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Liposomal Bupivacaine Use in Third Molar Impaction Surgery: INNOVATE Study

Stuart E. Lieblich, DMD;* and Hassan Danesi, MD†

*Clinical Professor, University of Connecticut School of Dental Medicine, Division of Oral and Maxillofacial Surgery, Avon, Connecticut, and †Pacira Pharmaceuticals, Inc, Parsippany, New Jersey

The analgesic efficacy and safety of liposomal bupivacaine (LB) in third molar extraction was evaluated in this phase 3, double-blind, placebo-controlled study of subjects undergoing bilateral third molar extraction. Subjects were randomized 2:1 to infiltration with LB (133 mg/10 mL) or placebo, and received opioid rescue medication as needed. Primary efficacy measure was cumulative area under the curve (AUC) of numeric rating scale (NRS) pain severity scores through 48 hours (AUC of $NRS_{0–48}$) postsurgery. Other measures included AUC of $NRS_{0–24}$, AUC of $NRS_{0–72}$, and AUC of $NRS_{0–96}$, and incidence of adverse events. There were 150 subjects in the primary efficacy population ($n = 99$ LB, $n = 51$ placebo) and 89 in the per-protocol population ($n = 59$ LB, $n = 30$ placebo). Least-squares mean for AUC of $NRS_{0–48}$ was 172.3 LB versus 194.7 placebo ($P = .227$) in the primary efficacy population and 120.8 LB versus 183.3 placebo ($P = .023$) in the per-protocol population. At all time points, between-group differences in AUC of NRS scores were significant in the per-protocol population (LB lower than placebo, $P < .05$) but not in the primary efficacy population. The adverse event profile was similar between groups. LB produced significantly lower cumulative pain scores versus placebo at all time points in the per-protocol analysis but not in the primary efficacy analysis because of protocol violations. This study indicates significant improvement in pain scores in the third molar model, but because of extensive protocol violations additional studies are warranted to demonstrate effectiveness.

Key Words: Oral surgery; Third molar; Bupivacaine; Tooth extraction; Postoperative pain; Nonnarcotic analgesics; Impacted tooth.

Each year, an estimated 5 million people undergo surgery for removal of impacted teeth in the United States.[1] Postsurgical pain is a common consequence of oral surgery and can significantly interfere with recovery, as well as with activities of daily living, for several days after surgery.[2,3] More lengthy, complex surgeries have been reported to be associated with more postsurgical pain, trismus, and swelling than shorter, less-difficult procedures.[4] Inadequate management of acute postsurgical pain has been associated with a wide array of negative outcomes, including delayed recovery and even increased risk for development of chronic pain.[5–7] In light of the high prevalence and burdensome clinical impact of pain following oral surgery, as well as the presurgical anxiety that affects many patients, effective management of postsurgical pain is a primary consideration for clinicians.[2,8,9] Opioids are commonly prescribed for pain management in dental settings, including third molar extractions,[10,11] but multiple therapeutic options may be needed to address the various sources of pain and inflammation that contribute to symptoms of pain following oral surgery.[12–14] Combinations of analgesics have been shown to provide improved analgesia over unimodal pain management.[15–18] Furthermore, opioids carry the risk of burdensome adverse effects, including nausea, vomiting, constipation, urinary retention, respiratory depression, central nervous system effects, and pruritus, as well as high potential for misuse, abuse, and diversion.[15,19,20]

The development and use of local anesthetics for intraoperative anesthesia and postsurgical analgesia is considered one of the most important advancements in dental

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Address correspondence to Dr Stuart E. Lieblich, Clinical Professor, Avon Oral and Maxillofacial Surgery, LLP, 34 Dale Road, Avon, CT 06001-3659; stul@comcast.net.

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science during the past century.[21] Infiltration with local anesthetics at the surgical site represents an effective approach to postsurgical analgesia that can be used as part of a multimodal approach to pain management. Local administration minimizes the risk of systemic adverse events (AEs); however, the efficacy of local anesthetics is limited by their short duration of action (typically ≤8–10 hours).[22] Liposomal bupivacaine (EXPAREL, bupivacaine liposome injectable suspension; Pacira Pharmaceuticals, Inc, Parsippany, NJ) is a novel prolonged-release formulation of bupivacaine indicated for infiltration into the surgical site to produce postsurgical analgesia.[23] Liposomal bupivacaine is provided as a 13.3-mg/mL solution in either a 20-mL vial (total bupivacaine, 266 mg) or a 10-mL vial (total bupivacaine, 133 mg). Approximately 3% of the total bupivacaine included in each vial is free bupivacaine, with the remainder encapsulated into the multivesicular liposomes that comprise DepoFoam delivery technology.[24] Each liposome is made up of multiple drug-containing vesicles, each of which is surrounded by a lipid bilayer.[25] This prolonged-release technology allows localized release of bupivacaine over several days following a single administration, resulting in a bimodal plasma concentration-versus-time curve, with a peak about 1 hour after administration (representing free extraliposomal bupivacaine), followed by a gradual rise to a second peak at around 12–36 hours later (representing gradual release of liposomal bupivacaine). The concentration of bupivacaine decreases slowly and is detectable for up to 72–96 hours, depending on the site of administration.[26]

Phase 2 and 3 clinical studies conducted across a range of surgical models have demonstrated the efficacy of liposomal bupivacaine for prolonged postsurgical analgesia,[27,28] while demonstrating a tolerability profile similar to that of bupivacaine HCl.[29] Since its approval in 2011, liposomal bupivacaine has been used in more than 2 million surgical patients.

