Liposomal Bupivacaine via Femoral Nerve Block in the Adductor **Canal for Total Knee Arthroplasty**

Jeff Gadsden,¹ Mark Hamilton,² Gary Schwartz,³ Jeff Gonzales,⁴ Jacob Hutchins,⁵ Partha Saha.⁶ Jia Song.⁶ Mary DiGiorgi.⁶ Roy Winston⁶

¹Duke University Medical Center, Durham, NC; ²Northside Hospital-Forsyth, Cumming, GA; ³Maimonides Medical Center, Brooklyn, NY; ⁴Guardian Anesthesia Services and Enhanced Recovery Anesthetic Consultants, Parker, CO; ⁵University of Minnesota Medical Center, Minneapolis, MN; ⁶Pacira BioSciences, Inc., Tampa, FL

OBJECTIVE

To compare the postoperative analgesic effect of liposomal bupivacaine (LB) 133 mg admixed with bupivacaine hydrochloride (HCl) 50 mg (LB133-ADMIX group) versus bupivacaine HCl 50 mg (BUP50 group) when administered via femoral nerve block in the adductor canal (ACB) in participants undergoing primary unilateral total knee arthroplasty (TKA)

CONCLUSIONS

- **1** In this phase 3 study investigating ACBs with LB 133 mg vs bupivacaine HCl 50 mg, LB 133 mg resulted in significant reductions in both pain and opioid consumption from 0 to 96 hours after surgery
- **2** The concurrent reductions in pain and opioid consumption are notable because they are interdependent variables, and participants had lower pain scores without higher opioid consumption
- 3 This study was designed to isolate the effects of the ACB study intervention by use of a simplified pain management protocol
- 4 LB 133 mg was well tolerated, with a similar safety profile to bupivacaine HCl 50 mg

PRESENTING AUTHOR: Jeff Gonzales; jeffrey.gonzales@pacira.com

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REFERENCES: 1. Fillingham YA et al. J Arthroplasty. 2022;37(9):1691-1696. 2. Fillingham YA et al. J Arthroplasty. 2022;37(10):1906-1921 e1902.

BACKGROUND

- Clinical practice guidelines recommend use of regional nerve blocks such as ACB for TKA¹
- ACBs can provide postoperative analgesia with reduced opioid consumption and contribute to improved recovery compared with femoral nerve blocks by preserving quadriceps strength after surgery²
- LB is a formulation of the local anesthetic bupivacaine that enables gradual release of bupivacaine for prolonged periods of analgesia
- More data are needed to determine the impact of LB admixed with bupivacaine HCI via ACB for TKA on pain intensity scores and opioid consumption

METHODS

STUDY DESIGN

Figure 1. Study design.

Cohort 1 (Efficacy, Safet

Screening (≤45 days before surger Participants undergoing prima unilateral TKA for degenerat knee OA • \geq 18 years of age ASA physical status classification ≤ 3 • BMI \geq 18 and <40 kg/m

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- A total of 166 participants were randomized and treated (cohort 1: n=45; cohort 2: n=121)
- 6 participants discontinued from cohort 1 because of participant withdrawal (n=4), adverse event (AE; n=1), or failure to meet continuation criteria (n=1)
- Participant demographics and baseline characteristics are shown in Table 1

Table 1. Demographics and Baseline Characteristics

Cohort 1		Cohorts 1 + 2			
LB133-ADMIX (n=24)	BUP50 (n=21)	LB133-ADMIX (n=85)	BUP50 (n=81)	Total ^a (N=166)	
61.5 (51-75)	63 (45-80)	62 (44-75)	62 (37-83)	62 (37-83)	
12 (50.0)	8 (38.1)	42 (49.4)	39 (48.1)	81 (48.8)	
16 (66.7)	17 (81.0)	64 (75.3)	66 (81.5)	130 (78.3)	
21 (87.5)	19 (90.5)	67 (78.8)	63 (77.8)	130 (78.3)	
2 (8.3)	2 (9.5)	14 (16.5)	15 (18.5)	29 (17.5)	
2 (8.4)	0	8 (9.4)	6 (7.4)	14 (8.4)	
32.5 (5.0)	33.3 (4.8)	31.4 (4.8)	32.7 (5.0)	32.1 (4.9)	
8.0 (3, 10)	8.0 (1, 10)	8.0 (2, 10)	8.0 (0, 10)	8.0 (0, 10)	
5.0 (0, 10)	5.0 (1, 8)	5.0 (0, 10)	5.0 (0, 10)	5.0 (0, 10)	
	LB133-ADMIX (n=24) 61.5 (51-75) 12 (50.0) 16 (66.7) 21 (87.5) 2 (8.3) 2 (8.4) 32.5 (5.0) 8.0 (3, 10)	LB133-ADMIX (n=24)BUP50 (n=21)61.5 (51-75)63 (45-80)12 (50.0)8 (38.1)16 (66.7)17 (81.0)21 (87.5)19 (90.5)2 (8.3)2 (9.5)2 (8.4)032.5 (5.0)33.3 (4.8)8.0 (3, 10)8.0 (1, 10)	LB133-ADMIX (n=24)BUP50 (n=21)LB133-ADMIX (n=85)61.5 (51-75)63 (45-80)62 (44-75)12 (50.0)8 (38.1)42 (49.4)16 (66.7)17 (81.0)64 (75.3)21 (87.5)19 (90.5)67 (78.8)2 (8.3)2 (9.5)14 (16.5)2 (8.4)08 (9.4)32.5 (5.0)33.3 (4.8)31.4 (4.8)8.0 (3, 10)8.0 (1, 10)8.0 (2, 10)	LB133-ADMIX (n=24)BUP50 (n=21)LB133-ADMIX (n=85)BUP50 (n=81)61.5 (51-75)63 (45-80)62 (44-75)62 (37-83)12 (50.0)8 (38.1)42 (49.4)39 (48.1)16 (66.7)17 (81.0)64 (75.3)66 (81.5)21 (87.5)19 (90.5)67 (78.8)63 (77.8)2 (8.3)2 (9.5)14 (16.5)15 (18.5)2 (8.4)08 (9.4)6 (7.4)32.5 (5.0)33.3 (4.8)31.4 (4.8)32.7 (5.0)8.0 (3, 10)8.0 (1, 10)8.0 (2, 10)8.0 (0, 10)	

