CONFIDENTIAL

PROTOCOL INN-CB-022

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

Original: 12 March 2017
Amendment 1: 17 May 2017

Sponsor:

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AMENDMENT 1 PROTOCOL CHANGES

Issued to address minor errors and omissions the following changes were made to the 12March 2017 version of the protocol:
Changed the number of sites expected to participate in the study from 5 to 8 (Synopsis)
Clarified the use of analgesics to allow the investigator to use their discretion for how long the patients remain on analgesics (Synopsis, Sections 5.10.3, 5.10.4)
Added the requirement to obtain a baseline for the ECG continuous monitoring prior to the surgery during the screening period. (Synopsis, Table 1, Section 5.11.2)
Clarified that the Holter monitor must be set up prior to the surgery on Day 1 to allow the recording to be on at the time of administration of INL-001 or Marcaine (Sections 5.11.3.1.1, 5.12.6, 8.1.2))
Added the collection of a blood sample for pharmacokinetic assessment before Time 0 (Section 5.11.3.1.1)
Clarified the version of MeDRA to be used is 18 (Synopsis, Section 8.2.1)
Clarified the study objectives that the study will use the same material as that used in the Phase III program (Section 2)
Clarified that only subjects will remain blinded in the study (Section 5.3)
Clarified that the site can destroy unused product once accountability has been completed and approval provided (Section 5.6)
Corrected the pregnancy test requirements to be females of child bearing potential and not females ≥ 55 years of age (Sections 5.11.2, 5.11.3.1.1, 5.12.5)
Deleted mention of a central lab since local labs are to be used (Section 5.12.4)
Added timing windows for the pharmacokinetic blood draws, for the completion of vital signs and for the evaluations of AEs associated with bupivacaine toxicity (Sections 5.12.7, 5.12.8.1, 5.13)
Corrected the volume of blood to be collected from 30 ml to 70 ml and added a reference to the PK manual for more detailed instructions (Section 5.13)
Updated the contact details for Innocoll (Section 7)
Added a PK evaluation to include percentage extrapolation (100x[AUC0-∞-AUC0-last]/AUC0-∞) (Section 8.1.3)

PROTOCOL SYNOPSIS

Name of Sponsor/Company: Innocoll Pharmaceuticals
Name of Finished Products: **Study Device:** INL-001 (bupivacaine hydrochloride [HCl] collagen-matrix implant)
Study Number: INN-CB-022
Title of Study: A Randomized, Single Blind Study to Investigate the Pharmacokinetics, Relative Bioavailability and Safety of INL-001 Bupivacaine Hydrochloride (HCl) Collagen-Matrix Implant 300 mg Compared to Marcaine™ 0.25% (bupivacaine HCl) 175 mg Infiltration After Open Hernioplasty
Study Centers: Approximately 8 sites in the United States
Study Period: Screening through end of study (EOS): Approximately 7 weeks
Objectives: The primary objectives of this study are to estimate the: • Pharmacokinetic profile of the INL-001 bupivacaine HCl collagen-matrix implant 300 mg after open hernioplasty. • Relative bioavailability of the INL-001 bupivacaine HCl collagen-matrix implant compared to Marcaine™ 0.25% infiltration. The secondary objective of this study is to assess the safety and tolerability of the INL-001 bupivacaine HCl collagen-matrix implant after placement in the surgical site during open hernioplasty, with particular emphasis on signs and symptoms of bupivacaine toxicity.

Name of Sponsor/Company: Innocoll Pharmaceuticals
Name of Finished Products: **Study Device:** INL-001 (bupivacaine hydrochloride [HCl] collagen-matrix implant)
Study Number: INN-CB-022
Methodology/Study Design: This is a multicenter randomized, single-blind, controlled study. Prior to surgery on Day 1, 48 subjects who continue to meet study entry criteria will be randomized just prior to surgery in a 2:1 ratio to receive either 3 x 100 mg INL-001 bupivacaine HCl collagen-matrix implants (total bupivacaine HCl dose 300 mg) or Marcaine 0.25% (bupivacaine HCl 175 mg) infiltration. Subjects will then undergo open hernioplasty according to standard procedure. If the surgeon encounters a significant surgical complication or other clinically significant medical condition during surgery, the test article may not be administered at the investigator's discretion, and the subject will be considered randomized but not enrolled or treated. Following surgery, subjects will be transferred to a post-anesthesia care unit (PACU) and/or other postoperative recovery area for observation where they may receive parenteral morphine as needed (rescue medication for breakthrough pain). Once subjects can tolerate oral medication, they will be started on a standardized oral analgesic regimen of acetaminophen 650 mg 3 times daily for as long as clinically required and will be prescribed immediate-release morphine (15 mg) to manage breakthrough pain only when it occurs. Subjects will remain in the PACU until they are stable and can be discharged to the clinic. Subjects will remain housed in the clinic at least until after the 72 hour blood sample has been collected for pharmacokinetic (PK) analysis on Day 4. Subjects discharged after the 72 hour blood draw will be instructed to return to the clinic to complete the 96 hour PK blood draw on Day 5. Follow-up safety assessments will include clinic visits on Day 7, Day 15 and Day 30. Pharmacokinetic blood samples will be collected from subjects before surgery and at predetermined time points up to 96 hours after administration of study drug. Safety assessments will include frequent assessment of vital signs through 72 hours, continuous electrocardiogram (ECG) monitoring for at least 24 hours, oxygen saturation levels, and adverse events (AEs) reporting with particular emphasis on the signs and symptoms of CNS and cardiovascular bupivacaine toxicity as described in Section 5.12.6. The surgical wound will be assessed frequently for adverse events associated with altered or delayed wound healing.
Number of Subjects Planned: 48 subjects
INL-001 Implant: Lyophilized bupivacaine HCl collagen-matrix implant (approximately 5 × 5 cm). Each implant contains 100 mg bupivacaine HCl.
Bupivacaine HCl Infiltration: Marcaine™ 0.25% (bupivacaine HCl) 175 mg.
Duration of Treatment: INL-001 bupivacaine HCl collagen-matrix implant and Marcaine ™ 0.25% (bupivacaine HCl) are single use products. The INL-001 collagen-matrix implant is bioresorbable and does not require removal.

Name of Sponsor/Company: Innocoll Pharmaceuticals

Name of Finished Products:
Study Device: INL-001 (bupivacaine hydrochloride [HCl] collagen-matrix implant)

Study Number: INN-CB-022

Inclusion Criteria: To be eligible for inclusion into this study, subjects must:

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

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Name of Finished Products:
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Exclusion Criteria:

A subject will be excluded from study participation if he/she:

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

Pharmacokinetic Variables:

NOTE: Time 0 is the time when the first INL-001 bupivacaine HCl collagen-matrix is implanted or the time of Marcaine 0.25% infiltration. Time 0 must be recorded on the electronic case report form (eCRF) for all treated subjects.

The following PK parameters will be calculated for each subject:

- Maximum (peak) plasma concentration (Cmax)
- Time to maximum (peak) plasma concentration (Tmax)
- Lag-time (tlag)
- Terminal half-life ($t_{½z}$)
- Terminal phase rate constant (λz)
- Area under the plasma concentration-time curve (AUC) from Time 0 to last time of last
- quantifiable plasma concentration (AUC0-last)
- AUC from Time 0 to infinity ($AUC_{0-\infty}$)

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Name of Finished Products:
Study Device: INL-001 (bupivacaine hydrochloride [HCl] collagen-matrix implant)

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Safety Assessments: The following variables are safety endpoints:

- Clinical laboratory assessments (screening only)
- ECG (screening and continuous ECG monitoring for at least 24 hours pre surgery during the screening period and post administration of study drug)
- Oxygen saturation levels
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature)
- Adverse events: Mapped to preferred term using the Medical Dictionary for Regulatory Activities (MedDRA)
- Special AEs related to bupivacaine toxicity and wound healing

Statistical Methods:

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

Analyses Populations:

Randomized Population: The randomized population will consist of all subjects who receive a randomization number, regardless of whether or not they receive test article.

Safety Population: The safety population will consist of all subjects who receive INL-001 bupivacaine collagen-matrix implant or Marcaine 0.25% infiltration. Subjects will be analyzed according to the treatment they actually receive.

Pharmacokinetic Population: The PK population will consist of all subjects who receive INL-001 bupivacaine collagen-matrix implant or Marcaine 0.25% infiltration and have at least 1 post-implantation/infiltration blood sample obtained. Subjects will be analyzed according to the treatment they actually receive.

Per Protocol Pharmacokinetic Population: The PK population will consist of all subjects in the pharmacokinetic population who have no major PK-related protocol deviations, and have sufficient data to calculate the Cmax, AUC0-∞, and AUC0-tlast for INL-001 or Marcaine. Subjects will be analyzed according to the actual treatment they receive.

Efficacy Population: Efficacy was not assessed in this study.

Safety: Safety variables include assessment of AEs, serious adverse events (SAEs), bupivacaine toxicity AEs, wound healing AEs, oxygen saturation levels, ECG data, vital signs, and baseline clinical laboratory parameters. These analyses will be conducted on the safety population.

