Poster #1831

Long-Term Safety of SABER®-Bupivacaine in Arthroscopic Subacromial Decompression

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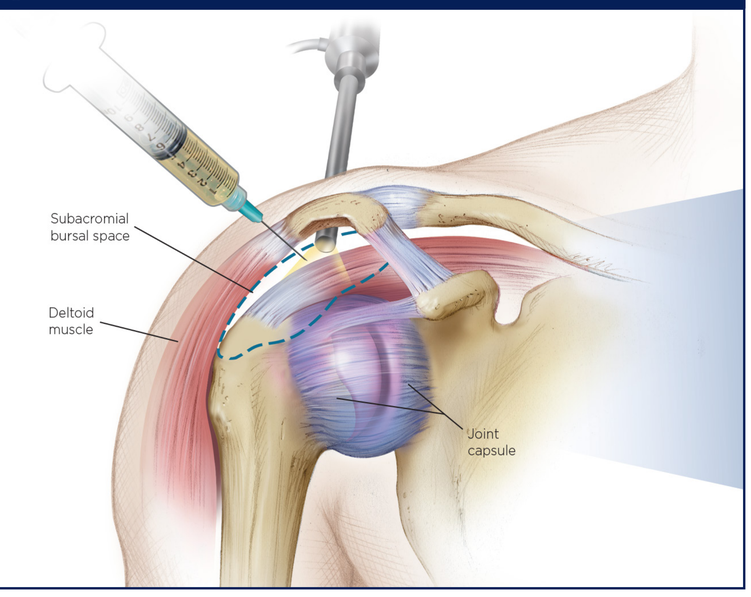
INTRODUCTION

- The ability of local anesthetics to provide effective analgesia after shoulder arthroscopy is limited both by their relatively short durations of action and by reports of chondrolysis following continuous joint infusion[1-4]
- **Sucrose acetate isobutyrate extended-release bupivacaine (SABER®-Bupivacaine)** is an investigational long-acting analgesic formulation containing bupivacaine 660 mg (13.2% wt/vol) in a single 5 mL dose
- After local instillation, it releases bupivacaine continuously to the surgical site for 72 hours, followed by gradual resorption of the depleted biocompatible matrix
- Several short-term studies have assessed the effect of SABER-Bupivacaine on postoperative pain[5,6]; the objective of this analysis is to examine its long-term safety when instilled into the subacromial space following arthroscopic subacromial decompression (ASD) (**Figure 1**)

Figure 1. Instillation



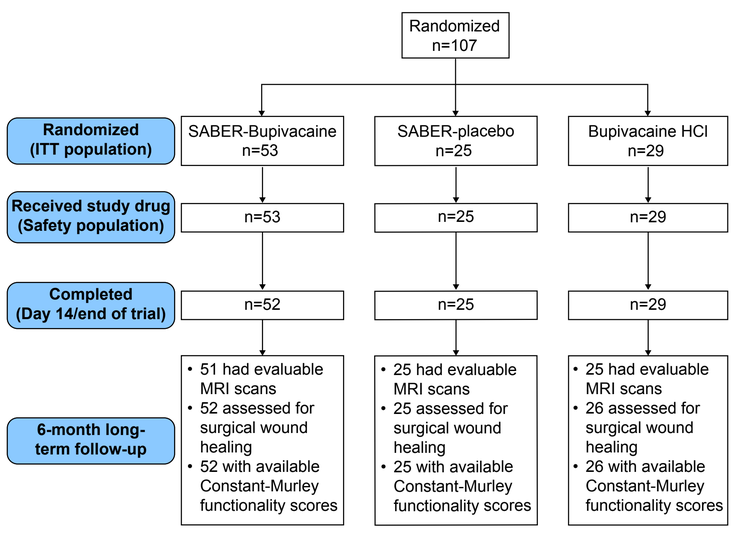
METHODS

- The long-term safety of SABER-Bupivacaine in ASD was examined in 2 separate studies, 1 conducted in Europe and 1 in Australasia

