FDA Briefing Document

Meeting of Anesthetic and Analgesic Drug Products Advisory Committee

January 16, 2020

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. The new drug application (NDA) 204803 for POSIMIR (bupivacaine extended-release solution for instillation) 660 mg/ 5mL (132mg/mL), 13.2% for post-surgical analgesia, has been brought to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee

January 16, 2020

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Division Director Memo

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIOLOGY, ADDICTION MEDICINE AND PAIN MEDICINE

M E M O R A N D U M

DATE: December 20, 2019

FROM: Rigoberto Roca, MD
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Neuroscience, CDER, FDA

TO: Chair, Members of the Anesthetic and Analgesic Drug Products Advisory Committee, and Invited Guests

RE: Overview of the January 16, 2020 AADPAC meeting to discuss NDA 204803 (Posimir)

At this meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), we will be discussing Durect Corporation's complete response to a Complete Response Letter (CRL) issued February 12, 2014, for NDA 204803 (bupivacaine extended-release solution). The NDA was originally submitted on April 12, 2013, and the proposed indication was for administration into the surgical incision to produce post-surgical analgesia. In addition, the Applicant claimed that the drug product is an extended-release solution of bupivacaine. The application was not approved after the first review cycle, and a Complete Response action letter was issued. The following is an excerpt from the CRL that identified the deficiencies:

> The application does not contain sufficient information to demonstrate that POSIMIR is safe when used in the manner described in the proposed label. Specifically, we have identified the following deficiencies:
>
> 1. There were adverse events related to the shoulder joint and surrounding tissues in subjects who underwent follow-up assessments at 18 months, after their arthroscopic subacromial decompression surgery. There were insufficient data due to the limited number of subjects and the lack of an appropriate comparator to permit a determination of whether SABER-bupivacaine causes adverse reactions affecting the joint or the surrounding structures to a clinically relevant greater extent than either bupivacaine HCl or a non-SABER containing placebo.

2. The risk of bruising, hematoma, pruritus, and dehiscence occurred following administration of SABER-containing products (SABER-bupivacaine and SABER-placebo) substantially more often than following administration of bupivacaine HCL. There were insufficient data to determine whether the risk is greater with SABER-bupivacaine than for either bupivacaine HCl or a non-SABER containing placebo following the surgical procedures studied and whether the risk was greater with only certain surgical procedures.
3. There was a marked increased risk of neurologically related adverse events, i.e., dizziness, dysgeusia, headache, hypoesthesia, paresthesia, and somnolence, which occurred with substantially greater frequency following administration of SABER-containing products compared to bupivacaine HCl. There were insufficient data to determine whether the risk is greater with SABER-bupivacaine than for either bupivacaine HCl or a non-SABER containing placebo following each of the surgical procedures studied and clinical impact of these reactions, e.g., whether they delayed discharge from the post-anesthesia care unit or affected time to ambulation.

Thereafter, the Applicant sought a formal dispute resolution on November 21, 2014. The appeal was denied by ODEII Deputy Director, Mary (Parks) Thanh Hai, MD, on January 15, 2015. The denial of appeal letter included the following (verbatim):

> "In reviewing your FDRR and additional materials cited earlier, I believe efficacy is present with Posimir but it is modest and inconsistent across different surgical procedures. My conclusion on efficacy preclude complete dismissal of the safety concerns raised by the Division."

Durect Corporation (the Applicant) submitted a Complete Response to the CRL on June 26, 2019 to address the safety deficiencies noted in the action letter, as well as, the concerns regarding inconsistent efficacy findings across surgical models.

Durect undertook actions to address the issues identified by the Agency as identified in the Complete Response cover letter.

1. Conducted a new clinical study entitled, A **P**lacebo-controlled (Part 1) or Active-controlled (Part 2) Trial of SAB**ER**®-Bupivacaine for the Management of Po**S**toperat**I**ve Pain Following Laparo**S**copic Cholecys**T**ectomy (PERSIST), to address the Agency's safety concerns.
2. Gathered and analyzed specific follow-up safety data from trials already conducted
3. Reassessed the entire body of clinical studies comprising the POSIMIR clinical program to definitively determine which studies were conducted under conditions allowing them to be considered adequate and well controlled and, thus, suitable to be included in the Agency's assessment of the benefit-to-harm calculus, and which studies were merely exploratory learning experiences that helped shape the clinical program

There are a lot of data for consideration with this Complete Response resubmission. The efficacy of Posimir is based on the local effects of bupivacaine while the safety is based on both local effects (e.g., inflammation at the surgical site and extended duration of the polymer at the site of administration) and on systemic levels (e.g., risk of local anesthetic systemic toxicity (LAST) and the release of benzyl alcohol from the formulation). To support the request for an indication as an extended release solution of bupivacaine, an amide local anesthetic, for single-dose administration installation into the surgical site to produce post-surgical anesthesia, we will present the pivotal studies and other studies in the drug development program, including the new PERSIST clinical study.

