonwhite and 65% of white patients reported at least one TEAE. The majority of TEAEs were mild to moderate in severity. For the nervous system SOC, there was a higher incidence of TEAEs for nonwhite patients than for white patients treated with any dose of INL-001, 39% versus 29%. For the injury, poisoning and procedural complications SOC, which includes wound-related issues, the incidence of TEAEs was similar for both racial groups.

The Applicant also evaluated the incidence of adverse events by history of prior hernia in the Phase 3 studies and by dose and type of surgery in all Phase 1, 2, and 3 studies. Briefly, there did appear to be an increased incidence of incision site issues, including swelling, erythema, and pain, in patients with a history of prior hernia in the Phase 3 studies. This is not surprising, however, given the increased surgical dissection likely required for a repeat hernia repair procedure. The more concerning wound-related adverse events, including post-procedural discharge, wound dehiscence or inflammation, appeared to occur with a similar frequency between the groups. Most TEAEs were reportedly mild to moderate in severity. A larger number of patients without a history of prior hernia repair experienced a severe TEAE compared to patients without that history.

As previously mentioned, the relationship between the surgical procedure performed and the occurrence of wound-related issues was evaluated. There was initial concern that an increase in wound-related adverse events contributed to the decision to not extensively evaluate XaraColl® in patients undergoing abdominal hysterectomy in the Phase 3 studies. It does not appear that was the case. Specifically, of the TEAEs that were reported in patients undergoing hysterectomy, none related to wound healing were reported with a higher incidence than observed for patients undergoing herniorrhaphy. There was a higher incidence of nausea and vomiting in the hysterectomy group. Most TEAEs were reported as mild to moderate in severity.

For the low number of patients who underwent other surgical procedures, including laparoscopic or other abdominal procedures, there did not appear to be an increased incidence of wound-related TEAEs. There was the single patient in Study INN-CB-004 who experienced the SAE of severe hypotension requiring removal of the bupivacaine collagen-matrices. Aside from that report, the majority of TEAEs were reported as mild to moderate in severity.

8.6. Specific Safety Studies/Clinical Trials

The Applicant did not conduct additional safety studies.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

Carcinogenicity studies with the drug substance, bupivacaine, or the XaraColl® product have not been conducted. Refer to the pharmacology-toxicology review by Dr. Gary Bond for additional information regarding the adequacy of the Applicant's nonclinical drug development program.

8.7.2. Pregnancy and Lactation

The Applicant did not conduct clinical studies in pregnant or lactating women. The following information was submitted to support the drug product label.

Pregnancy
Innocoll recommends that XaraColl® not be used during pregnancy unless the potential benefit(s) outweigh the risk(s). Nonclinical studies have indicated that subcutaneous administration of bupivacaine HCl to pregnant rats and rabbits resulted in developmental toxicity, and decreased rat pup survival.

The Applicant reviewed the published literature, including any clinical trials evaluating bupivacaine administration in pregnant women. Reportedly, there were no clinical studies identified that evaluated the effects of bupivacaine on women during the first or second trimesters of pregnancy. The studies identified focused on third trimester exposure, primarily during labor and delivery after administration of epidural or intrathecal bupivacaine, and the impact on maternal hemodynamics and fetal heart rate. As discussed below, because of XaraColl®'s formulation and the impossibility of using it as an epidural, spinal, or paracervical anesthetic, these adverse events and toxicities would not be observed.

In vitro studies have demonstrated a decreased amount of circulating plasma proteins in pregnant women, specifically α_1-acid glycoprotein (AAG), resulting in less protein binding and an increased amount of free circulating bupivacaine. Because the free bupivacaine is pharmacologically active, the risk of bupivacaine toxicity may be increased in this population. The intermediate duration local anesthetics, such as lidocaine and mepivacaine, are affected less by changes in protein binding during pregnancy, hence there is a lower risk of toxicity with use of these agents.

Labor and delivery
Bupivacaine, along with other local anesthetics, readily and rapidly cross the placenta and there have been reports of alterations of the central nervous system, peripheral vascular tone, and cardiac function in the parturient, fetus, and neonate. Additionally, maternal hypotension is a

well-documented adverse event with neuraxial administration of bupivacaine, as in the case of epidural or spinal anesthesia. Adequate pre-procedure hydration and patient positioning may prevent or reduce the severity of the hypotension. Maternal hypotension can result in observed fetal heart rate changes, requiring intervention.

While the formulation of XaraColl® prevents its off-label use for epidural or spinal anesthesia, it could be used off-label during cesarean deliveries for the management of post-operative pain. The potential adverse events observed after this off-label use would most closely mimic those observed after local anesthetic wound infiltration and not necessarily result in maternal hypotension or fetal bradycardia.

Lactation

Bupivacaine HCl has been reported to be excreted in human breast milk, suggesting nursing infants could be exposed. However, there is no available information on the effects of the drug on breastfed neonates or on the production of breast milk. Because of the potential neonatal exposure, administration of XaraColl® in this population should be based on a benefit-risk evaluation, including consideration for the unknown risk(s) presented to the infant. The Applicant's PK data from Study INN-CB-022 indicated that the peak systemic exposure to the bupivacaine in the XaraColl® matrices ranges from 1.5 to 24 hours (median 3 hours) after implantation, longer than that observed in the same study after local bupivacaine wound infiltration (range 0.5 to 4 hours, median 1 hour). These results would support the conservative recommendation that if use of this product cannot be avoided in lactating women, expressed breast milk should be discarded for up to 24 hours after XaraColl® implantation.

Additionally, while there may be neonatal exposure to administered bupivacaine during breast feeding, the negative impact of poorly controlled pain on breastfeeding must also be considered. The study by Wilson *et al* demonstrated a positive effect on breastfeeding initiation when post-partum pain was controlled via bupivacaine epidural or combined spinal-epidural anesthesia.

8.7.3. Pediatrics and Assessment of Effects on Growth

The safety and efficacy of XaraColl® has not been evaluated in pediatric patients. The Applicant submitted an initial pediatric study plan (iPSP) on January 27, 2016, and it was agreed upon on June 17, 2016. The proposed pediatric studies evaluating XaraColl® and the proposed deferral requests are as follows:

- Study INN-CB-020: a multicenter, randomized controlled study to evaluate the pharmacokinetics, safety, and efficacy of INL-001 for post-operative analgesia in children 2 to <17 years of age who are undergoing open inguinal hernia repair surgery.
  - This study has been initiated, as per the Agreed iPSP.
  - The Applicant is requesting to defer submission of the ongoing study until December 2018, after a regulatory decision regarding this application has been made.

- Study INN-CB-021: a multicenter, single-dose, randomized, blinded study in children 0 to <2 years of age who are scheduled for open inguinal hernia repair surgery.
  - The Applicant is requesting a deferral for initiation of this planned study until data from Study INN-CB-020 are available, and neonatal and infant dosing is determined.
  - The projected date for final protocol submission is November 2018, and study initiation projected for January 2019.

8.7.4. Overdose

Local anesthetic systemic toxicity (LAST)

Local anesthetics such as bupivacaine HCl have a well-characterized toxicity profile, commonly referred to as LAST, which generally relates to high systemic concentrations. The relative risk of experiencing LAST is dependent on many factors, including systemic absorption from different sites of administration. Specifically, inadvertent intravascular administration is associated with the highest plasma concentration and results in the fastest onset and typically most severe signs and symptoms, followed by intercostal nerve block, caudal/epidural block, brachial plexus block, and lastly subcutaneous administration (Open Anesthesia, 2018).

The toxicities associated with local anesthetic administration initially manifest as central nervous system (CNS) symptoms followed by cardiovascular system symptoms (CVS). Historically, it has been reported in the published literature that plasma concentrations of bupivacaine ≥2000 ng/mL may result in CNS toxicity and concentrations ≥4000 ng/mL may result in CVS toxicity; however, there have been reports of LAST symptoms occurring at concentrations much lower than those commonly referenced. Because the prolonged release bupivacaine products, such as XaraColl®, have a different, and potentially more variable, pharmacokinetic profile than that observed with the immediate release products, the Agency agrees with the findings by Scott *et al* (1989), suggesting that bupivacaine toxicity may be observed at systemic concentrations >1000 ng/mL. Case in point, the female patient in Study INN-CB-004, previously discussed in Section 8.4.2, Serious Adverse Events, appeared to experience bupivacaine toxicity at a much lower systemic concentration than the historic level of ≥2000 ng/mL (peak concentration was 900 ng/mL).

The following table summarizes the CNS and CVS symptoms commonly associated with bupivacaine toxicity.

Table 53. CNS and CVS Symptoms of Bupivacaine and Other Local Anesthetic Toxicity

Symptom
CNS
– Tinnitus, blurred vision, tongue paresthesias, circumoral numbness, lightheadedness
– Nervousness, agitation, restlessness, disorientation, tremor
– Tonic-clonic seizures
– CNS depression, respiratory failure
– Coma
CVS
– Decreased electrical excitability, conduction disturbances including heart block, myocardial contraction, PR interval, QRS, and QT prolongation
– Bradycardia
– Arteriolar dilation, hypotension
– Ventricular fibrillation, CV collapse
– Death

Source: Adapted from Gadsden, 2017.

There are weight-based dosing guidelines aimed at reducing the risk of LAST. Specifically, the maximum recommended dose of bupivacaine with or without epinephrine should not exceed 2 to 3 mg/kg, with an approximate duration of action of 1.5 to 8 hours.

Treatment of LAST

As described in the review article by Christie *et al* (2015), the management of LAST begins with immediate recognition of the associated signs and symptoms and resuscitation measures focused on maintaining airway, breathing, and circulation, as per Advanced Cardiac Life Support (ACLS) guidelines. Cardiopulmonary resuscitation (CPR) may be necessary in cases of cardiac arrest. Seizures should be treated with benzodiazepines, thiopental, or possibly propofol depending the hemodynamic status of the patient. Cardiac arrhythmias, conduction blocks, and hypotension can be managed according to ACLS protocols, however lidocaine should not be administered in this situation.

The development of Intralipid®, a lipid emulsion comprised of soya oil, glycerol, and egg phospholipids, has positively impacted the resuscitation outcomes after documented cases of LAST and the American Society of Regional Anesthesia (ASRA) includes lipid emulsion therapy, such as Intralipid®, in the practice advisory on local anesthetic systemic toxicity (Neal *et al*, 2010). Cardiopulmonary bypass, while not used often, is still a viable treatment option in the setting of refractory toxicity in the critically ill patient.

While the likelihood of developing local anesthetic systemic toxicity with XaraColl® may be low, the following recommendations should be followed:

- XaraColl® should only be administered to patients undergoing open IHR
- the dose of bupivacaine should not exceed the recommended 2 to 3 mg/kg
- additional local anesthetic medications should not be administered in combination with

XaraColl® or within 96 hours of administration
- resuscitation medications, including a lipid emulsion such as Intralipid®, and equipment should be immediately available in the clinical settings where XaraColl® will be administered.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

XaraColl® has not been marketed anywhere in the world at the time of this NDA review, therefore no post-marketing information is available. The clinical concerns surrounding bupivacaine are well-documented and relate primary to the development of LAST.

8.8.2. Expectations on Safety in the Postmarket Setting

The single potential clinical issue that may be described in the post-market setting is the development of fibrotic or granulation tissue after XaraColl® implantation and the impact on future surgical exploration and dissection if clinically indicated.

8.8.3. Additional Safety Issues From Other Disciplines

At the time of this clinical review, there did not appear to be additional safety concerns expressed from other disciplines.

8.9. Integrated Assessment of Safety

The two main safety concerns surrounding the clinical use of the bupivacaine collagen-matrix product that were extensively evaluated during review of this NDA included the risk of the development of LAST and the potential adverse impact on wound healing.

The systemic bupivacaine concentration at which LAST can develop is debatable and appears to depend on many factors, including the route and site of administration and the underlying medical condition of the treated patient. Historically, ≥2000 ng/mL was the systemic level concerning for the development of neurotoxicity and ≥4000 ng/mL for the development of cardiotoxicity. As described in the article by Scott *et al* (1989), however, bupivacaine toxicity can develop at systemic concentrations >1000 ng/mL and it is well-known that due to the high degree of protein binding and strong affinity for cardiac Na^+ channels, the management of bupivacaine toxicity can be challenging and prolonged.