Safety Analyses: The Medical Dictionary for Regulatory Activities (MedDRA Version 18) will be used

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to classify all AEs with respect to system organ class (SOC) and preferred term (PT). A treatment-emergent adverse event (TEAE) will be defined as any AE that occurred after implantation/infiltration. The number and percentage of subjects with AEs will be displayed for each treatment group by system organ class (SOC) and preferred term. Summaries in terms of severity and relationship to treatment will also be provided. Serious AEs will be summarized separately in a similar fashion. In the case of multiple occurrences of the same AE within the same subject, each subject will be counted only once for each SOC and preferred term. All AEs and SAEs will be listed by subject. An assessment of the occurrence of AEs with respect to bupivacaine plasma concentrations will be performed. Oxygen saturation levels will be summarized descriptively (sample size, mean, SD, CV, median, minimum, and maximum). ECG data including: RR, PR, QRS, and QTc intervals will be summarized descriptively. Vital signs and any other appropriate quantitative safety data will be presented descriptively by treatment group at each time point for the baseline and post-baseline evaluations, as well as change from baseline, using descriptive statistics (sample size, mean, SD, CV, median, minimum, and maximum). **Pharmacokinetics:** Individual plasma concentrations of bupivacaine will be tabulated for each scheduled sampling time and summarized descriptively using the arithmetic mean, associated standard deviation (SD) coefficient of variances (CV %), geometric mean, median, minimum and maximum. All concentrations below the lower limit of quantification (LOQ) will be set to zero for the purpose of calculating descriptive statistics. Pharmacokinetic parameters of bupivacaine will be listed for each subject. A descriptive summary for each parameter will include arithmetic mean, SD, CV (%), geometric mean, median, minimum and maximum (refer to Section 8.2.2 for details).

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AE	Adverse event
AIC	Anterior iliac crest
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AUC0-∞	AUC from Time 0 to infinity
AUC0-last	Area under the plasma concentration-time curve from Time 0 to last time of last quantifiable plasma concentration
ASA	American Society of Anesthesiologists
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BLQ	Below level of quantification
BSE	Bovine spongiform encephalopathy
CBC	Complete blood count
CFR	Code of Federal Regulations
eCRF	Electronic case report form
Cmax	Maximum plasma concentration
CRO	Clinical Research Organization
CV	Coefficient of variation
CYP	Cytochrome P450
EIU	Exposure in-utero
GCP	Good Clinical Practice
HCl	Hydrochloride
INl-001	Bupivacaine HCl collagen-matrix implant
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IR	Immediate release
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
MCHC	Mean corpuscular hemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical rating scale
NSAID	Nonsteroidal anti-inflammatory drugs

Abbreviation	Definition
PACU	Post Anesthesia Care Unit
PI	Pain Intensity
PK	Pharmacokinetic
PO	Per os, by mouth
Qualified designee	Qualified by education and training to perform the study procedure (eg, subinvestigator, nurse).
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
TAP	Transversus abdominis plan
TEAE	Treatment-emergent adverse events
Time 0	The time when the first INL-001 bupivacaine HCl collagen-matrix is implanted or the time of Marcaine 0.25% infiltration. Time 0 must be recorded on the eCRF for all treated subjects.
t1/2	Apparent first order terminal elimination half-life
tlag	Lag-time
t1/2z	Terminal half-life
λz	Terminal phase rate constant
Tmax	Time to maximum plasma concentration
TSE	Transmissible spongiform encephalopathy
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
WBC	White blood cell

1. INTRODUCTION

1.1. Postsurgical Pain

Postsurgical pain is a form of acute pain from surgical trauma that causes an inflammatory reaction and initiation of an afferent neuronal barrage (Gupta et al., 2010). Pain after surgery is a combined constellation of unpleasant sensory, emotional and mental experiences precipitated by the surgical trauma and associated with autonomic, endocrine-metabolic, physiological and behavioral responses (Gupta et al., 2010). Tissue trauma stimulates hypersensitivity of the central nervous system, resulting in pain within the immediate surgical field and in other areas directly affected by the surgical procedure (eg, the incision site).

Evidence suggests that surgery suppresses the immune system and that this suppression is proportionate to the invasiveness of the surgery (Ramsey, 2000). Effective postsurgical analgesia can reduce this deleterious effect and is an essential component in the care of the surgical patient. Inadequate pain control, apart from being inhumane, can result in increased patient morbidity or mortality (Gupta et al., 2010).

Optimal management of postsurgical pain requires an understanding of the pathophysiology of pain, the methods available to reduce pain, the invasiveness of the surgical procedure, and inherent patient factors, such as anxiety and depression, which are often associated with increased pain (Lovich-Sapola et al., 2015). Postsurgical pain management must be an integral part of perioperative care and should be based on sound physiologic and pharmacologic principles (Jain and Datta, 1997).

From 1992 to 2012, the total number of surgeries at community hospitals in the United States (US) increased by 17 percent to about 26.8 million surgeries (Surgeries in Hospital-Owned Outpatient Facilities, 2012), and approximately 1 million hernia repair surgeries are performed each year in the US (Co-Factor analysis, 2016). Although significant improvement has been made in the treatment of postsurgical pain, surveys still show that many patients still receive inadequate postsurgical analgesia (Rawal, 2001). Inadequate pain management can lead to poorer outcomes in the immediate postsurgical period and can also result in increased risk for chronic postsurgical pain (ie, pain that lasts beyond the typical healing period of 1 to 2 months). Chronic postsurgical pain is now recognized as a significant issue after surgery and may occur in over 30% of patients after some operations, particularly amputations, thoracotomy, mastectomy, and inguinal hernia repairs (Lovich-Sapola et al., 2015).

The standard pillar of postoperative treatment of moderate to severe pain has been the use of opioids. However, adverse reactions related to opioids including constipation, nausea, vomiting, respiratory depression, and addiction make their use unfavorable (Ramsey, 2000; Jain and Datta, 1997). There are data that suggest opioids should be avoided when not needed, because perioperative opioid therapy may be associated with an increased likelihood of long-term opioid use, with its attendant risks (Chou et al., 2016).

Acute postoperative pain and its treatment with opioids raise important concerns for the millions of patients who undergo major surgery every year (Clarke et al., 2014). A retrospective analysis

of 39,140 opioid-naïve patients who underwent major surgery found that almost 50% of these patients were discharged from the hospital with an opioid prescription, and that 1 in 30 of these patients continued to take opioids for more than 3 months (Clarke et al., 2014). Similarly, in 391,139 opioid-naïve patients who underwent short-stay surgery, 7.1% were newly prescribed opioids within 7 days of hospital discharge and 7.7% were prescribed opioids at 1 year after surgery. During this time period, oxycodone use increased from 5.4% within 7 days of surgery to 15.9% at 1 year (Alam et al., 2012).

The use of procedure-specific, multimodal perioperative pain management provides the basis for enhanced postsurgical pain control, optimization of analgesia while decreasing the requirement for opioids, decrease in adverse effects, and improved patient satisfaction (Lovich-Sapola et al, 2015). Preventive analgesia plays an important role in postsurgical pain management (Vadivelu et al., 2014), and available data indicate that afferent neural blockade with local anesthetics, such as bupivacaine, is the most effective analgesic technique (Ramsey, 2000).

Bupivacaine, introduced in 1963, is a widely used amide local anesthetic with a prolonged duration of action. Amides are relatively stable in solution and are slowly metabolized by hepatic amidases. Bupivacaine is therefore typified by a rapid onset and longer duration of action. Bupivacaine affects sensory nerves more than motor nerves and can also be used to provide several days of effective analgesia without motor blockade. Bupivacaine is approved for use in the United States and Europe as a local anesthetic (Section 1.2.1).

The advantages of effective pain management during and after surgery include patient comfort and satisfaction, earlier mobilization, fewer pulmonary and cardiac complications, a reduced risk of deep vein thrombosis, faster recovery with less likelihood of the development of neuropathic pain, and reduced cost of care (Ramsey, 2000).

Local placement of the INL-001 collagen matrix implant at multiple layers within the soft tissue layers during surgery offers a novel way to deliver bupivacaine HCl directly to the surgical site to produce effective postsurgical analgesia for the reduction of postsurgical pain and the requirement for opioid analgesics.

1.2. INL-001 Bupivacaine HCl Collagen-Matrix Implant

INL-001 (also known as XARACOLL®), is a sterile, resorbable and biodegradable Type 1 purified bovine collagen matrix implant comprised of 75 mg of Type 1 collagen purified from bovine Achilles tendons.

Each implant contains 100 mg bupivacaine HCl (equivalent to 88.8 mg of bupivacaine) that is homogeneously dispersed (Summary Report RPD-SYN136) in an approximately 5 x 5 cm matrix of 5 mm thickness. Because bupivacaine HCl is homogeneously dispersed within the matrix, it can be cut before placement into the surgical site using sterile technique. INL-001 is a drug (bupivacaine HCl)-device (Type I collagen) combination product.

1.2.1. Bupivacaine HCl

Bupivacaine, an amide local anesthetic with a prolonged duration of action, was introduced in the United States in 1963, and is currently indicated for the production of local anesthesia by percutaneous infiltration, peripheral nerve block, and central neural block (caudal or epidural). It

is also indicated for pain relief because sensory nerve block is more marked than motor block. Its long duration of action and its tendency to provide more sensory than motor block have made it a popular drug for providing prolonged analgesia during labor or during the postoperative period. Amides are relatively stable in solution and are slowly metabolized by hepatic amidases. Bupivacaine is therefore typified by a rapid onset and long duration of action.

