# SABER™-Bupivacaine, a novel extended-release formulation of bupivacaine for postoperative pain control demonstrates dose-response, safety and no impact on surgical wound healing following inguinal herniorrhaphy

Hadj A., Nicholson D., Moodie J., Turner R., Watts R., Abrouk N., Langecker P., Lissin D.

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## Introduction

SABER-Bupivacaine is an extended release formulation of bupivacaine in a resorbable matrix which provides delivery of bupivacaine at the site of administration over a period of 3 days. The formulation consists of three components: common local anesthetic bupivacaine (12%), organic matrix sucrose acetate isobutyrate, and a diluent, benzyl alcohol. Clinical benefits and safety of continuous infusions of bupivacaine into the surgical wound via elastomeric pumps was demonstrated following a variety of surgical procedures (Liu, 2006), including inguinal hernia repair (Lau, 2003; Sanchez, 2004). SABER-Bupivacaine formulation, a translucent thick solution, is designed to provide continuous delivery of bupivacaine once placed in the surgical wound at the same rate of 10-20 mg/h as delivered by elastomeric pumps through indwelling catheters. Multiple trials are ongoing to investigate safety and efficacy of SABER-Bupivacaine in various surgical procedures.

A 2-week, randomized, placebo-controlled, double-blind study of SABER-Bupivacaine instilled into the wound in patients undergoing open inguinal hernia repair was conducted at 5 clinical sites in Australia and New Zealand and subsequently extended to include 3 and 6-months follow-up evaluations of surgical wound healing and scar formation. Initial trial results were reported at the American Hernia Society Annual Meeting (2008 Hernia Repair, Poster 37). This poster describes the new long-term safety data generated during the trial extension and provides an overall summary of trial results.

## Methodology

Male or female patients, 18-65 years of age (n=124), undergoing open inguinal hernia repair under general anesthesia were enrolled in a multi-center, randomized, double blind, placebo-controlled trial. The trial comprised 3 treatment groups (SABER-Bupivacaine 2.5mL [330mg], SABER-Bupivacaine 5.0mL [660mg], and SABER-Placebo 2.5 or 5.0 mL) in order to evaluate dose-response and the safety of SABER™-Bupivacaine. A follow-up period (post double-blind treatment) included surgical wound healing evaluations at 3 and 6 months after surgery. Patients in all treatment groups had similar demographics, baseline characteristics, and general health profile.

Supplemental rescue analgesia was provided to all patients on demand with oral Tramadol 50-100 mg (maximum 400 mg daily) for treatment of moderate to severe pain or acetaminophen (1 g every 6 h) for mild pain.

All 124 randomized patients underwent elective, open, unilateral, tension-free herniorrhaphy using polypropylene mesh (Lichtenstein, 1989; Kurzer, 2003) with the exception of one patient who did not have the surgery. Surgical incision length varied between 6 and 10 cm (mean=6.47 cm, median=6.5 cm, SD=1.09 cm). Investigational product was instilled prior to wound closure.

Outcome Measures: pain intensity on movement evaluated using a numerical rating scale (0=no pain; 10=worst pain possible), collected several times a day. The adapted modified Brief Pain Inventory (Schurr, 2004) was completed once daily, including symptoms questionnaire of opioid-related side effects and early signs of bupivacaine toxicity. Surgical site healing and local tissue conditions were evaluated at follow up visits. Vital signs, physical examinations and safety laboratory assays were performed as part of safety assessments. A 12-lead ECG was performed at screening and when clinically indicated to evaluate and record all clinically significant abnormalities. In a subset of patients continuous ECG monitoring for 24 hours postoperatively was performed (n=56) and pharmacokinetic samples were collected (n=28).

## Statistics

Sample Size: 124 patients were randomized in the trial to receive one of the following three treatment groups: SABER-Bupivacaine 2.5 mL (n= 45), SABER-Bupivacaine 5.0 mL (n=47), and SABER-Placebo (n= 32). The safety summary patients set comprised 123 patients, while the Intention-To-Treat (ITT) analysis set comprised 122 patients which was the basis for the efficacy summaries.

The power computations anticipated a relative treatment effect of 0.67 would be detected based on the Mean Pain Intensity on Movement AUC normalized over the first 72 hours (assuming 80% power and 5% significance level).

Efficacy Endpoints: There were 2 co-primary efficacy endpoints: the mean pain intensity on movement area under the curve (AUC) normalized over the first 72 hours post surgery, and the proportion of patients who received opioid rescue medications during the study. Primary null hypotheses were no difference between treatment groups in terms of mean pain intensity on movement AUC and proportion of patients receiving opioid rescue medication.

