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ORIGINAL RESEARCH

Pharmacokinetics and Safety of INL-001 (Bupivacaine HCl) Implants Compared with Bupivacaine HCl Infiltration After Open Unilateral Inguinal Hernioplasty

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ABSTRACT

Introduction: Surgical site infiltration with bupivacaine HCl results in short-lived analgesia for postsurgical pain and carries the risk of systemic bupivacaine toxicity due to accidental intravascular injection. INL-001 is a bupivacaine HCl collagen-matrix implant that provides extended delivery of bupivacaine directly at the site and avoids the risk of accidental injection. Here, we examine the pharmacokinetic (PK) and safety profile of INL-001 placement during unilateral open inguinal hernioplasty.

Methods: This multicenter, single-blind study (NCT03234374) enrolled patients undergoing open inguinal hernioplasty to receive three INL-001 implants, each containing 100 mg bupivacaine HCl (n = 34) or local infiltration of 0.25% bupivacaine HCl 175 mg (n = 16). Acetaminophen was provided in the postsurgical period and supplemented by opioids for breakthrough pain, as needed. PK blood samples were taken before surgery and up to 96 h after drug administration.

Results: INL-001 demonstrated a prolonged rate of absorption and clearance of bupivacaine compared with 0.25% bupivacaine HCl 175 mg, as demonstrated by a longer time to peak plasma concentration and terminal elimination half-life. Peak plasma concentration with INL-001 300 mg was comparable to bupivacaine HCl 175 mg and well below levels associated with systemic bupivacaine toxicity. The most common adverse events (AEs) in both groups were associated with general anesthesia and the postsurgical setting. No AE was related to the implant, including those associated with wound healing.

Conclusions: These findings demonstrate that INL-001 provides immediate and extended delivery of bupivacaine and is well tolerated in patients undergoing open inguinal hernioplasty with no adverse effect on wound healing.

Trial registration: Clinicaltrials.gov identifier, NCT03234374.

Keywords: Bupivacaine HCl; Collagen-matrix implant; INL-001; Postsurgical pain; Xaracoll

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Key Summary Points

Why carry out this study?

Patients undergoing open inguinal hernia repair experience acute postsurgical pain. Use of opioids to control postsurgical pain has inherent risks; pain relief following surgical site infiltration of bupivacaine HCl is relatively short lived, has a risk of accidental intravascular administration, and may result in subsequent systemic bupivacaine toxicity. INL-001 (Xaracoll®), a unique collagen implant that delivers bupivacaine HCl over time into the surgical site, was developed and studied to address medical need.

This study was performed to characterize the pharmacokinetics of INL-001 as well as to provide additional safety information, including the impact of INL-001 on incision site healing and monitoring for the occurrence of systemic bupivacaine toxicity.

What was learned from the study?

INL-001 rapidly releases bupivacaine into the systemic circulation upon placement at the surgical site, and systemic bupivacaine levels were observed through 96 h of postsurgical pain management.

There were no findings suggestive of an adverse effect on incision site healing, and there were no signs or symptoms of systemic bupivacaine toxicity in this study.

This study demonstrates that the bupivacaine HCl implant, INL-001, is an effective and well-tolerated treatment for postsurgical pain control in patients undergoing open inguinal hernia repair.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13200230.

INTRODUCTION

Early and satisfactory postsurgical analgesia is important because suboptimal acute-pain management can lead to increased patient morbidity, impaired physical function and quality of life, increased cost of care, and a transition from acute to chronic pain and delayed recovery [1]. Local anesthetics (LA) are commonly used during open inguinal herniorrhaphy, but management is difficult and often inadequate [2, 3]. Historically, opioids have been the mainstay of postsurgical pain management and, while effective for certain types of pain, their use poses significant risks [1, 4].

Infiltration of the surgical site with LAs, such as bupivacaine hydrochloride (HCl), is frequently part of a multimodal pain management regimen to limit opioid use [5]. However, surgical site infiltration produces short-lived analgesia because analgesic efficacy depends on the anesthetic remaining in the vicinity of the nerves [6, 7]. Furthermore, there are safety risks with infiltration, including local anesthetic systemic toxicity (LAST) due to accidental intravascular injection and dosing errors, which can be serious or fatal [6, 8–12]. The dose and rate of bupivacaine HCl infiltration are the pharmacokinetic (PK) parameters most closely associated with the risk for toxicity [6, 10]; however, there is no method of monitoring administration procedures to eliminate this risk [6].

INL-001, a 5 cm × 5 cm × 0.5 cm bioresorbable implant comprised of collagen containing 100 mg of homogeneously dispersed bupivacaine HCl [13], is indicated in adults for placement into the surgical site to produce postsurgical analgesia for up to 24 h following open inguinal hernia repair [14]. It is a single-application, ready-to-use product designed for

the management of acute postsurgical pain through the immediate and extended release of bupivacaine [13]. Preclinical studies demonstrated significant reabsorption within 1 month and no microscopically observable collagen at 2 months. Additional studies have demonstrated that commonly used surgical materials are not affected by INL-001 (unpublished data, Innocoll Inc.).

Local placement of INL-001 within multiple soft tissue layers during surgery offers a novel way to deliver bupivacaine HCl directly to the source of pain, while avoiding the risk of dosing errors and inadvertent intravascular injection.