Adverse reactions to bupivacaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma concentrations, which may be due to overdosage, slow metabolic degradation or unintentional intravascular injection. Toxicity related to bupivacaine is characterized by numbness of the tongue, light-headedness, dizziness and tremors, potentially followed by convulsions and cardiovascular disorders.

From the published literature, it can be concluded that signs of central nervous system toxicity are usually evident before the appearance of cardiovascular toxicity with central nervous system and cardiovascular toxicities generally not seen until bupivacaine levels are ≥2000 ng/mL and ≥4000 ng/mL, respectively (Scott, 1975; Tucker and Mather, 1979).

1.2.2. Type I Collagen

Collagen is the most abundant protein in the human body and is used as a naturally safe and effective biomaterial in a wide variety of medical devices and delivery systems for bioactive agents (Ramshaw et al., 2001; Lee et al, 2001). Collagen implants are enzymatically degraded into constituent amino acids, with most reutilized for protein synthesis and the remainder excreted as urea (Bailey, 2000).

Collagen products have been approved as devices in the US and other parts of the world to aid in the management of wound healing, for cosmetic reconstruction and as absorbable hemostatic agents. The histological and biochemical fate of implanted collagen have been well studied. The collagen matrix is biocompatible, and collagen implants show minimal inflammatory and immunogenic responses (Cooperman and Michaeli, 1985; Delustro et al., 1987; DeLustro et al., 1986) and are progressively degraded and replaced in the wound with native collagen (Anselme et al., 1990).

The INL-001 collagen implant utilizes a proprietary collagen matrix technology known as COLLARX®. The COLLARX technology uses purified bovine-derived collagen for the manufacture of INL-001. The INL-001 collagen is extracted from bovine Achilles tendons, obtained exclusively from New Zealand closed herds that have been certified as transmissible spongiform encephalopathy (TSE) free and *negligible for the risk of bovine spongiform encephalopathy (BSE)* in accordance with Regulation (EC) No. 999/2001.

In the INL-001 56-day nonclinical toxicology study in rats (WIL134502) utilizing drug product made for Phase 2 material, the INL-001 collagen matrix was present at the incision site in all INL-001 animals at the Day 3 necropsy and in most animals at the Day 14 necropsy. These findings were confirmed microscopically. During the Day 28 necropsy, none of the INL-001 matrix was noted grossly or microscopically in any animal implanted with INL-001. There was no evidence of the matrix in the remaining INL-001 animals during necropsy on Day 56. These

findings suggest that complete resorption of the collagen matrix occurs between 14 and 28 days after implantation.

The very low potential for an antigenic response from Type 1 collagen is due to the almost identical amino acid sequencing between animal Type 1 collagen (eg, bovine) and human collagen and to the positioning of antigenic determinates outside of the triple helix (Serano, 1992). Because nearly all current collagen-containing implants are composed of Type 1 collagen, collagen-induced autoimmunity is not generally considered a potential concern.

Adverse reactions reported for collagen products that have been used for hemostasis include hematoma, potentiation of infection, wound dehiscence, inflammation and edema. Across the 10 Phase 1/2/3 INL-001 clinical studies, there was no increased incidence of wound infection or wound dehiscence after placement of up to 4 collagen matrices at multiple layers within the surgical site.

1.3. Findings From the INL-001 Clinical Program

1.3.1. Pharmacokinetics of INL-001 in Adults

The rate and extent of systemic bupivacaine absorption is dependent upon the total dose and concentration administered, the route of administration, and the vascularity of the administration site.

Following implantation of INL-001 100 mg, 150 mg, 200 mg, and 300 mg in different surgical models, there was a rapid rise in observed plasma bupivacaine concentrations with quantifiable concentrations observed in all subjects at the first time point (0.5 hours) after implantation. Bupivacaine HCl concentrations increased approximately proportionally with increasing doses of INL-001

Results from the adult pharmacokinetic study (Leiman et al., 2016) that investigated the pharmacokinetics, relative bioavailability and safety of INL-001 200 mg and INL-001 300 mg compared to infiltration of bupivacaine HCl 150 mg with epinephrine after open hernioplasty (INN-CB-013) using drug product material for Phase 2 studies showed that:

- Mean bupivacaine plasma concentrations were higher in the INL-001 300 mg group compared with the INL-001 200 mg and bupivacaine HCl 150 mg with epinephrine infiltration group throughout the 96-hour observation period. Mean bupivacaine plasma concentrations in the INL-001 300 mg group peaked 3 hours after implantation of the matrices.
- Areas under the plasma concentration time curve were dose proportional for INL-001 200 mg and INL-001 300 mg groups relative to the bupivacaine HCL 150 mg with epinephrine infiltrate group.
- The relative maximum concentrations (Cmax) for INL-001 200 mg and INL-001 300 mg were approximately 80% of the Cmax for the bupivacaine HCl 150 mg with epinephrine infiltrate. The mean terminal half-life (t1/2) of the INL-001 200 mg and INL-001 300 mg were 17 hour and 18 hours, respectively, compared with 9 hours for the bupivacaine HCl 150 mg with epinephrine infiltrate.

No subject who received INL-001 300 mg showed any signs or symptoms of systemic bupivacaine toxicity. The highest plasma concentration (777 ng/mL) after implantation of 3 INL-001 matrices (bupivacaine 300 mg) was well below the threshold concentration (ie, ≥2000 ng/mL) that has been associated with signs and symptoms of bupivacaine central nervous system (CNS) toxicity.

1.3.2. Phase 3 Clinical Studies in Adults

1.3.2.1. Efficacy

To demonstrate the efficacy of INL-001 for postsurgical analgesia, the sponsor examined the data from 2 identical, large, well-controlled, Phase 3 studies that were conducted in the United States (INN-CB-014 and INN-CB-016).

Findings from the 2 identical multicenter, double-blind, placebo-controlled Phase 3 studies independently demonstrate the effectiveness of locally placed INL-001 in reducing both pain intensity and the need for opioid rescue medication after surgery and together demonstrate the reproducibility of the treatment effects.

The INL-001 treatment response was comparable and consistent across both pivotal studies. In each study, subjects treated with INL-001 had statistically significantly less pain from Time 0 through the first 24 hours compared with subjects treated with placebo (SPI24; $p \leq 0.0004$; primary endpoint). The treatment effect of INL-001 was observed within the first hour after local placement of the matrices into the surgical site. That is, subjects who received INL-001 had statistically significantly less pain within the first hour after local placement of study drug compared with subjects who received placebo ($p<0.0001$). These reductions in pain intensity were coupled with less total opioid analgesic medication usage in the INL-001 treatment group compared with the placebo group. A noteworthy finding is that approximately one-third of INL-001 subjects did not require any opioid medication throughout the 72-hour postoperative period compared with 17% of subjects who received placebo.

Subjects in the INL-001 group combined used statistically significantly ($p \leq 0.0004$) less opioid rescue medication and had statistically significantly ($p=0.0007$) less opioid-related TEAEs (ie, nausea, vomiting, and constipation) over the post implantation period compared to subjects in the placebo group. This statistically significant reduction in opioid-related TEAEs after treatment with INL-001 is a clinically meaningful finding.

1.3.2.2. Safety

Safety findings from 2 identical Phase 3 studies demonstrated the safety of INL-001 300 mg for postsurgical analgesia. The most commonly reported treatment-emergent adverse events (TEAEs) were characteristic of those associated with general anesthesia, the surgical procedure, and/or rescue opioid analgesia use. Most TEAEs were not considered related to the study drug.

One death from an acute myocardial infarction occurred in the placebo group. This death was not considered related to study drug and was the only death that occurred across the entire INL-001 clinical program. None of the 404 subjects who received INL-001 300 mg had a serious adverse event that was considered related to study drug. Among the 404 subjects who received INL-001 300 mg, none presented with a constellation of symptoms that was indicative of

bupivacaine systemic toxicity. No subject who received INL-001 300 mg experienced bradycardia or other cardiac events related to INL-001. No clinically meaningful effects of INL-001 on vital sign parameters were observed.

Most reports of incision site swelling and incision site pain were mild or moderate, and none were attributed to the study drug. All TEAEs related to wound healing were typical of events associated with the hernia surgical procedure under study. Across the Phase 1/2/3 studies, 2.9% (17/578) subjects in the INL-001 group and 2.5% 7/280) subjects in the placebo group had wound dehiscence and/or wound infection events. None of these events were deemed related to study drug.

In a review of 1440 patients with a primary unilateral inguinal or femoral hernia repair who responded to a questionnaire about postoperative complications, infection was reported by 7.4% (105/1414) of patients and wound rupture was reported by 4.1% (49/1431) (Fränneby, 2008). Another systematic review of open inguinal hernia repair found rates of infection ranging from 3% to 5% (Sanchez-Manuel, 2003). Among the 578 subjects who received INL-001 in the Phase 1/2/3 studies, there were no safety signals suggestive of systemic or local tissue toxicity.

Subjects in the INL-001 300 mg group used statistically significantly less opioid rescue medications, which correlated with statistically significantly (p=0.0004) less opioid-related TEAEs over the post implantation period compared to subjects in the placebo group. This statistically significant reduction in opioid-related TEAEs is considered a clinically meaningful finding.