Secondary efficacy endpoints included: mean pain intensity AUC over the first 48 hours, overall treatment satisfaction, mean total opioid consumption (coded into morphine equivalent daily dose), and mean functional activities. A 1-way nonparametric Analysis of Variance (ANOVA) using a two-sided Wilcoxon test was used to compare the mean pain intensity AUC between treatment groups. The proportion of patients who received opioid rescue medication was analyzed using a two-sided Cohran-Mantel-Haenszel (CMH) test stratified by study site.

## Analgesic Effects

SABER-Bupivacaine 5.0 mL significantly improved normalized AUC of pain intensity on movement as compared to placebo during first 72 hours (mean 2.47 vs. 3.60; p=0.0033), and first 48 hours (mean 2.52 vs. 3.86; p=0.0007), while the differences between SABER-Bupivacaine 2.5 mL and placebo exhibited a trend in favor of SABER-Bupivacaine 2.5 mL (not statistically significant).

Positive and consistent trends were also observed with normalized AUC of pain intensity at rest for the same time periods. Most patients in each treatment group were satisfied or very satisfied with treatment, and mean scores for each functional activity improved from Day 1 to 5 in all 3 treatment groups.

Overall, opioid rescue analgesia after surgery was used in 53.2% of patients in the SABER-Bupivacaine 5.0 mL group, 72.1% of patients in the SABER-Bupivacaine 2.5 mL group, and 71.9% of patients in the placebo group. Reduction of percentage of patients resorting to rescue analgesia in the higher dose group, albeit not statistically significant, was positively correlated with overall reduction in daily opioid dose. Secondary endpoints measuring opioid analgesic medication consumption were met at a statistically significant level. During the periods of 1-24 hours, 24-48 hours and 48-72 hours post-operatively, placebo patients consumed approximately 3.5 (p=0.0009), 2.9 (p=0.0190) and 3.6 (p=0.0172) times more supplemental opioid analgesic medications, respectively, than patients treated with SABER-Bupivacaine 5.0 mL. Reduction trends of opioid consumption were supportive for the lower SABER-Bupivacaine dose group, 2.5 mL, but did not reach statistical significance.

In addition, the median time to first use of supplemental opioid analgesic medications after surgery, estimated based on the Kaplan-Meier survival curves, for the placebo patients was approximately 2.7 hours versus >72 hours for the patients in the SABER-Bupivacaine 5.0 mL group (p=0.0197, two-sided log-rank test).

Clinically, reduction of opioid consumption translated into lower incidence of opioid-related side effects. Symptoms typically associated with opioid use reported during the trial were constipation, somnolence, dizziness, nausea and vomiting. A general reduction of frequency of each of these symptoms was observed with increase of SABER-Bupivacaine dose.

## General Safety and Toxicity Monitoring

Pharmacokinetics of SABER-Bupivacaine were characterized by gradual increase of plasma bupivacaine concentrations with no burst. Maximum levels were reached approximately 13-17 hours after dosing and gradually decreased over 72 hours. Mean Cmax 466.79 ± 226.31 ng/mL and 866.57 ± 426.61 ng/mL for 2.5 mL and 5.0 mL doses, respectively. Levels increased proportionally with the dose administered.

There were no serious adverse events (SAEs) designated by investigators as related or possibly related to SABER-Bupivacaine. SAEs were reported in 6.8% (3/44), 4.3% (2/47), and 3.1% (1/32) of SABER-Bupivacaine 2.5 mL, SABER-Bupivacaine 5.0 mL, and placebo groups, respectively, and included acute coronary syndrome, syncopal episodes, and a post-operative wound complication.

The incidence of all AEs probably or possibly related to treatment from screening to Day 14 was 18.2% (8/44) in the SABER-Bupivacaine 2.5 mL group, 27.7% (13/47) in the SABER-Bupivacaine 5.0 mL group, and 28.1% (9/32) in the placebo group, and all were mild or moderate in severity.

Nervous system adverse events were reported by 66% (29/44) patients on 2.5 mL dose, 53% (25/47) on 5.0 mL dose, and 72% (23/32) on placebo. Cardiac adverse events were experienced by 23% (10/44) patients on 2.5 mL dose, 32% (15/47) on 5.0 mL dose, and 22% (7/32) on placebo. There were 5 vasovagal syncopal episodes during recovery from general anesthesia among patients from all dose groups, including placebo. Cardiovascular causes of syncopies were ruled out. Electrocardiographically, administration of SABER-Bupivacaine did not result in clinically relevant wave morphology changes or duration of RR, PR, QRS, and QTc intervals.