The risks of developing LAST after administration of XaraColl® are related to the following:
- The variable PK profile for XaraColl®, as determined in the Applicant's PK/BA study. Specifically, C_{max} ranged from approximately 663 ng/mL to 1230 ng/mL and T_{max} ranged from approximately 1.5 to 24 hours. This variability makes safety monitoring recommendations challenging.
- The pharmacodynamic response does not correlate with systemic bupivacaine

concentrations. This could potentially result in patients with toxic bupivacaine levels without any meaningful postsurgical analgesia.

- Open herniorrhaphy is often performed on an outpatient basis, such that many patients will be in an unmonitored setting during the time of peak systemic exposure and potential toxicity. This further complicates postsurgical safety assessments.
- The total maximum dose of bupivacaine delivered via the collagen-matrix is greater than that recommended in the Marcaine™ product label.

While the clinical concerns surrounding the development of LAST with administration of XaraColl® are on-going, there are four reasons why I recommend approval. First, the Applicant's drug development program included 612 patients exposed to a dose of XaraColl® and 469 patients received the maximum recommended dose, 300 mg bupivacaine HCl, and there was only a single patient who experienced what appeared to be LAST. Second, a comprehensive evaluation of adverse events likely associated with early neurotoxicity, including dysgeusia and tinnitus, indicated that the incidence was similar in both the XaraColl® treatment and placebo groups. Furthermore, a larger number of placebo-treated patients in Study INN-CB-016 experienced both dysgeusia and tinnitus when compared to XaraColl®-treated patients. Third, the evaluation of continuous 24-hour Holter data from the PK/BA study did not suggest an increased incidence of ECG changes indicative of bupivacaine-induced cardiotoxicity. Specifically, there were reportedly no abnormal ECG findings at or near the individual T_{max} and no adverse events suggesting bupivacaine-induced cardiotoxicity. Additionally, there were no ECG changes or cardiac adverse events reported for the patient with the highest observed plasma concentration, 1230 ng/mL, after XaraColl® administration.

And lastly, I believe the risk of developing LAST can be mitigated by adequate safety monitoring of all treated patients and limited use of XaraColl® in the surgical population most extensively evaluated, open inguinal hernia repair with mesh. The safety monitoring must include standard ASA monitoring post-operatively until such time as facility-issued discharge criteria have been met and discharge instructions and education provided. The discharge instructions should be detailed and comprehensive such that patients and caregivers are confident they are able to recognize the early signs and symptoms of bupivacaine-induced neurotoxicity. And while not an ideal risk mitigation strategy for presumed LAST, surgical removal of the matrices is a unique option that is not available after other routes of bupivacaine administration.

The potential adverse impact on wound healing was the other main safety concern associated with administration of XaraColl® that was thoroughly evaluated during the clinical review of this NDA. An evaluation of the surgical procedure performed, amount of implanted collagen per matrix, history of previous ipsilateral hernia repair, safety information from other research INDs, and information from the published literature was conducted to determine any associated risk of wound-related adverse events. Initial review of the Applicant's Phase 1, 2, and Phase 3 studies indicated an increased incidence of wound-related adverse events in patients treated with the collagen implant, either as the bupivacaine collagen-matrix or as the placebo collagen-matrix, when compared to patients treated with a comparator, such as

bupivacaine wound infiltration. Refer to Table 45 for summary of the wound-related adverse events for these studies. Specifically, incision site swelling and pain were reported with the highest incidence. Given the size and composition of the collagen implant, however, it is not surprising that there would be an increased incidence of these adverse events when compared to bupivacaine wound infiltration, for example. Wound dehiscence and post-procedural discharge, which appear to be more serious and may indicate a wound infection, were also reported with a higher incidence in patients who received the collagen matrices; however, the overall numbers were low and appear consistent with reports in the published literature after the same surgical procedure without the implanted collagen matrix. Analysis of wound-related adverse events by surgery type did not indicate an increased incidence in patients undergoing hysterectomy, an initial consideration given the selection of a single surgical population for evaluation in the pivotal Phase 3 studies.

Increasing amounts of Type I collagen per matrix did not appear to increase the incidence of wound-related adverse events. The majority of patients, 77%, received three, 75 mg matrices, for a total collagen dose of 225 mg. While the number of patients exposed to other amounts of collagen is low, those treated with 280 mg did not appear to have an increased incidence of wound-related adverse events. History of previous ipsilateral hernia repair with mesh did appear to result in a higher percentage of patients with incision site swelling and pain when compared to patients without this history. This is not surprising, however, given the increased surgical dissection typically required during repeat procedures, resulting in increased swelling and pain. The incidence of more clinically significant wound-related adverse events such as post-procedural discharge and dehiscence was similar for patients with and without a history of previous hernia repair. There have been (b) (4) INDs submitted using products with the CollaRX® technology, and while they were all subsequently withdrawn, it does not appear for reasons related to wound-healing. Review of information from the published literature suggests that the incidence of wound-related adverse events reported with use of XaraColl® appears the same or lower compared to reports from studies in open herniorrhaphy in which XaraColl® was not used.

A final consideration regarding the use of XaraColl® during open inguinal hernia repair with mesh is the potential for scar tissue or adhesions to develop at the site of implantation and the potential impact on future surgical dissection. The results of the non-clinical studies have indicated complete dissolution of the implant at Day 56 post-implantation and did not suggest an increased amount of fibrotic tissue at the time of necropsy on either Day 35 or Day 56. Understandably, the Phase 3 studies did not the evaluate the ease or difficulty of surgical re-exploration after treatment with XaraColl®. With the exception of the single patient who required removal of the matrices on post-operative day 1 secondary to presumed LAST, no other patients were reported as having a repeat surgical exploration or dissection after XaraColl® implantation. Evaluation of this potential clinical issue will likely be addressed in the post-market surveillance program.

The safety concerns of LAST and wound-healing have been adequately evaluated during the

Applicant's drug development program. The risks of LAST can likely be mitigated with the strategies discussed above and the adverse events related to wound healing appear consistent with reports from the published literature for patients undergoing the same surgical procedure without XaraColl® implantation. Therefore, I conclude that XaraColl® is a safe treatment option for surgical patients undergoing open inguinal hernia repair with mesh and should be approved for use in this surgical population.

9. Advisory Committee Meeting and Other External Consultations

There were no Advisory Committee Meetings or other external consultations requested during the clinical review of this NDA submission.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The proposed label for XaraColl® underwent several initial revisions, however, was not finalized based on the decision to issue a Complete Response Letter. Additional review and edits will be performed during the second cycle submission. As previously mentioned, the indication is too broad and will likely include only inguinal hernia repair with mesh, as evaluated during the Phase 3 studies.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not indicated at this time. If the Agency becomes aware of future safety concerns, one may become necessary.

12. Postmarketing Requirements and Commitments

There will be no PMRs issued for this NDA.

13. Appendices

13.1. References

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13.2. Financial Disclosure

Covered Clinical Studies: INN-CB-014, INN-CB-016

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 39		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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/

ALLISON MEYER
11/30/2018

MARTHA A VAN CLIEF
11/30/2018
Signing for Dr. Renee Petit-Scott, Primary Reviewer

RIGOBERTO A ROCA
11/30/2018

Division Summary Review for Regulatory Action and Cross-Discipline Team Leader Review

Date	November 30, 2018
From	Martha A. Van Clief, MD; Rigoberto Roca, MD
Subject	Cross-Discipline Team Leader Review and Division Summary Review
NDA/BLA # and Supplement#	209511
Applicant	Innocoll Pharmaceutical
Date of Original Submission	October 31, 2016 Refuse-to-File letter issued December 23, 2016
Date of Resubmission	February 02, 2018
PDUFA Goal Date	December 2, 2018
Proprietary Name	XaraColl®
Established or Proper Name	Bupivacaine HCl Collagen matrix-implant
Dosage Form	Implant
Applicant Proposed Indication/Population	For placement into the surgical site to produce postsurgical analgesia following (b) (4)
Applicant Proposed Dosing Regimen	Three collagen matrices, each containing 100 mg of bupivacaine HCl, should be placed (b) (4) at the surgical site (b) (4) and can be cut using aseptic technique before placement into the surgical site
Regulatory Action	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Renee Petit-Scott, MD
Statistical Review	Yi Ren, PhD; David Petullo, PhD
Pharmacology Toxicology Review	Gary Bond, PhD; Jay Chang, PhD; Dan Mellon, PhD
OPQ Review	Valerie Ampacher, PharmD, Debasis Ghosh, PhD, Tarun Mehta, MSc, Yan Zheng, PhD, Elizabeth Bearr, PhD, Sandra Suarez, PhD, Haritha Mandula, PhD, Steven Kinsley, PhD, Christina Capacci-Daniel, Caryn McNabb, Michael Tollon
CDRH	Lixin Liu; Cynthia Chang; David Krause
OSE/DMEPA	Cameron Johnson, PharmD; Otto Townsend, PharmD

CDTL = Cross-Discipline Team Leader
CDRH = Center for Devices and Radiological Health
DMEPA = Division of Medication Error Prevention and Analysis
OND = Office of New Drugs
OPQ = Office of Pharmaceutical Quality
OSE = Office of Surveillance and Epidemiology

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

The bupivacaine hydrochloride (HCl) collagen-matrix implant, hereinafter referred to as bupivacaine collagen-matrix, INL-001, or XaraColl®, manufactured by Innocoll Technologies, Incorporated, is a combination product containing bupivacaine HCl and purified bovine collagen, which when implanted, releases drug over time. The proposed indication for Xaracoll® is "for the placement into the surgical site to produce postsurgical analgesia following (b) (4) **The collagen device component of the product matrix serves as an inert delivery system and releases the bupivacaine HCl through dissolution and diffusion from the porous matrix. The purported benefit for Xaracoll® is the extended release of bupivacaine from the collagen-matrix which results in an extended duration of analgesia.**

Inadequate management of postsurgical pain is a serious condition and may result in delayed recovery, ineffective rehabilitation, and extended hospitalization. Patients that are not adequately treated may develop postsurgical complications, such as, pneumonia, deep venous thrombosis, infection, or delayed healing. Furthermore, poor management of acute postsurgical pain may lead to the development of a chronic pain condition; and the use of opioids for postsurgical analgesia may lead to opioid use disorder.

The applicant conducted two Phase 3 studies (INN-CB-014 and INN-CB-016). The two studies were identically designed as placebo-controlled studies in adult patients with acute postsurgical pain after open inguinal hernioplasty under general anesthesia.
In each of the two studies, approximately 300 patients were stratified by gender and history of previous hernia repair using mesh and randomly assigned to receive either INL-001 (three 100 mg collagen matrices for a total of 300 mg of bupivacaine) or three placebo collagen matrices at a 2:1 ratio within each stratum.

The primary efficacy endpoint was timeweighted sum of pain intensity from 0 to 24 hours (SPI24), which is an appropriate endpoint for evaluating postsurgical analgesia. The key secondary efficacy endpoints were total use of opioid analgesia from 0 to 24 hours (TOpA24), sum of pain intensity from 0 to 48 hours (SPI48), total use of opioid analgesia from 0 to 48 hours (TOpA48), sum of pain intensity from 0 to 72 hours (SPI72), and total use of opioid analgesia from 0 to 72 hours (TOpA72). These secondary efficacy endpoints are relevant to determine the duration of postsurgical analgesia and to evaluate if there is any reduction in the use of postsurgical opioids.
The results from the combined analysis of the primary endpoint of time-weighted mean SPI24 for the Phase 3 studies was statistically significantly different for the XaraColl® treatment group compared to the placebo group. Specifically, there appeared to be approximately a 22% reduction in SPI24 in patients treated with XaraColl® compared to those treated with placebo. The weakness of these trials is that there was no active comparator, therefore, the magnitude of the reduction may be less when compared to bupivacaine

which is typically used for surgical wound infiltration for postsurgical analgesia.

