SABER®-Bupivacaine

Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee

16 January 2020

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SABER-Bupivacaine

SPONSOR PRESENTATION

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Speaker	Topic
Tong J. Gan, MD, MHS, FRCA, MBA Professor and Chairman, Dept. of Anesthesiology Stony Brook School of Medicine	Clinical context
Neil Verity, PhD Executive Director, Pharmacology DURECT Corporation Project leader and principal scientist	Introduction to clinical program
Jon Meisner, MD Sr. Medical Director, Medical Affairs DURECT Corporation	Efficacy and safety
Asok Doraiswamy, MD, FACS Methodist Hospital of Southern California Huntington Memorial Hospital	General surgeon's perspective
Harold Minkowitz, MD Memorial Hermann Katy Hospital Memorial Hermann Memorial City Medical Center	Anesthesiologist's perspective

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Reserve speakers

Speaker	Title/Affiliation
James M. Anderson, MD, PhD	Professor of Pathology Case Western Reserve University
Nathaniel Katz, MD, MS	Adjunct Assistant Professor of Anesthesia, Tufts University School of Medicine Chief Science Officer, WCG-Analgesic Solutions
Lynne Steinbach, MD	Emeritus Professor of Radiology on Full Recall Department of Radiology and Biomedical Imaging University of California San Francisco
Julie Thacker MD, FACS, FASCRS	Associate Professor with Tenure Department of Surgery Duke University School of Medicine
Linval DePass, PhD, DABT, ATS Fellow	Principal Scientist and Executive Director, Nonclinical Safety, DURECT Corporation
David J. Ellis, MD, PhD	Vice President, Clinical Development DURECT Corporation
William B. Krebs, PhD	Consulting Statistician DURECT Corporation

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Post-operative pain

CLINICAL CONTEXT

Tong J. Gan, MD, MHS, FRCA, MBA
Professor and Chairman, Dept. of Anesthesiology
Stony Brook School of Medicine
Stony Brook, NY

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Better postoperative analgesics can improve outcomes

- >50 million surgical procedures per year in US[1]
- Up to 70% of patients experience moderate to severe pain after surgery[2], especially during first 72 hours when pain is most severe
- Poorly controlled pain following surgery can result in multiple negative outcomes and delay recovery
- Inadequately controlled postoperative pain can lead to persistent postsurgical pain, with incidence estimated at 30%-50%

[1] Brummett, et al, 2017
[2] Meissner, 2015

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Consensus Guidelines recommend multimodal management to manage acute postsurgical pain[1]

- Combination of pharmacological and nonpharmacological modalities (local anesthetics and systemic analgesics)
- Many hospitals have implemented multimodal regimens as part as Enhanced Recovery After Surgery (ERAS)
- Goal to control pain and reduce the need for opioids

[1] Chou et al., 2016

DURECT

Local anesthetics relatively simple and safe but not without limitation

- Up to 78% of patients administered local anesthetic during surgery for pain control[1]
- Bupivacaine most frequently used local anesthetic (~70% of local anesthetic use)[1]

[1] DRG Claims Analysis conducted in 2016, incorporating 2015 data

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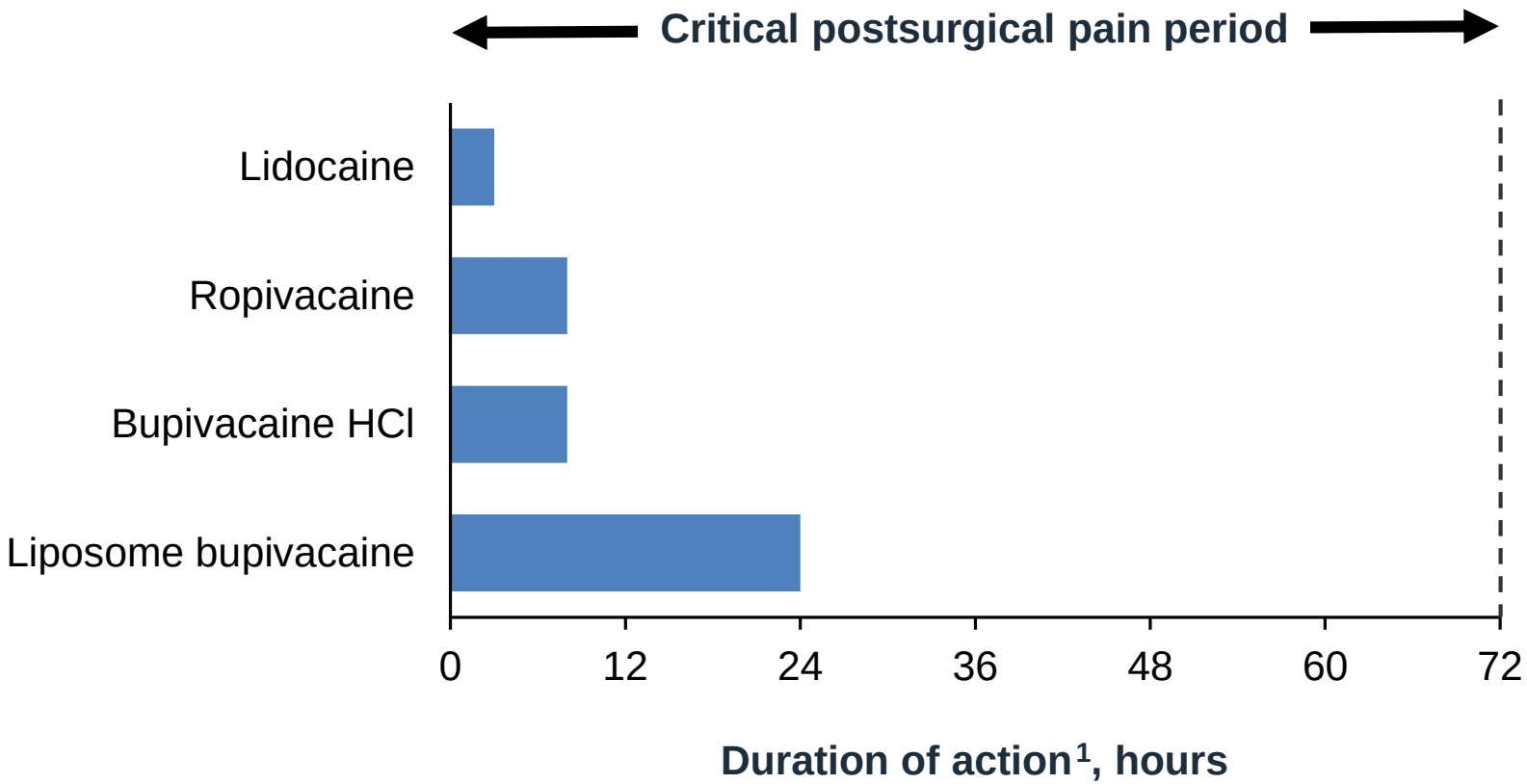
Available local anesthetics do not cover critical postsurgical pain period



[1] Duration of action data extracted from the respective product labels.

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Opioid analgesics widely used for postsurgical pain

- Up to 90% of patients who undergo surgery are given opioids for pain management[1]
- Opioids important analgesics for moderate-to-severe pain, but also with significant limitations[2]
  - Associated with AEs, including nausea and vomiting, constipation, sedation, and respiratory depression
  - Do not address source of pain at surgical site and fail to block pain signals to CNS

[1] Hill, 2017
[2] ASA Guidelines, 2012

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Finding opioid alternatives an important goal

- Patients receiving an opioid Rx within 7 days of short-stay surgery were 44% more likely to become long-term opioid users than those not receiving a prescription[1]
- 6% of patients prescribed opioids perioperatively continued to use them at 90-180 days, compared with 0.4% of controls[2]
  - Equates to >2 million persistent postoperative opioid users per year
- Development of non-opioid analgesic protocols is both a clinical goal (ERAS) and a public health goal

[1] Alam, 2012
[2] Brummett, 2017

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Value of a local anesthetic with sustained pain relief lasting 72 hours

- Helps cover the period of greatest postoperative pain
- Can be incorporated into multi-modal regimens to promote opioid-free analgesia
- Consistent with ERAS principles
- May help reduce or potentially eliminate side effects and sequelae associated with opioids

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SABER-Bupivacaine

INTRODUCTION

Neil Verity, PhD
Executive Director, Pharmacology
DURECT Corporation
Project leader and principal scientist

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SABER-Bupivacaine development goals

Target profile	
Indication	• Acute postoperative pain
Mode of action	• Extended-release bupivacaine
Administration	• Instilled directly into the surgical incision (needle-free) • Option to inject into anatomic spaces under visual guidance • Single dose, single administration
Efficacy goal	• Continuous, clinically-relevant pain reduction over 72 hours relative to placebo control
Safety goals	• Stable bupivacaine release rate • Safe bupivacaine systemic exposure • No effect on wound healing

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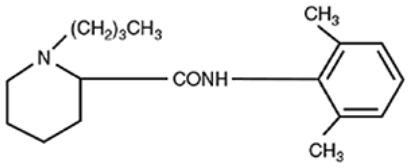
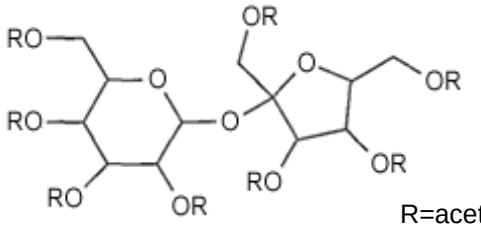
3-component solution

BUPIVACAINE



- Amide-type local anesthetic approved in 1972
- 13.2% by volume
  - 660 mg bupivacaine base in 5 mL solution (equivalent by weight to bupivacaine HCl 743 mg)
  - Sufficient for sustained release over 72 hours

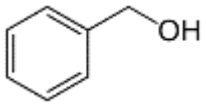
SAIB



R=acetate or isobutyrate

- Sucrose acetate isobutyrate
- Nonpolymeric, sugar-based matrix
  - Retention and stable release of bupivacaine for 72 hours
  - Biocompatible and biodegradable
  - Generally regarded as safe for oral use (GRAS)

BENZYL ALCOHOL



- Solvent reduces viscosity for instillation
- Common excipient in parenteral products
- 12- to 24-hour systemic clearance

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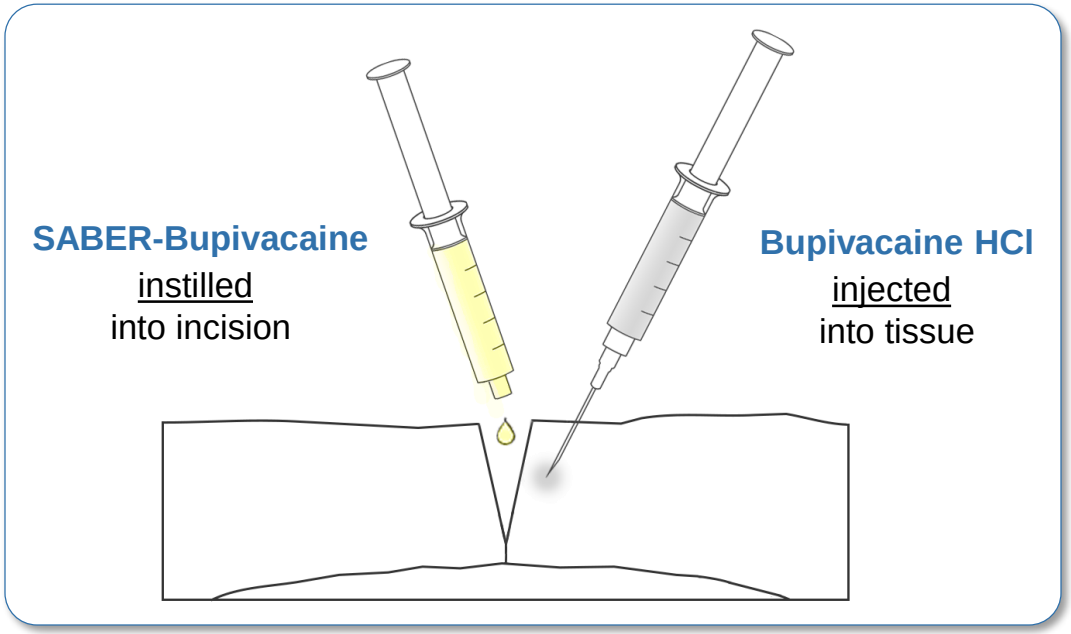
Dosing and administration

- One-time administration by surgeon just prior to skin closure, with patient under anesthesia
  - Instilled into incision without a needle = safer for patient and surgical team
  - May also be injected into targeted anatomic space under visual guidance
- Single 5-mL dose



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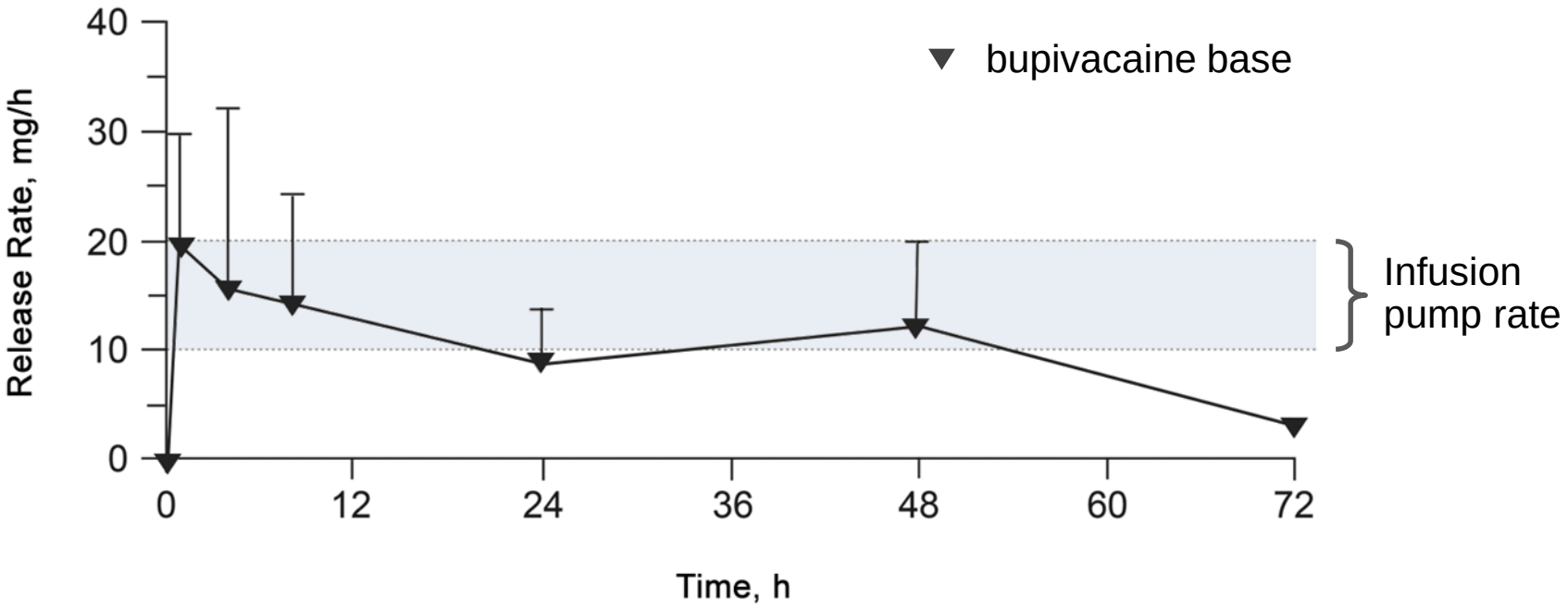
Bupivacaine release rate in human subjects

Release of bupivacaine base from SABER-Bupivacaine



- Continuous release of bupivacaine over 72 hours
- Dose and rate similar to wound infusion catheter
- No dose dumping

Source: ISE Figure 32.

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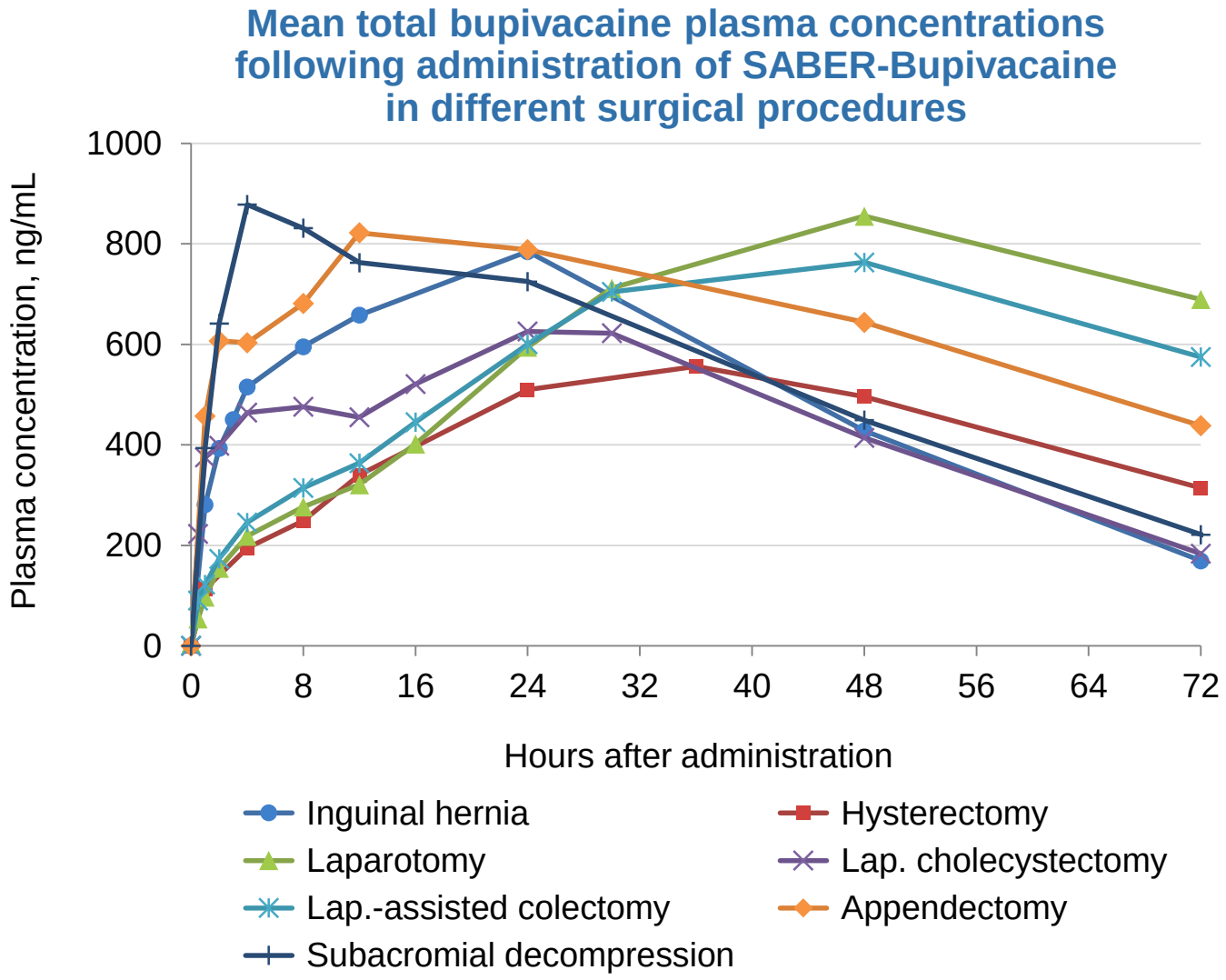
Consistent plasma bupivacaine levels



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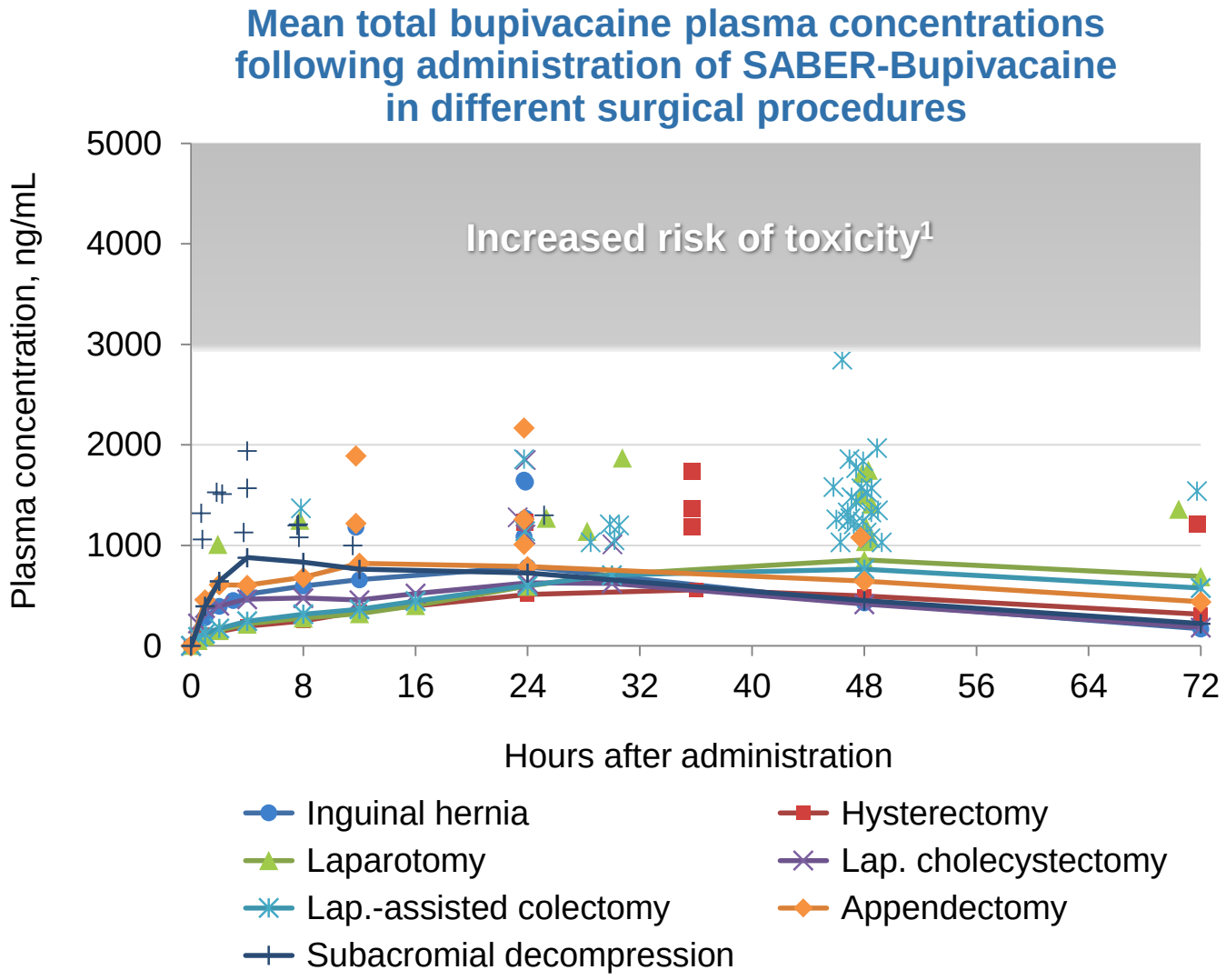
No C_{max} outliers in range of increased toxicity risk



[1] Mather, 1971; Munson, 1972; Munson, 1975; Denson, 1984.

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Extensive clinical program

- 14 studies (and 1 safety extension study) completed
- 876 SABER-Bupivacaine exposures
- Multiple surgical models
  - Abdominal surgery: 7 studies / 466 subjects dosed
  - Inguinal hernia repair: 4 studies / 250 subjects dosed
  - Shoulder surgery: 3 studies / 155 subjects dosed
  - Healthy volunteers: 1 study / 5 subjects dosed
- Total of 1,463 subjects in all treatment groups

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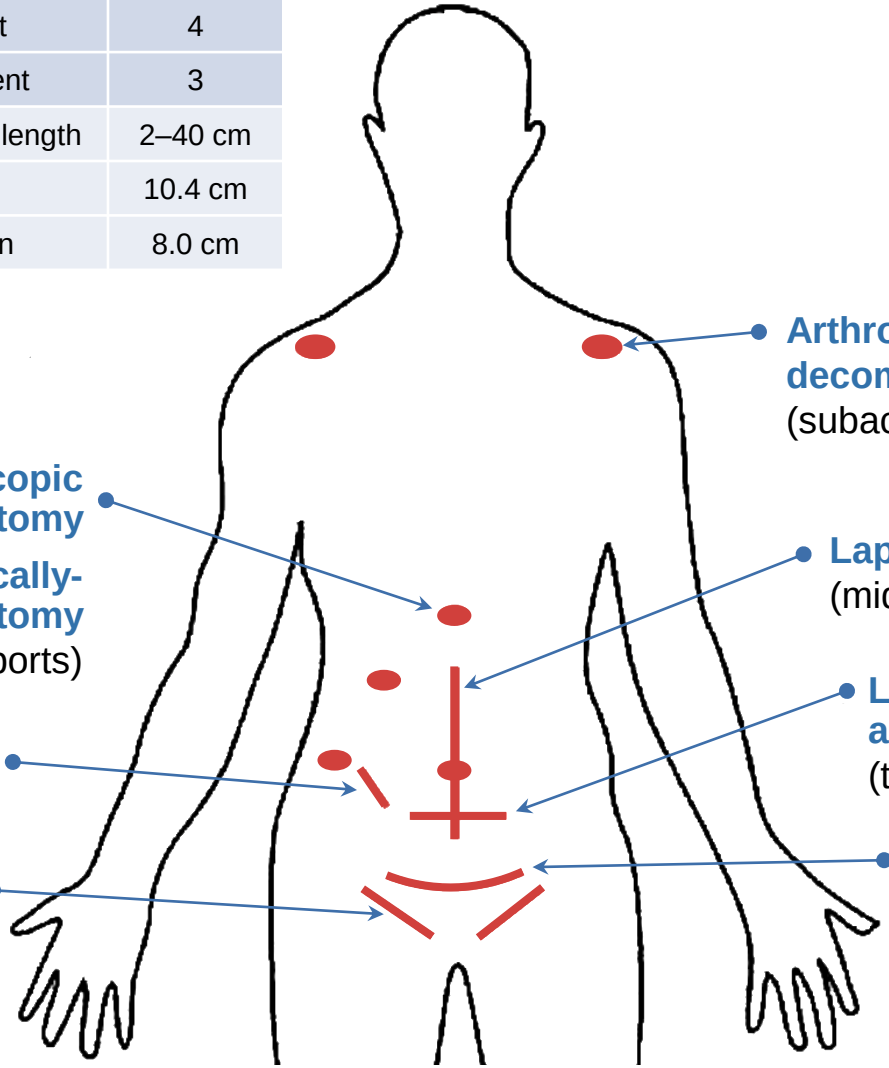
Representative range of surgical models

Surgical pain models			
Soft tissue	6	Inpatient	4
Orthopedic	1	Outpatient	3
Open	4	Incision length	2–40 cm
Endoscopic	2	Mean	10.4 cm
Combined	1	Median	8.0 cm



Arthroscopic subacromial decompression
(subacromial space)

Laparoscopic cholecystectomy

Laparoscopically-assisted colectomy
(laparoscopy ports)

Laparotomy
(midline linear incision)

Laparoscopically-assisted colectomy
(transverse hand port)

Open appendectomy

Open inguinal hernia repair

Abdominal hysterectomy
(Pfannenstiel incision)

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SABER-Bupivacaine summary

Efficacy	• More efficacious than placebo: 2 pivotal trials • Opioid use reduced: 2 pivotal trials • More efficacious (12-24 hours) and possibly longer-lasting than bupivacaine HCl: meta-analysis
Surgeries	• SABER-Bupivacaine safe & effective in a variety of surgeries
Adverse events	• Unremarkable except bruise-like discoloration
LAST	• No appreciable risk
Benzyl alcohol	• No appreciable risk
Wound issues	• No clinical harm due to SAIB deposition • No excess surgical site complications, normal wound healing • Bruise-like discoloration; no clinical consequences
Chondrolysis	• No appreciable risk
Risk-benefit	• Analgesic effect vs. placebo (pivotal and meta-analysis) • Analgesic effect vs. bupivacaine HCl (exploratory) • Decreased opioid use (pivotal and meta-analysis) • Benefits outweigh clinically inconsequential bruise-like discoloration

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SUMMARY OF DATA SUPPORTING SAFETY AND EFFICACY

Jon Meisner, MD
Executive Director, Clinical Development
DURECT Corporation

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Regulatory history

- 2007: End of Phase II
  - Efficacy to be established by comparison with placebo
  - Clinical program not designed for comparison with active control
  - Success in 1 soft-tissue model and 1 bony model required for general surgical indication
- 2013: New Drug Application (NDA) submitted by Sponsor
- 2014: Complete Response Letter (CRL) received
  - FDA unable to formulate benefit-to-harm calculus
  - Questions regarding efficacy profile and 3 issues related to safety
- 2019: full response to CRL submitted by Sponsor
  - Efficacy data systematically re-evaluated to resolve ambiguities
  - Newly-collected safety data integrated into the complete dataset, and dataset completely re-analyzed to address safety issues raised in CRL
  - Entirely new integrated summaries of efficacy and safety (ISE and ISS)
- Today: meeting of Advisory Committee

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FDA briefing book vs Sponsor briefing book

Sources of data and analyses presented to Advisory Committee

FDA[1]	Sponsor
• Conclusions made during original NDA review cycle regarding the safe administration of the product	—
• Additional safety analyses presented in the End-of-Review Cycle Meeting package and Formal Dispute Resolution Request	—
• ISS in the original NDA submission	—
• Safety data from the PERSIST study	• Safety data from the PERSIST study
—	• Revised and updated 2019 ISE
—	• Revised and updated 2019 ISS

[1] FDA Response to DURECT Errata Request, January 9, 2020.