The Infiltration Trial in Third Molar Extraction Observing the Analgesic Effect of EXPAREL (INNOVATE) study was conducted to assess the efficacy, safety, and tolerability of a single administration of liposomal bupivacaine in subjects undergoing bilateral third molar extraction. Here, we report the results for the primary efficacy outcome measure, as well as selected secondary and tertiary efficacy outcomes and overall safety results for the study.

METHODS

Study Design

This was a phase 3, randomized, double-blind, placebo-controlled, parallel-group study (US National Institutes of Health clinical trials identifier NCT02517905) conducted in subjects undergoing elective bilateral third molar extraction under local anesthesia at 3 study centers in the United States. Each study site obtained approval of a central institutional review board (Aspire Institutional Review Board, Santee, Calif), and the study was conducted according to the International Council for Harmonisation Guidelines for Good Clinical Practice; all subjects provided written informed consent before any study procedures were performed.

Study Subjects

Male and nonpregnant female adults (≥18 years of age) with American Society of Anesthesiologists physical status classification 1, 2, or 3 who were scheduled to undergo bilateral third molar extraction (extraction of all 4 third molars) under local anesthesia, with or without nitrous oxide/oxygen inhalation sedation, were eligible to participate in the study. Study participants were required to have full or partial bony impaction of at least 1 mandibular third molar.

Candidates for the study were excluded if they had a history of allergy or contraindication to amide-type local anesthetics, epinephrine, or opioids; a positive test result from an urine drug screen; a history of any disease or condition or recent use of any drug that, in the opinion of the investigator, might increase the risk of surgery or interfere with study evaluations; recent history of antibiotic use (intravenous, 45 days; oral, 30 days) for reasons other than dental prophylaxis; any use of long-acting opioids, nonsteroidal anti-inflammatory drugs, aspirin, or acetaminophen within 3 days before screening; or any use of opioids within 24 hours before screening.

Study Procedures and Treatment Regimens

A screening visit was conducted within 30 days before surgery and included assessment of medical/surgical history, signing of informed consent, physical and dental examination, vital sign measurement, pregnancy testing for women of childbearing potential, urine drug screen, and 12-lead electrocardiogram.

On the day of surgery (day 1), a centralized randomization system was used to preoperatively assign subjects in a 2: 1 ratio to receive either liposomal bupivacaine (133 mg/10 mL) or matching placebo (sterile normal saline, 10 mL). Administration of study drug was performed in a blinded manner. Syringes containing liposomal bupivacaine or placebo were masked so that the operator could not detect which solution was being infiltrated. A unique randomization code for each subject was generated by the centralized system, which then sent the codes to participating study sites. Blood samples for pharmacokinetic

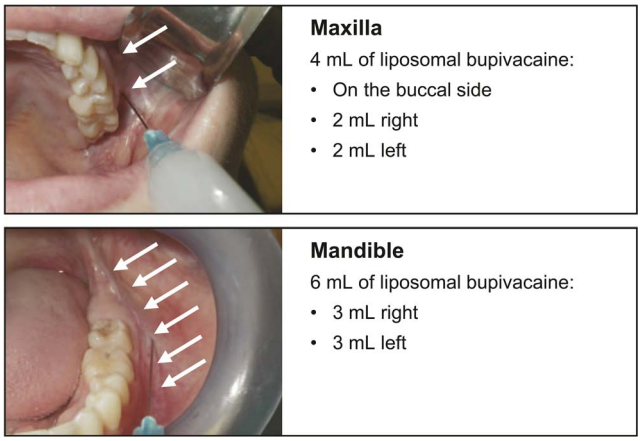

Figure 1. Infiltration technique. Arrows denote illustrative infiltration sites. Images courtesy of Stuart E. Lieblich, DMD.

analyses were obtained from all subjects prior to study drug administration; at 15 and 30 minutes and 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 84, and 96 hours after the beginning of study drug administration; and on days 7 and 10.

