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A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of a bupivacaine hydrochloride implant in patients undergoing abdominoplasty

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ABSTRACT

Introduction Surgical site infiltration with bupivacaine hydrochloride (HCl) is a standard element of postoperative analgesia for soft tissue surgeries, but results in short-lived analgesia. A novel bupivacaine implant, XARACOLL (bupivacaine HCl), is Food and Drug Administration approved for treatment of acute postsurgical pain following adult inguinal herniorrhaphy. This study examined the efficacy and safety of the bupivacaine implant (300 mg) compared with placebo for postsurgical pain after abdominoplasty.

Methods In this double-blind, placebo-controlled study, patients undergoing abdominoplasty were randomized to three 100 mg bupivacaine implants or three placebo collagen implants, in a 1:1 ratio, implanted intraoperatively. No other analgesics were administered into the surgical site. Patients were allowed opioids and acetaminophen for postoperative pain. Patients were followed for up to 30 days after treatment. Primary outcome: the analgesic effect of the bupivacaine implants through 24 hours postsurgery, measured by the sum of time-weighted pain intensity (SPI24). Prespecified key secondary outcomes included SPI48 and SPI72, percentage of opioid-free patients through 24, 48, and 72 hours, and adverse events, which were tested sequentially to control for multiplicity (ie, if the first variable failed to reach significance, no subsequent variables were declared statistically significant).

Results The bupivacaine implant patients (n=181) reported statistically significant lower SPI24 (mean (SD) SPI24=102 (43), 95% CI 95 to 109) compared with placebo patients (n=184; SPI24=117 (45), 95% CI 111 to 123, p=0.002). SPI48 was 190 (88, 95% CI 177 to 204) for INL-001 and 206 (96, 95% CI 192 to 219) for placebo, and not significantly different between groups. The subsequent secondary variables were therefore declared not statistically significant. SPI72 was 265 (131, 95% CI 244 to 285) for INL-001 and 281 (146, 95% CI 261 to 301) for placebo. The opioid-free percentage of patients at 24, 48, and 72 hours was 19%, 17%, and 17% for INL-001 and 6.5% for placebo patients (at all timepoints). The only adverse event occurring in ≥5% of patients and for which proportion INL-001 >placebo was back pain (7.7% vs 7.6%).

Conclusion The study design was limited by not containing an active comparator. Compared with placebo, INL-001 provides postoperative analgesia that is temporally aligned with the period of maximal postsurgical pain in abdominoplasty and offers a favorable safety profile.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The bupivacaine hydrochloride implant (INL-001) is Food and Drug Administration approved for use in adults for placement into the surgical site to produce postsurgical local analgesia for up to 24 hours following open inguinal hernia repair.

WHAT THIS STUDY ADDS

⇒ In abdominoplasty, bupivacaine implants provide postoperative analgesia through 24 hours.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Future research needs to determine whether the bupivacaine implants provide additional analgesia compared with standard bupivacaine infiltration.

Trial registration number NCT04785625.

INTRODUCTION

Approximately 80% of patients who undergo surgery will experience acute postoperative pain which, if inadequately managed, can be associated with delayed recovery time, and an increase in healthcare costs.[1]

While opioids are used in postoperative pain management, recent efforts to improve acute postsurgical pain management have focused on limiting opioid use to reduce the risk for opioid-related adverse events (AEs).[2] It has also been reported that postoperative opioid treatment can lead to persistent opioid use among opioid-naïve patients, with rates of 5.9%–6.5%.[3] A multimodal approach to analgesia, involving the administration of drugs with a variety of mechanisms of action, is recommended to decrease the need for opioids, and the infiltration of local anesthetics, such as bupivacaine, at the surgical site has become a common component of multimodal analgesic strategies.[4] However, local anesthetic infiltration into the surgical site induces short-lived analgesia (4–8 hours).[5] Infiltration also carries other risks such as preparation

dosing errors and accidental intravascular injection that can result in local anesthetic systemic toxicity, associated with significant morbidity and mortality.[6–9]

XARACOLL (Innocoll Pharmaceuticals, Ireland), also known as INL-001, is a US Food and Drug Administration (FDA)-approved bioresorbable proprietary collagen-matrix drug-delivery implant containing bupivacaine hydrochloride (HCl) for treatment of postsurgical pain for up to 24 hours following open inguinal hernia repair. The collagen-matrix is composed of type I purified bovine collagen and acts as an extended drug delivery system, releasing bupivacaine immediately and over time in the surgical wound. Each implant contains 100 mg of bupivacaine HCl and the approved dose consists of three implants placed into the surgical site (total dose 300 mg). Two phase III studies showed improvement in pain intensity through 24 hours and less opioid use through 72 hours postsurgery, compared with placebo.[10 11] Whereas these studies established INL-001's ability to safely reduce pain intensity and opioid use following open inguinal hernia repair surgery, there was limited data evaluating its analgesic properties in other soft tissue surgeries.

Abdominoplasty is a commonly performed surgical procedure with significant postoperative pain.[12 13] It is a recognized model for characterizing a drug's effect on acute postoperative soft tissue pain and has been validated as an FDA-accepted registration model.[14] This phase III study evaluated the postoperative analgesic efficacy and safety of INL-001 in patients undergoing abdominoplasty.

METHODS

This was a multicenter, randomized, double-blind, placebo-controlled efficacy and safety study of INL-001 (300 mg) for postsurgical pain in patients undergoing abdominoplasty. The study was registered on ClinicalTrials.gov (March 8, 2021; NCT04785625) and conducted from April 2021 (first patient enrolled: April 29, 2021) to October 2021 (last patient complete: October 27, 2021) at four centers in the USA (https://clinicaltrials.gov/ct2/show/NCT04785625). The primary objective of the study was to evaluate the analgesic effect of treatment with INL-001 compared with placebo collagen matrix implants. The secondary objective was to assess the safety and tolerability of INL-001.