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SABER-Bupivacaine

SUMMARY OF DATA SUPPORTING EFFICACY

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Adequate and well-controlled (AWC) clinical trials

SABER-Bupivacaine efficacy studies were systematically evaluated to determine which were adequate and well controlled and which were not

AWC definition from US Code (21 CFR § 314.126)

1. Objectives and methods of analysis clearly stated in protocol and clinical study report
2. Valid comparison with control to assess quantitative drug effect; study design precisely described
3. Subjects selected have the disease or condition being studied
4. Method of assigning patients to treatment groups minimizes bias and assures comparability
5. Experimenter and subject bias minimized (e.g., blinding)
6. Well-defined and reliable methods of assessment of subject response
7. Adequate analysis of results
8. Test drug standardized (identity, strength, quality, purity, dosage form)

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SABER-Bupivacaine efficacy studies

Results of systematic evaluation

6 Adequate and Well-controlled (AWC)	5 Not AWC
PIVOTAL • CLIN-808-006-0006 Open mesh inguinal hernia repair • BU-002-IM Arthroscopic subacromial decompression SUPPORTIVE • BU-001-IM Open abdominal hysterectomy • C803-025, Cohort 3 Laparoscopically-assisted colectomy • C803-028, Part 1 Laparoscopic cholecystectomy • C803-017 Arthroscopic subacromial decompression	• CLIN005-0006 Rotator cuff repair (predominantly arthroscopic subacromial decompression) • CLIN005-0010 Open inguinal hernia repair • C803-025, Cohort 1 Laparotomy • C803-025, Cohort 2 Laparoscopic cholecystectomy • C803-028, Part 2 Laparoscopic cholecystectomy

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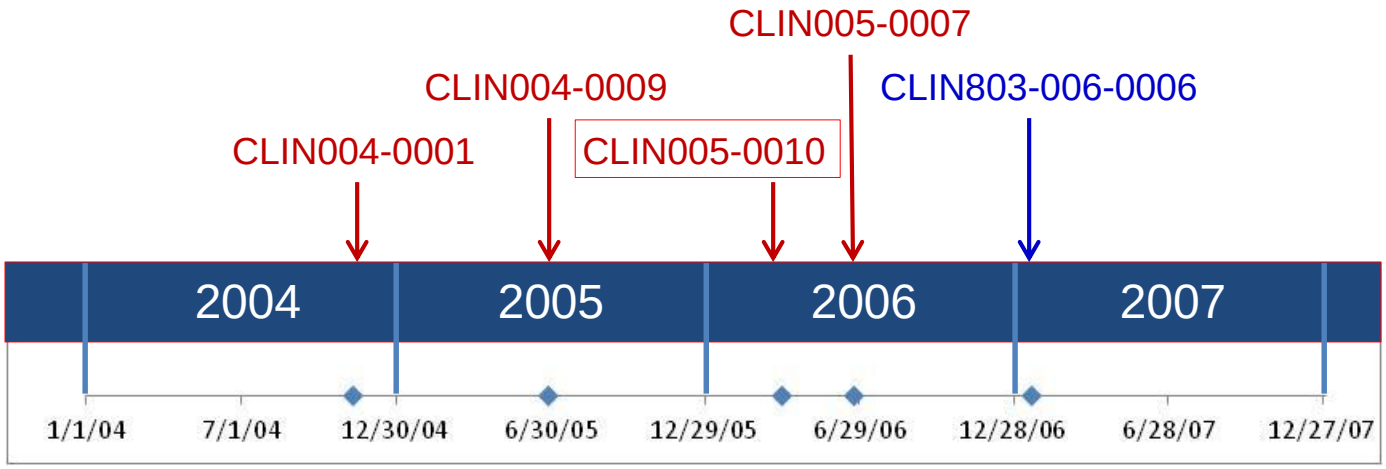
Timeline of hernia trials



Early experiences to explore dose and administration technique (NOT adequate and well controlled)

Confirmatory pivotal study (adequate and well controlled)

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CLIN005-0010: not adequate and well controlled

- Early learning experience
- Explored 2 doses and 3 modes of administration
  - Trial as designed: (1) deep injection or (2) subcutaneous injection
  - Amended mid-trial: (3) instillation into inguinal canal

Reasons not AWC	
Design deficiencies (AWC criterion #2)	• Efficacy endpoints not clearly defined • Mid-trial addition of “instillation” cohort not prospectively planned • No sample size calculation for “instillation” cohort • Mid-trial change in dose from 5 mL to 7.5 mL, and back to 5 mL not prospectively planned
Conduct deficiencies (AWC criterion #6)	• Primary endpoint data subject to inaccuracy and bias (subject-recorded at home on paper diaries)
Analysis deficiencies (AWC criterion #7)	• Primary endpoint assessment based on PP population • 120-hour primary pain endpoint inappropriate for 72-hour product • Inappropriate pooling of placebo patients from separate randomization pools

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PERSIST, Part 2: not adequate and well-controlled; not stand-alone trial

Reasons not AWC	
Design deficiencies (AWC criterion #2)	• Mid-trial change in comparator from saline placebo (Part 1) to bupivacaine HCl (Part 2) not prospectively planned (FDA request, Jan 2016) • Numerous subsequent unplanned changes at FDA request – Jan 2016: Add 3 new solicited symptoms to subject questionnaire – May 2016: Monitor vital signs and 0_2 sat. for min. 2 hours in PACU – Jan 2016, Sep 2016, Feb 2017: Add/revise study stopping criteria – Feb 2017: Extend follow-up to 60 days
Analysis deficiencies (AWC criterion #7)	• Mid-trial change from 72-hour to 48-hour pain endpoint not prospectively planned • No concurrent placebo control, so no assay sensitivity • Primary efficacy endpoint based on 0-48 hour pain data; not integrable with 0-72 hour results from AWC efficacy studies • Inappropriate pooling of Part 1 and Part 2 SABER-Bupivacaine treatment arms for secondary endpoints

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ADEQUATE AND WELL-CONTROLLED EFFICACY TRIALS

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6 AWC trials: common design elements

- Randomized, controlled, double-blind, multicenter, parallel-group
- Pain on movement scores (0-10 numeric scale) recorded in e-diaries at prespecified intervals
  - No baseline postoperative pain score
- Rescue analgesia (IV or oral opioid) upon request
- Primary collection period for efficacy data: 0-72 hours

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6 AWC trials: common endpoints across studies

Type	Endpoint	Study
Primary	Mean pain on movement over 72 hours	All
Co-primary	Percent who took rescue opioids over 0-15 days	CLIN803-006-0006
Co-primary	Cumulative opioid consumption over 72 hours (IV morphine mg equivalents)	BU-002-IM BU-001-IM C803-025, Cohort 3 C803-017
Key secondary	Cumulative opioid consumption over 72 hours (IV morphine mg equivalents)	C803-028, Part 1
Secondary	Time to first use of rescue opioids	All

Pivotal

DURECT

6 AWC trials: efficacy populations

Study ID	Surgical model	Treatment arms				Total
		SABER-Bupivacaine 2.5 mL	SABER-Bupivacaine 5 mL	Placebo	Bupivacaine HCl 50-100 mg	
CLIN803-006-0006	Inguinal hernia repair	43	47	32	—	122
BU-002-IM	Subacromial decompression	—	53	25	29	107
BU-001-IM	Abdominal hysterectomy	—	61	27	27	115
C803-025, Cohort 3	Laparoscopically-assisted colectomy	—	126	77	—	203
C803-028, Part 1	Laparoscopic cholecystectomy	—	46	46	—	92
C803-017	Subacromial decompression	—	40	20	—	60
	Totals	43	373	227	56	699

Pivotal

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PIVOTAL STUDIES

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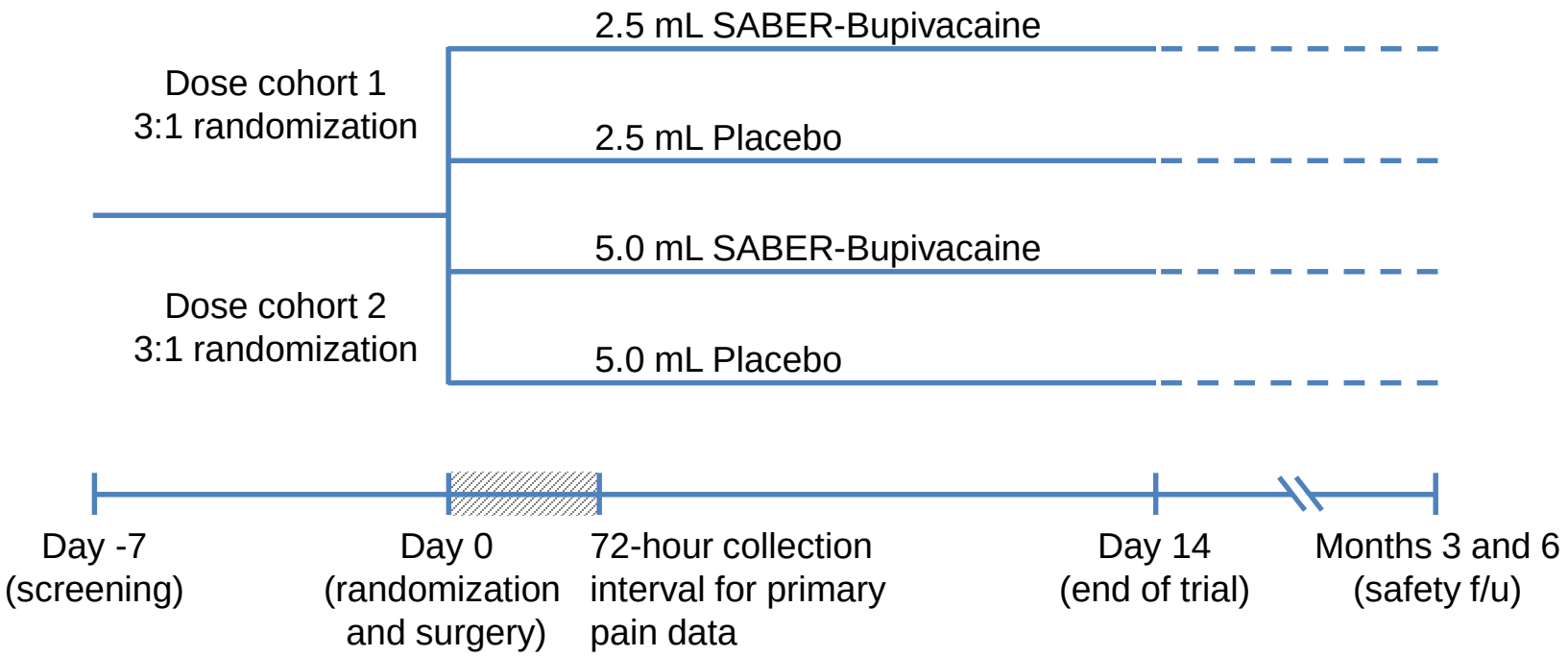
Pivotal soft tissue model: inguinal hernia repair

Study CLIN803-006-0006



- Study population: adults undergoing elective open mesh inguinal hernia repair
- 2 doses studied for determination of dose response
- Prespecified comparison: SABER-Bupivacaine vs pooled placebo
- Tramadol or acetaminophen given upon request for breakthrough pain

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CLIN-803-006-0006: inguinal hernia repair

Disposition and demographics

	SABER-Bupiv 2.5 mL	SABER-Bupiv 5 mL	Placebo 2.5 mL or 5 mL	Study Total
Subject disposition				
Randomized, dosed	44	47	32	123
Safety population	44	47	32	123
Efficacy population	**43**	**47**	**32**	**122**
Discontinued for adverse event or lack of efficacy	0	0	0	0
Discontinued for other reasons	3	0	1	4
3-month follow-up	34	42	26	102
6-month follow-up	32	38	24	94
Demographics and baseline characteristics				
Mean (range) age, years				49.3 (20-79)
Male sex				97%
White race				95%
Mean (range) BMI, kg/m^2				26.6 (19-39)

BMI, body mass index; ITT, intention-to-treat
Source: ISE Table 3 and Table 4.

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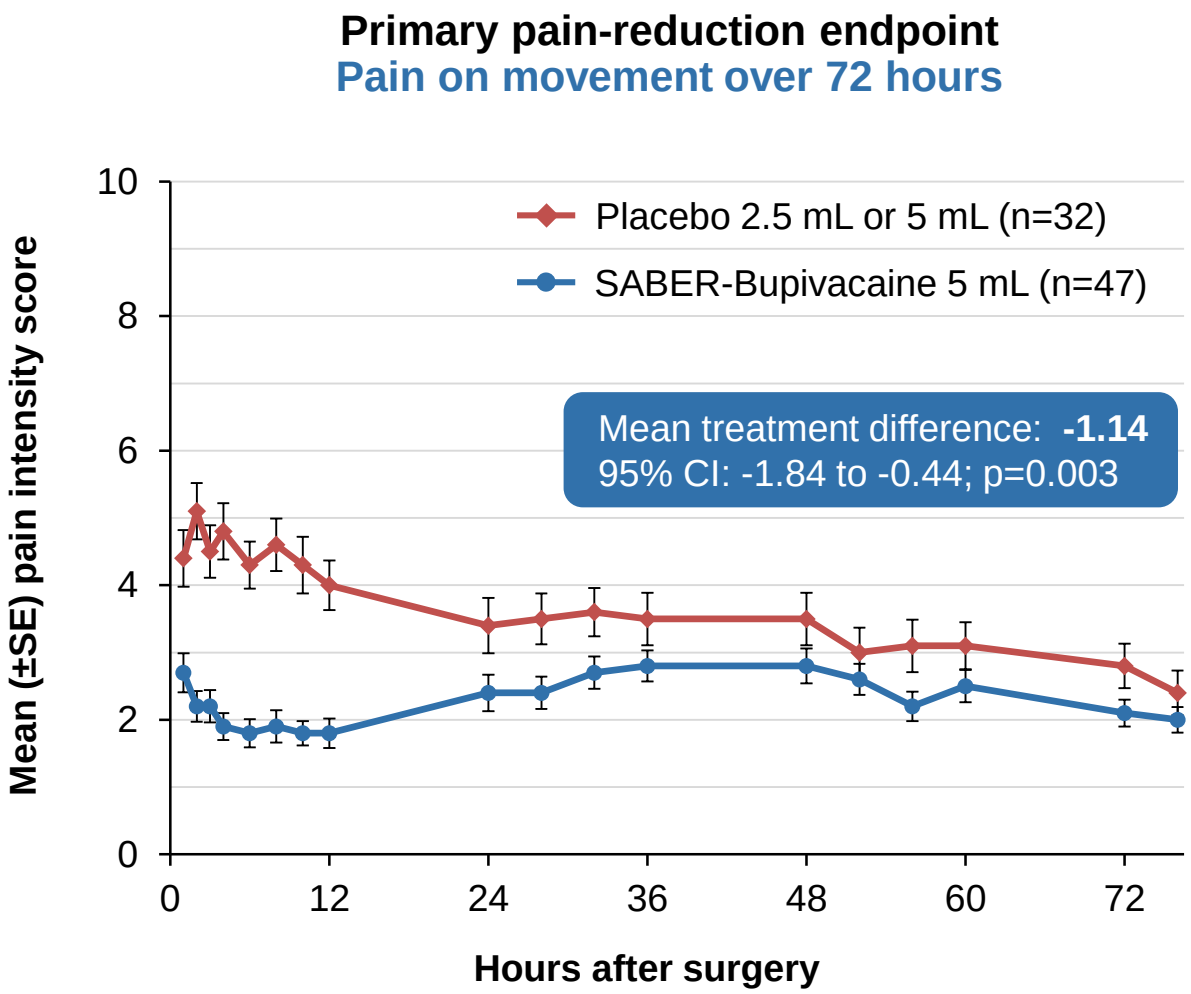
Hernia repair: pain reduced over 72 hours



Treatment difference based on normalized AUC1-72.

Source: CLIN-803-006-0006 CSR, Section 14.2, Table 3/1.1.

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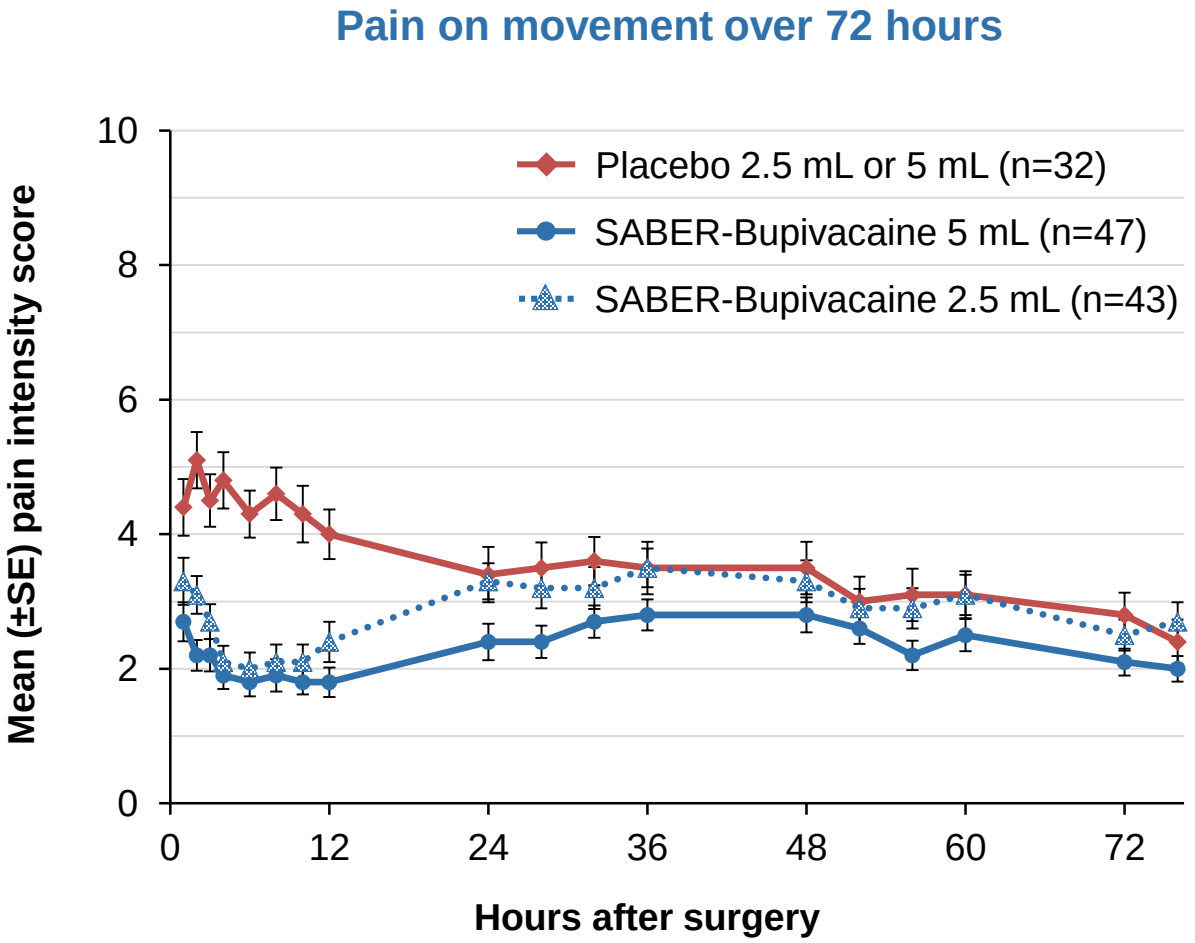
Dose-response: diminished activity with 2.5 mL dose



Mean 72-h treatment difference vs placebo

-1.14, p=0.003

-0.53, p=0.237

Recommended dose = 5 mL

Source: CLIN-803-006-0006 CSR, Section 14.2, Table 3/1.1; ISE Table 5.

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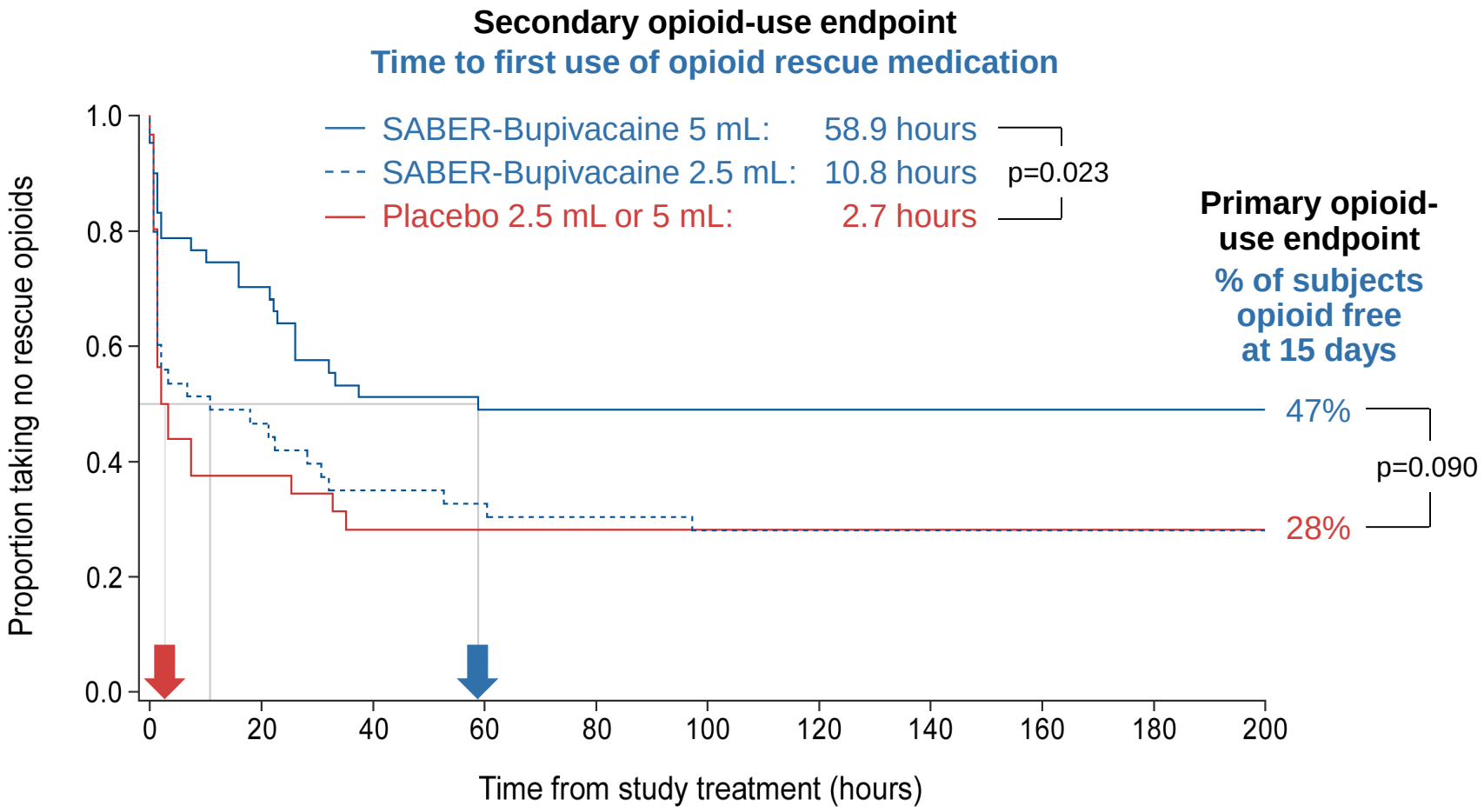
Hernia repair: delayed first request for opioid rescue



P-value for time to first use based on Kaplan-Meier survival estimates and log-rank test; p-value for % opioid free based on Cochran-Mantel-Haenszel test.
Source: ISE Figure 5 and Table 6.

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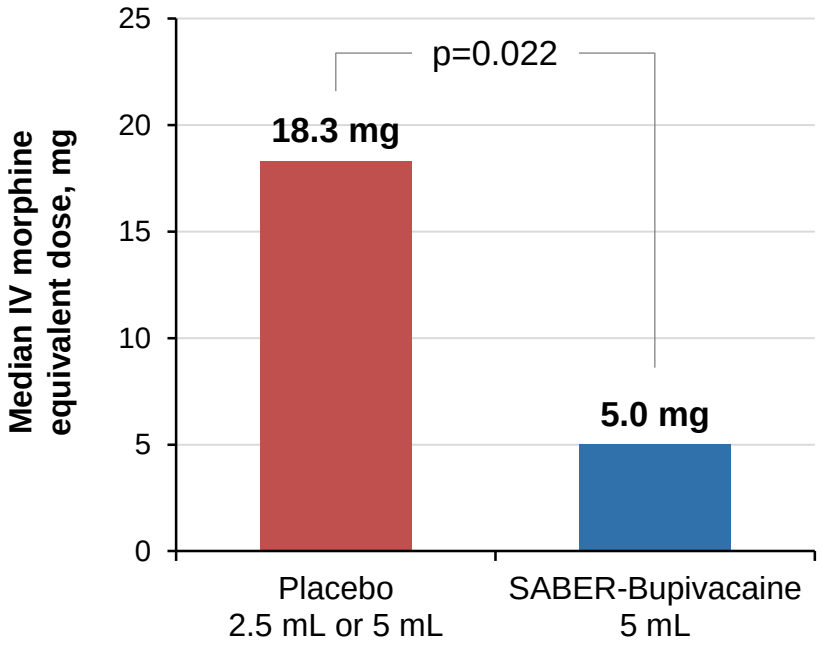
Hernia repair: less opioid use after surgery

Secondary opioid-use endpoint

Cumulative IV morphine-equivalent opioid dose
0-15 days postoperatively



IV, intravenous
P-value based on Wilcoxon rank-sum test.
Source: CLIN-803-006-0006 CSR Addendum #4, Table A4.2.

