A PHASE 3 RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF EXPAREL™, AN EXTENDED RELEASE BUPIVACAINE LOCAL ANALGESIC, IN BUNIONECTOMY

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ABSTRACT

Summary: EXPAREL, an extended release liposomal bupivacaine, resulted in significantly extended postoperative pain relief and decreased opioid use compared to placebo.

Introduction: This FDA-approved Phase 3 clinical trial compared EXPAREL, an experimental extended release liposomal bupivacaine-based analgesic, to placebo for the prevention of pain after bunionectomy procedures.

Methods: After obtaining IRB approval, 193 consenting patients undergoing bunionectomy were randomly assigned to receive either a single injection of placebo (n=96) or 120 mg EXPAREL (n=97) administered via wound infiltration at the conclusion of the surgical procedure. The severity of pain was assessed after surgery at specified predetermined time points using a numeric rating scale (NRS) at rest for pain with 0=no pain and 10=worst possible pain. The NRS scores were used to calculate the area under the curve (AUC) from immediately post op (time 0) through multiple postoperative time points. Other endpoints included number of patients requiring no parenteral opioid analgesic (rescue) medications, number of patients who were pain free (NRS=<1) postoperatively, and median time to first opioid use (rescue).

Results: The AUC for the NRS pain scores from the start of study drug injection demonstrated a statistically significant advantage to EXPAREL over placebo at 24 hours ($p=0.0005$) and 36 hours ($p<0.03$). A larger percentage of EXPAREL-treated patients avoided opioid rescue medication during the first 24 hours after surgery (7% vs 1%; $p<0.05$). Statistically significantly more EXPAREL-treated patients were pain free at 2, 4, 8, and 48 hours. The median time to first opioid use was also significantly delayed in favor of EXPAREL (4 hours vs 7 hours; $p<0.0001$). Treatment emergent adverse events (TEAEs) were reported by 60% of EXPAREL-treated patients compared to 68% in the placebo group; there were no deaths in either group, although there was one discontinuation due to a TEAE in the placebo group.

Discussion and Conclusion: EXPAREL, an investigational long-acting local analgesic, provided extended pain relief and decreased opioid use after bunionectomy compared to placebo, and therefore may offer clinically meaningful advantages in providing postoperative pain relief.

INTRODUCTION

- EXPAREL, an extended-release liposomal bupivacaine-based analgesic injection uses multivesicular liposomal [DepoFoam®] technology to release bupivacaine over several days
- DepoFoam utilizes membrane components that are natural, well tolerated, and cleared by normal metabolic pathways
- DepoFoam is <3% lipid, biodegradable, and biocompatible
- DepoFoam is a proven product delivery technology used in two commercially available products
  - Particle suspension in isotonic aqueous solution
  - Can target release for 1 to 30 days
  - Can be 10 to 30 µm in diameter
  - Does not alter native molecule
  - Can be infiltrated with fine-gauge needles

Figure 1. DepoFoam – Multivesicular Liposomes

METHODS

Study Design

- A phase 3, multicenter, parallel-group, placebo-controlled, randomized, double-blind study to evaluate the efficacy and safety of the intraoperative administration of EXPAREL compared with placebo
- Postsurgical opioid rescue medication consisted of 1–2 tablets of 5 mg oxycodone/325 mg acetaminophen q 4–6 hours as needed to a maximum of 12 tablets per day
- During the first 24-hour period, a single IV dose of ketorolac (15–30 mg) could be administered if necessary
- Patients who did not receive adequate pain control with this regimen were removed from the study and followed for safety only

Dosing

- Dose selection for this study was empirical
- Maximum volume that can be injected into a 3 cm surgical site without disrupting the integrity of the wound edge is approximately 8 mL
- A dose of 120 mg (8 mL) of EXPAREL was infiltrated

Patients

- Patients were male and female; ≥18 and ≤72 years of age
- Demographics and baseline characteristics were similar between groups
- The prevalence of enrolled females is consistent with the predominance of this condition in females
- Patients were scheduled to undergo primary unilateral first metatarsal osteotomy without hammertoe
- Patients were able to receive Mayo block for intraoperative local analgesic
- Patients provided informed consent and agreed to comply with all study visits and complete all assessments

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Table 1. Subject Demographics and Baseline Characteristics

Variable Statistics or Category	EXPAREL 120 mg (n=97)	Placebo (n=96)	Total (N=193)
Age (years)			
Mean	42.4	43.3	42.8
Standard Deviation	12.65	13.35	12.98
Minimum	18	19	18
Median	45	43	44
Maximum	65	72	72
Age Category (years) [n (%)]			
<40 Years	39 (40.2)	44 (45.8)	83 (43.0)
40–<65 Years	57 (58.8)	47 (49.0)	104 (53.9)
≥65 Years	1 (1.0)	5 (5.2)	6 (3.1)
Gender [n (%)]			
Male	22 (22.7)	12 (12.5)	34 (17.6)
Female	75 (77.3)	84 (87.5)	159 (82.4)
Race [n (%)]			
American Indian or Alaska Native	1 (1.0)	0	1 (0.5)
Black or African American	25 (25.8)	21 (21.9)	46 (23.8)
Asian	1 (1.0)	2 (2.1)	3 (1.6)
Native Hawaiian or Pacific Islander	0	0	0
White or Caucasian	66 (68.0)	72 (75.0)	138 (71.5)
Multiple	4 (4.1)	1 (1.0)	5 (2.6)
Ethnicity [n (%)]			
Hispanic or Latino	25 (25.8)	26 (27.1)	51 (26.4)
Not Hispanic or Latino	72 (74.2)	70 (72.9)	142 (73.6)
BMI (kg/m^2)			
n	97	96	193
Mean	28.11	27.63	27.87
Standard Deviation	5.796	5.729	5.753
Minimum	16.6	17	16.6
Median	27.43	26.75	27.01
Maximum	41.5	41.5	41.5