All randomized subjects received a preoperative inferior alveolar nerve block and infiltration around the long buccal nerve using lidocaine 2% with epinephrine 1: 100,000. The maxillary teeth received buccal and palatal infiltration with the same agent. In addition, topical benzocaine or intraoperative nitrous oxide could be administered at the discretion of the investigator. Study drug was administered after the lidocaine nerve block, at the end of surgery. Infiltration sites are illustrated in Figure 1; of the 10 mL of study drug solution (liposomal bupivacaine or placebo), 4 mL (2 mL per side) was infiltrated into the maxilla and 6 mL (3 mL per side) into the mandible, according to the following guidelines. (a) Maxilla: 2 points of infiltration (submucosal and supraperiosteal), separated by 6–8 mm, were identified at the apex of each extracted third molar socket (total of 4 infiltration sites), and 1 mL of study drug solution was infiltrated in each site. (b) Mandible: after readaptation and closure of the mucoperiosteal flap, the external oblique ridge was palpated to identify the buccinator muscle attachment; 4 infiltration points (6–8 mm apart) were selected along the buccinator muscle attachment line, and 0.5 mL of study drug solution was infiltrated approximately 5 mm deep into the muscle at each infiltration point (total of 2 mL per side for this step). Then, at the point of greatest subperiosteal reflection, just lateral to the third molar socket, 1.5 cm deep, 2 infiltrations of 0.5 mL each were administered as the needle was withdrawn (total of 1 mL per side for this step).

Oral oxycodone 5–10 mg was available to all subjects as needed (maximum every 4 hours) for control of postsurgical breakthrough pain; no other analgesics were permitted during the first 96 hours after surgery. Subjects remained at the study site for 96 hours after study drug administration, returned for follow-up visits on days 7 and 10, and were contacted by telephone on day 30.

Assessments

The date, time of administration, and amount of opioid rescue medication taken by each subject through 96 hours after surgery was documented. Pain intensity was assessed using an 11-point numeric rating scale (NRS; 0 = no pain, 10 = worst possible pain) at 15 and 30 minutes and 1, 2, 4, 6, 8, 12, 24, 48, 72, and 96 hours after surgery, and immediately before each administration of opioid rescue analgesic medication. Subjects' satisfaction with postsurgical pain control was assessed using a 5-point Likert scale (1 = extremely dissatisfied; 5 = extremely satisfied) at 24, 48, 72, and 96 hours after the beginning of study drug administration and on day 10. AEs were documented through day 30.

Outcome Measures

The primary efficacy measure was the cumulative area under the curve (AUC) of NRS pain severity scores through 48 hours (AUC of $NRS_{0–48}$) postsurgery. Secondary efficacy measures included the cumulative pain intensity scores through 24 hours (AUC of $NRS_{0–24}$) and 72 hours (AUC of $NRS_{0–72}$) postsurgery. Tertiary efficacy measures included AUC of $NRS_{0–96}$, time to first use of opioid rescue medication, total amount of opioid analgesics through 48 hours after surgery, and subjects' satisfaction with postsurgical pain control. Pharmacokinetics were also assessed through day 10. Safety outcomes assessed included the incidence of AEs through day 30, as well as intermittent vital signs, 12-lead electrocardiography, and neurological assessments during the first 96 hours after surgery.

Data Analysis

A sample size of 50 subjects per group was expected to have 90% power to detect a difference in mean cumulative NRS pain scores of 66 using a 2-group *t* test with a 0.05 2-sided significance level. However, the size of the liposomal bupivacaine group was increased to 100 to reduce the threshold for AE detection to 3%, and the size of the placebo group was increased to accommodate additional collection of pain scores before all rescue medication requests.

The safety population included all subjects who received study drug. The prespecified primary efficacy (intent-to-treat [ITT]) population included all subjects in the safety population

who underwent the planned surgery and who were enrolled after the study protocol was amended (September 2, 2015). The per-protocol population was defined after the study was completed, as a result of a large number of protocol violations observed during the study; this population included all subjects in the primary efficacy population who were without any major protocol deviations. The pharmacokinetic population included all subjects in the safety population who received liposomal bupivacaine, provided sufficient samples for pharmacokinetic analyses, and did not have protocol deviations that could impact the results.

The primary efficacy outcome measure was analyzed using an analysis of variance model fitting effects for treatment, site, and treatment-by-site interaction. If the interaction term was not significant, it was dropped from the model and the main effects model (terms for treatment and site only) was to be the final analysis. If the interaction term was significant, further analyses were performed exploring the interaction. The treatment difference, its 95% CI, and probability value were reported for the final model.

Secondary efficacy outcome measures were analyzed using a hierarchical, fixed-sequence, stepwise testing procedure performed in a sequentially rejective fashion; if the first test was significant at the 0.05 level, then, and only then, the next secondary efficacy measure was tested, and so forth. Between-group comparisons and 95% CIs for secondary efficacy measures involving continuous variables were analyzed using an analysis of variance model similar to that used for the primary efficacy outcome analysis. Between-group comparisons for time from start of study drug administration to first use of opioid rescue medication through 96 hours were conducted using a log-rank test and summarized with Kaplan-Meier estimates. Postsurgical opioid consumption amounts were converted into intravenous morphine equivalent amounts before analysis. Between-group comparisons of demographic variables at baseline were conducted using Student's *t* test for continuous variables and a Cochran-Mantel-Haenszel test for categorical data. Between-group comparisons of AE rates were conducted using the Fisher exact test. The 2-sided significance level for between-group differences was set at a probability value of 0.05. Pharmacokinetic parameters were estimated from the plasma bupivacaine measurements using noncompartmental analysis.