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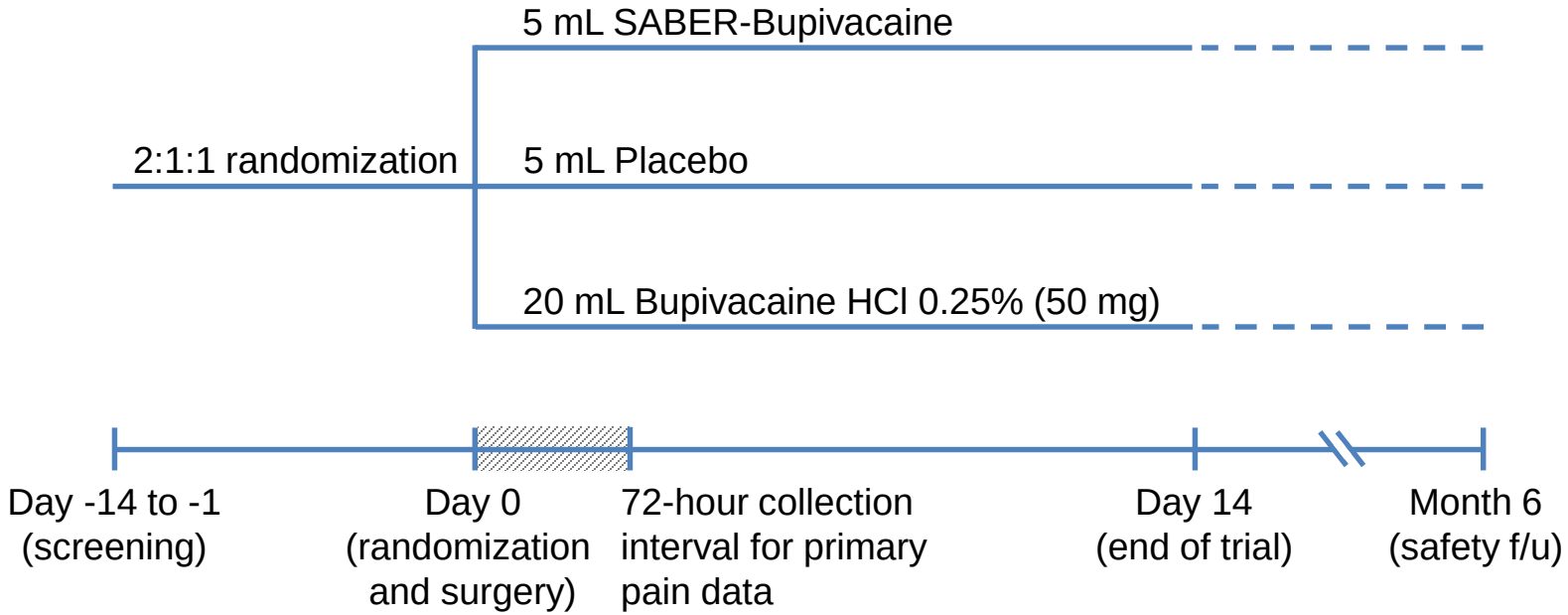
Pivotal orthopedic model: arthroscopic subacromial decompression (shoulder)

Study BU-002-IM



- Study population: adults undergoing arthroscopic subacromial decompression
- Bupivacaine HCl arm for assay sensitivity; not powered for efficacy
- IV or oral morphine upon request for breakthrough pain; all subjects received background acetaminophen at 6-hour intervals
- MRIs and examinations of shoulder function obtained at baseline and 6 months

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BU-002-IM: arthroscopic subacromial decompression

Disposition and demographics

	SABER-Bupivacaine	Placebo	Bupivacaine HCl	Study Total
Subject disposition				
Randomized, dosed	53	25	29	107
Safety population	53	25	29	107
Efficacy population	**53**	**25**	**29**	**107**
Discontinued	0	0	0	0
6-month follow-up	52	25	26	103
Demographics and baseline characteristics				
Mean (range) age, years				50.2 (21-70)
Female sex				60%
White race				96%
Mean (range) BMI, kg/m^2				26.5 (19-42)
Mean Constant-Murley functionality score				43.3

BMI, body mass index
Source: ISE Table 13 and Table 14.

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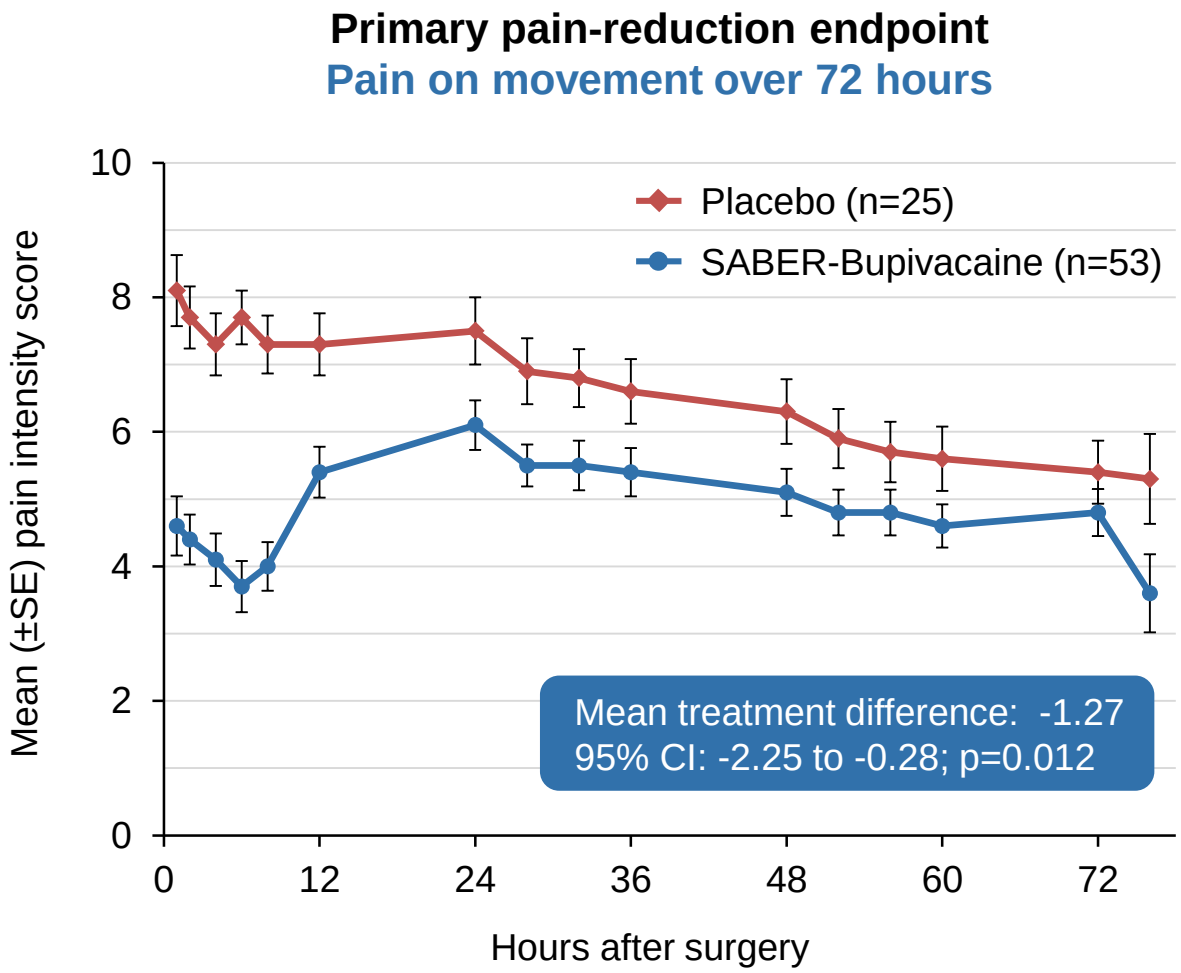
Subacromial decompression: pain reduced over 72 hours



Source: ISE Figure 8.

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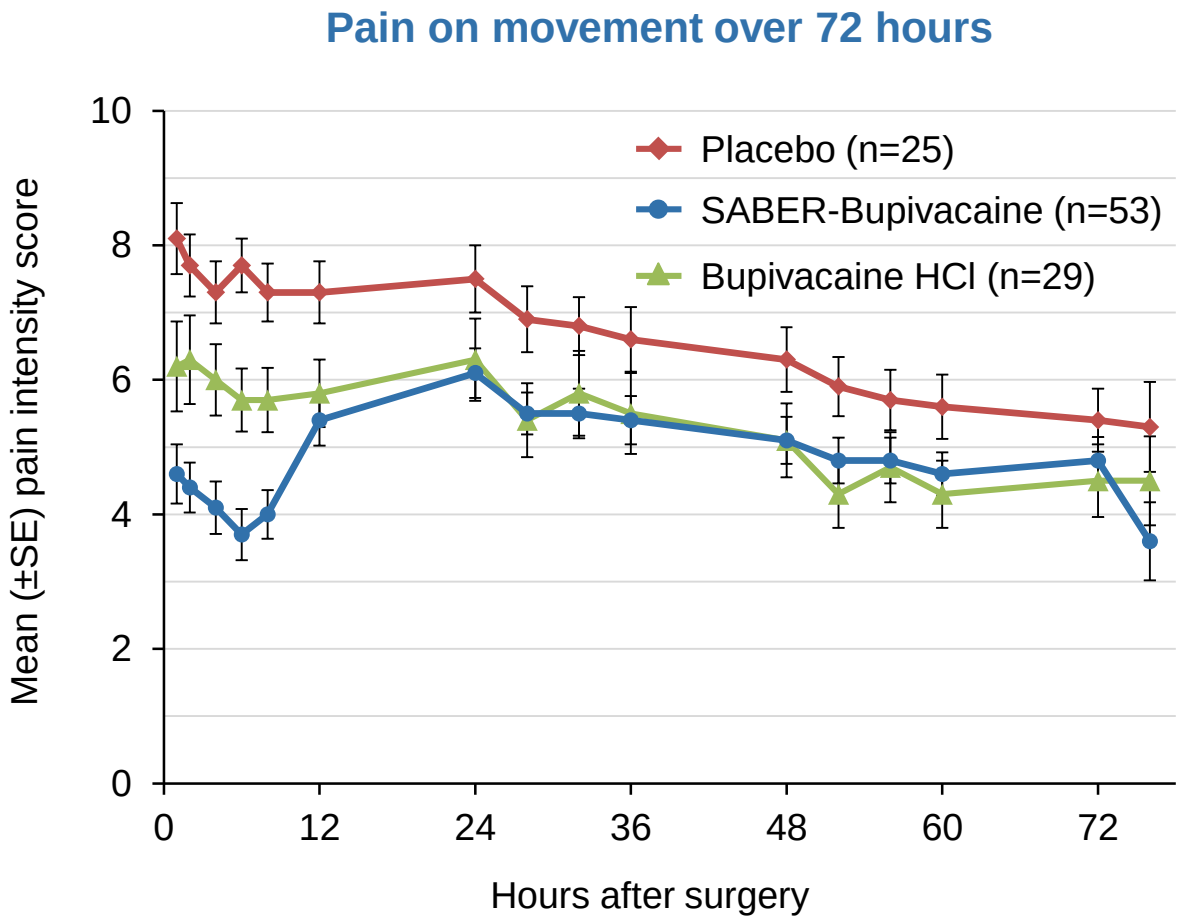
Subacromial decompression: possible early benefit vs bupivacaine HCl



Source: ISE Figure 8.

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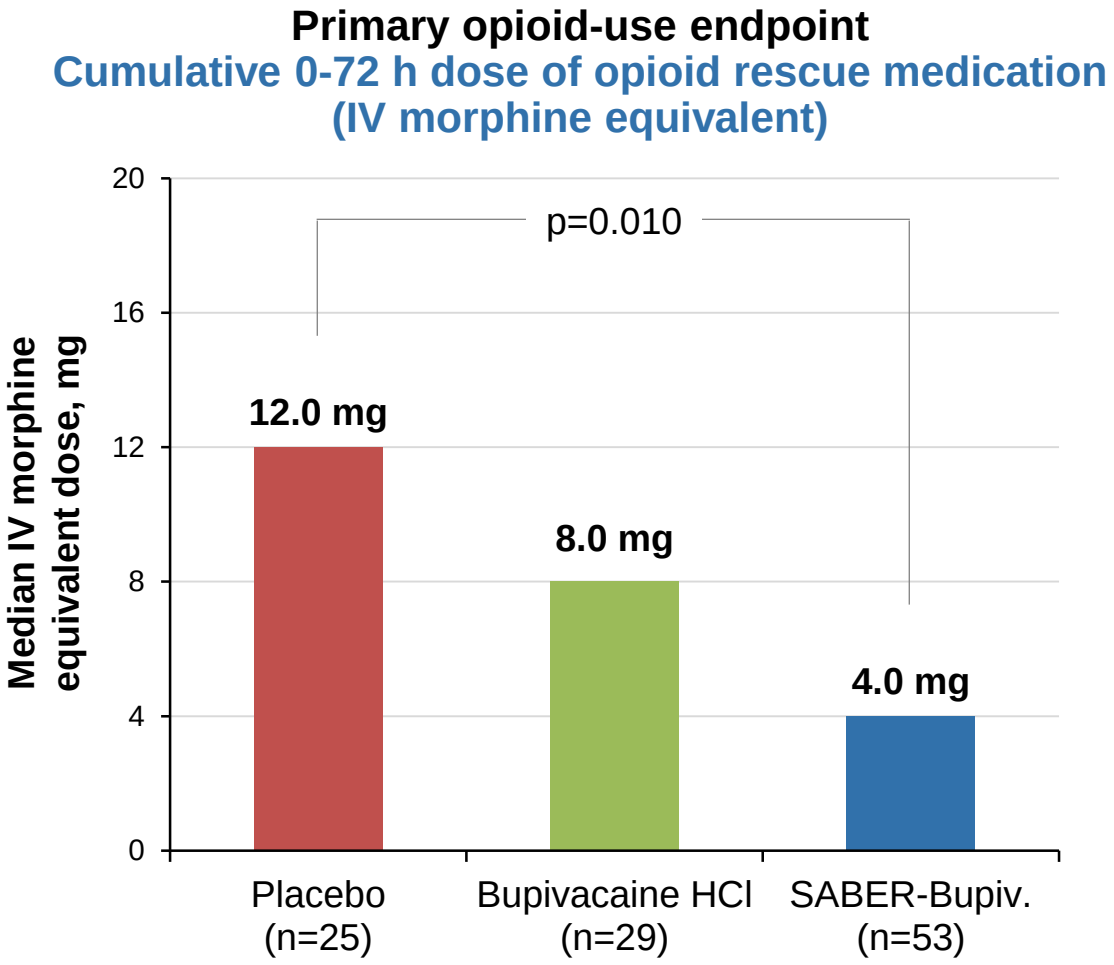
Subacromial decompression: less opioid use after surgery



IV, intravenous

P-value based on Hodges-Lehmann estimates for median difference and Wilcoxon rank-sum test

Source: ISE Table 16.

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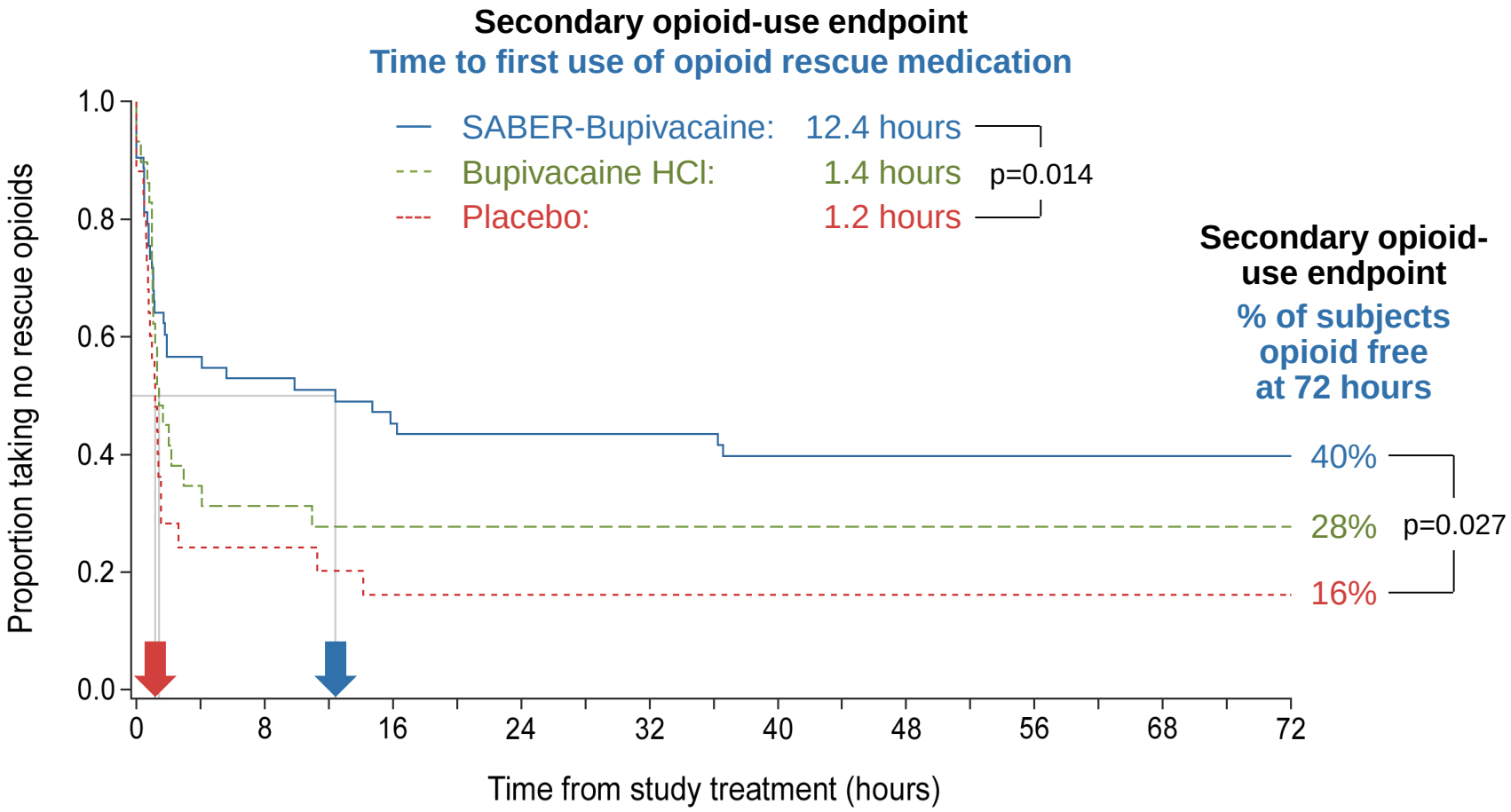
Subacromial decompression: delayed first request for opioid rescue



P-value based on Kaplan-Meier survival estimates and log-rank test.

Source: ISE Table 17 and Figure 9.

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COLLECTIVE EVIDENCE OF EFFECTIVENESS

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4 adequate and well-controlled supportive trials

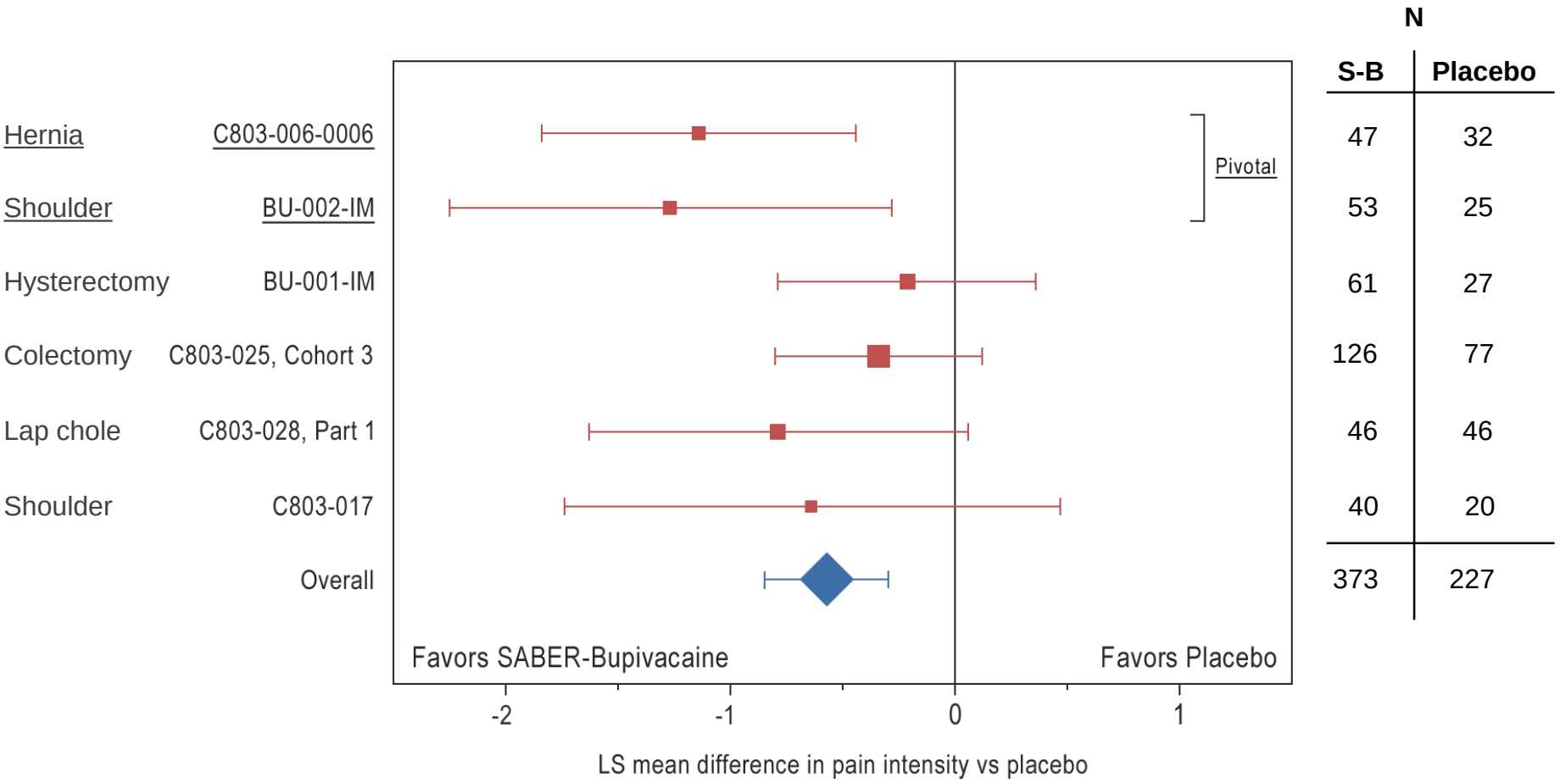
Trial	Postoperative pain model	N		
		SABER-Bupivacaine	Placebo	Bupivacaine HCl
BU-001-IM	Open abdominal hysterectomy	61	27	27
C803-025, Cohort 3	Laparoscopically-assisted colectomy	126	77	–
C803-028, Part 1	Laparoscopic cholecystectomy	46	46	–
C803-017	Arthroscopic subacromial decompression	40	20	–

- Point estimates for primary pain endpoint favored SABER-Bupivacaine over placebo

DURECT

Meta-analysis of AWC trials: reduced pain over 72 h

Pain on movement 0-72 h post-treatment

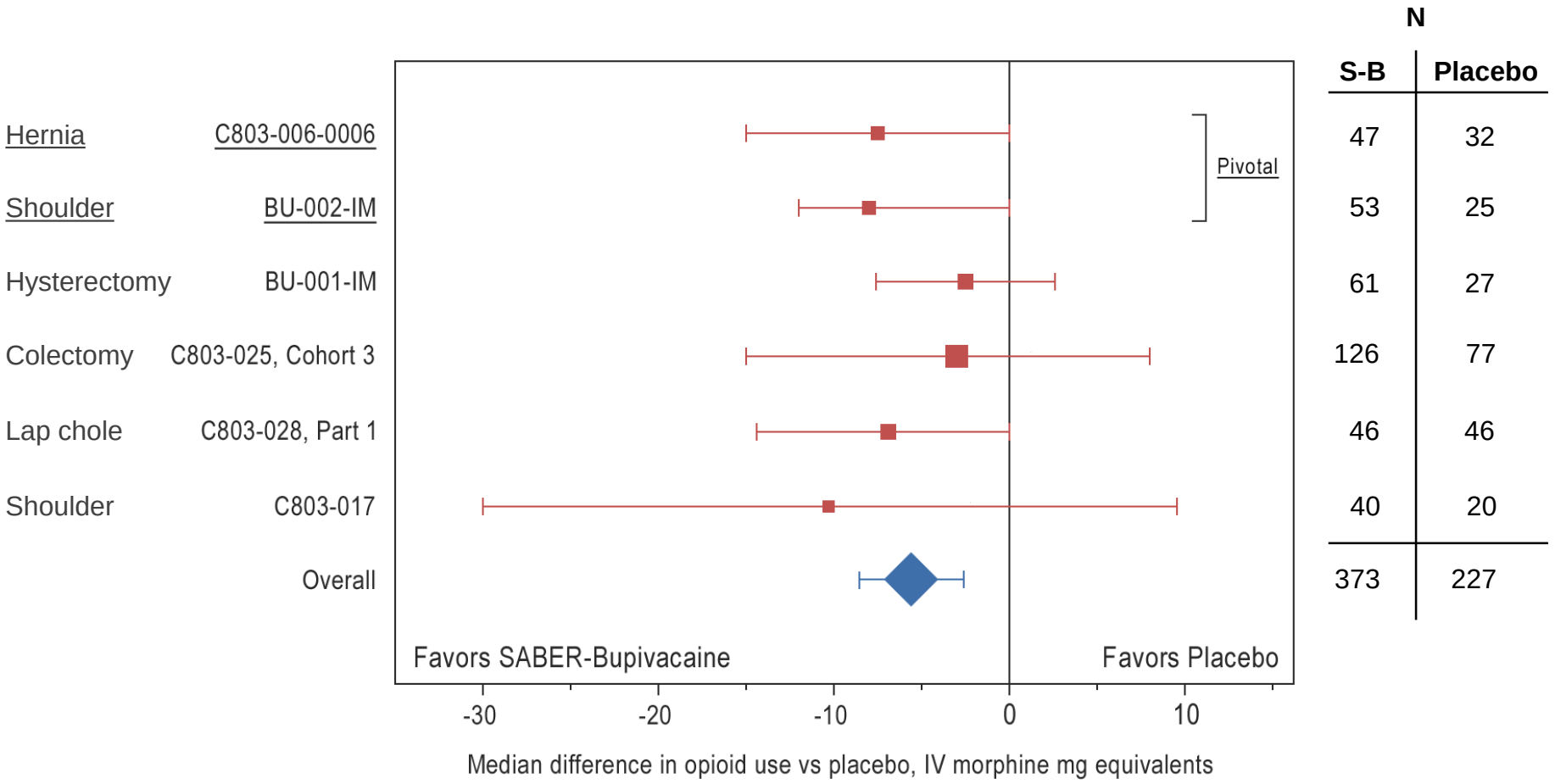


Point estimates and 95% confidence intervals are shown; 0-10 numeric pain rating scale.
Source: ISE Figure 21.

