Clinical Study Protocol

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of a 300-mg Dose of the INL-001 (Bupivacaine Hydrochloride) Implant in Patients Undergoing Abdominoplasty

Study Number:	INN-CB-024
Test Investigational Medicinal Product (Study Drug):	INL-001 (bupivacaine hydrochloride) implant
Phase:	3
IND Number:	77,127
Protocol Approval Date:	09 June 2021
Sponsor:	Innocoll Pharmaceuticals Limited Unit 9, Block D Monksland Business Park Monksland Athlone Co. Roscommon N37 VW42 Ireland Tel: 353-90-648-6834
Monitor:	Lotus Clinical Research, LLC 100 W California Boulevard Unit #25 Pasadena, California 91105 USA Office: 626-568-8727

Confidentiality Statement

AMENDMENT HISTORY

The protocol for Study INN-CB-024 (original protocol dated 29 January 2021) has been amended and reissued as follows:

Original	29 January 2021
Amendment 01	19 May 2021
Amendment 02	09 June 2021

SUMMARY OF CHANGES
AMENDMENT 02

The primary purpose of this amendment is to address:

- collecting blood samples and performing electrocardiography (ECG) when a patient has systemic bupivacaine toxicity
- assessment of adverse events related to the surgical wound

Revisions were made to the sections of the protocol as indicated below.

CLINICAL STUDY PROTOCOL SYNOPSIS

The protocol synopsis was revised to reflect changes made to the main body of the protocol.

3 STUDY DESIGN

The protocol was changed to explain that blood samples for bupivacaine concentrations will be collected and 12-lead ECG will be performed **at any time** that a patient is determined to have systemic bupivacaine toxicity—not just at the discretion of the investigator.

7 ASSESSMENT OF SAFETY

With regard to adverse events related to the surgical wound (ie, wound healing), the protocol was changed to indicate that certain listed signs and symptoms (5 of the 9), if exhibited by a patient, will always be recorded as an adverse event(s), whereas others listed will be assessed as an adverse event(s) at the discretion of the investigator/subinvestigator.

SUMMARY OF CHANGES
AMENDMENT 01

The primary purpose of this amendment is to:

- clarify the use of rescue pain medication (opioid and acetaminophen)
- add an exclusion criterion explaining that, in the opinion of the investigator, a patient having any other condition would warrant exclusion from the study
- add clarifications and make minor corrections as warranted

Revisions were made to the sections of the protocol as indicated below.

CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS

The sponsor's medical expert was changed.

CLINICAL STUDY PROTOCOL SYNOPSIS

The protocol synopsis was revised to reflect changes made to the main body of the protocol.

LIST OF ABBREVIATIONS

The list was revised accordingly.

1 INTRODUCTION AND BACKGROUND

A reference to the XARACOLL prescribing information was added where the product's indication and dose are described.

3 STUDY DESIGN

The duration of study participation for each patient was changed from a maximum of 75 (±4) days to a maximum of 75 (±3) days.

The use of rescue medication for pain was clarified as follows: As needed, a patient may receive rescue medication for pain at any time during the inpatient and outpatient portions of the study as described; however, these medications should **not** be taken concomitantly (ie, not at the same time).

The following was added for clarity as a footnote to Table 1 regarding electrocardiography (ECG) and blood sampling in the case of signs and/or symptoms suggestive of systemic bupivacaine toxicity: At any time that a patient is determined to be exhibiting signs and/or symptoms suggestive of systemic bupivacaine toxicity, at the discretion of the investigator, a bupivacaine blood sample will be collected and 12-lead ECG will be performed. The patient may be treated at the discretion of the investigator, including obtaining repeat bupivacaine blood concentrations, 12-lead ECG [electrocardiography], or removal of the implants.

4 SELECTION AND WITHDRAW OF PATIENTS

An inclusion criterion regarding methods of birth control was clarified to include the use of an intrauterine device (IUD).

An exclusion criterion was added explaining that, in the opinion of the investigator, a patient having any other condition would warrant exclusion from the study.

Section 4.3.2 was renamed to correctly reflect that it includes assessment of signs and symptoms potentially indicative of bupivacaine toxicity and the information around Common Terminology Criteria for Adverse Events (CTCAE) was corrected.

5 TREATMENT

The batch/lot numbers, expiry, and manufacturer for the study drugs (INL-001 and placebo) were added.

The use of rescue medication for pain was clarified as follows: As needed, a patient may receive rescue medication for pain at any time during the inpatient and outpatient portions of the study as described; however, these medications may **not** be taken concomitantly (ie, not at the same time).

The following statement was added for clarity: In the case of a suspected unexpected serious adverse reaction (SUSAR), unblinding of the sponsor will be performed according to the safety management plan.

Clarification was added to indicate that the sole responsibility of the Interim Data Monitoring Committee (IDMC) is to calculate the recommended sample size adjustment under prespecified decision rules in accordance with its charter.

7 ASSESSMENT OF SAFETY

The assessment of the severity of an adverse event was corrected to reflect the use of CTCAE.

Clarification was added regarding assessment of signs and symptoms potentially indicative of bupivacaine toxicity, wound grading (using the Southampton Wound Grading System), and wound healing being performed by a physician (ie, the investigator or subinvestigator).

Clarification was added regarding the adverse event assessment of wound-healing−related signs and symptoms.

At the 30-day follow visit, only blood (not urine) samples will be collected for clinical laboratory testing.

Clarification was added that electrocardiograms will be read by a physician (ie, the investigator or subinvestigator).

9 STATISTICAL METHODS

An analysis set was added for **all patients** to indicate the data entered into the electronic data capture system that will be used for the patient disposition displays and may include data from patients who did not meet screening criteria.

As it is defined in the study design sections of the protocol, clarification was added regarding the 2- or 4-hour window around administration of rescue medication for intravenous morphine (2 hours) and oxycodone (4 hours)

The version of the Medical Dictionary for Regulatory Activities (MedDRA) was changed from 21.1 to 18.

For the interim analysis, all decisions will be made on the basis of sum of pain intensity through 24, 48, **and/or** 72 hours (SPI24, SPI48, and/or SPI72). The protocol previously stated "through SPI24, SPI48, **or** SPI72."

For the first sensitivity analysis, clarification was added that the shorter censoring time will be 2 hours for oxycodone and acetaminophen, and 1 hour for intravenous morphine. Clarification was added regarding reason(s) for patient discontinuation.

Additional statistical parameters were listed for the primary analysis.

INVESTIGATOR AGREEMENT

Protocol Dated: 09 June 2021

IND 77,127

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of a 300-mg Dose of the INL-001 (Bupivacaine Hydrochloride) Implant in Patients Undergoing Abdominoplasty

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Telephone: _____

I have read this protocol and agree to conduct this clinical trial as outlined herein. I will ensure that all subinvestigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with Innocoll and any appointed contract research organizations (CROs) during the study. I will adhere to the Declaration of Helsinki and its amendments, the International Council for Harmonisation (ICH) principles of Good Clinical Practice (GCP), including archiving of essential study documents, and all United States Food and Drug Administration (US FDA) regulations (for study centers in the US) or European Directives (for study centers in the European Union [EU]) and other applicable regulations and guidelines of the country in which the study is conducted.

INVESTIGATOR AGREEMENT

Signature of Principal Investigator: _____

Date: _____

Sponsor's Authorized Representative: Gwendolyn E. Niebler, DO
Chief Medical Officer
Innocoll Pharmaceuticals Limited

Signature/Date: Gwendolyn Niebler (Jun 9, 2021 12:15 EDT) Jun 9, 2021

CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS

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CLINICAL STUDY PROTOCOL SYNOPSIS

Study INN-CB-024

Title of Study: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of a 300-mg Dose of the INL-001 (Bupivacaine Hydrochloride) Implant in Patients Undergoing Abdominoplasty

Sponsor: Innocoll Pharmaceuticals Limited

Investigational New Drug (IND) Number: 77,127

New Drug Application (NDA) Number: 209511

Test Investigational Medicinal Product (Study Drug) Dose, Pharmaceutical Form, Route of Administration, and Administration Rate: The test study drug used in this study is the INL-001 [XARACOLL® (bupivacaine hydrochloride) implant] (batch/lot 20002310; expiry September 2022; manufacturer Syntacoll GmbH, Donaustr 24, 93342 Saal/Donau, Germany).

INL-001 contains 300 mg of bupivacaine hydrochloride (HCl) (three 100-mg implants), equivalent to 266.4 mg of bupivacaine, and is implanted in a single administration.

Comparison/Reference Investigational Medicinal Product: The comparison study drug used in this study is the placebo (drug-free/collagen) implant (batch/lot 20000210; expiry September 2022; manufacturer Syntacoll GmbH, Donaustr 24, 93342 Saal/Donau, Germany).

Type of Study (Phase): Efficacy and safety (Phase 3)

Indication: Placement in the surgical site to produce postsurgical analgesia following abdominoplasty

Number of Investigational Centers Planned: Up to 8

Countries Planned: United States (US)

Planned Study Period: The study is expected to start at a time to be determined, with an estimated enrollment period of approximately 6 months, including an interim analysis. Screening to the end of the study for each patient will be a maximum of 75 (±3) days.

Planned Number of Patients: Up to approximately 432 patients will be screened in order to randomize 372 patients to achieve a minimum of 360 patients randomized and treated [180 evaluable patients per treatment group]).

Study Population: Men and women 18-65 years of age

Primary Objective: The primary objective of the study is to evaluate the analgesic effect of treatment (ie, efficacy) with INL-001 implants compared with placebo implants after placement into the surgical site during abdominoplasty.

Secondary Objectives: The secondary objective is to assess the safety and tolerability of INL-001 implants after placement in the surgical site during abdominoplasty.

General Study Design: This is a multicenter, randomized, double-blind, placebo-controlled efficacy and safety study of the INL-001 (bupivacaine HCl) implant, at 300 mg, in patients following abdominoplasty. On the day of surgery (study day 1), eligible patients will be randomly assigned to treatment in a 1:1 ratio to receive either INL-001 (three 100-mg implants

containing a total dose of 300 mg of bupivacaine HCl) or 3 placebo collagen implants. Patients will then undergo abdominoplasty under general anesthesia and have INL-001 or placebo implanted intraoperatively.

The duration of study participation for each patient will be a maximum of 75 (±3) days, consisting of a screening period (up to 45 days before surgery), an inpatient period (preoperative, intraoperative, immediately postoperative) of approximately 4 days, and an outpatient follow-up period (up to 30 days [±3 days] after treatment) including an end-of-study visit. Efficacy assessments will be made through 72 hours after treatment (after implant placement). Posttreatment (time measured from Time 0 [placement of first implant]) safety assessments will be made throughout the study after the informed consent form (ICF) is signed, and as specifically scheduled through 72 hours posttreatment, on day 7 (±1 day) (telephone), on day 15 (±3 days) (clinic visit), and on day 30 (±3 days) (clinic visit). Unless the investigator determines further hospitalization is necessary, the patient will be discharged on the day occurring 72 hours (day 4) after surgery.

During the screening period, all patients will provide informed consent and undergo eligibility and other screening and safety assessments (medical history including review of prior medications, physical examination, urine drug screen, serum pregnancy test for women of childbearing potential, clinical laboratory tests [hematology, chemistry, urinalysis], vital signs measurement, and 12-lead electrocardiography [ECG]). Vital signs include body temperature, pulse, systolic and diastolic blood pressure, respiration rate, and oxygen saturation measured by pulse oximetry. The reason(s) a patient does not meet screening criteria will be recorded, if applicable. Recording of adverse events and concomitant medication use will commence once a patient signs the ICF.

On the day of surgery (day 1), patient eligibility will be reconfirmed before the start of surgery (including medical history, urine drug screen, urine pregnancy test for women of childbearing potential, vital signs), patients will be randomly assigned to treatment with study drug (INL-001 or placebo collagen implant), and adverse events and prior/concomitant medications will be reviewed.

Patients will undergo an abdominoplasty with rectus sheath plication using standard surgical procedures conducted under general anesthesia, with no other local anesthetic used at the surgical site. All patients should undergo an abdominoplasty procedure with an incision that does not extend above the umbilicus. The approach should be anterior. The incision should in general be from one anterior superior iliac spine (ASIS) to the other. The exact incision length may vary depending on the patient's anatomy and the desired cosmetic outcome. All packs/gauze should be removed and adequate hemostasis must be achieved prior to skin closure. Surgical drains should be placed at the discretion of the surgeon and their use recorded. Ancillary procedures (eg, liposuction, breast augmentation/reduction) are prohibited.

The time of the first placement of study drug (placement of first implant) is considered Time 0 and will be recorded. Use of analgesic and all medications during surgery will be recorded. At the surgeon's discretion, if a significant surgical/medical complication is encountered during

surgery, study drug will not be implanted and the patient will be considered enrolled but not treated.

After surgery, patients will be transferred to a postanesthesia care unit (PACU) or other postoperative recovery area for monitored observation. The times patients enter and are discharged from the PACU will be recorded to calculate time to discharge from the PACU. Patients will be monitored with pulse oximetry starting in the PACU through 24 hours posttreatment. After leaving the PACU (time in PACU to be at the discretion of the investigator), patients will be placed in the postoperative unit or clinical research unit for domiciled observation. Vital signs, including body temperature, pulse, systolic and diastolic blood pressure, respiration rate, and oxygen saturation measured by pulse oximetry, will be assessed at multiple time points through discharge, and in the clinic on days 15 and 30; 12-lead ECG will be done on day 30.

Adverse event and concomitant medication information, including use of rescue medication, will be collected throughout the study (inpatient and outpatient). Surgical wound healing assessments will be made at 24, 48, and 72 hours after Time 0 and on days 7, 15, and 30 using the specified list and assessed for and recorded as adverse events as appropriate. The Southampton Wound Grading System will also be completed 72 hours posttreatment/prior to discharge (±4 hours) and on days 15 and 30. Assessment for signs and symptoms potentially indicative of systemic bupivacaine toxicity will be made after Time 0 at the following time points: 0.5, 1, 2, 3, and 4 hours (each ±15 minutes), and 5, 7, 9, 12, 15, 18, 24, 48, and 72 hours (each ±1 hour), and days 7 (±1 day) and 15 (±3 days) using the specified list and assessment made and recorded as adverse events as appropriate.

At any time that a patient is determined to have systemic bupivacaine toxicity, a bupivacaine blood sample will be collected and 12-lead ECG will be performed. Systemic bupivacaine toxicity will be recorded as an adverse event. The patient may be treated at the discretion of the investigator, including obtaining repeat bupivacaine blood levels, 12-lead ECG, or removal of the implants.

After surgery, patient reports of pain intensity using an 11-point numeric pain rating scale (NPRS) will be recorded at multiple time points through 72 hours posttreatment. Scheduled pain intensity scores will be recorded after Time 0 at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 20, 24, 28, 32, 36, 48, and 72 hours. Each assessment prior to hour 10 has a ±15-minute window; each assessment after and including hour 10 has a ±30-minute window. The 0.5-hour and 1-hour NPRS assessments may be omitted if, on the basis of clinical judgement, the patient is not yet awake and alert enough to appropriately answer the NPRS after surgery. Pain intensity assessments scheduled between 2400 (midnight) and 0600 (6 am) may be limited to collection every 4 hours if the patient is sleeping. However, consecutive pain assessments may not be missed, and the hour 12, 24, 48, and 72 posttreatment pain assessments must be completed even if they fall between 2400 (midnight) and 0600 (6 am). A pain intensity score will also be collected before **any** rescue pain medication use.

Patients will be permitted rescue medication to manage breakthrough pain when it occurs. Oral acetaminophen at 1000 mg every 4-6 hours as needed for pain (maximum daily dosage 3000 mg) and/or oxycodone 5-mg tablet(s) may be given (not to exceed 10 mg in a 4-hour period during the inpatient stay). Immediately prior to receiving **any** rescue medication, a pain intensity score must be recorded. If the NPRS score is 4 or less, patients will be discouraged from taking opioid rescue medication; however, rescue medication may be requested and provided at any time. If patients require opioid rescue medication, but are unable to take oral medications, they will be permitted to receive intravenous (iv) morphine (2-3 mg) every 3 hours until they are able to take oral rescue medication. As assessed by the investigator, if a patient's pain is not relieved by oxycodone and/or acetaminophen, the patient is not yet eligible for further treatment with oxycodone and/or acetaminophen, and more than 3 hours have passed since the previous iv morphine dose, a patient may receive a dose of iv morphine (2-3 mg) for pain relief. If the pain remains unrelieved or increases in intensity before additional rescue medication is allowed, additional treatment options will be discussed with the medical monitor.

Following discharge, to report an adverse event, a patient will contact study staff by telephone and report adverse event information, including incidence, duration, and any associated treatment. Patients with pain intensity scores of 4 or more at discharge will be given a written prescription for immediate-release oxycodone at a dosage of 5-10 mg every 4-6 hours as needed as rescue medication for breakthrough pain. Patients prescribed opioid rescue medication will also be permitted to take oral acetaminophen at 1000 mg every 4-6 hours (maximum daily dosage 3000 mg) and/or ibuprofen at 400 mg every 4-6 hours as needed for pain, on an outpatient basis. Patients with pain intensity scores of less than 4 at discharge will be instructed to take oral acetaminophen at 1000 mg every 4-6 hours as needed for pain (maximum daily dosage 3000 mg) and/or ibuprofen at 400 mg every 4-6 hours as needed for pain, on an outpatient basis. Patients who do not receive a written prescription for oxycodone upon discharge will be permitted to request immediate-release oxycodone 5-10 mg if their pain is unrelieved by acetaminophen. Use of opioids, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), or any other medications after discharge from the hospital will be recorded, with data reviewed by study staff at subsequent contacts.