EFFICACY: PAIN INTENSITY AND OPIOID CONSUMPTION

- From 0 to 96 hours after surgery, the least squares mean (LSM) standard error (SE) area under the curve (AUC) of the numerical rating scale (NRS) pain intensity score (the primary endpoint) was 568.9 (20.1) in the LB133-ADMIX group and 634.7 (20.0) in the BUP50 group (LSM difference vs BUP50, -65.8 [95% confidence interval (CI), -118.7, -12.9]; *P*=0.0074)
- From 0 to 96 hours, total opioid consumption was significantly lower in the LB133-ADMIX group versus the BUP50 group (LSM, 101.8 [95% CI, 89.1, 116.3] vs 132.8 [95% CI, 116.3, 151.7] MMEs; LSM ratio compared with BUP50, 0.77 [95% CI, 0.64, 0.92]; *P*=0.0018)
- Total opioid consumption was also consistently lower in the LB133-ADMIX group in 24-hour increments (Figure 2)
- Pain intensity scores were generally lower over time in the LB133-ADMIX group than the BUP50 group, particularly from 30 to 96 hours (Figure 2)

• This phase 3, multicenter, randomized, double-blind, active-controlled study (NCT05139030) enrolled 2 cohorts (Figure 1)

ty, PK) and Cohort 2 (Effica	acy, Safety) Efficacy Endpoints	Primary	 AUC of current NRS pain intensity scores 0-96 h after surgery
	ndmixed with HCl 50 mgª	Secondary	 Total opioid consumption 0-96 h after surgery Time to first opioid consumption Worst and average NRS pain intensity scores at 24, 48, 72, and 96 h after surgery
R 1:1 Bupivacaine	HCl 50 mg ^b	Exploratory	• Current NRS pain intensity scores 0-96 h after surgery
	Additiona	Safety	AEs and SAEs through postoperative day 14
	Endpoin		 AUC of bupivacaine plasma concentration versus time 0-168 h after surgery C_{max} T_{max}
		-	

^aLB 133 mg administered as 10 mL (133 mg) of LB admixed with 10 mL (50 mg) of bupivacaine HCI. ^bBupivacaine HCI 50 mg administered as 10 mL (50 mg) of bupivacaine HCI admixed with 10 mL of normal saline AE, adverse event; ASA, American Society of Anesthesiologists; AUC, area under the curve; BMI, body mass index; Cmax maximum plasma concentration; HCl, hydrochloride; LB, liposomal bupivacaine; NRS, numerical rating scale; OA, osteoarthritis; PK, pharmacokinetics; SAE, serious AE; TKA, total knee arthroplasty; T_{max} time of maximum plasma concentration.