The safety database in the drug development program consisted of 612 subjects and patients exposed to INL-002. Bupivacaine is a widely-used local anesthetic with a long history of clinical use and a large safety database spanning decades. The two safety issues of greatest concern with administration of XaraColl® include the development of local anesthetic systemic toxicity (LAST), which is a concern with all local anesthetics, and potential adverse effects on wound healing. Despite the bupivacaine dose in XaraColl® being greater than the maximum recommended dose in the bupivacaine product label, there were no reported cases of LAST in the Applicant's Phase 3 studies. Review of the neurological assessment data and the 24-hour ECG data captured via Holter monitoring did not identify any suspected cases of bupivacaine toxicity. Risk mitigation strategies for the development of LAST after treatment with XaraColl® include the following:

1. **Limited surgical use – the product label should recommend use of XaraColl® only in the surgical population for which the safety and efficacy were thoroughly evaluated. Because the PK profile was variable when used in a single surgical model, it is likely there would be variability among different surgical sites, with bupivacaine absorption from more vascular sites presenting a possible safety issue.**

2. **Monitor for sign and symptoms related to LAST and have resuscitative medications and equipment readily available. An additional treatment strategy for LAST that is specific to Xaracoll® is surgical removal of the implants. Removal of the matrices will not treat toxicity associated with already absorbed bupivacaine, but will prevent further release, thereby limiting on-going exposure and the need for ongoing treatment for LAST.**

3. **Patient education since a large number of patients may be in an unmonitored setting at the time of maximal plasma concentration. There should be adequate patient education prior to discharge regarding signs and symptoms that may be related to early LAST.**

4. **Limit the use of concurrent local anesthetics for 96 hours after administration of Xaracoll, since the risk of local anesthetic systemic toxicity is additive.**

The second safety concern associated with administration of XaraColl® is the potential adverse impact wound healing. However, information from the published literature, including clinical studies, case reports, and epidemiological studies, have indicated that the frequency of more clinically significant wound-related adverse events, such as dehiscence and discharge, as reported in the Applicant's Phase 3 studies is consistent with the rate of wound complications after inguinal herniorrhaphy.

From the clinical perspective, XaraColl® bupivacaine collagen-matrix has been shown to be a safe and effective short-term, ≤24 hours, treatment for postsurgical pain in patients undergoing open unilateral inguinal hernia repair with mesh.

However, deficiencies were identified from Dr. Bond, Pharmacology/Toxicology reviewer and from the Office of Product Quality (OPQ) and are presented here (adapted from Dr. Bond's review and the OPQ review). The applicant did not provide the following:

1. **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.**
2. **A valid in vivo micronucleus assay for bupivacaine. Specifically, the high dose selected for the assay did not result in frank toxicity.**
3. **Adequate extractables/leachables evaluation to support the safety of the proposed container closure system. Specifically, although the extraction study, submitted September 20, 2018 (SDN 33), was capable of detecting compounds at the requested safety concern threshold of (b) (4) mcg/day, many of the compounds detected above this safety threshold were not identified. Further, the Applicant did not provide adequate leachables data from multiple batches at release where compounds identified in the extraction study were targeted using validated methods.**
4. **Adequate justification for the proposed specification for (b) (4) in the drug product formulation.**
5. **A complete leachables assessment. An analytical method for the detection of leachables has not been provided an (b) (4) ore a correlation between the extractables and leachables cannot be made. Leachables testing should be performed on (b) (4) manufactured product**

Therefore, I concur with the Pharmacology/Toxicology and OPQ reviewers, that the deficiencies identified during their respective reviews precludes the approval of this NDA because we cannot adequately evaluate the safety of the drug product.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acute pain is a normal response to a surgical procedure, due tissue trauma. Postsurgical pain can be self-limiting and may often only requires short term treatment. However, the duration of treatment may vary depending on the specific surgical procedure. • Inadequate management of postsurgical pain is a serious condition and may result in delayed recovery, ineffective rehabilitation, and extended	**Effective management of acute postsurgical pain is essential to prevent the development of postsurgical complications, chronic pain conditions, and opioid use disorder.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	hospitalization. • Patients that are not adequately treated may develop postsurgical complications, such as, pneumonia, deep venous thrombosis, infection, or delayed healing. • Poor management of acute postsurgical pain may lead to the development of a chronic pain condition. The transition to chronic pain is complex and not completely understood, however, it appears that biological mechanisms are involved including neuroplasticity, pain modulation, and central sensitization. • Chronic pain leads to emotional suffering and increased financial expenses, to include, direct healthcare costs, absenteeism, lost productivity and the need for social services support. (Meissner, 2015)	
Current Treatment Options	• Current treatment options for postsurgical pain include the following: 1. opioid analgesics 2. non-opioid analgesics 3. local anesthetics for wound infiltration, peripheral nerve blockade, or neuraxial anesthesia • Opioid analgesics are first-line therapy for post -surgical pain. However, they are associated with undesirable side effects, such as, sedation, nausea, vomiting, and constipation. • The use of opioid for postsurgical pain may lead to long-term use and abuse. Studies have reported that an opioid-naïve patient who receives an opioid prescription within 7 days of a low-risk surgery were 44% more likely to become long-term opioid users within one year compared with those that did not receive a prescription. (Alam, 2012) • Non-opioids alone are usually not adequate for postsurgical analgesia. More often they are use as adjuncts for postsurgical pain to reduce the need for opioid analgesics. • The use of local anesthetics via infiltration or nerve block is preferred, when applicable, because their use may eliminate the need for potent opioids. However, the limitation of local anesthetics is their duration of	**The current treatments for postsurgical analgesia have serious drawbacks.** • **Opioids have undesirable side effects and their use may lead to opioid abuse disorder.** • **Non-opioids are not adequate to manage postsurgical analgesia except for minor procedures.** • **Local anesthetics are effective but are limited by their short duration of action that does not meet the need for several days to a week of analgesia.** **Extended release formulations of local anesthetics may address an unmet need if the duration of analgesia can extend to cover the period of moderate to severe postsurgical pain.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	action of 8 to 12 hours after surgery, thus, requiring the use of potent opioids to manage postsurgical pain. • Of the local anesthetics available for postsurgical pain management, lidocaine, ropivacaine, and bupivacaine, with and without epinephrine, are the most commonly used. Ropivacaine and bupivacaine are considered longer-acting than lidocaine and generally provide up to eight hours of postsurgical pain relief when administered via wound infiltration. • There are currently no approved local anesthetics with an extended release or slow release profile that have demonstrated reliable prolonged postsurgical analgesia. A continuous infusion of a dilute concentration of bupivacaine via a peripheral nerve or neuraxial catheter appears to be the only available mechanism to prolong the duration of action of bupivacaine.	**While there are several marketed, approved bupivacaine products for use in the management of postsurgical pain, none have an extended release profile that reliably prolongs postsurgical analgesia beyond that observed after administration of immediate release bupivacaine.**
Benefit	• The applicant conducted two Phase 3 studies (INN-CB-014 and INN-CB-016). The two studies were identically designed as placebo-controlled studies in adult patients with acute postsurgical pain after open inguinal hernioplasty under general anesthesia • The study population were healthy males or females, age 18 years or older. In each of the two studies, approximately 300 patients were stratified by gender and history of previous hernia repair using mesh and randomly assigned to receive either INL-001 (three 100 mg collagen matrices for a total of 300 mg of bupivacaine) or three placebo collagen matrices at a 2:1 ratio within each stratum. • The primary efficacy endpoint was timeweighted sum of pain intensity from 0 to 24 hours (SPI24), which is an appropriate endpoint for evaluating postsurgical analgesia. • The key secondary efficacy endpoints were total use of opioid analgesia from 0 to 24 hours (TOpA24), sum of pain intensity from 0 to 48 hours (SPI48), total use of opioid analgesia from 0 to 48 hours (TOpA48), sum of pain intensity from 0 to 72 hours (SPI72), and total use of opioid analgesia from 0 to 72 hours (TOpA72). These	**The Phase 3 studies meet the evidentiary standard, because placebo-controlled trials are considered acceptable for an adequate and well-controlled study [21 CFR 314.126].** **Approval of the bupivacaine collagen-matrix would offer clinicians an additional bupivacaine product to administer for postsurgical pain management after a commonly performed surgical procedure, inguinal herniorrhaphy. It may provide longer postsurgical analgesia than currently approved products.** **Additional benefits of XaraColl® include the following:** • **Bupivacaine is a widely-used local anesthetic with a long history of clinical use**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	secondary efficacy endpoints are relevant to determine the duration of postsurgical analgesia and to evaluate if there is any reduction in the use of postsurgical opioids. • The results from the combined analysis of the primary endpoint of time-weighted mean SPI24 for the Phase 3 studies was statistically significantly different for the XaraColl® treatment group compared to the placebo group. Specifically, there appeared to be approximately a 22% reduction in SPI24 in patients treated with XaraColl® compared to those treated with placebo. • The weakness of these trials is that there was no active comparator. Bupivacaine has been used for decades in the treatment of post-operative pain when administered for wound infiltration, peripheral nerve blockade, or neuraxial anesthesia/analgesia. It is an effective local anesthetic with a well-established safety profile as documented in premarket clinical studies and in the published literature in the form of clinical studies, case reports, and epidemiological studies. Therefore, there is no direct comparison to bupivacaine which is typically used for postsurgical analgesia, to reduce the requirement of postsurgical opioids. • XaraColl® would provide clinicians an additional, potentially longer-acting bupivacaine product for use in the management of postsurgical pain. The results from the Applicant's Phase 3 studies have demonstrated improved sum of pain intensity over 24 hours after XaraColl® implantation when compared to placebo treatment, and the PK/BA study results suggested a different release profile than the currently marketed bupivacaine products. • The data for the secondary endpoints related to reduction of opioid use from the Phase 3 studies does not appear to be clinically meaningful. If an active comparator had been used in the Phase 3 trials the reduction in opioid use probably would have been minimal.	**and a large safety database spanning decades** • **Variable matrix size, due to cutting, will permit implant into a variety of surgical wounds** • **In the event of LAST, the matrices can be surgically removed, which is not a treatment option after wound infiltration, peripheral nerve blockade, or neuraxial block** • **The Phase 3 studies did demonstrate a clinically meaningful difference in time to first opioid rescue analgesia between the XaraColl® and placebo groups; e.g., 10 hours in Study INN-CB-014** **The totality of the impact of adequate postsurgical pain management on health care outcomes is likely immeasurable and the benefits are likely to extend beyond individual patient outcomes, potentially impacting overall cost and societal burden of poorly managed pain.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety database in the drug development program consisted of 612 subjects and patients exposed to INL-002. • The two safety issues of greatest concern with administration of XaraColl® include the development of local anesthetic systemic toxicity (LAST), which is a concern with all local anesthetics, and potential adverse effects on wound healing. LAST • Factors influencing the development of LAST include the site of administration and total dose administered. The proposed maximum dose of bupivacaine in XaraColl®, 266.4 mg, is higher than the recommend dose in the bupivacaine product label, 175 mg without epinephrine. Use of a higher than currently recommended dose may lead to increased incidence of LAST depending on the surgical location, specifically if the surrounding tissue is highly vascular. • Because the PK profile of XaraColl® appeared variable in the single surgical population evaluated, use of the product in other surgical models or for other painful conditions is not recommended. While bupivacaine has a long history of clinical use and the safety profile is well-established, it is highly cardiotoxic due to its strong affinity for cardiac Na^+ channels and the high degree of protein binding. Systemic exposure to increased amounts of bupivacaine poses the greatest risk for the development of toxicity and XaraColl® implantation into highly vascular sites is likely to increase the risk above what has been characterized in the Applicant's Phase 3 clinical studies evaluating inguinal herniorrhaphy. • An additional concern regarding the variable PK profile of XaraColl® is the likelihood of patients being in an unmonitored setting around C_{max}, a time when the risk of toxicity is the highest. This can potentially be mitigated by adequate and comprehensive patient education regarding the signs and symptoms associated with bupivacaine toxicity.	**Despite the bupivacaine dose in XaraColl® being greater than the maximum recommended dose in the bupivacaine product label, there were no reported cases of LAST in the Applicant's Phase 3 studies. The only case of presumed LAST was reported for a 57-year-old female patient who received either 150 mg or 200 mg during bladder sling surgery. While this case is concerning and emphasizes the variable PK profile of XaraColl® when used in different surgical locations, it is reassuring that no other patient experienced bupivacaine toxicity, even with the highest doses administered.** **Review of the neurological assessment data and the 24-hour ECG data captured via Holter monitoring did not identify other cases of bupivacaine toxicity.** **Risk mitigation strategies for the development of LAST after treatment with XaraColl® include the following:** • **Limited surgical use – the product label should recommend use of XaraColl® only in the surgical population for which the safety and efficacy were thoroughly evaluated, unilateral inguinal hernioplasty. Because the PK profile was variable when used in a single surgical model, it is likely there would be variability among different**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Drug-Drug interactions with other local anesthetics are a concern because the toxicity of local anesthetics are additive. Wound Healing • While the published literature contains contradictory information regarding the impact of exogenously administered collagen on wound healing, the data from the Applicant's development program appears adequate to address wound healing after open inguinal herniorrhaphy. Specifically, 816 patients who underwent inguinal herniorrhaphy received the collagen-matrix, either as component of XaraColl® or the placebo matrix. • There was initial concern regarding the increased number of wound-related adverse events in patients who received the collagen matrix when compared to patients who received a comparator treatment without the matrix. Closer evaluation, however, revealed that the adverse events with the greatest increased incidence, incision site pain and swelling, may have been anticipated given the size and composition of XaraColl®. • Adverse events that are likely considered more serious, such as wound dehiscence and discharge, appear to have occurred with a similar frequency as that reported in the published literature. • Non-clinical and OPQ deficiencies were identified from Dr. Bond, Pharmacology/Toxicology reviewer and from the Office of Product Quality (OPQ) and are presented her (adapted from Dr. Bond's review and the OPQ review). The applicant did not provide the following: 1. 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	**surgical sites, with bupivacaine absorption from more vascular sites presenting a possible safety issue.** • **Available resuscitative medications and equipment – as with all local anesthetics, administration of XaraColl® should occur only those clinical settings that have immediate access to resuscitative equipment and medications, including lipid emulsion therapy, in the event of LAST. An additional treatment strategy for LAST that is not an option for other routes of bupivacaine administration is surgical removal of the implants.** • **Patient education – because a large number of patients may be in an unmonitored setting around the time of maximal plasma concentration, there should be adequate patient education prior to discharge regarding signs and symptoms that may be related to early LAST.** • **Limit the use of concurrent local anesthetics for 96 hours after administration of Xaracoll, since the risk of local anesthetic systemic toxicity is additive.** **The potential adverse impact of XaraColl® on wound healing was of initial concern. However, review of the totality of the data presented, including the Applicant's clinical development program of 892 patients**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the rat model do not test exposures that provide coverage for the human exposures via your product. 2. 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. 3. Adequate extractables/leachables evaluation to support the safety of your proposed container closure system. Specifically, although your extraction study, submitted September 20, 2018 (SDN 33), was capable of detecting compounds at the requested safety concern threshold of (b) (4) mcg/day, you did not identify many of the compounds detected above this safety threshold. Further, you did not provide adequate leachables data from multiple batches at release where compounds identified in the extraction study were targeted using validated methods. 4. Adequate justification for the proposed specification for (b) (4) in the drug product formulation. 5. A complete leachables assessment. An analytical method for the detection of leachables has not been provided and therefore a correlation between the extractables and leachables cannot be made. Leachables testing should be performed on (b) (4) manufactured product (b) (4) (b) (4)	**treated with a dose of collagen-matrix appears to support the safe use of XaraColl® in the surgical population evaluated, inguinal herniorrhaphy.** **The deficiencies identified from the Pharmacology/Toxicology and OPQ reviewers preclude the approval of this application, because we cannot adequately determine the safety of the drug product.**