NOTE: As needed, a patient may receive rescue medication for pain at any time during the inpatient and outpatient portions of the study as described; however, these medications should **not** be taken concomitantly (ie, not at the same time).

Method of Randomization and Blinding: Eligible patients will be randomly assigned to treatment in a 1:1 ratio to receive either INL-001 or placebo collagen implants. Patients will not be aware of their treatment allocation and all study staff involved in efficacy and safety assessments will be blinded to treatment assignments until after database lock and release of unblinding randomization codes. Emergency unblinding is allowable if deemed necessary by the investigator, and discussed and agreed with the study medical monitor, for the safety of the patient and will be fully documented and included in protocol deviations. Patients will be stratified by study center and body mass index (BMI) (<30 kg/m^2 and ≥ 30 kg/m^2). In the case of a suspected unexpected serious adverse reaction (SUSAR), unblinding of the sponsor will be performed according to the safety management plan.

Duration of Patient Participation and Maximal Exposure to Study Drug: The duration of study participation for each patient will be a maximum of 75 (±3) days, consisting of a screening period (up to 45 days before surgery), an inpatient period (preoperative, intraoperative, postoperative) lasting 4 days, and an outpatient follow-up period (up to 30 days after treatment [±3 days]) including an end-of-study visit.

End of Study: End of study is defined as the last visit of the last patient.

Plans for Treatment or Care After the Patient Has Ended Participation in the Study: This study includes procedures and assessments through day 30 after implantation of study drug and includes no further treatment after this time point.

Inclusion Criteria: Patients will be eligible for participation in the study if they have provided written informed consent and all of the following inclusion criteria are met before surgery:

(a) Must be a man or woman who is 18-65 years of age.

(b) Has a body mass index of 18-35 kg/m^2.

(c) Must qualify for an abdominoplasty with rectus sheath plication, in the opinion of the surgeon.

(d) Has a planned (nonemergency) abdominoplasty, with an incision that does not extend beyond the umbilicus, to be performed using standard surgical technique under general anesthesia.

(e) If the patient is a woman of childbearing potential, is not lactating or pregnant (negative serum pregnancy test result during screening and a negative urine pregnancy test before surgery [day 1]).

(f) If patient is a woman, any of the following apply:

- is not of childbearing potential (defined as postmenopausal for ≥1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy])
- is practicing at least 1 of the following medically acceptable methods of birth control and agrees to continue with the regimen throughout the duration of the study:
  - —oral, implantable, or injectable contraceptives for 3 consecutive months before randomization
  - —intrauterine device (IUD) for 3 consecutive months before randomization
  - —total abstinence from sexual intercourse (≥1 complete menstrual cycle before the screening visit)
  - —double barrier (condom, sponge, diaphragm,)

(g) Has a physical status classification I (healthy) or II (mild systemic disease) according to the American Society of Anesthesiologists.

(h) Has the ability and willingness to comply with all study procedures including being domiciled for at least 72 hours after surgery and to comply with all study procedures including use of a diary.

(i) Is willing to use only permitted medications throughout the study.

(j) Is willing to use opioid analgesia, if needed.

(k) Must be able to fluently speak and understand English or Spanish and be able to provide meaningful written informed consent for the study.

Exclusion Criteria: A patient will not be eligible for participation in the study if any of the following criteria are met before surgery:

(a) Has a known hypersensitivity to amide-type local anesthetics, fentanyl, morphine, oxycodone, acetaminophen, NSAIDs, or bovine products.

(b) Is scheduled for other significant concurrent surgical procedures (eg, gastrointestinal resection or additional cosmetic procedures concurrent with abdominoplasty).

(c) Has undergone major surgery within 3 months before the scheduled abdominoplasty or plans to undergo another surgical procedure within 30 days after study surgery.

(d) Has used aspirin or aspirin-containing products within 7 days before surgery. Aspirin at a dose of 325 mg or less is allowed for cardiovascular prophylaxis if the patient has been on a stable dosage regimen for 30 days or more before the screening visit.

(e) Has used local anesthetics, systemic steroids, anticonvulsants, alpha-adrenergic agonists, or monoamine oxidase inhibitors (MAOIs) within 10 days before study surgery. Antidepressant medications (eg, selective serotonin re-uptake inhibitors [SSRIs]) will be allowed for depression provided the patient has been on a stable dosage regimen for 30 days or more before screening procedures and intends to remain on the same regimen for the duration of study participation.

(f) Has used an opioid analgesic on an extended daily basis (≥5 mg oral morphine equivalents per day for 3 or more days a week) within 4 weeks before surgery. Patients who, in the opinion of the investigator, may be developing physical dependency or opioid tolerance will be excluded.

(g) Has used any analgesic other than acetaminophen or NSAIDs within 24 hours before surgery that, in the opinion of the investigator, may confound the assessment of pain. Acetaminophen may be used on the day of surgery but is subject to preoperative restrictions for oral intake.

(h) Has any chronic painful condition (eg, fibromyalgia), as determined by the investigator, that may confound the assessment of pain associated with the abdominoplasty procedure.

(i) Chronically uses pain medication other than acetaminophen and NSAIDs or selective cyclooxygenase-2 (COX-2) inhibitors more than 5 times per week within 4 weeks before surgery and cannabinoids used for analgesia within 4 weeks before surgery.

(j) Has a physical or mental condition that, in the opinion of the investigator, may confound the assessment of postsurgical pain after abdominoplasty.

(k) Shows evidence of tolerance or physical dependency to sedative-hypnotic medications.

(l) Has a known or suspected history of drug abuse or substance-use disorder.

(m) Has a urine drug screen (at screening or on day of surgery) positive for drugs of abuse or misuse, with the exception of cannabinoids and amphetamines prescribed or purchased over the counter to manage a condition. Patients reporting or testing positive for past use of cannabinoids will not necessarily be excluded, unless they appear under the influence

of cannabinoids at the time of screening or on the day of surgery, in the judgment of the investigator.

(n) Has liver function test (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) values greater than 3 times the upper limit of normal, or a history of cirrhosis. Patients who, in the opinion of the investigator, have liver function test results of concern should also be excluded.

(o) Has any clinically significant unstable cardiac disease or has evidence of a clinically significant 12-lead ECG abnormality (eg, ventricular hypertrophy, clinically significant arrhythmia at screening, or an implantable cardioverter-defibrillator [ICD]).

(p) Has any clinically significant unstable, neurologic, immunologic, renal, or hematologic disease (eg, uncontrolled diabetes or significantly abnormal laboratory findings) or any other condition (eg, malignancy or active coronavirus disease 2019 [COVID-19] infection) that, in the opinion of the investigator, could compromise the patient's welfare, ability to communicate with the study staff, or otherwise contraindicates study participation.

(q) Has current malignancy and currently receiving systemic chemotherapy or radiotherapy, or cancer diagnosis within 5 years before screening (excluding squamous or basal cell carcinoma of the skin that has been clinically stable and fully excised in a curative procedure).

(r) Has an open workman's compensation claim.

(s) Has participated in a clinical study (investigational or marketed product) within 30 days before surgery.

(t) Has any other condition that, in the opinion of the investigator, would warrant exclusion from the study.

Statistical Considerations

Sample Size Rationale: The sample size was chosen primarily on the basis of previous clinical study data for INL-001 in inguinal hernia repair, but also with the consideration of the results of other bupivacaine-containing products studied in abdominoplasty. Sample size is estimated at 360 patients, with 180 patients per treatment group. The effect size with INL-001 in the combined results of 2 clinical Phase 3 studies in postoperative analgesia after open inguinal hernia repair was 0.525 for sum of pain intensity (SPI) through 24 hours (SPI24). The effect size with INL-001 was 0.25. With the historical SPI through 48 hours (SPI48) effect size of 0.25, 360 evaluable patients will yield a power of at least 66%; however, it is believed that a greater separation between the INL-001 and placebo treatment groups will be observed for abdominoplasty given that postoperative pain is more severe and longer lasting than with inguinal hernia repair, yielding greater power. This is increased to 372 patients to allow for some attrition of patients randomized to those randomized and treated; all randomized and treated patients will be evaluable and included in the modified intent-to-treat (mITT) analyses.

Efficacy Analysis: The SPI (area under the concentration-time curve [AUC] of pain intensity) as measured by the NPRS through various time points up to 72 hours posttreatment will be calculated using the trapezoidal method with NPRS scores and the actual assessment times in hours. The primary efficacy variable will be SPI24, but the same general rules and calculations

will apply for all $SPI_{0\text{-time}}$. For SPI24 calculation, both scheduled and unscheduled values (if available) from Time 0 through 24 hours posttreatment will be used in the calculation. For patients who receive rescue medication, just prior to it being administered, a pain score will be obtained; this will be included in the calculation of the SPI. Pain score(s) for the duration of the rescue efficacy following treatment with an opioid rescue medication will be excluded from the calculation if they are lower than the pain score just prior to rescue medication administration; those that are equal to or higher will be included. This period will be 2 hours following iv morphine and 4 hours following oxycodone.

All efficacy comparisons will be based on the comparison of INL-001 vs placebo. The primary efficacy variable, SPI24, will be analyzed using an analysis of covariance (ANCOVA) model with treatment as the main effect and a covariate for BMI. Summary statistics (sample size, mean, standard deviation [SD], median, minimum, maximum, and 25^{th} and 75^{th} percentiles) will be presented along with the p-values from the ANCOVA model. To account for the interim analysis and potential sample size increase, the method of Cui et al 1999 will be employed. For the final analysis and resulting p-value, the data will be split for those patients included in the interim analysis and those not included in the interim analysis; data from these groups will be analyzed completely independently, then combined using the inverse normal method to test the null hypotheses that there is no difference between the treatment groups. For maximum statistical efficiency, the weights are defined prospectively according to the square root of the planned proportion of participants in the 2 stages, relative to the preplanned total enrollment of 360 patients, as $w_i=\sqrt{0.5}$. The calculation of these weights is fixed and will not be changed due to unblinded data; likewise, in the case of deviations from the planned proportions due to enrollment overrun, the weights will remain fixed. An approach identical to the primary efficacy analysis will be used for each of the continuous key secondary variables and the same statistics will be presented.

For key secondary outcomes of proportions, each proportion, the difference, and 95% confidence intervals (CIs) will be reported; difference will be tested with the 2-proportion Z test (and with the Cui-Hung-Wang [CHW] method applied to account for the interim analysis). In the case of low counts (any expected cell count ≤5), a Fisher's Exact test will be used. All continuous secondary efficacy variables will be summarized with appropriate descriptive statistics (sample size, mean, SD, coefficient of variation [CV], median, minimum, maximum, and 25^{th} and 75^{th} percentiles) and analyzed using ANCOVA models with treatment as the main effect and a covariate for BMI. Summary graphs of efficacy data including total use of opioid analgesia (TOpA) and NPRS scores by treatment group (arithmetic means and standard error [SE]) vs nominal time will be plotted). All categorical efficacy variables will be summarized with counts and proportions and compared by Cochran-Mantel-Haenszel tests (for ordered variables), Pearson chi-squared, or Fisher's exact tests as needed. The time to first use of opioid rescue medication, time to discharge from the PACU, and time to no longer using rescue medication during the study will be summarized using Kaplan-Meier methods. Log rank tests will be used to compare treatment groups. The median time to discharge will be estimated together with the associated 95% CI. Models containing additional blocking factors or covariates may be fit as secondary analyses.

Safety Analyses: Safety variables include assessment of adverse events (including assessment for signs and symptoms of systemic bupivacaine toxicity and assessment of wound healing), clinical laboratory test results, vital signs measurements (including body temperature, pulse, systolic and diastolic blood pressure, respiration rate, and oxygen saturation measured by pulse oximetry), ECG findings, surgical wound grading, and concomitant medications. These analyses will be conducted for the safety population. No formal statistical tests will be performed on safety evaluations.

Multiple Comparisons and Multiplicity: The key secondary efficacy variables will be tested sequentially each at the 0.05 level to control the overall Type-I error rate. Specifically, each key secondary variable will be tested in order. The next key secondary variable will be tested if the prior secondary variable comparison is statistically significant.

Planned Interim Analysis: An interim analysis will be performed when approximately 50% of the initially planned population is evaluable with respect to efficacy. This interim analysis will be performed by unblinded personnel separate from those responsible for the conduct and analysis of the study; all decisions will be made on the basis of SPI24, SPI48, and SPI72. An independent committee will review the data and recommend to the sponsor one of the following: increase the sample size by up to 180 patients or keep the current sample size and continue.

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LIST OF ABBREVIATIONS

Abbreviation	Term
%CV	percentage coefficient of variation
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASIS	anterior superior iliac spine
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	AUC from Time 0 extrapolated through infinity
AUC_{0-last}	AUC from Time 0 through last observed concentration
BMI	body mass index
BSE	bovine spongiform encephalopathy
CBC	complete blood count
CDMS	clinical data management system
CFR	Code of Federal Regulations
CHW	Cui-Hung-Wang (method)
CI	confidence interval
C_{max}	maximum observed plasma concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
COX-2	cyclooxygenase-2
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
EC	European Community
ECG	electrocardiogram/electrocardiography
EOS	end of study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
h	hour(s)
HCl	hydrochloride
IB	Investigator's Brochure
ICD	implantable cardioverter-defibrillator
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Interim Data Monitoring Committee
IND	Investigational New Drug (application)
INN	International Nonproprietary Name
IRB	Institutional Review Board

Abbreviation	Term
ITT	intent-to-treat
IUD	intrauterine device
iv	intravenous(ly)
LAST	local anesthetic systemic toxicity
LOCF	last observation carried forward
LS	least squares
m	minute(s)
MAOI	monoamine oxidase inhibitor
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
mITT	modified intent-to-treat
n	number
NPRS	numeric pain rating scale
NSAID	nonsteroidal anti-inflammatory drug
OTC	over-the-counter
PACU	postanesthesia care unit
POpA	parenteral opioid analgesia
RSI	reference safety information
SAP	statistical analysis plan
SAS	Statistical Analysis Software®
SD	standard deviation
SE	standard error
SOC	system organ class
SOP	standard operating procedure
SPI24, SPI48, SPI72	sum of pain intensity through 24, 48, 72 hours
SSRI	selective serotonin re-uptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
T_{max}	time to maximum observed concentration
TOpA	total use of opioid analgesia
TSE	transmissible spongiform encephalopathy
UDS	urine drug screen
US/USA	United States/United States of America
USP	United States Pharmacopeia
WBC	white blood cell

1 INTRODUCTION AND BACKGROUND

1.1 Background

Management of acute pain is a significant concern in the postsurgical period, with nearly 90% of patients experiencing acute postsurgical pain as reported in a retrospective study (Gan et al 2014). In general, if acute postsurgical pain is not appropriately managed, it can lead to physiologic dysfunction across many organ systems including the central nervous, cardiopulmonary, and immune systems. Inadequately managed acute postsurgical pain can also promote the development of chronic postoperative pain (Gan 2017), which can place a significant burden on the health care system.

Recent efforts to improve acute postsurgical pain management have focused on limiting the use of opioids to reduce the risk for opioid-related adverse events and the risk of developing an opioid addiction. Instead, a multimodal approach to analgesia is used which involves the administration of drugs with a variety of mechanisms of action to improve the effectiveness of analgesia (Chou et al 2016). Infiltration of local anesthetics, such as bupivacaine, at the surgical site has become a common component of multimodal analgesic strategies. However, locally injected bupivacaine hydrochloride (HCl) injection has a short duration of action (4-8 hours) (McGee 2010) that is insufficient to manage acute postoperative pain, which can last for several days depending on the surgery (Svensson et al 2000, Scully et al 2018). In addition, administration of liquid forms of bupivacaine increases the risk for accidental intravascular injection, which can result in local anesthetic systemic toxicity (LAST) which is associated with significant morbidity and mortality (Goyal and Shukla 2012). Therefore, there is an unmet medical need for non-liquid formulations of bupivacaine that can deliver drug overtime into a surgical site postoperatively.

The use of INL-001 addresses this unmet medical need by using an implant to deliver bupivacaine into the surgical site. INL-001 has received marketing approval from the United States (US) Food and Drug Administration (FDA) for use in open inguinal hernia repair and Innocoll is undertaking a development program in order to obtain FDA approval to expand the approved indication for INL-001 to use in soft-tissue surgeries beyond inguinal hernia repair (XARACOLL Prescribing Information 2020, Innocoll Pharmaceuticals Limited). Innocoll is conducting this additional efficacy and safety study with INL-001 in abdominoplasty, which when combined with data from inguinal hernia repair, will serve to describe a range of soft-tissue surgeries for which INL-001 use would be effective and safe.

Abdominoplasty was chosen as the additional soft-tissue surgery “model” for several reasons. Surgical procedures of the abdominal region have been identified as among the most painful soft-tissue surgical procedures, and this pain is often related to the length of the incision site (Chung et al 1997, Chia et al 2002). Abdominoplasty is a common abdominal surgery and has one of the longest incisions among surgical procedures, going from one anterior superior iliac crest to the contralateral anterior superior iliac crest.