Study population

Men and women (aged 18–65 years), with a body mass index (BMI) of 18–35 kg/m^2 undergoing elective abdominoplasty surgery with rectus sheath plication, were eligible for participation. Patients were excluded from the study if they had known hypersensitivity to amide-type local anesthetics, fentanyl, morphine, oxycodone, acetaminophen, non-steroidal anti-inflammatory drugs, or bovine products, were scheduled for other significant concurrent surgical procedures, had undergone major surgery within 3 months before the scheduled abdominoplasty, or planned to undergo another surgical procedure within 30 days after the study surgery.

During the screening period (up to 45 days before surgery), eligibility was confirmed, and informed consent provided. Patients were monitored during an inpatient period of approximately 4 days and an outpatient follow-up period of up to 30 days (phone-call on day 7 and a clinic visit on days 15 and 30).

Randomization and blinding

Randomization was stratified by study center and BMI (<30 kg/m^2 and ≥30 kg/m^2). On the day of surgery, eligible patients were randomly assigned (1:1) to treatment with INL-001 (three 100 mg implants containing a total dose of 300 mg of bupivacaine HCl) or placebo collagen implants, which were identical in appearance and provided in blinded, numbered kits to the investigative site. A centralized blocked randomization was performed using an electronic randomization system. Site staff, including surgeons, the study sponsor personnel including the statistician, and patients were blinded to treatment. No unblinding to treatment occurred during the study. Unblinding was conducted by an independent data management group after all patients completed the study and the database was locked.

Intervention and procedures

Abdominoplasty was performed according to standard surgical techniques under general anesthesia, with no other local anesthetic used at the surgical site (online supplemental material 1 contains the anesthesia protocol). The abdominoplasty procedure was performed with an anterior approach, and with an incision not extending above the umbilicus. In general, the incision was from one anterior superior iliac spine to the other, but the exact incision length could vary depending on the patient's anatomy. Drains could be placed at the discretion of the investigator, but ancillary procedures (eg, liposuction) at the same time were prohibited.

Prior to incision closure, the INL-001 or placebo implants were placed in the surgical site. Following tissue removal and repair of the abdominal musculature, two implants were placed on the rectus diastasis at the site of rectus sheath plication and one implant was placed below the abdominal incision between Scarpa's fascia and the subcutaneous fat. The implants were, to the greatest extent possible, placed so they spanned the fascia that was exposed prior to surgical closure. Implants could be cut in two halves to accommodate placement. Patients in both treatment groups were permitted rescue medication (opioids—morphine or oxycodone, and/or acetaminophen) to manage breakthrough pain (see online supplemental material 2).

Outcome measures

Efficacy

Pain intensity was measured using a patient-completed 11-point Numerical Pain Rating Scale (NPRS; 0 (no pain) to 10 (worst possible pain)). NPRS scores were recorded at prespecified multiple timepoints through 72 hours post-treatment. These timepoints were: 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 20, 24, 28, 32, 36, 48, and 72 hours after treatment (placement of implants). Pain intensity was also recorded prior to rescue pain medication use.

The sum of pain intensity (SPI) was calculated from time 0 (placement of implants) through 24 hours post-treatment (SPI24), through 48 hours (SPI48), and through 72 hours (SPI72). SPI was calculated using area under the curve (AUC) of pain intensity (NPRS) and the actual assessment times in hours (ie, the pain-time curve). The primary efficacy outcome measure for the study was SPI24. SPI48 and SPI72 were considered key secondary efficacy outcome measures. Pain scores obtained prior to rescue medication use were also included in the calculation of SPI. Pain scores subsequent to the administration of pain medication rescue use were censored through the duration of efficacy of the rescue (2 hours for morphine, 4 hours for acetaminophen, oxycodone), with the exception that pain scores in this period that were higher than the rescue pain score were retained. This approach assumes that the pain profile without rescue would have transitioned linearly from