The safety and efficacy of INL-001 have been evaluated in 11 clinical trials, with 892 patients having received INL-001 implants (612 INL-001; 280 placebo implants). In two pivotal phase 3 studies, MATRIX-1 and MATRIX-2 ($N = 624$ patients, 411 treated with INL-001 and 208 treated with placebo), the primary efficacy endpoint of the sum of pain intensity from 0 to 24 h (SPI24) after open inguinal hernioplasty was investigated [13]. Patients in these studies received either INL-001 or placebo implants and were discharged shortly after surgery. Individually, both studies demonstrated that INL-001 300 mg significantly reduced SPI24 (MATRIX-1, $p \leq 0.0004$; MATRIX-2, $p < 0.0001$) and led to significantly less total use of opioids in the first 24 h after surgery (MATRIX-1, $p < 0.0001$; MATRIX-2, $p < 0.0001$), compared with placebo [13]. The MATRIX-2 study demonstrated significant reductions in pain ($p = 0.0270$) and total opioid use ($p = 0.0003$) through 48 h with INL-001, and the MATRIX-1 study demonstrated a similar magnitude of effect in the reduction of pain without reaching significance ($p = 0.0568$). There was no statistically significant treatment effect for INL-001 compared with placebo for pain reduction or total use of opioids through 72 h (not tested in MATRIX-1; MATRIX-2, $p = 0.1490$); however, there was a higher proportion of patients who did not receive opioid rescue analgesia in the INL-100 versus placebo group in both studies. In MATRIX-1, through 72 h after surgery, 36% of INL-001-treated patients and 22% of placebo-treated patients did not use any opioids (MATRIX-2 values were 28% and 12%, respectively) [13]. Based on overall data, INL-001 received approval by the US Food and Drug Administration (FDA) with an indication for use in adults for placement into the surgical site to produce postsurgical analgesia for up to 24 h following open inguinal hernia repair.

The primary objective of this study (NCT03234374) was to evaluate the PK profile of INL-001 300 mg compared with 0.25% bupivacaine HCl 175 mg infiltration. The maximum concentration was identified as a key PK parameter for comparison because it is generally thought to be the primary driver of systemic bupivacaine toxicity [10]. The secondary objective of this study was to assess the safety and tolerability of INL-001, with emphasis on wound healing and the signs and symptoms of bupivacaine toxicity.

METHODS

This multicenter, randomized, single-blind, active comparator-controlled study (NCT03234374 posted on July 31, 2017, at https://clinicaltrials.gov/ct2/show/NCT03234374?term=inl-001&draw=2&rank=1) enrolled men and women aged ≥ 18 years that were undergoing elective unilateral inguinal hernioplasty via open laparotomy. The repair of multiple hernias through a single incision was permitted. This trial enrolled patients across five sites in the US from June through August 2017. Patients were randomized to receive either three INL-001 (Xaracoll®, Innocoll Pharmaceuticals Ltd., Athlone, Ireland) 100 mg bupivacaine HCl implants, for a total of 300 mg bupivacaine HCl ($n = 35$), or local infiltration of 0.25% bupivacaine HCl (Marcaine) 175 mg ($n = 17$).

The protocol and statement of informed consent were approved by an Institutional Review Board (IRB) prior to each center's initiation (see Table S1 in Supplementary materials). All procedures were conducted in accordance with the Declaration of Helsinki, and the study was conducted in compliance with Good Clinical Practice guidelines. Informed consent was obtained from all participants. In addition, eligible individuals must have had the ability and

willingness to comply with study procedures and to use only permitted medications (including opioids).

Patients were excluded from enrollment if they had a known hypersensitivity to amide local anesthetics, morphine, acetaminophen, or bovine products. Patients were also excluded if they were scheduled for bilateral inguinal hernia repair or another significant surgical procedure concomitantly. In addition, eligible patients could not have undergone major surgery within 3 months of initial treatment nor were they permitted to have another laparotomy procedure planned for within the 30-day postsurgical period. Also, patients with a known or suspected history of alcohol or drug abuse or misuse within 3 years of screening or a clinically significant unstable cardiac, neurologic, immunologic, renal, hepatic, or hematologic disease or any other significant condition were excluded.

Enrolled patients underwent elective unilateral inguinal hernioplasty via open laparotomy according to standard procedures. In the INL-001 group, three implants (each containing 100 mg of bupivacaine HCl) were cut in half; these six implants were placed in protocol-defined locations in the surgical site. After the hernia sac was reduced and the mesh was ready for insertion, three of the six implants were placed into the hernia repair site below the site of mesh placement. The mesh placement was completed per the surgeon's typical technique. The external oblique aponeurosis was closed, and the remaining three implants were placed between the fascia/muscle closure and skin closure. The subcutaneous tissue and skin were closed per the surgeon's preferred method. If the surgeon encountered a significant surgical or medical complication, there was the option not to administer the study drug; this patient would be considered randomized, but not enrolled or treated. The comparator group was treated with 0.25% bupivacaine HCl 175 mg infiltrated into the muscular planes of the transverse abdominis and interior oblique muscles as well as the surrounding subcutaneous tissues. This dose of bupivacaine HCl (175 mg) was chosen because it represents a common clinically used dose per the prescribing information for bupivacaine HCl injection (Marcaine) and was the dose predicted to most closely result in a maximum concentration similar to that of INL-001 300 mg.

Following surgery, patients were transferred to a postanesthesia care unit (PACU) until stable and then moved to the clinic where they were allowed to receive parenteral morphine, if needed, as a rescue medication for breakthrough pain. Once patients were able to tolerate oral medication, they were started on a standardized oral analgesic regimen of acetaminophen 650 mg three times daily (TID). They were prescribed immediate-release morphine (15 mg) to manage breakthrough pain.

