SUPPLEMENTAL METHODS

Study Sites

The 13 study sites were Brigham and Women's Hospital (Boston, MA), Massachusetts General Hospital (Boston, MA), Columbia University Medical Center (New York, NY), Duke University (Durham, NC; 2 sites), Stanford University (Stanford, CA), Henry Ford Health Systems (Detroit, MI), INOVA Fairfax Hospital (Falls Church, VA), University of Minnesota (Minneapolis, MN), Saint Peter's University Hospital (New Brunswick, NJ), Loma Linda University Medical (Loma Linda, CA), West Virginia University (Morgantown, WV), and Kaweah Delta Health (Visalia, CA).

Study Drug and Multimodal Regimen

At the time of skin incision closure, 15 mg of intravenous ketorolac and 1000 mg of intravenous acetaminophen were administered. Within 90 minutes of surgery end, a bilateral, 2-point classic TAP block with LB 266 mg plus BUPI HCl 50 mg or BUPI HCl 50 mg alone (30 mL each side; 60 mL total for each) was performed under ultrasound guidance by experienced physicians, primarily staff anesthesiologists.[1] Subcutaneous lidocaine could be administered at the area of the needle insertion site if needed for patient comfort. The TAP infiltration included 2 steps; TAP needle placement and saline hydrodissection followed by study drug mixture infiltration into the TAP. Confirmatory ultrasound images were taken after the needle position had been established and after infiltration. Beginning 6 hours after skin incision closure, 650 mg of oral acetaminophen and 600 mg of oral ibuprofen were given every 6 hours for up to 72 hours or until hospital discharge. Opioid pain medication to treat postsurgical pain was permitted if requested by the patient and consisted of immediate-release oxycodone initiated at 5–10 mg every 4 hours or as needed. If unable to tolerate or initial rescue medication failure was

experienced, intravenous morphine initiated at 1–2 mg or hydromorphone initiated at 0.3–0.5 mg could be administered every 4 hours or as needed.

Randomization and Blinding

A centralized randomization system was used to generate treatment assignments. Patients and research personnel collecting data were blinded to allocation; only designated unblinded pharmacists responsible for preparing study drugs received the unblinded randomization assignments. The individuals administering treatments may have been able to identify the preparations containing LB because LB is a milky aqueous suspension. Those preparing or administering study drugs were not allowed to perform any of the study assessments or reveal the treatment to any other members of the study team.

Tertiary End Points

Tertiary efficacy end points included AUC of the VAS pain intensity scores from 0–12, 0–24, 0–48, 24–48, 24–72, and 48–72 hours; the sum of VAS pain intensity scores at rest from end of surgery through 72 hours; the sum of VAS pain intensity scores from 0–12, 0–24, 0–48, 24–48, 24–72, and 48–72 hours; integrated rank assessment using the VAS pain intensity score at rest at 24, 48, and 72 hours after surgery and the total amount of postsurgical opioids consumed from end of surgery through 24, 48, and 72 hours; OBAS[2] at each assessed time point; time spent in the postanesthesia care unit; time to first unassisted ambulation; proportion of individuals meeting Modified Post Anesthesia Discharge Scoring System criteria for discharge readiness; overall assessment of patient satisfaction with postsurgical pain control; responses to the 15-item quality of recovery questionnaire (Table 1)[3]; and number of unscheduled phone calls or office visits related to pain through day 14.

Statistical Analysis

Statistical analyses of study end points were prespecified in the statistical analysis plan. For the primary end point, comparison between groups was assessed using an analysis of covariance (ANCOVA) model with treatment and site as the main effects and age and height as covariates. Additionally, the percent reduction in total postsurgical oral MED was determined on the basis of the least squares mean for each group estimated from the ANCOVA model. No multiplicity adjustments were made for efficacy.