2. Introduction and Background

This document will serve as the Cross-Discipline Team Leader (CDTL) review of this new drug application (NDA), as well as the Division Summary (DD) review for the decision on the regulatory action.

The Applicant, Innocoll, Inc., has submitted a new drug application (NDA) for Xaracoll®, bupivacaine HCl collagen-matrix implant. The Applicant is proposing to rely on the Agency's finding of efficacy and safety for Marcaine™ (NDA 016964); therefore, this submission is a 505 (b)(2) submission. The current indication for the Marcaine™, the approved product is "for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures."

This document will also capture the final outcomes of any items that were still under discussion at the time Dr. Petit-Scott's review was finalized.

As noted in Dr. Petit-Scott's review, the bupivacaine hydrochloride (HCl) collagen-matrix implant, Xaracoll®, is a combination product containing bupivacaine HCl and purified bovine collagen, which when implanted into the soft tissue at the surgical site, releases the drug product, bupivacaine HCl over time. The Applicant's proposed indication is for placement into the surgical site to produce postsurgical analgesia following (b) (4). Bupivacaine HCl is an amide local anesthetic and local anesthetics block the generation and conduction of nerve impulses, thereby, producing local anesthesia and analgesia. The proposed dosing regimen for Xaracoll® is the placement of 3 collagen matrices, each containing 100 mg of bupivacaine HCl, in 2 or 3 anatomic layers at the surgical site.

The regulatory history and interactions are well-summarized in Dr. Petit-Scott's review. Innocoll Technologies, Inc., submitted IND 77127 in March 2007, for evaluation of the bupivacaine collagen-matrix in surgical patients. The following table, reproduced from Dr. Petit-Scott's review, is a high-level summary of the key interactions between Innocoll and the Agency regarding the clinical development program.

Summary of Pre-Submission and Submission Regulatory Activities

Meeting/Communication/Date	Event/Key Clinical Issues
IND 77127 submitted, March 2007	
End of Phase 2 Meeting/December 5, 2011	• Phase 3 study constructs reasonable, 200 mg and 300 mg proposed doses • Primary endpoint of integrated assessment of pain- (b) (4) • Pharmacokinetic and Bioavailability (PK/BA) study reasonable but should be concluded prior to Phase 3 studies (cardiotoxicity and neurotoxicity should be fully evaluated prior to Phase 3 study initiation) • Post-operative analgesic indication may be too broad

Meeting/Communication/Date	Event/Key Clinical Issues
	• Wound healing and effects of (b) (4) on suture and mesh needs to be evaluated
Type C Meeting/WRO/July 6, 2015	• Xaracoll® 300 mg bupivacaine collagen-matrix acceptable • Safety database needs to contain at least 500 exposed subjects • Primary endpoint should be Summed Pain Intensity Difference at 24 hours (SPID24) • Hierarchical testing acceptable for multiple endpoints • Standard acetaminophen dosing post-operatively acceptable
Initial Pediatric Study Plan (iPSP) Received/January 27, 2016	Written feedback in the form of a tracked-changes document was sent to the Sponsor.
Type C Meeting/WRO/April 20, 2016	• Pooling of data in the ISS and ISE is acceptable • Primary and secondary efficacy endpoints should be expressed as Summed Pain Intensity (SPI) versus Summed Pain Intensity Difference (SPID) • Screening laboratory values need to be included • Case Report Forms (CRFs) and patient narratives should be submitted for all subjects who experienced an SAE, discontinued due to an adverse event, or died
Agreed iPSP/June 17, 2016	No additional advice provided.
NDA 209511 Submission/October 31, 2016	NDA received.
Refuse to File NDA 209511/December 23, 2016	There no refuse to file clinical issues identified. The refuse to file issues included the following: • Reliance on which bupivacaine product needed clarification • PK/BA study was not conducted with the to-be-marketed formulation • There were a variety of sterilization and packaging issues described by the Chemistry, Manufacturing, and Controls (CMC) review team • The nonclinical review team had several issues including inadequate nonclinical data to qualify the safety of the to-be-marketed formulation and inadequate extractable/leachable evaluation • Xaracoll® is a drug-device combination product and there was no biocompatibility information included in the New Drug Application (NDA) submission
NDA 209511 Resubmission/February 2, 2018	NDA received.
NDA 209511 Filed/April 17, 2018	Potential clinical review issues include the following: • The incidence of wound-related issues is higher in subjects treated with collagen matrix compared to

Meeting/Communication/Date	Event/Key Clinical Issues
	subjects treated with comparators (no collagen matrix) • Adequacy of cardiotoxicity evaluation • Phase 3 studies were identical in design and surgical population, therefore the results less strongly support a broad postsurgical analgesic indication • DRUG INTERACTIONS section of the label needs to included comprehensive information regarding the use of additional local anesthetics

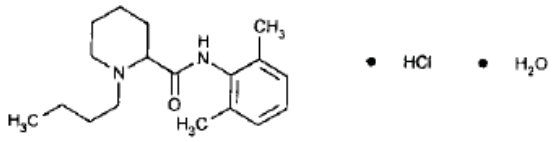
Source: Dr. Petit-Scott's Clinical Review

3. Product Quality

The following overview is adapted from the Office of Product Quality (OPQ) Quality Assessment Review:

Drug Substance:

The drug substance, bupivacaine hydrochloride, is a local anesthetic which can produce moderate to prolonged anesthesia. The drug substance is chemically known as 1-butyl-*N*-(2,6-dimethylphenyl)-2-piperidine carboxamide hydrochloride monohydrate. It has the following chemical structure, molecular formula and molecular weight:



Molecular formula

$C_{18}H_{28}N_2O \cdot HCl \cdot H_2O$

Relative molecular mass

342.90	monohydrate
324.89	anhydrous
288.43	free base anhydrous

It is a white (b) (4) crystalline powder with high melting point. It is soluble in water. (b) (4) (b) (4) All CMC information regarding drug substance has been referenced to DMF (b) (4) The Applicant provided a letter of authorization from the DMF holder to use the information contained in the DMF for the evaluation of the NDA. Based on last DMF review (08/22/2018), the DMF (b) (4) is adequate. Although, the CMC information in the DMF includes impurity information, the sponsor provided structures of four identified process/ degradation impurities including the information on their origin, fate and controls

in the NDA. The drug substance is a USP and Ph. Eur. monographed product. The proposed specification and tests are consistent with the compendial standards.

The **drug substance review team** concluded that adequate information is provided in the application and in the Type II DMF (b) (4) to ensure identity, strength, purity and quality of drug substance. Based on the stability data, as provided in the DMF (b) (4) the **proposed retest date of** (b) (4) **months** when stored at (b) (4) (b) (4) is adequate (See Drug Substance Review by Debasis Ghosh and Donna Christner in panorama for additional information).

Drug Product:

The drug product, Xaracoll (bupivacaine HCl collagen-matrix implants) 300 mg is supplied as three sterile surgical implants (5 cm x 5 cm x 0.5 cm), each containing 100 mg of bupivacaine HCl and 75 mg of Type I purified collagen in individually sealed blisters. Type I purified collagen serves as an inert delivery system and releases the bupivacaine through dissolution and diffusion from the porous matrix. The implant consists of purified type I bovine collagen (b) (4) (b) (4) (b) (4) The applicant intends to store Xaracoll at 20-25°C (68-77°F), excursions permitted between 15-30°C (59-86°F). A shelf life of 24 months from the date of manufacturing is proposed.

Based on the assessment by drug product review team, the proposed **shelf life of 24 months when stored in the proposed container closure system at room temperature can be granted.**

The **Biopharmaceutics Team (**ONDP) assessed the multi-point dissolution profile comparison for the Phase 3 lots and commercial lot and concluded that the quality of the product is acceptable. The details of the review by Kalpana Paudel and Kelly Kitchens can be found in panorama.

The Process Review Team (OPF) indicated that the commercial batch formula reflects the proposed composition, the commercial batch record, and the commercial scale and concluded that the information provided by the applicant is adequate. The details of the review by Tarun Mehta and Ubrani Venkataram can be found in panorama.