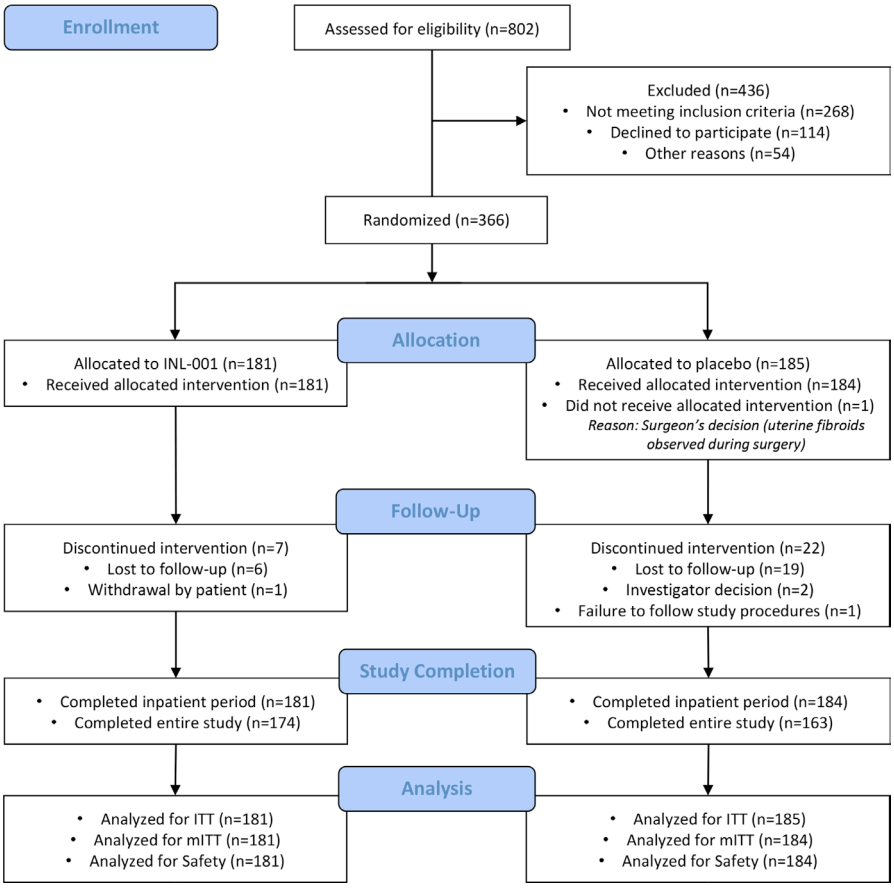

Figure 1 Flow diagram of study population. ITT, intent-to-treat; mITT, modified ITT.

the pre-rescue value to the first value after the duration of effect for the rescue; the censoring removes the dip in pain scores attributable to rescue.

Opioid use was collected throughout the study. The proportion of patients who were opioid free for 0–24, 0–48, and 0–72 hours after surgery were prespecified key secondary efficacy outcomes.

Safety

Patients were monitored for AEs through day 30 after surgery. AEs were a prespecified secondary outcome measure of this study. Following hospital discharge, patients reported AEs by telephone and provided incidence, duration, and any associated treatment. Additionally, AE information was recorded during the follow-up phone call (day 7) and visits (days 15 and 30). AEs were assessed for severity and relatedness to treatment.

In addition, a signs and symptoms checklist (online supplemental material 3) was used at prespecified timepoints (hours 0.5, 1, 2, 3, 4, 5, 7, 9, 12, 15, 18, 24, 48, and 72, and days 7 and 15) to systematically assess for any AEs suggestive of systemic bupivacaine toxicity. Blood samples could be collected to assess for bupivacaine plasma concentrations at the discretion of the investigator (online supplemental material 4).

Wound healing was assessed by use of a signs and symptoms checklist (online supplemental material 3) at 24, 48, and 72 hours, and days 7, 15 and 30, to systematically assess for any AEs indicative of adverse wound healing. An additional assessment of wound healing was done through the completion of the Southampton Wound Grading System[15] 72 hours postsurgery and at days 15 and 30 (online supplemental material 5).

Additional safety variables included clinical laboratory test results, vital signs, electrocardiography findings, and concomitant medications.

Sample size

Sample size calculation was based on previous clinical studies for INL-001 in inguinal hernia repair.[10] The effect size of these inguinal hernia repair studies were 0.53 for SPI24 (based on a least squares means (LSmeans) difference of 24.5 with SD 46.5) and 0.25 for SPI48 (based on an LSmeans difference of 23.4 with SD 92.4). Using a two-sample t-test with a 95% CI, a sample size of 360 was expected to yield a power of >99% for SPI24, the prespecified primary outcome measure, and this drove the sample size choice. The power to show separation at 48 hours was recognized as low (66%) but it was thought that the ultimate power of the study to detect a difference at that timepoint might be higher given that abdominoplasty is generally a more painful procedure than inguinal hernia.

Analysis populations

The intent-to-treat (ITT) population consisted of patients randomly assigned to study treatment who may have received any dose of study drug (INL-001 or placebo). The ITT population was used for disposition patient-count purposes. The modified ITT (mITT) population consisted of all patients randomly assigned to study treatment who received any dose of study drug (INL-001 or placebo) and was used for efficacy analysis. The safety population consisted of all patients who received any dose of study drug (INL-001 or placebo) and was used for safety analyses.

Table 1 Demographic and other baseline characteristics

Demographic and other baseline characteristics	Study treatment		
	INL-001 (n=181)	Placebo (n=184)	Total (n=365)
Sex at birth, n (%)			
Male	0	3 (1.6)	3 (0.8)
Female	181 (100)	181 (98.4)	362 (99.2)
Age at screening (years)			
Mean (SD)	43.3 (9.0)	43.1 (9.0)	43.2 (9.0)
Median	43.0	43.0	43.0
Minimum, maximum	20, 65	20, 65	20, 65
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	4 (2.2)	4 (2.2)	8 (2.2)
Black or African-American	44 (24.3)	49 (26.6)	93 (25.5)
Native Hawaiian or other Pacific Islander	1 (0.6)	0	1 (0.3)
White	130 (71.8)	128 (69.6)	258 (70.7)
Other	2 (1.1)	3 (1.6)	5 (1.4)
Ethnicity group, n (%)			
Hispanic or Latino	77 (42.5)	79 (42.9)	156 (42.7)
Not Hispanic or Latino	101 (55.8)	102 (55.4)	203 (55.6)
Not reported	2 (1.1)	0	2 (0.5)
Unknown	1 (0.6)	3 (1.6)	4 (1.1)
Height (cm)			
Mean (SD)	161.7 (6.7)	162.5 (7.2)	162.1 (7.0)
Median	161.3	161.3	161.3
Minimum, maximum	144.6, 185.4	142.0, 185.4	142.0, 185.4
Weight (kg)			
Mean (SD)	71.9 (10.6)	72.9 (9.8)	72.4 (10.2)
Median	72.2	72.4	72.2
Minimum, maximum	45.8, 101.7	50.8, 106.9	45.8, 106.9
BMI (kg/m^2)			
Mean (SD)	27.4 (3.1)	27.6 (2.8)	27.5 (3.0)
Median	27.6	27.9	27.8
Minimum, maximum	19.4, 34.8	19.9, 33.6	19.4, 34.8
BMI strata, n (%)			
<30 kg/m^2	144 (79.6)	146 (79.3)	290 (79.5)
>30 kg/m^2	37 (20.4)	38 (20.7)	75 (20.5)
Length of incision			
Mean (SD)	34.1 (10.1)	35.3 (10.0)	34.7 (10.0)
Median	32.0	34.8	33.0
Minimum, maximum	11, 64	15, 36	11, 64
Treatment compliance			
Three implants placed, n (%)*	180 (99.4)	183 (99.5)	363 (99.5)
Any implants cut, n (%)	180 (99.4)	183 (99.5)	363 (99.5)
First implant cut, n (%)	66 (36.5)	65 (35.3)	131 (35.9)
Second implant cut, n (%)	52 (28.7)	58 (31.5)	110 (30.1)
Third implants cut, n (%)	150 (82.9)	153 (83.2)	303 (83.0)