At the January 2020, meeting, the Committee will be asked to consider the following points:

1. **Whether the Applicant has provided sufficient information to support the proposed indication.**

2. **Whether there are issues with this Complete Response resubmission that warrant additional studies and, if so, should these studies be conducted before or after approval.**

3. **Whether the efficacy, safety, and overall risk-benefit profile of Posimir support the approval of this application.**

The Division and the Agency are grateful to the members of the committee and our invited guests for taking time from your busy schedules to participate in this important meeting. Thank you in advance for your advice, which will aid us in making the most informed and appropriate decision possible.

Glossary of Terms

AC	advisory committee
AE	adverse event
AR	adverse reaction
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRL	Complete Response Letter
CRT	clinical review template
CSR	clinical study report
DMC	data monitoring committee
DRL	Discipline Review Letter
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert

PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

Brief Regulatory Summary: Drug Development Program to the Original NDA Submission on April 12, 2013

Posimir is formulated as a 12% solution (132 mg bupivacaine/mL) with a maximum administration volume of 5 mL allowing for 660 mg of bupivacaine to be instilled within a site. Posimir contains two principal excipients, benzyl alcohol ((BA) 22% (220 mg/mL)) to reduce viscosity on initial instillation, and sucrose acetate isobutyrate ((SAIB) 66% (725 mg/mL)) for the formation of a depot matrix for the extended release of bupivacaine.

DURECT Corporation opened IND 066086 on October 23, 2002. The original formulation of their drug product included (b) (4), a compound with carcinogenic potential. In the nonclinical studies conducted by the Applicant, tissue inflammation and necrosis were observed, and the Division advised the Applicant to change the formulation based on these findings prior to initiating studies in humans. The IND was withdrawn, and a clinical study was conducted outside the United States which did not demonstrate analgesia. The product was subsequently reformulated using BA and the (b) (4) was removed. The IND was reopened on December 23, 2005, with Phase 2 study protocols.

On October 27, 2006 the Sponsor was notified by the Division, via a teleconference, of a partial clinical hold on IND 0066086 related to potentially toxic bupivacaine plasma levels in the following completed studies:

- In Study CLIN004-001 (inguinal herniorrhaphy), the administration of SABER-bupivacaine 7.5 mL (990 mg) with bupivacaine HCl 25 mg resulted in a mean Cmax of 954 ng/mL (plasma bupivacaine level).
- In CLIN004-0009 (inguinal herniorrhaphy) the administration of SABER-bupivacaine 7.5 mL and bupivacaine HCl 25 mg resulted in a mean Cmax of 1300 ng/mL and a range extending to 2200 ng/mL.

The Sponsor was advised to hold all doses of SABER-bupivacaine 7.5 mL for the ongoing studies, CLIN005-0010 and CLIN005-0006.

The Sponsor submitted a response to the clinical hold letter on November 17, 2006, agreeing to cease clinical investigation of the SABER-bupivacaine7.5 mL dose, to eliminate the use of additional bupivacaine or other local anesthetics with SABER-bupivacaine, to modify the method of administration to instillation into the surgical wound, and hourly vital signs and solicited adverse events collection for up to 48 hours after administration.

The Sponsor submitted a request for a Special Protocol Assessment (SPA) on August 4, 2008. The SPA is a process in which sponsors request agreement with FDA on the design and size of certain clinical trials, clinical studies, or animal studies to determine if they adequately address scientific and regulatory requirements for a study that could support marketing approval.[1] An

[1] https://www.fda.gov/media/97618/download

SPA agreement indicates concurrence by FDA with the adequacy and acceptability of specific critical elements of overall protocol design for a study intended to support a future marketing application. The submitted protocol C803-017 was a Phase 3 study to evaluate patients undergoing arthroscopic shoulder surgery. The request was denied on September 18, 2008. The following advice was conveyed to the Sponsor:

- Provide a rationale as to how administered bupivacaine will not enter the joint capsule
- A non-SABER placebo should be included in the clinical evaluations
- A broad postsurgical indication must include a wide range of evaluated surgical procedures.

The Sponsor did not resubmit the protocol but opted to conduct the study as a Phase 2.

December 27, 2006 the Sponsor proposed to conduct two Phase 3 studies in support of NDA submission. The Sponsor was advised that the NDA would need 400 patient exposures to local wound infiltration and 500 for a novel route of administration, including intra-articular.

