FA-15

Liposomal Bupivacaine Administered as a Sciatic Nerve Block in the Popliteal Fossa for Bunionectomy

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OBJECTIVE

To investigate the efficacy, safety, and pharmacokinetics of liposomal bupivacaine (LB) administered as a sciatic nerve block in participants undergoing bunionectomy

CONCLUSIONS

1. In an adaptive study design that used a simplified pain management protocol designed to isolate the effects of the study interventions, LB 133 mg demonstrated significant reductions in pain intensity in the first 96 hours after surgery compared with bupivacaine hydrochloride (HCl) 50 mg when administered as a sciatic nerve block in participants undergoing bunionectomy
2. LB 133 mg was also associated with reduced opioid consumption and a higher proportion of participants being opioid free 0-96 hours after surgery
3. LB 133 mg was well tolerated with a similar safety profile to bupivacaine HCl 50 mg

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REFERENCES: 1. Korwin-Kochanowska K et al. *Reg Anesth Pain Med.* 2020;45(9):702-708. **2.** Golf M et al. *Adv Ther.* 2011;28(9):776-788. **3.** EXPAREL (bupivacaine liposome injectable suspension) [US package insert]. Pacira BioSciences, Inc.; 2021.

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BACKGROUND

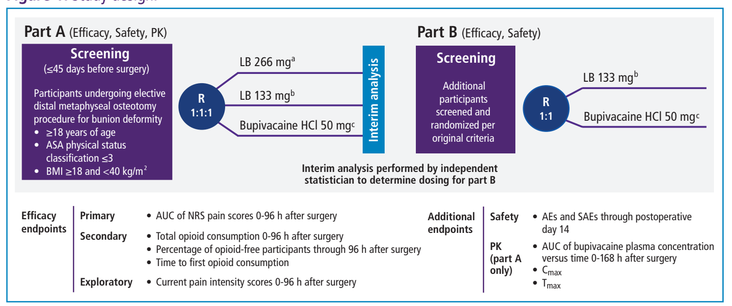
- Current guidelines for postoperative pain management after bunionectomy recommend systemic analgesia (eg, paracetamol, nonsteroidal anti-inflammatory drugs, steroids) and ankle block or wound infiltration for regional analgesia, with opioids reserved for breakthrough pain[1]
- LB is a long-acting formulation of bupivacaine that delivers extended postsurgical analgesia, which can help decrease opioid use for breakthrough pain
  - In a previous phase 3 trial, LB via wound infiltration reduced pain intensity and opioid use relative to placebo up to 36 and 24 hours after bunionectomy, respectively[2]
- While LB is currently approved for use via local infiltration and as an interscalene brachial plexus nerve block for postsurgical analgesia,[3] data regarding use of LB as a sciatic nerve block for postsurgical pain after bunionectomy are limited

METHODS

STUDY DESIGN

- This phase 3, multicenter, randomized, double-blind, active-controlled study (NCT05157841) was conducted in 2 parts using an adaptive study design (Figure 1)
- Part A was to be completed and analyzed before enrollment in part B was initiated
  - In part A, the efficacy, safety, and pharmacokinetics of LB were evaluated in participants undergoing bunionectomy
  - The efficacy and safety of LB (at the dose established in part A) compared with bupivacaine HCl were evaluated in part B

Figure 1. Study design.



[a]LB 266 mg administered as 20 mL (266 mg) of LB mixed with 10 mL of normal saline. [b]LB 133 mg administered as 10 mL (133 mg) of LB mixed with 20 mL of normal saline. [c]Bupivacaine HCl 50 mg administered as 20 mL of 0.25% bupivacaine HCl mixed with 10 mL of normal saline. AE, adverse event; ASA, American Society of Anesthesiologists; AUC, area under the curve; BMI, body mass index; C_{max}, maximum plasma concentration; HCl, hydrochloride; LB, liposomal bupivacaine; NRS, numerical rating scale; SAE, serious adverse event; T_{max}, time to maximum plasma concentration.