*Two of three implants were placed in one patient in each group as one implant was accidentally dropped and unusable.
BMI, body mass index.

Statistical analysis

Patient demographics, baseline characteristics, efficacy, and safety variables are summarized using descriptive statistics.

Efficacy variables were compared between groups (INL-001 vs placebo). For continuous variables, an analysis of covariance was used with treatment as the main effect (two levels) and a covariate for BMI (continuous). For outcomes of proportions, the difference was tested with the Pearson's χ^2. In case of low counts (any expected cell count ≤5), a Fisher's exact test was used. For the safety variables, no formal statistical tests are performed.

Multiplicity

Prespecified key secondary efficacy variables were tested sequentially at the 0.05 level to control the overall type I error rate. Each key secondary efficacy variable was tested in order:

1. SPI48.

Table 2 Primary and key secondary efficacy variables (mITT population): pain intensity and opioid use

	INL-001	Placebo	INL-001 vs placebo	P value
Primary efficacy variable				
SPI24; mean (SD)	102.1 (42.9)	117.0 (45.2)	−14.8 (−23.8 to −5.7)*	<0.01
95% CI	95.7 to 108.6	110.5 to 123.3		
Secondary efficacy variables				
SPI48; mean (SD)	190.4 (87.7)	205.8 (95.9)	−15.2 (−34.1 to 3.7)*	0.12
95% CI	177.1 to 204.0	192.4 to 219.0		
SPI72; mean (SD)	264.60 (131.35)	281.10 (146.28)	−16.2 (−44.8 to −12.5)*	NA†
95% CI	244.4 to 285.1	260.8 to 301.1		
Opioid free 24; n (%)	34 (18.8)	12 (6.5)	12.3 (5.6 to 19.0)‡	NA†
Opioid free 48; n (%)	31 (17.1)	12 (6.5)	10.6 (4.1 to 17.2)‡	NA†
Opioid free 72; n (%)	31 (17.1)	12 (6.5)	10.6 (4.1 to 17.2)‡	NA†

SPI (24, 48, 72)=sum of pain intensity (from time 0 through 24, 48, 72 hours).
*Least squares mean difference (95% CI) based on ANCOVA model with body mass index as covariate.
†Because of the multiplicity algorithm, all secondary efficacy variables tested after SPI48 were declared not statistically significant.
‡Difference (95% CI) based on the Pearson's χ^2 test.
ANCOVA, analysis of covariance; mITT, modified intent-to-treat; NA, not applicable.

2. Proportion of patients who were opioid free post-treatment through 24 hours.
3. Proportion of patients who were opioid free post-treatment through 48 hours.
4. SPI72.
5. Proportion of patients that were opioid free post-treatment through 72 hours.

If a variable failed to reach statistical significance, no subsequent variables would be declared statistically significant.

RESULTS

Of the 802 patients screened, 366 patients were randomly assigned to the study groups (mITT population; INL-001=181, placebo=184). All treated patients completed the full inpatient period. In total, 174 INL-001 patients (96.1%) and 163 placebo patients (88.1%) completed the entire study (figure 1). Demographics and baseline characteristics were similar between groups (table 1).

Efficacy results

Primary outcome: SPI24

INL-001 patients reported statistically significantly lower mean SPI24 compared with placebo patients (mean (SD; 95% CI) SPI24=102 (42; 96 to 109) vs 117 (45; 111 to 123); p=0.002; table 2).

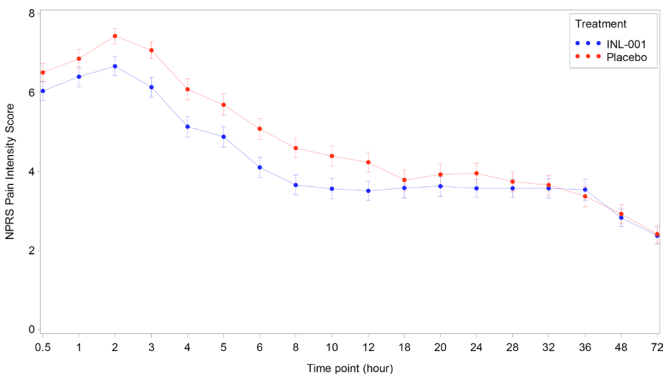

Figure 2 Mean (±95% CI) of Numerical Pain Rating Scores (NPRS) by treatment and timepoint.

Key secondary outcomes: SPI48, SPI72 and percentage opioid free

SPI48 (mean (SD; 95% CI)) was 190 (88; 177 to 204) for INL-001 and 206 (96; 192 to 219) for placebo and was not significantly different between groups (p>0.05, see table 2). Therefore, the subsequent variables were declared not statistically significantly different between groups. SPI72 was 265 (131; 244 to 285) for INL-001 and 281 (146; 261 to 301) for placebo.