EUROPEAN STUDY

- This randomized, double-blind, active- and placebo-controlled trial was conducted at 9 sites in Austria, Denmark, Germany, Latvia, and Sweden
- Eligible patients were ≥18 years of age and undergoing ASD under general anesthesia (**Figure 2**)
- An intact rotator cuff was confirmed in all patients by prestudy magnetic resonance imaging (MRI) to minimize exposure of the intra-articular cartilage to bupivacaine
- Patients were randomized 2:1:1 to receive 1 of the following, administered subacromially at the close of surgery by percutaneous injection under direct arthroscopic visualization:
  - SABER-Bupivacaine 13.2% 5 mL
  - Bupivacaine hydrochloride (HCl) 0.25% 20 mL
  - SABER-placebo 5 mL (SABER formulation without bupivacaine)
- Long-term safety assessments 6 (±1) months after ASD included:
  - Surgical-site healing and local tissue evaluation
  - Shoulder MRI
  - Change from baseline in Constant-Murley functionality scores

Figure 2. European Study: Flow Diagram

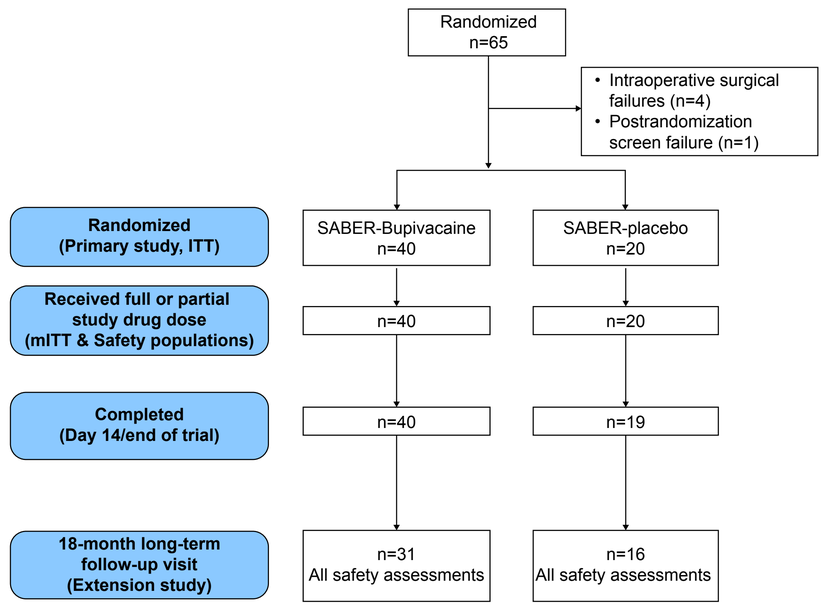


ITT, intention-to-treat.

AUSTRALASIAN STUDY

- This was a long-term extension of a randomized, double-blind, placebo-controlled study conducted at multiple sites in Australia and New Zealand
  - The primary 28-day trial enrolled patients 18 to 65 years of age undergoing ASD under general anesthesia (**Figure 3**)
  - Patients whose preoperative MRIs showed a major or full-thickness rotator cuff tear were excluded
  - At the close of surgery, SABER-Bupivacaine or SABER-placebo was percutaneously instilled into the subacromial space under direct arthroscopic visualization
  - Safety assessments at 18 months included pain intensity on movement, surgical-site healing and local tissue evaluation, shoulder MRI, and frequency and severity of adverse events (AEs)

Figure 3. Australasian Study: Flow Diagram



mITT, modified intention-to-treat.