In addition, abdominoplasty is a well-established acute pain model that has been demonstrated to be sensitive to demonstrating a drug effect. The open surgical approach and large size of the surgical field with abdominoplasty lends itself to use of a drug-device combination like INL-001. Also, abdominoplasty was also chosen to study because it is considered a more vascular surgery than inguinal hernia repair (O’Dey et al 2004). Vascularity of a surgical site is thought to

influence the potential for systemic absorption of bupivacaine, which can have safety implications. There is a desire to assess safety as related to potential systemic bupivacaine absorption after release of bupivacaine from INL-001. This study in abdominoplasty will allow for an evaluation of the safety of INL-001 in a more vascular soft-tissue surgery.

1.2 Investigational Medicinal Product: INL-001 Implant

The INL-001 implant received marketing approval from the FDA in August 2020. INL-001 [registered as XARACOLL® (bupivacaine hydrochloride) implant] is a single-application drug-device combination product that is comprised of a collagen drug delivery vehicle and the active ingredient, an amide local anesthetic (ie, bupivacaine HCl). It is indicated for use in adults for placement into the surgical site to produce postsurgical analgesia for up to 24 hours following open inguinal hernia repair. The approved dose is 300 mg (three 100-mg implants (XARACOLL Prescribing Information 2020).

The active pharmaceutical ingredient in INL-001, bupivacaine, blocks the generation and the conduction of nerve impulses by increasing the threshold for electrical excitation in the nerve by slowing the propagation of the nerve impulse and by reducing the rate of rise of the action potential (XARACOLL Prescribing Information 2020).

INL-001 utilizes a proprietary collagen-matrix technology composed of a sterile, resorbable, and biodegradable Type I purified bovine collagen-matrix (Angele et al 2004) and the active ingredient, bupivacaine HCl. The Type I collagen in INL-001 is extracted from bovine Achilles tendons obtained exclusively from closed herds in New Zealand that have been certified as transmissible spongiform encephalopathy (TSE) free and negligible for the risk of bovine spongiform encephalopathy (BSE) in accordance with Regulation European Community (EC) No. 999/200 (Ministry for Primary Industries/Biosecurity New Zealand 2019).

INL-001 is formulated using 75 mg of Type I collagen with 100 mg of bupivacaine HCl (equivalent to 88.8 mg of bupivacaine) in an approximately 5 × 5 × 0.5-cm implant. The dose of INL-001 to be evaluated in this study is three 100-mg implants for a total dose of 300 mg.

1.3 Study Rationale

This study is intended to demonstrate postoperative analgesic efficacy and safety of INL-001 versus placebo collagen implant in patients undergoing abdominoplasty. This study, along with existing data and data from another new study, is intended to be used to provide adequate information to demonstrate that INL-001 is effective and safe in soft-tissue surgeries beyond inguinal hernia repair.

1.4 Findings From Nonclinical and Clinical Studies

Brief summaries of pertinent nonclinical pharmacology, pharmacokinetics, and toxicology data and clinical studies of INL-001 are provided in the following sections. More detailed information is provided in the Investigator's Brochure (IB).

1.4.1 Nonclinical Studies

Bupivacaine has been widely used as a local anesthetic and has demonstrated efficacy in animal models in multiple species (Li et al 2013, Hersh et al 1992). The pharmacology of bupivacaine is well understood.

The distribution, metabolism, and excretion of bupivacaine across species is characterized in the literature including data showing that, following absorption, bupivacaine is rapidly and readily distributed to tissues, with the highest concentrations in highly perfused tissues. In general, the metabolic profile of bupivacaine is similar across species although quantitatively different, with no novel metabolite identified in humans (Goehl et al 1973, Carson 2000). The excretion of bupivacaine in monkeys and humans is predominantly in the urine; in rats, excretion in urine and feces is generally similar; and in dogs, only small amounts of excretion of bupivacaine in the urine have been reported. The dog excretion data in the literature for bupivacaine is consistent with excretion data obtained in the dog following implantation of INL-001, which showed approximately 0.16% of the bupivacaine dose was collected in the urine over a 72-hour period. The genotoxicity of bupivacaine HCl was evaluated in 4 in vitro studies and 2 in vivo studies, with no safety concerns identified.

Clinically significant pharmacokinetic drug interactions with bupivacaine have been reported with verapamil, diazepam, and cimetidine in humans, animals, and/or in vitro test systems. These interactions occurred with bupivacaine administered epidurally or intravenously (iv).

The uniformity of bupivacaine in the INL-001 implant and the release of bupivacaine from the implant was evaluated in in vitro and/or in vivo assessments. The in vitro uniformity study demonstrated that bupivacaine content is homogeneously dispersed throughout INL-001. An in vitro dissolution study of a whole matrix found that bupivacaine was released as early as 5 minutes and complete release of bupivacaine occurred by 24 hours. An in vivo study showed the in vitro drug release profile was similar to that seen in vivo in dogs with INL-001 implanted into the abdomen and subcutaneous tissues through a surgical incision.

Two studies were conducted in which INL-001 was surgically implanted in rats followed by a 56-day postsurgical period to assess potential local and systemic effects, determine potential effects on wound healing, and characterize the resolution of any implant-related findings. The initial study was conducted with early development drug product and the second study with the clinical Phase 3/commercial formulation using generally the same study design. INL-001 was well tolerated following implantation. By day 28 following INL-001 implantation, attrition of the implant was approximately 95% and the implant was not observed microscopically by day 56 after dosing. INL-001−associated findings were limited to observations at the injection site, including transient edema through day 10 and microscopic findings associated with the repair process.

Biocompatibility studies were conducted with extracts from INL-001 and the drug-free implant; these studies did not identify any safety concerns. There was no evidence of acute systemic toxicity or effects on body temperature (ie, pyrogenicity) associated with administration of drug-free implant extract or evidence of skin irritation, sensitization, or genotoxicity following exposure to bupivacaine implant extract.

1.4.2 Clinical Studies

The clinical pharmacology, efficacy, and safety of INL-001 (at single doses of 100, 150, 200, and 300 mg) have been evaluated in 11 completed clinical studies (Phases 1-3) in adults, including 2 well-controlled pivotal Phase 3 studies of INL-001 in open inguinal hernia repair, at its recommended approved dose (three 100-mg bupivacaine HCl implants) (XARACOLL Prescribing Information 2020).

In a pharmacokinetic/relative bioavailability study in patients following inguinal hernioplasty (Study INN-CB-022), the commercial formulation of INL-001 at a dose of 300 mg was compared with Marcaine 0.25% injection at a dose of 175 mg (the maximum recommended single dose). Quantifiable bupivacaine concentrations were evident at the first posttreatment time point measured (30 minutes) for all patients treated with INL-001 or Marcaine. Bupivacaine concentrations were detectable through the 96-hour posttreatment time point (last time point) in both treatment groups but at higher concentrations with INL-001 than with Marcaine. Pharmacokinetic analysis led to the following additional conclusions:

- For the INL-001 treatment group, the mean maximum observed plasma concentration (C_{max}) (minimum, maximum) was 663.412 ng/mL (274.00 ng/mL, 1230.00 ng/mL) compared with a mean C_{max} (minimum, maximum) for the Marcaine treatment group of 641.000 ng/mL (275.00 ng/mL, 1140.00 ng/mL).
- For the INL-001 treatment group, the median time to maximum observed plasma concentration (T_{max}) was 3.03 hours with a mean terminal elimination half-life ($t_{1/2}$) of 18.95 hours compared with a T_{max} of 1.01 hours and a mean $t_{1/2}$ of 9.08 hours for the Marcaine treatment group.
- For INL-001, the geometric means for area under the concentration-time curve (AUC) through last observed concentration ($AUC_{0\text{-last}}$) was 18186.9 h•ng/mL and the AUC extrapolated through infinity ($AUC_{0\text{-}\infty}$) was 19012.5 h•ng/mL. For Marcaine, the geometric means for $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ were 8836.9 h•ng/mL and 8920.1 h•ng/mL, respectively.

In clinical studies of an earlier bupivacaine collagen implant formulation, following implantation of INL-001 at 100, 150, and 200 mg in various abdominopelvic surgeries, quantifiable bupivacaine plasma concentrations were observed from 30 minutes after placement (at the first posttreatment time point). Bupivacaine concentrations increased in a slightly higher than dose-proportional manner with increasing doses of INL-001.

The efficacy of INL-001 was evaluated in 2 multicenter, double-blind, placebo-controlled Phase 3 studies in adults that independently demonstrated the effectiveness of locally placed INL-001 (300 mg implanted in layers at the surgical site) in reducing both pain intensity and the need for opioid rescue analgesia after surgery; together, these studies demonstrate the reproducibility of the INL-001 treatment effects (Studies INN-CB-014 and INN-CB-016). In each study, INL-001 achieved the primary endpoint, with patients treated with INL-001 experiencing statistically significantly less pain ($p \leq 0.0004$) as evaluated by the (time-weighted) sum of pain intensity through 24 hours (SPI24). These reductions in pain intensity were coupled with less total opioid rescue analgesic medication use in the INL-001 treatment group compared with the placebo implant group. In data pooled from the 2 pivotal studies, patients used statistically significantly ($p \leq 0.0004$) less opioid rescue analgesia and had statistically significantly ($p=0.0007$) fewer opioid-related treatment-emergent adverse events (ie, nausea, vomiting, and constipation) over the postimplantation period compared with subjects in the combined placebo implant group.

The existing INL-001 safety database is derived from a clinical development program of 11 studies conducted in soft-tissue surgeries in adults, including the 2 positive Phase 3 studies in inguinal hernia repair. A total of 892 adult patients have received collagen-matrix implants in this program (612 INL-001 and 280 placebo implants). Of the 892 patients, 816 patients underwent inguinal hernia repair, 69 patients underwent hysterectomy, and 7 patients underwent other types of soft-tissue surgeries (ie, nonlaparoscopic benign gynecological procedure other than hysterectomy or elective surgery requiring a vertical or transverse abdominal incision).

Across these 11 studies:

- Adverse events occurring at an incidence of 2% or more patients following administration of INL-001 at 300 mg and at a higher incidence than placebo implants, respectively, were somnolence (19.2% vs 13.9%), dizziness (16.4% vs 13.9%), incision site swelling (13% vs 10.7%), incision site pain (11.7% vs 11.4%), restlessness (7.7% vs 6.8%), dysgeusia (7.5% vs 4.6%), vision blurred (4.9% vs 2.1%), headache (4.7% vs 2.1%), tremor (4.5% vs 2.1%), postprocedural discharge (4.3% vs 3.6%), scrotal swelling (2.8% vs 1.8%), seroma (2.6% vs 1.8%), oral hypoesthesia (2.6% vs 1.4%), pyrexia (2.3% vs 1.8%), and wound dehiscence (2.1% vs 1.8%).

- In these studies, adverse events considered by the investigator to be treatment related following INL-001 placement in the surgical site occurred at a rate of 1.5% or less. The only treatment-related adverse event that occurred in 1% or more of all patients who received INL-001 at 300 mg was dysgeusia (1.3%), which also occurred in 0.7% of patients in the placebo group.

- Across the INL-001 clinical development program, 16 patients experienced 1 or more serious adverse events: 11 patients in the INL-001 (including earlier formulation) treatment group and 5 patients in the placebo implant or other comparator group. Serious adverse events reported in the INL-001 treatment group included wound infection and seroma. One patient had the INL-001 implant removed after placement of an earlier formulation of bupivacaine collagen matrix implant during bladder sling surgery (see event described below).

- There were no verbatim reports of systemic bupivacaine toxicity or LAST during any inguinal hernia repair study done as part of the development program for INL-001. The safety assessments conducted during the development program included monitoring adverse events, measurement of vital signs, and assessments with multiday cardiac Holter monitors. These assessments revealed no constellation of neurologic or cardiovascular (CV) signs or symptoms to suggest systemic bupivacaine toxicity in patients undergoing open inguinal hernia repair receiving INL-001.

  One patient experienced signs and symptoms thought to be consistent with LAST approximately 4 hours after administration of an earlier formulation of the INL-001 (at 150 mg) following bladder sling surgery. Treatment included administration of lipid emulsion and surgical removal of the INL-001 implants.

- Across the INL-001 clinical development program, incision-site adverse events occurring with an incidence of 2% or more in either the INL-001 (including earlier formulation) or placebo group compared with a non-implant comparator treatment group (n=52) included swelling, pain, other complication, postprocedural discharge, erythema, dehiscence, and inflammation.

1.5 Known and Potential Benefits and Risks to Patients

Complete information may be found in the IB provided to each investigator. Each investigator must become familiar with all information in the IB before commencing this study.

The potential benefits to participating patients with acute postsurgical pain following abdominoplasty are (1) that they may experience a reduction in acute postoperative pain as a result of treatment with INL-001, (2) that they will understand they are contributing to the scientific knowledge that may lead to expansion of the treatment options for patients' acute postsurgical pain, and (3) because INL-001 is implanted (not injected) into the surgical site, accidental intravascular injection/surgical site infiltration that often leads to bupivacaine's most serious potential central nervous system (CNS) and CV systemic toxicities may be prevented.

The potential risks of study participation include those associated with exposure to INL-001 per the FDA-approved labeling and the risks of medical evaluation, including venipuncture and other risks associated with the required medical procedures.

Because individual patient factors may impact the safety of an amide local anesthetic such as bupivacaine, there is a potential risk for severe life-threatening adverse effects associated with the local administration of bupivacaine. Therefore, INL-001 should be administered in a setting where trained personnel and equipment are available to promptly treat patients who show evidence of CNS or CV toxicity. Monitoring cardiovascular and neurologic status, as well as vital signs, should be performed during and after placement of INL-001.

Allergic-type reactions are rare and may occur as a result of sensitivity to bupivacaine or to other formulation ingredients. These reactions are characterized by signs of urticaria, pruritus, erythema, angioedema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly anaphylactoid-like symptoms (including severe hypotension). Cross-sensitivity among members of the amide-type local anesthetic group has been reported.

2 STUDY OBJECTIVES

The primary objective of the study is to evaluate the analgesic effect of treatment (ie, efficacy) with INL-001 implants compared with placebo implants after placement into the surgical site during abdominoplasty.

The secondary objective is to assess the safety and tolerability of INL-001 implants after placement in the surgical site during abdominoplasty.

3 STUDY DESIGN

3.1 General Study Design

This is a multicenter, randomized, double-blind, placebo-controlled efficacy and safety study of the INL-001 (bupivacaine HCl) implant, at 300 mg, in patients following abdominoplasty. On the day of surgery (study day 1), eligible patients will be randomly assigned to treatment in a 1:1 ratio to receive either INL-001 (three 100-mg implants containing a total dose of 300 mg of bupivacaine HCl) or 3 placebo collagen implants. Patients will then undergo abdominoplasty under general anesthesia and have INL-001 or placebo implanted intraoperatively.

The duration of study participation for each patient will be a maximum of 75 (±3) days, consisting of a screening period (up to 45 days before surgery), an inpatient period (preoperative, intraoperative, immediately postoperative) of approximately 4 days, and an outpatient follow-up period (up to 30 days [±3 days] after treatment) including an end-of-study visit. Efficacy assessments will be made through 72 hours after treatment (after implant placement). Posttreatment (time measured from Time 0 [placement of first implant]) safety assessments will be made throughout the study after the informed consent form (ICF) is signed, and as specifically scheduled through 72 hours posttreatment, on day 7 (±1 day) (telephone) , on day 15 (±3 days) (clinic visit), and on day 30 (±3 days) (clinic visit). Unless the investigator determines further hospitalization is necessary, the patient will be discharged on the day occurring 72 hours (day 4) after surgery.

During the screening period, all patients will provide informed consent and undergo eligibility and other screening and safety assessments (medical history including review of prior medications, physical examination, urine drug screen, serum pregnancy test for women of childbearing potential, clinical laboratory tests [hematology, chemistry, urinalysis], vital signs measurement, and 12-lead electrocardiography [ECG]). Vital signs include body temperature, pulse, systolic and diastolic blood pressure, respiration rate, and oxygen saturation measured by pulse oximetry. The reason(s) a patient does not meet screening criteria will be recorded, if applicable. Recording of adverse events and concomitant medication use will commence once a patient signs the ICF.

On the day of surgery (day 1), patient eligibility will be reconfirmed before the start of surgery (including medical history, urine drug screen, urine pregnancy test for women of childbearing potential, vital signs), patients will be randomly assigned to treatment with study drug (INL-001 or placebo collagen implant), and adverse events and prior/concomitant medications will be reviewed.

Patients will undergo an abdominoplasty with rectus sheath plication using standard surgical procedures conducted under general anesthesia (see anesthesia protocol below in Section 5.1.1), with no other local anesthetic used at the surgical site. All patients should undergo an abdominoplasty procedure with an incision that does not extend above the umbilicus. The approach should be anterior. The incision should in general be from one anterior superior iliac spine (ASIS) to the other. The exact incision length may vary depending on the patient's anatomy and the desired cosmetic outcome. All packs/gauze should be removed and adequate hemostasis must be achieved prior to skin closure. Surgical drains should be placed at the discretion of the surgeon and their use recorded. Ancillary procedures (eg, liposuction, breast augmentation/reduction) are prohibited.

Placement of study drug is detailed below in Section 5.1.2. The time of the first placement of study drug (placement of first implant) is considered Time 0 and will be recorded. Use of analgesic and all medications during surgery will be recorded. At the surgeon's discretion, if a significant surgical/medical complication is encountered during surgery, study drug will not be implanted and the patient will be considered enrolled but not treated.