PK Assessments

Patients remained at the clinic at least until the 72-h blood sample was collected. After discharge, patients returned to the clinic to complete the 96-h blood draw. For PK assessment, blood samples were collected before Time 0 (the time of implantation or infiltration) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 36, 48, 72, and 96 h after Time 0. The following PK parameters for bupivacaine were assessed when possible: maximum (peak) plasma concentration (C_{max}), time to maximum (peak) plasma concentration (T_{max}), lag-time (t_{lag}), terminal elimination half-life ($t_{1/2}$), terminal phase rate constant (λ_z), area under the plasma concentration-time curve (AUC) from Time 0 to time of last quantifiable plasma concentration ($AUC_{0–last}$), AUC from Time 0 to infinity ($AUC_{0–\infty}$), and percentage extrapolation ($AUC_{extrap\%}$) ($100 \times [AUC_{0–\infty} - AUC_{0–last}]/AUC_{0–\infty}$).

The λ_z was not presented for patients who did not exhibit a terminal elimination phase in their concentration-time profiles. To estimate λ_z, linear regression of the concentration in logarithm scale vs. time was performed using at least three data points. Uniform weighting was selected to perform the regression analysis to estimate λ_z.

Safety Assessments

Safety assessments included the following: physical examinations performed at screening; postsurgical assessment of vital signs through 72 h; 24-h continuous electrocardiogram (ECG) obtained at screening, prior to surgery, and 24 h following study drug administration; measurement of oxygen saturation levels prior to surgery and for at least 12 h after study drug administration; and adverse event (AE) reporting. Once discharged from the clinic, patients were instructed to return to the clinic on days 5, 7, 15, and 30 for follow-up safety assessments.

The number and percentage of patients who reported one or more treatment-emergent AEs (TEAEs), serious AEs, drug-related TEAEs, or TEAEs leading to removal of the implants were summarized for each treatment group. TEAEs were defined as any AE that occurred after implantation/infiltration. The Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 was used to classify all AEs according to system organ class (SOC) and preferred term (PT). Patients reporting more than one AE for a given MedDRA PT or SOC were counted only once for that term or SOC using the most severe incident.

In addition, the safety endpoints included the following two specific assessments: one focused on the signs and symptoms typically associated with wound healing and the other focused on the signs and symptoms associated with potential bupivacaine toxicity. The number and percentage of patients with signs and symptoms related to impaired wound healing and potential bupivacaine toxicity were summarized descriptively at each scheduled time point for each treatment. Specific signs and symptoms potentially associated with wound healing were assessed during the 4-day inpatient observation period and through the 30-day outpatient period.

Systemic bupivacaine toxicity is generally identified by a constellation of central nervous system and cardiovascular AEs. Signs and symptoms reported as potentially indicative of bupivacaine toxicity (i.e., anxiety, blurred vision, change in the level of consciousness, depression, dizziness, drowsiness, incoherent speech, light-headedness, metallic taste, numbness and tingling of the mouth and lips, respiratory difficulty, restlessness, tinnitus, and tremors) were collected at the following time points after Time 0 (or more frequently if needed) in both treatment groups: 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 h (± 15 min); and then 15, 18, 24, 36, 48, and 72 h (± 1 h).

Statistical Analysis

The randomized population consisted of all patients, whether or not they received treatment. The safety population consisted of all patients who received INL-001 or 0.25% bupivacaine HCl infiltration. The PK population consisted of all patients who received INL-001 or 0.25% bupivacaine HCl infiltration and had at least one postimplantation/infiltration blood sample obtained. The per-protocol PK population consisted of all patients in the PK population who had no major PK-related protocol deviation and had sufficient data to calculate the C_{max}, $AUC_{0-\infty}$, and AUC_{0-last}.

Continuous data were summarized using descriptive statistics. Geometric mean and geometric mean percent coefficient of variation (CV%) were also provided for the summary of C_{max} and AUC. Patients with 0 values were excluded from the calculation of geometric mean and geometric mean CV%.

RESULTS

Fifty-two patients were randomized to the study. Of the 35 patients in the INL-001 group, 34 (97.1%) completed the study and 1 (2.9%) was randomized but not enrolled. Of the 17 patients in the 0.25% bupivacaine HCl infiltration group, 16 (94.1%) completed the study and 1 (5.9%) was randomized but not enrolled (Fig. 1).

The 50 patients enrolled comprised the safety, PK, and per-protocol PK populations, all of whom received INL-001 or 0.25% bupivacaine HCl infiltration, had at least one postimplantation/infiltration blood sample obtained, had no major PK-related protocol deviation, and had sufficient data to calculate the C_{max},