The **Microbiology** review team stated that the submission is recommended for **approval** on the basis of sterility assurance. Details can be found in the review by Yan Zheng and Elizabeth Bearr.

The **Facility reviewer** (**OPF**) has made **acceptable** recommendations for **drug product** manufacturing and testing sites based on inspectional history. The details of the Facility review by Christina Capacci-Daniel can be found in panorama.

The **Facility reviewer** from the **Center for Devices and Radiological Health** (**CDRH**) recommended VAI (Voluntary Action Indicated). However, the final classification has been deferred to CDER.

Biocompatibility of collagen matrix component of Xaracoll was assessed by Lixin Liu of **CDRH** following an Inter-center consult request from CDER (ICCR2018- 03014). The CDRH team concluded that there were no deficiencies concerning the biocompatibility test reports for the collagen component of Xaracoll. Refer to the review by Lixin Liu for details.

Conclusion and Recommendation (verbatim from the Quality Review Assessment)

Based on the assessment of CMC information by **drug product review team**, except the following deficiency, the applicant provided adequate CMC information to ensure the quality of drug product for the intended use. While evaluating the compatibility of primary container closure system (blister package), the drug product reviewer identified an incomplete leachable assessment with primary container closure system. It has been noted that the sponsor did not submit an analytical method for the leachables. The review team indicated that leachable assessment is critical due to the proposed drug product manufacturing process. (b) (4) (b) (4) We note that the sponsor recommended the extractables study of the secondary packaging be a (b) (4) The complete response will be due to the lack of leachables data at several timepoints throughout stability including (b) (4) manufactured product. Based on this deficiency, drug product review team recommended a 'Complete Response'.

Based on the Labeling review by drug product review team, the labels (package inserts, container and cartons) comply with all regulatory requirements from a CMC perspective (see Labeling review by Valerie Amspacher and Julia Pinto in panorama)

Based on assessment by drug product review team, the claim of categorical exclusion for environmental assessment is acceptable (see drug product review by Valerie Amspacher and Julia Pinto in panorama)

I concur with the drug product review team that there has been an incomplete assessment of the leachables for the primary container closure system (blister package). The review team's recommended comments regarding the deficiency to be conveyed to the applicant are reproduced in Section 15.

4. Nonclinical Pharmacology/Toxicology

The following narrative is reproduced from Dr. Bond's Review, Section 1.2 Brief Discussion of Non-Clinical Findings.

There are no nonclinical concerns with the drug substance specifications. The proposed drug product specifications are not incompliance with the recommendations outlined in ICH M7 for mutagenic impurities. Specifically, the proposed specifications for (b) (4) (b) (4) at NMT (b) (4) ppm, which results in a potential total daily intake of NMT (b) (4) mcg per device, technically exceeds the ICH M7 threshold of toxicological concern of (b) (4) mcg/day for an acute use product if it released entirely on the first day of dosing. , The actual drug product batch analyses suggest that the specification may be able to be tightened. This should be addressed in the second cycle. All other drug product specifications are acceptable. The Applicant also adequately addressed the safety of all (b) (4) and elemental impurities in accordance with ICH Q3C and Q3D.

The drug product technically contains a novel excipient, bovine collagen, because this compound is not currently listed in the FDA Inactive Ingredients Database (IID) for use in a subcutaneously implanted device. The Applicant conducted biocompatibility studies in accordance with the International Standards Organization (ISO) which were reviewed by CDRH to address their regulatory requirements. As a novel excipient, CDER requires adequate justification for the safety of this excipient as well in accordance with CDER guidance. Given the fact that collagen is an endogenous compound and the body is well equipped to metabolize and process this material, only local tissue toxicity studies with the formulation were deemed necessary to inform the safety of this novel excipient.

To characterize the systemic and local safety of the drug product formulation, the Applicant conducted an extensive literature review for bupivacaine and submitted a pivotal GLP 56-day rat toxicology study testing the local tissue effects of the to-be-marketed bupivacaine collagen sponge implant in a wound closure model. They also evaluated would healing qualitatively in this study. The new GLP toxicology study results suggest the potential for a clear local tissue response which includes microscopic evidence of marked necrosis of tissue surrounding the implant and a chronic-active inflammatory state consistent with the implantation of a foreign material. Mild to moderate necrosis was noted in the saline group, the bupivacaine injection control group, and the collagen matrix alone implant group. Only the bupivacaine collage implant groups demonstrated marked local tissue necrosis. There was no clear impact on wound healing in this study based on clinical and gross macroscopic observations alone suggesting that the enhanced local tissue response did not translate into significant clinical impact. The existing human local safety data should be leveraged to confirm that these local changes are not considered clinically adverse. The implanted material was no longer clearly present in tissue somewhere between 35 and 56 days post implantation.

During development, the Division noted that although not required for approval of the product, the standard battery of genetic toxicity studies for bupivacaine would ideally be completed to appropriately inform labeling. The Applicant completed the requested studies. Bupivacaine HCl was negative for genotoxicity in a standard test battery: 1) in vitro reverse mutation assay in bacterial cells (Ames), 2) in vitro mammalian cell gene mutation test (L5178Y/TK+/- mouse lymphoma assay), and 3) in vivo clastogenicity assay in rodent (micronucleus assay). However, the high dose tested in the in vivo study did not result in frank toxicity, therefore the study is not considered valid based on

current standards. (b) (4) Given the apparent greater exposure to bupivacaine via this product relative to the referenced product (2 times the AUC0-last), this study can be required to be completed as per OND policy.

The Applicant submitted a literature review of the published studies to address the requirements outlined in the Pregnancy Labeling and Lactation Rule (PLLR). Review of the published studies submitted did not identify data that substantively changed the overall conclusions of the referenced reproductive and developmental toxicity studies in the Marcaine labeling. As such, no additional labeling recommendations are provided at this time.

The final recommendation of the pharmacology/toxicology team was that the application not be approved due to inadequate non-clinical data to justify the safety of Xaracoll. The review team's final conclusion is well-summarized in Dr. Bond's recommendations (reproduced from Dr. Bond's review):

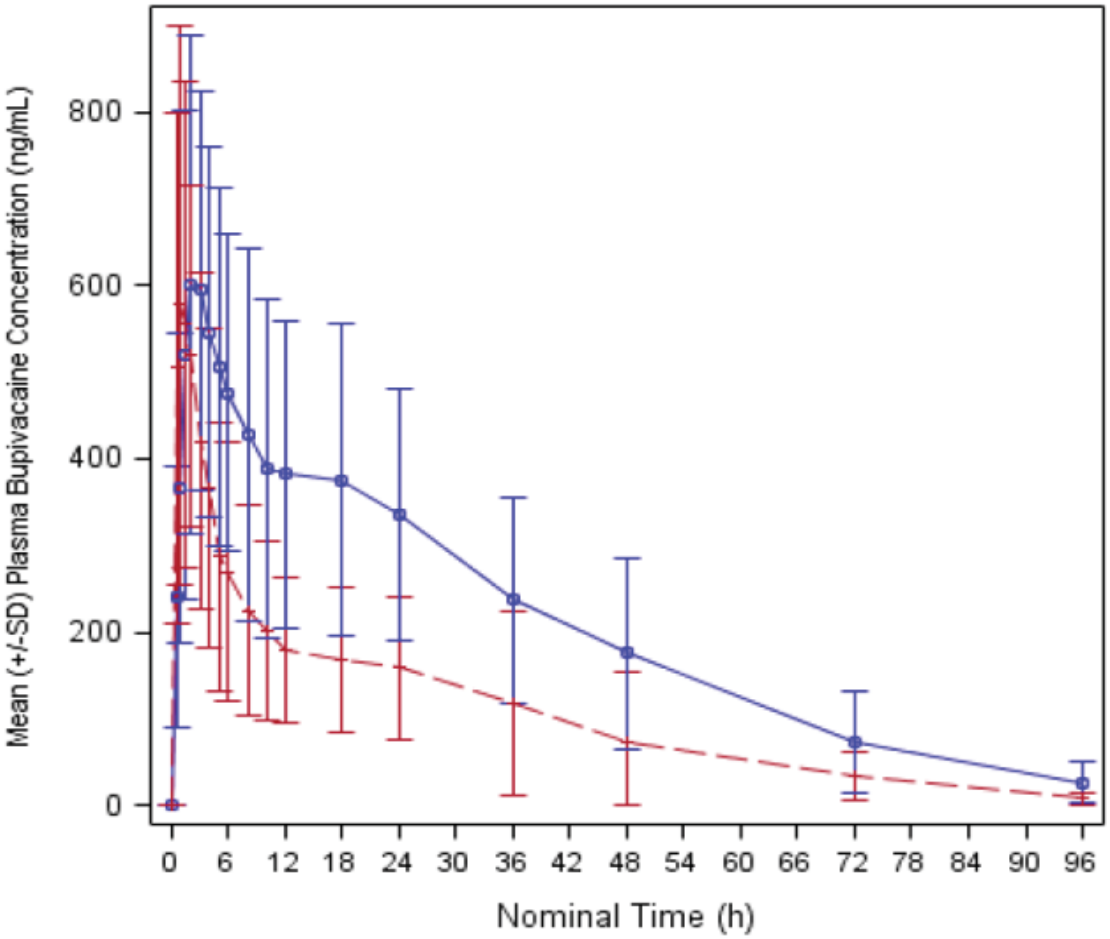
> The Applicant has not submitted adequate extractables/leachables data to characterize the safety of the drug product container closures system. Second, the existing toxicology study does not provide adequate coverage for the proposed systemic toxicity of bupivacaine via this product, particularly because the AUC0-last for this product exceeds that of the referenced drug product. As such, adequate toxicity data in two species are required. Third, the in vivo micronucleus assay did not test adequate doses to be considered valid and will be required to be repeated unless justified otherwise. Finally, the Applicant did not provide adequate safety justification for the levels of (b) (4) in the final drug product taking into considerations the recommendations outlined in ICH M7.

I concur with the review team that there are non-clinical deficiencies that preclude the approval of this NDA. The review team's recommended comments regarding the deficiencies to be conveyed to the applicant are in Section 15.

5. Clinical Pharmacology

As noted in Dr. Lee's review, the Applicate submitted study INN-CB-022, a multicenter, randomized, single-blind, active comparator-controlled study, conducted in patients undergoing open hernioplasty surgery to 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.

> The following figure from Dr. Lee's review (reproduced from NDA submission noted as Post-text Figure 14.2.1.1a) represents the PK profile from Study INN-CB-022.
>
> 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.

This figure demonstrates the following information (reproduced from Dr. Lee's review):

- 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, were higher after that time period in comparison with the Marcaine 0.25% treatment group.

The following table (reproduced from Dr. Lee's review) shows the PK parameters from INN-CB-022:

Summary of the Mean (SD) Plasma Bupivacaine Parameters by Treatment – Per-Protocol PK Populations.

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)

This table demonstrates the following (reproduced from Dr. Lee's review):

- 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%.

The general pharmacology and pharmacokinetic characteristics are reproduced from Dr. Lee's review and are obtained from the Marcaine Label as he notes.

The following was reproduced from the CLINICAL PHARMACOLOGY section of the Marcaine Label (headings added by this reviewer):

Mechanism of Action

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.

Pharmacodynamics

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.

The following was reproduced from the PHARMACOKINETICS section of the Marcaine Label (headings added by this reviewer):

Absorption
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 (b) (4) p to 7 hours. The duration of anesthetic effect is prolonged by the addition of epinephrine 1:200,000.

(b) (4)

Distribution
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.

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.

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.

Metabolism
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.

Excretion
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.

The following literature information from Clinical Pharmacology Online was reproduced from Dr. Lee's review:

- 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.

Drug Interactions
Dr. Lee states in his review that, "No dedicated Xaracoll pharmacokinetic studies were conducted to evaluate drug interactions."

However, it is known that the toxic effects of local anesthetics are additive. Therefore, bupivacaine HCl administered together with Xaracoll may impact the overall systemic exposure of bupivacaine.