Unlike other currently marketed local anesthetics, which are injected directly into the soft tissue, the INL-001 collagen matrix is placed at multiple layers in the soft tissue (eg, between the fascia, muscle, and skin) during the surgical procedure. Because INL-001 is implanted into the surgical site, unintended intravascular injection that often leads to the drug's most serious potential central nervous system and cardiovascular systemic toxicities is prevented. Placement of the INL-001 collagen matrix directly into the surgical site makes INL-001 a safe and effective way to deliver bupivacaine HCl locally to the surgical site to provide postsurgical analgesia.

The purpose of this additional pharmacokinetic study is to further characterize the pharmacokinetics of the INL-001 to-be-marketed formulation relative to the reference listed drug (Marcaine™ 0.25%) and to collect additional INL-001 safety data, with particular emphasis on signs and symptoms of bupivacaine toxicity.

2. STUDY OBJECTIVES

The primary objectives of this study are to estimate the:

- Pharmacokinetic profile of the INL-001 bupivacaine HCl collagen-matrix implant 300 mg during and after open hernioplasty.
- Relative bioavailability of the INL-001 bupivacaine HCl collagen-matrix implant compared to Marcaine™ 0.25% infiltration.

The secondary objective of this study is to assess the safety and tolerability of the INL-001 bupivacaine HCl collagen-matrix implant after placement in the surgical site during open hernioplasty, with particular emphasis on signs and symptoms of bupivacaine toxicity.

The study objectives of this study are similar to those from the previous adult pharmacokinetic study (INN-CB-013). This study however will utilize clinical trial material manufactured identically to that used in the Phase 3 studies.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan Description

This is a multicenter randomized, single-blind, controlled study. Prior to surgery on Day 1, 48 subjects who continue to meet study entry criteria will be randomized just prior to surgery in a 2:1 ratio to receive either 3 x 100 mg INL-001 bupivacaine HCl collagen-matrix implants (total bupivacaine HCl dose 300 mg) or Marcaine 0.25% (bupivacaine HCl) 175 mg infiltration. Subjects will then undergo open hernioplasty according to standard procedure. If the surgeon encounters a significant surgical complication or other clinically significant medical condition during surgery, the test article may not be administered at the investigator's discretion, and the subject will be considered randomized but not enrolled or treated.

Following surgery, subjects will be transferred to a post-anesthesia care unit (PACU) and/or other postoperative recovery area for observation where they may receive parenteral morphine as needed (rescue medication for breakthrough pain). Once subjects can tolerate oral medication, they will be started on a standardized oral analgesic regimen of acetaminophen 650 mg 3 times daily and will be prescribed immediate-release morphine (15 mg) to manage breakthrough pain only when it occurs. Subjects will remain in the PACU until they are stable and can be discharged to the clinic.

Subjects will remain housed in the clinic at least until after the 72 hour blood sample has been collected for PK analysis on Day 4. Subjects discharged after the 72 hour blood draw will be instructed to return to the clinic to complete the 96 hour PK blood draw on Day 5. Follow-up safety assessments will include clinic visits on Day 7, Day 15 and Day 30.

Pharmacokinetic blood samples will be collected from subjects before surgery and at predetermined time points up to 96 hours after administration of study drug. Safety assessments will include frequent assessment of vital signs through 72 hours, continuous electrocardiogram (ECG) monitoring for at least 24 hours, oxygen saturation levels, and adverse events (AEs) reporting with particular emphasis on the signs and symptoms of CNS and cardiovascular bupivacaine toxicity as described in Section 5.12.6. The surgical wound will be assessed frequently for adverse events associated with altered wound healing.

Table 1: Study INN-CB-022 Assessments

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

h=hour; Time 0=The time when the first INL-001 bupivacaine HCl collagen-matrix is implanted or the time of Marcaine 0.25% infiltration.
NOTE: Time 0 must be recorded on the eCRF for all treated subjects.

a Update before surgery.
b Refer to Section 5.12.7.
c Before surgery. Results must be negative before surgery can proceed.
d 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 patient confirmed eligible within the screening window

4. SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects must meet all of the inclusion criteria specified in Section 4.1 and none of the exclusion criteria specified in Section 4.2 of the protocol to be eligible for participation in this study.

4.1. Subject Inclusion Criteria

To be eligible for inclusion into this protocol, subjects must:

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

4.2. Subject Exclusion Criteria

A subject will be excluded from study participation if prior to surgery he/she:

1. Has a known hypersensitivity to amide local anesthetics, morphine, acetaminophen, or bovine products.
2. Is scheduled for bilateral inguinal hernioplasty or other significant concomitant surgical procedure.
3. Has undergone major surgery within 3 months of the scheduled hernioplasty or plans to undergo another laparotomy procedure within the 30 day postoperative period.
4. Has known or suspected history of alcohol or drug abuse or misuse within 3 years of screening or evidence of tolerance or physical dependency on opioid analgesics or sedative-hypnotic medications.
5. Has any clinically significant unstable cardiac, neurological, immunological, renal, hepatic or hematological disease or any other condition that, in the opinion of the investigator, could compromise the subject's welfare, ability to communicate with the study staff or otherwise contraindicate study participation.

6. Has venous access difficulties that may preclude the frequent pharmacokinetic sampling requirements of the study.
7. Has participated in a clinical trial (investigational or marketed product) within 30 days of surgery.

4.3. Subject Withdrawal Criteria

Each subject has the right to withdraw from the study at any time without prejudice. If a subject withdraws from the study, the reason(s) should be stated in the subject's medical record and recorded onto the electronic case report form (eCRF).

The investigator or sponsor may discontinue any subject's participation if he or she feels it is necessary for any reason, including any adverse event, clinically significant adverse change in any laboratory test, or failure to comply with the protocol including inability to follow the visit schedule.

Subjects who withdraw from the study or who are discontinued for any reason should have a final evaluation (Day 30 end of study) performed either before withdrawal or as soon as possible after discontinuation.

5. PROCEDURES AND TREATMENTS

5.1. Randomization

Before surgery on Day 1, 48 eligible subjects will be randomized in a 2:1 ratio to receive either 3 x 100 mg INL-001 bupivacaine HCl collagen-matrix implants or Marcaine 0.25% (bupivacaine HCl) 175 mg infiltration.

5.2. Dose Rationale

The aims of this study are to estimate the pharmacokinetic (PK) profile, relative bioavailability (BA) and safety of the commercial dose of the INL-001 bupivacaine HCl collagen-matrix implant (300 mg) compared to Marcaine 0.25% infiltration (175 mg).

5.3. Blinding

This is a single-blind study in which the study subject is blinded to treatment group. All precautions will be taken to ensure that the blinding of the treatment group is maintained throughout the study period. Unblinding to the subject will not be permitted unless it is deemed necessary for appropriate treatment of a medical emergency.

5.4. Identity of Investigational Products

5.4.1. INL-001 Bupivacaine HCl Collagen-Matrix Implant

The INL-001 bupivacaine HCl collagen-matrix is an approximately 5 × 5 x 0.5 cm off-white to white, porous matrix that contains 100 mg of bupivacaine HCl in a lyophilized matrix of Type I collagen. All study drug matrices are terminally sterilized.

5.4.2. Marcaine™ 0.25% (Bupivacaine HCl) Infiltration

Marcaine 0.25% for infiltration is available in sterile isotonic solution containing sodium chloride. Marcaine 0.25% contains 2.5 mg of bupivacaine HCl/mL. The sponsor will supply the Marcaine 0.25% for this study.

5.5. Packaging and Labeling

The test article will be labeled with the sponsor name and address, description of contents, storage conditions and any other applicable item required by national and regional guidelines/regulations. The label will contain the statement: “Investigational Product: To be used in a clinical investigation only” or other similar/appropriate statement.

5.6. Storage and Disposition of Investigational Supplies

INL-001 should be stored at 20 C to 25°C (68 F to 77°F). INL-001 must not be used after the retest date or if sterile packaging is opened or damaged. Marcaine 0.25% for infiltration should be stored according to the manufacturer’s specifications.

All unused clinical supplies will be appropriately stored in a secure place until used or returned to Innocoll. The investigator agrees not to supply the investigational drug to any person except to those subjects enrolled in the study. Upon termination of the study, all used and unused investigational drug and remaining materials supplied by Innocoll will be returned for destruction or destroyed at the site as instructed by the clinical monitor.

5.7. Investigational Drug Accountability

Innocoll or its agent will maintain a master log of investigational drug dispensed to the investigative sites. The investigator or qualified designee will keep records documenting the following:

- date of receipt
- identification of each investigational drug (batch number/serial number or unique code)
- expiry date, if applicable
- date(s) of use
- subject identification
- date on which the investigation drug was returned/explanted from the subject, if applicable
- date of return of unused, expired, or damaged investigation drugs, if applicable

All unused INL-001 matrices (portions or whole) and all used and unused Marcaine 0.25% vials will be retained for drug accountability purposes until notified.

An investigational drug inventory form must be kept current by the study designated person and must be made available to the clinical monitor, Innocoll employees, IRB/IEC, and regulatory agencies for routine inspection and accountability during monitoring visits. When instructed by Innocoll, the investigator will agree to return all original containers of unused investigational drugs to Innocoll or their designee.