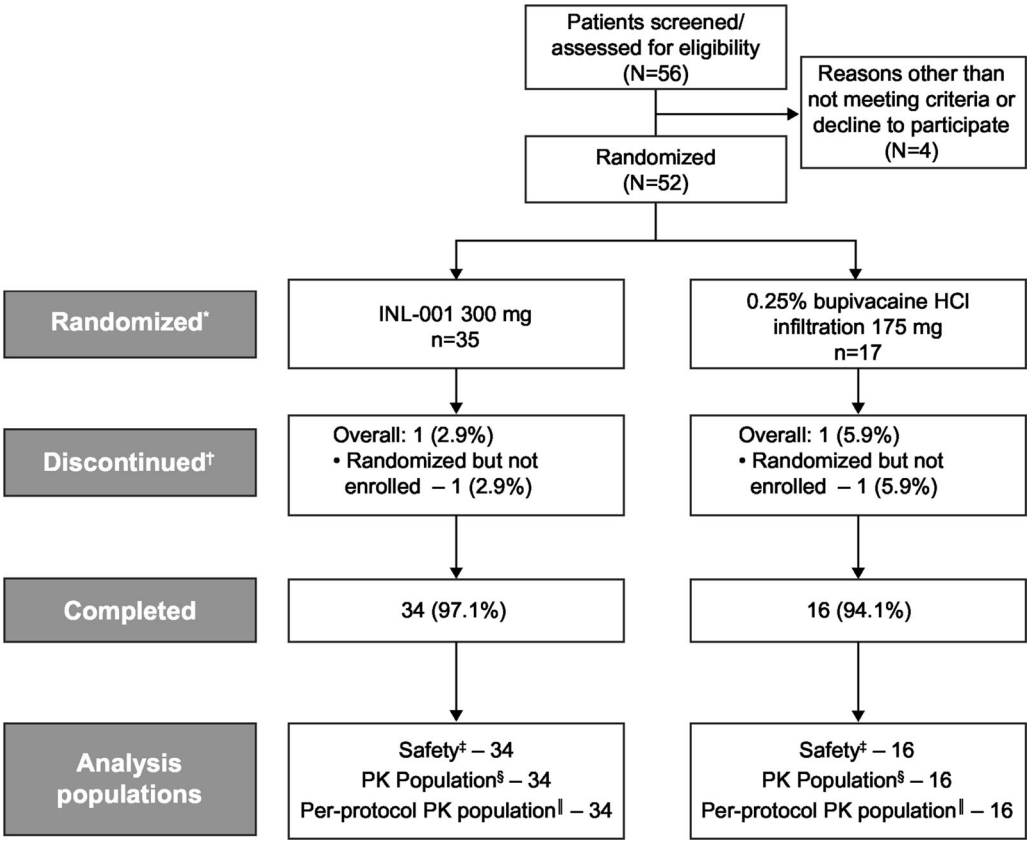

Fig. 1 Study flow diagram. *HCl* hydrochloride, *PK* pharmacokinetic. Asterisk: Randomized population = all patients who received a randomization number, regardless of whether they received the study drug. Dagger: Patients were considered randomized, but not enrolled or treated if the investigator encountered a condition during surgery which prevented placement of an implant. Double dagger: Safety population = all patients who received INL-001 bupivacaine HCl collagen-matrix implant or 0.25% bupivacaine HCl infiltration. Section sign: PK population = all patients who received study drug and had ≥ 1 postimplantation/infiltration blood sample obtained. Double verticle line: Per-protocol PK population = all patients in the PK population with no major PK-related protocol deviations and who had sufficient data to calculate

AUC_{0-last}, and $AUC_{0-\infty}$ for either INL-001 or 0.25% bupivacaine HCl infiltration. Table 1 summarizes demographic and baseline characteristics by treatment for the safety population. Demographics were comparable across the treatment groups, and most patients were male (98.0%) and white (92.0%); the mean ± standard deviation (SD) age was 44.3 ± 14.0 years. No clinically significant abnormalities were reported for the physical examinations performed at screening.

Pharmacokinetics

There were quantifiable bupivacaine concentrations at the first time point measured (0.5 h) for all patients treated with INL-001 and 0.25% bupivacaine HCl infiltration. Bupivacaine concentrations were detectable through 96 h in both treatment groups. The mean bupivacaine concentration was higher in patients receiving 0.25% bupivacaine HCl infiltration for the first 1.5 h (504.881 ng/mL at 0.5 h; 577.560 ng/mL at 1.0 h; 555.875 ng/mL at 1.5 h) compared with the INL-001 group (240.672 ng/mL at 0.5 h; 367.091 ng/mL at 1.0 h; 520.515 ng/mL

Table 1 Patient demographics (safety population)

Demographics/baseline characteristics	INL-001 300 mg *n* = 34	0.25% Bupivacaine HCl infiltration 175 mg *n* = 16
Age, years, mean (SD)	45.6 (14.8)	41.6 (12.2)
Sex, *n* (%)		
Male	33 (97.1)	16 (100)
Female	1 (2.9)	0
Race, *n* (%)		
White	31 (91.2)	15 (93.8)
Black	3 (8.8)	0
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (6.3)
Ethnicity, *n* (%)		
Hispanic or Latino	7 (20.6)	3 (18.8)
Non-Hispanic or Latino	27 (79.4)	13 (81.3)
BMI, kg/m^2, mean (SD)	27.4 (5.0)	27.8 (4.9)

BMI body mass index, *HCl* hydrochloride, *SD* standard deviation

at 1.5 h), as shown in Fig. 2a. From 2 through 96 h, the mean bupivacaine concentrations were lower in the 0.25% bupivacaine HCl infiltration group (518.875 ng/mL at 2 h, 420.688 ng/mL at 3 h; gradually reduced to 118.581 ng/mL by 36 h and 5.378 ng/mL at 96 h) compared with the INL-001 group (601.636 ng/mL at 2 h, 595.212 at 3 h; gradually reduced to 237.600 ng/mL at 36 h and 26.948 ng/mL at 96 h; Fig. 2b).