I concur with the review team that the information submitted in support of the application is acceptable from the clinical pharmacology perspective.

6. Clinical Microbiology

Xaracoll is not a therapeutic antimicrobial therefore clinical microbiology date were neither required or submitted.

7. Clinical/Statistical- Efficacy

The Applicant has conducted two Phase 3 clinical studies to support the efficacy of their product, INN-CB-014 and INN-CD-016. Appendix 1 and 2 describe the studies conducted during the drug development program. The design of the pivotal Phase 3 studies are well described in Dr. Petit-Scott's and Dr. Ren's individual reviews and will only be briefly summarized here.

The following description is adapted from Dr. Ren's review.

> The Phase 3 studies (INN-CB-014 and INN-CB-016) were multicenter, randomized, double-blind, and placebo-controlled studies in adult patients with acute postsurgical pain. The studies were identically designed to evaluate the efficacy and safety and tolerability of INL-001 after its implantation into surgical wound. The surgical model in both studies was open inguinal hernioplasty with mesh conducted under general anesthesia. The study population were healthy males or females, age 18 years or older. In each of the two studies, approximately 300 patients were stratified by gender and history of previous hernia repair using mesh and randomly assigned to receive either INL-001 (three 100 mg collagen matrices for a total of 300 mg of bupivacaine) or three placebo collagen matrices at a 2:1 ratio within each stratum. The primary efficacy endpoint was timeweighted sum of pain intensity from 0 to 24 hours (SPI24). The key secondary efficacy endpoints were total use of opioid analgesia from 0 to 24 hours (TOpA24), sum

of pain intensity from 0 to 48 hours (SPI48), total use of opioid analgesia from 0 to 48 hours (TOpA48), sum of pain intensity from 0 to 72 hours (SPI72), and total use of opioid analgesia from 0 to 72 hours (TOpA72).

Demographics and baseline characteristics are presented in the tables below for each study (reproduced from Dr. Ren's review).

Study INN-CB0014: Demographic and Baseline Characteristics (Intent-to-Treat Population)

	INL-001 (N=204)	Placebo (N=101)	Total (N=305)
Age (years): n (%)			
< 65	174 (85.3)	83 (82.2)	257 (84.3)
≥ 65	30 (14.7)	18 (17.8)	48 (15.7)
Mean (SD)	53.1 (12.8)	53.3 (14.0)	53.1 (13.2)
Min, max	19, 83	21, 86	19, 86
Gender: n (%)			
Male	196 (96.1)	97 (96.0)	293 (96.1)
Female	8 (3.9)	4 (4.0)	12 (3.9)
Ethnicity: n (%)			
Hispanic or Latino	77 (37.7)	38 (37.6)	115 (37.7)
Not Hispanic or Latino	127 (62.3)	62 (61.4)	189 (62.0)
Missing	0 (0)	1 (1.0)	1 (0.3)
Race: n (%)			
White	185 (90.7)	91 (90.1)	276 (90.5)
Black or African American	15 (7.4)	7 (6.9)	22 (7.2)
Asian	2 (1.0)	2 (2.0)	4 (1.3)
Other	2 (1.0)	1 (1.0)	3 (1.0)
Body Mass Index (kg/m2)			
Mean (SD)	27.1 (3.9)	27.3 (4.6)	27.1 (4.1)
Min, max	18.7, 39.6	19.2, 42.1	18.7, 42.1
Missing, n (%)	2 (1.0)	1 (1.0)	3 (1.0)
Previous Hernia Repair using Mesh: n (%)			
Yes	20 (9.8)	12 (11.9)	32 (10.5)
No	184 (90.2)	89 (88.1)	273 (89.5)

Source: Modified CSR Table 7, Study INN-CB-014
SD: standard deviation

Study INN-CB-016: Demographic and Baseline Characteristics (Intent-to-Treat Population)

	INL-001 (N=213)	Placebo (N=106)	Total (N=319)
Age (years): n (%)			
< 65	180 (84.5)	92 (86.8)	272 (85.3)
≥ 65	33 (15.5)	14 (13.2)	47 (14.7)
Mean (SD)	50.7 (13.7)	48.5 (13.9)	50.0 (13.8)
Min, max	18, 85	19, 75	18, 85
Gender: n (%)			
Male	208 (97.7)	103 (97.2)	311 (97.5)
Female	5 (2.3)	3 (2.8)	8 (2.5)
Ethnicity: n (%)			
Hispanic or Latino	44 (20.7)	23 (21.7)	67 (21.0)
Not Hispanic or Latino	169 (79.3)	83 (78.3)	252 (79.0)
Race: n (%)			
White	182 (85.4)	90 (84.9)	272 (85.3)
Black or African American	23 (10.8)	12 (11.3)	35 (11.0)
Asian	4 (1.9)	3 (2.8)	7 (2.2)
Other	3 (1.4)	1 (0.9)	4 (1.2)
Missing	1 (0.5)	0 (0)	1 (0.3)
Body Mass Index (kg/m2)			
Mean (SD)	26.8 (4.0)	27.2 (5.1)	27.0 (4.4)
Min, max	17.8, 40.8	17.4, 45.9	17.4, 45.9
Missing, n (%)	4 (1.9)	0 (0)	4 (1.2)
Previous Hernia Repair using Mesh: n (%)			
Yes	22 (10.3)	10 (9.4)	32 (10.0)
No	189 (88.7)	96 (90.6)	285 (89.3)
Missing	2 (0.9)	0 (0)	2 (0.6)

Source: Modified CSR Table 7, Study INN-CB-016
SD: standard deviation

The following tables describes the patient disposition information for both studies (reproduced from Dr. Ren's review).

Patient Disposition, Study INN-CB-014

	INL-001	Placebo	Total
Randomized	204	101	305
Completed the study	196 (96.1%)	100 (99.0%)	296 (97.1%)
Discontinued the study	8 (3.9%)	1 (1.0%)	9 (2.9%)
Adverse event	1 (0.5%)	0	1 (0.3%)
Lost to follow-up	4 (2.0%)	1 (1.0%)	5 (1.6%)
Other	3 (1.5%)	0	3 (1.0%)

Source: Study INN-CB-014 CSR Table 4

Patient Disposition, Study INN-CB-016

	INL-001	Placebo	Total
Randomized	213	106	319
Completed the study	203 (95.3%)	103 (97.2%)	306 (95.9%)
Discontinued the study	10 (4.7%)	3 (2.8%)	13 (4.1%)
Adverse event	0	1 (0.9%)	1 (0.3%)
Lost to follow-up	5 (2.3%)	1 (0.9%)	6 (1.9%)
Other	5 (2.3%)	1 (0.9%)	6 (1.9%)

Source: Study INN-CB-016 CSR Table 4

The primary efficacy endpoint was the summed pain intensity (SPI24). The subjects who received the bupivacaine collagen-matrices had statistically significantly less pain over the first

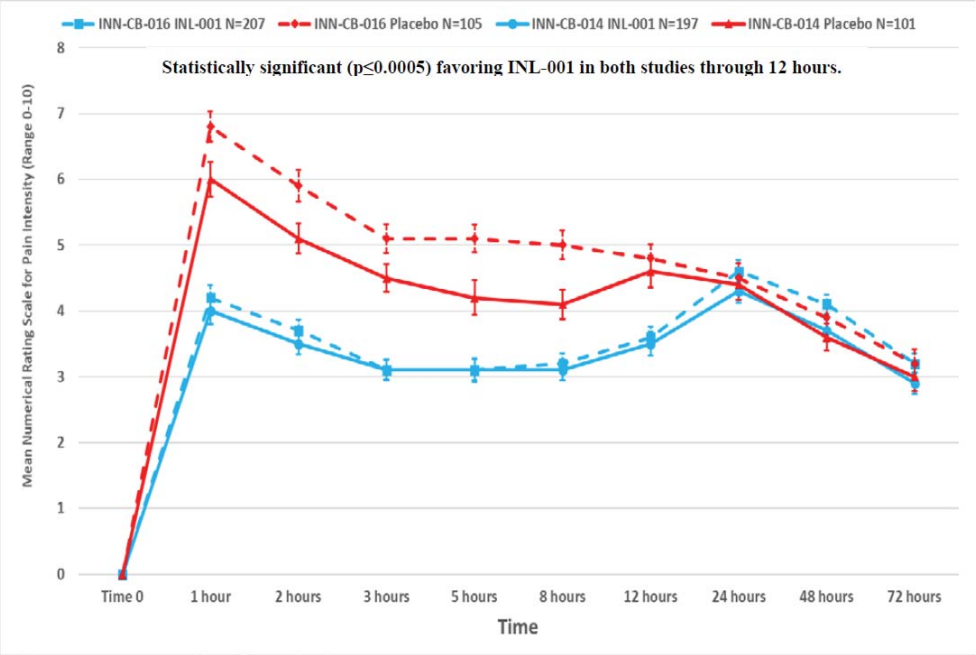
24 hours post-operatively when compared to subjects who were treated with the placebo collagen-matrices. The primary efficacy endpoint results are described in the following table.

Primary Endpoint: Time-Weighted Sum of Pain Intensity from Time 0 through 24 hours – Studies INN-CB-014 and INN-CB-016, Modified Intent-to-Treat Population

	INN-CB-014		INN-CB-016	
Primary efficacy variable Statistic	**INL-001 N=197**	**Placebo Collagen-Matrix Implants N=101**	**INL-001 N=207**	**Placebo Collagen-Matrix Implants N=105**
SPI24				
Mean (SD)	85.9 (47.18)	106.8 (48.20)	88.3 (47.01)	116.2 (44.04)
Median	82.2	107.5	84.4	119.3
Minimum, maximum	0, 224.4	6.6, 230.4	0, 219.8	23.5, 213.3
Observed p-value[a]	0.0004	-	<0.0001	-

Data source: INN-CB-014 Tables 14.2.1.1 and 14.2.1.2; INN-CB-016 Tables 14.2.1.1 and 14.2.1.2
a p-value based on ANOVA model with treatment, gender, and history of previous ipsilateral hernia repair as main effects.
Reproduced from the applicant submission, page 42 in Summary of Clinical Efficacy

The following table demonstrates the Mean Numerical Rating Scale of Pain Intensity over the 72-hour post-implantation period for studies INN-CB-014 and INN-CB-016 (Modified Intent-to-Treat Population)



Data source: CSR INN-CB-014 Table 14.2.3.1 and Table 14.2.3.2; CSR INN-CB-016 Table 14.2.3.1 and Table 14.2.3.2
p-values from an ANOVA model with treatment, gender, and history of previous ipsilateral hernia repair as main effects.
Applicant's submission, page 47 of Summary of Clinical Efficacy

The graph above shows that the results were consistent for both studies with the Xaracoll curves overlapping during the first 24 hours. It also demonstrates that at 24 hours the placebo and Xaracoll treatment groups converge with no further benefit from Xaracoll from 24 to 72 hours.

The key secondary endpoint was total use of opioid analgesia from time 0 to 24 hours (TOpA24). Subjects in both studies required statistically less opioid rescue analgesia from Time 0 through 24 hours compared to subjects who received placebo collagen-matrix implants as demonstrated in the table below. The other secondary endpoints did not reach statistical significance based on hierarchal testing.

Key efficacy variable Statistic	INN-CB-014		INN-CB-016	
	INL-001 N=197	Placebo Collagen-Matrix Implants N=101	INL-001 N=207	Placebo Collagen-Matrix Implants N=105
TOpA24, mg IV morphine equivalent				
Median	5.0	10.0	5.0	14.0
Minimum, maximum	0, 47.0	0, 40.0	0, 70.0	0, 53.0
Observed p-value[a]	<0.0001	-	<0.0001	-
p-value based on sequential testing	*	-	*	-

Adapted from Applicant's submission, Summary of Clinical Efficacy, page 44.

The applicant collected data on exploratory efficacy endpoints. The table below demonstrates that in both studies, the time to first use of opioid analgesia was statistically significantly longer in the Xaracoll group compared to the placebo collagen-matrix implant group.