$AUC_{0\text{-}72}$ for VAS pain intensity was analyzed using an ANCOVA model with treatment and site as main effects and age and height as covariates to determine if LB plus BUPI was noninferior to BUPI alone. The least squares means for treatment difference and 95% confidence intervals (CIs) were used in a step-down statistical approach. To test for noninferiority, a margin of 36 was set on the upper bound of the 95% CI. This noninferiority margin was set on the basis of an average pain intensity score difference of 0.5, which was considered a clinically nonsignificant difference over 72 hours and is a smaller margin than what has been reported in previous studies.[4,5] From this, a noninferiority margin was calculated through integral transformation (0.5 × 72 hours = 36). If noninferiority was determined, then superiority was tested. If the upper bound of the 95% CI was <0, then superiority was determined. If superiority was determined, then the 1-sided superiority test *P* value is shown. If the superiority test failed, only the 1-sided noninferiority test *P* value is shown. This methodology was used for AUC of the VAS pain intensity scores at all time points, with noninferiority margins corresponding to an average pain intensity score difference of 0.5 over the respective time interval.

The percentage of opioid-spared and opioid-free patients was analyzed using a logistic regression model with treatment, site, age, and height as explanatory variables. Time to first opioid rescue was calculated from the end of surgery to first opioid medication and analyzed

using a Cox regression model with treatment and site as factors and age and height as covariates.

SUPPLEMENTAL METHODS REFERENCES

1. Go R, Huang YY, Weyker PD, Webb CA. Truncal blocks for perioperative pain management: a review of the literature and evolving techniques. *Pain Manag.* 2016;6(5):455-468.
2. Lehmann N, Joshi GP, Dirkmann D, et al. Development and longitudinal validation of the overall benefit of analgesia score: a simple multi-dimensional quality assessment instrument. *Br J Anaesth.* 2010;105(4):511-518.
3. Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology.* 2013;118(6):1332-1340.
4. Jenkins MG, Murphy DJ, Little C, McDonald J, McCarron PA. A non-inferiority randomized controlled trial comparing the clinical effectiveness of anesthesia obtained by application of a novel topical anesthetic putty with the infiltration of lidocaine for the treatment of lacerations in the emergency department. *Ann Emerg Med.* 2014;63(6):704-710.
5. Miki K, Ikemoto T, Hayashi K, et al. Randomized open-label [corrected] non-inferiority trial of acetaminophen or loxoprofen for patients with acute low back pain. *J Orthop Sci.* 2018;23(3):483-487.

Table 1. Quality of Recovery 15-item Questionnaire

Part A. How have you been feeling in the last 24 hours? (0 = none of the time [poor] and 10 = all of the time [excellent])
Able to breathe easily
Been able to enjoy food
Feeling rested
Have had a good sleep
Able to look after personal toilet and hygiene unaided
Able to communicate with family and friends
Getting support from hospital doctors and nurses
Able to return to work or usual home practices
Feeling comfortable and in control
Having a feeling of general well-being
Part B. Have you had any of the following in the last 24 hours? (0 = all of the time [poor] and 10 = none of the time [excellent])
Moderate pain
Severe pain
Nausea or vomiting
Feeling worried or anxious
Feeling sad or depressed