At the periods 0–24, 0–48, and 0–72 hours, 18.8% (n=34), 17.1% (n=31), and 17.1% (n=31) of INL-001 patients remained opioid free. For all periods, 6.5% (n=12) of placebo patients remained opioid free (table 2). A statistically significant difference between groups for prespecified secondary outcome measures was not achieved.

Pain scores over time are provided in figure 2 and descriptive values for additional SPI timepoints are provided in online supplemental material 6.

Safety results

The safety population consisted of 181 INL-001 and 184 placebo patients. The incidence of AEs was similar between treatment groups (INL-001: 84%; placebo: 87%). No patients in either treatment group had an AE leading to discontinuation, death, or removal of the implants. Table 3 lists the AEs that occurred in ≥2% of patients and had higher occurrence in the INL-001 vs placebo group. Most patients reported AEs as mild or moderate (1% of INL-001 and 2% of placebo patients had an AE considered severe) and most AEs were considered unrelated to treatment (6% of INL-001 and 8% of placebo patients had an AE considered definitely or probably related to treatment). AEs considered definitely related to treatment were mild and resolved during the study.

A review of AEs derived from the systematic assessment of any signs or symptoms of bupivacaine toxicity during the study did not indicate that any patient experienced systemic bupivacaine toxicity. Eight patients (four in each group) had bupivacaine plasma concentrations assessed (all ≤135 ng/mL) (see online supplemental material 4).

The most common (≥ 2% overall) AEs derived from the systematic assessment of wound healing during the study were: wound dehiscence (INL-001: n=21 (11.6%); placebo: n=24 (13.0%)), incision site swelling (INL-001: n=5 (2.8%); placebo: n=5 (2.7%)), incision site erythema (INL-001: n=5 (2.8%);

Table 3 Adverse events occurring in ≥2% of patients and for which INL-001 >placebo

	INL-001 (n=181)		Placebo (n=184)		Total (n=365)	
	N	%	N	%	N	%
Dysgeusia	4	2.2	3	1.6	7	1.9
Incision site swelling	5	2.8	5	2.7	10	2.7
Incision site erythema	5	2.8	4	2.2	9	2.5
Postprocedural discharge	5	2.8	2	1.1	7	1.9
Back pain	14	7.7	14	7.6	28	7.7
Pain in extremity	4	2.2	0	0.0	4	1.1
Pruritus generalized	5	2.8	3	1.6	8	2.2
Rash	4	2.2	2	1.1	6	1.6
Orophyaryngeal pain	8	4.4	3	1.6	11	3.0
Increased blood pressure	6	3.3	3	1.6	9	2.5

placebo: n=4 (2.2%)), postprocedural discharge (INL-001: n=5 (2.8%); placebo: n=2 (1.1%)), incision site edema (INL-001: n=8 (4.4%); placebo: n=9 (4.9%)).

Most wound-healing AEs were mild or moderate. There was one serious AE reported in the study. The patient (placebo) experienced a wound infection at a drain site that required hospitalization. The patient recovered. The majority of reported wound dehiscence events occurred at one center and was likely influenced by surgical postoperative management and medical experience of the assessor. Results from the Southampton Wound Grading System are provided in online supplemental material 5.

There were no clinically meaningful effects on laboratory test results, vital sign parameters, physical examinations, electrocardiography parameters, and concomitant medication (other than described for rescue pain medication).

DISCUSSION

Treatment with INL-001 was associated with significantly less pain during the first 24 hours following abdominoplasty surgery compared with placebo. This is similar to the results of open inguinal hernia studies conducted with INL-001[10] and is clinically relevant since the first 24 hours after surgery are generally the most painful for soft tissue surgeries like abdominoplasty.[16–19]

The primary analgesic outcome of this study was pain intensity, specifically SPI24 resulting from repeat pain intensity measurements. While there is no established clinical threshold for SPI endpoints, repeat measurement of pain intensity with analysis over a period of time was chosen as the primary efficacy outcome based on the FDA recommendation to use a well-defined and reliable patient-reported outcome measure of the subject's pain intensity which allows for frequent pain intensity measurements at preselected timepoints during the trial to measure the effect of a non-opioid analgesic effect over time.[20] In addition, SPI is a common measure in pain trials.[14 20–23]

This study was underpowered for the first key secondary endpoint (SPI48) in the statistical hierarchy and not powered for the remaining key secondary endpoints of this study. There was in increase in pain intensity variability between patients as time from surgery increased, which is not surprising given the subjective nature of pain measurement and differences in recovery between patients postoperatively. This variability impacted the ability to demonstrate statistical significance. Given the numeric differences in favor of INL-001 on the key secondary endpoints, further study of these outcomes with INL-001 could be warranted.

In this study, INL-001 was well tolerated. The percentage of INL-001 patients (84%) reporting any AEs was similar to the placebo group (87%). The types of AEs in this study are expected after surgery, general anesthesia, or abdominoplasty specifically, or can be seen with opioid use.[14 18 19 24 25] In addition, the incidence and types of AEs were comparable or lower than reported in placebo or bupivacaine-treated groups in other abdominoplasty studies.[14 18 19 24 25]

There was no evidence of systemic bupivacaine toxicity when INL-001 was used in abdominoplasty. As with other surgeries, there is a recognized risk of postoperative adverse wound healing after abdominoplasty. The incidence of wound-related AEs in this study was low and consistent with the abdominoplasty literature.[14 18 19 25–27] Wound dehiscence was the most reported AE associated with the surgical wound, but the incidence was consistent with that reported in another abdominoplasty study that administered saline or bupivacaine in the surgical site[24] and occurred mostly at one investigator site.