DURECT

Meta-analysis of AWC trials: reduced opioid use

Cumulative opioid use 0-72 h post-treatment



Point estimates and 95% confidence intervals are shown; values in IV morphine mg equivalents.
Source: ISE Figure 22.

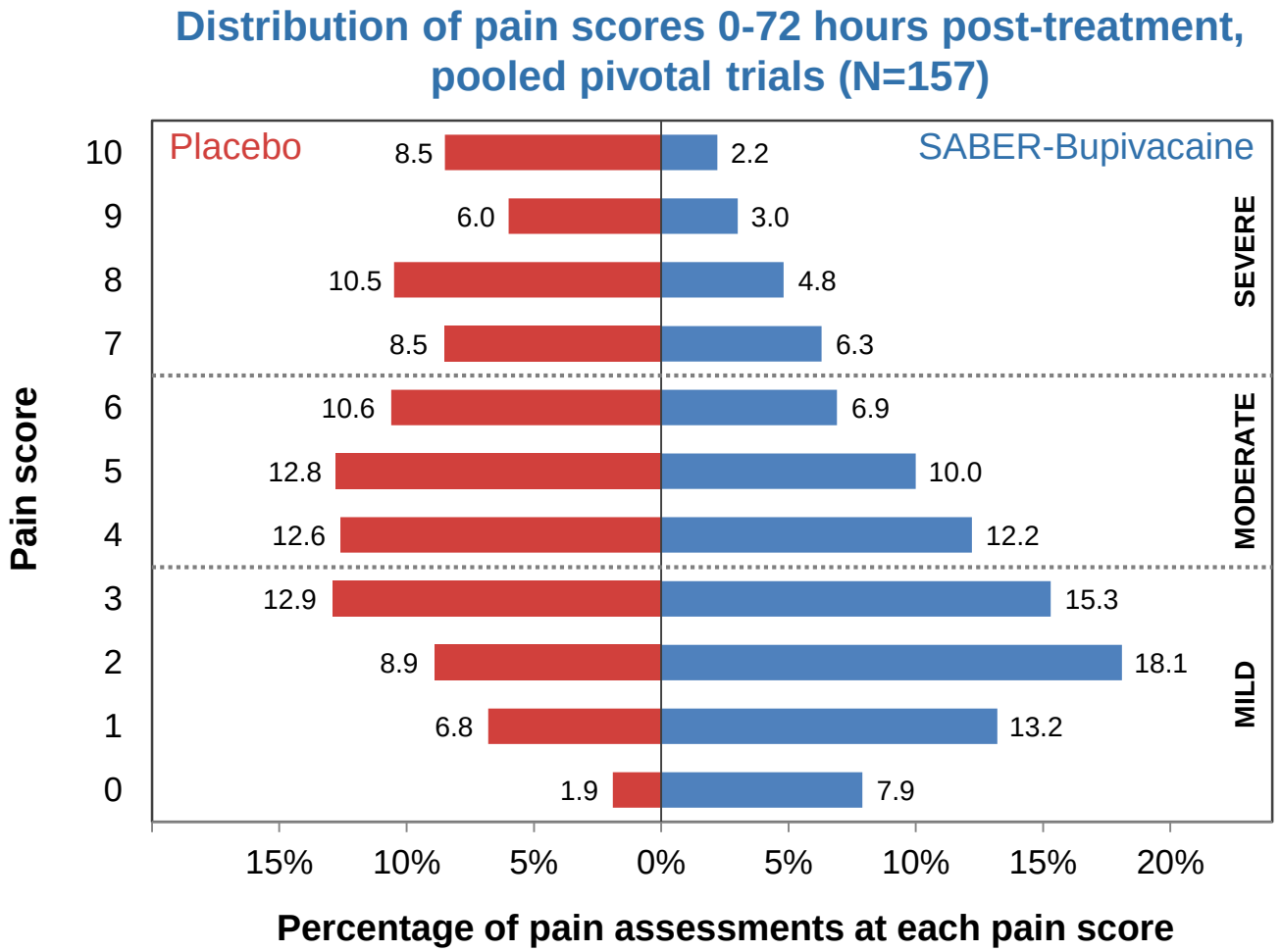
DURECT

SABER-Bupivacaine

ADDITIONAL EFFICACY MEASURES

DURECT

Pain severity shifted from higher to lower



p<0.001 for the correlation between pain score and treatment group

Placebo group = 57 subjects (906 pain reports); SABER-Bupivacaine group = 100 subjects (1578 pain reports). Pain scores adjusted for prior use of opioid rescue by a windowed substitution method. P-value based on Mantel-Haenszel chi-square test for the correlation between pain score value and treatment group.

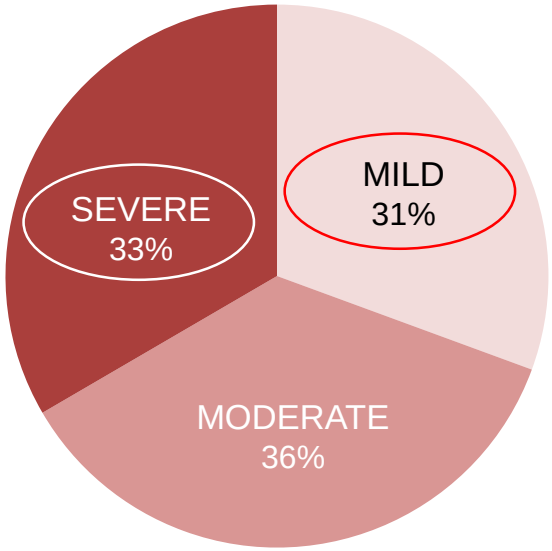
Source: ISE Figure 36.

DURECT

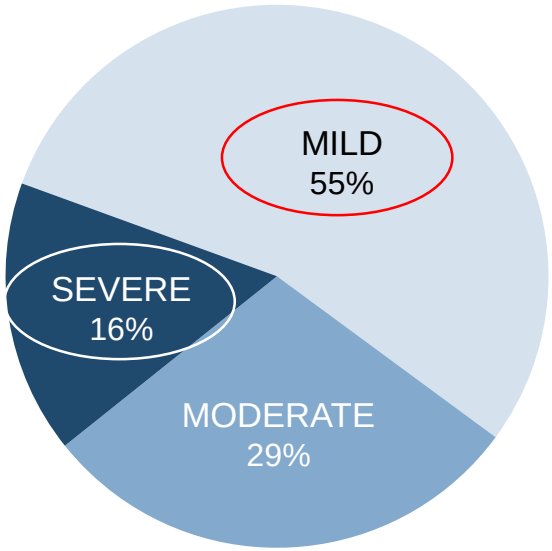
More mild pain reports, fewer severe pain reports

Distribution of mild, moderate, and severe pain scores over 0-72 hours, pooled pivotal trials (N=157)

Placebo



SABER-Bupivacaine

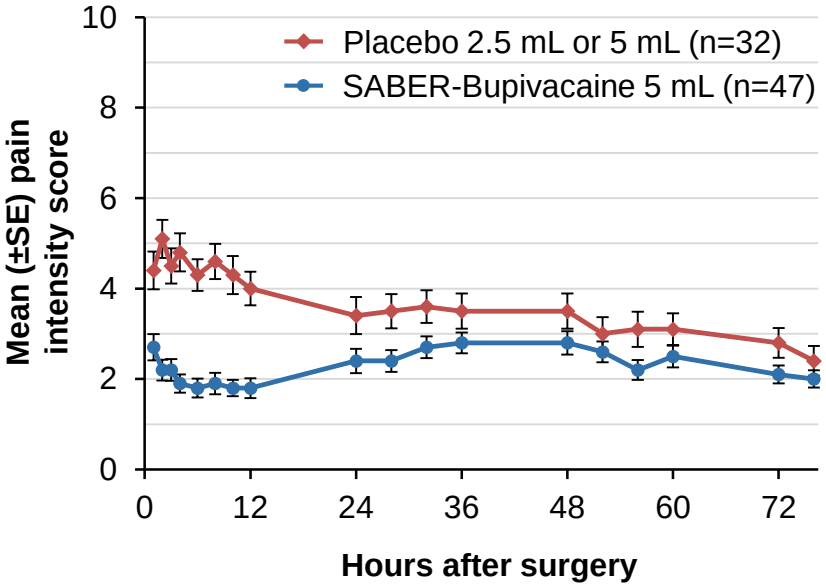


Pain scores adjusted for opioid rescue medication use by a windowed substitution method.
Source: ISE Table 106.

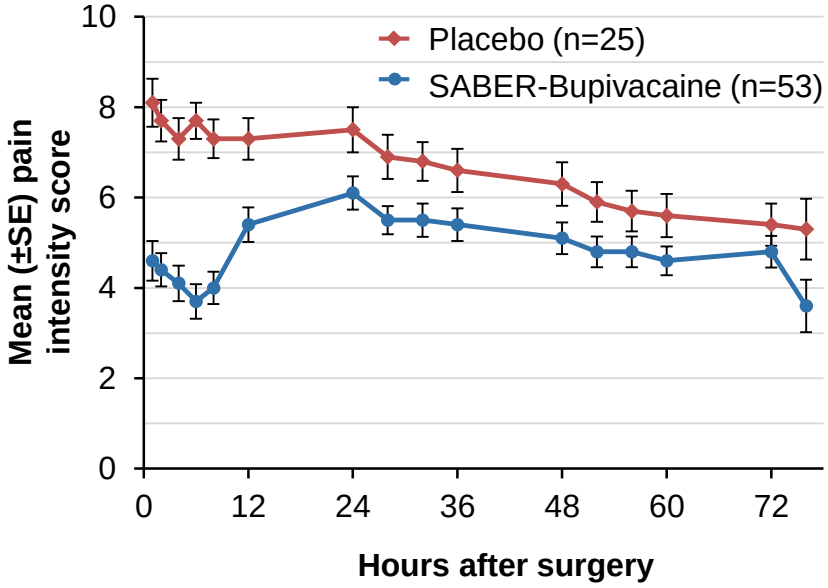
DURECT

72-hour duration of action: pivotal trials

CLIN803-006-0006
Inguinal hernia repair



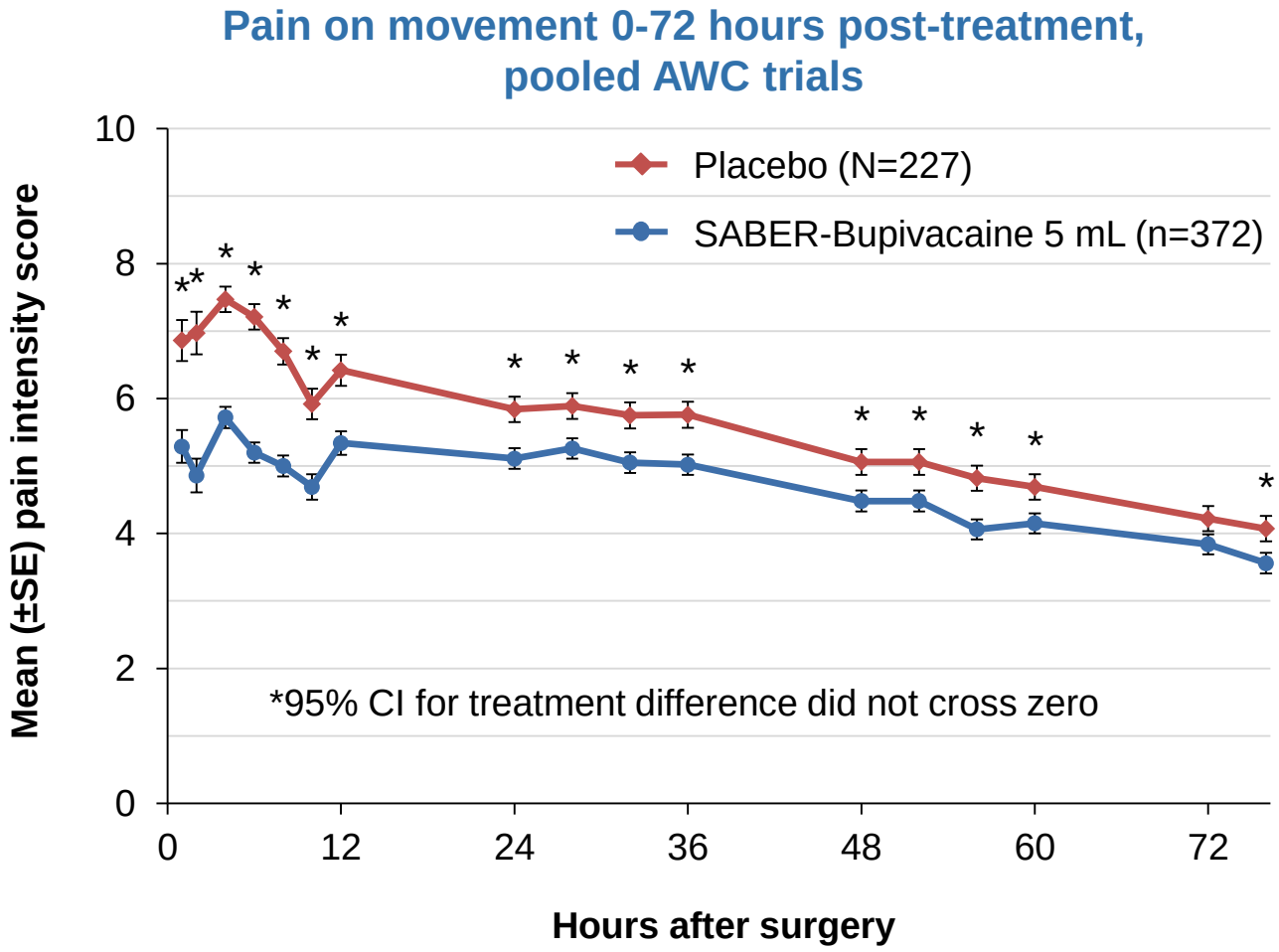
BU-002-IM
Subacromial decompression



- Treatment difference through 72 hours evident in 2 pivotal trials; however, sample sizes too small for point-by-point comparison

DURECT

72-hour duration of action: 6 AWC trials



AWC, adequate and well-controlled; CI confidence interval; SE, standard error.

The placebo group consisted of 165 subjects treated with SABER-placebo 5 mL, 16 subjects treated with SABER-placebo 2.5 mL, and 46 subjects treated with saline placebo.

Source: ISE Figure 35.

DURECT

SABER-Bupivacaine

EXPLORATORY COMPARISON WITH IMMEDIATE-RELEASE BUPIVACAINE

DURECT

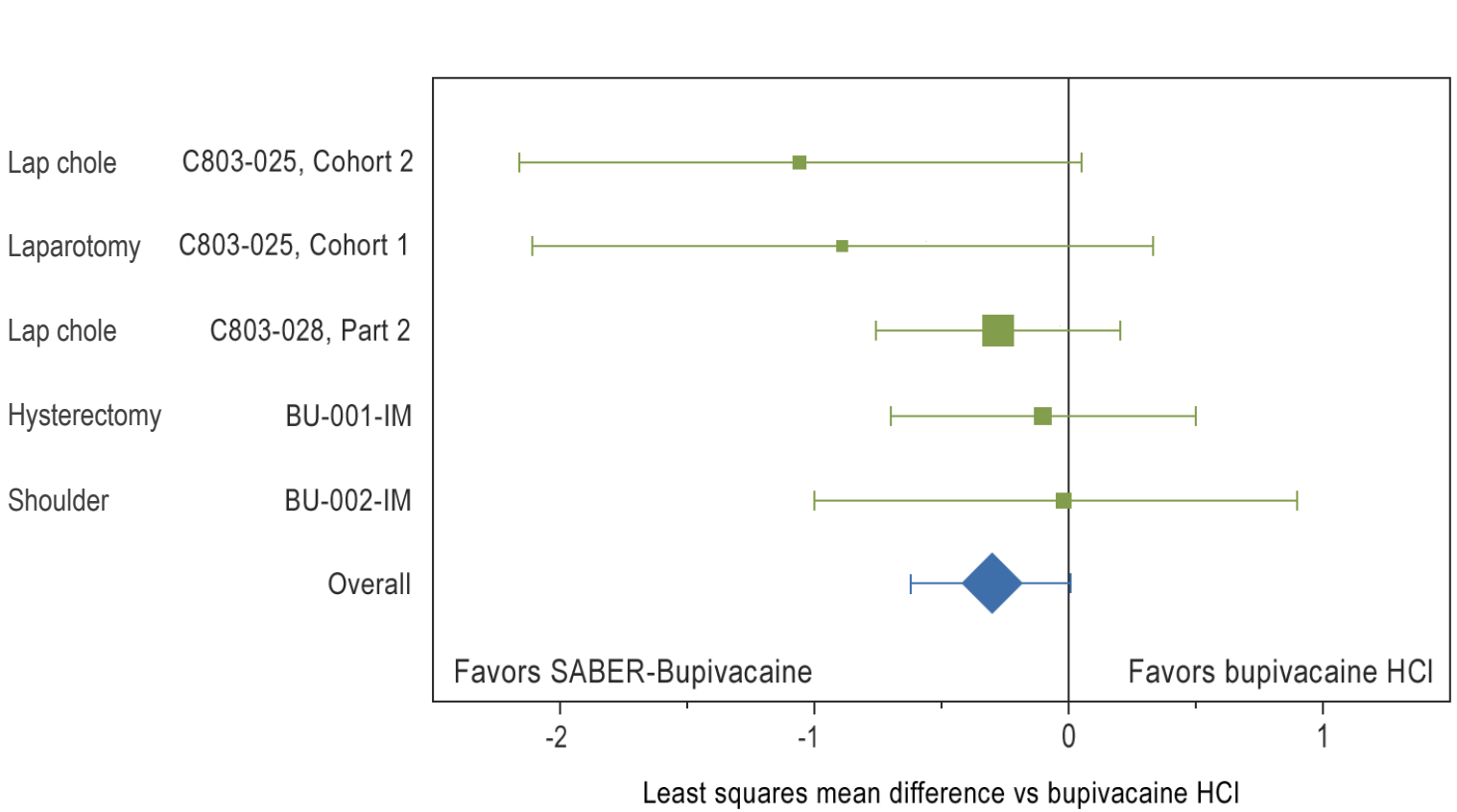
All clinical trials with a bupivacaine HCl arm

Trial	Postoperative pain model	N		
		SABER-Bupivacaine	Bupivacaine HCl	Placebo
BU-001-IM	Open abdominal hysterectomy	61	27	27
BU-002-IM	Subacromial decompression	53	29	25
C803-025, Cohort 1	Laparotomy	26	17	–
C803-025, Cohort 2	Laparoscopic cholecystectomy	30	20	–
C803-028, Part 2	Laparoscopic cholecystectomy	148	148	–

DURECT

Point prevalence favors SABER-Bupivacaine in bupivacaine HCl-controlled trials

Pain on movement 0-72 h post-treatment (Exploratory comparisons; not adequate and well controlled)

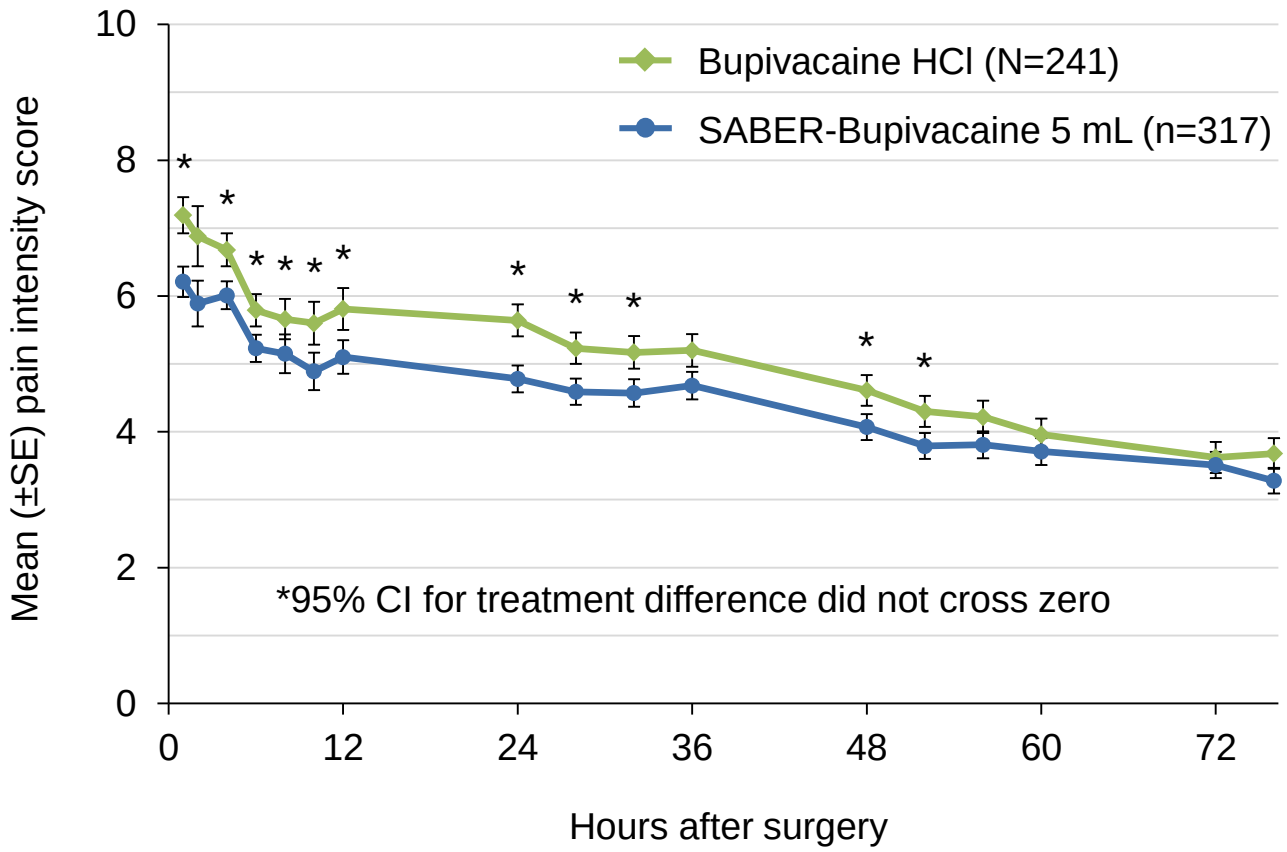


	S-B	Bup HCl	
	N	N	Dose
Lap chole, C803-025, Cohort 2	30	20	150 mg
Laparotomy, C803-025, Cohort 1	26	17	150 mg
Lap chole, C803-028, Part 2	148	148	75 mg
Hysterectomy, BU-001-IM	61	27	100 mg
Shoulder, BU-002-IM	53	29	50 mg
Overall	318	241	

DURECT

Exploratory analysis suggests extended duration of action vs bupivacaine HCl

Pain intensity on movement 0-72 hours post-treatment, pooled bupivacaine HCl-controlled trials



CI confidence interval; SE, standard error.

DURECT

SABER-Bupivacaine

EFFICACY CONCLUSIONS

DURECT

Primary efficacy conclusions

- Clinically relevant 72-hour mean pain reduction demonstrated in 2 adequate and well-controlled pivotal trials vs placebo control
- Meta-analysis of 6 AWC trials showed superiority to placebo
- Clinical meaningfulness of analgesia substantiated by reduced and delayed opioid use relative to placebo
- Reduced the proportion of subjects who experienced severe postoperative pain compared with placebo

DURECT

Exploratory efficacy conclusions

- Meta-analysis of 5 trials with a bupivacaine HCl control arm produced an overall point estimate favoring SABER-Bupivacaine over bupivacaine HCl for mean 72-hour pain reduction
- Data pooled from 5 trials with a bupivacaine HCl control arm indicated that SABER-Bupivacaine may prolong the duration of analgesia relative to bupivacaine HCl

DURECT

SABER-Bupivacaine

SUMMARY OF DATA SUPPORTING SAFETY

DURECT

Safety population

Subjects treated in clinical program

Study Drug	Dose	N
SABER-Bupivacaine	2.5 mL	50
SABER-Bupivacaine	5 mL	735
SABER-Bupivacaine	7.5 mL	4
SABER-Bupivacaine + bupivacaine HCl	5 mL - 7.5 mL + 50 mg - 75 mg	87
Bupivacaine HCl	6.25 mg-150 mg	272
SABER-placebo (vehicle control)	2.5 mL-10 mL	268
Saline placebo	5 mL	47
Total		1,463

DURECT

Methodological complexities addressed in the 2019 Complete Response submission

- Heterogeneous set of clinical trials
  - Wide range of surgical procedures
  - Differing patient populations
  - Differing control comparators
  - Differing terminology used to describe the same adverse event (AE)
  - Adverse events spontaneously reported in some trials but solicited by investigators in others → solicited AEs occur at higher rates than spontaneously-reported AEs

- The problem: confounding between variables can produce misleading or erroneous results

DURECT

Sponsor actions to address methodological complexities

- Safety data from the entire clinical program exhaustively reviewed and, where necessary, re-analyzed to address issues of confounding
- New trial (C803-028, laparoscopic cholecystectomy, N=388) conducted to examine safety issues of specific concern to FDA
  - Results evaluated separately
  - Results also folded into aggregate analysis, since non-vehicle control population (bupivacaine HCl and saline placebo) vastly expanded

SABER-Bupivacaine

ADVERSE EVENTS PROFILE

Source: 2019 Integrated Summary of Safety (ISS)

DURECT

Deaths and serious treatment-emergent AEs

	Trials with bupivacaine HCl control		Trials with placebo control	
	SABER-Bupivacaine (N=321)	Bupivacaine HCl 50-150 mg (N=242)	SABER-Bupivacaine (N=342)	Placebo* (N=216)
Any TEAE	85%	90%	97%	98%
Any serious TEAE	7%	5%	6%	8%
Any severe TEAE	10%	7%	10%	12%
Any TEAE leading to discontinuation	0%	1%	0%	0%
Number of subjects who died	0	0	1	0

*Vehicle control

Narrative summary of death: 82 year-old man with history of Parkinson's disease-related gut dysmotility and megacolon died 40 days after colectomy from unresolved ileus. Judged unrelated to study drug.