RESULTS

Subjects

A total of 166 subjects were randomized and 162 received study treatment (liposomal bupivacaine, $n = 105$; placebo, $n = 57$); 150 were included in the primary efficacy population (liposomal bupivacaine, $n = 99$; placebo, $n = 51$), and 89 were treated per protocol (liposomal bupivacaine, $n = 59$; placebo, $n = 30$) (Figure 2). Seventy-three subjects were excluded from the analysis because of major protocol violations, which included ≥1 of the scheduled NRS assessments either missing or not completed; ≥1 rescue medication dose without an NRS assessment at time of rescue dose or within 15 minutes prior; ≥3 doses of oxycodone given on a scheduled basis or as standard care (ie, not given as needed for breakthrough pain) within any 12-hour period within 96 hours after surgery; any dental work (oral surgery, tooth repair/fillings) within 14 days of study surgery; posttraumatic stress disorder; use of any analgesic or nonsteroidal anti-inflammatory drug not allowed by the study protocol within 96 hours after surgery; plasma bupivacaine concentrations <100 ng/mL at 8 hours after surgery in subjects assigned to the liposomal bupivacaine group; or administration of rescue medication with an NRS score <4 immediately prior to administration of rescue medication. Demographics are summarized in Table 1. The placebo and liposomal bupivacaine groups were generally well matched at baseline. The placebo group had a slightly higher proportion of females and the liposomal bupivacaine group had a slightly higher proportion of African American subjects; however, there were no significant differences between the groups on any demographic parameter.

Efficacy: Primary Efficacy (ITT) Population

The primary efficacy measure, least-squares mean (SEM) AUC of $NRS_{0–48}$, was 172.3 (10.7) in the liposomal bupivacaine group compared with 194.7 (15.0) in the placebo group ($P = .227$). Between-group differences in cumulative pain scores were not statistically different at 24, 72, or 96 hours after surgery (Figure 3A). Results for opioid-related outcome measures are summarized in Table 2. The proportion of subjects who required rescue medication was slightly higher in the liposomal bupivacaine group compared with placebo (82 vs 77%; $P = .539$), and median time to first use of opioid rescue medication was longer (3.9 vs 3.1 hours) and least-squares mean total opioid consumption through 48 hours after study drug administration was lower (6.1 vs 6.9 mg; $P = .932$) in the liposomal bupivacaine group compared with the placebo group. Mean scores for subjects' satisfaction with postsurgical pain control were between 3.2 and 3.4 in both treatment groups throughout the study (Figure 4A).

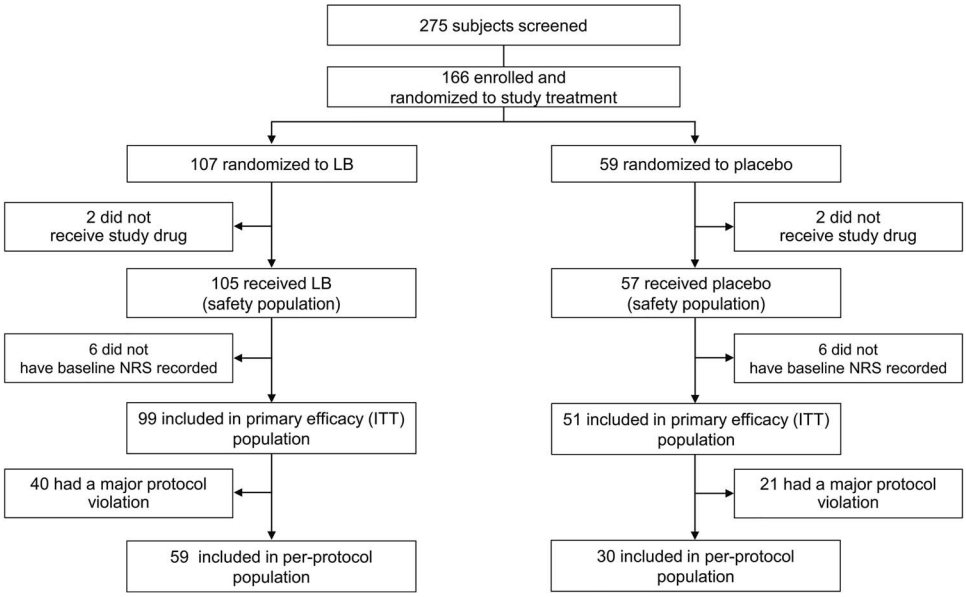

Figure 2. Study population: disposition of subjects LB indicates liposomal bupivacaine; NRS, numeric rating scale; and ITT, intent-to-treat.