The INL-001 group had an extended median T_{max} (3.0 h) and mean $t_{1/2}$ (19.0 h) compared with the 0.25% bupivacaine HCl infiltration group (T_{max}, 1.01 h; $t_{1/2}$, 9.08 h; Table 2). The C_{max} was similar between the INL-001 and 0.25% bupivacaine HCl infiltration groups (663.412 ng/mL and 641.000 ng/mL, respectively). The INL-001 group vs. 0.25% bupivacaine HCl infiltration group had higher geometric means for AUC_{0-last} (18,186.9 h*ng/mL vs. 8836.9 h*ng/mL, respectively) and $AUC_{0-\infty}$ (19,012.5 h*ng/mL vs. 8920.1 h*ng/mL, respectively). The highest individual bupivacaine plasma concentration observed in the INL-001 treatment group (1230.00 ng/mL) was comparable to the highest observed in the 0.25% bupivacaine HCl infiltration treatment group (1140.00 ng/mL).

TEAEs

TEAEs were reported by 97.1% of patients in the INL-001 group and 93.8% of patients in the 0.25% bupivacaine HCl infiltration group (Table 3). The most common TEAEs in the INL-001 and 0.25% bupivacaine HCl infiltration groups were somnolence (55.9%, 62.5%), dizziness (35.3%, 43.8%), constipation (23.5%, 6.3%), vision blurred (23.5%, 18.8%), and dysgeusia (11.8%, 25.0%), respectively. Most TEAEs were considered mild in severity for both the INL-001 (76.5%) and 0.25% bupivacaine HCl (68.8%) treatment groups. There was only one TEAE classified as moderate in severity (incision site inflammation) in the INL-001 group and none classified as severe in either treatment group. No patient in the study discontinued because of a TEAE, and there was no serious AE.

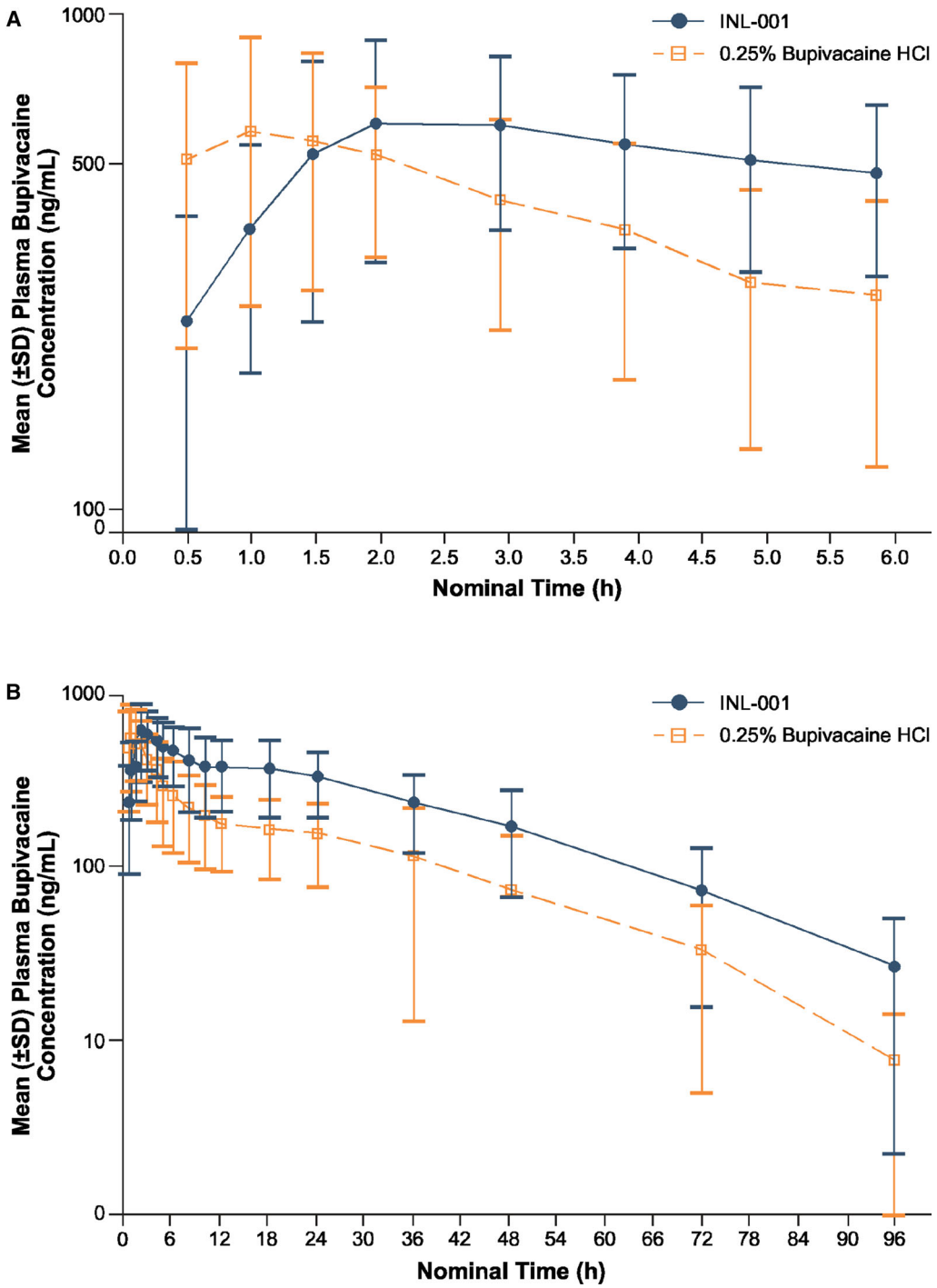

Fig. 2 Mean (± SD) plasma bupivacaine concentrations by treatment on semi-logarithmic scale (PK population). **a** Expanded initial postsurgical period of 0 to 6 h. **b** Full period of PK measurements from 0 to 96 h postsurgery. Note: If the actual sampling time (measured from dosing) was outside of the collection window for nominal time points, the corresponding concentration was excluded from concentration vs. time descriptive summaries and plots but was still used in the calculation of PK parameters. The lower limit of quantitation for bupivacaine was 1 ng/mL. *HCl* hydrochloride, *PK* pharmacokinetic, *SD* standard deviation