Assessments

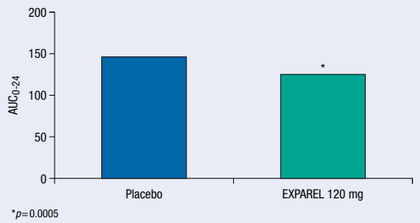
- Pain intensity scores were rated by the patients on an 11-point numeric rating scale (NRS) at 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours
- NRS pain intensity scores were recorded at first use of rescue pain medication
- Postsurgical opioid rescue medication use (time and dose) was recorded through 72 hours
- Subject satisfaction with postsurgical pain relief at 24 and 72+8 hours was also recorded
- Safety parameters included vital signs, clinical laboratory values, wound healing and TEAEs and SAEs

Primary & Secondary Measures of Efficacy

- The primary measure of efficacy was the AUC of NRS scores through 24 hours (AUC_{0-24} of NRS-R Pain Intensity Scores)
- Secondary measures of efficacy included the following:
  - AUC of NRS scores through 36, 48, 60, and 72 hours
  - Proportion of patients pain-free at 24 hours and other time points (NRS ≤ 1)
  - Proportion of patients who received no rescue pain medication
  - Total consumption of opioid rescue medication (mg) through 24, 36, 48, 60, and 72 hours
  - Time to first use of opioid rescue medication

RESULTS

Figure 2. Statistically Significant Reduction in Pain (as measured by Primary Endpoint: AUC_{0-24} of NRS-R pain intensity scores)



*$p=0.0005$

- The study met its primary efficacy endpoint with a statistically significant reduction in AUC through 24 hours in the patients receiving EXPAREL compared to placebo ($p=0.0005$)

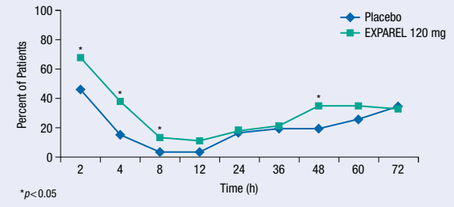
Table 2. AUC at All Time Points

	AUC_{0-24}	AUC_{0-36}	AUC_{0-48}	AUC_{0-60}	AUC_{0-72}
EXPAREL 120 mg	125*	199*	272	339	402
Placebo	146	221	292	359	421

*$p<0.05$

- The difference continued to be statistically significant through 36 hours

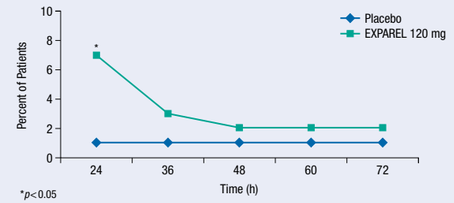
Figure 3. Percentage of Patients Who Were Pain Free (NRS=0 or 1)



*$p<0.05$

- The difference between treatment groups was statistically significant at 2, 4, 8, and 48 hours

Figure 4. Percentage of Patients Requiring No Rescue Medication



*$p<0.05$

- Statistical significance favoring the EXPAREL group was demonstrated through 24 hours

Time to First Opioid Use

- The median time to first use of opioid rescue medication was 7.15 hours for the EXPAREL group and 4.28 hours for the placebo group ($p<0.0001$).

SAFETY RESULTS

- EXPAREL was well tolerated in patients who received postsurgical treatment for pain following bunionectomy
- Most TEAEs were not related to study medication and were mild or moderate in severity
- There was no statistical difference between treatment groups in wound assessments (erythema, drainage, edema, and induration)

EXPAREL on Wound Healing

- The potential effects of EXPAREL on orthopedic wound healing were examined during a follow-up visit 4–6 weeks after bunionectomy
- Follow-up radiographs and office notes were collected for 82% of patients
- No patients demonstrated any evidence of malunion or non-union

CONCLUSIONS

- This study met its primary endpoint with a statistically significant reduction in pain (as measured by AUC_{0-24} of NRS-R pain intensity scores) in patients receiving EXPAREL compared to placebo ($p=0.0005$)
- A larger percentage of patients treated with EXPAREL avoided opioid rescue pain medication during the first 24 hours after surgery compared to placebo (7% vs 1%; $p<0.05$)
- Statistically significantly more patients treated with EXPAREL were pain free at 2, 4, 8, and 48 hours compared to placebo
- Opioid rescue use was statistically significantly delayed with EXPAREL and there was less opioid consumed over the first 24 hours after surgery
- EXPAREL was well tolerated in patients who received postsurgical treatment for pain following bunionectomy
- Most TEAEs were not related to study medication and were mild or moderate in severity
- No patients demonstrated any evidence of malunion or non-union