Efficacy: Per-Protocol Population

Because of the potential for confounding effects arising from the large number of protocol violations in both treatment groups, efficacy results were also analyzed using an analysis of variance interaction model to determine the impact of the violations on efficacy outcomes, and are reported for the per protocol population. With respect to the primary efficacy outcome measure, least-squares mean (SEM) AUC of $NRS_{0–48}$ was significantly lower in the liposomal bupivacaine group (120.8 [13.9]) compared with the placebo group (183.3 [23.0]; $P = .023$). Cumulative pain scores were also significantly lower in the liposomal bupivacaine group compared with placebo at 24, 72, and 96 hours after surgery ($P < .05$) (Figure 3B). Results for opioid-related outcome measures are summarized in Table 2. As in the primary efficacy population, the proportion of subjects who required rescue medication was similar between the liposomal bupivacaine and placebo groups (73 and 67%, respectively; $P = .733$), as were the median time to first use of opioid rescue medication (4.3 and 3.4 hours, respectively) and the least-squares mean total opioid consumption through 48 hours after study drug administration (2.9 and 3.2 mg, respectively; $P = .736$). Mean scores for subjects' satisfaction with postsurgical pain control were between 3.4 and 3.6 in both treatment groups throughout the study (Figure 4B), with no statistically significant between-group differences observed at any time point ($P >$ .431 at each time point).

Pharmacokinetics

Pharmacokinetics results are summarized in Table 3. Plasma bupivacaine concentrations were detectable for >96 hours. The mean (SD) maximum plasma bupivacaine concentration observed following administration of liposomal bupivacaine was 313 (89) ng/mL, which is well below the plasma levels at which systemic toxicity would be expected to occur (2000–4000 ng/mL).[30,31]

Table 1. Subject Demographics

	Safety Population			*Per-Protocol Population*		
Parameter	*Liposomal Bupivacaine,* n = *105*	*Placebo,* n = *57*	*P*	*Liposomal Bupivacaine,* n = *59*	*Placebo,* n = *30*	*P*
Age, mean (SD), y	20.9 (3.8)	20.9 (4.8)	.973	20.8 (3.9)	20.5 (5.3)	.836
Female, No. (%)	53 (50.5)	33 (57.9)	.368	30 (50.8)	17 (56.7)	.605
Race, No. (%)			.573			.203
White	94 (89.5)	53 (93.0)		53 (89.8)	29 (96.7)	
African American	9 (8.6)	1 (1.8)		4 (6.8)	0	
Other	2 (1.9)	3 (5.3)		2 (3.4)	1 (3.3)	
Body mass index, mean (SD), kg/m^2	25.8 (6.9)	24.5 (4.7)	.182	26.1 (7.8)	24.6 (4.7)	.247

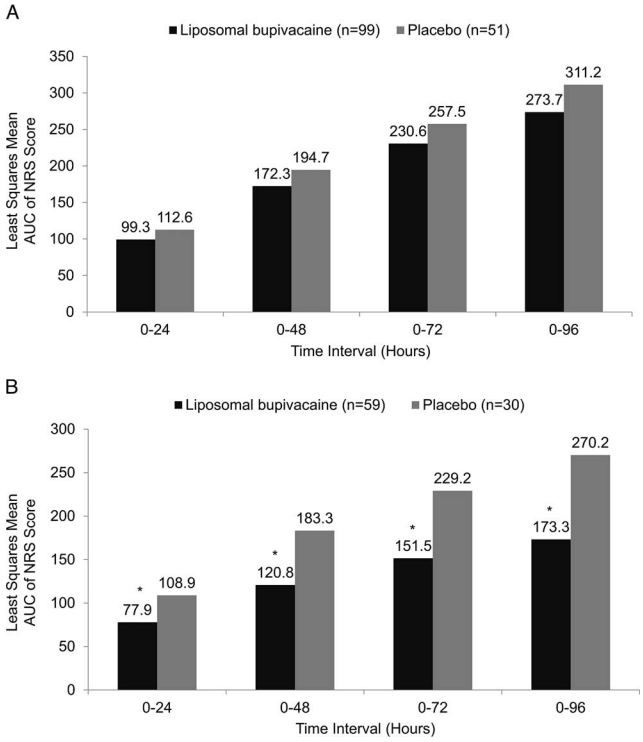

Figure 3. A. Cumulative AUC of NRS pain intensity scores at 24, 48, 72, and 96 hours postsurgery (primary efficacy [ITT] population). AUC indicates area under the curve; NRS, numeric rating scale; and ITT, intent-to-treat. B. Cumulative AUC of NRS pain intensity scores at 24, 48, 72, and 96 hours postsurgery (per-protocol population). *$P < .05$ versus placebo.