DURECT

Methods of collecting AEs varied across trials

Collection method	Control group: Bupivacaine HCl	Control group: Placebo
Solicited	Solicited AEs Bupivacaine HCl-controlled trials	Solicited AEs Placebo-controlled trials
Spontaneously reported	Spontaneously-reported AEs Bupivacaine HCl-controlled trials	Spontaneously-reported AEs Placebo-controlled trials

DURECT

Treatment-emergent adverse events (TEAEs) with incidence ≥5% in either treatment group

Spontaneously-reported in bupivacaine HCl-controlled studies

Preferred Term	SABER-Bupivacaine 5 mL (N=321)	Bupivacaine HCl 50-150 mg (N=242)
Post-procedural contusion	202 (62.9%)	119 (49.2%)
Nausea	85 (26.5%)	79 (32.6%)
Vomiting	38 (11.8%)	27 (11.2%)
Procedural pain	34 (10.6%)	37 (15.3%)
Headache	34 (10.6%)	16 (6.6%)
Constipation	27 (8.4%)	22 (9.1%)
Dizziness	27 (8.4%)	21 (8.7%)
Pyrexia	22 (6.9%)	17 (7.0%)
Diarrhoea	19 (5.9%)	11 (4.5%)
Somnolence	18 (5.6%)	16 (6.6%)
Dysgeusia	17 (5.3%)	10 (4.1%)
Back pain	8 (2.5%)	17 (7.0%)

Bupivacaine HCl-controlled studies: BU-001-IM (hysterectomy); BU-002-IM (shoulder arthroscopy); C803-025, Cohort 1 (laparotomy); C803-025, Cohort 2 (laparoscopic cholecystectomy); C803-028, Part 2 (laparoscopic cholecystectomy).

DURECT

TEAEs with incidence ≥5% in either treatment group

Solicited in bupivacaine HCl-controlled studies

Preferred Term	SABER-Bupivacaine 5 mL (N=321)	Bupivacaine HCl 50-150 mg (N=242)
Somnolence	76 (23.7%)	66 (27.3%)
Constipation	65 (20.2%)	58 (24.0%)
Headache	53 (16.5%)	49 (20.2%)
Nausea	47 (14.6%)	50 (20.7%)
Dizziness	44 (13.7%)	43 (17.8%)
Dysgeusia	31 (9.7%)	24 (9.9%)
Pruritus	31 (9.7%)	27 (11.2%)
Paraesthesia	20 (6.2%)	21 (8.7%)
Vomiting	16 (5.0%)	20 (8.3%)

Bupivacaine HCl-controlled studies: BU-001-IM (hysterectomy); BU-002-IM (shoulder arthroscopy); C803-025, Cohort 1 (laparotomy); C803-025, Cohort 2 (laparoscopic cholecystectomy); C803-028, Part 2 (laparoscopic cholecystectomy).

DURECT

TEAEs with incidence ≥5% in either treatment group

Spontaneously-reported in placebo-controlled studies

Preferred Term	SABER-Bupivacaine 5 mL (N=342)	Vehicle control 2.5-10 mL (N=216)
Nausea	146 (42.7%)	90 (41.7%)
Post-procedural contusion	81 (23.7%)	46 (21.3%)
Headache	51 (14.9%)	40 (18.5%)
Vomiting	50 (14.6%)	25 (11.6%)
Somnolence	43 (12.6%)	39 (18.1%)
Dizziness	43 (12.6%)	30 (13.9%)
Constipation	39 (11.4%)	22 (10.2%)
Pyrexia	27 (7.9%)	19 (8.8%)
Pruritus	23 (6.7%)	16 (7.4%)
Diarrhoea	23 (6.7%)	13 (6.0%)
Incision site erythema	22 (6.4%)	13 (6.0%)
Abdominal distension	19 (5.6%)	14 (6.5%)
Bradycardia	18 (5.3%)	7 (3.2%)
Post procedural discharge	17 (5.0%)	9 (4.2%)
Insomnia	17 (5.0%)	9 (4.2%)
Back pain	14 (4.1%)	15 (6.9%)
Hypokalemia	14 (4.1%)	12 (5.6%)
Dysgeusia	8 (2.3%)	11 (5.1%)

Placebo-controlled studies: CLIN005-0002 (appendectomy); CLIN005-0006 (shoulder arthroscopy); CLIN005-0010 (inguinal hernia repair); CLIN803-006-0006 (inguinal hernia repair); C803-017 (shoulder arthroscopy); c803-025, Cohort 3 (laparoscopically-assisted colectomy).

DURECT

TEAEs with incidence ≥5% in either treatment group

Solicited in placebo-controlled studies

Preferred Term	SABER-Bupivacaine 5 mL (N=342)	Vehicle control 2.5-10 mL (N=216)
Constipation	83 (24.3%)	54 (25.0%)
Somnolence	74 (21.6%)	54 (25.0%)
Pruritus	59 (17.3%)	37 (17.1%)
Dizziness	54 (15.8%)	38 (17.6%)
Nausea	47 (13.7%)	34 (15.7%)
Tinnitus	25 (7.3%)	14 (6.5%)
Dysgeusia	24 (7.0%)	18 (8.3%)
Paraesthesia	19 (5.6%)	14 (6.5%)
Vomiting	16 (4.7%)	9 (4.2%)
Hypoaesthesia	15 (4.4%)	12 (5.6%)

Placebo-controlled studies: CLIN005-0002 (appendectomy); CLIN005-0006 (shoulder arthroscopy); CLIN005-0010 (inguinal hernia repair); CLIN803-006-0006 (inguinal hernia repair); C803-017 (shoulder arthroscopy); c803-025, Cohort 3 (laparoscopically-assisted colectomy).

DURECT

SABER-Bupivacaine

TOPICS OF SPECIAL INTEREST

DURECT

Topic #1: risk of bupivacaine toxicity

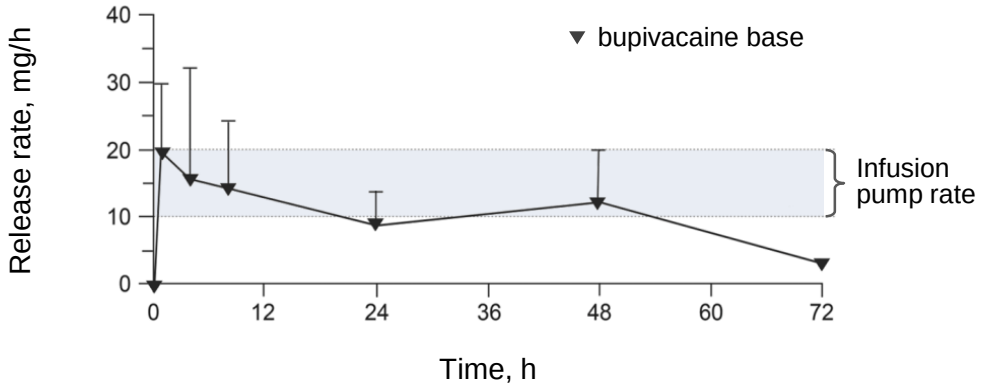
One dose of SABER-Bupivacaine contains 660 mg of bupivacaine base.

Question: What is the risk of local anesthetic systemic toxicity (LAST)?

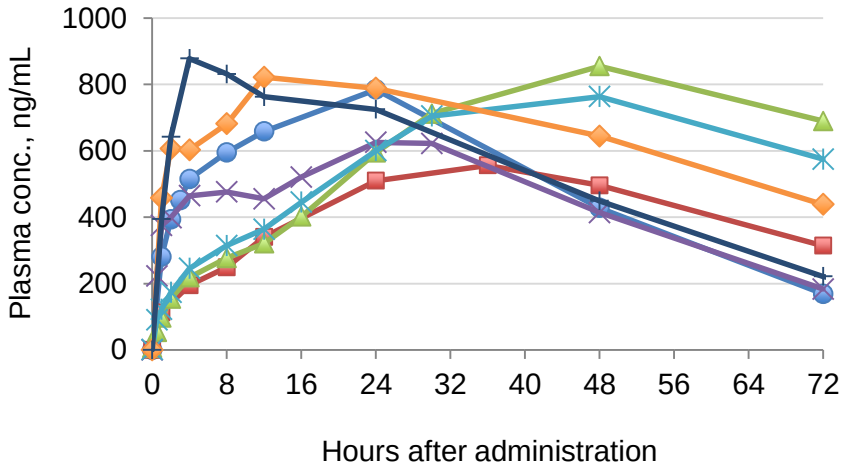
DURECT

Predictable systemic exposure

- Slow, stable release from SAIB depot
- No dose dumping



- Consistent PK profile
  - Mean C_{max} values similar irrespective of procedure
  - T_{max} values vary within proscribed range



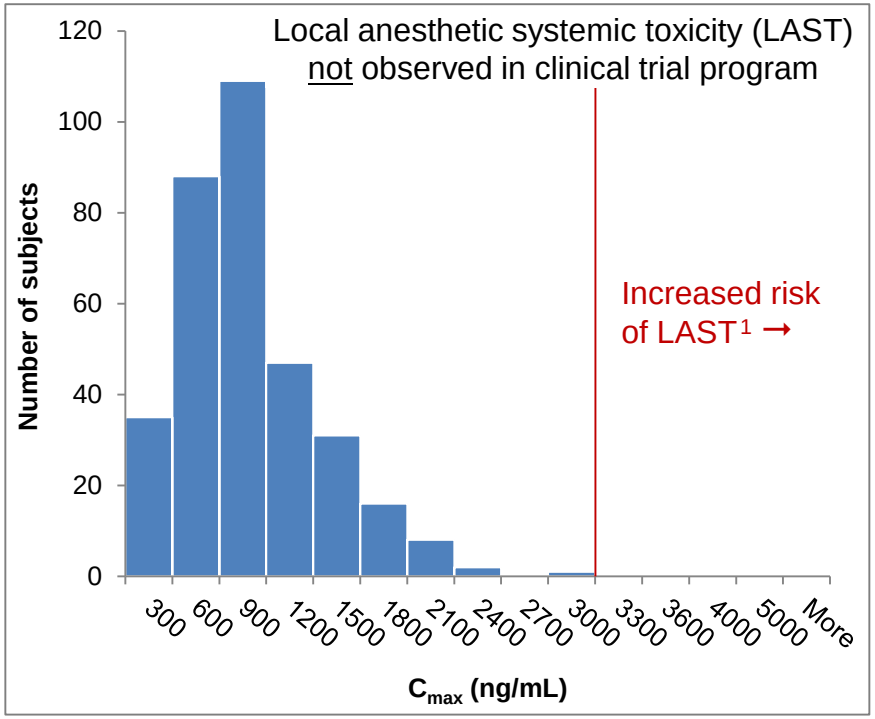
- <u>Very low risk of inadvertent intravascular injection</u>

DURECT

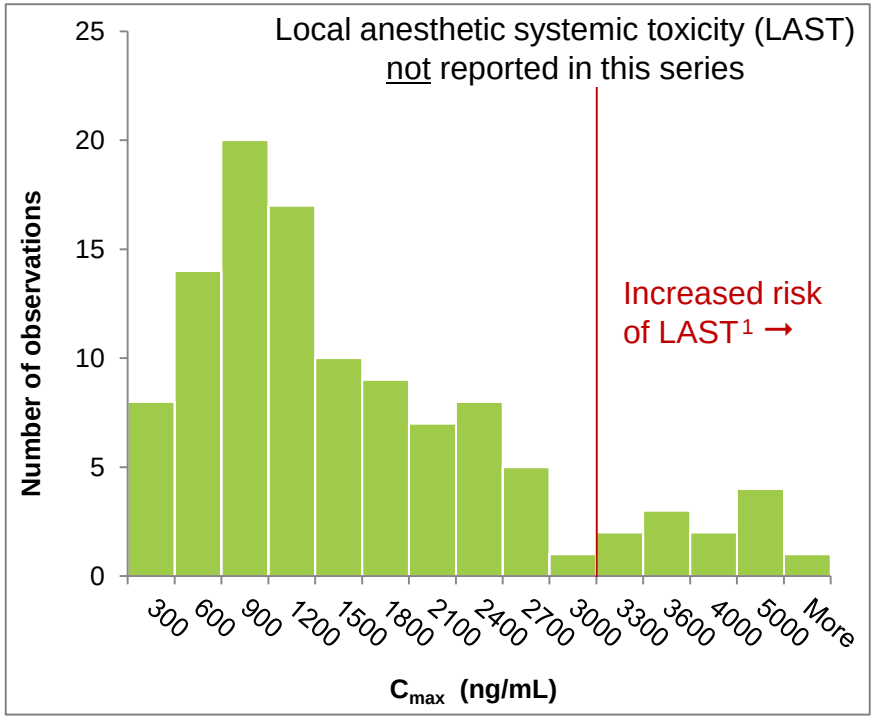
Upper C_{max} range lower than that seen in literature

Distribution of peak plasma concentrations: SABER-Bupivacaine vs immediate-release bupivacaine

SABER-Bupivacaine 5 mL
All PK subjects (N=335)



Bupivacaine HCl 20-300 mg
42 published papers, 1970-2018



PubMed search terms = bupivacaine pharmacokinetics, bupivacaine population pharmacokinetics, bupivacaine plasma levels

[1] Mather, 1971; Munson, 1972; Munson, 1975; Denson, 1984.

DURECT

Evidence of CNS LAST not observed in SABER-Bupivacaine clinical trials

CNS presentations of LAST in case reports (ASRA Practice Advisory, 2017)

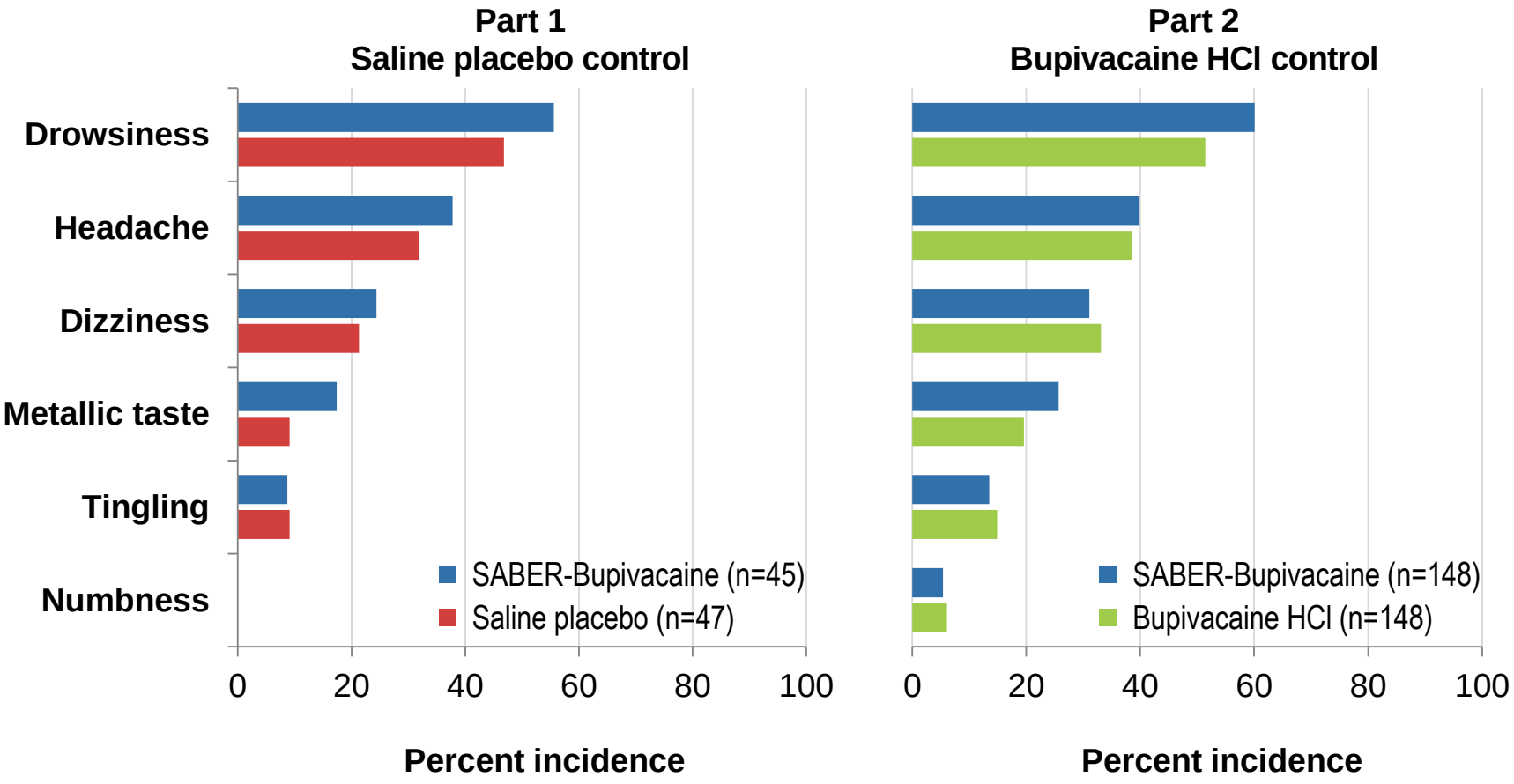
Symptom	Incidence in SABER-Bupivacaine clinical trials
Prodromal (e.g., perioral numbness, tinnitus, metallic taste)	• Equal incidence in SABER-Bupivacaine and placebo groups; not correlated with concentration
Agitation	• 1 subject with agitation in each of placebo and SABER-Bupivacaine groups (plasma conc. 326 ng/mL)
Seizure	• Seizure not reported in any subject
Loss of consciousness	• Loss of consciousness reported in 1 subject following vasovagal event unrelated to LAST

Neal, et al, *Reg Anesth Pain Med*, 2018

DURECT

C803-028 (PERSIST): No meaningful imbalance in 6 CNS symptoms of LAST

Solicited by e-diary in PERSIST (laparoscopic cholecystectomy)

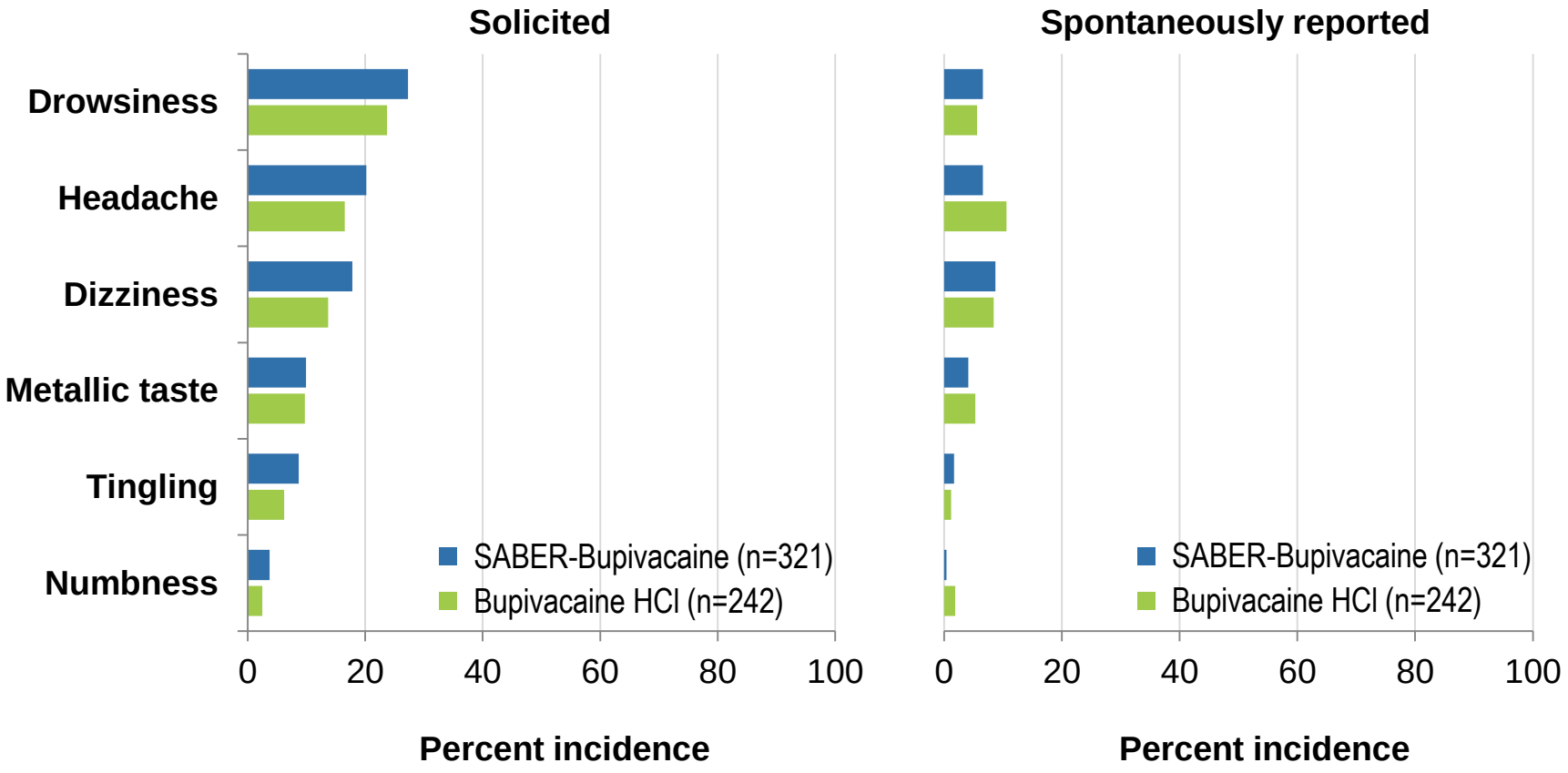


Source: C803-028 CSR, Table 14.3.1.9.1.

DURECT

2019 overall analysis: no clear pattern of differences

AEs reported in studies with bupivacaine HCl arm
SABER-Bupivacaine 5 mL vs bupivacaine HCl 50-150 mg



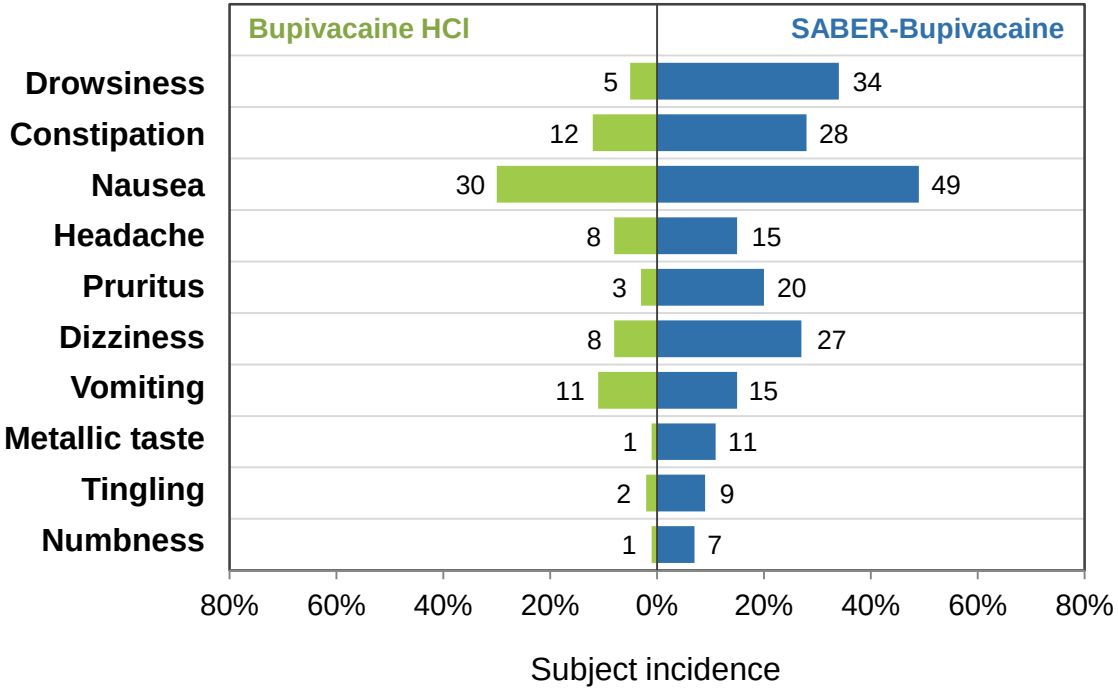
Source: 2019 ISS, Table 43 and Appendix 2, Table 8.2.

DURECT

2013 ISS confounded by mixing of solicited and spontaneously-reported AEs

Combined solicited and spontaneously-reported AEs

Safety population, all SABER-Bupivacaine Studies, 2013 ISS
SABER-Bupivacaine (N=683), bupivacaine HCl (N=124)



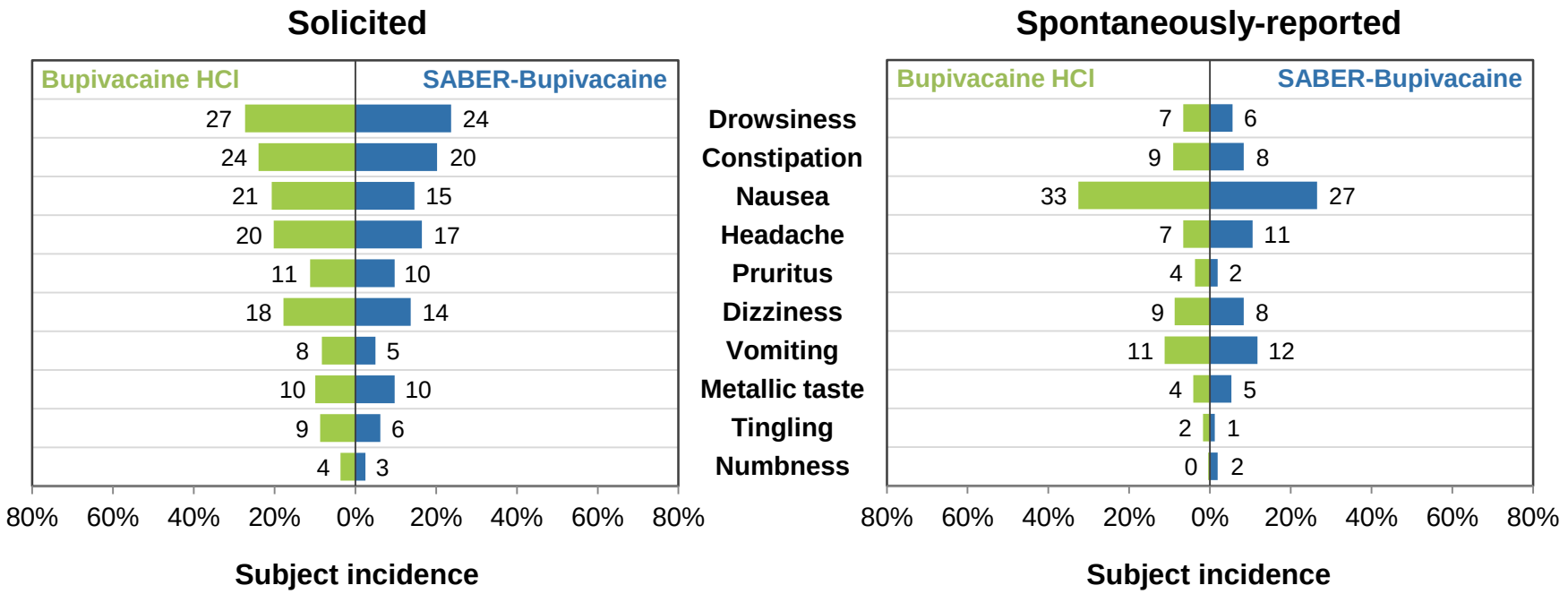
Bupivacaine HCl < SABER-Bupivacaine
Confounded data

Source: 2013 ISS, Table 13.

DURECT

2019 ISS: no clear pattern of differences

AEs reported in bupivacaine HCl-controlled studies
SABER-Bupivacaine 5 mL (N=321) vs bupivacaine HCl 50-150 mg (N=242)



Bupivacaine HCl > SABER-Bupivacaine

Both groups comparable

Source: 2019 ISS, Table 43 and Appendix 2, Table 8.2.

