# Post-operative pain control with extended-release bupivacaine formulation. Clinical Trial Results in Inguinal Hernia Repair.

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## Introduction

SABER™-Bupivacaine (POSIDUR™) is a semi-viscous solution of sucrose acetate isobutyrate formulation containing 12% bupivacaine, an amide-type local anesthetic. SABER-Bupivacaine, created by DURECT Corporation, is intended to provide prolonged post-surgical pain relief, reduce reliance on opioid analgesic medications, and improve post-operative recovery by slowly releasing bupivacaine over a period of several days.

Continuous infusions of local anesthetics into the surgical wound utilizing various catheter and pump systems have demonstrated utility and clinical benefits of such treatment approach in a variety of surgical procedures. SABER-Bupivacaine is designed to provide continuous delivery of bupivacaine to local tissues where it is applied. Clinical trials in different surgical settings are ongoing to investigate the safety and efficacy of SABER™-Bupivacaine as part of the clinical development program.

Current results of the Phase IIb, dose-finding, randomized controlled trial in patients undergoing open inguinal hernia repair demonstrate utility of the product, systemic and local safety, and the analgesic and opioid-sparing effects of SABER-Bupivacaine when deposited at the surgical site in doses up to 5.0 mL (660 mg bupivacaine).

## Methodology

Study Design: multicenter, randomized, double-blind, parallel-group, placebo-controlled, dose-finding. All study staff and patients were blinded to the study treatment throughout the study.

Participants: male and female patients, in good general health, 18 to 65 years of age, who were to undergo elective open unilateral tension-free Lichtenstein-type inguinal hernia repair under general anesthesia.

Drug administration: at the surgical site prior to the wound closure.

Outcome Measures: pain intensity on movement evaluated using a numerical rating scale (0=no pain; 10=worst pain possible), collected 4 times a day. The adapted modified Brief Pain Inventory 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).

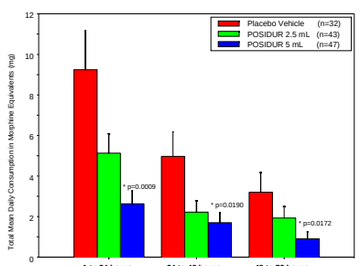
Sample Size: 120 evaluable subjects in three treatment groups: SABER-Bupivacaine 2.5 mL (n=42), SABER-Bupivacaine 5.0 mL (n=47), and SABER-Placebo (n=31). It was anticipated that a relative treatment effect of 0.67 would be detected based on the Mean Pain Intensity on Movement AUC over the period of 1 to 72 hours with 80% power and a 5% significance level.

Endpoints: There were 2 co-primary efficacy endpoints: the mean pain intensity on movement area under the curve (AUC) over the time period 1 to 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 or opioid rescue medication. Secondary endpoints included: mean pain intensity AUC over the time period of 1 to 48 hours, overall treatment satisfaction, mean total opioid dose (coded into morphine equivalent daily dose), and mean functional activities. A 1-way nonparametric ANOVA based on the 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 Cohran-Mantel-Haenszel (CMH) test.

## Opioid-Sparing Effects

Patients in all treatment groups had access to rescue opioid medications. All opioid medications were converted to Morphine Equivalent doses for analysis.

Overall, opioid rescue analgesia after surgery was used in 53.2% (25/47; 95% CI: 38.1%, 67.9%) of patients in the SABER-Bupivacaine 5.0 mL group, 72.1% (31/43; 95% CI: 56.3%, 84.7%) of patients in the SABER-Bupivacaine 2.5 mL group, and 71.9% (23/32; 95% CI: 53.3%, 86.3%) 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.




In addition, the median time to first use of supplemental opioid analgesic medications after surgery, calculated using Log-Rank test for comparison of Kaplan-Meier survival curves, for the placebo patients was 2.7 hours versus >72 hours for the patients in the SABER-Bupivacaine 5.0 mL group (p=0.0197). Reduction trends of opioid consumption were supportive for the lower SABER-Bupivacaine dose group, but did not reach statistical significance.