Safety

Overall, all subjects (100%) in both treatment groups experienced ≥1 AE; however, the majority of AEs in both the liposomal bupivacaine and placebo groups were mild in severity (93.3 and 94.7%, respectively). There were no serious AEs or discontinuations due to an AE reported in either treatment group. An overview of the AEs reported by ≥5% of study subjects is provided in Table 4. The most frequently reported AEs were oral hypoesthesia, dysgeusia, and nausea. The incidence of dysgeusia was significantly higher in the liposomal bupivacaine group compared with placebo (76 vs 56%; $P = .012$), and the incidence of headache was significantly lower in the liposomal bupivacaine group compared with placebo (6 vs 16%; $P = .047$). The incidence of alveolar osteitis was low in both the liposomal bupivacaine and placebo groups (1.9 vs 3.5%; $P = 0.614$).

DISCUSSION

In this randomized, placebo-controlled study of the safety and analgesic efficacy of liposomal bupivacaine in the setting of bilateral impacted third molar extraction, surgical site infiltration of liposomal bupivacaine was well tolerated, but was not associated with a significant improvement compared with placebo on any of the outcome measures assessed in the primary (ITT) efficacy analysis. When the study data were analyzed with subjects representing protocol violations removed (per-protocol efficacy analysis), treatment with liposomal bupivacaine resulted in lower least-squares mean cumulative NRS pain intensity scores during the first 48 hours after surgery (primary efficacy measure) compared with placebo. Least-squares mean scores remained significantly lower compared with placebo through 96 hours after surgery, without negatively impacting opioid consumption or subjects' satisfaction with postsurgical pain control. It is likely that the observed results were confounded by the unexpectedly large number of protocol violations that occurred during the study.

The most important limitation of the study was the relatively high number of protocol violations that occurred, which, as suggested by the differences between the ITT and per-protocol analysis, significantly impacted the outcomes of the study. Because this was the first formal evaluation of liposomal bupivacaine in the setting of dental surgery, more robust studies with a standardized administration

Table 2. Opioid-Related Outcome Measures†

Parameter	*Primary Efficacy (ITT) Population*		*Per-Protocol Population*	
	Liposomal Bupivacaine, n = *99*	*Placebo*, n = *51*	*Liposomal Bupivacaine*, n = *59*	*Placebo*, n = *30*
Subjects requiring rescue medication, *n* (%)	81 (82)*	39 (77)	43 (73)**	20 (67)
Time to first use of opioid rescue medication, median (95% CI), hours	3.9 (3.5, 4.2)	3.1 (2.7, 3.6)	4.3 (4.1, 6.1)	3.4 (2.8, NE)
Total postsurgical opioid consumption through 48 hours, LSM (SEM), mg	6.1 (1.1)***	6.9 (1.2)	2.9 (1.2)****	3.2 (1.3)

† ITT indicates intent-to-treat; NE, not estimated; and LSM, least squares mean.
* $P = .539$.
** $P = .733$.
*** $P = .932$ versus placebo.
**** $P = .736$ versus placebo.

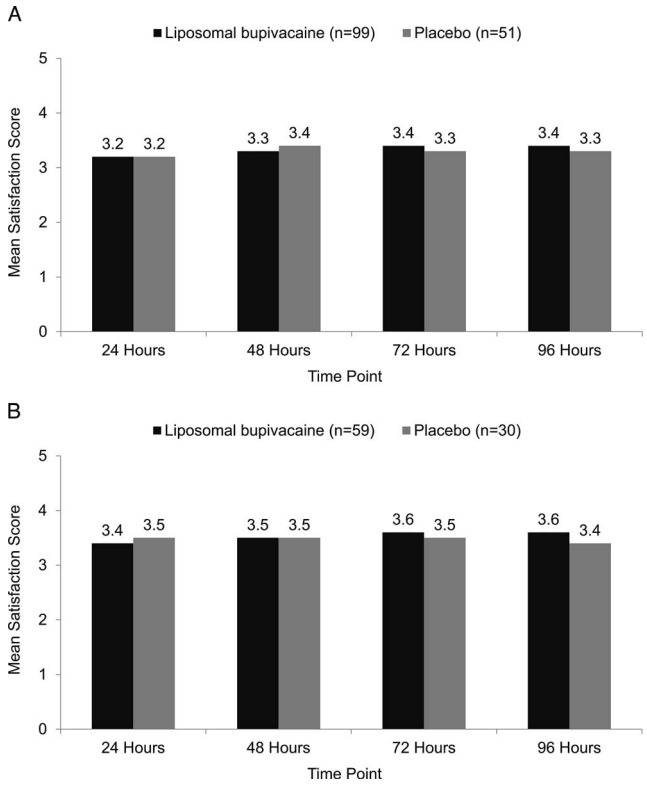

Figure 4. A. Mean scores for subjects' satisfaction with postsurgical pain control assessed using a 5-point Likert scale where 1 = extremely dissatisfied and 5 = extremely satisfied (primary efficacy [intent-to-treat] population) B. Mean scores for subjects' satisfaction with postsurgical pain control assessed using a 5-point Likert scale where 1 = extremely dissatisfied and 5 = extremely satisfied (per-protocol population).

technique and analgesic protocol may be helpful to fully validate the results observed in this exploratory study. Despite the fact that the sample size did not reach the number of subjects defined in the a priori power calculation for the efficacy analyses, there was a fairly strong efficacy signal in favor of liposomal bupivacaine observed on the cumulative pain score assessments, although this observation was not borne out in the opioid-related outcome assessments. Reasons for the lack of statistically significant between-group differences in median time to first use of opioid rescue medication and least-squares mean total amount of opioid consumption observed in this study are unclear. This study was not powered to detect statistical differences in these outcome measures.