DURECT

Evidence of cardiac LAST not observed in SABER-Bupivacaine clinical trials

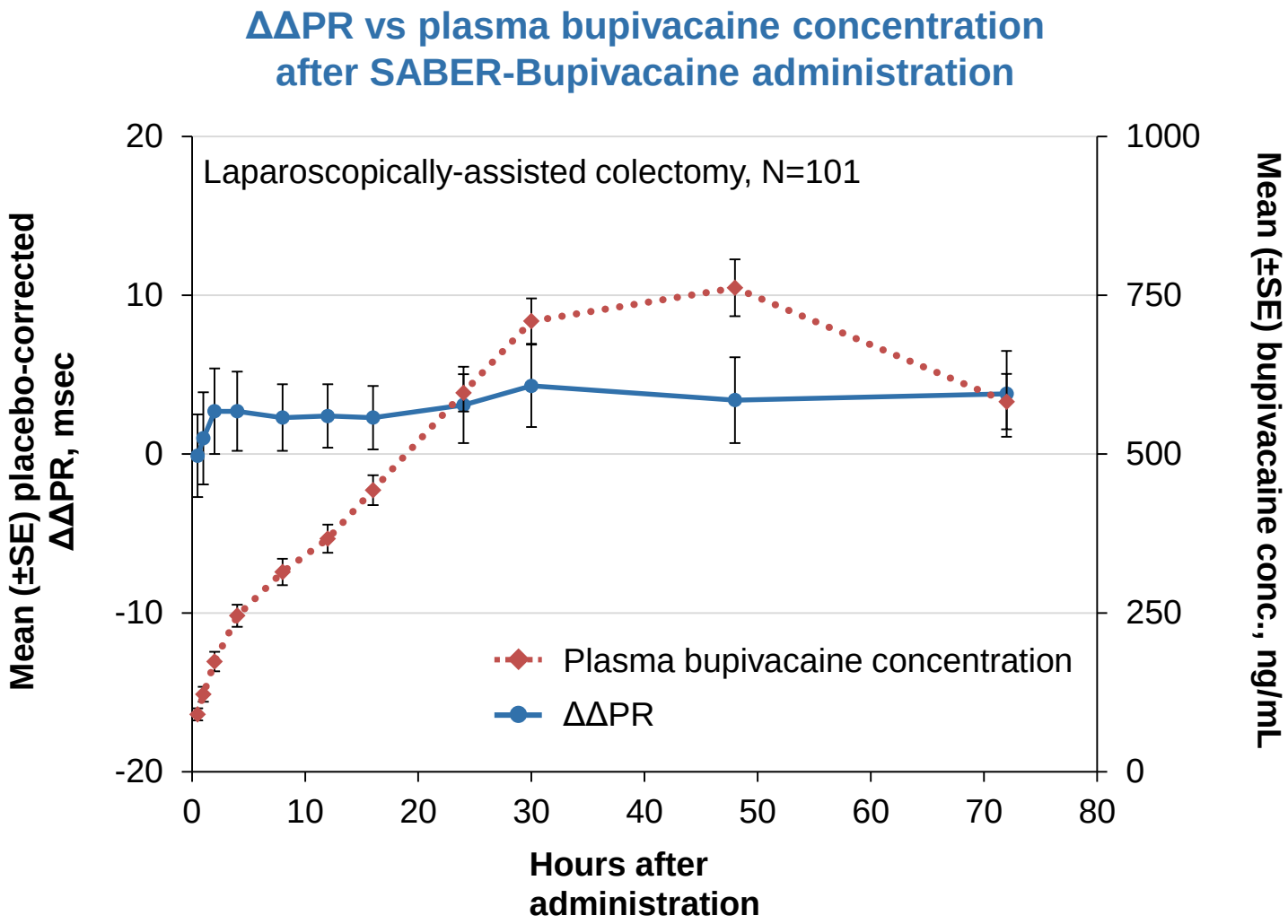
Cardiovascular presentations of LAST in case reports (ASRA Practice Advisory, 2017)

Symptom	Incidence in SABER-Bupivacaine clinical trials
Bradycardia and/or hypotension	• Treatment-related bradycardia or hypotension not seen on ECG or vital signs monitoring
Conduction delays	• No change in HR, PR, QRS, or QTcF seen on serial EGG
Arrhythmia	• Arrhythmias and proarrhythmic events did not vary among groups on 72-hour Holter monitoring
Cardiac arrest	• Cardiac arrest not reported in any subject

Neal, et al, *Reg Anesth Pain Med*, 2018

DURECT

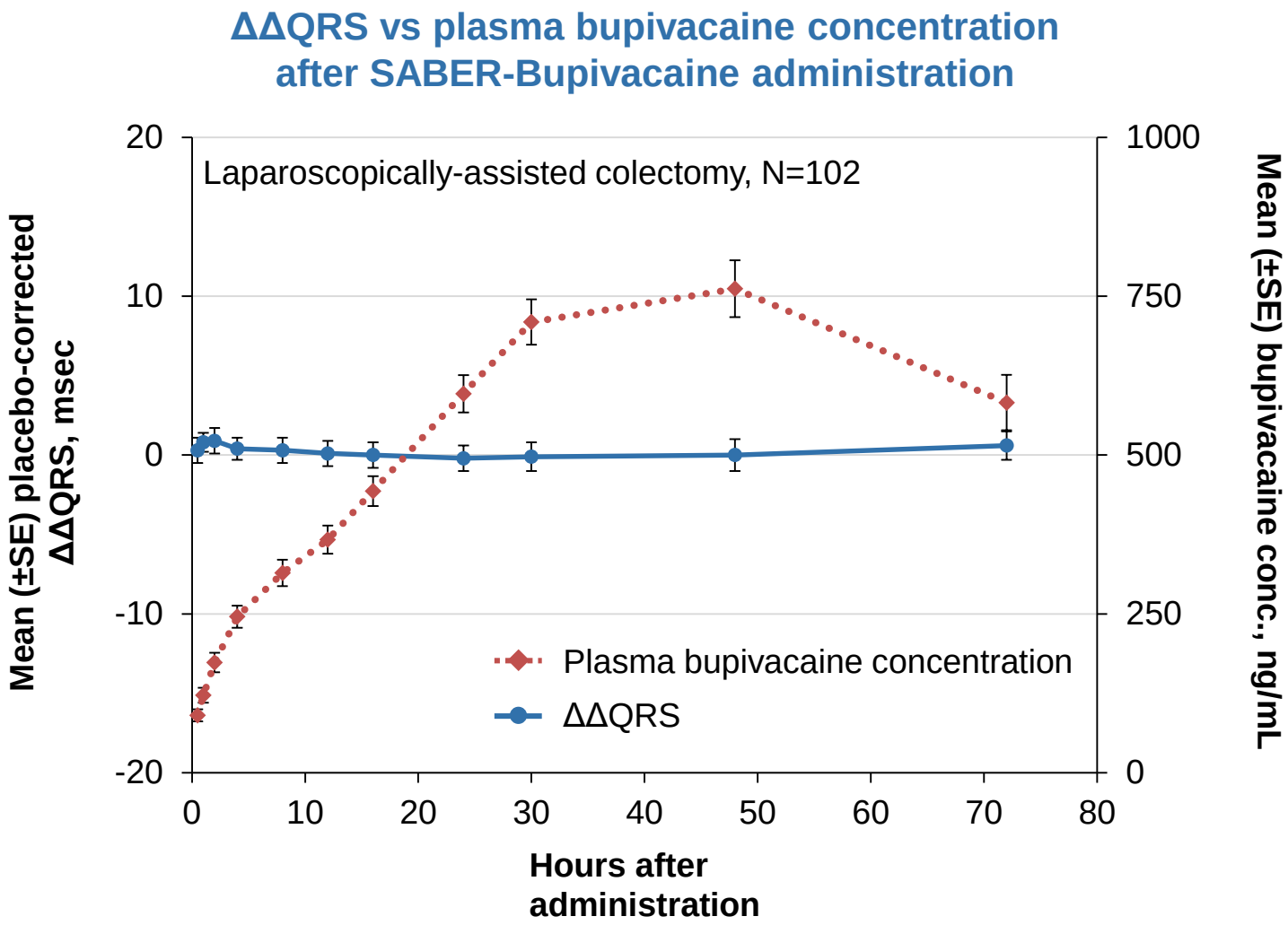
Changes in PR interval not correlated with PK



C803-025, Cohort 3: laparoscopically-assisted colectomy (N=129).

DURECT

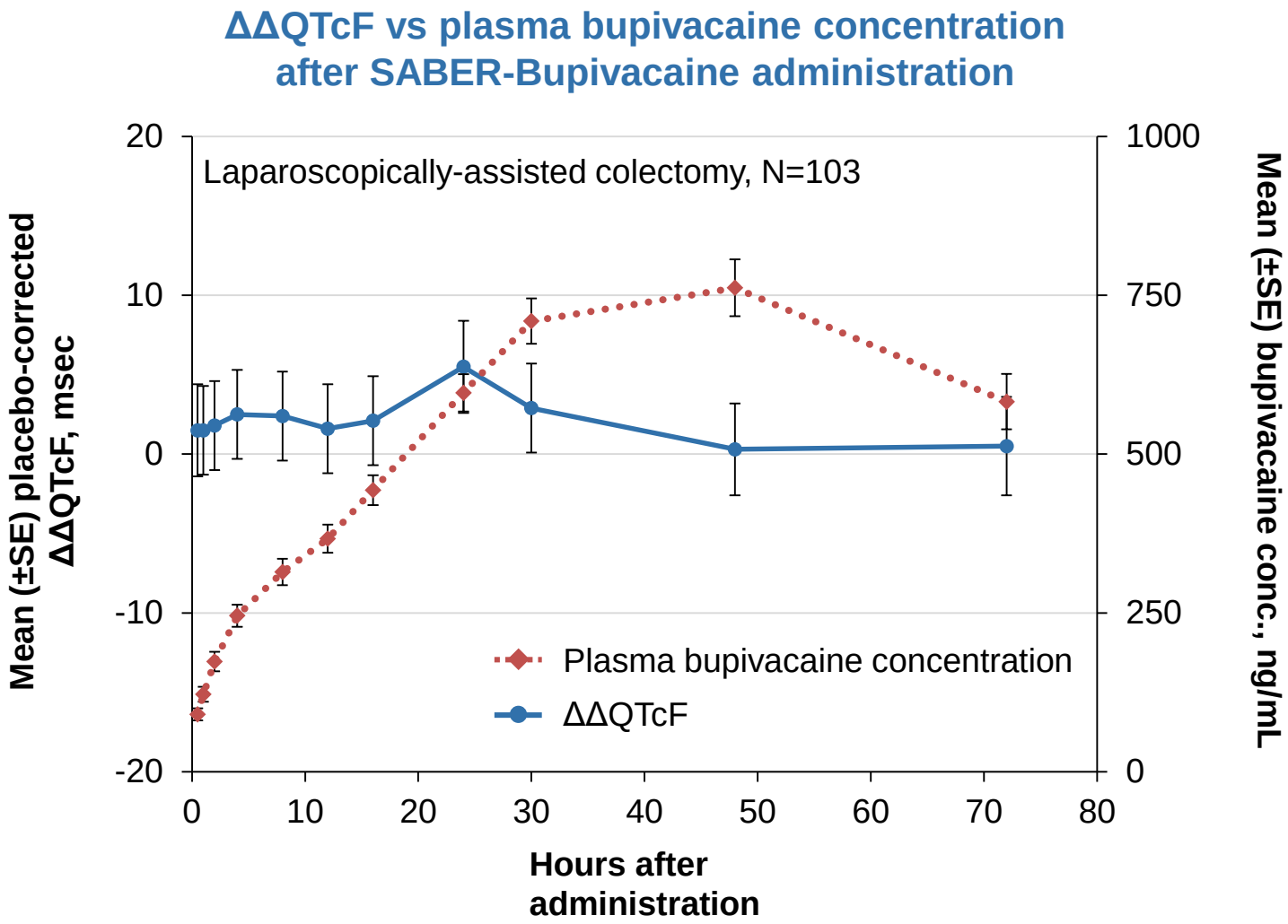
Changes in QRS interval not correlated with PK



C803-025, Cohort 3: laparoscopically-assisted colectomy (N=129).

DURECT

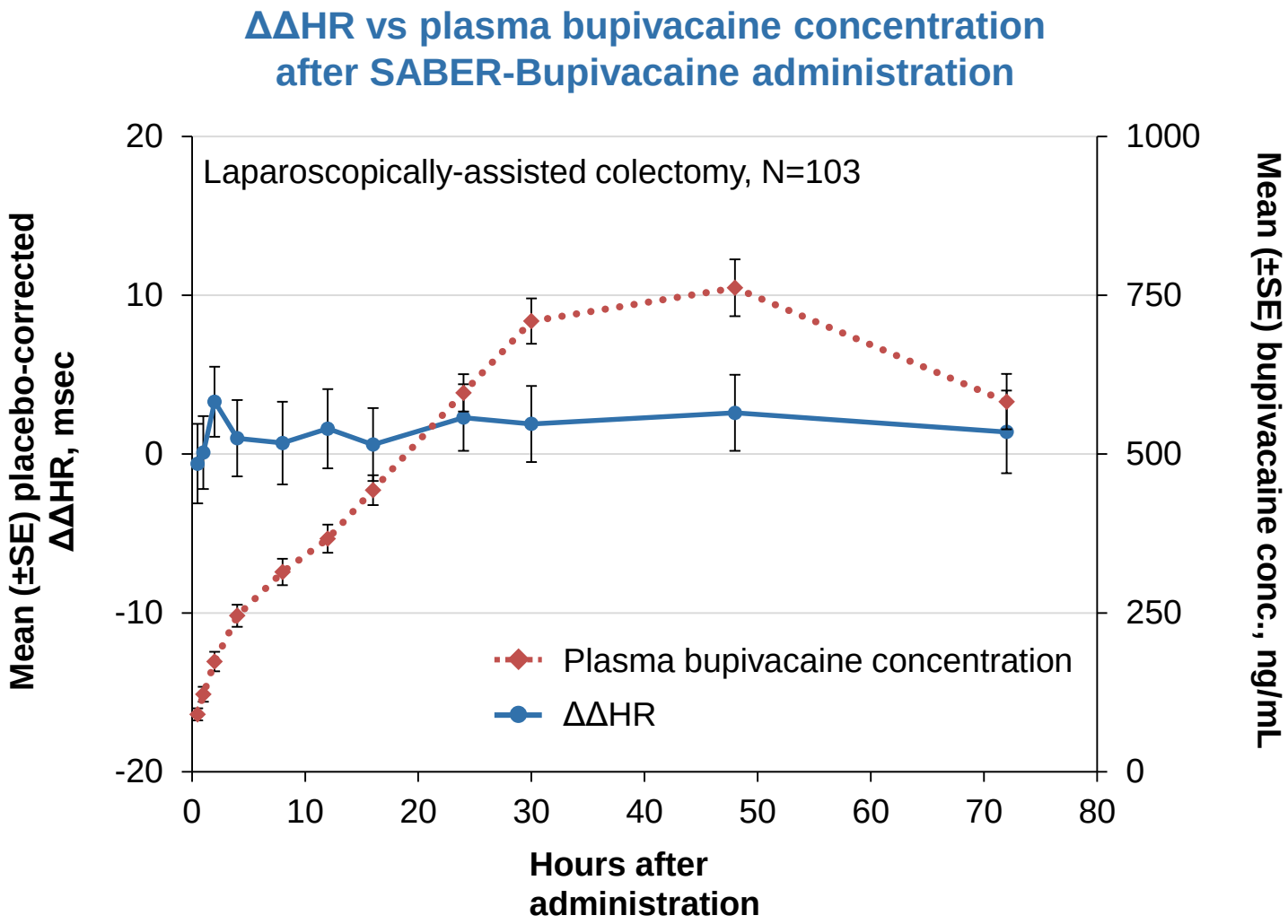
Changes in QT interval not correlated with PK



C803-025, Cohort 3: laparoscopically-assisted colectomy (N=129).

DURECT

Changes in heart rate not correlated with PK



C803-025, Cohort 3: laparoscopically-assisted colectomy (N=129).

DURECT

No signal for cardiac LAST on 72-h Holter monitoring

C803-025, Cohort 3: laparoscopically-assisted colectomy
SABER-Bupivacaine n=123, placebo n=75

- **Heart rate**

  "... [T]here does not appear to be a clear dose response. All changes between placebo and SABER-Bupivacaine appear to be similar."

- **Supraventricular arrhythmias**

  "... [T]he change from baseline on placebo, as compared to SABER-Bupivacaine, revealed no clear evidence of dose related effects."

- **Ventricular arrhythmias and proarrhythmia**

  "... [T]here were no clear differences between the findings in the SABER-Bupivacaine dose group compared to placebo."

DURECT

Conclusion: LAST

Question:	**What is the risk of local anesthetic systemic toxicity (LAST)?**
Conclusion:	**LAST has not been observed in 876 subjects exposed to SABER-Bupivacaine in clinical trials**
Summary of findings:	• Predictable systemic exposure – Mean C_{max} <900 ng/mL for all surgeries – Mean T_{max} 4 h to 48 h depending on surgery – Lower peak concentrations than immediate-release bupivacaine, per published case reports • No evidence of LAST seen in clinical trials – No LAST signal at peak plasma concentration 1500-2850 ng/mL (27 of 337 PK subjects) – No neurologic or cardiac symptoms/signs of LAST • Low risk of inadvertent intravascular injection

DURECT

Topic #2: potential benzyl alcohol effects

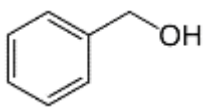
SABER-Bupivacaine contains benzyl alcohol.

Question: Does the benzyl alcohol component of SABER-Bupivacaine cause adverse effects?

DURECT

Benzyl alcohol: background

BENZYL ALCOHOL



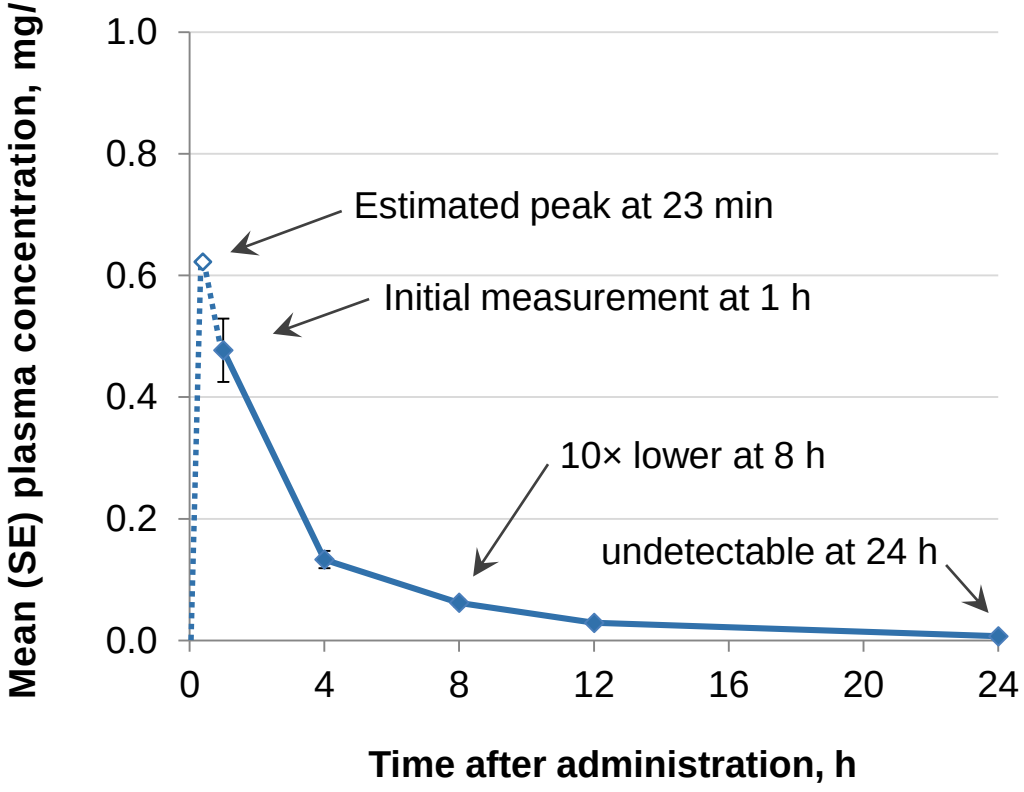
- Solvent reduces viscosity for instillation
- 12- to 24-hour systemic clearance

- *Reminder:* benzyl alcohol is found in numerous approved prescription and OTC drugs (oral, IV, and topical) intended for adults and children (but not neonates, who lack metabolic apparatus)

DURECT

Benzyl alcohol systemic exposure

Pharmacokinetics of benzyl alcohol after instillation of SABER-Bupivacaine into the surgical incision (BU-001-IM, abdominal hysterectomy; PK cohort n=24)



Benzyl alcohol mean C_{max}

- At 1 h: 0.5 mg/L
- Estimated peak: 0.62 mg/L
  (curve fit with 2-compartment model)
- Well within the asymptomatic range based on animal studies[1] and previously approved products containing benzyl alcohol[2]

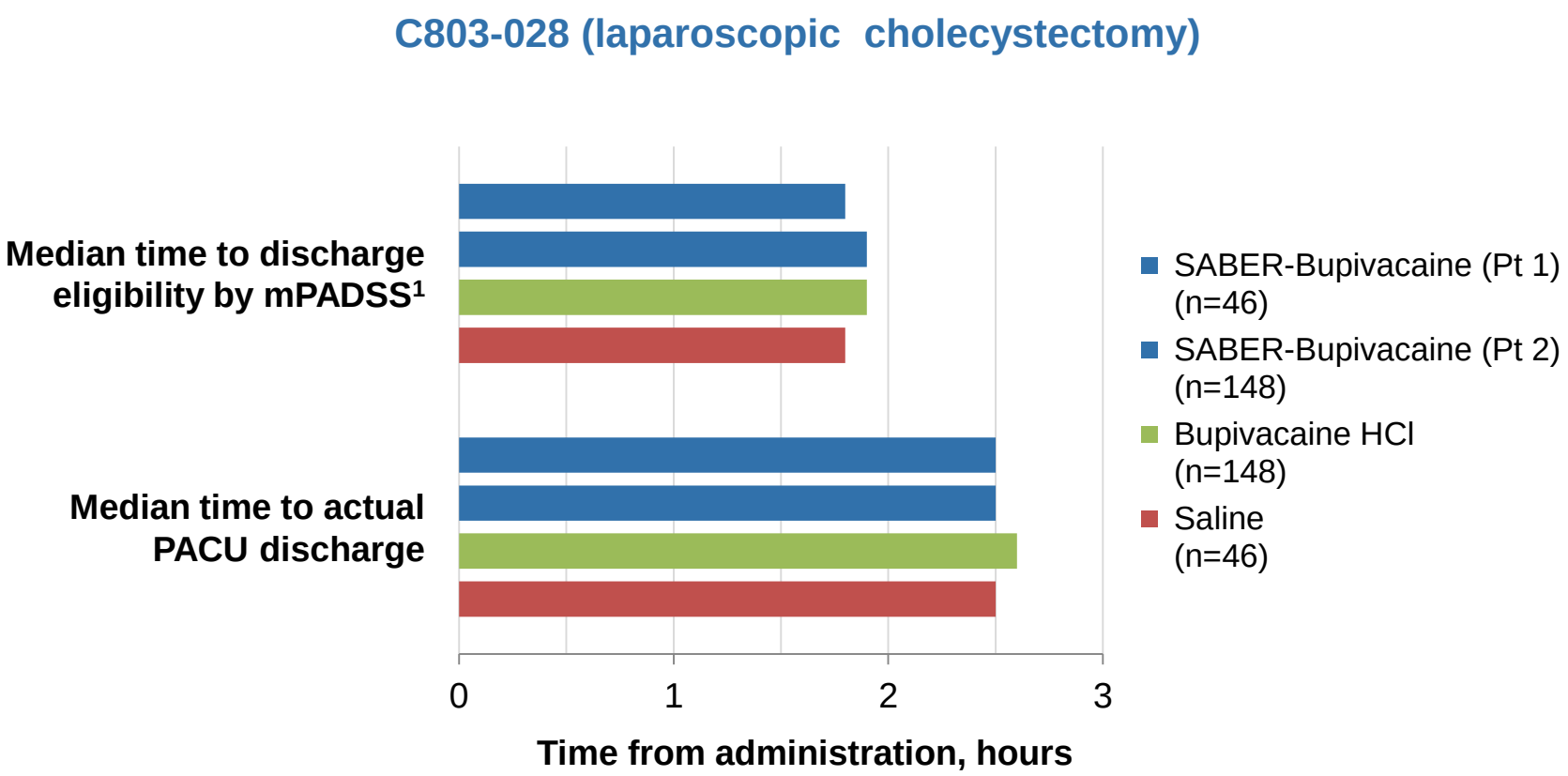
- ULEFSIA® (benzyl alcohol) lotion, for topical use, approved 2009: **1.97 to 2.99 mg/L** measured 0.5 h after application in 6 months to 3 years age group[2]

SABER-Bupivacaine PK: BU-001-IM (open abdominal hysterectomy); n=24 for PK cohort.

[1] EMA, Committee for Human Medicinal Products (CHMP), 2017.
[2] ULEFSIA prescribing information, revised July 2012.

DURECT

PACU recovery times did not vary by treatment group

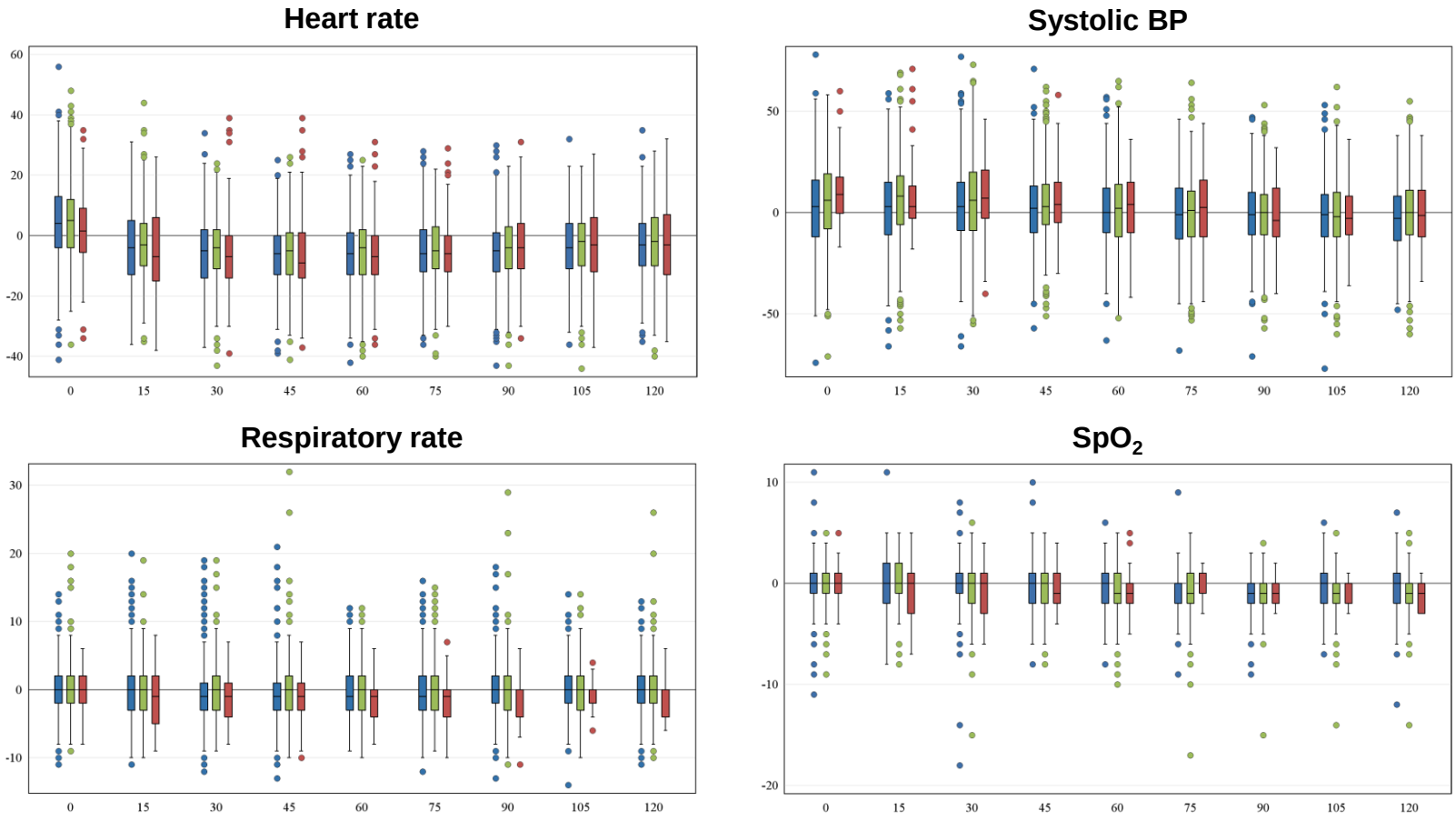


[1] Awad, 2006.