5.8. Implantation/Infiltration of Study Drug

5.8.1. INL-001 Bupivacaine HCl Collagen-Matrix Implant

Three x 100 mg INL-001 collagen-matrix implants will be placed in the surgical site prior to wound closure on Day 1 as follows:

1. Use sterile scissors to cut each of the three 5 cm x 5 cm x 0.5 cm collagen matrices in half for a total of 6 half collagen matrices each measuring approximately 2.5 cm x 5 cm x 0.5 cm in size.
2. After the hernia sac is reduced and the mesh is ready for insertion, place 3 half collagen matrices (150 mg bupivacaine HCl) into the hernia repair site below the site of mesh placement. Complete the mesh placement per the surgeon's typical technique.
3. Close the muscle/fascial layer and place the remaining 3 half collagen matrices (150 mg bupivacaine HCl) between the fascia/muscle closure and the skin closure. The skin incision should be closed in the usual fashion.

If the surgeon encounters a significant surgical complication or other clinically significant medical condition during surgery, INL-001 may not be implanted at the investigator's discretion, and the subject will be considered randomized but not enrolled or treated.

5.8.2. Marcaine™ 0.25% (Bupivacaine HCl) Infiltration

Marcaine 0.25% infiltration (70 mL=175 mg of bupivacaine HCl) will be administered according to standard practice or as follows:

- Infiltrate approximately 25 mL into the muscular planes (transverse abdominis and interior oblique muscles)
- Infiltrate approximately 45 mL into the surrounding subcutaneous tissues

5.9. Management of Local Anesthetic Emergencies

Local anesthetics should only be administered by clinicians who are well versed in the diagnosis and management of dose-related toxicity and other acute emergencies that might arise from administration of local anesthetics (ie, bupivacaine HCl). The investigative site must also insure the immediate availability of oxygen, other resuscitative drugs, cardiopulmonary resuscitative equipment, and the personnel resources needed for proper management of toxic reactions and related emergencies.

As described in Section 5.12.6 through Section 5.12.8.1, subjects will be carefully monitored for untoward cardiovascular, respiratory, and state of consciousness changes. At the first sign of an untoward change, oxygen should be administered. The treatment of local anesthetic toxicity may include the following as determined by the physician and in accordance with the institution:

- Airway management
- Seizure suppression (eg, benzodiazepines)
- Management of cardiac dysrhythmias
- Lipid emulsion therapy
- Possible removal of the bupivacaine HCl collagen-matrix implants

5.10. Prior and Concomitant Medications/Procedures

5.10.1. Prior Medications and Procedures

All prior medications taken within 21 days before randomization on Day 1 will be recorded. Any relevant prior surgeries will also be recorded on the Prior/Concomitant Procedures eCRF page.

5.10.2. Concomitant Medications and Procedures

All medications (including over-the-counter medications, parenteral or oral rescue medication, and antiemetics) taken by the subject on Day 1 through the end of the study (Day 30) will be recorded on the eCRF.

Additionally, any diagnostic, therapeutic or surgical procedures performed during the study period (Day 1 through Day 30) should be recorded on the eCRF including the date, indication for and description of the procedure.

5.10.3. Restricted or Prohibited Medications Before and During Surgery

Treatment with the following medications before study entry or during surgery are restricted or prohibited as follows:

- All analgesics except acetaminophen are prohibited within 24 hours of surgery. Acetaminophen may be used the day of surgery but is subject to preoperative restrictions for oral intake.
- A preoperative dose of an antiemetic for nausea prophylaxis is allowed, but antiemetic medications should only be given postoperatively to treat actual reports of nausea.
- Aspirin or aspirin-containing products are prohibited within 7 days of surgery. Aspirin at a dose of ≤ 325 mg is allowed for cardiovascular prophylaxis if the subject has been on a stable dose regimen for at least 21 days before Day 1.
- The use of any investigational product within 30 days of surgery is prohibited.
- Any anesthetics (except for propofol, midazolam and short acting agents) including epidural or local infiltrations are prohibited. Subjects who require the use of other anesthetics intraoperatively including any local IV anesthetic to reduce the burning effect of the propofol infusion will be prohibited from receiving the test article.
- Doses of up to 100 mcg of fentanyl may be utilized intraoperatively: Other opioid analgesics should be avoided pre- or intraoperatively.
- Epidural anesthesia and local anesthetic infiltration are prohibited.

5.10.4. Morphine and Acetaminophen

While in the PACU, subjects may receive parenteral morphine as needed (rescue medication for breakthrough pain) and on request for pain control at recommended incremental doses of 1 to 2 mg. Subjects will also be prescribed morphine 15 mg IR tablets to be taken only if needed for breakthrough pain up to a maximum of 1 tablet every 3 hours.

Once subjects can tolerate oral medication, they will start a standardized oral analgesic regimen of acetaminophen 650 mg TID until discharged from the inpatient unit or deemed not clinically indicated. If the initial dose of acetaminophen on the day of surgery (Day 1) is administered before noon, subjects will be instructed to take acetaminophen 650 mg twice more during that day, approximately 6 hours apart. If the initial dose of acetaminophen is administered after noon, subjects will be instructed to take acetaminophen 650 mg once more approximately 8 hours after the initial dose.

All doses of parenteral or oral rescue medication and acetaminophen will be recorded on the eCRF.

5.11. Assessments by Visit

5.11.1. Informed Consent

Signed and dated informed consent will be obtained from each subject before any study procedures are undertaken. Details about how the informed consent will be obtained and documented are provided in Section 9.3, Subject Information and Consent.

5.11.2. Screening Period (Day -21 to Day -1)

Subjects meeting the relevant eligibility criteria listed in Section 4 may be enrolled in the study after the nature and purpose of the protocol have been explained and written informed consent to participate has been voluntarily provided by the subject. The following procedures will be performed and documented during the screening period:

1. Medical history (Section 5.12.1)
2. Prior and concomitant medications/procedures (Section 5.10)
3. Physical examination including measurement of body weight and height (Section 5.12.2)
4. Vital sign measurements (Section 5.12.7)
5. 12-lead electrocardiogram (ECG) (Section 5.12.3)
6. Collection of samples for:
    a. Clinical laboratory testing (Section 5.12.4)
    b. Serum pregnancy testing only if female of childbearing potential (Section 5.12.5)
7. Adverse events (Section 6)
8. After the patients have been confirmed eligible a continuous ECG (via Holter monitor) for 24 hours should be obtained prior to Day1 of the surgical procedure

5.11.3. Inpatient Period (Day 1 through Day 4)

5.11.3.1. Hernioplasty Surgery (Day 1)

5.11.3.1.1. Preoperative

The following procedures will be performed and documented preoperatively:

1. Update medical history
2. Concomitant medications/procedures (Section 5.10)
3. Vital sign measurements (Section 5.12.7)
4. Collection of a blood sample for pharmacokinetic assessment before Time 0 (Section 5.13)
5. Urine pregnancy testing, if female of childbearing potential (Section 5.12.5)
6. Establish continued eligibility for treatment (Section 4)
7. Adverse events (Section 6)

8. Set up the continuous ECG (Holter monitor) just prior to surgery.

5.11.3.1.2. Intraoperative

The following procedures will be performed and documented intraoperatively:

1. Open hernioplasty repair under general anesthesia according to the investigator's standard surgical practice
2. Implantation of INL-001 or infiltration with Marcaine 0.25% according to randomization (Section 5.1). Record Time 0.
3. Concomitant medications/procedures (Section 5.10)
4. Vital sign measurements (Section 5.12.7)
5. Continuous 12-lead ECG monitoring (Section 5.12.6)
6. Oxygen saturation levels (Section 5.12.6)
7. Collection of blood samples for pharmacokinetic assessment (Section 5.13)
8. Assessment of bupivacaine toxicity (Section 5.12.8.1)
9. Adverse events (Section 6)

5.11.3.1.3. Immediate Postoperative Period (End of Surgery Through Day 2)

The following procedures will be performed and documented during the immediate postoperative period (ie, end of surgery through Day 2):

1. Concomitant medications/procedures (Section 5.10)
2. Vital sign measurements (Section 5.12.7)
3. Continuous 12-lead ECG monitoring (Section 5.12.6)
4. Oxygen saturation levels (Section 5.12.6)
5. Collection of blood samples for pharmacokinetic assessment (Section 5.13)
6. Assessment of bupivacaine toxicity (Section 5.12.8.1)
7. Wound healing assessments (Section 5.12.8.2)
8. Adverse events (Section 6)

Other relevant information regarding the subject's condition, as determined by the investigator will be recorded.

5.11.3.1.4. Postoperative Days 3 and 4

The following procedures will be performed and documented on postoperative Days 3 and 4:

1. Concomitant medications/procedures (Section 5.10)
2. Vital sign measurements (Section 5.12.7)
3. Collection of blood samples for pharmacokinetic assessment (Section 5.13)
4. Assessment of bupivacaine toxicity (Section 5.12.8.1)

5. Wound healing assessments (Section 5.12.8.2)
6. Adverse events (Section 6)

Other relevant information regarding the subject's condition, as determined by the investigator will be recorded.