After surgery, patients will be transferred to a postanesthesia care unit (PACU) or other postoperative recovery area for monitored observation. The times patients enter and are discharged from the PACU will be recorded to calculate time to discharge from the PACU. Patients will be monitored with pulse oximetry starting in the PACU through 24 hours posttreatment. After leaving the PACU (time in PACU to be at the discretion of the investigator), patients will be placed in the postoperative unit or clinical research unit for domiciled observation. Vital signs, including body temperature, pulse, systolic and diastolic blood pressure, respiration rate, and oxygen saturation measured by pulse oximetry, will be assessed at multiple time points through discharge, and in the clinic on days 15 and 30; 12-lead ECG will be done on day 30.

Adverse event and concomitant medication information, including use of rescue medication, will be collected throughout the study (inpatient and outpatient). Surgical wound healing assessments will be made at 24, 48, and 72 hours after Time 0 and on days 7, 15, and 30 using the specified list and assessed for and recorded as adverse events as appropriate. The Southampton Wound Grading System will also be completed 72 hours posttreatment/prior to discharge (±4 hours) and on days 15 and 30. Assessment for signs and symptoms potentially indicative of systemic bupivacaine toxicity will be made after Time 0 at the following time points: 0.5, 1, 2, 3, and 4 hours (each ±15 minutes), and 5, 7, 9, 12, 15, 18, 24, 48, and 72 hours (each ±1 hour), and days 7 (±1 day) and 15 (±3 days) using the specified list and assessment made and recorded as adverse events as appropriate.

At any time that a patient is determined to have systemic bupivacaine toxicity, a bupivacaine blood sample will be collected and 12-lead ECG will be performed. Systemic bupivacaine toxicity will be recorded as an adverse event. The patient may be treated at the discretion of the investigator, including obtaining repeat bupivacaine blood levels, 12-lead ECG, or removal of the implants.

After surgery, patient reports of pain intensity using an 11-point numeric pain rating scale (NPRS) will be recorded at multiple time points through 72 hours posttreatment. Scheduled pain intensity scores will be recorded after Time 0 at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 20, 24, 28, 32, 36, 48, and 72 hours. Each assessment prior to hour 10 has a ±15-minute window; each assessment after and including hour 10 has a ±30-minute window. The 0.5-hour and 1-hour NPRS assessments may be omitted if, on the basis of clinical judgement, the patient is not yet awake and alert enough to appropriately answer the NPRS after surgery. Pain intensity assessments scheduled between 2400 (midnight) and 0600 (6 am) may be limited to collection every 4 hours if the patient is sleeping. However, consecutive pain assessments may not be missed, and the hour 12, 24, 48, and 72 posttreatment pain assessments must be completed even if they fall between 2400 (midnight) and 0600 (6 am). A pain intensity score will also be collected before **any** rescue pain medication use.

Patients will be permitted rescue medication to manage breakthrough pain when it occurs. Oral acetaminophen at 1000 mg every 4-6 hours as needed for pain (maximum daily dosage 3000 mg)

and/or oxycodone 5-mg tablet(s) may be given (not to exceed 10 mg in a 4-hour period during the inpatient stay). Immediately prior to receiving **any** rescue medication, a pain intensity score must be recorded. If the NPRS score is 4 or less, patients will be discouraged from taking opioid rescue medication; however, rescue medication may be requested and provided at any time. If patients require opioid rescue medication, but are unable to take oral medications, they will be permitted to receive intravenous (iv) morphine (2-3 mg) every 3 hours until they are able to take oral rescue medication. As assessed by the investigator, if a patient's pain is not relieved by oxycodone and/or acetaminophen, the patient is not yet eligible for further treatment with oxycodone and/or acetaminophen, and more than 3 hours have passed since the previous iv morphine dose, a patient may receive a dose of iv morphine (2-3 mg) for pain relief. If the pain remains unrelieved or increases in intensity before additional rescue medication is allowed, additional treatment options will be discussed with the medical monitor.

Following discharge, to report an adverse event, a patient will contact study staff by telephone and report adverse event information, including incidence, duration, and any associated treatment. Patients with pain intensity scores of 4 or more at discharge will be given a written prescription for immediate-release oxycodone at a dosage of 5-10 mg every 4-6 hours as needed as rescue medication for breakthrough pain. Patients prescribed opioid rescue medication will also be permitted to take oral acetaminophen at 1000 mg every 4-6 hours (maximum daily dosage 3000 mg) and/or ibuprofen at 400 mg every 4- 6 hours as needed for pain, on an outpatient basis. Patients with pain intensity scores of less than 4 at discharge will be instructed to take oral acetaminophen at 1000 mg every 4-6 hours as needed for pain (maximum daily dosage 3000 mg) and/or ibuprofen at 400 mg every 4- 6 hours as needed for pain, on an outpatient basis. Patients who do not receive a written prescription for oxycodone upon discharge will be permitted to request immediate-release oxycodone 5-10 mg if their pain is unrelieved by acetaminophen. Use of opioids, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), or any other medications after discharge from the hospital will be recorded, with data reviewed by study staff at subsequent contacts.

NOTE: As needed, a patient may receive rescue medication for pain at any time during the inpatient and outpatient portions of the study as described; however, these medications should **not** be taken concomitantly (ie, not at the same time).

A detailed table of procedures and assessments is provided in Table 1.

3.2 Planned Number of Patients and Countries

Up to approximately 432 patients will be screened in order to randomize 372 patients to achieve a minimum of 360 patients randomized and treated [180 evaluable patients per treatment group]). Details about the definition of evaluable patients and sample size are given in Section 9.

The study is expected to start at a time to be determined, with an estimated enrollment period of approximately 6 months, including an interim analysis. Screening to the end of the study for each patient will be approximately 75 (±3) days.

3.3 Justification for Study Design and Selection of Population

This is a randomized, double-blind, placebo-controlled study designed primarily to assess the efficacy and safety of INL-001 in adult patients scheduled for abdominoplasty. The study design employed in this study has previously been used successfully in 2 clinical Phase 3 studies conducted to demonstrate the efficacy and safety of INL-001 to manage acute postoperative pain in patients undergoing open inguinal hernia repair. The rationale for studying patients undergoing abdominoplasty was previously provided in Section 1.3.

3.4 Stopping Rules for the Study

Innocoll reserves the right to discontinue the study for safety or administrative reasons at any time.

The study will be stopped, until further benefit-risk evaluation is made, if 2 patients require removal of the INL-001 implants due to suspected systemic bupivacaine toxicity as outlined below in Section 4.3.2.

During the conduct of the study, serious adverse events will be reviewed (see Section 7.1.5), as they are reported from the investigational centers, to identify safety concerns.

The study may also be terminated by the sponsor for any reason at any time. For example, the sponsor could terminate the study in the event of:

- new toxicologic or pharmacologic findings or safety issues from any source (eg, other clinical studies, postmarketing experience) that invalidate the earlier positive benefit-risk assessment
- discontinuation of the development of the investigational medical product

If the entire study is stopped or if elements of the study are stopped, the patients whose participation is terminated early will be monitored according to withdrawal criteria and procedures (see Section 4.3).

If the study is terminated prematurely, investigator(s) will inform their patients and arrange their appropriate follow-up.

3.5 Schedule of Study Procedures and Assessments

Study procedures and assessments by visit with their respective time points are presented in Table 1. Detailed descriptions of each method of procedures and assessments are provided in Section 6 (efficacy assessments) and Section 7 (safety assessments). The end of study is defined as the last visit of the last patient.

Table 1: Schedule of Procedures/Assessments

Procedure/Assessment [a]	Screening period (up to 45 days before surgery)	Day of surgery (day 1)		In-patient postoperative period [b] (hours relative to Time 0 implantation and day is relative to day of surgery)			Out-patient postoperative period (relative to day of surgery)		
		Immediate preoperative period	Intraoperative period	Day 2 (through 24 h)	Day 3 (through 48 h)	Day 4 (through 72 h)	Day 7 ±1 d (telephone)	Day 15 ±3 d (clinic visit)	Day 30/ EOS ±3 d (clinic visit)
Written informed consent	X								
Study-drug kit number assignment (after preoperative assessments)		X (enrolled)							
Demographics/Medical history	X	X (update)							
Inclusion/Exclusion criteria	X	X							
Urine drug screen (results before study-drug kit assignment)	X	X							
Pregnancy test (for women of childbearing potential) (results before study-drug kit assignment)	X (serum)	X (urine)							X (urine)
Prior/Concomitant medications (including opioids and other analgesics)	X	◄----------							----------►
Clinical laboratory tests	X (blood/urine)								X (blood only)
Vital signs (see details and time points below)	X	X		X	X	X		X	X
Electrocardiography (12 lead)	X								X
Physical examination (screening body weight and height/posttreatment weight only)	X								X
Adverse events	X	◄----------							----------►

Continued on next page.

Procedure/Assessment [a]	Screening period (up to 45 days before surgery)	Day of surgery (day 1)		In-patient postoperative period [b] (hours relative to Time 0 implantation and day is relative to day of surgery)			Out-patient postoperative period (relative to day of surgery)		
		Immediate preoperative period	Intraoperative period	Day 2 (through 24 h)	Day 3 (through 48 h)	Day 4 (through 72 h)	Day 7 ±1 d (telephone)	Day 15 ±3 d (clinic visit)	Day 30/ EOS ±3 d (clinic visit)
Surgery/Implantation			X (Time 0 is recorded implantation time of first implant)						
Assessment of signs and symptoms potentially indicative of systemic bupivacaine toxicity (see time points below)				X	X	X	X	X	
Assessment of signs and symptoms related to wound healing				X	X	X (prior to discharge)	X	X	X
Southampton Wound Grading System						X (prior to discharge)		X	X
Numeric pain rating scale (NPRS) (see time points below)				X	X	X			
Discharge [c]						X			

Footnotes to table and detailed time points on next page.

Footnotes to table and detailed time points:

[a] Procedures and assessments have timing windows that may go beyond those specified.

[b] The times patients enter and are discharged from the postanesthesia care unit (PACU) will be recorded.

[c] Patients will be discharged after all procedures/assessments have been completed. Whether a patient is prescribed opioid pain medication at hospital discharge will be recorded.

d=day(s); EOS=end of study; h=hour(s); m=minute(s).

Time points for record of vital signs measurements after Time 0: 0.5 hour (±5 m); 1, 2, 4 hours (±15 m); 8, 12 hours (±2 h); 24, 48 hours (±3 h); 72 hours (±4 h) (prior to discharge); days 15 (±3 d) and 30 (±3 d). (Vital signs include body temperature, pulse, systolic and diastolic blood pressure, respiration rate, and oxygen saturation measured by pulse oximetry.) NOTE: Measurements from 0.5 through 12 hours will/may occur on day 1.

Time points for assessment of signs and symptoms potentially indicative of systemic bupivacaine toxicity after Time 0: 0.5, 1, 2, 3, and 4 hours (each ±15 m); 5, 7, 9, 12, 15, 18, 24, 48, and 72 hours (each ±1 h); and days 7 (±1 day) and 15 (±3 days). NOTE: Assessments from 0.5 through 18 hours will/may occur on day 1. At any time that a patient is determined to have systemic bupivacaine toxicity, a bupivacaine blood sample will be collected and 12-lead ECG will be performed. Systemic bupivacaine toxicity will be recorded as an adverse event. The patient may be treated at the discretion of the investigator, including obtaining repeat bupivacaine blood concentrations, 12-lead ECG, or removal of the implants.

Time points for NPRS for pain intensity after Time 0: 0.5, 1, 2, 3, 4, 5, 6, 8 hours (each ±15 m); 10, 12, 18, 20, 24, 28, 32, 36, 48, 72 hours (each ±30 m). (The 0.5-hour and 1-hour NPRS assessment may be omitted if, on the basis of clinical judgment, the patient is not yet awake and alert enough to appropriately answer the NPRS after surgery. In the case of use of a rescue pain medication, scores will also be obtained within 15 minutes before **any** rescue medication use.) NOTE: Assessments done 0.5 through 20 hours will/may occur on day 1. No NPRS scores will be collected after discharge.

3.5.1 Screening Period (Up to 45 Days Before Day of Surgery)

The following will take place:

- written informed consent
- demographics/medical history
- inclusion/exclusion criteria
- urine drug screen (UDS)
- serum pregnancy test (for women of childbearing potential)
- prior medications (including analgesic medication)
- clinical laboratory tests (hematology, chemistry, urinalysis)
  (Laboratory tests may be repeated at the discretion of the investigator to confirm accuracy.)
- vital signs (body temperature, pulse, systolic and diastolic blood pressure, respiration rate, and oxygen saturation measured by pulse oximetry)
- electrocardiogram (ECG)
- physical examination (including body weight and height)
- adverse events (recorded after informed consent obtained)
- training on data collection in patient diary

3.5.2 Day of Surgery (Day 1)

3.5.2.1 Immediate Preoperative Period

The following will take place:

- study-drug kit number assigned after preoperative assessments (patient enrolled)
- demographics/medical history (update)
- inclusion/exclusion criteria
- UDS (results available before study-drug kit number assignment)
- urine pregnancy test (for women of childbearing potential/results available before study-drug kit number assignment)
- prior medications (including opioids and other analgesic medication)
- vital signs (body temperature, pulse, systolic and diastolic blood pressure, respiration rate, and oxygen saturation measured by pulse oximetry)
- adverse events

3.5.2.2 Intraoperative

The following will take place and be recorded:

- concomitant medications (including anesthetics, opioids, or other analgesic medication)
- adverse events
- surgery/implantation (placement of first implant recorded as Time 0)
- placement of surgical drain(s)

3.5.3 Inpatient Postoperative Period (Relative to Time 0/Through 72 Hours or Discharge)

The following will take place:

- concomitant medications (including opioids and other analgesic medication)
- vital signs (body temperature, pulse, systolic and diastolic blood pressure, respiration rate, and oxygen saturation measured by pulse oximetry) (hours after Time 0): 0.5 (±5 minutes); 1, 2, 4 (±15 minutes); 8, 12 (±2 hours); 24, 48 (±3 hours); 72 hours (±4 hours)
- adverse events
- assessment of signs and symptoms potentially indicative of systemic bupivacaine toxicity (hours after Time 0): 0.5, 1, 2, 3, and 4 (each ±15 minutes), and 5, 7, 9, 12, 15, 18, 24, 48, and 72 (each ±1 hour)
  (Use of specific list in Section7.1.6.1 and assess/record as adverse events as appropriate.)
- assessment of wound healing (hours after Time 0): 24, 48, 72 (each ±4 hours)
  (Use of specific list in Section 7.1.6.2 and assess/record as adverse events as appropriate.)
- Southampton Wound Grading System (hours after Time 0): 72 (±4 hours)
  (Assess for and record as adverse events as appropriate.)
- NPRS (hours after Time 0): 0.5, 1, 2, 3, 4, 5, 6, 8 (each ±15 minutes); 10, 12, 18, 20, 24, 28, 32, 36, 48, 72 (each ±30 minutes)
  NOTE: The 0.5-hour and 1-hour NPRS assessments may be omitted if, on the basis of clinical judgement, the patient is not yet awake and alert enough to appropriately answer the NPRS after surgery. Pain intensity assessments scheduled between 2400 (midnight) and 0600 (6 am) may be limited to collection every 4 hours if the patient is sleeping. However, consecutive pain assessments may not be missed, and the hour 12, 24, 48, and 72 posttreatment pain assessments must be completed even if they fall between 2400 (midnight) and 0600 (6 am). A pain intensity score will also be collected before **any** rescue pain medication use. No NPRS scores will be collected after discharge.

- hospital discharge: after all assessments scheduled for 72 hours after Time 0 have been completed and patient diary has been provided to collect the occurrence of outpatient adverse events and concomitant medication use, which will be recorded in the case report form (CRF)
  NOTE: At hospital discharge, patients provided written prescription for opioid rescue medication will be recorded.
- dispense patient diary

3.5.4 Outpatient Postoperative Period

3.5.4.1 Day 7 (±1 Day) Telephone Contact

The following will take place:

- concomitant medications (including opioids and other analgesic medication)
- adverse events
- assessment of signs and symptoms potentially indicative of systemic bupivacaine toxicity (Use of specific list in Section 7.1.6.1 and assess/record as adverse events as appropriate.)
- assessment of wound healing
  (Use of specific list in Section 7.1.6.2 and assess/record as adverse events as appropriate.)

3.5.4.2 Day 15 (±3 Days) Clinic Visit

The following will take place:

- concomitant medications (including opioids and other analgesic medication)
- vital signs (body temperature, pulse, systolic and diastolic blood pressure, respiration rate, and oxygen saturation measured by pulse oximetry)
- adverse events
- assessment of signs and symptoms potentially indicative of systemic bupivacaine toxicity (Use of specific list Section 7.1.6.1 and assess/record as adverse events as appropriate.)
- assessment of wound healing
  (Use of specific list in Section 7.1.6.2 and assess/record as adverse events as appropriate.)
- Southampton Wound Grading System
  (Assess for and record as adverse events as appropriate.)

3.5.4.3 Day 30/End of Study (±3 Days) Clinic Visit

The following will take place:

- urine pregnancy test (for women of childbearing potential)
- concomitant medications (including opioids and other analgesic medication)
- clinical laboratory tests (hematology and chemistry)

- vital signs (body temperature, pulse, systolic and diastolic blood pressure, respiration rate, and oxygen saturation measured by pulse oximetry)
- ECG
- adverse events
- physical examination
- assessment of wound healing
  (Use of specific list in Section 7.1.6.2 and assess/record as adverse events as appropriate.)
- Southampton Wound Grading System
  (Assess for and record as adverse events as appropriate.)