Pre-NDA Meeting was held on July 31, 2012. The following key clinical advice was provided:

- Only one adequate and well-controlled study may be acceptable if the results were adequately robust and able to withstand sensitivity analyses.
- The single study must provide evidence of efficacy and safety of SABER-bupivacaine when administered during a variety of surgical procedures.
- The single study must allow a determination of the adequacy of the dosing paradigm to be used with SABER-bupivacaine.
- Wound discoloration needs to be further evaluated.
- SABER-bupivacaine effect on the QTc interval needs to be characterized.

The Applicant submitted NDA 204803 on April 12, 2013, pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

The following Clinical and Statistic Summary will discuss key Agency interactions with the Applicant from the original NDA submission to the current NDA re-submission.

In Appendix A, the complete regulatory summary will be available. At the end of the complete regulatory summary there is a timeline of the key interactions between the Agency from the End-of-Review meeting until the submission of the final amendment to the PERSIST study.

Clinical and Statistical Summary

Overview

Posimir® (also referred to as SABER-Bupivacaine in this document) consists of a new formulation of bupivacaine, a currently approved marketed product. Posimir is formulated as a 12% w/w solution (132 mg bupivacaine/mL), which is equivalent to 13.2% w/v due to the fact that the density of SABER-Bupivacaine is 1.1 g/mL at 25ºC. The proposed maximum administration volume that is to be administered to a surgical site is 5 mL, equivalent to 660 mg of bupivacaine.

The purpose of formulating the bupivacaine within a sucrose-based biodegradable matrix (sucrose acetate isobutyrate, also known as SAIB), is in order for the SAIB to form a depot that will allow the bupivacaine to be released into the adjacent tissues over the course of 72 hours.

The Applicant is seeking the following indication: post-surgical analgesia, to be accomplished by administration of Posimir by instillation into the surgical incision such that the product is fully contained within the surgical wound following wound closure.

This document is organized to provide the following information:

1. Original NDA review, to include a summary of the drug development program and a high-level summary of the efficacy.
    a. Summary of the efficacy findings in the two pivotal studies and supportive studies conducted in inguinal hernia repair and arthroscopic subacromial decompression.
    b. The deficiencies identified by the primary clinical reviewer and recommendation of a Complete Response (CR)
    c. The Discipline Review Letter (DLR) sent to the Applicant identifying the primary clinical reviewer's deficiencies and the response of the Applicant.
    d. The Complete Response Letter (CRL) and identified deficiencies.
2. The Formal Dispute Resolution Request (FDRR) submitted by the Applicant and the denial by the Deputy Office Director.
3. Follow-up communication between the Division and Sponsor/Applicant
4. Complete Response NDA re-submission
    a. Summary of the new PERSIST study conducted to provide additional supportive efficacy and safety data.
    b. Summary of key interactions with the Applicant related to the design of the PERSIST study
    c. Overview of safety related deficiencies identified in the Complete Response Letter (CRL) and data submitted by the Applicant to respond to the deficiencies.

Original NDA Submission

Efficacy Original NDA Submission

The clinical program submitted in support of the efficacy of Posimir consisted of seven trials, with the to-be-marketed formulation and methods of administration. The studies were intended to demonstrate the efficacy of Posimir in two different types of procedures – orthopedic and soft tissue surgeries. The control treatment groups for these studies consisted primarily of SABER-placebo (also referred to by the review team as "placebo"), which is the SABER vehicle without the bupivacaine component, or an active comparator, immediate-release bupivacaine hydrochloride.

The following table from Dr. Petit-Scott's review includes the seven randomized, double-blind, controlled trials supporting the claimed effects of statistically significant reduction in pain intensity on movement and reduced need for opioids over a 72-hour period after surgery.

Summary of Studies Evaluating Efficacy (Original NDA Submission)

Study Number	Phase	Comparator	Surgical Procedure	Pivotal
CLIN803-006-0006	2	SABER-placebo	inguinal hernia repair	Y
CLIN005-0010	2	SABER-placebo	inguinal hernia repair	N
BU-002-IM	2	SABER-placebo and bupivacaine HCl	arthroscopic subacromial decompression	Y
CLIN005-0006	2	SABER-placebo	arthroscopic subacromial decompression	N
C803-017	2b	SABER-placebo	arthroscopic subacromial decompression	N
C803-025 Cohort 3	3	SABER-placebo	lap-assisted colectomy	N
C803-025 Cohorts 1 and 2	3	Bupivacaine HCl	laparotomy (cohort 1), lap chole (cohort 2)	N
BU-001-IM	2	SABER-placebo and bupivacaine HCl	total abdominal hysterectomy	N