TREATMENT ADMINISTRATION AND PERMITTED ANALGESIC MEDICATIONS

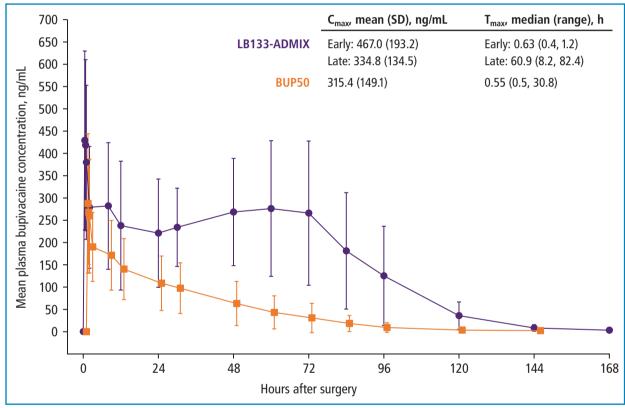
- The study drug was administered as an ACB ~90 minutes before surgery
- Oral celecoxib 200 mg was administered within 4 hours before surgery, and spinal anesthesia with 0.5% bupivacaine HCl (\geq 15 mg) was administered immediately before surgery
- After study drug administration, all participants received local anesthetic containing 15 mL (37.5 mg) of 0.25% bupivacaine HCl for infiltration between the popliteal artery and capsule of the knee. Participants received two doses of 1000 mg intravenous (IV) acetaminophen: 1 dose at the time of surgical incision and 1 postoperative dose ~8 hours later
- Participants were not permitted to receive nonsteroidal anti-inflammatory drugs within 96 hours after surgery or opioids except oxycodone (up to a maximum of 10 mg) or IV morphine (initiated at 2 mg) or hydromorphone (initiated at 0.2 mg) as needed for breakthrough pain

STATISTICAL ANALYSES

- Statistical tests were conducted in hierarchical order using an analysis of covariance model with treatment as the main effect
- All tests were 1-sided with a significance level of 0.025

Figure 2. Current NRS pain intensity scores over time and opioid consumption over each 24-hour period from 0 to 96 hours after surgery in the LB133-ADMIX and BUP50 groups.

Figure 3. Mean plasma bupivacaine concentration from 0 to 168 hours after surgery.

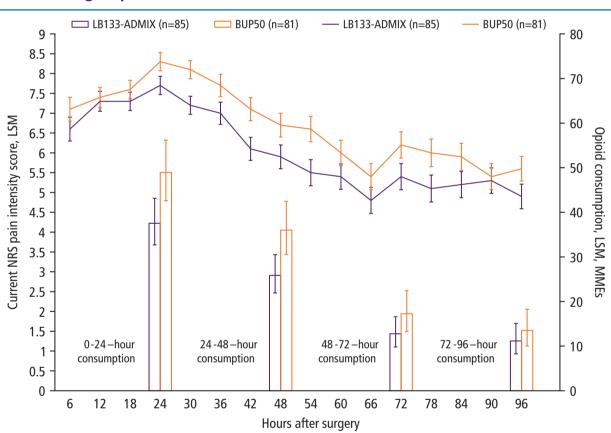


Error bars are the standard deviation. C_{max} maximum plasma concentration; BUP50, bupivacaine hydrochloride 50 mg group; LB133-ADMIX, liposomal bupivacaine 133 mg admixed with bupivacaine hydrochloride 50 mg group; SD, standard deviation; T_{max}, time of maximum plasma concentration.

Table 2. AEs (Cohort 1 + 2)

	LB133-ADMIX, n (%)ª (n=86)	BUP50, n (%)ª (n=80)
ny AE	77 (89.5)	71 (88.8)
Mild AE	51 (59.3)	51 (63.8)
Moderate AE	24 (27.9)	19 (23.8)
Severe AE	2 (2.3)	1 (1.3)
AEs by preferred term (≥10%	6 of Participants in Either Treatment Group)
Nausea	34 (39.5)	30 (37.5)
Constipation	30 (34.9)	31 (38.8)
Muscle spasms	11 (12.8)	9 (11.3)
Insomnia	5 (5.8)	13 (16.3)
Headache	13 (15.1)	2 (2.5)
Hypotension	3 (3.5)	8 (10.0)

bupivacaine hydrochloride 50 mg group.



Lines: see values on left y-axis; error bars are the standard error. Bars: see values on right y-axis; error bars are the 95% confidence interval. BUP50, bupivacaine hydrochloride 50 mg group; LB133-ADMIX, liposomal bupivacaine 133 mg admixed with bupivacaine hydrochloride 50 mg group; LSM, least squares mean; MME, morphine milligram equivalent; NRS, numerical rating scale.

PHARMACOKINETICS

• The peak plasma concentration profile in the BUP50 group exhibited 1 peak, after which plasma concentrations decreased; the peak plasma concentration profile for the LB133-ADMIX group exhibited a biphasic peak (Figure 3)

SAFETY

- The frequency of AEs was similar between the LB133-ADMIX and BUP50 groups, with most AEs being mild to moderate in severity (Table 2)
- 1 participant in the BUP50 group discontinued because of severe AEs (acute myocardial infarction and atrial fibrillation) considered unrelated to treatment No deaths occurred during the study
- The rate of treatment-related AEs was low and similar between groups (LB133-ADMIX: 3.5%; BUP50: 2.5%)

), ng/mL	T _{max} , median (range), h
.2)	Early: 0.63 (0.4, 1.2)
.5)	Late: 60.9 (8.2, 82.4)
	0.55 (0.5, 30.8)