4 SELECTION AND WITHDRAWAL OF PATIENTS

Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow patients to be enrolled are not granted by Innocoll.

4.1 Patient Inclusion Criteria

Patients will be eligible for participation in the study if they have provided written informed consent and all of the following inclusion criteria are met before surgery:

(a) Must be a man or woman who is 18-65 years of age.

(b) Has a body mass index of 18-35 kg/m^2.

(c) Must qualify for an abdominoplasty with rectus sheath plication, in the opinion of the surgeon.

(d) Has a planned (nonemergency) abdominoplasty, with an incision that does not extend beyond the umbilicus, to be performed using standard surgical technique under general anesthesia.

(e) If the patient is a woman of childbearing potential, is not lactating or pregnant (negative serum pregnancy test result during screening and a negative urine pregnancy test before surgery [day 1]).

(f) If patient is a woman, any of the following apply:

- is not of childbearing potential (defined as postmenopausal for ≥1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy])
- is practicing at least 1 of the following medically acceptable methods of birth control and agrees to continue with the regimen throughout the duration of the study:
  - —oral, implantable, or injectable contraceptives for 3 consecutive months before randomization
  - —intrauterine device (IUD) for 3 consecutive months before randomization
  - —total abstinence from sexual intercourse (≥1 complete menstrual cycle before the screening visit)
  - —double barrier (condom, sponge, diaphragm)

(g) Has a physical status classification I (healthy) or II (mild systemic disease) according to the American Society of Anesthesiologists.

(h) Has the ability and willingness to comply with all study procedures including being domiciled for at least 72 hours after surgery and to comply with all study procedures including use of a diary.

(i) Is willing to use only permitted medications throughout the study.

(j) Is willing to use opioid analgesia, if needed.

(k) Must be able to fluently speak and understand English or Spanish and be able to provide meaningful written informed consent for the study.

4.2 Patient Exclusion Criteria

A patient will not be eligible for participation in the study if any of the following criteria are met before surgery:

(a) Has a known hypersensitivity to amide-type local anesthetics, fentanyl, morphine, oxycodone, acetaminophen, NSAIDs, or bovine products.

(b) Is scheduled for other significant concurrent surgical procedures (eg, gastrointestinal resection or additional cosmetic procedures concurrent with abdominoplasty).

(c) Has undergone major surgery within 3 months before the scheduled abdominoplasty or plans to undergo another surgical procedure within 30 days after study surgery.

(d) Has used aspirin or aspirin-containing products within 7 days before surgery. Aspirin at a dose of 325 mg or less is allowed for cardiovascular prophylaxis if the patient has been on a stable dosage regimen for 30 days or more before the screening visit.

(e) Has used local anesthetics, systemic steroids, anticonvulsants, alpha-adrenergic agonists, or monoamine oxidase inhibitors (MAOIs) within 10 days before study surgery. Antidepressant medications (eg, selective serotonin re-uptake inhibitors [SSRIs]) will be allowed for depression provided the patient has been on a stable dosage regimen for 30 days or more before screening procedures and intends to remain on the same regimen for the duration of study participation.

(f) Has used an opioid analgesic on an extended daily basis (≥5 mg oral morphine equivalents per day for 3 or more days a week) within 4 weeks before surgery. Patients who, in the opinion of the investigator, may be developing physical dependency or opioid tolerance will be excluded.

(g) Has used any analgesic other than acetaminophen or NSAIDs within 24 hours before surgery that, in the opinion of the investigator, may confound the assessment of pain. Acetaminophen may be used on the day of surgery but is subject to preoperative restrictions for oral intake.

(h) Has any chronic painful condition (eg, fibromyalgia), as determined by the investigator, that may confound the assessment of pain associated with the abdominoplasty procedure.

(i) Chronically uses pain medication other than acetaminophen and NSAIDs or selective cyclooxygenase-2 (COX-2) inhibitors more than 5 times per week within 4 weeks before surgery and cannabinoids used for analgesia within 4 weeks before surgery.

(j) Has a physical or mental condition that, in the opinion of the investigator, may confound the assessment of postsurgical pain after abdominoplasty.

(k) Shows evidence of tolerance or physical dependency to sedative-hypnotic medications.

(l) Has a known or suspected history of drug abuse or substance-use disorder.

(m) Has a urine drug screen (at screening or on day of surgery) positive for drugs of abuse or misuse, with the exception of cannabinoids and amphetamines prescribed or purchased over the counter to manage a condition. Patients reporting or testing positive for past use of cannabinoids will not necessarily be excluded, unless they appear under the influence of cannabinoids at the time of screening or on the day of surgery, in the judgment of the investigator.

(n) Has liver function test (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) values greater than 3 times the upper limit of normal, or a history of cirrhosis. Patients who, in the opinion of the investigator, have liver function test results of concern should also be excluded.

(o) Has any clinically significant unstable cardiac disease or has evidence of a clinically significant 12-lead ECG abnormality (eg, ventricular hypertrophy, clinically significant arrhythmia at screening, or an implantable cardioverter-defibrillator [ICD]).

(p) Has any clinically significant unstable, neurologic, immunologic, renal, or hematologic disease (eg, uncontrolled diabetes or significantly abnormal laboratory findings) or any other condition (eg, malignancy or active coronavirus disease 2019 [COVID-19] infection) that, in the opinion of the investigator, could compromise the patient's welfare, ability to communicate with the study staff, or otherwise contraindicates study participation.

(q) Has current malignancy and currently receiving systemic chemotherapy or radiotherapy, or cancer diagnosis within 5 years before screening (excluding squamous or basal cell carcinoma of the skin that has been clinically stable and fully excised in a curative procedure).

(r) Has an open workman's compensation claim.

(s) Has participated in a clinical study (investigational or marketed product) within 30 days before surgery.

(t) Has any other condition that, in the opinion of the investigator, would warrant exclusion from the study.

4.3 Withdrawal Criteria and Procedures for the Patient

4.3.1 General Guidelines

Patients may choose to withdraw from the study at any time; however, because of the nature of the study drug, unless under extreme circumstances, patients cannot discontinue treatment once INL-001 is implanted during the surgical procedure. A patient is considered treated once at least 1 implant is placed. The investigator may determine at any time whether it is in the best interest for the health of the patient to remove the implant.

If a significant surgical complication or other clinically significant medical condition is encountered during surgery, INL-001 may not be implanted, at the surgeon's discretion, and the patient will be considered enrolled but not treated. This will be documented in the CRF.

All patients are free to withdraw from participation in this study at any time, for any reason, and without prejudice to their continued care; however, this generally means they are choosing not to continue performing study-related procedures/assessments. If a patient withdraws consent after surgery, efficacy assessments may be stopped, but whenever possible, safety information will be collected and patients will be asked to continue with all study procedures and visits if they are willing. Patients who do not have adequate pain relief from the protocol-allowed rescue medication regimen should be given standard of care analgesic medications at the discretion of the investigator. Vital signs measurements and pain intensity score should be obtained at the time of this event and prior to the administration of standard-of-care rescue medication. If willing, patients should be encouraged to remain in the clinical research unit for the duration of the

inpatient portion of the study and all study assessments should continue according to the protocol time points, including pain intensity scores. Patients should be treated with standard of care after withdrawal from, or termination of, the study as appropriate.

Investigators should attempt to obtain information about patients in the case of withdrawal from the study. Results of any evaluations and observations, together with a narrative describing the reason(s) for withdrawal from the study, must be recorded in the source documents. The CRF must document the primary reason for withdrawal from the study.

The investigator may terminate a patient's participation in the study for any of the following reasons:

- Patient withdraws consent and refuses to continue procedures/assessments.
- Patient's clinical condition requires additional treatment that, in the opinion of the investigator, is incompatible with the protocol.
- After reasonable attempts to make contact, the patient is lost to follow-up.
- Patient takes prohibited concomitant medications, as defined in this protocol.

Patients must be withdrawn from the study if any of the following events occur prior to study drug implantation:

- Patient develops an illness that would interfere with his/her continued participation.
- Patient is noncompliant with the study procedures and assessments or administration of study drug, in the opinion of the investigator.
- A female patient has a confirmation of pregnancy during the study from a positive pregnancy test.

If the reason for withdrawal from the study is an adverse event and/or clinically significant abnormal laboratory test result, monitoring will be continued as applicable (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The specific event or test result (including repeated test results, as applicable) must be recorded both on the source documentation and in the CRF; both the adverse events page and the relevant page of the CRF will be completed at that time.

The patient will be monitored as applicable (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). As soon as possible, the investigator must inform the sponsor about each patient who is being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a patient is withdrawn from the study for multiple reasons that include adverse events, the relevant page of the CRF should indicate the withdrawal was related to an adverse event. An exception to this requirement will be the occurrence of an adverse event that, in the opinion of the investigator, is not severe enough to warrant discontinuation but requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be "need to take a prohibited medication," and would not indicate the adverse event.

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records and transcribed to the CRF.

4.3.2 Assessment of Bupivacaine Toxicity and Removal of Implants Due to Bupivacaine Systemic Toxicity

Patients in this study will be domiciled in a monitored setting at least through 72 hours posttreatment. In addition to the general adverse event monitoring in this setting, patients will be specifically queried and assessed for signs and symptoms potentially indicative of systemic bupivacaine toxicity at multiple time points during the study using the following list of signs and symptoms:

- respiratory difficulty
- change in level of consciousness
- restlessness
- anxiety
- difficulty speaking or being understood
- lightheadedness
- numbness and tingling of the mouth and lips
- metallic taste
- tinnitus (ringing in ears)
- dizziness
- changes in vision
- tremors
- depression
- drowsiness

Assessment of patients for signs and symptoms potentially indicative of systemic bupivacaine toxicity will be made after Time 0/implantation at the following time points: 0.5, 1, 2, 3, and 4 hours (each ±15 minutes); 5, 7, 9, 12, 15, 18, 24, 48, and 72 hours (each ±1 hour); and on days 7 and 15.

If any of these signs or symptoms are assessed (and recorded) as an adverse event(s), the severity of the adverse event(s) will be scored based on the adverse event grading scale of the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 as follows:

Grade	Description
1	**Mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	**Moderate**; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3	**Severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living
4	**Life-threatening consequences**: urgent intervention indicated
5	**Death related to adverse event**

If a patient experiences a grade 4 adverse event of any of the following:

- respiratory difficulty
- change in level of consciousness
- cardiovascular event
- 3 or more of the other signs and symptoms on the list concurrently

bupivacaine plasma concentrations will be obtained and the investigator may request that the patient's treatment be unblinded. If the patient received INL-001, the investigator may make the decision to remove the implants as part of the patient's treatment plan for these adverse events. If at all possible, the investigator should discuss the case with the medical monitor before proceeding.

The decision to return a patient to the operating room in order to remove INL-001 implants will be an individualized assessment made on the basis of multiple patient factors (eg, age, comorbidities, hemodynamic statues). The determination regarding returning a patient to the operating room for removal of INL-001 implants will be made by the investigator.

4.4 Replacement of Patients

There is no provision for replacing patients.

4.5 Rescreening

A patient who is screened but not enrolled, such as because inclusion/exclusion criteria were not met or enrollment did not occur within the specified time, may be considered for screening again if, for example, there is a change in the patient's medical background or a modification of study inclusion and exclusion criteria.

Patients may have individual parameters retested at the discretion of both the investigator and the sponsor.

If the patient is rescreened, another ICF must be signed.

4.6 Screening Failure

Screening failures are defined as potential participants who consent to participate in the study but are not subsequently enrolled in the study. Minimal information to be recorded includes demography and screening failure details, including eligibility criteria.

5 TREATMENT

Additional information about study drug handling, administration, accountability, and disposition may be found in the study pharmacy manual.

5.1 Investigational Medicinal Product Used in the Study and Other Treatment Information

The test study drug used in this study is the INL-001 [XARACOLL® (bupivacaine hydrochloride) implant] (batch/lot 2000231; expiry September 2022; manufacturer Syntacoll GmbH, Donaustr 24, 93342 Saal/Donau, Germany).

The comparison study drug used in this study is the placebo (drug-free/collagen) implant (batch/lot 20000210; expiry September 2022; manufacturer Syntacoll GmbH, Donaustr 24, 93342 Saal/Donau, Germany).

INL-001 is a drug-device combination product containing 100 mg of bupivacaine HCl per implant, equivalent to 88.8 mg of bupivacaine, for placement in the surgical site. The dose to be evaluated is three 100-mg implants (300 mg bupivacaine HCl), equivalent to 266.4 mg of bupivacaine. Each implant is 5 cm × 5 cm × 0.5 cm in size and is white to off-white in color. Placebo implants contain collagen but no bupivacaine. Implants are terminally sterilized.

Additional details may be found in the IB for INL-001.

5.1.1 Anesthetic Protocol

The standardized anesthetic regimen will include general anesthesia with fentanyl (maximum dose of 4 mcg/kg) and propofol (dose at discretion of the anesthesia provider), with or without volatile anesthetics or muscle relaxants. The standardized anesthetic regimen is a guide that should be followed to minimize interpatient variability to the greatest extent possible. However, it is understood that hemodynamic fluctuations and other intraoperative events may necessitate some deviation from this standard regimen. Neuraxial techniques, such as epidural and spinal anesthesia, are not allowed. No epinephrine is permitted during the procedure. No local anesthetic other than INL-001 (study drug) in the surgical field or regional anesthesia is permitted. Lidocaine HCl 1% injection at a dose of no more than 20 mg may be administered once through iv access to decrease venous irritation (eg, as caused by propofol) at the time of surgical anesthesia. Intraoperatively, fentanyl (maximum dose of 4 mcg/kg) is permitted for analgesia. No other analgesic agents may be used during the procedure including, but not limited to, opioids (other than fentanyl), acetaminophen (oral or iv), NSAIDs (eg, ketorolac or COX-2 inhibitors), ketamine, pregabalin, and others. A preoperative dose of an antiemetic, ondansetron iv 4 mg, for nausea prophylaxis is allowed; however, postoperative antiemetic medications should be given to treat only patients who report nausea and/or vomiting. Administration of fentanyl should be avoided 30 minutes prior to the anticipated conclusion of the procedure if medically acceptable in the judgement of the anesthesiologist.

5.1.2 Placement of Study Drug

Following tissue removal and repair of the abdominal musculature, 2 implants should be placed on the rectus diastasis at the site of rectus sheath plication and 1 implant should be placed below the abdominal incision between Scarpa's fascia and the subcutaneous fat. The implants should, to the greatest extent possible, be placed so they span the fascia that is exposed prior to surgical closure. Implants may be divided to accommodate placement, but an individual implant may not be cut into more than 2 halves.

5.2 Preparation, Handling, Labeling, Storage, and Accountability for the Study Drug

5.2.1 Storage and Security

The investigator or designee must record that appropriate temperature conditions have been maintained for the study drug received and that any discrepancies are reported and resolved before use of the study drug.

Study drug must be stored at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F). Brief exposure to temperatures up to 40°C (104°F) may be tolerated provided the mean kinetic temperature does not exceed 25°C (77°F) (United States Pharmacopeia [USP] Controlled Room Temperature); however, such exposure should be minimized.

To prevent theft or diversion, study drug must be stored securely locked in an appropriate enclosure. Any actual or suspected theft or diversion must be reported to the sponsor immediately.

5.2.2 Clinical Supply Label

The study drug will be labeled with the sponsor's 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.

Supplies of study drug will be labeled according to the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) and will include any locally required statements.

5.2.3 Accountability

The investigator will ensure that adequate records showing the receipt, dispensing, return, or other disposition of the study drug, including the date, quantity, batch or code number, and identification of study patients (number and initials) who receive the study drug are maintained. The investigator will not supply the study drug to any person except subinvestigators (as submitted to the local regulatory authority), designated staff, and patients in this study. The investigator will not dispense the study drug from any sites other than those submitted to the local regulatory authority. The study drug will not be relabeled or reassigned for use by other patients.

Each study drug shipment will include a packing slip listing the contents of the shipment, return instructions, and any applicable forms.

The investigator is responsible for ensuring deliveries of the study drug and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with the Code of Federal Regulation (CFR) or national and local regulations, and used in accordance with this protocol.

Only patients enrolled in the study may receive the study drug and only authorized staff at the investigational center may supply or administer the study drug, which must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions or appropriate instructions with access limited to the investigator and authorized staff at the investigational center.

The investigator, institution, or head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

A record of study drug accountability (ie, study drug and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee with an account given for any discrepancies. Upon completion of the study, unused study drug will be returned to the sponsor's designee.

5.3 Justification for Study Drug

The dose of INL-001 to be evaluated in this study (ie, three 100-mg implants, for a total dose of 300 mg of bupivacaine HCl) was selected on the basis of completed efficacy, safety, and pharmacokinetic studies in which a 300-mg dose of INL-001 was shown to be well tolerated in patients undergoing inguinal hernia repair, another open soft-tissue surgery, in 2 pivotal Phase 3 double-blind studies (Studies INN-CB-014 and INN-CB-016). A dose of 300 mg is the FDA-approved dose for use in open inguinal hernia repair. This dose is anticipated to provide an appropriate benefit-risk level in abdominoplasty. Refer to the IB for further information.

5.4 Other Medicinal Products Used in the Study

For intraoperative medication use, refer to the anesthetic protocol described in Section 5.1.1. No local anesthetic in the surgical field other than INL-001 (study drug) or regional anesthesia is permitted. Intravenous lidocaine HCl 1% injection at a dose of no more than 20 mg may be administered once through iv access to decrease venous irritation (eg, as caused by propofol).