SUPPLEMENTAL TABLES

Supplemental Table 1. Inclusion and Exclusion Criteria

Type	Criteria
Inclusion	1. Women 18 years of age and older at screening
	2. Term pregnancies of 37- to 42-weeks gestational age, scheduled to undergo elective cesarean delivery
	3. ASA physical status 2 or 3
	4. Able to provide informed consent, adhere to the study visit schedule, and complete all study assessments
Exclusion	1. Patients who, in the opinion of the study site principal investigator, have a high-risk pregnancy (eg, multiple gestations, pregnancy resulting from in vitro fertilization, gestational diabetes, prolonged bed rest required for medical reasons)
	2. Patients with a pregnancy-induced medical condition or complication (eg, hypertension, pre-eclampsia, chorioamnionitis)
	3. Patients with ≥3 prior cesarean deliveries
	4. Prepregnancy body mass index >50 kg/m^2 or otherwise not anatomically appropriate to undergo a TAP block
	5. Allergy, hypersensitivity, intolerance, or contraindication to any of the study medications for which an alternative is not named in the protocol (eg, amide-type local anesthetics, opioids, bupivacaine, NSAIDs, spinal anesthesia)
	6. Planned concurrent surgical procedure with the exception of salpingo-oophorectomy or tubal ligation
	7. Severely impaired renal or hepatic function (eg, serum creatinine level >2 mg/dL [176.8 μmol/L], blood urea nitrogen level >50 mg/dL [17.9 mmol/L], serum AST level >3 times the ULN or ALT level >3 times the ULN
	8. Patients at an increased risk for bleeding or a coagulation disorder (defined as platelet count less than 80,000 × 10^3/mm^3 or international normalized ratio greater than 1.5)
	9. Concurrent painful physical condition that may require analgesic treatment (such as long-term, consistent use of opioids) in the postsurgical period for pain that is not strictly related to the surgery and that may confound the postsurgical assessments
	10. Clinically significant medical disease in either the mother or baby that, in the opinion of the investigator, would make participation in a clinical study inappropriate. This includes any psychiatric or other disease in the mother that would constitute a contraindication to participation in the study or cause the mother to be unable to comply with the study requirements
	11. History of, suspected, or known addiction to or abuse of illicit drug(s), prescription medicine(s), or alcohol within the past 2 years

12. Administration of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the patient's participation in this study

13. Previous participation in a liposomal bupivacaine study

14. Any clinically significant event or condition uncovered during the surgery (eg, excessive bleeding, acute sepsis) that might render the subject medically unstable or complicate the subject's postsurgical course[a]

15. Received the epidural component of CSE anesthesia during participation in the study[a]

[a]Ineligible to receive study drug and was withdrawn from the study if patient met these criteria during surgery.
ALT, alanine aminotransferase; ASA, American Society of Anesthesiology; AST, aspartate aminotransferase; CSE, combined spinal epidural; NSAID, nonsteroidal anti-inflammatory drug; TAP, transversus abdominis plane; ULN, upper limit of normal.

Supplemental Table 2. Overall Benefit of Analgesia Score Questionnaire

Number	Question
1	Please rate your current pain at rest 0 = minimal pain to 4 = maximum imaginable pain
2[a]	Please grade any distress and bother from vomiting in the past 24 hours 0 = not at all to 4 = very much
3[a]	Please grade any distress and bother from itching in the past 24 hours 0 = not at all to 4 = very much
4[a]	Please grade any distress and bother from sweating in the past 24 hours 0 = not at all to 4 = very much
5[a]	Please grade any distress and bother from freezing in the past 24 hours 0 = not at all to 4 = very much
6[a]	Please grade any distress and bother from dizziness in the past 24 hours 0 = not at all to 4 = very much
7	How satisfied are you with your pain treatment during the past 24 hours 0 = not at all to 4 = very much

[a]Opioid-spared was defined a priori as taking ≤15 mg oral morphine equivalent dose after surgery with an OBAS of 0 for questions 2 through 6.
OBAS, Overall Benefit of Analgesia Score questionnaire.[1]

Supplemental Table 3. Patient Demographics and Baseline Characteristics (Noncomplying Patients)[a]

	LB + BUPI HCl (n=25)	BUPI HCl alone (n=25)
Age, median (range), y	35 (22–45)	31 (24–41)
Race, n (%)		
White	15 (60.0)	16 (64.0)
Black/African American	2 (8.0)	6 (24.0)
Asian	1 (4.0)	1 (4.0)
Other/Multiple	7 (28.0)	2 (8.0)
Weight, mean (SD), kg	94.8 (17.2)	84.8 (15.1)
Height, mean (SD), cm	164.0 (7.5)	162.0 (5.7)
ASA classification, n (%)		
2	24 (96.0)	23 (92.0)
3	1 (4.0)	2 (8.0)
Prior cesarean delivery, n (%)		
0	8 (32.0)	9 (36.0)
1	11 (44.0)	9 (36.0)
2	6 (24.0)	7 (28.0)

[a]Patients excluded from the PCA.
ASA, American Society of Anesthesiologists; BUPI, bupivacaine; HCl, hydrochloride; LB, liposomal bupivacaine; PCA, protocol complaint analysis; SD, standard deviation.