RESULTS

EUROPEAN STUDY

- All 107 randomized patients received treatment and completed both the initial component of the trial and the 6-month safety evaluation (**Table 1**)

Table 1. European Study: Patient Demographics at Enrollment

	SABER-Bupivacaine n=53	SABER-Placebo n=25	Bupivacaine HCl n=29	Total n=107
Sex, n				
Female/Male	33/20	14/11	17/12	64/43
Age, years				
Mean (range)	50.1 (28–70)	48.6 (24–63)	51.6 (21–70)	50.2 (21–70)
Race, n				
Asian	0	1	0	1
Hispanic	2	0	0	2
White	50	24	29	103
Other	1	0	0	1
Body Mass Index, kg/m²				
Mean (range)	26.8 (20.3–35.3)	25.8 (19.3–34.5)	26.6 (21.5–41.5)	25.5 (19.3–41.5)

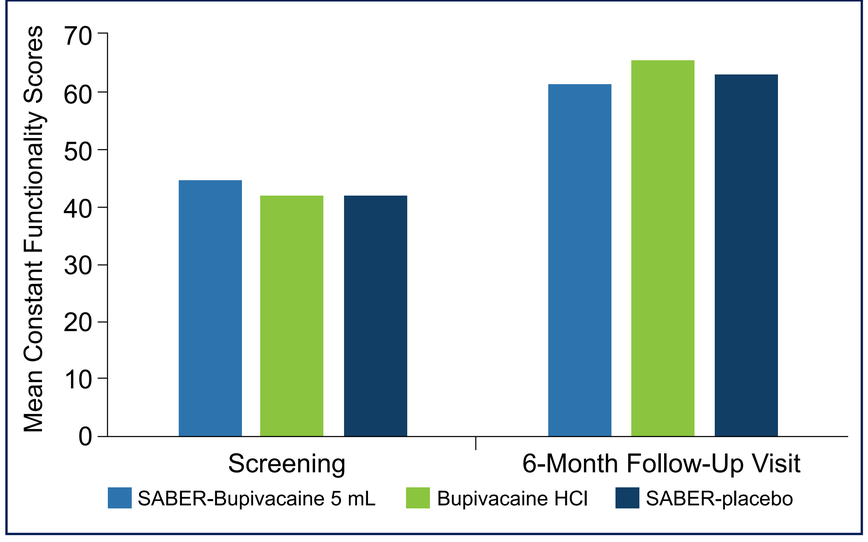
- At 6 months, 101 patients had evaluable MRI scans and 103 were assessed for surgical wound healing
- No safety concerns were identified in MRI results or surgical-site evaluations
- Shoulder MRI evaluations for most patients were improved or unchanged from baseline (**Table 2**); in the few cases in which worsening was observed, it was generally mild and considered unrelated to study treatment
- Compared with pretreatment baseline, MRI studies showed no new degenerative changes to the glenohumeral joint or cartilage, or to the rotator cuff

Table 2. European Study: Shoulder MRI Evaluations at the 6-Month Follow-Up Visit

MRI Change from Baseline	SABER-Bupivacaine n=51		SABER-Placebo n=25		Bupivacaine HCl n=25	
	n	%	n	%	n	%
Improved	6	11.8	2	8.0	6	24.0
No change	31	60.8	14	56.0	9	36.0
Worsened						
Mild	12	23.5	5	20.0	9	36.0
Moderate	2	3.9	4	16.0	0	0.0
Severe	0	0.0	0	0.0	1	4.0

- No evidence of cartilage loss or chondrolysis was found
- Constant-Murley functionality scores indicated increases in functionality from baseline to 6-month follow-up in all 3 groups (**Figure 4**)

Figure 4. European Study: Mean Constant-Murley Functionality Scores at Screening and 6-Month Follow-Up