TREATMENT ADMINISTRATION AND PERMITTED ANALGESIC MEDICATIONS

- The study drug was administered as a popliteal sciatic nerve block ~90 minutes before surgery
- Celecoxib 200 mg orally was permitted within 4 hours before surgery
- All participants received a Mayo field block (20 mL of 0.5% bupivacaine HCl) after study drug administration, 1000 mg of intravenous (IV) acetaminophen at the time of incision, and a single postoperative 1000-mg dose of IV acetaminophen ~8 hours after incision
- No other analgesic agents were permitted within 96 hours after surgery 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 performed in a hierarchical order with an analysis of covariance model performed for part A and part B separately
- All statistical comparisons were 1-sided tests at an α level of 0.025 unless otherwise specified

RESULTS

PARTICIPANTS

- A total of 185 participants were randomized and treated across both parts of the study
- In part A, 22 participants were enrolled in each treatment group
  - There were 5 discontinuations from part A because of participant withdrawal (n=3), adverse event (AE; n=1), and other reasons (n=1)
- In part B, additional participants were randomized to the LB 133 mg (at the selected dose from part A) and bupivacaine HCl 50 mg treatment groups, resulting in 163 total participants receiving LB 133 mg (n=81) or bupivacaine HCl 50 mg (n=82) across parts A and B
  - There were no discontinuations in part B
- Participant demographics and baseline characteristics are shown in Table 1

Table 1. Demographics and Baseline Characteristics

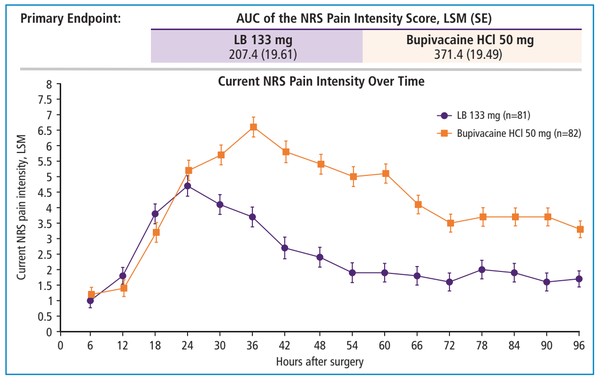
	Part A			Part A + B		
	LB 266 mg (n=22)	LB 133 mg (n=22)	Bupivacaine HCl 50 mg (n=22)	LB 133 mg (n=81)	Bupivacaine HCl 50 mg (n=82)	Total[a] (N=185)
Age, median (range), y	50.5 (23-63)	53.5 (21-67)	46 (23-65)	52 (18-75)	47.5 (21-76)	50 (18-76)
Female, n (%)	21 (95.5)	20 (90.9)	17 (77.3)	74 (91.4)	68 (82.9)	163 (88.1)
Not Hispanic or Latino, n (%)	12 (54.5)	12 (54.5)	9 (40.9)	55 (67.9)	50 (61.0)	117 (63.2)
Race, n (%)						
White	16 (72.7)	14 (63.6)	18 (81.8)	47 (58.0)	49 (59.8)	112 (60.5)
Black	4 (18.2)	7 (31.8)	4 (18.2)	25 (30.9)	28 (34.1)	57 (30.8)
Asian	0	0	0	4 (4.9)	1 (1.2)	5 (2.7)
Other[b]	2 (9.1)	1 (4.5)	0	5 (6.2)	4 (4.9)	11 (5.9)
Average pain intensity (NRS), mean (SD)[c]	3.9 (2.23)	3.8 (2.07)	3.8 (2.19)	3.4 (2.10)	3.8 (2.33)[d]	3.7 (2.22)[d]

[a]Total includes all participants in the LB 266 mg group (part A), all participants receiving LB 133 mg (part A + B), and all participants receiving bupivacaine HCl 50 mg (part A + B). [b]Includes American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, and other/multiple/not reported/unknown. [c]In the last 30 days. [d]Data unavailable for 1 participant in the bupivacaine HCl 50 mg group.
HCl, hydrochloride; LB, liposomal bupivacaine; NRS, numerical rating scale; SD, standard deviation.

EFFICACY: PAIN INTENSITY 0-96 HOURS AFTER SURGERY

- In part A, the least squares mean (LSM) standard error (SE) area under the curve (AUC) of the numerical rating scale (NRS) pain intensity score difference from bupivacaine HCl 50 mg was significant for LB 133 mg (–189.0 [62.27]; P=0.0012) but not for LB 266 mg; therefore, LB 133 mg was selected for part B
- In the combined population from parts A and B, the LSM [SE] AUC of the NRS pain intensity score difference from bupivacaine HCl 50 mg for LB 133 mg was –164.0 [27.74]; P<0.00001), representing a 44% reduction (Figure 2)
- Current NRS pain intensity scores were comparable between the LB 133 mg and bupivacaine HCl 50 mg groups for the first 24 hours after surgery; thereafter, pain scores were lower in the LB 133 mg group

Figure 2. NRS pain intensity after surgery for the LB 133 mg and bupivacaine HCl 50 mg groups (part A + B).