Time to First Use of Rescue Opioid Analgesia – Studies INN-CB-014 and INN-CB-016, Modified Intent-to Treat Population

Parameter Statistic	INN-CB-014		INN-CB-016	
	INL-001 N=197	Placebo Collagen- Matrix Implants N=101	INL-001 N=207	Placebo Collagen- Matrix Implants N=105
Subjects who used rescue opioid from Time 0 through 72 hours, n (%)	126 (64.0)	79 (78.2)	150 (72.5)	92 (87.6)
Time to FOpA (hours)				
Median (95% CI)[a]	10.7 (5.2, 17.8)	1.0 (0.9, 1.1)	6.2 (2.0, 12.0)	0.9 (0.8, 1.0)
Hazard ratio (95% CI)[b]	0.52 (0.39, 0.70)		0.43 (0.33, 0.56)	
Log rank p-value[c]	<0.0001		<0.0001	

Data source: CSR INN-CB-014 Table 14.2.5.1 and CSR INN-CB-016 Table 14.2.5.1

a The 95% CI for median was computed using the Brookmeyer-Crowley method.
b The hazard ratio and 95% CI were based on a Cox proportional hazards regression model with treatment, gender, and history of previous ipsilateral hernia repair as exploratory variables.
c p-value (2-sided) was obtained using stratified log rank test based on stratification factors of gender and history of previous ipsilateral hernia repair.

Reproduced from applicant's submission, page 48 in the Summary of Clinical Efficacy

In addition, the applicant evaluated the subjects that did not need rescue opioid analgesia. The results are summarized in the table below.

Percentage of Subjects Who Did Not Use Rescue Opioid Analgesia – Studies INN-CB-014 and INN-CB-016, Modified Intent-to-Treat

Parameter Statistic	INN-CB-014		INN-CB-016	
	INL-001 N=197	Placebo Collagen-Matrix Implants N=101	INL-001 N=207	Placebo Collagen-Matrix Implants N=105
Subjects who did not use rescue opioid analgesia, n (%)				
Time 0 through PACU discharge	115 (58.4)	29 (28.7)	110 (53.1)	18 (17.1)
Time 0 through 24 hours	82 (41.6)	22 (21.8)	74 (35.7)	13 (12.4)
Time 0 through 48 hours	72 (36.5)	22 (21.8)	59 (28.5)	13 (12.4)
Time 0 through 72 hours	71 (36.0)	22 (21.8)	57 (27.5)	13 (12.4)

Data source: CSR INN-CB-014 Table 14.2.2.9 and CSR INN-CB-016 Table 14.2.2.9

Reproduced from applicant's submission, page 54 in the Summary of Clinical Efficacy

From Time 0 to PACU discharge, the Xaracoll group demonstrated that over 50% of the patients did not require opioids. However, at 24 and 48 hours the percentage difference between the Xaracoll group and placebo group declined. This finding is consistent with the Mean Numerical Rating Scale of Pain Intensity curves above, where the Xaracoll curves start to rise at 8 hours and converge with the placebo curves at 24 hours. Therefore, the opioid reduction reported does not indicate a clinically meaningful reduction in perioperative opioid use.

The Applicant has provided the substantial evidence of effectiveness required by law [see 21 CFR 314.126(a)(b)] to support approval. I agree with Dr. Petit-Scott's conclusion below (reproduced from her review):

> The Phase 3 studies conducted by the Applicant did demonstrate a statistically significant difference between XaraColl® and placebo matrices on the primary efficacy endpoint and some key secondary efficacy endpoints. However, the effect of XaraColl® on post-operative opioid use is likely not clinically relevant (b) (4) (b) (4) because standard of care wound infiltration was not the comparator group.

8. Safety

The safety database in the drug development program consisted of 612 subjects and patients exposed to INL-002. The types of safety assessments that were included in the Phase 1 pharmacokinetic studies and the Phase 3 clinical trial are well-described in Dr. Petit-Scott's review.

Adequacy of Applicant's Clinical Safety Assessments (adapted from Dr. Petit-Scott's submission)

- There were no issues with the data integrity or the overall quality of the submission.
- The clinical study reports (CSR) provided definitions for adverse events (AE), FDA-defined serious adverse events (SAE), and treatment emergent adverse events (TEAE). However, the Applicant specified that a hospital admission based on a complication of a pre-existing condition or an admission for a diagnostic evaluation of an adverse event would not qualify the adverse event as an SAE. The adverse

events were categorized by severity and causality relationships with documentation. The AEs determined not to be related to the study drug were evaluated for a relationship to the surgical procedure, opioid analgesic use, or other.

Key Safety Results

Dr. Petit-Scott noted in her review that greater "than 90% of subjects in both treatment groups experienced at least one treatment-emergent adverse event (TEAE), with a slightly larger percentage in the INL-001 group (97% versus 94%). Somnolence was the most common TEAE reported in both groups with a similar incidence. There were no TEAEs that led to discontinuation and all TEAEs were mild or moderate in severity. There were no reported serious adverse events (SAE)."

There was one patient death reported across the drug development program. There were seven SAEs documented in the Applicant's Phase 3 studies. Two occurred in Study INN-CB-014 and five occurred in Study INN-CB-016. For Study INN-CB-016 three patients were in the treatment group and two were in the placebo group. The following summaries are adapted from Dr. Petit-Scott's review:

> The reported death was a 42-year-old male with a several cardiac risk factors who treated for a right inguinal hernia during Study INN-CB-016. He was randomized to the placebo group and had three collagen matrices implanted. The patient developed hypertension, tachycardia, and ST elevation on the ECG intraoperatively. He was eventually diagnosed with an anterolateral myocardial infarction and severe anoxic encephalopathy. He died study day 20.
>
> There was a single subject across the entire drug development program who experienced signs and symptoms that are seen with local anesthetic systemic toxicity (LAST). The patient was a 57-year-old female with a significant past medical history who presented for a bladder sling procedure. Approximately four hours post-operatively, the patient developed chest pain, hypotension, and notable QT prolongation on ECG. Bupivacaine toxicity was suspected, and the patient was treated with intralipid. Eight bupivacaine HCl levels were measured during the first 6 hours after onset of symptoms and ranged from 54 to 143 ng/mL. At 22 hours post-operatively the bupivacaine level was 900 ng/mL. After a poor response to therapy, the patient returned to the operating room for removal of the matrices. Thereafter, her condition improved and she was discharged in stable condition on POD 4.

The two main safety concerns related the clinical use of the bupivacaine collagen-matrix product that were evaluated during review of this NDA included the risk of the development of local anesthetic systemic toxicity (LAST) and the potential adverse impact on wound healing (adapted from Dr. Petit-Scott's review).

> LAST
>
> In Study INN-CB-014, the dictionary coded AE terms that were included as possibly related to LAST included the following (similar terms grouped together):

- Altered state of consciousness, anxiety, dizziness, dizziness postural, anxiety, procedural anxiety, tremor, restlessness
- Tinnitus
- Chills, cold sweat
- Non-cardiac chest pain
- Dysgeusia, hypoesthesia and paresthesia oral
- Hypotension
- Vision blurred, visual impairment

There were 59 patients (29%) in the INL-001 group and 22 patients (22%) in the placebo group who experienced signs and/or symptoms that *could* be considered part of the constellation of LAST. While there appears to be a slight increased incidence of these AEs in the INL-001 treatment group, it is likely not clinically relevant. Well-documented AEs that are strong predictors of LAST, such as tinnitus and dysgeusia (metallic taste), appear to have occurred with similar frequency between the INL-001 treatment and placebo groups. Additionally, there was one patient in the placebo group that reported both tinnitus and dysgeusia, which were unlikely related to implantation of the placebo matrices.

In Study INN-CB-016, the dictionary coded AE terms that were included as possibly related to LAST included the following (similar terms grouped together):

- Anxiety, restlessness, dizziness, tremor
- Tinnitus
- Chest discomfort
- Dysgeusia, hypoesthesia and paresthesia oral
- Hypotension and procedural hypotension
- Vision blurred, vision impairment

There were 57 patients (27%) in the INL-001 group and 41 patients (39%) in the placebo group who experienced signs and/or symptoms that *could* be considered part of the constellation of LAST. Therefore, in study INN-CB-016 the placebo group reported more adverse events than the INL-001 group which supports the safety of INL-001.

Incision Site Issues

All Incision Site Issues for All Clinical Studies

Preferred Term	All INL-001, N=612, n (%)	Placebo Collagen-Matrix, N=280, n (%)	Comparator Treatment, N=52, n (%)
Swelling	61	30 (11%)	0 (0)
Pain	(10%)	32 (11%)	0 (0)
Other	57 (9%)	16 (6%)	0 (0)
complication	26 (4%)	11 (4%)	0 (0)
Erythema	15 (3%)		

Preferred Term	All INL-001, N=612, n (%)	Placebo Collagen-Matrix, N=280, n (%)	Comparator Treatment, N=52, n (%)
Post-procedural discharge	20 (3%)	10 (4%)	1 (2%)
Dehiscence	12 (2%)	5 (2%)	0 (0)
Inflammation	9 (2%)	6 (2%)	0 (0)
Infection	7 (1%)	2 (1%)	0 (0)
Hematoma	5 (1%)	1 (0.4%)	0 (0)

Source: Adapted from Applicant's Summary of Clinical Safety, p. 55 (PDF), NDA 209511
Comparator treatment included bupivacaine HCl 150 mg with epinephrine wound infiltration, bupivacaine HCl 175 mg wound infiltration, ON-Q Painbuster® pump, and standard of care.
Reproduced from Dr. Petit-Scott's review

Dr. Petit-Scott concluded the following (adapted from Dr. Petit-Scott's review):

> Incision site swelling and pain were reported with the highest incidence. Given the size and composition of the collagen implant, however, it is not surprising that there would be an increased incidence of these adverse events when compared to bupivacaine wound infiltration, for example. Wound dehiscence and post-procedural discharge, which appear to be more serious and may indicate a wound infection, were also reported with a higher incidence in patients who received the collagen matrices; however, the overall numbers were low and appear consistent with reports in the published literature after the same surgical procedure without the implanted collagen matrix.

I concur with Dr. Petit-Scotts final assessment of the safety profile of Xaracoll®, adapted from her review:

> The safety concerns of LAST and wound-healing have been adequately evaluated during the Applicant's drug development program and the data does not indicate an increased incidence of LAST compared to bupivacaine. Wound healing is consistent with reports from the published literature for patients undergoing the same surgical procedure without XaraColl® implantation. Therefore, I conclude that XaraColl® is a safe treatment option for surgical patients undergoing open inguinal hernia repair with mesh and should be approved for use in this surgical population.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application, as there were no issues in this application that required presentation or discussion at an advisory committee meeting.

10. Pediatrics

The Applicant submitted an initial pediatric study plan (iPSP) on January 27, 2016 and it was agreed upon on September 23, 2016. The proposed pediatric studies evaluating XaraColl® and the proposed deferral requests are as follows (reproduced from Dr. Petit-Scott's review):

- Study INN-CB-020: a multicenter, randomized controlled study to evaluate the pharmacokinetics, safety, and efficacy of INL-001 for post-operative analgesia in children 2 to <17 years of age who are undergoing open inguinal hernia repair surgery.

  This study has been initiated, with limited enrollment to date per the applicant, as noted in the submission.

  The Applicant is requesting to defer submission of the ongoing study until December 2018, after a regulatory decision regarding this application has been made.
- Study INN-CB-021: a multicenter, single-dose, randomized, blinded study in children 0 to <2 years of age who are scheduled for open inguinal hernia repair surgery.

  The Applicant is requesting a deferral for initiation of this planned study until data from Study INN-CB-020 are available, and neonatal and infant dosing is determined.

  The projected date for final protocol submission is November 2018, and study initiation projected for January 2019.

11. Other Relevant Regulatory Issues

Dr. Petit-Scott's review includes the following information concerning patents and exclusivity:

> There are no outstanding patents or exclusivity periods, as indicated in the Approved Drug Products with Therapeutic Equivalence Evaluations publication, commonly referred to as the Orange Book.