The high rate of AEs observed in both groups was not unexpected, because hypoesthesia, an expected, indeed an intended, clinical outcome of local anesthetic administration, was captured as an AE. When asked, "Are you experiencing anything out of the ordinary?" as part of the AE assessments, virtually every subject in both treatment groups affirmed they had numbness in the surgical area. More broadly, the similarity between groups with respect to the incidence of hypoesthesia and other AEs suggests liposomal bupivacaine was generally well tolerated in this study. The relatively high incidence of dysgeusia observed in this study (76% in the liposomal bupivacaine group vs 56% with placebo; $P = .012$) is probably due to effects from the local anesthetics used in the study.

Consistent with previous clinical studies of liposomal bupivacaine, there were no signals indicating systemic toxicity in this study in spite of the fact that subjects received 133 mg of bupivacaine contained within the DepoFoam structures. The prolonged-release characteristics of liposomal bupivacaine help to maintain plasma bupivacaine levels well below the 2000–4000 ng/mL threshold for systemic toxicity.[30,31] For example, in the current study, the observed mean (SD) maximum plasma bupivacaine concentration following the 133-mg doses was 313 (89) ng/mL, which is comparable to maximum plasma bupivacaine concentration levels observed across previous studies of liposomal bupivacaine.[26]

In conclusion, the results from this study of liposomal bupivacaine for postsurgical analgesia in subjects undergoing bilateral impacted third molar extraction are encouraging, but additional investigation in prospective, randomized studies that incorporate clearly defined administration technique, rigorous data collection, and protocol compliance will be necessary to fully characterize the clinical profile of liposomal bupivacaine in this surgical setting.

Table 3. Pharmacokinetic Parameters for Liposomal Bupivacaine (Pharmacokinetic Population)*

Parameter	*Liposomal Bupivacaine 133 mg/10 mL*, n = *103*†
C_{max}, mean (SD), ng/mL	313 (89)
T_{max}, median (minimum, maximum), h	1.0 (0.2, 29.6)
$AUC_{0-\infty}$, mean (SD), h·ng/mL	7600 (2611)‡
$t_{1/2}$, mean (SD), h	8.7 (3.1)‡

* C_{max} indicates maximum observed plasma concentration; T_{max}, time to attain C_{max}; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time of study drug administration to infinity; and $t_{1/2}$, apparent terminal elimination half-life.

† Included all subjects in the safety population who received liposomal bupivacaine, provided sufficient samples for pharmacokinetic analyses, and did not have protocol deviations that could impact the results.

‡ $n = 99$.

Table 4. Adverse Events Reported by ≥5% of Subjects in Either Treatment Group (Safety Population)

Adverse Event, Preferred Term	*Liposomal Bupivacaine* (n = *105), No. (%)*	*Placebo* (n = *57), No. (%)*	*P*
Hypoesthesia, oral	104 (99.0)	57 (100)	1.000
Dysgeusia	80 (76.2)	32 (56.1)	.012
Nausea	32 (30.5)	16 (28.1)	.857
Vomiting	18 (17.1)	9 (15.8)	1.000
Muscle contractions, involuntary	16 (15.2)	12 (21.1)	.388
Dizziness	11 (10.5)	8 (14.0)	.610
Postprocedural edema	10 (9.5)	7 (12.3)	.599
Muscle twitching	8 (7.6)	4 (7.0)	1.000
Headache	6 (5.7)	9 (15.8)	.047

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REFERENCES

1. Friedman JW. The prophylactic extraction of third molars: a public health hazard. *Am J Public Health*. 2007;97:1554–1559.

2. Snyder M, Shugars DA, White RP, Phillips C. Pain medication as an indicator of interference with lifestyle and oral function during recovery after third molar surgery. *J Oral Maxillofac Surg*. 2005;63:1130–1137.

3. Bienstock DA, Dodson TB, Perrott DH, Chuang SK. Prognostic factors affecting the duration of disability after third molar removal. *J Oral Maxillofac Surg*. 2011;69:1272–1277.

4. de Santana-Santos T, de Souza-Santos JAS, Martins-Filho PRS, da Silva LCF, de Oliveira e Silva ED, Gomes ACA. Prediction of postoperative facial swelling, pain and trismus following third molar surgery based on preoperative variables. *Med Oral Patol Oral Cir Bucal*. 2013;18:e65–e70.

5. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology*. 2012;116:248–273.

6. Pluijms WA, Steegers MA, Verhagen AF, Scheffer GJ, Wilder-Smith OH. Chronic post-thoracotomy pain: a retrospective study. *Acta Anaesthesiol Scand*. 2006;50:804–808.

7. Poleshuck EL, Katz J, Andrus CH, et al. Risk factors for chronic pain following breast cancer surgery: a prospective study. *J Pain*. 2006;7:626–634.

8. Huang D, Wun E, Stern A. Current treatments and advances in pain and anxiety management. *Dent Clin North Am*. 2011;55:609–618.

9. Hersh EV, Kane WT, O'Neil MG, et al. Prescribing recommendations for the treatment of acute pain in dentistry. *Compend Contin Educ Dent*. 2011;32:22, 24–30; quiz 31-22.

10. Volkow ND, McLellan TA, Cotto JH, Karithanom M, Weiss SR. Characteristics of opioid prescriptions in 2009. *JAMA*. 2011;305:1299–1301.

11. Moore PA, Nahouraii HS, Zovko JG, Wisniewski SR. Dental therapeutic practice patterns in the U.S. II. Analgesics, corticosteroids, and antibiotics. *Gen Dent*. 2006;54:201–207.

12. Au AH, Choi SW, Cheung CW, Leung YY. The efficacy and clinical safety of various analgesic combinations for postoperative pain after third molar surgery: a systematic review and meta-analysis. *PLoS One*. 2015;10:e0127611.

13. Gordon SM, Mischenko AV, Dionne RA. Long-acting local anesthetics and perioperative pain management. *Dent Clin North Am*. 2010;54:611–620.

14. Donaldson M, Goodchild JH. Appropriate analgesic prescribing for the general dentist. *Gen Dent*. 2010;58:291–297; quiz 298–299.

15. Tufts Health Care Institute. The role of dentists in preventing opioid abuse: executive summary. Available at: http://opioidriskmanagement.com/opioid/mar10docs/executivesummary.pdf. Accessed July 7, 2016.

16. Bailey E, Worthington H, Coulthard P. Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth, a Cochrane systematic review. *Br Dent J*. 2014;216:451–455.

17. Joshi GP, Beck DE, Emerson RH, et al. Defining new directions for more effective management of surgical pain in the United States: highlights of the Inaugural Surgical Pain Congress™. *Am Surg*. 2014;80:219–228.

18. Ong CK, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. *Anesth Analg*. 2010;110:1170–1179.

19. Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication-assisted therapies—tackling the opioid-overdose epidemic. *N Engl J Med*. 2014;370:2063–2066.

20. Katz NP, Birnbaum HG, Castor A. Volume of prescription opioids used nonmedically in the United States. *J Pain Palliat Care Pharmacother*. 2010;24:141–144.

21. Moore PA, Hersh EV. Local anesthetics: pharmacology and toxicity. *Dent Clin North Am*. 2010;54:587–599.

22. Golembiewski J, Dasta J. Evolving role of local anesthetics in managing postsurgical analgesia. *Clin Ther*. 2015;37:1354–1371.

23. Exparel [prescribing information]. Parsippany, NJ: Pacira Pharmaceuticals, Inc; 2015.

24. Chahar P, Cummings KC III. Liposomal bupivacaine: a review of a new bupivacaine formulation. *J Pain Res*. 2012;5:257–264.

25. Howell SB. Clinical applications of a novel sustained-release injectable drug delivery system: DepoFoam technology. *Cancer J*. 2001;7:219–227.

26. Hu D, Onel E, Singla N, Kramer WG, Hadzic A. Pharmacokinetic profile of liposome bupivacaine injection following a single administration at the surgical site. *Clin Drug Investig*. 2013;33:109–115.

27. Bergese SD, Ramamoorthy S, Patou G, Bramlett K, Gorfine SR, Candiotti KA. Efficacy profile of liposome bupivacaine, a novel formulation of bupivacaine for postsurgical analgesia. *J Pain Res*. 2012;5:107–116.

28. Dasta J, Ramamoorthy S, Patou G, Sinatra R. Bupivacaine liposome injectable suspension compared with bupivacaine HCl for the reduction of opioid burden in the postsurgical setting. *Curr Med Res Opin*. 2012;28:1609–1615.

29. Viscusi ER, Sinatra R, Onel E, Ramamoorthy SL. The safety of liposome bupivacaine, a novel local analgesic formulation. *Clin J Pain*. 2014;30:102–110.

30. Jorfeldt L, Lofstrom B, Pernow B, Persson B, Wahren J, Widman B. The effect of local anaesthetics on the central circulation and respiration in man and dog. *Acta Anaesthesiol Scand*. 1968;12:153–169.

31. Bardsley H, Gristwood R, Baker H, Watson N, Nimmo W. A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. *Br J Clin Pharmacol*. 1998;46:245–249.