5.11.4. Outpatient Follow-up Period (Day 5 through Day 30)

5.11.4.1. Day 5

The following procedures will be performed and documented on postoperative Day 5:

1. Concomitant medications/procedures (Section 5.10)
2. Vital sign measurements (Section 5.12.7)
3. Collection of blood sample for 96-hour pharmacokinetic assessment (Section 5.13)
4. Wound healing assessments (Section 5.12.8.2)
5. Adverse events (Section 6)

5.11.4.2. Day 7 (± 1 day)

The following procedures will be performed during the Day 7 follow-up visit:

1. Concomitant medications/procedures (Section 5.10)
2. Vital sign measurements (Section 5.12.7)
3. Wound healing assessments (Section 5.12.8.2)
4. Adverse events (Section 6)

5.11.4.3. Day 15 (± 3 days)

The following procedures will be performed during the Day 15 follow-up visit:

1. Concomitant medications/procedures (Section 5.10)
2. Vital sign measurements (Section 5.12.7)
3. Wound healing assessments (Section 5.12.8.2)
4. Adverse events (Section 6)

5.11.4.4. Day 30 (± 3 days) End of Study

The following procedures will be performed during the Day 30 follow-up visit:

1. Concomitant medications/procedures (Section 5.10)
2. Vital sign measurements (Section 5.12.7)
3. Wound healing assessments (Section 5.12.8.2)
4. Adverse events (Section 6)

After all Day 30 procedures are completed the subject may be discharged from the study. As described in Section 6.4, any adverse event that is ongoing at the Day 30 follow-up visit will be followed to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause (ie, concurrent condition or medication) or, in the opinion of the investigator, further evaluation is not warranted.

5.12. Demographic and Safety Assessments

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

5.12.1. Medical History

During the screening period, the investigator or qualified designee will obtain a medical history that includes relevant diagnoses and/or procedures/therapies with onset/resolutions dates.

Medical history will be updated with any relevant information before the surgical procedure on Day 1.

5.12.2. Physical Examination

During the screening visit, the investigator or qualified designee will perform a complete physical examination (by body system) on each subject. Height and body weight will be measured and recorded at screening.

5.12.3. 12-Lead Electrocardiogram

During the screening period, subjects will have a 12-lead electrocardiogram (ECG) performed.

A qualified physician will interpret, sign, and date the ECGs. Electrocardiogram assessments must be 'within normal limits' or interpreted as 'abnormal, not clinically significant' for the subject to be included in the study. ECG findings will be documented as normal; abnormal, clinically significant; or abnormal, not clinically significant. The investigator or qualified designee must sign and date the ECG, thereby acknowledging review of ECG results.

5.12.4. Clinical Laboratory Testing

During the screening visit, blood and urine samples will be collected for local clinical laboratory testing as shown in Table 2.

Table 2: Clinical Laboratory Parameters

Hematology	Clinical Chemistry	Urinalysis
Hematocrit	Blood urea nitrogen	Specific gravity
Hemoglobin	Creatinine	Ketones
Red blood cell count	Total bilirubin	pH
Red blood cell morphology	Alanine aminotransferase (ALT)	Protein
White blood cell count	Aspartate aminotransferase (AST)	Blood
Neutrophils	Alkaline phosphatase	Glucose
Lymphocytes	Sodium	
Monocytes	Potassium	
Basophils	Calcium	
Eosinophils	Chloride	
Platelets	Phosphate	
	Serum bicarbonate	
	Uric acid	
	Total cholesterol	
	Total protein	
	Glucose	
	Triglycerides	
	Albumin	

The investigator or qualified designee will evaluate each laboratory value for clinical significance. A subject with a clinically significant laboratory value should be followed until there is a satisfactory resolution of the abnormality, or until the subject's condition has stabilized. The investigator or qualified designee must sign and date laboratory reports acknowledging review of laboratory results.

5.12.5. Pregnancy Testing

All women of child-bearing potential will have a serum pregnancy test at screening and a urine pregnancy test (dipstick) before surgery on Day 1. Results must be available before the surgical procedure on Day 1. Subjects with positive results at screening or Day 1 will be excluded from participating in the study.

5.12.6. Monitoring for Signs of Bupivacaine Toxicity in the Immediate Postoperative Period

On Day 1, subjects will be monitored for signs/symptoms of bupivacaine toxicity as follows:

- Continuous ECG monitoring (via Holter monitor) set up prior to surgery to allow monitoring from Time 0 through 24 hours or longer, if clinically indicated.
- Heart rate and respiratory rate: Continuously from Time 0 through 12 hours or longer, if clinically indicated. Record values every 15 minutes through Hour 3 and then every hour through Hour 12. Abnormal values will be recorded as an adverse event.
- Oxygen saturation via pulse oximetry: Continuously from Time 0 through 12 hours or longer, if clinically indicated. Record values every 15 minutes through Hour 3 and then every hour through Hour 12. Abnormal values will be recorded as an adverse event.

- Blood pressure (systolic/diastolic): Monitor every 15 minutes from Time 0 through Hour 3 and record. Then monitor each hour through Hour 12 and record. Abnormal values will be recorded as an adverse event.
- Body temperature: Monitor according to the investigator's standard practice and in keeping with hospital policy.
- AEs associated with bupivacaine toxicity (Section 5.12.8.1).

5.12.7. Vital Signs

Blood pressure (systolic/diastolic), respiratory rate, heart rate and body temperature will be assessed during the screening period, at baseline (before surgery on Day 1), and on the Day 5, Day 7, Day 15, and Day 30 follow-up visits. During the inpatient period, vital signs will be assessed as shown in Table 3.

Table 3: Vital Sign Assessments During the Inpatient Period (Day 1 through Day 4)

Parameter	**Time Point (+/- 5minute window up to and including hour 3 and then a +/- 15 minute window for all remaining time points)**
Heart rate	Continuously from Time 0 through 12 hours (record every 15 minutes through Hour 3 then every hour through Hour 12) and at 18, 24, 36, 48, and 72 hours after Time 0 and record.
Respiratory rate	Continuously from Time 0 through 12 hours (record every 15 minutes through Hour 3 then every hour through Hour 12) and at 18, 24, 36, 48, and 72 hours after Time 0 and record.
Diastolic/systolic blood pressure	Every 15 minutes starting at Time 0 and continuing through Hour 3 and every hour through Hour 12, and at 18, 24, 36, 48, and 72 hours after Time 0. Record each value.
Body temperature	According to the investigator's standard practice and in keeping with hospital policy

5.12.8. Adverse Events of Interest

5.12.8.1. Adverse Events Associated with Bupivacaine Toxicity

The subject will be asked if he/she has had any 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 (as applicable) at the following time points after Time 0 (or more frequently if needed): 0.5, 1 , 2 , 3, 4 5, 6, 7, 8, 9, 10, 11, 12 hours ±15 minutes and then 15, 18, 24, 36, 48, and 72 hours (±1 hour).

5.12.8.2. Wound Healing

5.12.8.2.1. Inpatient

Each day during the inpatient period (Day 1 through Day 4), the investigator or qualified designee will inspect the surgical wound site for the following signs of wound infection and dehiscence:

- Discharge or leakage of fluid
- Redness or inflammation spreading from the edges of the wound
- Warmth in the area around the wound
- Swelling in the area around the wound
- Separation of the edges of any part of the wound

The subject will also be asked if he/she has wound pain or soreness in addition to the discomfort experienced following surgery.

5.12.8.2.2. Outpatient

During the outpatient follow-up evaluations on Day 5, Day 7, Day 15, and Day 30, the subject will be asked the following questions to evaluate for signs of wound infection and wound dehiscence:

1. Have you noticed problems with the site of the hernia repair surgery since we last spoke?
2. Have you noticed any of the following at the site of the hernia repair since we last spoke?
    - Any discharge or leakage of fluid
    - Pain or soreness in addition to the discomfort experienced following the operation
    - Redness or inflammation spreading from the edges of the wound
    - Warmth in the area around the wound
    - Swelling in the area around the wound
    - Separation of the edges of any part of the wound

In addition, have any of the following occurred:

- Have you been to a health care provider about the wound
- Have you been prescribed antibiotics for an infection in the wound
- Have you been admitted to a hospital with an infection of the surgical wound

5.13. Pharmacokinetic Assessments

Blood samples will be collected for the determination of pharmacokinetics at the following time points: 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. (There is a +/- 5 minute time window for the PK time points up to and including 5 hours after time 0 and a +/- 15 minute time window for the remaining time points). Time 0 is the time

when the first INL-001 bupivacaine HCl collagen-matrix is implanted or the time of the Marcaine 0.25% injection. Approximately 70 mL of blood will be drawn from each subject for the PK analysis.

Detailed procedures for collection, handling and storage of collected pharmacokinetic samples are provided in the PK lab manual.

5.14. Efficacy Assessments

Efficacy of INL-001 will not be assessed during this study.

5.15. End of Study

The end of study is when the last subject completes the Day 30 end of study visit.

5.16. Discussion and Justification of Study Design

This study is designed to compare the pharmacokinetics of INL-001 to the reference drug, Marcaine 0.25%. This study will also evaluate the safety of INL-001, particularly with respect to any potential cardiac and neurological effects of INL-001 in subjects undergoing hernioplasty.

Both components of the INL-001 implant (collagen and bupivacaine) have been in clinical use worldwide for several decades. The INL-001 implant is a Type I collagen matrix (25 cm^2) with homogeneously dispersed bupivacaine HCl 100 mg that is being developed for postoperative analgesia. It has been demonstrated that INL-001 provides subjects with pain relief at the surgical site without the adverse effects from elevated systemic bupivacaine levels that have been associated with local nerve block or incisional infiltration.