A limitation is that this study did not contain an active comparator treatment arm. Patients used rescue medication as needed, rather than on a scheduled basis as might be done in clinical practice to allow for a clearer assessment of efficacy. Additionally, most patients were female, however, this is not unexpected for abdominoplasty surgery.[14]

CONCLUSION

This study showed that, compared with placebo, INL-001 was effective in providing postoperative analgesia in abdominoplasty, a model of soft tissue surgery. Treatment with INL-001 was well tolerated in this patient population, with no evidence of systemic bupivacaine toxicity or impaired wound healing. These results may support expanding the indication of INL-001 for use in soft tissue surgeries beyond inguinal hernia repair.

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manuscript. NSi also declares that he serves on the board and that he is part owner (holding stock or stock options) of the parent company of Lotus Clinical Research LLC (ERG Holding Co). HSM declares that he has received support from Innocoll Pharmaceuticals, Durect, and Pain Reform; grants or contracts from Innocoll Pharmaceuticals, Pacira Pharmaceuticals, Heron Therapeutics, Acacia Pharma, and Vertex Pharmaceuticals; consulting fees from Avenue Therapeutics; and payment or honoraria from Pacira Pharmaceuticals, AcelRx Pharmaceuticals, and Heron Therapeutics. DL declares that he received support for the present manuscript from Pacira Pharmaceuticals, Heron Therapeutics, Merck, Innocoll Pharmaceuticals, AcelRx Pharmaceuticals, Acacia Pharma (including consulting fees), Durect, The Medicines Company, and Pain Reform. BV declares that he is an employee of a contract research organization that is paid to provide statistical services to Innocoll Pharmaceuticals. NSk and GN declare that, at the time of the study, they were an employee of Innocoll Pharmaceuticals and that they have patents planned, issued, or pending with Innocoll Pharmaceuticals, and stock or stock options from Innocoll Pharmaceuticals.

Patient consent for publication Not applicable.

Ethics approval The protocol and statement of informed consent were approved by the Institutional Review Boards (WCG IRB-IRB00000533) prior to each center's initiation. All procedures were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki Declaration and its later amendment or comparable ethical standards. The study was conducted in compliance with the International Council for Harmonization principles of Good Clinical Practice and other applicable local regulations and guidelines. Written informed consent was obtained from all patients included in the study.

Provenance and peer review Not commissioned; externally peer reviewed.

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Supplementary Material 1

Anesthesia protocol

As per generally accepted operating procedures, a standardized anesthetic regimen, including general anesthesia with fentanyl (maximum dose of 4 mcg/kg) and propofol (dose at discretion of the anesthesia provider), was included in the trial. Epinephrine, however, was not permitted during the procedure, and no local anesthetics other than XARACOLL in the surgical field or regional anesthesia were permitted either. Lidocaine HCl 1% injection at a dose of no more than 20 mg was allowed to be administered once through intravenous (iv) access to decrease venous irritation at the time of surgical anesthesia. Intraoperative fentanyl was also permitted for analgesia. No other analgesic agents were to be used during the procedure including, but not limited to, opioids (other than fentanyl), acetaminophen (oral or iv), NSAIDs (e.g., ketorolac or COX-2 inhibitors), ketamine, pregabalin, and others. A preoperative dose of an antiemetic, ondansetron iv 4 mg, for nausea prophylaxis was allowed; however, postoperative antiemetic medications were to be given to treat only patients who reported nausea and/or vomiting. Administration of fentanyl was to be avoided 30 minutes prior to the anticipated conclusion of the procedure if medically acceptable in the judgement of the anesthesiologist.

Supplementary Material 2

Rescue Medication protocol

Patients were permitted rescue medication to manage breakthrough pain when it occurred. Oral acetaminophen at 1000 mg every 4-6 hours (maximum daily dosage 3000 mg) and/or oxycodone 5 mg tablet(s) (not to exceed 10 mg in a 4-hour period during the inpatient stay) could be given on an as needed basis for pain. Immediately prior to receiving any rescue medication, a pain intensity score was recorded. If the NPRS score was 4 or less, patients were discouraged from taking opioid rescue medication; however, rescue medication could be requested and provided at any time. If patients required opioid rescue medication, but were unable to take oral medications, they were permitted to receive intravenous morphine (2-3 mg) every 3 hours until they were able to take oral rescue medication. A pain intensity score was collected before any rescue medication use.

Patients with pain intensity scores of 4 or more at discharge were 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 were also 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 were 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 did not receive a written prescription for oxycodone upon discharge were permitted to request immediate-release oxycodone 5-10 mg if their pain was unrelieved by acetaminophen or NSAIDs. All concomitant medication use during participation in the study was recorded. Following discharge on Day 4, scheduled patient check-ins took place throughout the outpatient postoperative period to monitor recovery. These check-ins occurred on Day 7 (±1 day), 15 (±3 days), and 30 (±3 days); the Day 7 check-in was conducted via telephone, whereas the Day 15 and Day 30 check-ins were conducted in a clinical setting.