DURECT

Vital signs and SpO_2: change from baseline similar between treatment groups

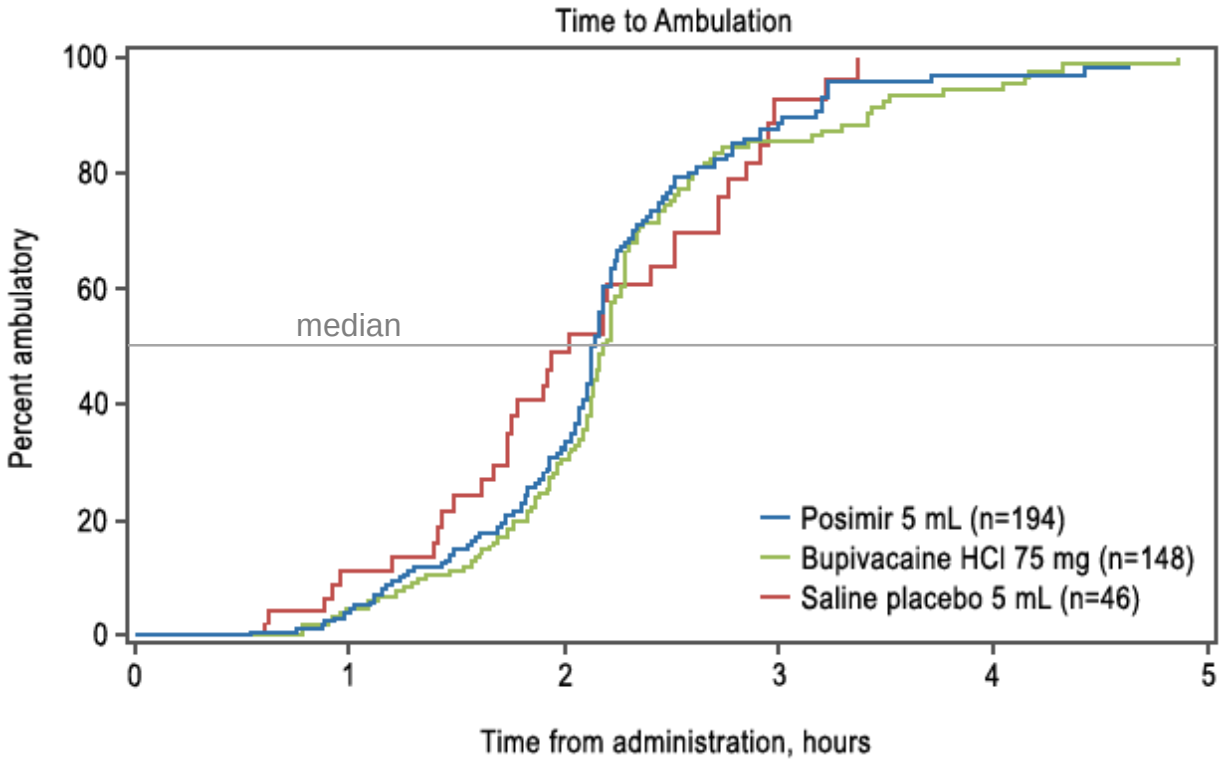
Δ pre/post-anesthesia at 15 min intervals during the first 2 hours after surgery, C803-028 (laparoscopic cholecystectomy)



DURECT

Time to ambulation in PACU: no difference between SABER-Bupivacaine and bupivacaine HCl

Ambulation with steady gait and no dizziness, consistent with pre-op level (mPADSS activity level score 2 of 2)
C803-028 (laparoscopic cholecystectomy)

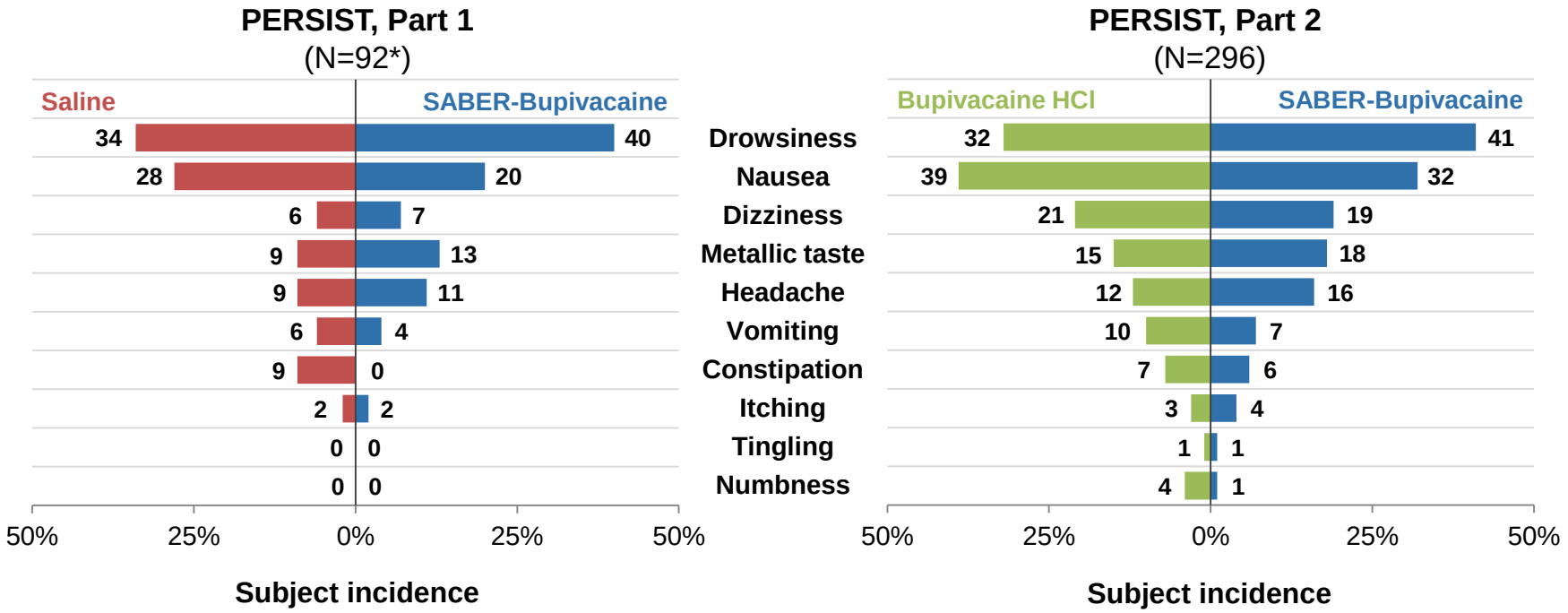


mPADSS assessments recorded every 15 min during period of greatest benzyl alcohol exposure

DURECT

No meaningful difference in 10 solicited symptoms during period of greatest benzyl alcohol exposure

Symptoms solicited by LogPad 6 hours after SABER-Bupivacaine administration



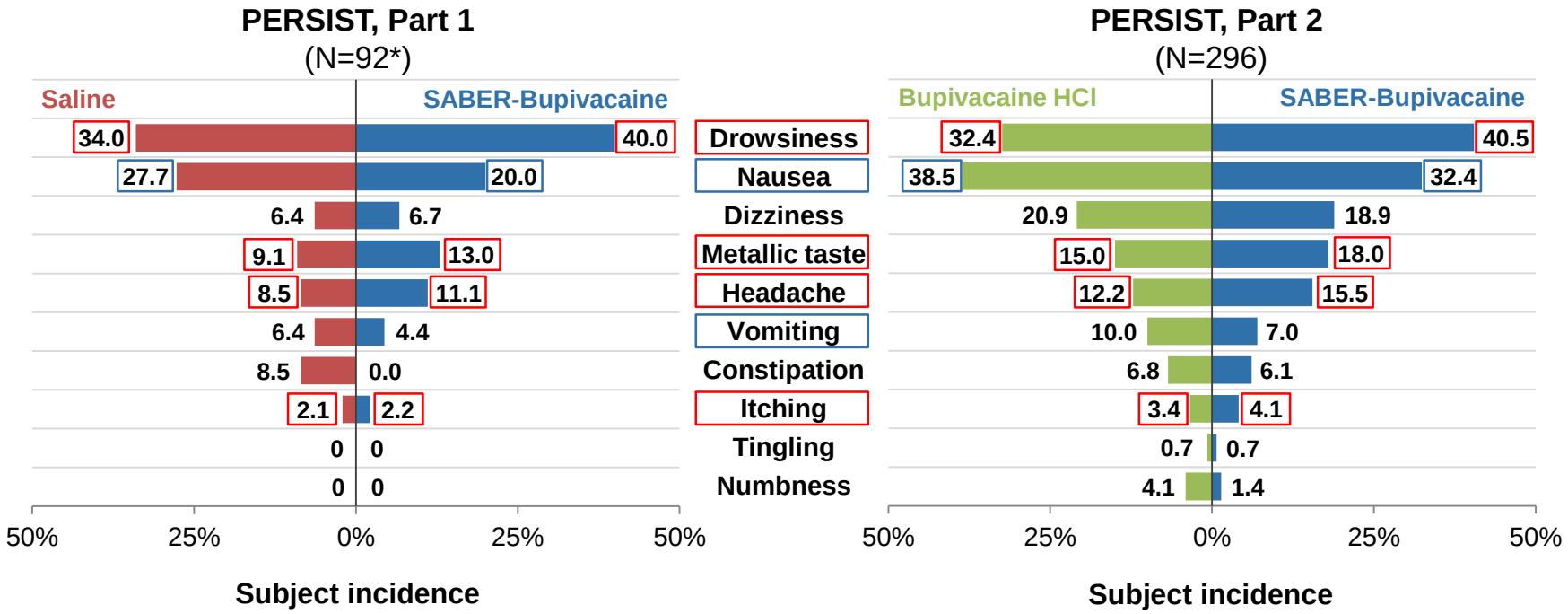
"Have you experienced any of the following symptoms today?"

*N=45 for dysgeusia, paresthesia, and hypoesthesia, which were added to the solicitation list after Part 1 had begun.

DURECT

No meaningful difference in 10 solicited symptoms during period of greatest benzyl alcohol exposure

Symptoms solicited by LogPad 6 hours after SABER-Bupivacaine administration



"Have you experienced any of the following symptoms today?"

*N=45 for dysgeusia, paresthesia, and hypoesthesia, which were added to the solicitation list after Part 1 had begun.

DURECT

Conclusion: potential benzyl alcohol effects

Question:	**Does the benzyl alcohol component of SABER-Bupivacaine cause adverse effects?**
Conclusion:	**Adverse effects have not been detected**
Summary of findings:	• Safe systemic exposure – Mean C_{max} ~0.62 mg/L at 1 hour – Plasma levels down 10-fold at 8 hours; undetectable at 24 hours – Peak concentration well within asymptomatic range • Evaluations in new laparoscopic cholecystectomy study (C803-028) – Time to PACU discharge eligibility and time to actual PACU discharge: no differences – Vital signs and O_2 saturation: no differences during first 2 hours after administration (highest benzyl alcohol levels) – 10 solicited symptoms: no meaningful differences – Drowsiness may have been a feature, not a bug

DURECT

Topic #3: Potential SAIB effects

SABER-Bupivacaine contains sucrose acetate isobutyrate (SAIB).

Question: Does the SAIB component of SABER-Bupivacaine cause adverse effects?

DURECT

Some SAIB effects observed in rats and rabbits

- Rabbit study
  - NZW rabbits given 2 subcutaneous injections each of SABER-Bupivacaine or vehicle control
  - 0.75 mL/kg or 2.4 mL per rabbit, equivalent to 53 mL for 70 kg human
  - Residual SAIB found in 1/6 of injection sites at 39 weeks and 1/3 to 1/2 of injection sites at 52 weeks
- Rat study
  - Foreign body reaction observed following subcutaneous injection
  - Erroneously described in study report as “granulomatous inflammation,” even though consistent with foreign body reactions seen with all approved depot formulations

DURECT

SAIB effects not observed in humans

- Clinical studies
  - MRI of healed surgical incisions 6 months after abdominal hysterectomy showed no evidence of retained SAIB or local tissue abnormalities
  - Shoulder MRIs 6 and 18 months after shoulder arthroscopy (2 separate trials) showed no evidence of retained SAIB or local tissue abnormalities
  - Physical examination of the surgical site 3 and 6 months after inguinal hernia repair and 6 months after abdominal hysterectomy produced no abnormal findings
  - Histologic examination 1-3 days after open abdominal surgery (C803-027) showed no tissue or cellular pathology in the vicinity of the incision

Conclusion: potential SAIB effects

Question:	**Does the SAIB component of SABER-Bupivacaine cause adverse effects?**
Conclusion:	**Adverse effects were not detected in clinical studies**
Summary of findings:	• Rabbit data showed persistence of SAIB, but neither physical exam nor MRI showed any human correlate – Human subjects received 10-fold smaller volume spread over a relatively larger tissue bed in a biologically active space • Rat data showed foreign body reaction at injection site comparable with other approved depot formulations – Associated complications not observed in human subjects – Single-use nature of SABER-Bupivacaine mitigates risk

DURECT

Topic #4: Potential effects on wound healing

SABER-Bupivacaine is placed directly into the surgical incision.

Question: Does SABER-Bupivacaine impair wound healing?

DURECT

Potential wound-healing concerns

- Acute recovery period
  - Dehiscence
  - Hematoma
  - Infection
  - Peri-incisional bruising
- Long-term recovery
  - Quality of healing
- Sponsor actions
  - Reviewed data related to surgical site complications
  - Performed new study in laparoscopic cholecystectomy; included structured serial surgical site examinations
  - Folded all into updated 2019 ISS
  - Reviewed pertinent surgical literature

Clinically-important dehiscence comparable between treatment groups

- 22 subjects with superficial dehiscence
- 2 subjects with fascial dehiscence
- 3 subjects required surgical intervention (all with underlying risk factors)

Subjects with dehiscence reported as AEs: combined bupivacaine HCl- and placebo-controlled trials

	SABER-Bupivacaine 2.5 or 5 mL (N=707)	SABER-placebo 2.5-10 mL (N=268)	Bup HCl 50-150 mg (N=242)	Saline 5 mL (N=47)
Total reported, n (%)	16 (2.3%)	5 (1.9%)	3 (1.2%)	0 (0.0%)
Superficial	14 (2.0%)	5 (1.9%)	3 (1.2%)	0 (0.0%)
Fascial	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Required intervention, n (%)	**2 (0.28%)**	**1 (0.37%)**	**0 (0.00%)**	**0 (0.00%)**
Upper bound of 95% CI	(0.89%)	(1.77%)	(1.24%)	(6.18%)

Source: ISS Table 37 and Table 38.

DURECT

Dehiscence rates low relative to published rates

Published superficial dehiscence rates

Incision type	Reported rate	Reference
Laparotomy	3.2%	Trimbos et al, 1992
Sternotomy	5.8%	Zeitani et al, 2004
C-section	15.1%	Cetin et al, 1997
Abd hysterectomy	17.3%	Mahana et al, 2013
Orthopedic surgery	41.0%	Uckay et al, 2011
Lap cholecystectomy	5.1%-9.1%	Na, 2015
Lap cholecystectomy	20%	Neri, 2008

Published fascial dehiscence rates

Incision type	Reported rate	Reference
Laparotomy	1.2%	Carlson, 1997
Laparotomy	3.4%	Webster et al, 2003
Laparotomy	5.9%	Waqar, 2005
Midline incision	<1% acceptable ≥4 still reported	Israelsson and Millbourn, 2012
Midline laparotomy	3.5%	Lima et al, 2019

SABER-Bupivacaine superficial rates

Linear abdominal incisions	5.8%	SABER-Bupivacaine trials (N=400) [a]
Lap cholecystectomy	1.4%	SABER-Bupivacaine trials (N=438) [b]

SABER-Bupivacaine fascial rates

Linear abdominal incisions	0.5%	SABER-Bupivacaine trials (N=400) [a]

[a] Combined hysterectomy, laparotomy, laparoscopically-assisted colectomy, appendectomy trials

[b] Combined laparoscopic cholecystectomy trials

DURECT

No dehiscence signal upon structured wound exam

- Newly-conducted trial PERSIST (laparoscopic cholecystectomy) with prespecified structured wound-healing exam
  - Most concentrated application of study drug per unit incision length
  - Blinded exam at each post-op visit (days 0, 3, 7, 14, 30, 60)

Subjects with dehiscence: PERSIST (safety population)

	Part 1		Part 2	
	SABER-Bupiv (N=45)	Saline (N=47)	SABER-Bupiv (N=148)	Bup HCl (N=148)
Superficial, n (%)	0 (0%)	0 (0%)	**2 (1.4%)**	**3 (2.0%)**
Fascial, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Required intervention, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

60-day exam limited to 45 subjects in each treatment group.

Source: ISS Table 37 and Table 38.

DURECT

No change in suture strength based on *in vitro* studies

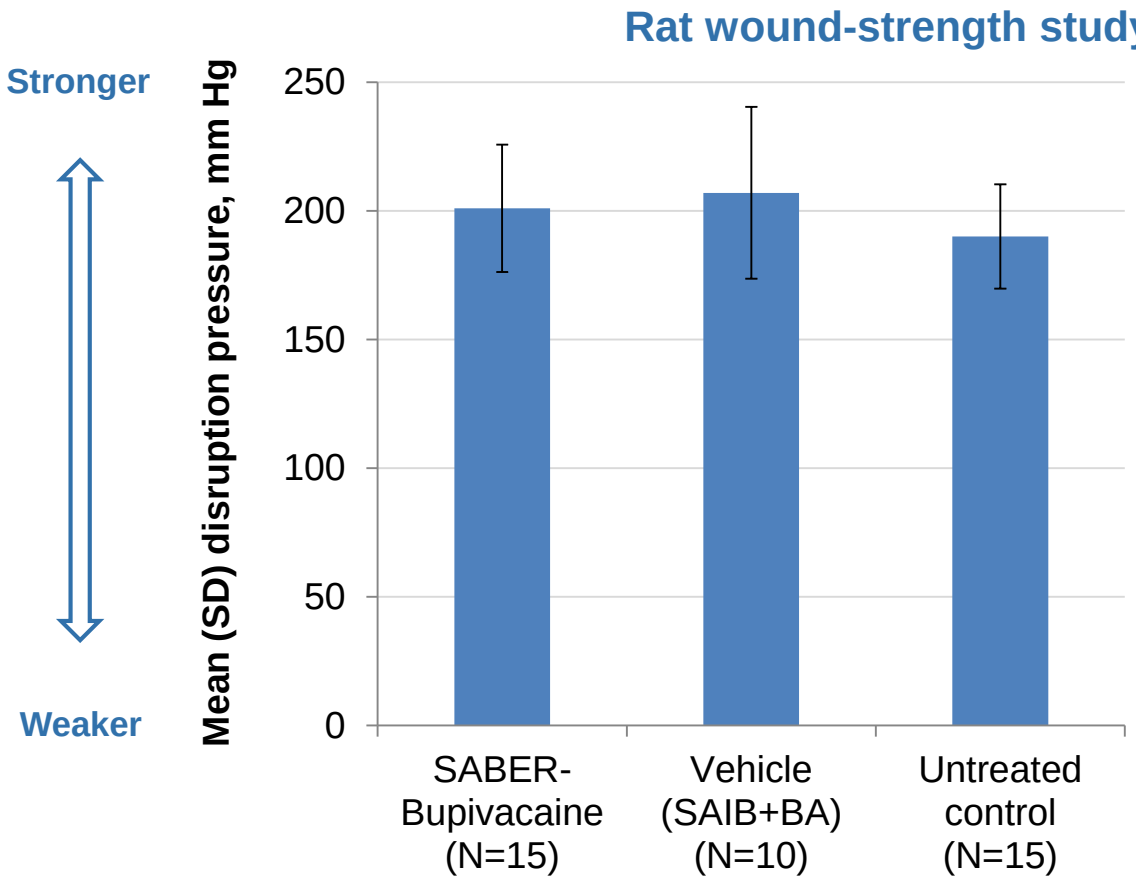
Sutures studied for compatibility with SABER-Bupivacaine

Description of Sutures Manufacturer / Name	Material	Absorbable / Non-absorbable	Monofilament / Multi-strand (color)	Size
Ethicon / SILK	Silk	Non-absorbable	Multi-strand braid (black)	3/0
Ethicon / ETHILON™	Nylon	Non-absorbable	Monofilament (black)	3/0
CP Medical / POLYPRO®	Polypropylene	Non-absorbable	Monofilament (blue)	3/0
CP Medical / PLAIN GUT	Gut, Plain	Absorbable (collagen)	Monofilament	3/0
Ethicon / CHROMIC GUT	Gut, Chromic	Absorbable	Monofilament	6/0
Ethicon / VICRYL™ Plus	Polyglactin 910	Absorbable	Multi-strand braid	3/0
CP Medical / MONO-DOX®	Polydioxanone	Absorbable	Monofilament (violet)	3/0
CP Medical / MONOSWIFT®	Poly (glycolide-co-caprolactone)	Absorbable	Monofilament (violet)	3/0
CP Medical / VISORB®	Polyglycolic Acid	Absorbable	Multi-strand braid (violet)	3/0

Source: 2013 NDA, Section 3.2.P.2.6.2.

DURECT

No effect on wound integrity in animal studies



Methods

- Male Sprague-Dawley rats
- 2.5 cm full-thickness incisions on each dorsolateral flank under general anesthesia
- Wounds instilled with test solution, then closed with skin sutures
- Wound strength evaluated on Day 7
- Dose: 0.125 mL/300 g rat (equiv. to 29 mL/70 kg human)

DURECT

Clinically relevant hematomas not increased

Subjects with hematoma (safety population: all trials, 2019 ISS)

	SABER-Bupivacaine 5 mL (N=663)	SABER-placebo 2.5-10 mL (N=268)	Bup HCl 50-150 mL (N=242)	Saline 5 mL (N=47)
Total reported, n (%)	22 (3.3%)	6 (2.2%)	3 (1.2%)	0 (0.0%)
Required drainage, n (%)	**3 (0.45%)**	3 (1.12%)	**2 (0.83%)**	0 (0.0%)

Published hematoma rates

Surgical procedure	Reported rate	Reference
Laparoscopic cholecystectomy	2.9%	Pan et al, 2013
Laparoscopic cholecystectomy	3.7%-6.0%	Cheng et al, 2013
Laparoscopic inguinal hernia repair	5.1%	Panton and Panton, 1994
Open inguinal hernia repair	5%-10%	Stucky et al, 2015
Open inguinal hernia repair	2.4%	Zhang et al, 2013
Abdominal surgery	4.4%-7.7%	Kakkar et al, 1997
Cesarean section	4.7%-6.9%	Nuthalapaty et al, 2013
Reduction mammoplasty	5%	Carpelan et al, 2014

Source: ISS Tables 28, 29, 30, and 31.

DURECT

Infection rates similar when SABER-Bupivacaine compared with non-SABER controls

Trials with non-SABER controls, 2019 ISS

Adverse event, n (%)	Bupivacaine HCl-controlled trials[a]		Saline placebo-controlled trials[b]	
	SABER-Bupivacaine 5 mL (N=321)	Bupivacaine HCl 50-150 mg (N=242)	SABER-Bupivacaine 5 mL (N=45)	Saline placebo 5 mL (N=47)
Incision-site infection	7 (2.2%)	4 (1.7%)	0 (0.0%)	0 (0.0%)
Incision-site cellulitis	2 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any surgical site infection	**9 (2.8%)**	**4 (1.7%)**	**0 (0.0%)**	**0 (0.0%)**
95% CI for incidence	(1.5%-5.3%)	(0.7%-4.2%)	(0.0%-6.5%)	(0.0%-6.4%)

[a] Laparotomy, abdominal hysterectomy, laparoscopic cholecystectomy, and subacromial decompression.
[b] Laparoscopic cholecystectomy.

- Infections treated with IV (~25%), oral (~75%), and/or topical antibiotics and local wound care; none required return to OR
- 1 post-laparotomy subject in the SABER-Bupivacaine group had an SAE of severe infection, with a complicated course that resolved after treatment with antibiotics and opening of the incision to drain pus.
- All other infections were rated mild or moderate in severity.

DURECT

Infection rates comparable between groups in large- and small-incision surgeries

Trials with bupivacaine HCl control

Adverse event, n (%)	Laparotomy[a]		Laparoscopic cholecystectomy[b]	
	SABER-Bupivacaine 5 mL (N=26)	Bupivacaine HCl 150 mg (N=17)	SABER-Bupivacaine 5 mL (N=178)	Bupivacaine HCl 75 or 150 mg (N=168)
Incision-site infection	4 (15.4%)	2 (11.8%)	3 (1.7%)	2 (1.2%)
Incision-site cellulitis	0 (0.0%)	0 (0.0%)	2 (1.1%)	0 (0.0%)
Any surgical site infection	**4 (15.4%)**	**2 (11.8%)**	**5 (2.8%)**	**2 (1.2%)**
95% CI for incidence	(6.6%-34.8%)	(3.8%-36.4%)	(1.3%-6.4%)	(0.4%-4.2%)

[a] C803-025, Cohort 1 CSR
[b] C803-025, Cohort 2 CSR and C803-028, Part 2 CSR

- Rates similar to those reported in the surgical literature
  - Open abdominal surgery 3.1%-20.9%[1]
  - Laparoscopic cholecystectomy 0.8%-2.8%[2]

[1] Foster, 2018; Xiao, 2015; Clarke-Pearson, 2013; Bennett-Guerrero, 2010; Mäkinea, 2001.
[2] Fahrner, 2014; Keus, 2009; Shea, 1996.