Supplemental Table 4. Total Opioid Consumption Through 72 hours (Primary End Point) and Other Time Points After Cesarean Delivery (PCA Set)

	LB plus BUPI HCl (n=71)	BUPI HCl alone (n=65)
Primary End Point		
MED through 72 hours, LSM (SE), MED mg	15.5 (6.67)	32.0 (6.25)
Treatment difference, LSM (SE)	−16.5 (7.28)	
95% CI of treatment difference	−30.8, −2.2	
P value	0.012	
Secondary End Points		
MED through 24 hours, LSM (SE), MED mg	2.4 (1.82)	5.6 (1.70)
Treatment difference, LSM (SE)	−3.2 (1.99)	
95% CI of treatment difference	−7.1, 0.7	
P value	0.054	
MED through 48 hours, LSM (SE), MED mg	9.1 (4.46)	20.5 (4.18)
Treatment difference, LSM (SE)	−11.4 (4.87)	
95% CI of treatment difference	−20.0, −1.9	
P value	0.010	
MED through Day 7, LSM (SE), MED mg	23.3 (9.75)	45.8 (9.13)
Treatment difference, LSM (SE)	−22.4 (10.65)	
95% CI of treatment difference	−43.3, −1.6	
P value	0.018	
Through Day 14, LSM (SE), MED mg	28.2 (11.20)	47.8 (10.49)
Treatment difference, LSM (SE)	−19.6 (12.23)	
95% CI of treatment difference	−43.6, 4.3	
P value	0.054	

BUPI, bupivacaine; CI, confidence interval; HCl, hydrochloride; LB, liposomal bupivacaine; LSM, least squares mean; MED, morphine equivalent dose; PCA, protocol compliant analysis; SE, standard error.

Supplemental Table 5. AUC of VAS Pain Intensity Scores at Various Time Points (PCA Set)

AUC of VAS pain intensity scores, LSM (SE)	LB plus BUPI HCl (n=71)	BUPI HCl alone (n=65)	LSM treatment difference (95% CI)	*P* value for noninferiority
0-12 h	7.7 (1.4)	7.0 (1.3)	0.7 (−2.3, 3.7)	<0.001
0-24 h	27.7 (4.7)	32.6 (4.4)	−5.0 (−15.1, 5.2)	<0.001
0-36 h	55.7 (8.5)	69.3 (7.9)	−13.6 (−31.7, 4.53)	<0.001
0-48 h	95.4 (12.7)	114.8 (11.9)	−19.4 (−46.7, 7.9)	<0.001
12-24 h	19.9 (3.6)	25.6 (3.4)	−5.7 (−13.5, 2.1)	0.002
12-36 h	44.7 (7.1)	57.6 (6.7)	−12.9 (−28.2, 2.3)	<0.001
12-48 h	87.7 (11.8)	107.8 (11.1)	−20.1 (−45.4, 5.3)	0.002
12-72 h	140.2 (20.3)	171.5 (19.0)	−31.3 (−74.8, 12.3)	0.003
24-36 h	23.9 (4.0)	30.5 (3.7)	−6.6 (−15.1, 1.8)	0.002
24-48 h	67.8 (9.0)	82.2 (8.4)	−14.4 (−33.6, 4.8)	0.004
36-48 h	19.2 (3.9)	26.6 (3.7)	−7.4 (−15.8, 1.0)	<0.001
48-72 h	52.5 (9.6)	63.7 (8.9)	−11.2 (−31.6, 9.2)	0.013

The AUC of VAS pain intensity score at 72 hours was a secondary end point. Other time points are tertiary end points.