AUSTRALASIAN STUDY

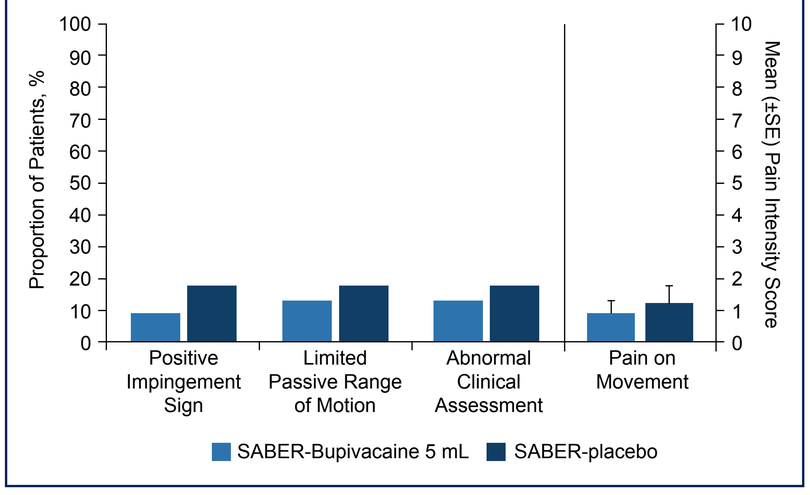
- Of the 60 patients who received treatment in the primary study, 47 were evaluated in the 18-month long-term extension study (**Table 3**)

Table 3. Australasian Study: Patient Demographics at Enrollment

	SABER-Bupivacaine n=31	SABER-Placebo n=16	Total n=47
Sex, n			
Female/Male	17/14	8/8	25/22
Age, years			
Mean (range)	46.4 (27–66)	47.9 (30–68)	46.9 (27–68)
Race, n			
Asian	1	0	1
Caucasian	28	16	44
Aborigine/Torres Strait Islander	1	0	1
Other	1	0	1
Body Mass Index, kg/m²			
Mean (range)	27.1 (19–34)	29.1 (23–42)	27.8 (19–42)

- No subject showed evidence of surgical-site infection, bleeding, discoloration, or dehiscence
- Shoulder examinations at 18 months revealed no safety concerns, and findings were similar between groups (**Figure 5**)
- Overall, no safety concerns were identified based on 18-month MRI results
  - MRI studies showed no new degenerative changes to the glenohumeral joint or cartilage compared with pretreatment baseline and no residual traces of study drug
  - Mild, nonprogressive chondral loss at the humeral head was noted in 2 patients, 1 in the SABER-Bupivacaine group and 1 in the SABER-placebo group; neither finding was considered related to the study drug or reported as an AE

Figure 5. Australasian Study: Shoulder Examination by Treatment Group at 18 Months Postdose



- The number, type, relationship, and severity of treatment-emergent AEs (TEAEs) reported were similar between treatment groups (**Table 4**)

Table 4. Australasian Study: Summary of TEAEs at 18 Months Postdose

	SABER-Bupivacaine n=31		SABER-Placebo n=16	
	Number of Patients	Number of Events	Number of Patients	Number of Events
Patients reporting at least 1 TEAE	2	2	2	2
Bursitis	0	0	1	1
Degenerative cartilage disease	1	1	0	0
Tendon rupture	0	0	1	1
Hyperglycemia	1	1	0	0

TEAEs were defined as AEs with onset during the 18-month study period but after completion of the primary trial.

CONCLUSIONS

- In these 2 studies of SABER-Bupivacaine with long-term follow-up, no safety concerns were identified at the 6-month or 18-month postdose assessments compared with placebo or bupivacaine HCl
- There was no evidence of bupivacaine-related chondrolysis or rotator cuff injury based on patient history, clinical exam, and MRI results
- Taken together with the short-term safety and efficacy results from the primary studies, these long-term safety results support the potential role of SABER-Bupivacaine as a primary component of multimodal postoperative analgesia in arthroscopic subacromial decompression

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DISCLOSURES

R.S. Page's institution has received educational support from De Puy-Synthes and research support from Integra Health
A. Malone, A. Hadj, J. Grohs, and S. Rasmussen have nothing to disclose
D. Ellis is an employee of DURECT

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