The purpose of this additional pharmacokinetic study is to further characterize the pharmacokinetics of the INL-001 to-be-marketed formulation relative to the reference listed drug (Marcaine 0.25%) and to collect additional INL-001 safety data, with particular emphasis on signs and symptoms of bupivacaine toxicity.

5.17. Appropriateness of Measures

Standard statistical, clinical, and laboratory procedures will be utilized in this study.

6. ADVERSE EVENTS

Throughout the study, the investigator will monitor each subject for evidence of investigational drug intolerance and for the development of clinical and/or laboratory evidence of an AE. An AE assessment will be made by the investigator on a routine basis throughout the study.

All AEs that occur during the course of the study must be reported in detail on the subject's chart (source document), appropriate eCRFs, and on any other report form required by national law.

6.1. Definitions

6.1.1. Adverse Event

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered an investigational drug and which does not necessarily have a causal relationship with the drug. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational drug, whether or not the event is considered causally related to the use of the drug. Such an event can result from use of the investigational drug as stipulated in the protocol or labeling of the investigational drug. Any worsening of a pre-existing condition or illness is considered an AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be clinically significant AEs.

A treatment-emergent AE is defined as any AE with onset or worsening reported by a subject from the time the investigational drug is implanted until completion of or discharge from the study (see Section 4.3 for details regarding premature discontinuation).

6.1.2. Serious Adverse Event

Any AE that results in 1 or more of the following is considered a serious adverse event (SAE):

1. Death - Includes death of a fetus due to miscarriage/spontaneous abortion and elective abortion in the subject.
2. Life Threatening Situation - The subject was at immediate risk of death at the time of the event. It does not refer to the hypothetical risk of death if the AE was more severe or was to progress.
3. Inpatient Hospitalization - This includes any new hospital admission during the study or prolongation of an existing hospitalization. The following are not considered serious due to inpatient hospitalization:
    a. Trips to the ER that do not include a hospital admission
    b. Optional admission not associated with a precipitating medical AE (eg, cosmetic surgery)
    c. Admission for treatment of a pre-existing condition that has not worsened or had an increase in severity or frequency (eg, cataract surgery)
    d. Pre-planned treatments or surgical procedures noted in the baseline source documentation
4. Persistent or Significant Disability/Incapacity - Any AE having an outcome that is associated with a substantial disruption of the ability to carry out normal life functions. This includes the inability to work. This is not intended to include transient, interruptions of daily activities.
5. Congenital Anomaly/Birth Defect in a child of the subject.
6. Other Medically Important Events - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse

event when, based upon medical judgment, they may jeopardize the subject and/or may require intervention to prevent one of the outcomes listed in 1 through 5 above.

If any serious, life-threatening, or fatal adverse event occurs whether related to investigational drug or not, the investigator must notify Innocoll Pharmaceuticals within 24 hours by entry into the eCRF as an SAE and/or telephone, facsimile, email (see Section 6.5).

6.2. Adverse Event Severity

The severity of the adverse event will be graded using the following definitions:

- Mild - The adverse event is transient and easily tolerated by the subject.
- Moderate - The adverse event causes the subject discomfort and interrupts the subject's usual activities.
- Severe - The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

6.3. Relationship to Investigational Drug

The investigator must record the causal relationship of each adverse event in the eCRF, and on the serious adverse reporting form (if applicable). An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to an adverse event.

- Related: There is evidence to suggest a causal relationship between the drug and the adverse event.
- Not related: An adverse event is due to underlying or concurrent illness or effect of another drug or event and is not related to the study drug (eg, has a more likely alternate etiology and / or a temporal relationship does not suggest a causal relationship).

6.4. Adverse Event Collection Period

All (serious and non-serious) adverse events, whether elicited during study visits or spontaneously reported by the subject, that occur from the time the subject signs the study-specific informed consent form until completion of or discharge from the study will be collected.

Any AE will be followed to a satisfactory resolution until it becomes stable or until it can be explained by another known cause (ie, concurrent condition or medication) or, in the opinion of the investigator, further evaluation is not warranted. All findings relevant to the final outcome of an AE will be reported in the subject’s medical record.

6.5. Serious Adverse Event Reporting

In the event of an SAE, whether related to the investigational drug or not, the investigator will notify Innocoll Pharmaceuticals within 24 hours of being made aware of the SAE:

Medpace Clinical Safety

Medpace SAE hotline – USA:

Telephone: +1-800-730-5779, ext. 2999 **or** +1-513-579-9911, ext. 2999

Facsimile: +1-866-336-5320 **or** +1-513-579-0444

e-mail: medpace-safetynotification@medpace.com

All serious adverse events that the investigator considers related to study drug occurring after the study closes must be reported to the sponsor.

6.6. Sponsor Reporting Requirements to Regulatory Authorities

Adverse event reporting, including reporting of suspected unexpected serious adverse drug reactions (SUSARs), will be carried out in accordance with applicable local regulations.

6.7. Exposure During Pregnancy

An exposure during pregnancy (also referred to as exposure in-utero [EIU]) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to the investigational drug (maternal exposure).
2. A male has been exposed, either due to treatment or environmental, to the investigational drug prior to or around the time of conception and/or is exposed during his partner's pregnancy (paternal exposure).

If any study subject is found to be pregnant during the study the investigator must submit EIU information to Innocoll Pharmaceuticals within 24 hours of awareness of the pregnancy, irrespective of whether an adverse event has occurred.

Follow-up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. Innocoll Pharmaceuticals will follow the pregnancy until completion or until pregnancy termination (eg, induced abortion).

7. PROTOCOL DEVIATIONS

When a variation from the protocol is deemed necessary for an individual subject, the investigator or other physician in attendance must contact the Innocoll Pharmaceuticals designee listed below:

For medical issues contact:

Thomas Thompson, MD
Medpace, Inc.
Cell: +1.919.602.5726
E-mail: t.thompson1@medpace.com

For non-medical issues contact:

Suzanne Wilson
Innocoll Pharmaceuticals
Telephone Office: +1 267 324 3260
Mobile: +1 267 432 1003
E-mail: swilson@innocoll.com

Such contact with the Innocoll Pharmaceuticals designee must be made as soon as possible to permit a decision as to whether or not the subject is to continue in the study. The deviation from the protocol will be authorized only for that subject and will be documented in writing by both parties.

8. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

8.1. Statistical and Analytical Plans

8.1.1. Analysis Populations

8.1.1.1. Randomized Population

The randomized population will consist of all subjects who receive a randomization number, regardless of whether or not they receive test article.

8.1.1.2. Safety Population

The safety population will consist of all subjects who receive INL-001 bupivacaine collagen-matrix implant or Marcaine 0.25% infiltration. Subjects will be analyzed according to the treatment they actually receive.

8.1.1.3. Pharmacokinetic Population

The PK population will consist of all subjects who receive INL-001 bupivacaine collagen-matrix implant or Marcaine 0.25% infiltration and have at least 1 post-implantation/infiltration blood sample obtained. Subjects will be analyzed according to the treatment they actually receive.

8.1.1.4. Per Protocol Pharmacokinetic Population

The PK population will consist of all subjects in the pharmacokinetic population who have no major PK-related protocol deviations, and have sufficient data to calculate the Cmax, AUC0-∞, and AUC0-tlast for INL-001 or Marcaine. Subjects will be analyzed according to the actual treatment they receive.

8.1.1.5. Efficacy Population

Efficacy was not assessed in this study.

8.1.2. Safety Variables

The following variables are safety endpoints:

- Clinical laboratory assessments (screening only)
- ECG (screening and continuous ECTG monitoring for at least 24 hours pre and post administration of study drug
- Oxygen saturation levels
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature)
- Adverse events: Mapped to preferred term using the Medical Dictionary for Regulatory Activities (MedDRA)

- Special AEs related to bupivacaine toxicity and wound healing

8.1.3. Pharmacokinetic Variables

The following pharmacokinetic parameters will be assessed when possible:

- Maximum (peak) plasma concentration (Cmax)
- Time to maximum (peak) plasma concentration (Tmax)
- Lag-time (tlag)
- Terminal half-life (t½z)
- Terminal phase rate constant (λz)
- Area under the plasma concentration-time curve (AUC) from Time 0 to last time of last quantifiable plasma concentration (AUC0-last)
- AUC from Time 0 to infinity (AUC0-∞)
- Percentage extrapolation (100x[AUC0-∞-AUC0-last]/AUC0-∞)

8.1.4. Efficacy Variables

Efficacy was not assessed in this study.

8.2. Statistical Methodology

8.2.1. Safety Analyses

The Medical Dictionary for Regulatory Activities (MedDRA Version 18) will be used to classify all AEs with respect to system organ class (SOC) and preferred term (PT). A treatment-emergent adverse event (TEAE) will be defined as any AE that occurred after implantation/infiltration.

An overview of AEs will be provided that summarizes subject incidence of all TEAEs, serious TEAEs, test article-related TEAEs, test article-related serious TEAEs, and TEAEs leading to discontinuation of treatment (ie, removal of the test article).

The number and percentage of subjects that experienced 1 or more TEAEs, serious TEAEs, TEAEs related to test article, or TEAEs leading to discontinuation of treatment will be summarized for by SOC, PT, age group, and treatment group.

Summaries will be provided by maximum severity for the number and percentage of subjects with TEAEs and for subjects with test article-related TEAEs by system organ class, preferred term, age group, and treatment group.

