SABER®-Bupivacaine Reduced Pain Intensity for 72 Hours Following Abdominal Surgery Relative to Bupivacaine-HCl

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INTRODUCTION

- Early postsurgical pain typically peaks on the first postoperative day and shows some improvement over the first 72 hours[1]
- Many surgical procedures performed under general anesthesia therefore require complex postoperative pain management involving the use of strong opioids
  - — Unfortunately, up to 80% of patients experience an opioid-related adverse event (AE) which can extend the length of hospital stay and increase the likelihood of readmission[2]
  - — Postoperative opioid use also represents a common gateway to opioid addiction[3]
- Although local anesthetics can significantly reduce pain after surgery, they are typically short acting and provide little relief beyond the first postoperative day[4]
- There is therefore an unmet need for a simple-to-use, nonopioid treatment option that provides reliable pain relief over the postsurgical 72-hour period
- SABER-Bupivacaine (sucrose acetate isobutyrate extended-release–bupivacaine) is a semiviscous solution that contains the active ingredient bupivacaine (132 mg/mL), in a delivery platform composed of a biodegradable organic matrix and the solvent benzyl alcohol[5]
  - — The solvent diffuses on instillation, leaving an extended-release, in situ depot that delivers the local anesthetic at the surgical site throughout the first 72 postoperative hours[5]
- The Bupivacaine Effectiveness and Safety SABER Trial (BESST) was conducted to extend the existing clinical experience with SABER-Bupivacaine to patients undergoing major abdominal surgery

METHODS

Study Design and Treatment

- This was an international, multicenter, randomized, double-blind, parallel-group controlled, phase 3 trial in patients undergoing elective major abdominal surgery[5]
- Patients were enrolled in 1 of 3 cohorts, depending on the type of surgical procedure, with a 3:2 allocation ratio of SABER-Bupivacaine to control for all cohorts[5]
- Data from the 2 cohorts with Bupivacaine-HCl as an active comparator are reported here:
  - — Cohort 1 patients (n = 48) underwent open laparotomy, and the control was Bupivacaine-HCl (150 mg)
  - — Cohort 2 patients (n = 50) underwent laparoscopic cholecystectomy, and the control was Bupivacaine-HCl (150 mg)
- SABER-Bupivacaine 5 mL (132 mg/mL, 660 mg bupivacaine) was instilled directly into the surgical incisions, whereas Bupivacaine-HCl was infiltrated into the peri-incisional tissue[5]
- In the postoperative period, all patients had access to rescue opioids when pain intensity was rated at ≥4 points on a 0 to 10 numerical rating scale (moderate to severe pain)[5]
  - — Pain intensity at rest and on movement (sitting up in bed) was recorded with an electronic device (LogPad; PHT, Boston, MA)
- Safety was monitored by evaluation of vital signs, physical examination findings, safety laboratory test results, and AEs and included cardiovascular and neurologic event monitoring (standard 12-lead electrocardiogram [ECG] at screening and at final visit and 12-lead Holter monitoring before surgery to 72 hours after surgery) and assessment of surgical wound healing (day 7, final visit, and day 30) and local tissue conditions (days 7 and 14)

Primary End Points

- Coprimary end points were mean pain intensity on movement time-normalized area under the curve during the period 0 to 72 hours after dose ($AUC_{0\text{-}72}$), using both scheduled pain intensity and pain intensity prior to each opioid dose, and mean total intravenous morphine equivalent opioid dose during the period 0 to 72 hours after dose

RESULTS

Study Patients

- 98 patients were randomly assigned in Cohorts 1 and 2 (**Table 1**)

Table 1. Surgical Procedural Characteristics (safety population)

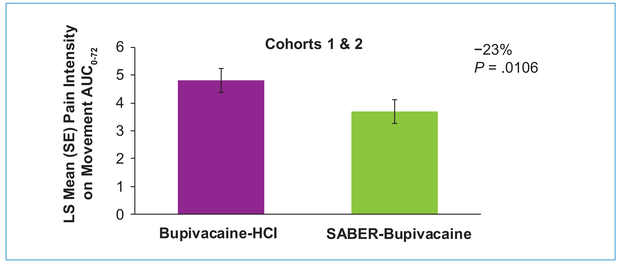
	Cohort 1 – Laparotomy		Cohort 2 – Cholecystectomy	
	SABER-Bupivacaine n = 30	Bupivacaine-HCl n = 18	SABER-Bupivacaine n = 30	Bupivacaine-HCl n= 20
Cumulative incision length, mean (SD), cm				
	19.6 (7.98)	20.7 (7.53)	3.9 (0.81)	3.8 (0.77)
Incisions, n (%)				
1	27 (90.0)	16 (88.9)	0	0
2	3 (10)	1 (5.6)	0	0
3	0	1 (5.6)	6 (20)	4 (20)
4	0	0	23 (76.7)	16 (80)
5	0	0	1 (3.3)	0
6	0	0	0	0
Duration of surgery, median (range), min				
	146 (55-320)	180.5 (63-239)	46 (28-120)	46 (27-96)

SD, standard deviation.