Dr. Petit-Scott's review includes the following information concerning regarding financial disclosures:

> Pepe Carmona, Chief Financial Officer, Innocoll Pharmaceuticals, signed FDA form 3454 on October 4, 2016, certifying that he has not entered into any financial arrangement with any of the listed clinical investigators. He further certified that none of the individual investigators has a proprietary interest in this drug product or a significant equity in the Sponsor per 21 CFR 54.2(b) or received payments in excess of what is permitted per 21 CFR 54.2(f).

Routine audits were conducted at three sites by the Division of Clinical Compliance and Evaluation in the Office of Scientific Investigations (OSI). Three of the sites were selected because of high enrollment and two of the three sites showed significant treatment effect.

The following table, reproduced from Dr. Blay's review, summarizes the information on the sites and the outcomes of the inspections:

Site #/ Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
Site #417 **Dr. Fadi Saba** Professional Health Care of Pinellas, Inc. 1839 Central Avenue St. Petersburg, FL 33713	INN-CB-014 Subjects: 50	10-20 Sep 2018	NAI
Site #420 **Dr. Jose Suarez** Medical Research Center 922 SW 82nd Avenue Miami, FL 33144	INN-CB-014 Subjects: 39	13-17 Aug 2018	NAI
Site #603 **Dr. Kenneth Deck** Alliance Research Centers 24012 Calle de la Plata, Ste. 203 Laguna Hills, CA 92653	INN-CB-016 Subjects: 45	1-5 Oct 2018	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations; Data unreliable

Dr. Blay's overall assessment of findings and recommendation were noted as follows:

> The clinical sites of Drs. Saba, Suarez, and Deck were inspected in support of this NDA. Based on the results of these inspections, the studies (Protocols INN-CB-014 and INN-CB-016) appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.
>
> The final compliance classification of the inspections of Drs. Saba, Suarez, and Deck was No Action Indicated (NAI).

12. Labeling

Consultations were obtained from the following: the Division of Medication Error Prevention and Analysis (DMEPA). Their recommendations were considered and incorporated into the label.

Discussions with the Applicant regarding the text of the label will be conducted during the next review cycle, however, the following information should be included in the label.

INDICATIONS AND USAGE
The applicant's proposal for a broad indication, i.e., placement into the surgical site to produce postsurgical analgesia (b) (4) is not supported by their drug development program. The applicant conduct the pivotal Phase 3 studies in the same surgical model, inguinal hernioplasty. Therefore, the indication should only include the use of Xaracoll in inguinal hernioplasty.

DOSEAGE AND ADMINISTRATION

The description of the dose of Xaracoll® for inguinal hernioplasty of 300 mg of bupivacaine HCL consists of three bupivacaine HCl implants, each containing 100 mg of bupivacaine HCl.

In following language should be included in the label:

(b) (4)

Xaracoll is a implant for placement into the surgical sites, therefore, placement instructions must be described in DOSAGE AND ADMINISTRATION.

WARNINGS AND PRECAUTIONS
The use of additional local anesthetics within 96 hours of the administration of Xaracoll® should be avoided.

13. Postmarketing Recommendations

There are no postmarketing recommendations at the time of this review.

14. Recommended Comments to the Applicant

Pharmacology/Toxicology Assessment (Reproduced from Dr. Bond's Review):

1. 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 this deficiency:
   Conduct adequate toxicology studies in two species that provide adequate coverage for the proposed human exposures via your drug product (AUC and Cmax).

2. You have not provided a valid in vivo micronucleus assay for bupivacaine. Specifically, the high dose selected for the assay did not result in frank toxicity.

   To address this deficiency:
   Repeat the in vivo micronucleus assay for bupivacaine testing doses that result in frank toxicity in accordance with the ICH guidance document: S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074931.pdf.

3. You have not provided an adequate extractables/leachables evaluation to support the safety of your proposed container closure system. Specifically, although your extraction study, submitted September 20, 2018 (SDN 33), was capable of detecting compounds at

the requested safety concern threshold of (b) (4) mcg/day, you did not identify many of the compounds detected above this safety threshold. Further, you did not provide adequate leachables data from multiple batches at release where compounds identified in the extraction study were targeted using validated methods.

To address this deficiency:
Identify the compounds detected in the extraction studies completed to date and evaluate the drug product stability batches for the presence of any extractable detected at (b) (4) mcg/day or higher. Provide a toxicological risk assessment for any leachable compound present in the drug product at (b) (4) mcg/day or greater.

4. You have not provided adequate justification for the proposed specification for (b) (4) (b) (4) in the drug product formulation.

   To address this deficiency:
   Either reduce the specification for (b) (4) to NMT (b) (4) mcg/day or provide an adequate toxicological risk assessment for this compound to justify the proposed specification in accordance with the ICH guidance document: M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf.

OPQ Assessment (reproduced from OPQ review):

5. An incomplete leachables assessment has been provided. An analytical method for the detection of leachables has not been provided and therefore a correlation between the extractables and leachables cannot be made. Leachables testing should be performed on (b) (4) manufactured product due to the manufacturing process which involves (b) (4)

   In order to resolve this deficiency:
   a. From the robust extractables profiles of both primary and secondary packaging, identify and determine the target leachables.
   b. Develop methods which can detect these leachables in the drug product.
   c. Test 3 batches of drug product at multiple timepoints on stability with emphasis on (b) (4) manufactured product that includes ink labeling on individual blisters as planned for commercial product.
   d. We refer you to USP <1663> and <1664>.

Deputy Division Director's Comments

I concur with the review team that the lack of adequate data to support the product's quality precludes approval of the application at this time.

References

Alam. (2012). Long-term Analgeis Use After Low-Risk Surgery. *Archives of Internal Medicine*, 172(5):425-430.

Meissner, W. (2015). Improving the management of post-operative acute pain: priorities for change. *Current Medical Research and Opinion*, 31:11, 2131-2143.

Appendix 1. Clinical Trials Supporting NDA 209511 (adapted from Dr. Petit-Scott's review)

Study Identity	Study Design	Regimen and Route	Primary Study Objective(s)	Study Population	No. of patients completed	No. and location of centers
Phase 3 Controlled Studies to Support Efficacy and Safety						
INN-CB-014	Phase 3, multi-center, randomized, double-blind, placebo-controlled	Surgical implantation of the following: INL-001 – three 100 mg bupivacaine implants (total dose 300 mg) Pbo – three placebo collagen implants	To compare the analgesic effect of INL-001 to the placebo-collagen implant for the management of acute post-operative pain after open laparotomy inguinal hernioplasty	Adult males and females scheduled to undergo an open unilateral inguinal herniorrhaphy	INL-001: 196 pbo-collagen: 100	20 U.S. sites
INN-CB-016	Phase 3, multi-center, randomized, double-blind, placebo-controlled	Surgical implantation of the following: INL-001 – three 100 mg bupivacaine implants (total dose 300 mg) Pbo – three placebo collagen implants	To compare the analgesic effect of INL-001 to the placebo-collagen implant for the management of acute post-operative pain after open laparotomy inguinal hernioplasty	Adult males and females scheduled to undergo an open unilateral inguinal herniorrhaphy	INL-001: 203 pbo-collagen: 103	19 U.S. sites
Phase 2 Controlled Studies to Support Efficacy and Safety						
INN-CB-003	Phase 2, multi-center, randomized, single-dose, double-blind, placebo-controlled	Surgical implantation of the following: INL-001 – two 50 mg bupivacaine implants (total dose 100 mg) Pbo – two placebo collagen implants	To compare the total use of opioid rescue analgesia over 24 hours after hernioplasty by treatment group	Adult males scheduled to undergo an open unilateral inguinal herniorrhaphy	INL-001: 24 pbo-collagen: 29	8 U.S. sites
INN-CB-010	Phase 2, multi-center, randomized,	Surgical implantation of the following: INL-001 – two 100 mg	To compare the sum of pain intensity after aggravated movement	Adult males scheduled to undergo an open	48	5 U.S. sites

Study Identity	Study Design	Regimen and Route	Primary Study Objective(s)	Study Population	No. of patients completed	No. and location of centers
	single-dose, double-blind, placebo-controlled	bupivacaine implants (total dose 200 mg) Pbo – two placebo collagen implants	over the first 72 hours after hernioplasty by treatment group	unilateral inguinal herniorrhaphy, performed according to standard surgical technique		
Clinical Pharmacology Studies						
INN-CB-013	Phase 2, randomized, single-dose, double-blind, active control	Surgical implantation of the following: INL-001 – two 100 mg bupivacaine implants (total dose 200 mg) INL-001 – three 100 mg bupivacaine implants (total dose 300 mg) Bupivacaine infiltration – 60 mL of 0.25% bupivacaine with epinephrine	To estimate the pharmacokinetic profile of two doses of INL-001 after open laparotomy hernioplasty To estimate the relative bioavailability of INL-001 compared to local bupivacaine infiltration	Adult males and females scheduled to undergo an open unilateral inguinal herniorrhaphy	2 INL-001: 25 3 INL-001: 24 Bupivacaine infiltration: 12	5 U.S. sites
INN-CB-022	Phase 1, randomized, single-dose, double-blind, active control	Surgical implantation of three 100 mg bupivacaine implants (total dose 300 mg) Bupivacaine infiltration – 70 mL of 0.25% Marcaine™	To estimate the PK profile of INL-001 during and after open hernioplasty To estimate the relative bioavailability of INL-001 compared with local bupivacaine infiltration	Adult males and females scheduled to undergo an open unilateral inguinal herniorrhaphy	3 INL-001: 34 Bupivacaine infiltration: 16	5 U.S. sites

Source: Adapted from *Tabular Listing of All Clinical Studies*, Applicant's submission, NDA 209511

Appendix 2. Additional Phase 1 and Phase 2 Clinical Studies Conducted by the Applicant (adapted from Dr. Petit-Scott's review)

Study number	Study design	Regimen and route	Study population	Number of patients
INN-CB-001	Phase 1, single-dose, open-label, PK, safety	Surgical implantation of three 50 mg bupivacaine implants (total dose 150 mg)	Adult females scheduled for hysterectomy for reasons other than known or suspected malignancy	12
INN-CB-002	Phase 2, randomized, single-dose, double-blind, placebo controlled	Surgical implantation of the following: INL-001 – three 50 mg bupivacaine implants (total dose 150 mg) Pbo – three placebo collagen implants Standard of care – same treatment as active and pbo groups but not implanted matrices	Adult females scheduled for hysterectomy or other non-laparoscopic benign gynecological procedure for reasons other than known or suspected malignancy	INL-001: 27 pbo-collagen: 15 standard care: 10
INN-CB-004	Phase 2, randomized, single-dose, double-blind, placebo controlled	Surgical implantation of the following: INL-001 – three 50 mg bupivacaine implants (total dose 150 mg) or four 50 mg bupivacaine implants (total dose 200 mg) Pbo – three or four placebo collagen implants	Adult males and females scheduled for elective surgery that required a vertical or transverse abdominal incision	3 INL-001: 1 4 INL-001: 2 3 pbo-collagen: 1 4 pbo-collagen: 1
INN-CB-005	Phase 2, randomized, single-dose, unblinded	Surgical implantation of three 50 mg bupivacaine implants (total dose 150 mg) Each matrix contained 70 mg bovine Type I collagen (total dose 210 mg or 280 mg) ON-Q PainBuster® bupivacaine HCl infused at 5 mL (12.5 mg)/hour for 72 hours (total dose 900 mg)	Adult females scheduled for hysterectomy or other non-laparoscopic benign gynecological procedure for reasons other than known or suspected malignancy	INL-001: 13 ON-Q: 13
INN-CB-011	Phase 2, single-dose, open-label	Surgical implantation of four 50 mg bupivacaine implants (total dose 200 mg)	Adult males scheduled to undergo an open or laparoscopic unilateral inguinal herniorrhaphy	10

Study number	Study design	Regimen and route	Study population	Number of patients
			or laparoscopic umbilical hernioplasty	

Source: Adapted from *Tabular Listing of All Clinical Studies*, Applicant's submission, NDA 209511

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/s/

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