In addition to routine collection of adverse events, early signs of CNS toxicity (dysgeusia, paresthesia and tinnitus) were collected by daily symptoms questionnaire, and cardiac safety was investigated by analysis of 12-lead electrocardiograms and telemetry data acquired pre- and post-dosing. Most CNS symptoms were reported by patients on the first day following drug administration and included dysgeusia 10% for 2.5 mL dose, 7% for 5.0 mL dose and 7% for placebo group; paresthesia 12% for 2.5 mL dose, 9% for 5.0 mL dose and 0% for placebo group; tinnitus 5% for 2.5 mL dose, 11% for 5.0 mL dose and 14% for placebo group.

Clinically significant laboratory abnormalities were infrequent and consisted of 1 positive glucose urine test at screening in the SABER-Bupivacaine 2.5 mL group and 1 high creatine kinase blood level at Day 14 in the placebo group.

Heart rate, blood pressure, respiratory rate, and temperature were similar from screening to Day 14 in all treatment groups, and the most common changes in all groups in physical exam findings were changes in gastrointestinal hernia and other gastrointestinal changes.

## Surgical Wound Healing

During the initial 2-week study period, procedural complications probably or possibly related to study treatment were reported 0% (0/32) in SABER-Placebo group, 2.3% (1/44) in 2.5 mL dose group, and 8.5% (4/47) in 5.0 mL dose group. During the entire study period incidence of these events was 15.6% (5/32) in placebo group, 34.1% (15/44) in 2.5 mL dose group, and 14.9% (7/47) in 5.0 mL dose group, and included hemorrhage and hematoma. There were no cases of wound dehiscence or infection. All events were transient, resolving with no treatment and predominantly mild in intensity. There were no severe local reactions reported. Incidence of procedural complications was not related to bupivacaine dose, volume of SABER-containing investigational product, incision length or participating surgeon.

Evaluation of local tissue conditions was as expected: 100%, 97.1% and 99% in placebo, 2.5 mL and 5.0 mL dose groups, respectively, at 3 months postoperatively (n=102). During the 6-month follow-up visit local tissue conditions were reported 100% as expected in all patients (n=94). Among all the patients who were not lost to follow-up at 3 and 6 months, assessment of surgical wound and scar formation demonstrated 100% healing as expected in all treatment groups.

## Conclusions

Administration of SABER-Bupivacaine by instillation through surgical wound layers in patients with inguinal herniorrhaphy was easily accomplished and did not result in significant changes to the surgical routine. Both doses of SABER-Bupivacaine, 2.5 mL and 5.0 mL, were safe and well-tolerated by comparison to placebo. The higher dose, 5.0 mL, demonstrated effective analgesia in the management of surgical wound pain and significantly improved mean pain intensity AUC on movement compared to placebo for 48 and 72 hours postoperatively. Patients treated with SABER-Bupivacaine 5.0 mL required significantly less opioid rescue medications as compared to placebo. Reduction of opioid rescue dose was associated with reduction of opioid-related side effects (constipation, somnolence, dizziness, nausea and vomiting). Efficacy trends in the SABER-Bupivacaine 2.5 mL group were positive, but not statistically significantly different from placebo. Administration of SABER-Bupivacaine had no impact on surgical wound healing. Evaluation of local tissue, formation of scar and overall healing assessed up to 6 months postoperatively was not adversely impacted by SABER-Bupivacaine or SABER-Placebo in this patient population.

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## References

Liu SS, Richman JM, Thirlby RC, Wu CL. Efficacy of continuous wound catheters delivering local anesthetic for postoperative analgesia: a quantitative and qualitative systematic review of randomized controlled trials. J Am Coll Surg. 2006 Dec;203(6):914-32.

Lichtenstein IL, Shulman AG, Amid PK, Montllor MM. The tension-free hernioplasty. Am J Surg. 1989 Feb;157(2):188-93.

Kurzer M, Belsham PA, Kark AE. The Lichtenstein repair for groin hernias. Surg Clin North Am. 2003 Oct;83(5):1099-117.

Lau H, Patil NG, Lee F. Randomized clinical trial of postoperative subfascial infusion with bupivacaine following ambulatory open mesh repair of inguinal hernia. Dig Surg. 2003;20(4):285-9. Epub 2003 May 15.

Sanchez B, Waxman K, Tatevossian R, Gamberdella M, Read B. Local anesthetic infusion pumps improve postoperative pain after inguinal hernia repair: a randomized trial. Am Surg. 2004 Nov;70(11):1002-6.

Schurr MJ, Gordon DB, Pellino TA, Scanlon TA. Continuous local anesthetic infusion for pain management after outpatient inguinal herniorrhaphy. Surgery. 2004 Oct;136(4):761-9.

For information regarding SABER-Bupivacaine clinical development, please contact:
Dmitri Lissin, MD, Sr. Director, Clinical Development
DURECT Corporation
2 Results Way, Cupertino, CA 95014
Tel. (408) 777-4907
e-mail: dmitri.lissin@durect.com