Error bars are the standard error. AUC, area under the curve; HCl, hydrochloride; LB, liposomal bupivacaine; LSM, least squares mean; NRS, numerical rating scale.

EFFICACY: OPIOID CONSUMPTION 0-96 HOURS AFTER SURGERY

- In the combined population of parts A and B, LB 133 mg was associated with a significant 61% reduction in LSM total opioid consumption and 5 times higher odds of being opioid free compared with bupivacaine HCl 50 mg 0-96 hours after surgery (Table 2)

Table 2. Opioid Consumption 0-96 Hours After Surgery (Parts A + B)

	LB 133 mg (n=81)	Bupivacaine HCl 50 mg (n=82)	P value
Total opioid consumption, MMEs			
LSM (95% CI)[a]	17.68 (13.71-22.80)	45.34 (35.14-58.51)	
LSM ratio from bupivacaine (95% CI)	0.39 (0.28-0.55)	–	<0.00001
Postsurgical opioid-free participants			
Opioid free, %[b]	24.4	6.0	
Not opioid free, %	75.6	94.0	
Odds ratio (95% CI)	5.04 (2.01-12.62)	–	0.0003

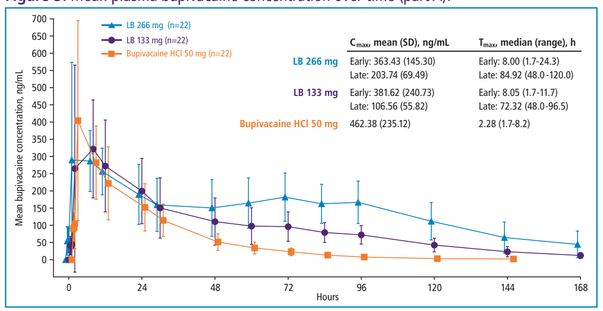
[a]From analysis of covariance with main effect of treatment and covariates of site (categorical) and age (continuous). Total dose was log-transformed in the analysis, and back-transformed total dose is reported. Note: zero dose was replaced with 3.75 mg to enable log-transformation. [b]LSM estimate using logistic regression with treatment as main effect and site as categorical and age as continuous covariates.
CI, confidence interval; HCl, hydrochloride; LB, liposomal bupivacaine; LSM, least squares mean; MME, morphine milligram equivalent.

- The median times to first rescue medication were 20.27 (range, 17.13-29.98) hours for LB 133 mg and 20.68 (range, 19.28-24.40) hours for bupivacaine HCl 50 mg; the hazard ratio of 0.65 was statistically significant (Cox 1-sided P=0.0089)

PHARMACOKINETICS (PART A)

- Both doses of LB were associated with biphasic peak bupivacaine plasma concentrations, whereas bupivacaine HCl 50 mg exhibited a single peak occurring ~3 times earlier than the LB treatment arms (Figure 3)
- Overall, bupivacaine dose-normalized exposure was similar across treatment groups

Figure 3. Mean plasma bupivacaine concentration over time (part A).



Error bars are the standard deviation. C_{max}, maximum plasma concentration; HCl, hydrochloride; LB, liposomal bupivacaine; T_{max}, time to maximum plasma concentration.

SAFETY

- The frequency of AEs was similar across treatment groups with all AEs being mild or moderate severity (Table 3)
- In part A, SAEs of hypertension and pyrexia were reported in 1 participant in the LB 266 mg group, and 1 participant in the bupivacaine HCl 50 mg group had an SAE of second-degree atrioventricular block; both participants discontinued from part A

Table 3. AEs

	Part A	Part A + B	
	LB 266 mg (n=22)	LB 133 mg (n=81)	Bupivacaine HCl 50 mg (n=82)
Any AE	13 (59.1)	42 (51.9)	45 (54.9)
Mild AE	7 (31.8)	32 (39.5)	35 (42.7)
Moderate AE	6 (27.3)	10 (12.3)	10 (12.2)
AEs by preferred term (≥5% of Participants in Any Treatment Group)			
Nausea	9 (40.9)	13 (16.0)	19 (23.2)
Constipation	3 (13.6)	10 (12.3)	16 (19.5)
Headache	1 (4.5)	8 (9.9)	4 (4.9)
Vomiting	5 (22.7)	4 (4.9)	7 (8.5)
Pruritus	1 (4.5)	6 (7.4)	5 (6.1)

Values are the number (%). AE, adverse event; HCl, hydrochloride; LB, liposomal bupivacaine.