Patients will be permitted rescue medication to manage breakthrough pain when it occurs. Oral acetaminophen at 1000 mg every 4-6 hours as needed for pain (maximum daily dosage 3000 mg) and/or oxycodone 5-mg tablet(s) may be given (not to exceed 10 mg in a 4-hour period during the inpatient stay). If the NPRS score is 4 or less, patients will be discouraged from taking opioid rescue medication; however, rescue medication may be requested and provided at any time. If patients require opioid rescue medication, but are unable to take oral medications, they will be permitted to receive iv morphine (2-3 mg) every 3 hours, as needed until they are able to take oral rescue medication. As assessed by the investigator, if a patient's pain is not relieved by oxycodone, the patient is not yet eligible for further treatment with oxycodone, and more than 3 hours have passed since the previous iv morphine dose, a patient may receive a dose of iv

morphine (2-3 mg) for pain relief. If the pain remains unrelieved or increases in intensity before additional rescue medication is allowed, additional treatment options will be discussed with the medical monitor.

Patients with pain intensity scores of 4 or more at discharge will be given a written prescription for immediate-release oxycodone at a dosage of 5-10 mg every 4-6 hours as needed as rescue medication for breakthrough pain. Patients prescribed opioid rescue medication will also be permitted to take oral acetaminophen at 1000 mg every 4-6 hours (maximum daily dosage 3000 mg) and/or ibuprofen at 400 mg every 4-6 hours as needed for pain, on an outpatient basis. Patients with pain intensity scores of less than 4 at discharge will be instructed to take oral acetaminophen at 1000 mg every 4-6 hours (maximum daily dosage 3000 mg) and/or ibuprofen at 400 mg every 4-6 hours as needed for pain, on an outpatient basis. Patients who do not receive a written prescription for oxycodone upon discharge will be permitted to request immediate-release oxycodone 5-10 mg if their pain is unrelieved by acetaminophen or NSAIDs. Use of opioids, acetaminophen, NSAIDs, or any other medications after discharge from the hospital will be recorded, with data reviewed by study staff at subsequent contacts.

Patients prescribed opioid rescue medication will be asked to record their use of this medication in a diary and will be instructed on the proper way to dispose of unused medications. (NOTE: Relevant FDA guidelines may be found at https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/ensuringsafeuseofmedicine/safedisposalofmedicines/ucm186187.htm.)

Patients may receive any treatment for a pre-existing condition or as required for appropriate patient management during the study if it is not listed as restricted according to inclusion/exclusion criteria.

In the event that a standard-of-care rescue medication or anesthesia medication listed in this protocol is not available due to supply/procurement issues, a medically acceptable alternative may be used after review and approval by the medical monitor and this will not be a protocol deviation.

NOTE: As needed, a patient may receive rescue medication for pain at any time during the inpatient and outpatient portions of the study as described; however, these medications should **not** be taken concomitantly (ie, not at the same time).

5.5 Treatment After the End of the Study

This study includes procedures and assessments through day 30 after implantation of study drug and includes no further treatment after this time point.

5.6 Restrictions

There are no specific restrictions in this study other than those listed in the inclusion/exclusion criteria (see Section 4.1 and Section 4.2) and in study treatment including analgesic medication use.

5.7 Prior and Concomitant Medications or Therapy

Treatment with the following medications before study entry or during the study is not allowed:

- Analgesics not included as part of this study and specified in the protocol are prohibited within 24 hours of surgery. A peri-operative dose of an antiemetic for nausea prophylaxis is allowed; however, postoperatively antiemetic medications should be given only to treat actual reports of nausea.
- Aspirin or an aspirin-containing product within 7 days of surgery is prohibited. Aspirin at a dose of 325 mg or less is allowed for cardiovascular prophylaxis if the patient has been on a stable dosage regimen for 30 days or more before screening procedures.
- Opioid analgesic for an extended daily basis (≥5 mg of oral morphine equivalent per day for 3 or more days a week) within 4 weeks before surgery is prohibited.
- Any investigational product within 30 days of surgery is prohibited.
- Pain medication before randomization that, in the opinion of the investigator, could confound pain assessments during the study, is prohibited. After randomization, all concomitant pain medications are prohibited except those specifically allowed by the protocol.
- Agents that could affect the analgesic response (such as central alpha agents [clonidine and tizanidine], corticosteroids, and anticonvulsant agents) within 10 days of surgery are prohibited. Antidepressant medications (eg, SSRIs) will be allowed for the treatment of depression provided the patient has been on a stable dosing regimen 30 or more days before screening and intends to remain on the same dosing regimen for the duration of the study.
- MAOIs within 10 days of surgery are prohibited.
- Systemic corticosteroids within 10 days of surgery are prohibited. Inhaled, ophthalmic, and topical corticosteroids are allowed.
- Local anesthetics (eg, lidocaine, other formulations of bupivacaine) are not permitted to be used in the surgical wound. Lidocaine HCl 1% injection at a dose of no more than 20 mg may be administered once through iv access to decrease venous irritation (eg, as caused by propofol) at the time of surgical anesthesia.
- Surgery will be conducted under general anesthesia with no local anesthetic placement other than study drug permitted in the surgical field (see anesthetic protocol in Section 5.1.1).

Rescue analgesia allowed for the treatment of breakthrough pain during the study is presented in Section 5.4.

Patients are not permitted to be concurrently enrolled in another clinical study.

Any prior or concomitant medication a patient has received within 45 days before study drug administration and through the end of the study, including follow-up, will be recorded in the CRF. Trade name and International Nonproprietary Name (INN, if available), indication, dose, and start and end dates of the administered study medication will be recorded.

At each visit after the screening visit, the investigator will ask patients whether they have taken any medications (other than the study drug), including over-the-counter (OTC) medications, vitamins, or herbal or nutritional supplements, since the previous visit.

5.8 Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance until completion of the study or patient withdrawal, according to the protocol. A check of compliance with study procedures will be performed during each visit after study drug placement and study drug accountability records will be completed.

If the investigator or the sponsor determines the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn from the study.

Exposure to study drug will be assessed as required.

5.9 Temporary Discontinuation of Study Drug

This is not applicable to this study.

5.10 Randomization and Blinding

Eligible patients will be randomly assigned to treatment in a 1:1 ratio to receive either INL-001 or placebo collagen implants. Patients will not be aware of their treatment allocation and all study staff involved in efficacy and safety assessments will be blinded to treatment assignments until after database lock and release of unblinding randomization codes. Emergency unblinding is allowable if deemed necessary by the investigator, and discussed and agreed with the study medical monitor, for the safety of the patient and will be fully documented and included in protocol deviations. Patients will be stratified by study center and body mass index (BMI) (<30 kg/m^2 and ≥ 30 kg/m^2). In the case of a suspected unexpected serious adverse reaction (SUSAR), unblinding of the sponsor will be performed according to the safety management plan.

5.11 Data Monitoring Committee (Interim Analysis)

An Interim Data Monitoring Committee (IDMC), statistical support group responsible for calculating the recommended sample size adjustment under the prespecified decision rules in accordance with its charter, will review the unblinded results of the interim analysis and return a recommendation for an increase in sample size, if needed. They will not participate in the conduct of the study in any other way and their communication will be limited to the study recommendations described in the interim analysis section below.

6 EFFICACY AND OTHER ASSESSMENTS

6.1 Efficacy Assessments

6.1.1 Pain Intensity

Pain intensity will be assessed using NPRS at specified time points during the study (see Table 1). The NPRS is an 11-point scale on which 0 indicates "no pain" and 10 indicates the "worst possible pain." All postsurgical medication use will be recorded. In the case of a rescue medication being used, an NPRS score will be obtained within 15 minutes before the patient is administered rescue medication. (See statistical methods in Section 9.5.)

The primary efficacy variable is the sum of time-weighted pain intensity (SPI) from Time 0 through 24 hours (SPI24) as assessed by the pain intensity score using an NPRS. SPI will also be calculated for other time points.

Key secondary pain intensity efficacy variables are as follows:

- SPI from Time 0 through 48 hours (SPI48)
- SPI from Time 0 through 72 hours (SPI72)

NOTE: For order of statistical analysis for key secondary efficacy variables see Section 9.5.

Other secondary pain intensity efficacy variables are as follows:

- SPI through the following posttreatment time points: 2, 3, 4, 5, 6, 8, 10, 12, 18, 20, 28, 32, 36 hours
- pain intensity at each scheduled time point

6.1.2 Opioid Use

Opioid use will be captured throughout the study (see Table 1). Various parameters will be calculated relating to opioid use, posttreatment through discharge and after discharge. (See statistical methods in Section 9.5.)

Key secondary opioid-use efficacy variables are as follows:

- proportion of patients who are opioid free through 24 hours
- proportion of patients who are opioid free through 48 hours
- proportion of patients that are opioid free through 72 hours

NOTE: For order of statistical analysis for key secondary efficacy variables see Section 9.5.

Other secondary opioid-use efficacy variables are as follows:

- proportion of patients who are opioid free from 24 through 48 hours, from 48 through 72 hours, and through day 7
- proportion of patients who do not receive opioid rescue medication at discharge

- proportion of patients who do not use opioids following discharge
- total use of opioid analgesia (TOpA) through the following posttreatment time points: 2, 4, 6, 8, 10, 12, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 42, 44, 46, 48, and 72 hours, and prior to discharge
- total use of parenteral opioid analgesia (POpA) from Time 0 through 24 hours
- time to first use of opioid rescue medication
- time to no longer using opioid rescue medication during the study
- proportion of patients who used any oral opioid rescue medication through the following posttreatment time points: 2, 4, 6, 8, 10, 12, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 42, 44, 46, 48, and 72 hours
- total rescue medication use through the following posttreatment time points: 2, 4, 6, 8, 10, 12, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 42, 44, 46, 48, and 72 hours
- proportion of patients who receive **any** rescue medication through 24, 48, and 72 hours

6.2 Other Assessments: Time to Discharge From the Postanesthesia Care Unit (PACU)

The times a patient enters and is discharged from the PACU will be recorded to measure time to discharge from the PACU, another secondary efficacy variable.

7 ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events (including assessments of signs and symptoms potentially indicative of bupivacaine toxicity and assessment of wound healing), clinical laboratory test results, vital signs measurements, physical examination findings (including body weight and height measurements), ECG findings, and use of concomitant medication. Safety variables will be collected at scheduled time points during the study as shown in Table 1.

7.1 Adverse Events

7.1.1 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product during a clinical study, which does not necessarily have a causal relationship with the treatment. An adverse event can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

In this study, an adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the condition under study, or of any concurrent disease, whether or not considered related to the study drug. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions that were present before study entry and do not worsen during this study will not be considered adverse events.

Any adverse event will be monitored 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 adverse event will be reported in the patient's medical record. Accordingly, an adverse event can include any of the following:

- intercurrent illness(es)
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions
- drug interactions
- events occurring during diagnostic procedures
- laboratory or diagnostic test abnormalities that result in withdrawal of the patient from the study (except for results of screening tests performed that lead to screening failure not considered adverse events), are associated with clinical signs and symptoms or a serious

adverse event, require medical treatment or further diagnostic work-up, or are considered by the investigator to be clinically significant

7.1.2 Recording and Reporting of Adverse Events

7.1.2.1 Starting Date, Stop date, and Duration of an Adverse Event

The definitions of adverse event start and stop dates and duration are:

- The **start date** is the date an adverse event is first noted.
- The **stop date** is the date the adverse event is known to be resolved. If it is not known to be resolved, it is indicated as ongoing.
- The **duration** of an adverse event is recorded as a time in minutes, hours, or days.

7.1.2.2 Actions Taken

None:	No action was taken.
Change study treatment:	This is not applicable to this study.
Treatment:	Specified medication (to be recorded) was used as a countermeasure.
Others:	Other actions, such as an operative procedure, were required because of the adverse event(s).

7.1.2.3 Definition of Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as one of the following:

- resolved
- resolved with sequelae
- ongoing
- death
- unknown

Death should be entered as the outcome of an adverse event only when the patient's death is definitely or probably related to the adverse event. (NOTE: The causal relationship of the adverse event to the study treatment is not to be considered in making this decision.) If the patient's death is definitely or probably related to more than 1 adverse event, the outcome of death should be indicated for each adverse event.

7.1.2.4 Documentation of Adverse Events

At each visit or evaluation time point, the investigator will monitor, inquire about, and/or evaluate adverse events using nonleading questions. The occurrence of all adverse events will be documented in the CRF with the following information, as appropriate:

- name or term of the adverse event
- start date
- stop date (or an indication of ongoing)
- how long persisted (optional)
- severity
- seriousness
- actions taken
- outcome
- investigator opinion regarding relationship to study drug

Adverse events should be documented from the time the patient provides informed consent. The adverse events will be documented as soon and as completely as possible in the appropriate CRF and in source documents. Follow-up information will be entered as soon as possible after it becomes available. The causality assessment will be assigned by the investigator and signed and dated when recorded.

Corrections to most adverse event details may be made but will be dated and signed according to ICH guidelines (except for changes in severity and/or seriousness, as noted in the following sections). If a suspected diagnosis has been ruled out, the investigator may change the adverse event term and should add a comment naming the original suspected diagnosis and the reason for the change.

A clinically relevant worsening of an adverse event (eg, relevant change in severity or seriousness) will result in new data entry. The original entry will be indicated as unresolved and given an end (stop) date reflecting the date the adverse event worsened and a comment will be entered stating the adverse event is continuing with changed severity/seriousness (eg, continues as “event name” with new onset date and new severity/seriousness). The onset (start) date of the new entry is also the date of worsening. The onset date of a serious adverse event is the date the event fulfills any criterion for seriousness.

Adverse events that occur during the study should be managed using established standards of care in order to protect the life and health of the patient.

For the purpose of recording any adverse event, the study period is defined for each patient as the time from signing the ICF to the end of the follow-up period. The end of the follow-up period for recording of adverse events is defined as day 30 after treatment with study drug. The period for reporting treatment-emergent adverse events is defined as the period after treatment with study drug until the end of follow-up period (day 30).

All adverse events that occur during the defined study period must be recorded both in the source documents and in the CRF, regardless of the severity/seriousness of the event or judged relationship to the study drug. For serious adverse events, the serious adverse event area of the CRF must be completed and the serious adverse event must be reported immediately (Section 7.1.5). The investigator does not need to actively monitor patients for adverse events after the defined study period.

Following discharge, to report an adverse event, a patient will contact study staff by telephone and report adverse event information, including incidence, duration, and any associated treatment.

At each contact with the patient, the investigator or designee must question the patient about adverse events by asking an open-ended question such as "Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe." All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible and when such diagnosis is made, all related signs, symptoms, and laboratory test findings will be recorded collectively as a single diagnosis in the CRF and, if it is a serious adverse event, on the serious adverse event area of the CRF.

The clinical course of each adverse event will be monitored at suitable intervals until resolved, stabilized, or returned to baseline; until the patient is referred for continued care to a health care professional; or until a determination of a cause unrelated to the study drug or study procedure is made.

The start and stop dates, duration (in case of adverse event duration of less than 24 hours start and stop times collected), action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded both in the source documentation and the CRF.

The relationship of each adverse event to the study drug and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below. Further details are given in the Safety Monitoring Plan for this study.

7.1.3 Severity of an Adverse Event

The severity of each adverse event must be recorded according to CTCAE (see Section 4.3.2).

7.1.4 Relationship of an Adverse Event to the Study Drug

Investigators will classify the relationship of an adverse event to the study drug as follows:

Definitely related:	An adverse event that is due to use of the study drug. The adverse event cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The temporal relationship is very suggestive.
Probably related:	An adverse event that can be reasonably attributed to the use of the study drug. An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s). The temporal relationship is suggestive.
Unlikely related:	An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), and/or the temporal relationship suggests that a causal relationship is unlikely.
Not related:	An adverse event that is not related to the use of the study drug.

If the investigator determines that an adverse event is unlikely to be or not be related to the study drug, the investigator will determine whether the adverse event is most likely to be related to the surgical procedure, opioid use, or something else.

7.1.5 Serious Adverse Events

For recording a serious adverse event, the study period is defined for each patient as described in Section 7.1.2.4. Serious adverse events occurring in a patient after the end of the follow-up period should be reported to the sponsor, if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.

7.1.5.1 Definition of a Serious Adverse Event

A serious adverse event is any untoward medical occurrence that, at any dose, has the following characteristics:

- results in death
- is life-threatening

  NOTE: An adverse event or adverse reaction is considered life-threatening if, in the opinion of either the investigator or sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- requires inpatient hospitalization or prolongation of existing hospitalization

  NOTE: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as a serious adverse event according to this criterion. Admission to the hospital for social or situational reasons (ie, no place to stay, lives too far away to come for

hospital visits) will not be considered inpatient hospitalization. An elective hospital admission to treat a condition present before exposure to the study drug, or a hospital admission for a diagnostic evaluation of an adverse event, **does not** qualify the condition or event as a serious adverse event.

- results in permanent (persistent) disability/incapacity
- if a patient exposed to the study drug gives birth to a child with congenital anomaly or birth defect
- is an important medical event

Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but which may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization.

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.

7.1.5.2 Expectedness

A serious adverse event that is not included in the IB under reference safety information (RSI) for expedited reporting purposes by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. This may also be determined using the product-prescribing information when it becomes available.

For the purpose of reporting a SUSAR, the edition of the IB at the time of occurrence of the SUSAR applies.