Supplementary Material 3

Signs and Symptoms checklist for AEs of special interest

Systemic Bupivacaine Toxicity	**Wound healing**
– Respiratory difficulty	– Purulent discharge or leakage of fluid from site
– Change in level of consciousness	– Pain or soreness
– Restlessness	– Redness or inflammation (edges of wound)
– Anxiety	– Warmth around the wound
– Difficulty speaking or being understood	– Swelling around the wound
– Light-headedness	– Separation of edges of the wound
– Numbness and tingling of mouth and lips	– Seen by health care provider about wound
– Metallic taste	– Prescribed antibiotics for infection of wound
– Tinnitus (ringing in ears)	– Admitted to hospital with infection of wound
– Dizziness	
– Changes in vision	
– Tremors	
– Depression	
– Drowsiness	

Supplementary Material 4

Plasma level concentrations assessed for bupivacaine toxicity

Investigators were instructed to collect blood samples for bupivacaine plasma concentrations if they felt the patient might be experiencing systemic bupivacaine toxicity. In addition, if the patient experienced a **grade 4 AE** (defined as *"life threatening consequences: urgent intervention indicated"*) 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

Eight patients had a blood sample collected, four in each treatment group, at the discretion of the investigator. There were no grade 4 AEs as descripted above and no verbatim reports of systemic bupvicaine toxicity. Bupivacaine plasma concentrations measured (all ≤135 ng/mL) for these patients were well below a level suggestive of systemic bupivacaine toxicity, which is general 2000 ng/mL or more[1,2].

[1] Bardsley, et al., *A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers.* British journal of clinical pharmacology, 1998. 46(3): p. 245-249.

[2] Jorfeldt, et al., *The effect of local anaesthetics on the central circulation and respiration in mand and dog.* Acta Anaesthesiologica Scandinavica, 1968. 12(4): p. 153-169.

Supplementary Material 5

Southampton Wound Grading System

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 haemoserous discharge**
A	At one point only (≤2cm)
B	Along wound (>2cm)
C	Large volume
D	Prolonged (>3 days)
MAJOR COMPLICATIONS	
IV	**Pus**
A	At one point only (≤2cm)
B	Along wound (>2cm)
V	**Deep or severe wound infection with/without tissue breakdown**
	Haematoma requiring aspiration

Wound (healing) grading using the Southampton Wound Grading System[3] was performed by the investigator (physician) at 72 hours (day 4) posttreatment, day 15, and day 30. Investigator judgment was used to determine if a finding was an adverse event (AE).

The counts and percentages of patients in each category of the Southampton Wound Grading Scale were reported at each time point that it was collected. Results are provided in the table below. On day 4 (prior to discharge), all patients (100%) had wounds graded 0, I, or II. On day

[3] Bailey, et al., *Community surveillance of complications after hernia surgery.* British Medical Journal, 1992. 304(6825): p. 469-471.

15, 85% of patients had wounds graded 0, I, or II; 10% grade III; 2% grade IV; and 0% grade V (3% was not assessed). On day 30, 84% of patients had grade 0, I, or II; 7% grade III, 1% grade IV; and 0% grade V (8% was not assessed).

Summary of Patients with Southampton Wound Grading System Findings by Treatment and Time Point (Safety Population)

Time point	Grade (appearance)	Study treatment		Total (N=365)
		INL-001 (N=181)	Placebo (N=184)	
Day 4 (prior to discharge)	0 (Normal healing)	136 (75.1)	134 (72.8)	270 (74.0)
	I Normal healing with mild bruising or erythema:	42 (23.2)	48 (26.1)	90 (24.7)
	a (some bruising)	22 (12.2)	24 (13.0)	46 (12.6)
	b (considerable bruising)	0	2 (1.1)	2 (0.5)
	c (mild erythema)	20 (11.0)	22 (12.0)	42 (11.5)
	II Erythema plus other signs of inflammation:	2 (1.1)	2 (1.1)	4 (1.1)
	a (at one point)	1 (0.6)	1 (0.5)	2 (0.5)
	b (around sutures)	0	1 (0.5)	1 (0.3)
	c (along wound)	1 (0.6)	0	1 (0.3)
	d (around wound)	0	0	0
	III Clear or haemoserous discharge:	0	0	0
	a (at one point only (≤2 cm))	0	0	0
	b (along wound (>2 cm)	0	0	0
	c (large volume)	0	0	0
	d (prolonged (>3 days))	0	0	0
	Major Complications:			
	IV Pus:	0	0	0
	a (at one point only (≤2 cm))	0	0	0
	b (along wound (>2 cm))	0	0	0
	V Deep or severe wound infection with or without tissue breakdown; haematoma requiring aspiration	0	0	0
	Not assessed	1 (0.6)	0	1 (0.3)
Day 15	0 (Normal healing)	127 (70.2)	129 (70.1)	256 (70.1)
	I Normal healing with mild bruising or erythema:	23 (12.7)	23 (12.5)	46 (12.6)
	a (some bruising)	8 (4.4)	11 (6.0)	19 (5.2)
	b (considerable bruising)	15 (8.3)	12 (6.5)	27 (7.4)
	c (mild erythema)	0	0	0
	II Erythema plus other signs of inflammation:	5 (2.8)	5 (2.7)	10 (2.7)
	a (at one point)	2 (1.1)	3 (1.6)	5 (1.4)
	b (around sutures)	2 (1.1)	0	2 (0.5)
	c (along wound)	1 (0.6)	2 (1.1)	3 (0.8)
	d (around wound)	0	0	0
	III Clear or haemoserous discharge:	19 (10.5)	17 (9.2)	36 (9.9)
	a (at one point only (≤2 cm))	17 (9.4)	16 (8.7)	33 (9.0)
	b (along wound (>2 cm)	2 (1.1)	1 (0.5)	3 (0.8)
	c (large volume)	0	0	0
	d (prolonged (>3 days))	0	0	0
	Major Complications:			
	IV Pus:	3 (1.7)	4 (2.2)	7 (1.9)
	a (at one point only (≤2 cm))	3 (1.7)	4 (2.2)	7 (1.9)
	b (along wound (>2 cm))	0	0	0