AUC, area under the curve; BUPI, bupivacaine; CI, confidence interval; h, hours since end of surgery; HCl, hydrochloride; LB, liposomal bupivacaine; LSM, least squares mean; PCA, protocol compliant analysis; SE, standard error; VAS, visual analog scale.

Supplemental Table 6. Additional Tertiary End Points (PCA Analysis Set)

	LB plus BUPI HCl (n=71)	BUPI HCl alone (n=65)	LSM treatment difference (95% CI)	*P* value[a]
Sum of VAS pain intensity scores, LSM (SE)				
0-72 h	19.7 (2.7)	23.4 (2.5)	−3.7 (−9.5, 2.0)	0.002[b]
Integrated rank assessment using SPIS at rest and OMED for rescue medications, LSM (SE)				
0-24 h	−37.2 (14.2)	−20.0 (13.3)	−17.2 (−47.6, 13.2)	0.133
0-48 h	−40.8 (16.0)	−10.2 (15.0)	−30.6 (−64.9, 3.6)	0.040
0-72 h	−40.9 (16.3)	−12.7 (15.2)	−28.3 (−63.1, 6.5)	0.056
OBAS total score, LSM (SE)[c]				
24 h	5.68 (0.51)	5.71 (0.48)	−0.03 (−1.13, 1.07)	0.477
48 h	2.25 (0.37)	2.60 (0.35)	−0.35 (−1.15, 0.45)	0.196
72 h	1.45 (0.36)	1.64 (0.36)	−0.19 (−0.93, 0.55)	0.305
Time spent in PACU, LSM (SE), h	2.2 (0.36)	2.4 (0.34)	−0.3 (−1.0, 0.5)	0.256
Time to first unassisted ambulation, h				
First quartile	13.5	10.8	-	0.470
Median	NA	16.1	-	
Third quartile	NA	NA	-	
MPADSS discharge readiness, %				
24 h	96.3	95.3	-	0.268
48 h	100.0	100.0	-	0.411
72 h	100.0	100.0	-	0.645
Patient satisfaction at 72 h, mean (SD)[d]	4.31 (0.81)	4.37 (0.81)	-	0.683
Overall QoR-15 at 72 h, LSM (SE)	125.2 (3.8)	123.5 (4.0)	1.8 (−5.2, 8.7)	0.308
Unscheduled phone calls, n (%)	0 (0.0)	0 (0.0)	-	0.560

[a]*P* values are from tests for difference between groups, except where otherwise noted. [b]From noninferiority test, based on noninferiority margin of 4.5. [c]OBAS total score was derived by adding all the scores of questions 1 to 6, adding 4 to that total, and subtracting the score of question 7 from the result. If a response was missing to any question in the OBAS, the total score was not calculated. [d]Using a 5-point Likert scale. BUPI, bupivacaine; CI, confidence interval; h, hours since end of surgery; HCl, hydrochloride; LB, liposomal bupivacaine; LSM, least squares mean; MPADSS, Modified Post Anesthesia Discharge Scoring System; NA, not applicable; OBAS, overall benefit of analgesia score; PACU, postanesthesia care unit; PCA, protocol compliant analysis; SD, standard deviation; SE, standard error; SPIS, sum of pain intensity scores; VAS, visual analog scale.

Supplemental Table 7. Total Opioid Consumption Through 72 Hours After Cesarean Delivery (All Treated Patients)

	LB plus BUPI HCl (n=96)	BUPI HCl alone (n=90)
MED through 72 hours, LSM (SE), MED mg	24.3 (6.03)	27.5 (5.84)
Treatment difference, LSM	−3.1	
95% CI of treatment difference	−15.7, 9.4	
P value[a]	0.312	

These data were a reanalysis of the primary end point in a population of all patients treated. [a]Test for treatment difference between groups.
BUPI, bupivacaine; CI, confidence interval; HCl, hydrochloride; LB, liposomal bupivacaine; LSM, least squares mean; MED, morphine equivalent dose; SE, standard error.