Efficacy Outcomes

- In the combined Cohort 1 and 2 populations, pain intensity on movement (excluding opioid rescue pain scores) was significantly lower with SABER-Bupivacaine compared with Bupivacaine-HCl (inferential analysis with analysis of variance [ANOVA])[5] (**Figure 1**)

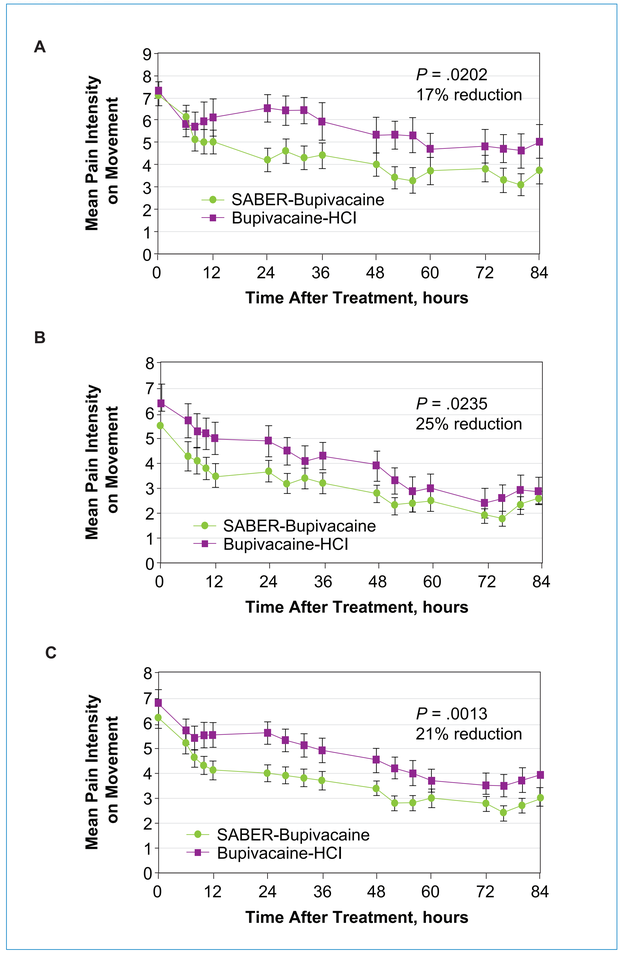
Figure 1. Pain intensity on movement areas under the curve (scheduled pain assessments only) were improved across the combined Cohort 1 and 2 populations (intention-to-treat population).



SE, standard error.

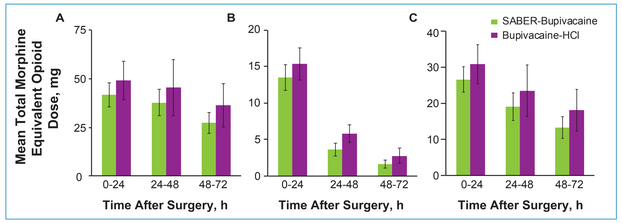
- Using a repeated-measures analysis, pain intensity on movement was significantly lower with SABER-Bupivacaine compared with Bupivacaine-HCl during the 0- to 72-hour observation period[5] (**Figure 2**)
  - — A repeated-measures analysis was used to partition variability resulting from individual patient differences, given the relatively short period of observation and the low attrition rate

Figure 2. Repeated-measures pain intensity on movement during the 0- to 72-hour period (intention-to-treat population). (A) Cohort 1, laparotomy; (B) Cohort 2, cholecystectomy; (C) Cohorts 1 and 2.



- Mean opioid use was lower in the SABER-Bupivacaine group than in the control group, but this difference was not statistically significant[5] (**Figure 3**)

Figure 3. Total morphine equivalent opioid medication dose (intention-to-treat population). (A) Cohort 1, laparotomy; (B) Cohort 2, cholecystectomy; (C) Cohorts 1 and 2.



Safety

- Overall, AEs were similar between SABER-Bupivacaine and control groups (**Table 2**)
  - — The Holter data showed no consistent treatment-related effects on any of the ECG intervals, including QTcF
  - — No consistent imbalances between treatment groups and no evidence of bupivacaine toxicity were observed (**Table 2**)

Table 2. Summary of Treatment-Emergent Adverse Events (TEAEs)

n (%)	Cohort 1[a]		Cohort 2[a]	
	SABER-Bupivacaine n = 30	Bupivacaine-HCl n = 18	SABER-Bupivacaine n = 30	Bupivacaine-HCl n = 20
≥1 TEAE	30 (100)	17 (94)	28 (93)	20 (100)
≥1 cardiovascular TEAE	4 (13)	7 (39)	2 (7)	2 (10)
≥1 neurologic TEAE	6 (20)	4 (22)	17 (57)	10 (50)
≥1 serious TEAE	9 (30)	4 (22)	0	1 (5)

CONCLUSIONS

- Patients treated with SABER-Bupivacaine after laparotomy and laparoscopic cholecystectomy surgery experienced clinically and statistically significant pain relief for 3 days compared with patients treated with standard bupivacaine
- Opioid use was lower in patients treated with SABER-Bupivacaine on all 3 days compared with bupivacaine-treated patients, but the difference was not statistically significant
- SABER-Bupivacaine was well tolerated
  - — There was no evidence of systemic bupivacaine toxicity, as assessed by AEs and results of laboratory testing and intensive Holter monitoring
- Overall, treatment with SABER-Bupivacaine provided a clinically meaningful reduction in pain intensity over a 72-hour postoperative period compared with bupivacaine

DISCUSSION

- SABER-Bupivacaine may provide a foundation for reliable 72-hour pain relief to help spare opioid use and its corresponding adverse events
- SABER-Bupivacaine has the potential to reduce readmissions and call-backs due to inadequate pain relief with shorter acting analgesia or opioid-related adverse events

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Financial Disclosure

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http://myqr.co/xhj1

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