Table 2 PK parameters (per-protocol PK population)

PK parameter	INL-001 300 mg *n* = 34	0.25% Bupivacaine HCl infiltration 175 mg *n* = 16
Median T_{max}, h (min, max)	3.0 (1.5, 24.0)	1.0 (0.5, 4.0)
Mean $t_{1/2}$, h (SD)	19.0 (5.9)	9.1 (3.8)
Mean C_{max}, ng/mL (SD; range)	663.4	641.0
	(263.8; 274–1230)	(262.7; 275–1140)
AUC_{0-last}, h * ng/mL), geometric mean (geometric CV%[a])	18,186.9 (39.0)	8836.9 (46.3)
$AUC_{0-\infty}$ h * ng/mL, geometric mean (geometric CV%[a])	19,012.5 (38.7)	8920.1 (46.7)

AUC area under the concentration-time curve, $AUC_{0-\infty}$ AUC from 0 to infinity, AUC_{0-last} AUC from Time 0 to the last quantifiable plasma concentration, C_{max} maximum (peak) plasma concentration, *CV* coefficient of variation, *HCl* hydrochloride, *PK* pharmacokinetic, *SD* standard deviation, $t_{1/2}$ terminal elimination half-life, T_{max} time to C_{max}
[a]Geometric CV% = 100 * $(\exp(SD^2) - 1)^{0.5}$, where SD was of the log-transformed data

For the INL-001 group, 17.6% of patients reported a treatment-related TEAE compared with 12.5% of patients in the 0.25% bupivacaine HCl infiltration group (Table 4). The most common treatment-related TEAEs in both groups were tremor (8.8%, 6.3%), dysgeusia (5.9%, 6.3%), and somnolence (5.9%, 6.3%) for the INL-001 and 0.25% bupivacaine HCl infiltration groups, respectively.

Wound Healing

There was no evidence of a meaningful adverse effect on wound healing in either treatment group at any time point. Specific signs and symptoms potentially associated with short-term postoperative wound healing as listed on the assessment were recorded, by treatment, during the 4-day observation period (Table 5). For the INL-001 treatment group, during protocol-defined wound-healing assessment time points, "wound pain or soreness" was reported by 2.9% of patients on day 3 and 5.9% of patients on day 4; "swelling in the area around the wound" was reported by 5.9% of patients on day 4. For the 0.25% bupivacaine HCl infiltration treatment group, "wound pain or soreness" was reported by 6.3% of patients on day 4; "swelling in the area around the wound" was reported by 6.3% of patients on days 1, 2, 3, and 4; "discharge or leakage of fluid" was reported by 6.3% of patients on day 1. Duration of individual incision site-related TEAEs was recorded. Three patients had incision site-related TEAEs that lasted > 10 days. One patient had mild symptoms of incision site swelling, warmth, and inflammation with a duration of 34–36 days, one patient had mild incision site inflammation for 11 days, and one patient with moderate incision site inflammation had this symptom for a duration of 14 days. The remaining TEAEs associated with the incision site or surgical wound had a duration of ≤ 4 days.

Specific signs and symptoms potentially associated with long-term wound healing, as listed on the assessment, were recorded, by treatment, during the outpatient visits through 30 days post-surgery (Table 5). Among these, for the INL-001 treatment group, "swelling in the area around the wound" was reported by 8.8% of patients each on days 5 and 7, one (2.9%) patient on day 15, and two (5.9%) patients on day 30. For the 0.25% bupivacaine HCl infiltration treatment group, "swelling in the area around the wound" was reported by 12.5% of patients each on days 5 and 7. "Problems with hernia repair surgery" was reported by 5.9% of patients on day 7 and by 2.9% of patients on day 15 for those treated with INL-001 and 6.3% of patients on day 7 for those treated with 0.25% bupivacaine HCl infiltration.

Table 3 Most common (≥ 5% in any treatment group) TEAEs by system organ class and preferred term (safety population)

System organ class preferred term	INL-001 300 mg *n* = 34	0.25% Bupivacaine HCl infiltration 175 mg *n* = 16
Patients with any TEAE, *n* (%)	33 (97.1)	15 (93.8)
Nervous system disorders	26 (76.5)	13 (81.3)
Somnolence	19 (55.9)	10 (62.5)
Dizziness	12 (35.3)	7 (43.8)
Tremor	6 (17.6)	3 (18.8)
Dysgeusia	4 (11.8)	4 (25.0)
Headache	4 (11.8)	1 (6.3)
Gastrointestinal disorders	12 (35.3)	4 (25.0)
Constipation	8 (23.5)	1 (6.3)
Oral hypoesthesia	3 (8.8)	2 (12.5)
Nausea	3 (8.8)	2 (12.5)
Oral paresthesia	3 (8.8)	2 (12.5)
Eye disorders	10 (29.4)	3 (18.8)
Vision blurred	8 (23.5)	3 (18.8)
Psychiatric disorders	7 (20.6)	4 (25.0)
Restlessness	6 (17.6)	2 (12.5)
Anxiety	2 (5.9)	1 (6.3)
Injury, poisoning, and procedural complications	6 (17.6)	1 (6.3)
Incision site complications	3 (8.8)	0
Ear and labyrinth disorders	3 (8.8)	1 (6.3)
Tinnitus	3 (8.8)	1 (6.3)
Cardiac disorders	2 (5.9)	2 (12.5)
Bradycardia	2 (5.9)	1 (6.3)

TEAEs were defined as any adverse event that occurred after implantation/infiltration. Adverse events were coded using the MedDRA (version 18.0)
HCl hydrochloride, *MedDRA* Medical Dictionary for Regulatory Activities, *TEAE* treatment-emergent adverse event

Other wound-healing signs and symptoms reported by those treated with INL-001 included the following: "warmth in the area around the wound" was reported by 11.8% of patients on day 5 and 2.9% of patients on days 7, 15, and 30. "Any wound pain or soreness" was reported by 8.8% of patients on day 5, 5.9% of patients on day 7, and 2.9% of patients on day 30.