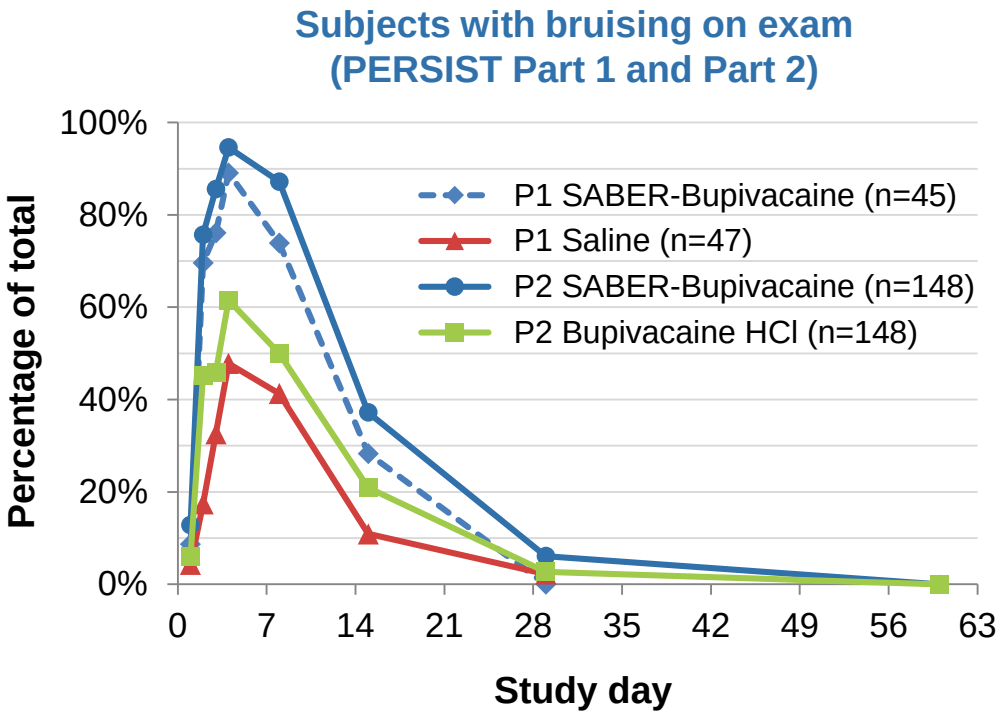
DURECT

SABER-Bupivacaine can produce bruise-like discoloration

- Peri-incisional bruising common after surgery
- “Bruise-like discoloration” is a different phenomenon
  - Surgical trauma plays minimal role
  - Area of discoloration not painful or tender to palpation
  - Histological examination showed red blood cells and fragments without additional pathology
  - Likely a result of bupivacaine-induced vasodilation, followed by lysis of RBCs and transport into subcutaneous tissue by benzyl alcohol
- Seen as red area surrounding incision
  - More pronounced with large, open incisions
  - No swelling, tenderness, or warmth; non-blanching
  - Treatment not required; not mistaken for infection or hematoma
  - Faded over 2-4 weeks with color changes and no sequelae (same as conventional bruise)

Characteristics of bruise-like discoloration

- Appeared 12-24 hours after surgery (too early for infection)
- Peak prevalence on day 4; resolution in nearly all subjects by day 30
- Greater incidence among SABER-Bupivacaine-treated subjects



Sources: ISS Figure 1; ISS Table 25; Appendix 10, Table 1 and Table 3.

DURECT

Bruise-like discoloration not tender to touch

Tenderness to palpation at peak discoloration
C803-027 (laparotomy or laparoscopically-assisted colectomy), N=10

Subject ID	Study Day	Location	Tenderness at discoloration (0-10 scale)	Pain at rest (0-10 scale)
01-001	3	Main surgical incision	0	0
01-002	2	Main surgical incision	0	0
01-003	4	Main surgical incision	2	2
01-004	3	Main surgical incision	0	0
01-005	2	Main surgical incision	0	6
01-006	2	Main surgical incision	0	0
01-007	2	Main surgical incision	0	0-2
	2	Other incision	0	0-2
01-008	2	Main surgical incision	1	0
	2	Other incision	0	0
01-009	2	Main surgical incision	8	8
01-010	2	Main surgical incision	9	8

Source: C803-027 CSR, Listing 19 and Listing 20.

DURECT

Nearly all surgical incisions healed as expected in all studies with long-term follow-up

Study	Follow-up period	Assessment method	SABER-Bupivacaine 5 mL		Bupivacaine HCl 50-150 mg	
			Available subjects	Healing NOT as expected	Available subjects	Healing NOT as expected
C803-028 Laparoscopic cholecystectomy	30 days 60 days	Physical exam	193 of 193 45 of 45	0 (0.0%) 0 (0.0%)	148 of 148 42 of 45	1 (0.7%)* 0 (0.0%)
CLIN803-006-0006 Inguinal hernia repair	3 months 6 months	Physical exam	42 of 47 38 of 47	0 (0.0%) 0 (0.0%)	—	—
BU-001-IM Abdominal hysterectomy	6 months	Physical exam MRI	60 of 60 10 of 60	2 (3.3%)† 0 (0.0%)	27 of 27 6 of 27	3 (11.1%)† 0 (0.0%)
BU-002-IM Subacromial decompression	6 months	Physical exam MRI	52 of 53 51 of 53	0 (0.0%) 1 (2.0%)‡	26 of 29 25 of 29	0 (0.0%) 0 (0.0%)
C803-017e Subacromial decompression	18 months	Physical exam MRI	31 of 40 27 of 40	0 (0.0%) 0 (0.0%)	—	—

* Umbilical incisional hernia
† Moderate to excessive scarring
‡ Mild edema of the deltoid muscle, distant from study drug administration site

DURECT

Conclusion: potential effects on wound healing

Question:	**Does SABER-Bupivacaine impair wound healing?**
Conclusion:	**No safety signal for clinically-important wound-related complications was seen with SABER-Bupivacaine treatment**
Summary of findings:	• Dehiscence: SABER-Bupivacaine (0.28%) vs bupivacaine HCl (0.0%); literature-reported rates: 1.2% to 5.9% • Hematoma: SABER-Bupivacaine (0.45%) vs bupivacaine HCl (0.83%); literature-reported rates: 2.4% to 10% • Infection: SABER-Bupivacaine (2.8%) vs bupivacaine HCl (1.7%); literature-reported rates: 0.8% to 20.9% • Bruise-like discoloration: more frequent with SABER-Bupivacaine treatment, but self-resolving and not clinically concerning • Abnormal healing: rarely observed at long-term follow-up, and no relation to treatment group

DURECT

Topic #5: chondrolysis of the shoulder joint

Bupivacaine HCl infused into the shoulder joint has caused chondrolysis in clinical practice.

Question	Is there a risk that SABER-Bupivacaine could cause chondrolysis or other shoulder-related complications if instilled subacromially?

DURECT

Chondrolysis: clinical context

- Caused by infusion into the intra-articular space at high flow rates of concentrated (0.5%) bupivacaine, for a period of days after surgery[1]
- Symptoms include joint pain, stiffness, and limited range of motion[2]
  - Symptoms develop as early as 2 months after surgery
  - Pain and progressive motion loss by 3 to 5 months
  - Cartilage loss on MRI or x-ray by 5 or 6 months
- Transient bupivacaine exposure (e.g., single intra-articular injections) not sufficient to cause chondrolysis[3]
  - Chondrolysis rarely reported before widespread use of pain pumps for post-surgical infusion into the shoulder joint
  - Subacromial infusion of bupivacaine (as opposed to intra-articular infusion) has not resulted in chondrolysis

SABER-Bupivacaine was administered into the subacromial space under arthroscopic visual guidance to ensure correct placement

[1] Matsen, 2013; Wiater, 2011; Anderson, 2010; Rapley, 2009; Hansen, 2007
[2] Provencher, 2011; Anderson, 2010; Hansen, 2007
[3] Busfield, 2014; Matsen, 2013; Anderson, 2010

DURECT

SABER-Bupivacaine administered subacromially in 3 arthroscopic shoulder surgery trials without complication

- BU-002-IM
  - 52 SABER-Bupivacaine subjects and 26 bupivacaine HCl subjects with baseline (pre-surgical) and 6-month shoulder MRIs
  - Blinded central reading of MRIs indicated no cartilage loss in the shoulder joint and no healing abnormalities in the surrounding tissues
  - Functional shoulder examinations were not consistent with chondrolysis
- C803-017 / C803-017e
  - 27 SABER-Bupivacaine subjects and 14 placebo subjects with 18-month shoulder MRIs; nearly all with pre-surgical MRIs for comparison
  - Blinded central reading of MRIs revealed "*no unexpected injuries or findings" and "no cartilage or bone lesions... that would be of concern"*
  - 3 subjects regarded by FDA in 2014 as possible cases of chondrolysis exhibited no relevant pathology
- CLIN005-0006
  - 62 SABER-Bupivacaine subjects and 44 placebo subjects without MRIs
  - 7-year phone survey and 10-year written survey of principal investigators indicated no cases of chondrolysis had been reported

DURECT

Conclusion: chondrolysis

Question:	**Is there a risk that SABER-Bupivacaine could cause chondrolysis or other shoulder-related complications?**
Conclusion:	**Clinical data suggest this concern is unwarranted**
Summary of findings:	• BU-002-IM: no evidence of chondrolysis or unexpected tissue abnormalities based on 6-month MRIs and functional shoulder exams (52 treated subjects) • C803-017: no evidence of chondrolysis or unexpected tissue abnormalities based on 18-month MRIs (27 treated subjects) • CLIN005-0006: no investigator reports of chondrolysis 7 and 10 years post-surgery (62 treated subjects)

DURECT

SABER-Bupivacaine

SAFETY SUMMARY

DURECT

Safety summary

Item	Findings
Adverse event profile	• Unremarkable, with exception of increased rate of bruise-like discoloration
Risk of LAST	• Clinical studies indicate stable release rate, predictable pharmacokinetics, reassuring C_{max} values, and no evidence of local anesthetic toxicity
Benzyl alcohol effects	• Benzyl alcohol rapidly cleared; clinical effects not observed
SAIB effects	• None of concern; animal study results not replicated in humans
Wound-related complications	• Clinically important differences in acute wound-related complications not observed (bruising excepted) • Healing “as expected” at long-term follow-up, with no differences between treatment groups
Chondrolysis	• No evidence of chondrolysis or other tissue pathology at 6 and 18 months after shoulder arthroscopy

DURECT

SABER-Bupivacaine

CLINICAL RELEVANCE OF EFFICACY AND SAFETY FINDINGS

DURECT

Clinical relevance of efficacy outcomes

- Clinically meaningful -1.14 and -1.27 mean 72-h pain reduction vs placebo seen in 2 adequate and well-controlled trials in soft-tissue and orthopedic surgery, respectively
- Meta-analysis of 6 adequate and well-controlled trials showed positive pain reduction compared with placebo control
- Reduced opioid use provided evidence that the observed analgesic effect was clinically meaningful
- Pain reduction was sustained for 72 hours after administration and affected the entire range of pain intensities from mild to severe
- Comparison with immediate-release bupivacaine was not a goal of the development program; however, exploratory analysis suggested the possibility of improved initial pain control and prolonged duration of analgesia relative to bupivacaine HCl

DURECT

Clinical relevance of safety outcomes

- Safety data developed from more than 800 adult subjects dosed with SABER-Bupivacaine
- Safety profile comparable to that of immediate-release bupivacaine, in widespread clinical use for nearly 50 years
- Possibility of bupivacaine toxicity and adverse reactions to inactive components of formulation carefully investigated
- Potential for adverse effects on wound healing, both acute and long term, thoroughly explored
- Bupivacaine-associated chondrolysis not observed, nor evidence of tissue abnormalities on MRI
- Safety dataset includes a range of surgical procedures and a heterogeneous patient population
- Needle-free instillation into the surgical incision reduces risk to patients and members of the surgical team

DURECT

Clinical relevance of patient populations

- Representative surgical populations studied
- No important safety or efficacy differences between subgroups
  - Age range: 18-87 years
    - <45 years: 30%
    - >65 years: 13%
  - Sex distribution
    - Female: 57%
    - Male 43%
  - Race distribution
    - Nonwhite subjects underrepresented, but no evidence of differential effect
  - BMI range: 14.1-61.2 mg/kg^2
    - 30% ≤25 mg/kg^2
    - 9% >35 mg/kg^2

DURECT

Clinical relevance of surgical procedures

- Representative surgical pain models studied (6 AWC trials)
  - 4 soft-tissue procedures, 2 orthopedic procedures
  - 2 open procedures, 3 endoscopic procedures, and 1 combined procedure
  - 2 major inpatient procedures, 4 outpatient procedures
  - Range of cumulative incision lengths from 2 to 40 cm (mean 10.4 cm)
- Efficacy demonstrated in both soft-tissue and bony models
- Safety profile consistent across procedures

DURECT

SABER-Bupivacaine conclusion

Efficacy	• More efficacious than placebo: 2 pivotal trials • Opioid use reduced: 2 pivotal trials • More efficacious (12-24 hours) and possibly longer-lasting than bupivacaine HCl: meta-analysis
Surgeries	• SABER-Bupivacaine safe & effective in a variety of surgeries
Adverse events	• Unremarkable except bruise-like discoloration
LAST	• No appreciable risk
Benzyl alcohol	• No appreciable risk
Wound issues	• No clinical harm due to SAIB deposition • No excess surgical site complications, normal wound healing • Bruise-like discoloration; no clinical consequences
Chondrolysis	• No appreciable risk
Risk-benefit	• Analgesic effect vs. placebo (pivotal and meta-analysis) • Analgesic effect vs. bupivacaine HCl (exploratory) • Decreased opioid use (pivotal and meta-analysis) • Benefits outweigh clinically inconsequential bruise-like discoloration

DURECT

SABER-Bupivacaine

GENERAL SURGEON'S PERSPECTIVE

Asok Doraiswamy, MD, FACS
Methodist Hospital of Southern California
Huntington Memorial Hospital
Pasadena, CA

DURECT

General surgeon’s perspective

- Principal investigator in 2 laparoscopic cholecystectomy trials
- 43 patients administered SABER-Bupivacaine
- Needle-free administration technique straightforward and safe
- Positive clinical experience
- Bruising not a concern; readily distinguishable from more concerning complications
- Outpatient surgery = 40% of practice; potential for sending patients home with smaller opioid prescriptions extremely important

SABER-Bupivacaine

ANESTHESIOLOGIST'S PERSPECTIVE

Harold Minkowitz, MD
Memorial Hermann Katy Hospital
Memorial Hermann Memorial City Medical Center
Houston, TX

DURECT

Anesthesiologist's perspective

- Pain management experts
- Aims
  - Safely manage pain
  - Reduce reliance on systemic opioids
  - Embrace multimodal analgesia and Enhanced Recovery After Surgery
- Principal investigator, and reviewed clinical trial data in detail
- SABER-Bupivacaine fits current guidelines for postoperative pain management
  - Sustained local anesthetic release for baseline analgesia
  - Component of non-opioid treatment plan
  - Low-risk safety profile
- Important addition to analgesic armamentarium

SABER®-Bupivacaine

Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee

16 January 2020

DURECT

SABER-Bupivacaine + Bupivacaine HCl Group: composition

Trial	SABER-Bupivacaine Dose (mL)	Bupivacaine HCl Dose (mg)	Number of Subjects
CLIN004-0001 hernia	5.0 mL	50 mg	5
	7.5 mL	50 mg	45
CLIN004-0009 hernia	5.0 mL	75 mg	6
	7.5 mL	75 mg	26
CLIN005-0006 shoulder	7.5 mL	0	3
CLIN005-0010 hernia	7.5 mL	0	1
CLIN005-0008 healthy volunteers	5.0 mL	0	5
TOTAL			91

NOTE: The CLIN005-0008 trial was a 3 way crossover (IV bupivacaine HCL, Bupivacaine TTS, and SC SABER-Bupivacaine, 5mL)

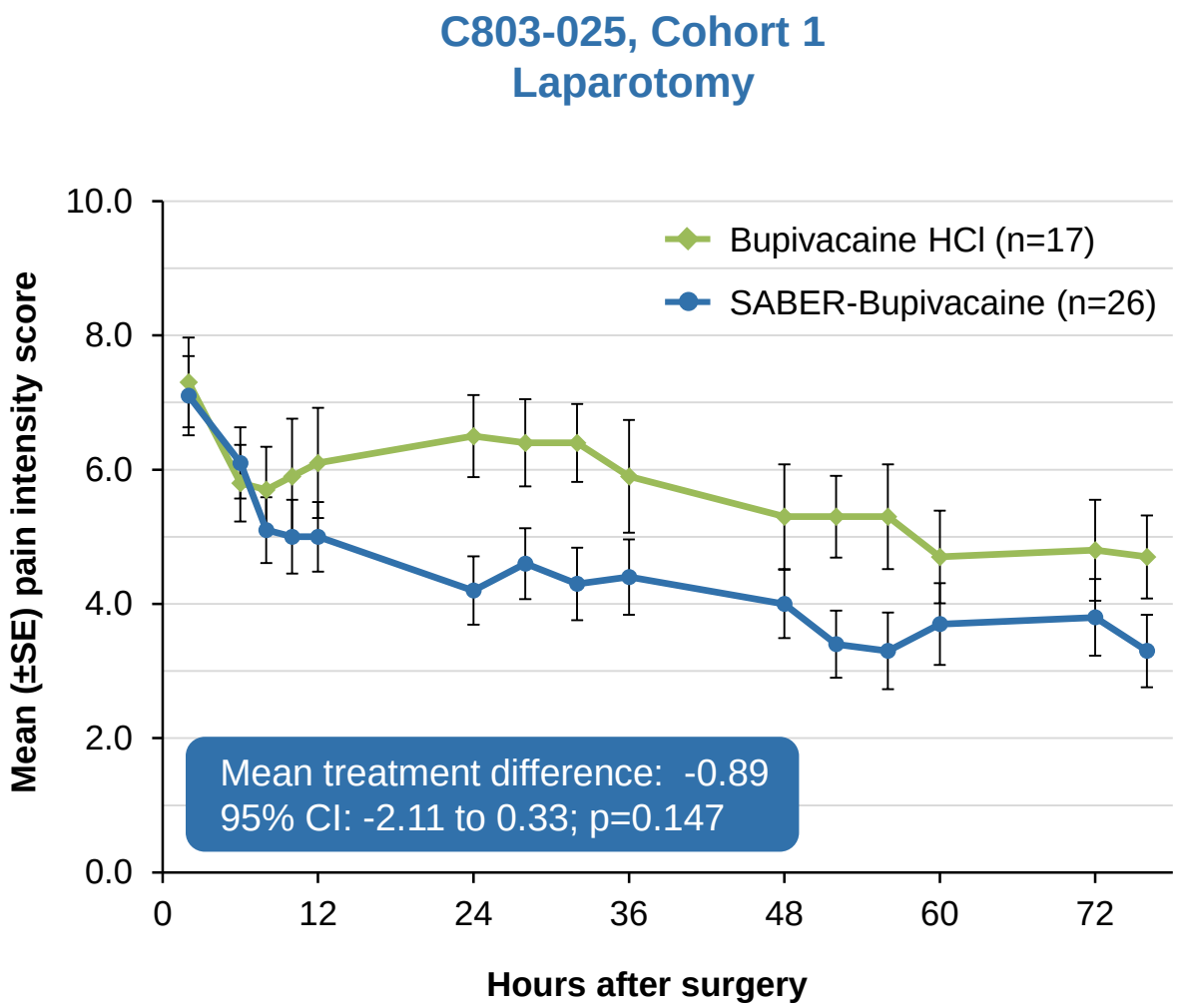
DURECT

Trials with subjects >65 and >75 years old

Trial	Number of Subjects > 65	Number of Subjects > 75
BU-001-IM (hysterectomy)	1	0
BU-002-IM (shoulder)	7	0
C803-017 (shoulder)	2	0
C803-025 (laparotomy, laparoscopic cholecystectomy, and laparoscopically-assisted colectomy)	81	21
C803-027 (laparoscopically-assisted colectomy)	3	3
C803-028 (laparoscopic cholecystectomy)	34	2
CLIN004-0009 (hernia)	4	0
CLIN005-0006 (shoulder)	16	2
CLIN005-0010 (hernia)	15	3
CLIN-803-006-0006 (hernia	4	1
Total	**167**	**32**

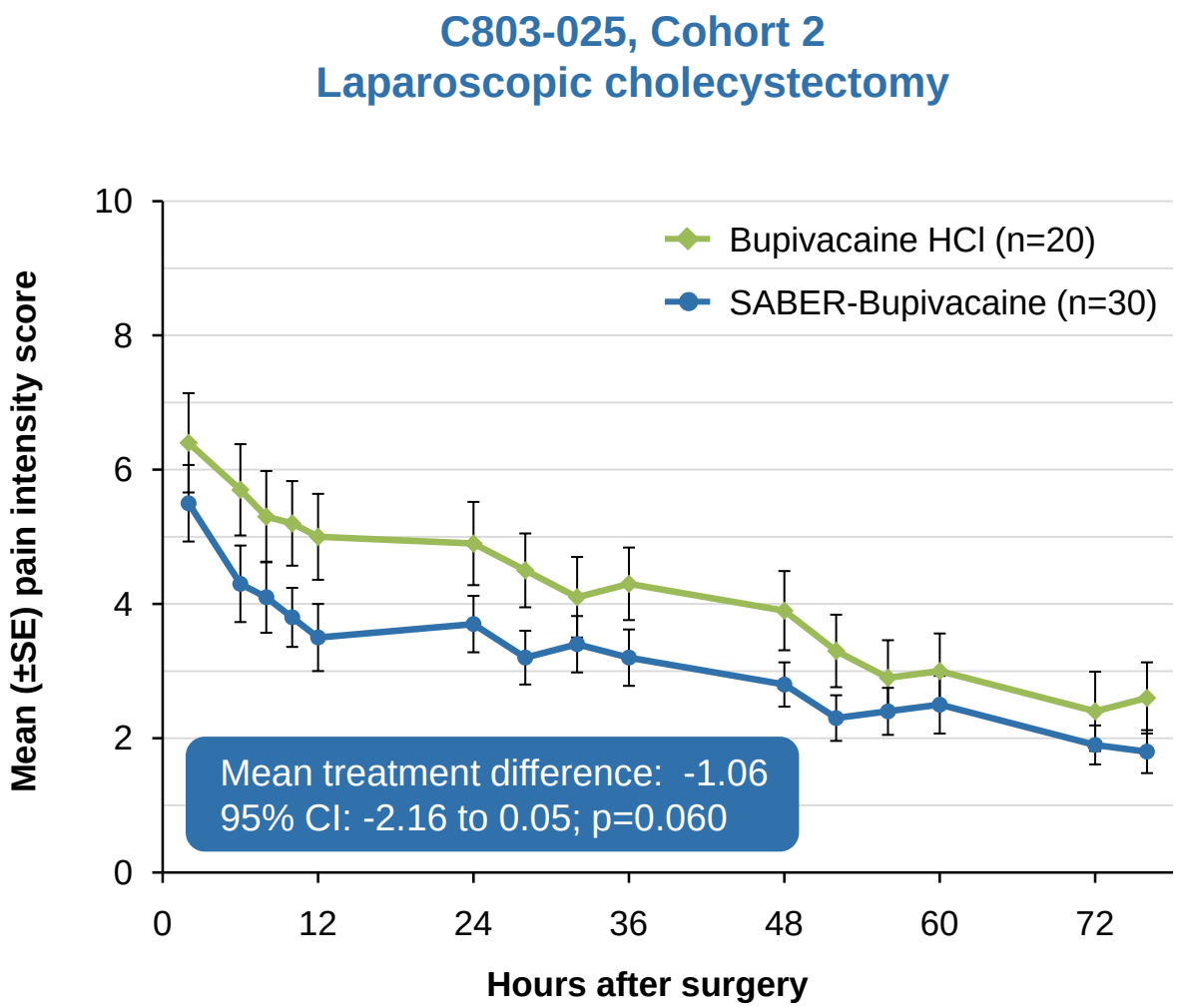
DURECT

C803-025, Cohort 1: pain over time



DURECT

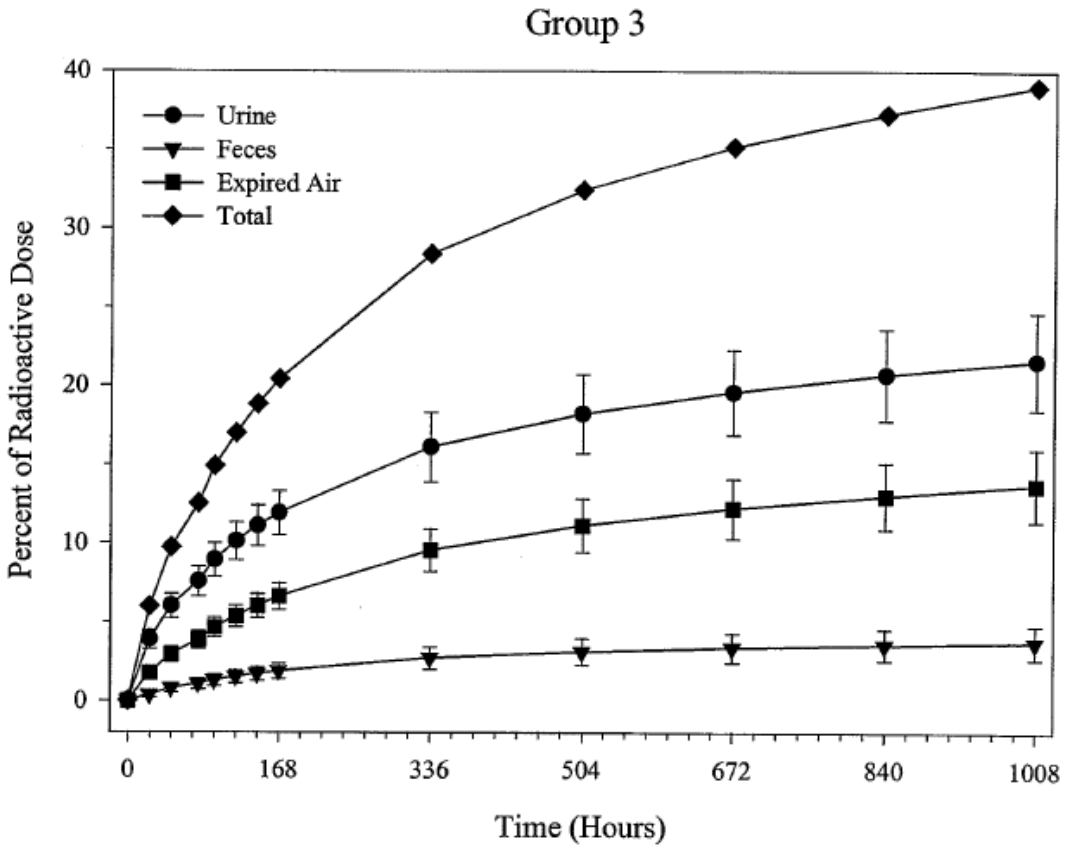
C803-025, Cohort 2: pain over time



DURECT

Metabolic excretion of 14C-SAIB in rats

Figure 5
Mean cumulative percent of radioactive dose at specified intervals following a single subcutaneous dose of ^{14}C-SAIB (311 mg/kg) to male Sprague Dawley rats (Group 3)



DURECT