Supplementary Table 8. AUC of VAS Pain Intensity Scores Through 72 Hours After Cesarean Delivery (All Treated Patients)

	LB plus BUPI HCl (n=96)	BUPI HCl alone (n=90)
$AUC_{0\text{-}72}$, LSM (SE)	158.8 (19.1)	168.3 (18.4)
Treatment difference, LSM (SE)	−9.6 (20.20)	
95% CI of treatment difference	−49.2, 30.0	
P value for noninferiority	0.012	

These data were a reanalysis of a secondary end point in a population of all patients treated. $AUC_{0\text{-}72}$, area under the curve through 72 hours; BUPI, bupivacaine; CI, confidence interval; HCl; hydrochloride; LB, liposomal bupivacaine; LSM, least squares mean; VAS, visual analog scale; SE, standard error.

Supplementary Table 9. Total Opioid Consumption Through 72 Hours

	LB plus BUPI HCl	BUPI HCl alone
MED in all patients excluded from the PCA, LSM (SE), mg[a]	52.1 (7.71)	10.5 (7.71)
Treatment difference	41.7 (11.08)	
95% CI of treatment difference	20.0, 63.4	
P value	<0.001	
MED in patients excluded because of incorrect TAP block placement, LSM (SE), mg[b,c]	70.7 (11.57)	9.7 (10.36)
Treatment difference	61.1 (16.97)	
95% CI of treatment difference	27.8, 94.3	
P value	<0.001	
MED in excluded patients with correct TAP block placement, but incorrect LA dosing or nonadherence to multimodal postsurgical analgesic regimen, LSM (SE), mg[b,d]	32.2 (7.41)	18.3 (8.34)
Treatment difference	13.9 (11.16)	
95% CI of treatment difference	−8.02, 35.72	
P value	0.11	
MED in excluded patients with adherence to multimodal postsurgical analgesic regimen, but incorrect LA dosing or TAP block placement, LSM (SE), mg[b,e]	65.9 (16.22)	12.4 (18.27)
Treatment difference	53.4 (27.88)	
95% CI of treatment difference	−1.21, 108.07	
P value	0.028	
MED in excluded patients with correct LA dosing, but incorrect TAP block placement and nonadherence to multimodal postsurgical analgesic regimen, LSM (SE), mg[b,f]	55.5 (8.35)	15.2 (8.35)
Treatment difference	40.3 (12.16)	
95% CI of treatment difference	16.45, 64.12	
P value	<0.001	

[a]LB plus BUPI HCl, n=25; BUPI HCl alone, n=25. [b]Some patients met multiple PCA exclusion criteria. [c]LB plus BUPI HCl, n=6; BUPI HCl alone, n=7. [d]LB plus BUPI HCl, n=19; BUPI HCl alone, n=18. [e]LB plus BUPI HCl, n=6; BUPI HCl alone, n=7. [f]LB plus BUPI HCl, n=19; BUPI HCl alone, n=19.

BUPI, bupivacaine; CI, confidence interval; HCl, hydrochloride; LA, local anesthetic; LB, liposomal bupivacaine; LSM, least squares mean; MED, morphine equivalent dose; PCA, protocol compliant analysis; SE, standard error; TAP, transversus abdominis plane.

Supplementary Table 10. Opioid Consumption Through 72 Hours in Patients Excluded From the PCA Due to Incorrect TAP Block Placement

LB plus BUPI HCl (n=6)	BUPI HCl alone (n=7)
112.5	37.5
105	15
90	7.5
82.5	7.5
15	0
0	0
	0

Values are the oral MED (in mg) for each patient who was excluded.
BUPI, bupivacaine; HCl, hydrochloride; MED, morphine equivalent dose; PCA, protocol compliant analysis.

SUPPLEMENTAL TABLES REFERENCE

1. Lehmann N, Joshi GP, Dirkmann D, et al. Development and longitudinal validation of the overall benefit of analgesia score: a simple multi-dimensional quality assessment instrument. *Br J Anaesth.* 2010;105(4):511-518.