Table 4 Summary of treatment-related TEAEs by system organ class and preferred term (safety population)

System organ class preferred term	INL-001 300 mg *n* = 34	0.25% Bupivacaine HCl infiltration 175 mg *n* = 16
Patients with any treatment-related TEAE, *n* (%)	6 (17.6)	2 (12.5)
Nervous system disorders	4 (11.8)	2 (12.5)
Tremor	3 (8.8)	1 (6.3)
Dysgeusia	2 (5.9)	1 (6.3)
Somnolence	2 (5.9)	1 (6.3)
Dizziness	1 (2.9)	0
Gastrointestinal disorders	2 (5.9)	0
Dry mouth	1 (2.9)	0
Hypoesthesia oral	1 (2.9)	0
Paresthesia oral	1 (2.9)	0
Injury, poisoning, and procedural complications	1 (2.9)	0
Incision site inflammation	1 (2.9)	0
Psychiatric disorders	1 (2.9)	0
Restlessness	1 (2.9)	0

TEAEs were defined as any adverse event that occurred after implantation/infiltration. Adverse events were coded using the MedDRA (version 18.0)
HCl hydrochloride, *MedDRA* Medical Dictionary for Regulatory Activities, *TEAE* treatment-emergent adverse event

"Redness or inflammation spreading from the edges" was reported by 2.9% of patients on days 5, 7, 15, and 30. "Discharge or leakage of fluid" and "separation of the edges of any part of the wound" were reported by 2.9% of patients on day 5. "See a healthcare provider about the wound" was reported by one (2.9%) patient on day 7.

Bupivacaine Toxicity

"Drowsiness" was the only sign or symptom of potential bupivacaine toxicity per the assessment reported by ≥ 15% of patients in both treatment groups. Following treatment with INL-001, "drowsiness" was reported by 11 (32.4%) patients after 1 h, six (17.6%) patients after 2 h, seven (20.6%) patients after 3 h, and eight (23.5%) patients after 4 h. Following treatment with the 0.25% bupivacaine HCl infiltration, drowsiness was reported by four (25.0%) patients after 0.5 h, seven (43.8%) patients after 1 h, four (25.0%) patients after 2 h, four (25.0%) patients after 3 h, and three (18.8%) patients after 5 h. "Drowsiness" generally resolved within 5–9 h post-surgery for patients in both treatment groups. In the 0.25% bupivacaine HCl infiltration treatment group, "metallic taste" was reported by three (18.8%) patients 1 h after treatment. All other signs and symptoms on the assessment were reported by < 15% of patients in the 0.25% bupivacaine HCl infiltration treatment group.

Vital Signs and Holter Monitor

No clinically significant abnormality was reported for the vital signs monitored during the study or the continuous ECG screening performed prior to surgery and following INL-

Table 5 Specific signs and symptoms potentially associated with wound healing (safety population) per utilized assessment

	INL-001 300 mg *n* = 34				**0.25% Bupivacaine HCl infiltration 175 mg *n* = 16**			
	Observation period, days				**Observation period, days**			
Short-term wound healing,[a] *n* of patients (%)	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Any wound pain or soreness	0	0	1 (2.9)	2 (5.9)	0	0	0	1 (6.3)
Swelling in the area around the wound	0	0	0	2 (5.9)	1 (6.3)	1 (6.3)	1 (6.3)	1 (6.3)
Discharge or leakage of fluid	0	0	0	0	1 (6.3)	0	0	0
Redness or inflammation spreading from the edges	0	0	0	0	0	0	0	0
Separation of the edges of any part of the wound	0	0	0	0	0	0	0	0
Warmth in the area around the wound	0	0	0	0	0	0	0	0
Long-term wound healing,[b] *n* of patients (%)	**5**	**7**	**15**	**30**	**5**	**7**	**15**	**30**
Warmth in the area around the wound	4 (11.8)	1 (2.9)	1 (2.9)	1 (2.9)	0	0	0	0
Any wound pain or soreness	3 (8.8)	2 (5.9)	0	1 (2.9)	0	0	0	0
Swelling in the area around the wound	3 (8.8)	3 (8.8)	1 (2.9)	2 (5.9)	2 (12.5)	2 (12.5)	0	0
Redness or inflammation spreading from the edges	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	0	0	0	0
Discharge or leakage of fluid	1 (2.9)	0	0	0	0	0	0	0
Problems with hernia repair surgery	0	2 (5.9)	1 (2.9)	0	0	1 (6.3)	0	0
See a healthcare provider about the wound	0	1 (2.9)	0	0	0	0	0	0
Prescribed antibiotics for an infection in the wound	0	0	0	0	0	0	0	0
Separation of the edges of any part of the wound	0	0	0	0	0	0	0	0
Admitted to a hospital with an infection of the surgical wound	0	0	0	0	0	0	0	0

HCl hydrochloride

[a] Signs and symptoms potentially associated with wound healing collected during the 4-day inpatient stay post-surgery. [b]Signs and symptoms potentially associated with wound healing collected during the 30-day outpatient visit post-surgery

001 implantation/0.25% bupivacaine HCl infiltration. No clinically meaningful trends in oxygen saturation were observed post-surgery.