Summary of Patients with Southampton Wound Grading System Findings by Treatment and Time Point (Safety Population)

Time point	Grade (appearance)	Study treatment		Total (N=365)
		INL-001 (N=181)	Placebo (N=184)	
	V Deep or severe wound infection with or without tissue breakdown; haematoma requiring aspiration	0	0	0
	Not assessed	4 (2.2)	6 (3.3)	10 (2.7)
Day 30	0 (Normal healing)	134 (74.0)	130 (70.7)	264 (72.3)
	I Normal healing with mild bruising or erythema:	14 (7.7)	12 (6.5)	26 (7.1)
	a (some bruising)	4 (2.2)	1 (0.5)	5 (1.4)
	b (considerable bruising)	10 (5.5)	11 (6.0)	21 (5.8)
	c (mild erythema)	0	0	0
	II Erythema plus other signs of inflammation:	9 (5.0)	6 (3.3)	15 (4.1)
	a (at one point)	3 (1.7)	1 (0.5)	4 (1.1)
	b (around sutures)	1 (0.6)	1 (0.5)	2 (0.5)
	c (along wound)	4 (2.2)	4 (2.2)	8 (2.2)
	d (around wound)	1 (0.6)	0	1 (0.3)
	III Clear or haemoserous discharge:	16 (8.8)	10 (5.4)	26 (7.1)
	a (at one point only (≤2 cm))	15 (8.3)	9 (4.9)	24 (6.6)
	b (along wound (>2 cm)	1 (0.6)	1 (0.5)	2 (0.5)
	c (large volume)	0	0	0
	d (prolonged (>3 days))	0	0	0
	Major Complications:			
	IV Pus:	1 (0.6)	4 (2.2)	5 (1.4)
	a (at one point only (≤2 cm))	1 (0.6)	4 (2.2)	5 (1.4)
	b (along wound (>2 cm))	0	0	0
	V Deep or severe wound infection with or without tissue breakdown; haematoma requiring aspiration	0	0	0
	Not assessed	7 (3.9)	22 (12.0)	29 (7.9)

Supplementary Material 6

Additional SPI outcomes

		INL-001	Placebo	INL-001 vs Placebo LS Mean Difference (95%CI)[a]	p-value
SPI2	Mean(SD)	9.68 (3.233)	10.51 (2.836)		
	95%CI	9.24 - 10.13	10.06 - 10.94	-0.82 (-1.44 - -0.19)	0.01
SPI3	Mean(SD)	16.2 (5.3)	17.85 (4.584)		
	95%CI	15.5-17.0	17.12 - 18.55	-1.6 (-2.61 - -0.58)	0.002
SPI4	Mean(SD)	22.4 (7.5)	24.8 (6.5)		
	95%CI	21.4-23.4	23.8-25.8	-2.45 (-3.88 - -1.01)	0.001
SPI5	Mean(SD)	28.1 (9.6)	31.6 (8.6)		
	95%CI	26.8-29.5	30.2-32.8	-3.36 (-5.22 - -1.50)	<0.001
SPI6	Mean(SD)	33.1 (11.4)	37.5 (10.4)		
	95%CI	31.6-34.7	35.9-39.1	-4.38 (-6.61 - -2.15)	<0.001
SPI8	Mean(SD)	41.3 (14.7)	47.8 (14.0)		
	95%CI	39.3-43.5	45.7-49.8	-6.4 (-9.33 - -3.47)	<0.001
SPI10	Mean(SD)	48.9 (18.2)	57.3 (17.7)		
	95%CI	46.3-51.5	54.7-59.9	-8.37 (-12.05 - -4.69)	<0.001
SPI12	Mean(SD)	56.4 (21.8)	66.5 (21.5)		
	95%CI	53.2-59.6	63.4-69.6	-10.09 (-14.54 - -5.65)	<0.001
SPI18	Mean(SD)	79.4 (32.2)	92.41 (32.873)		
	95%CI	74.7-84.2	87.64 - 97.06	-12.91 (-19.60 - -6.22)	<0.001
SPI20	Mean(SD)	81.7-92.3	100.41 (36.870)		
	95%CI	86.9 (35.7)	95.09 - 105.61	-13.38 (-20.85 - -5.92)	<0.001
SPI24	Mean(SD)	102.1 (42.9)	117.0 (45.2)		
	95%CI	95.7 – 108.6	110.5 – 123.3	−14.8 (−23.8, −5.7)	0.001
SPI28	Mean(SD)	117.21 (50.092)	133.10 (53.465)		
	95%CI	109.71 - 124.85	125.52 - 140.53	-15.74 (-26.40 - -5.08)	0.004
SPI32	Mean(SD)	132.49 (57.540)	148.82 (61.761)		
	95%CI	123.85 - 141.30	140.09 - 157.39	-16.16 (-28.45 - -3.88)	0.01
SPI36	Mean(SD)	147.88 (65.329)	163.70 (69.828)		
	95%CI	138.10 - 157.86	153.81 - 173.41	-15.63 (-29.54 - -1.71)	0.028
SPI48	Mean(SD)	190.4 (87.7)	205.8 (95.9)		
	95%CI	177.1 – 204.0	192.4 – 219.0	−15.2 (−34.1, 3.7)	0.12
SPI72	Mean(SD)	264.60 (131.35)	281.10 (146.28)		
	95%CI	244.4 – 285.1	260.8 – 301.1	−16.2 (−44.8, -12.5)	NA[b]

[a] Least Squares Mean Difference (95% Confidence Interval) based on ANCOVA model with Body Mass Index as covariate
[b] Because of the multiplicity algorithm, all secondary variables tested after SPI48 were declared not statistically significant