7.1.5.3 Reporting a Serious Adverse Event

7.1.5.3.1 Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events that occur during the study, regardless of the assessed relationship to study drug treatment, must be reported to the sponsor by the investigator within 24 hours after the investigator becomes aware of it. Completing the serious adverse event form and reporting the serious adverse event must not be delayed, even if all the information is not available. The investigator does not need to actively monitor patients for adverse events once the study has ended.

The serious adverse event form will be sent to the contract research organization (CRO) and sponsor representatives.

The following information will be provided to record the adverse event accurately and completely:

- study number
- investigator and investigational center identification

- patient number
- start date and detailed description of adverse event
- investigator's assessment of the relationship to study drug

Additional information may include:

- age and sex of patient
- date of implantation
- action taken
- outcome, if known
- severity
- explanation of assessment of relationship to study drug
- concomitant medication (including doses, routes of administration, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death
    - —cause of death (whether or not the death was related to study drug)
    - —autopsy findings (if available)

Healing of the surgical wound will be assessed throughout the study and if there is a wound-related event, it will be recorded as such.

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the study drug, study procedures, and underlying disease.

Additional information (follow-up) about any serious adverse event unavailable at the time of initial reporting should be provided by the investigator within 24 hours of the time it becomes known.

The investigator must ensure the Institutional Review Board (IRB) is also informed of the event, in accordance with national and local regulations.

7.1.5.3.2 Sponsor Responsibility

If a SUSAR is believed to be related to the study drug or study procedures, the sponsor will take appropriate steps to notify all investigators participating in the study and the appropriate competent authorities (and IRB, as appropriate).

In addition to notifying the investigators and competent authorities (and IRB, as appropriate), other action may be required, including:

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- modifying the existing consent form and informing all study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to treatment with INL-001

7.1.6 Protocol-defined Adverse Events and Safety Assessments of Special Interest

There are 2 specific safety areas of interest for this study, systemic bupivacaine toxicity and wound healing. Signs and symptoms potentially indicative of systemic bupivacaine toxicity and signs and symptoms related to healing of the surgical wound will be evaluated at specified time points using the lists below. Signs and symptoms will be assessed and recorded as described above for adverse events in general. In addition, wound grading will be performed at specified time points using the Southampton Wound Grading System (Bailey et al 1992).

7.1.6.1 Assessment of Signs and Symptoms Potentially Indicative of Systemic Bupivacaine Toxicity

Patients will be specifically queried and assessed by the investigator/subinvestigator (physician) for these signs and symptoms potentially indicative of bupivacaine toxicity at specified time points after implantation of study drug using the following list of signs and symptoms (see Table 1).

Have you had any of the following since we last spoke?

- respiratory difficulty
- change in level of consciousness
- restlessness
- anxiety
- difficulty speaking or being understood
- lightheadedness
- numbness and tingling of the mouth and lips
- metallic taste
- tinnitus (ringing in ears)
- dizziness
- changes in your vision
- tremors
- depression
- drowsiness

If a patient reports any of the above signs and symptoms, they will be assessed as to whether they qualify as adverse events and, if so, recorded as noted previously regarding adverse events. If the investigator determines that the patient experienced systemic bupivacaine toxicity, this will be recorded as an adverse event.

If any of these signs or symptoms are assessed (and recorded) as an adverse event(s), the severity of each adverse event must be recorded according to CTCAE (see Section 4.3.2).

7.1.6.2 Wound Healing

The following signs and symptoms associated with wound healing will be queried and assessed by the investigator/subinvestigator (physician) at specified time points after implantation of study drug (see Table 1):

- **purulent discharge or leakage of fluid from the site**
- 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**
- **had been seen by a health care provider about the wound**
- **had been prescribed nonprophylactic antibiotics for an infection in the wound**
- **had been admitted to a hospital with an infection of the surgical wound**

If a patient reports any of the above signs and symptoms, which are shown in **bold text**, they will be recorded as adverse events related to the surgical site. If a patient reports any of the other (not bolded) signs and symptoms, they will be assessed as to whether they qualify as adverse events and, if so, recorded as noted previously regarding adverse events (see above in Section 7.1).

7.1.6.3 Wound Grading

At 72 hours posttreatment, day 15, and day 30 the investigator/subinvestigator (physician) will complete the Southampton Wound Grading System. Investigator judgment will be used to determine if a finding is an adverse event. If an adverse event is identified during completion of this assessment that was not previously identified through the wound healing assessment, it will be assessed and recorded according to the adverse event criteria defined above.

Wound healing grade and appearance will be assessed as follows:

Grade	Appearance
0	Normal healing
I Normal healing with mild bruising or erythema:	
a	Some bruising
b	Considerable bruising
c	Mild erythema
II Erythema plus other signs of inflammation:	
a	At one point
b	Around sutures
c	Along wound
d	Around wound
III Clear or haemoserous discharge:	
a	At one point only (≤2 cm)
b	Along wound (>2 cm)
c	Large volume
d	Prolonged (>3 days)
Major complications	
IV Pus:	
a	At one point only (≤2 cm)
b	Along wound (>2 cm)
V Deep or severe wound infection with or without tissue breakdown; haematoma requiring aspiration	

7.1.7 Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure patient safety, after the patient's condition has stabilized and/or treatment has been administered, the investigator or other physician in attendance must contact the physician identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the CRO and sponsor, will decide whether the patient should continue to participate in the study.

7.2 Pregnancy

All women of reproductive age who participate in the study will be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Women will be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected. Becoming pregnant during study participation is not considered an adverse event; however, any complications during pregnancy within the course of the study may be considered an adverse event(s).

7.3 Medication Error and Special Situations Related to the Study Drug

Any administration of the study drug that is not in accordance with the study protocol or surgery manual should be reported on the CRF and in the patient's source documents as a deviation, regardless of whether or not an adverse event occurs as a result.

7.4 Clinical Laboratory Tests

Blood and urine samples for clinical laboratory tests will be collected at the screening visit; and blood samples only will be collected at the day-30 follow-up visit (see Table 1).

7.4.1 Hematology, Serum Chemistry, and Urinalysis

The following clinical laboratory tests will be performed:

Hematology (complete blood count [CBC])	**Serum chemistry:**	**Urinalysis**
Hematocrit Hemoglobin Platelet count White blood cell (WBC) count WBC differential (percentage and absolute): – basophils – eosinophils – lymphocytes – monocytes – neutrophils	Blood urea nitrogen Creatinine Total bilirubin Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase Sodium Potassium Calcium Chloride Phosphate Serum bicarbonate Total cholesterol Glucose (nonfasting) Albumin	Color and appearance Specific gravity pH Ketones Protein Blood Glucose

The following additional laboratory tests will also be performed:

- For women of childbearing potential, a serum sample for pregnancy test will be collected at screening, and a urine sample on the day of surgery (with results available before study-drug kit assignment) and on day 30.

All clinical laboratory test results outside the reference range will be assessed by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

A laboratory test result that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event and will be monitored as

described in Section 7.1, whether during or at the completion of participation. An event may include a laboratory or diagnostic test abnormality that results in the withdrawal of the patient from the study, the temporary or permanent withdrawal of medical treatment, or further diagnostic work-up. (NOTE: Abnormal laboratory or diagnostic test results at the screening visit that preclude a patient from entering the study or receiving study drug are not considered adverse events.)

Clinical laboratory tests (serum chemistry, hematology, and urinalysis) will be performed at the time points detailed in Table 1. Blood samples (approximately 16 mL total per patient) will be collected. Clinical laboratory tests will be performed using the central laboratory.

7.4.2 Urine Drug Screen

A urine drug screen will be performed at the screening visit and immediately before surgery (see Table 1). Urine screening will be done for drugs of abuse/misuse, with testing during the screening period and on the day of surgery (with results available before study-drug kit number assignment).

A positive result for any excluded drugs of misuse/abuse (see Section 4.2) or their metabolites without medical explanation will preclude the patient from enrollment or continued participation in the study.

7.5 Vital Signs

Vital signs, including body temperature, pulse, systolic and diastolic blood pressure, respiration rate, and oxygen saturation, will be measured/recorded at screening, preoperatively, and at the following posttreatment time points: 0.5 hours (±5 minutes); 1, 2, 4 hours (±15 minutes); 8, 12 hours (±2 hours); 24, 48, 72 hours (±4 hours) prior to discharge; day 15 (±3 days); and day 30 (±3 days) (see Table 1).

Oxygen saturation will be monitored by pulse oximetry during the inpatient study period. Oxygen saturation will be recorded at the individual time points listed above. Pulse oximeter alarms should be set according to clinic standards, with oxygen desaturation that occurs in concordance with the delay period and the specified limits recorded as an adverse event. Patients should be evaluated to ensure proper pulse oximeter placement and to ensure desaturation is not due to patient movement or device-related issues.

All vital sign results outside the reference ranges will be judged by the investigator as belonging to one 1 of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

7.6 Physical Examinations

A complete physical examination will be performed at screening and on day 30 (±3 days) after treatment (including screening body weight and height and posttreatment weight only) (see Table 1). A complete physical examination will include at a minimum skin, lungs, CV, respiratory, gastrointestinal, musculoskeletal, and neurological assessments. Any physical examination finding that is judged by the investigator as clinically significant (except at the screening visit) will be considered an adverse event, recorded in the CRF, and monitored as

described in Section 7.1.2. Investigators should pay special attention to clinical signs related to previous serious diseases.

7.7 Electrocardiography

A standard 12-lead ECG will be performed locally (by a physician [ie, the investigator or subinvestigator]) and recorded (after the patient has been supine for at least 5 minutes) at screening and on day 30 (±3 days) (see Table 1). All ECG recordings will be identified with the patient number, date, and time of the recording.

All ECG results outside of the reference ranges should be evaluated and will be judged as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

Any ECG finding that is judged as clinically significant (except at the screening visit) will be considered an adverse event, recorded on the source documentation and on the CRF, and monitored as described in Section 7.1.2.

8 ASSESSMENT OF PHARMACOKINETICS: NOT APPLICABLE

Pharmacokinetics are not assessed in this study.

9 STATISTICAL METHODS

This section describes the statistical analysis as foreseen at the time of planning the study. Changes, additions, and further details about the analyses will be described in the statistical analysis plan (SAP). After finalization of the SAP, any additional analyses or changes to analyses that may be required will be fully disclosed in the clinical study report (CSR).

9.1 Sample Size and Power Considerations

The sample size was chosen primarily on the basis of previous clinical study data for INL-001 in inguinal hernia repair, but also with the consideration of the results of other bupivacaine-containing products studied in abdominoplasty. Sample size is estimated at 360 patients, with 180 patients per treatment group. The effect size with INL-001 in the combined results of 2 clinical Phase 3 studies in postoperative analgesia after open inguinal hernia repair was 0.525 for SPI24. The effect size with INL-001 for SPI48 was 0.25. With the historical SPI48 effect size of 0.25, 360 evaluable patients will yield a power of at least 66%; however, it is believed that a greater separation between the INL-001 and placebo treatment groups will be observed for abdominoplasty given that postoperative pain is more severe and longer lasting than with inguinal hernia repair, yielding greater power. This is increased to 372 patients to potentially counter the effects of imputation for dropouts, but all randomized and treated patients will be evaluable and included in the modified intent-to-treat (mITT) analyses.

9.2 Analysis Sets

9.2.1 Intent-to-Treat Population

The intent-to-treat (ITT) population will consist of all patients randomly assigned to study treatment who may or may not have received any dose of study drug (INL-001 or placebo collagen implants). The ITT population will be used mainly for disposition patient-count purposes. Following the ITT principle, data from patients will be analyzed according to assigned treatment at randomization.

9.2.2 Modified ITT Population

The mITT population will consist of all patients randomly assigned to study treatment who receive any dose of study drug. Following the ITT principle, data from patients will be analyzed according to their assigned treatment at randomization. The mITT population will be the primary population for efficacy assessments.

9.2.3 Safety Analysis Set

The safety population will consist of all patients who receive any dose of study drug. Data will be analyzed according to treatment received. The safety population will be used for safety analyses.

9.2.4 All Patients

All patient data entered into the electronic data capture system will be used for the patient disposition displays and may include data from patients who did not meet screening criteria.

9.3 Data Handling Conventions

For all variables other than SPI, only the observed data from the patients will be used in the statistical analyses, ie, there is no plan to estimate missing data, unless otherwise specified. If conducted, detailed data imputation rules will be described in the SAP.

See Section 9.5 concerning SPI scores for the handing of missing data and rescue medications.

9.4 Study Population

The safety analysis set (see Section 9.6) will be used for all study population summaries unless otherwise specified. Summaries will be presented by surgery type and for all patients.

9.4.1 Patient Disposition

Data from patients screened; patients enrolled; patients enrolled but not treated; patients in the safety, ITT, and mITT analysis sets; patients who complete the study; and patients who withdraw from the study will be summarized using descriptive statistics. Data from patients who withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics.

9.4.2 Demographic and Baseline Characteristics

Patient demographic and baseline characteristics will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be provided. For categorical variables, patient counts, and percentages will be provided. Categories for missing data will be presented, if necessary. Patients will be stratified by study center and BMI (<30 kg/m^2 and ≥ 30 kg/m^2).

9.5 Efficacy Analysis

The estimand for the primary efficacy endpoint will use a hypothetical strategy. Intermittent missing values will be assumed to fall along a line connecting the observed values on either side of the missing value. For the intercurrent event of rescue medication, patients will have their pain recorded just prior to the administration of rescue medication; to estimate what the pain values may have been had the rescue not been administered, if all values are less than the pain score recorded just prior to administration of rescue medication, then the values collected during the period (4 hours) of efficacy of the rescue medication will be replaced with values falling on a line connecting the pain score recorded just prior to rescue medication administration to the first pain score outside the duration of efficacy of the rescue medication. However, pain scores that

are equal to or greater than the score measured just prior to administration will be included in the calculation. For the intercurrent event of discontinuation, data for patients who discontinue the study for lack of efficacy and for adverse events will be assumed to follow the distribution of the worst values observed to the point of withdrawal; data for patients withdrawing for other reasons will be assumed to follow the distribution of the values in their treatment group.

The SPI (AUC of pain intensity as measured by the NPRS) through various time points up to 72 hours posttreatment will be calculated using the trapezoidal method with NPRS scores and the actual assessment times in hours. The primary efficacy variable will be SPI24, but the same general rules and calculations will apply for all $SPI_{0\text{-time}}$. For SPI24 calculation, both scheduled and unscheduled values (if available) from Time 0 through 24 hours posttreatment will be used in the calculation. For patients who receive rescue medication, just prior to it being administered, a pain score will be obtained; this will be included in the calculation of the SPI. Pain score(s) for the duration of the rescue efficacy following treatment with an opioid rescue medication will be excluded from the calculation if they are lower than the pain score just prior to rescue medication administration; those that are equal to or higher will be included. This period will be 2 hours following iv morphine and 4 hours following oxycodone. Pain scores in this window that are less than the pain recorded just prior to rescue medication administration will be excluded from the calculation, and linear interpolation will be used to connect the pain just prior to rescue medication administration to the first measure outside of 2 or 4 hours after administration of iv morphine or oral oxycodone, respectively.

Assuming a patient has a 24-hour nominal value, their SPI value will be normalized to exactly 24 hours. Should the patient be missing the nominal 24-hour value, but has a subsequent NPRS score recorded, linear interpolation will be performed to impute the 24-hour value by connecting the prior and subsequent values and calculating where the 24-hour value would fall on that line. The previously stated rules around rescue medication use will be applied should the 24-hour value fall within the 2- or 4-hour window of rescue medication use; the NPRS score collected from the associated rescue medication use will serve as the prior point for the imputation and the first subsequent noncensored value will serve as the other anchor. If observed values are greater than or equal to the pre-rescue−medication value (and before the 24-hour cut-off), then they will be used.

If a patient withdraws from the study and does not continue to provide pain assessments or has no values following a missing/censored 24-hour value, multiple imputation methods will be employed using observed data and reason for withdrawal. First, all pain intensity values will be assigned to their nominal time points for the purposes of creating covariates for the multiple imputation; when a rescue medication was used, the scheduled values that fall in the censoring period will be replaced with the "pain right now" collected prior to the rescue use. This substitution will be employed only for executing the multiple imputation (MI) procedure for imputing values after withdrawal; the methods above will be used for the actual SPI calculation. Data for patients who discontinued early due to lack of efficacy or an adverse event(s) will be imputed using the distribution of the worst values observed to that point, conditioned on the nonmissing values. For patients who discontinue for any other reason, values will be imputed assuming missing at random; covariates will include all nonmissing pain-intensity assessments and imputation will be done within treatment group. For the multiple imputation stages, values will be imputed using 20 replicates and the Markov Chain Monte Carlo (MCMC) method implemented with the SAS (Statistical Analysis Software®) MI procedure. Patients who are

missing their 0.5-hour and/or 1-hour values will have that value imputed as the first nonmissing value and the SPI will be calculated as described. Full details of the SPI calculations will be in the SAP, including sensitivity analyses to test the robustness of the assumptions.

All efficacy comparisons will be based on the comparison of INL-001 vs placebo.

The primary efficacy variable, SPI24, will be analyzed using an analysis of covariance (ANCOVA) model with treatment as the main effect and a covariate for BMI (continuous). Summary statistics (sample size, mean, SD, median, minimum, maximum, and 25th and 75th percentiles) will be presented along with the least squares (LS) mean, standard error (SE), 95% CIs, difference in LS means, and p-values from the ANCOVA model.