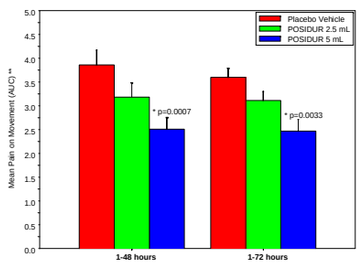
Clinically, reduction of opioid consumption translated into lower incidence of opioid-related side effects. Symptoms typically associated with opioid use reported during the trial were constipation, somnolence, dizziness, nausea and vomiting. A gradual reduction of frequency of each of these symptoms was observed with increase of SABER-Bupivacaine dose. The most frequent symptom, constipation, was reduced significantly as compared between 5.0 mL SABER-Bupivacaine dose and placebo, p=0.0034 (Chi-Square test).

| | Placebo n=32 | 2.5mL Dose n=44 | 5.0mL Dose n=47 |
|---|---|---|---|
| *Constipation* | 17 (53.1%) | 16 (36.4%) | 10 (21.3%) |
| *Somnolence* | 15 (46.9%) | 17 (38.6%) | 13 (27.7%) |
| *Dizziness* | 9 (28.1%) | 13 (29.5%) | 9 (19.1%) |
| *Nausea* | 9 (28.1%) | 13 (29.5%) | 8 (17.0%) |
| *Vomiting* | 2 ( 6.3%) | 3 (6.8%) | 1 (2.1%) |

Positive correlation between frequency and dose of opioid consumption and reduction of opioid-related adverse events indicates the clinically important opioid-sparing property of SABER-Bupivacaine.

## Analgesic Effects

SABER-Bupivacaine 5.0 mL significantly improved normalized AUC of pain intensity on movement as compared to placebo from 1 to 72 hours (mean 2.47 vs. 3.60; p=0.0033), and from 1 to 48 hours (mean 2.52 vs. 3.86; p=0.0007), while the differences between SABER-Bupivacaine 2.5 mL and placebo supported the positive trend (not statistically significant).




Positive trends were also demonstrated 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.

## Toxicity Monitoring

Bupivacaine pharmacokinetics is important for understanding systemic exposure and prevention of overdose. Rapid rise of plasma concentration (usually after IV injection) and high plasma levels > 2,000 ng/mL are associated with severe adverse neurological and then cardiovascular effects in humans (Bardsley et al, 1998; Knudsen et al, 1997; Jorfeldt et al, 1968).

Pharmacokinetics of SABER-Bupivacaine were characterized by maintenance of plasma bupivacaine concentrations below toxic levels, mean $C_{max}$ 466.79 ± 226.31 ng/mL and 866.57 ± 426.61 ng/mL for 2.5 mL and 5.0 mL doses, respectively. Levels have increased proportionally with the dose administered. No burst of drug delivery was observed. Maximum levels were reached approximately 13-17 hours after dosing and gradually decreased over 72 hours.

Nervous system adverse events were reported by 29 patients on 2.5 mL dose (66%), 25 on 5.0mL dose (53%), and 23 on placebo (72%). Cardiac adverse events were experienced by 10 patients on 2.5mL dose (23%), 15 on 5.0mL dose (32%), and 7 on placebo (22%). 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.

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, 7% for 5.0 mL and 7% for placebo; paresthesia 12% for 2.5 mL, 9% for 5.0 mL and 0% for placebo; tinnitus 5% for 2.5 mL, 11% for 5.0 mL and 14% for placebo. Electrocardiographically, administration of SABER-Bupivacaine did not result in clinically relevant wave morphology changes or duration of RR, PR, QRS, and QTc intervals.

## General Safety

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 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.

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 gastrointestinal changes.

The surgical site healed as expected and local tissue conditions were normal in most patients at all time points evaluated. Long term effects on wound-healing are being evaluated at 3 and 6 month follow-up visits via study protocol extension.

## Conclusions

- SABER-Bupivacaine 5.0 mL deposited directly at the surgical site was safe and effective in the management of pain in patients who underwent elective, open, unilateral, tension-free, inguinal hernia repair.
- SABER-Bupivacaine 5.0 mL significantly improved mean pain intensity AUC on movement compared with placebo post-surgery for 48 and 72 hours.
- Patients treated with SABER-Bupivacaine 5.0 mL required significantly less opioid rescue medications post-operatively compared with placebo.
- Reduction of opioid rescue dose was associated with reduction of opioid-related side effects (constipation, somnolence, dizziness, nausea and vomiting).
- Over the study period, SABER-Bupivacaine 5.0 mL prolonged the time to first opioid use compared with placebo.
- Efficacy trends in the SABER-Bupivacaine 2.5 mL group were positive, but not statistically significantly different from placebo.
- Patient satisfaction with overall pain treatment was observed in each treatment group throughout the duration of the study.
- Further investigations are planned using other surgical applications to confirm analgesic and opioid-sparing properties of SABER-Bupivacaine.

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