DISCUSSION

INL-001 is a drug-device combination that delivers bupivacaine HCl, utilizing a collagen-matrix drug delivery technology designed to be implanted in the surgical site at the time of elective open inguinal hernia repair. This study supports that INL-001 begins to release bupivacaine immediately upon placement in the surgical area and provides a continued release of bupivacaine over time, as evidenced by quantifiable bupivacaine concentrations at the first time point measured (0.5 h) through the last time point measured (96 h).

For the INL-001 dose of 300 mg of bupivacaine HCl, which has been shown to be effective for pain relief and well tolerated in clinical trials of open inguinal hernia repair [13], the mean maximum concentrations were comparable with a commonly used 175 mg dose of bupivacaine HCl. A prolonged rate of bupivacaine absorption and clearance was observed when delivered by INL-001 compared with 0.25% bupivacaine HCl infiltration, as demonstrated by the median time to maximum concentration being three times that of infiltrated bupivacaine HCl and the mean half-life being twice as long. At 36 h, the mean bupivacaine concentration with INL-001 was twice that of 0.25% bupivacaine HCl infiltration and five times greater at 96 h.

The peak bupivacaine plasma concentrations for both treatment groups (1230 ng/mL for the INL-001 group and 1140 ng/mL for the bupivacaine HCl infiltration group) were comparable. The highest individual bupivacaine plasma concentration observed in the INL-001 clinical development program was 38% and 69% lower than the threshold concentrations that have been associated with the signs and symptoms of bupivacaine central nervous system toxicity (> 2000 ng/mL) and cardiovascular toxicity (> 4000 ng/mL), respectively [6, 10]. There was also no clinical evidence of systemic bupivacaine toxicity in either treatment group in this study.

Overall, INL-001 was found to be well tolerated. Somnolence was the most common TEAE observed in both the INL-001 and the 0.25% bupivacaine HCl infiltration treatment groups. The most common AEs reported in both groups were expected in a post general anesthesia setting and with the use of opioids, consistent with the known profile of bupivacaine. Although there were signs and symptoms related to wound healing reported by individuals from both treatment groups, the frequency of post-surgical wound healing-related events was overall lower than that reported in the literature for inguinal hernia surgery [15]. Additionally, all but one of the wound healing-related events were mild in severity. Only one patient had wound-healing events whose symptoms lasted > 14 days, and all events related to the surgical wound were manageable and resolved.

Bupivacaine HCl and bovine type I collagen have established safety profiles and have been available and used for many years in the healthcare setting [16]. INL-001, as a drug-device combination, has a demonstrated safety profile consistent with each of these components. The collagen that makes up the collagen matrix of the implant is sourced from purified, biocompatible, bioresorbable bovine type I collagen. Bovine type I collagen is used in numerous clinical applications and shares a common amino acid structure and surface epitopes with human type I collagen, resulting in a negligible risk for an immune response. No risks or allergic reactions related to the collagen have been reported with the use of INL-001. Additionally, due to the unique bioresorbable implant formulation of INL-001, risks associated with liquid bupivacaine formulations such as accidental intravascular injection and preparation-related dosing errors are avoided.

The predominantly white and male patient population is a limitation to this study. A strength of this study is that it includes a dose of bupivacaine HCl that is commonly used in surgical infiltration as a comparator for evaluation of pharmacokinetics [13, 17–20]. Based on findings from the pivotal phase 3 MATRIX-1 and MATRIX-2 studies [13], INL-001 received

FDA approval for placement into the surgical site to produce postsurgical analgesia for up to 24 h following open inguinal hernia repair in adults. In the MATRIX studies, fewer patients needed opioids with INL-001 postoperatively through 72 h compared to placebo-treated patients [14]. The results from this study support the benefits of INL-001 by demonstrating prolonged bupivacaine exposure, which aligns with the significant reduction in both postsurgical pain and opioid consumption observed with INL-001 treatment in the MATRIX studies [13]. The AEs that did occur in the study described here were mild in severity (one moderate and no severe events in the INL-001 group), and the overall safety profile was similar to that seen in the MATRIX studies, with INL-001 being well tolerated.

CONCLUSIONS

This PK evaluation supports that INL-001 begins to release bupivacaine immediately upon placement in the surgical area, with a relatively rapid rise in the bupivacaine concentration, and provides an extended release of bupivacaine over time relative to 0.25% bupivacaine HCl 175 mg infiltration. Treatment with INL-001 was well tolerated, with no evidence of an adverse effect on wound healing or of bupivacaine toxicity in patients undergoing elective unilateral inguinal hernioplasty via open laparotomy.

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Compliance with Ethics Guidelines. The protocol and statement of informed consent were approved by an Institutional Review Board (IRB) prior to each center's initiation (see Table S1 in Supplementary materials). All procedures were conducted in accordance with the

Declaration of Helsinki and the study was conducted in compliance with Good Clinical Practice guidelines. Informed consent was obtained from all participants. In addition, eligible individuals must have had the ability and the willingness to comply with study procedures and to use only permitted medications (including opioids).

Data Availability. Deidentified patient data are available upon request from the corresponding authors.

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