To account for the interim analysis and potential sample size increase, the method of Cui et al 1999 will be employed. For the final analysis and resulting p-value, the data will be split for those patients included in the interim analysis and those not included in the interim analysis; data from these groups will be analyzed completely independently, then combined using the inverse normal method to test the null hypotheses that there is no difference between the treatment groups:

$$Z_1 = \Phi^{-1}(1 - p_1)$$

$$and\ Z_2 = w_1 Z_1 + w_2 \Phi^{-1}(1 - p_2)$$

where:
Z_1=the Z statistic for the first stage
Z_2=the combination test statistic at the end of the second stage
w_i=the weighting applied for each associated Z statistic
p_1=the first stage p-value
p_2=the second-stage p-value based on second-stage participants

For maximum statistical efficiency, the weights are defined prospectively according to the square root of the planned proportion of participants in the 2 stages, relative to the preplanned total enrollment of 360 patients, as $w_i=\sqrt{0.5}$. The calculation of these weights is fixed and will not be changed due to unblinded data; likewise, in the case of deviations from the planned proportions due to enrollment overrun (see interim analysis section below), the weights will remain fixed.

The key secondary efficacy variables include:

- SPI from Time 0 through 48 hours (SPI48)
- proportion of patients who are opioid free posttreatment through 24 hours
- proportion of patients who are opioid free posttreatment through 48 hours
- SPI from Time 0 through 72 hours (SPI72)
- proportion of patients who are opioid free posttreatment through 72 hours

An approach identical to the primary efficacy analysis will be used for each of the continuous key secondary variables and the same statistics will be presented. For key secondary outcomes of proportions, each proportion, the difference, and 95% confidence intervals (CIs) will be reported; the difference will be tested with the 2-proportion Z test (with Cui-Hung-Wang [CHW] method

applied to account for the interim analysis). In the case of low counts (any expected cell count ≤5), a Fisher's Exact test will be used; p-values will be transformed to an equivalent Z for applying the CHW method.

All continuous secondary efficacy variables will be summarized with appropriate descriptive statistics (sample size, mean, SD, coefficient of variation [CV], median, minimum, maximum, and 25th and 75th percentiles) and analyzed using ANCOVA models with treatment as the main effect and a covariate for BMI.

Summary graphs of efficacy data including TOpA and NPRS scores by treatment group (arithmetic means and standard error [SE]) vs nominal time will be plotted.

All categorical efficacy variables will be summarized with counts and proportions and compared by Cochran-Mantel-Haenszel tests (for ordered variables), Pearson chi-squared, or Fisher's exact tests as needed.

The time to first use of opioid rescue medication, time to discharge from the PACU, and time to no longer using rescue medication during the study will be summarized using Kaplan-Meier methods. Log rank tests will be used to compare treatment groups. The median time to discharge will be estimated together with the associated 95% CI.

Models containing additional blocking factors or covariates may be fit as secondary analyses.

9.6 Safety and Tolerability Analysis and Planned Method of Analysis

9.6.1 Safety and Tolerability Analysis

Safety variables include assessment of adverse events, clinical laboratory test results, vital signs measurements (including body temperature, pulse, systolic and diastolic blood pressure, respiration rate, and oxygen saturation measured by pulse oximetry), ECG findings, surgical wound grading, and concomitant medications. These analyses will be conducted for the safety population. No formal statistical tests will be performed on safety evaluations.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA), version 18 or later. The number and percentage of patients with adverse events will be displayed for each treatment group by system organ class (SOC) and preferred term. Summaries in terms of severity and relationship to study treatment will also be provided. Serious adverse events will be summarized separately in a similar fashion. In the case of multiple occurrences of the same adverse event for the same patient, the patient will be counted only once for each SOC and preferred term. All adverse events and serious adverse events will be listed by patient.

Adverse events collected from the assessments for systemic bupivacaine toxicity and wound healing will each be presented both as part of the adverse events overall and summarized separately. Additionally, the counts and percentages of patients in category of the Southampton Wound Grading Scale will be reported at each time point where it is collected.

Clinical laboratory test results, vital signs measurements, and any other appropriate quantitative safety data will be presented descriptively by treatment group at each time point for the baseline (screening) and postbaseline evaluations, as well as change from baseline, using descriptive statistics (number, mean, SD, median, minimum, and maximum).

ECG data including RR, PR, QRS, and QTc intervals will be summarized descriptively.

9.6.2 Planned Method of Analysis

The mITT analysis set (see Section 9.5) will be used for all efficacy analyses. In general, summaries will be presented overall and by surgery type.

The efficacy analysis will estimate the SPI24, SPI48, and SPI72.

9.7 Sensitivity Analysis

The following 2 sensitivity analyses will be performed:

- To investigate the impact of the assumed period of efficacy for the rescue medication, a shorter period of 2 hours following oxycodone and acetaminophen rescue medication administration, and 1 hour following morphine will be used in the imputation algorithm.
- To investigate the impact of the choice of reasons for discontinuation when imputing from the distribution of worst values, 2 additional analyses will be performed: the first will include data from patients who withdraw for “other” or “unknown” reasons in the group receiving values imputed from the distribution of worst value. (Additional items may also be included and detailed in the SAP.) The second will impute from the distribution of worst values for **all** withdrawn patients.

9.8 Multiple Comparisons and Multiplicity

The key secondary efficacy variables will be tested sequentially each at the 0.05-level to control the overall Type-I error rate. Specifically, each key secondary variable will be tested in order. The next key secondary variable will be tested if the prior secondary variable comparison is statistically significant. The order is as follows:

- SPI48
- proportion of patients who are opioid free posttreatment through 24 hours
- proportion of patients who are opioid free posttreatment through 48 hours
- SPI72
- proportion of patients that are opioid free posttreatment through 72 hours

9.9 Planned Interim Analysis

An interim analysis will be performed when approximately 50% of the initially planned population is evaluable with respect to efficacy. This interim analysis will be performed by unblinded personnel separate from those responsible for the conduct and analysis of the study; all decisions will be made on the basis of SPI24, SPI48 and/or SPI72. An independent committee will review the data and recommend to the sponsor one of the following:

- increase the sample size by up to 180 patients
- keep the current sample size and continue

SPI24 will be evaluated first. If the conditional power for SPI24 is at or over 90% with the current sample size, then the committee will base recommendations on SPI48 and/or SPI72. If the conditional power for SPI24 is between 20% and less than 90%, the committee will recommend increasing the sample size. This increase will be chosen by adding blocks of 10

patients with the goal of selecting the minimum number of patients such that the SPI24 conditional power is raised to at least 90%.

In the case that SPI24 conditional power is at or over 90%, SPI48 will be evaluated as above, ie, no change will be made if conditional power is at or over 90%; otherwise, the smallest increase that would raise its power over 90% will be chosen.

Likewise, if SPI48 conditional power is at or over 90%, SPI72 will be evaluated as above, ie, no change will be made if conditional power is at or over 90%; otherwise, the smallest increase that would raise its power over 90% will be chosen.

At each step, the subsequent SPI will also be checked. If its conditional power can be raised to over 90% with no more than an additional 30 patients beyond what the current step suggests, that will be the recommendation returned by the committee (again, in blocks of 10 patients). For example, if SPI24 is over 90% conditional power, but SPI48 required an increase of 38 patients and SPI72 required an increase of 63 patients, the recommended increase would be 70 patients (increases may only be done in blocks of 10 patients).

For SPI24, SPI48, and SPI72, if the conditional power at the current sample size is over 20% and the maximum increase of 180 patients falls short of raising the conditional power to at least 90%, the committee will recommend an increase of 180 patients No further information will be provided to the sponsor beyond this recommendation and the sponsor may choose to ignore the recommendation and leave the sample size unchanged.

Conditional power will be calculated using the following formula (Mehta and Pocock 2011):

$$CP(Z_1,\check{n}_2) = 1 - \Phi\left(\frac{Z_\alpha\sqrt{n_2} - Z_1\sqrt{n_1}}{\sqrt{\check{n}_2}} - \frac{Z_1\sqrt{\check{n}_2}}{\sqrt{n_1}}\right)$$

where Z_1 is the value of the Z score at the interim, n_1 is the actual sample size at the interim, n_2 is the total planned sample size (360 patients), and $\check{n}_2$ is the total planned sample size minus the actual sample size at the interim.

Due to the speed of enrollment, it is possible full enrollment of the initial sample size will be achieved prior to the completion of the interim analysis. A small overrun may be possible in this scenario, if the committee does not recommend an increase.

9.10 Reporting Deviations From the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the SAP, the CSR, or any combination of these, as appropriate, and in accordance with applicable national, local, and regional requirements and regulations.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 General Quality Control and Assurance Measures

Steps to assure the accuracy and reliability of data and documentation include the selection of qualified research organizations/institutions, study investigators and appropriate investigational centers, review of protocol procedures with the investigator and associated personnel prior to starting the study, and periodic monitoring visits of the centers by the CRO. The protocol cannot be altered or changed except through a formal protocol amendment approved by Innocoll, signed by the investigator(s), and approved by the IRB before implementation.

Data and documentation generated for this study will be reviewed for accuracy and completeness by the CRO during and after on-site monitoring visits and any discrepancies will be resolved with the investigator or designees, as appropriate.

All information recorded in the CRF will be supported by corresponding source documentation. Acceptable source documentation includes, but is not limited to, hospital records, clinic and medical office charts, laboratory data, recorded data from automated instruments, memoranda, and pharmacy dispensing records. In some cases, the source documents may be in electronic format.

10.2 Method of Determining Protocol Compliance

Study drug will be implanted in eligible patients during surgery. Therefore, study drug treatment compliance will not be evaluated.

Compliance with respect to protocol procedures and the use of other medications will be strictly monitored.

10.3 Monitoring Procedures

The CRO monitors will conduct visits to the study facilities to monitor the study. The investigator will allow these monitors and other authorized Innocoll personnel and representatives access to study documentation and to the clinical supplies dispensing and storage area. On request, the investigator will assist the monitors in their activities. Requests by regulatory agencies and the sponsor (or its designees) to inspect the study centers may be made. The investigator will allow inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

Periodically, the CRO monitor or other CRO or Innocoll personnel or representatives will visit the study center for the purpose of directly comparing the data in the CRF with the source documents. The investigator will make source documents (hard copy or electronic) available for this purpose.

The investigator will ensure accurate completion of the CRFs and will approve the CRFs. The CRFs will be signed by the investigator or a subinvestigator to attest that the information contained within is accurate and true.

11 ETHICS

11.1 Ethical Conduct of the Study

The sponsor will ensure the ethical conduct of the study according to the Declaration of Helsinki and its amendments; the ICH and principles of GCP, including archiving of essential study documents; and all US FDA regulations and other applicable local regulations and guidelines.

A properly constituted, valid IRB must review and approve the protocol, the ICF, and related patient information and recruitment materials before the start of the study.

It is the responsibility of the investigator(s) to ensure that written informed consent is obtained from a patient before any activity or procedure is undertaken that is not part of routine care.

11.2 Informed Consent

The investigator or a qualified person designated by the investigator, should fully inform the patient of all pertinent aspects of the study, including the written information approved by the IRB. All written and oral information about the study will be provided in a language as nontechnical as practical to be understood by the patient. The patient should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. This will be captured in the source documents.

Written informed consent will be obtained from each patient before any study specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The patient's willingness to participate in the study will be documented in the ICF, which will be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The investigator will keep the original ICFs, and copies will be given to the patients. It will also be explained to the patients that the patient is free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment.

11.3 Competent Authorities and Review Boards

Before this study starts, the protocol will be submitted to the US FDA and to the respective IRB for review. As required, the study will not start at a given investigational center before the IRB and FDA give written approval or a favorable opinion.

11.4 Confidentiality Regarding Study Patients

The investigator must ensure that the privacy of the patients (including their identity and all personal medical information) will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names. This will be accomplished by an identification number.

Personal medical information may be reviewed for the purpose of patient safety or for verifying data in the source documents and the CRF. This review may be conducted by the study monitor, the sponsor, properly authorized persons on behalf of the sponsor, and health authorities. Personal medical information will always be treated as confidential.

12 COMPLIANCE STATEMENT

This study will be conducted in full accordance with the ICH, GCP E6, and any applicable national and local laws and regulations (eg, 21CFR Parts 11, 50, 54, 56, 312, and 314). Any episode of noncompliance will be documented.

The investigator is responsible for performing the clinical study in accordance with this protocol and the applicable GCP guidelines referenced above for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this clinical study in accordance with the protocol will be documented in separate clinical study agreements with the sponsor and other forms, as required by national competent authorities in the country where each investigational center is located.

The investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the clinical study and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the involved clinical study personnel must be familiar with the background and requirements of the study and with the properties of the study drug, as described in the IB (or prescribing information for a marketed product).

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the clinical study at that investigational center and for contacts with study management, with the IRB, and with competent authorities.

13 DATA HANDLING AND RECORD KEEPING

13.1 Direct Access to Source Data and Documents

All patient data must have supportive original source documentation in the medical records, or equivalent, before the data are transcribed to the CRF. Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

If data are processed from other institutions or by other means (eg, clinical laboratory data) the results will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management).

The medical experts, study monitors, auditors, IRB, and inspectors from competent authorities (or their agents) will be given direct access to source data and documents (eg, medical charts/records, laboratory test results, printouts) for source data verification, provided patient confidentiality is maintained in accordance with national and local requirements.

The investigator must maintain the original records (ie, source documents) of each patient's data at all times. The investigator must maintain a confidential patient identification list that allows the unambiguous identification of each patient.

13.2 Data Collection

Data will be collected using CRFs specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21CFR Part 11 (USA). Before using the CDMS, it will be fully validated, and all users will receive training on the system and study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel; CRFs must be completed for each patient who provided informed consent. Patient identity should not be discernible from the data provided on the CRF.

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory) these data will be sent to the investigational center where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management). All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF. Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

For patients who enter a study but do not meet entry criteria, at a minimum, data for screening failure reason, demography, and adverse events from the time of informed consent will be entered in the CRF.

13.3 Data Quality Control

Data management tasks for this study are delegated to a CRO and these functions may be carried out as described in the standard operating procedures (SOPs) for clinical studies at that

organization. These SOPs will be reviewed by the sponsor before the start of data management activities.

Data will be verified by the study monitor using the data source. Data identified as erroneous or data that are missing will be referred to the investigational center for resolution through data queries. Any necessary changes will be made in the clinical database and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS and any discrepancies will be queried.

Applicable terms will be coded according to the coding conventions for this study.

Once 50% of the patients are enrolled (about 180 patients) and, after all data are entered in the database for these patients, the CDMS and all other study data will be "locked" to further additions or corrections without written authorization by Innocoll. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate including decisions made and agreed to concerning the patients whose participation was in violation of the protocol. All data collected will be approved by the investigator at the investigational center. This approval acknowledges review by the investigator and acceptance of the data as being complete and accurate.

At the conclusion of the study, after all data are entered in the database, the CDMS and all other study data will be "locked" to further additions or corrections with written authorization by Innocoll. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate including decisions made and agreed to concerning the patients whose participation was in violation of the protocol. All data collected will be approved by the investigator at the investigational center. This approval acknowledges review by the investigator and acceptance of the data as being complete and accurate.

13.4 Archiving of Case Report Forms and Source Documents

13.4.1 Sponsor Responsibilities

The original CRFs will be archived by the sponsor. Investigational center-specific CRFs will be provided to the respective investigational centers for archiving.

13.4.2 Investigator Responsibilities

The investigator must maintain all written and electronic records, accounts, notes, reports, and data related to the study and any additional records required to be maintained under country, state/province, or national and local laws until the CRO or sponsor notifies the institution in writing that records may be destroyed, including, but not limited to:

- full case histories
- signed ICFs
- patient identification lists
- CRFs for each patient on a per visit basis
- data from other sources (eg, central laboratory, ECG evaluation)

- safety reports
- financial disclosure reports/forms
- reports of receipt, use, and disposition of the study drug
- copies of all correspondence with the sponsor, the IRB, and any health authority

If, after 10 years from study completion, or earlier in the case of the investigational center closing or going out of business, the investigator reasonably determines that study record retention has become unduly burdensome and sponsor has not provided written notification of destruction, then the investigator may submit a written request to sponsor at least 60 days before any planned disposition of study records. After receipt of such request, the sponsor may make arrangements for appropriate archival or disposition, including requiring that the investigator deliver such records to the sponsor. The investigator shall notify the sponsor of any accidental loss or destruction of study records.

14 FINANCIAL INFORMATION AND INSURANCE

For covered clinical studies (refer to 21CFR54), the investigator will provide the sponsor with financial information required to complete the FDA 3454 form. Each investigator will notify the sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

15 FINAL CLINICAL STUDY REPORT AND PUBLICATION POLICY

15.1 Registration of the Clinical Study

In compliance with national and local regulations and in accordance with Innocoll standard procedures, this clinical study will be registered on trials registry websites before the first patient is enrolled.

15.2 Clinical Study Report and Publications

Innocoll will retain ownership of the data.

The final CSR will be written after completion of the study and will include a summary of the study results based on a statistical evaluation and clinical assessment.

All unpublished information given to the investigator by the sponsor shall not be published or disclosed to a third party without prior written consent of the sponsor.

The results of this study may be published or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results provided in "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (www.ICMJE.org). Publication of the results will occur in a timely manner according to applicable regulations. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual investigational center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and aligned with International Committee of Medical Journal Editors authorship requirements:

- substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
- drafting the work or revising it critically for important intellectual content
- final approval of the version to be published
- agreement to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

The publications team established by the sponsor will oversee this process.

No patent applications based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.

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