Special AEs, including AEs related to bupivacaine toxicity and AEs related to wound healing, will be summarized by age and treatment group.

Descriptive statistics will be presented by age and treatment group for each vital sign parameter for the actual and change from prior to surgery on Day 1 to each follow-up visit. Oxygen saturation levels will be listed and summarized. Clinical laboratory test findings and ECG data will be listed by age group for each subject.

8.2.2. Pharmacokinetic Analyses

Individual plasma concentrations of bupivacaine will be tabulated for each scheduled sampling time and summarized descriptively using the arithmetic mean, associated standard deviation (SD) coefficient of variances (CV %), geometric mean, median, minimum and maximum. All concentrations below the lower limit of quantification (LOQ) will be set to zero for the purpose of calculating descriptive statistics.

Individual plasma concentration-time profiles of bupivacaine will be plotted both on a semi-logarithmic and a linear scale. The mean plasma concentration-time profile and SD will also be presented graphically.

Actual blood sampling times for bupivacaine will be converted to a time from Time 0 (elapsed time). Individual elapsed times will be used in the PK analysis.

Pharmacokinetic parameters of bupivacaine will be listed for each subject. A descriptive summary for each parameter will include arithmetic mean, SD, CV (%), geometric mean, median, minimum and maximum.

Data permitting, the tlag, Cmax, Tmax, t1/2z, λz, AUC0-last, and AUC0-∞ will be assessed.

The Cmax and Tmax will be obtained directly from the concentration-time data. Where there are multiple identical maximum concentrations in a single profile, the Cmax value is defined as the first temporal occurrence. The tlag will be taken as the time of occurrence of the first quantifiable plasma bupivacaine concentration.

AUC0-last will be calculated using the linear trapezoidal rule from predose to the last quantifiable plasma concentration.

AUC0-∞ will be calculated according to the following equation:

$$AUC_{0-\infty} = AUC_{0-last} + \left(\frac{C_{last}}{\lambda_z} \right)$$

Where Clast is the last quantifiable concentration.

For the purpose of calculating AUC0-last, when 2 consecutive plasma concentrations below the LOQ are encountered after Tmax, all subsequent values will be excluded from the analysis. When embedded missing values occur, they will be excluded from the analysis. Quantifiable concentrations at predose, if any will be set to zero.

The proportion of AUC0-∞ due to extrapolation (AUCextr) will also be calculated, expressed as a percentage.

The terminal phase rate constant (λz) will be estimated by linear regression on the terminal phase of the log concentration-time profile. The number of data points included in the regression will be determined by visual inspection. A minimum of 3 data points in the terminal phase, excluding Cmax will be required to estimate λz.

The t1/2z will be calculated as:

$$t_{1/2,z} = \frac{log_e(2)}{\lambda_z}$$

The relative bioavailability (AUC0-last, AUC0-∞ and Cmax) of the INL-001 bupivacaine collagen-matrix implant (300 mg) will be calculated with respect to the Marcaine 0.25% (175 mg) infiltration using an ANOVA model with a term for treatment. The analysis of variance (ANOVA) model will be run on the dose-normalized natural log transformed values. The least squares means and the standard error values from the analyses will be used to construct the 90% confidence intervals for the relative bioavailability evaluations. The relative bioavailability will be calculated as:

$$F_{rel} = \frac{AUC_{test}}{AUC_{standard}} * \frac{Dose_{standard}}{Dose_{test}}$$

Test=INL-001; standard=Marcaine 0.25%

These analyses will be performed on the Per Protocol PK Population.

8.2.3. Efficacy Analyses

Efficacy will not be not assessed in this study.

8.2.4. Sample Size

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

9. ETHICS

9.1. Independent Ethics Committee or Institutional Review Board

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent, and all other forms of subject information related to the study (eg, advertisements used to recruit subjects) and any other necessary documents be reviewed by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB). IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of investigational drug shipment to a study site. Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design.

9.2. Ethical Conduct of the Study

The study will be conducted in accordance with GCP guidelines and the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/). At appropriate intervals, the clinical monitor will visit the site during the clinical study and assure that the investigator's obligations are being fulfilled.

Trial documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated-marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. For Phase 4 studies in countries in the ICH regions and for countries not in ICH Regions, trial documents should be retained for the length of time local GCP guidelines or law require. If there are no local laws, the site should retain the file for 5 years after completion of the study. Records include the Confidential Follow-up Forms and other documents such as informed consents, lab reports and other source documents, drug accountability forms, Ethics Committee approvals, protocols, and eCRFs.

9.3. Subject Information and Consent

For all investigators participating in the study, the study protocol and consent form must be approved by the investigator's Institutional Review Board/Independent Ethics Committee and a copy of the approved consent form must be supplied to Innocoll Pharmaceuticals. The subject will be asked to read the consent form or have the form read to him/her. If the subject decides to participate in the study, the subject will be asked to sign and date the form as evidence of consent. Each subject must voluntarily sign and date a consent form before participating in this study. It is the obligation of the investigator or his representative to explain the nature of the study to the subject. The investigator must document in the subject's medical chart that the subject has signed a consent form to participate in an investigational trial, a copy of the signed and dated consent form should be given to the subject or his/her representative, and the original should be retained with the subject's study records. The subjects may withdraw consent at any time throughout the course of the trial. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in the study.

The ICF will provide the new requirement as per 21CFR50.25(c) and will include the specific statement that refers to the trial's description on www.clinicaltrials.gov.

For investigators in the United States, the privacy protection of individually identifiable health information (Protected Health Information [PHI]) became a requirement under the Privacy Rules of the Health Insurance Portability and Accountability Act (HIPAA) effective April 14, 2003. Protected Health Information (eg, results of tests, exams and medical records etc.) generated during clinical studies may be communicated amongst several parties in generating final study reports. Accordingly, prior to a subject participating in a clinical study he must authorize the use and disclosure of his PHI by signing an authorization form.

PHI authorization must be approved by the investigator's Institutional Review Board or Privacy Board and a copy of the authorization form must be supplied to Innocoll Pharmaceuticals. The subject will be asked to read the PHI authorization form or have the forms read to him/her. If the subject decides to participate in the study, the subject will be asked to sign and date the form as evidence of consent. Each subject must voluntarily sign and date a PHI authorization before participating in this study. A designated and legally authorized representative may also sign and date the PHI authorization when necessary. The investigator will document in the subject's medical chart that the subject has signed a PHI authorization form to participate in an investigational trial, a copy of the PHI authorization, if not contained in the informed consent, will be given to the subject or his representative, and the original will be retained with the subject's study records.

10. SOURCE DOCUMENTS AND CASE REPORT FORMS COMPLETION

10.1. Source Documents and Access to Source Data/Documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 GCP, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of Innocoll Pharmaceuticals' study, each site will permit authorized representatives of the sponsor's, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source documents are all information, original records of clinical findings, observations, or other activity in a clinical trial necessary for reconstruction and evaluation of the trial. Examples of these original documents and data records include, but not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, x-rays, and subject files and records kept at the pharmacy , at the laboratories involved in the clinical trial.

All source documents and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Adverse events must be graded, assessed for severity and causality and reviewed by the site Principal Investigator or designee.

10.1. Electronic Case Report Forms (eCRFs) and Data Handling

Innocoll Pharmaceuticals will provide an Electronic Data Capture (EDC) system for this study. This system will be used to transmit the information collected in the performance of this study to Innocoll and to governmental agencies. eCRF data should be completed and available for review by Innocoll personnel or representative within a reasonable period of time after completion of each study visit.

Data entries will be corrected by changing the entry in the EDC system. Any changes or corrections to eCRF data will be electronically tracked and will include the reason for correction, who made the correction and the date/time stamp when the correction was made within the audit trail of the EDC system. The investigator will review the eCRFs for completeness and accuracy and electronically sign and date the eCRF data where indicated. Innocoll personnel or representatives will review eCRFs periodically for completeness and acceptability. The investigator will be provided with complete electronic copies of the data for his/her files at the conclusion of the study.

11. QUALITY CONTROL AND COMPLIANCE

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and applicable regulatory requirements. Reports will be submitted to Innocoll Pharmaceuticals on monitoring activities.

The investigators will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

Data management will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the sites(s) for clarification/resolution.

12. USE OF INFORMATION

All information concerning INN-CB-022 and Innocoll operations, such as Innocoll patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by Innocoll and not previously published, is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Innocoll in connection with the development of INL-001. This information may be disclosed as deemed necessary by Innocoll. To allow the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide Innocoll with complete test results and all data developed in this study.

This confidential information shall remain the sole property of Innocoll Pharmaceuticals, shall not be disclosed to others without the written consent of Innocoll, and shall not be used except in the performance of this study.

13. COMPLETION OF THE STUDY

The investigator will complete this study in satisfactory compliance with the protocol within the timeframe allotted in the financial contract. Delays in the completion and/or reporting of the study beyond this time must be mutually agreed upon in writing by both the investigator and Innocoll. It is agreed that, for reasonable cause, Innocoll may terminate this study prematurely, or the investigator may terminate participation in the study, provided that written notice is submitted at a reasonable time in advance of the intended termination.

14. INVESTIGATOR'S AGREEMENT

I have read the INN-CB-022 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Printed Name of Investigator

Signature of Investigator

Date

15. LIST OF REFERENCES

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