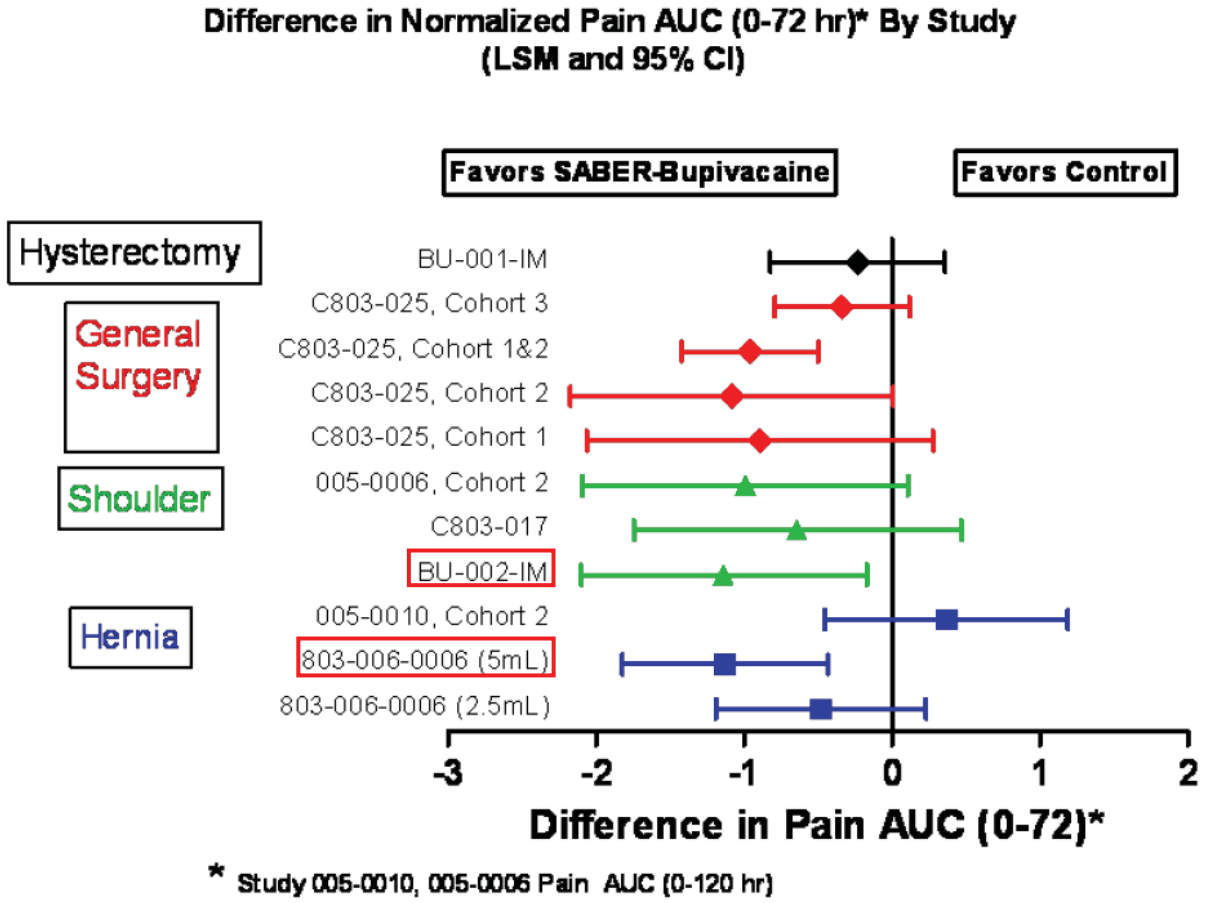
Source: Dr. Petit-Scott's Clinical Review and adapted from Dr. Arthur Simone's Clinical Review, p. 34 (PDF), Jan. 8, 2014.

The studies were conducted in several surgical models, specifically arthroscopic subacromial decompression, general surgery (soft tissue), and total abdominal hysterectomy. The applicant identified the following two studies as "pivotal":

- CLIN803-006-0006, a Phase 2 study in patients undergoing inguinal hernia repair
- BU-002-IM, a Phase 2 study in patients undergoing shoulder surgery

The following figure, reproduced from Dr. Simone's clinical review (found in Appendix C) and from the Applicant's submission, summarizes the efficacy results for normalized pain intensity AUCs for SABER-bupivacaine using a Forest Plot, in the supportive seven clinical studies. The pivotal studies are highlighted by a red border.

Forest Plot of Randomized, Double-Blind, Well-Controlled Trials form Individual Study Results



Source: Original Submission NDA 204803, ISS, Page 18.

The pivotal studies in inguinal hernia repair and arthroscopic subacromial decompression demonstrated efficacy on the primary endpoints of mean pain intensity (PI) on movement AUC over the time period 1 to 72 hours post-surgery (AUC_{72}). It is clear from the forest plots of studies from the development program that the same or similar surgical models showed inconsistent and modest efficacy. However, the studies were powered for modest improvement in mean pain intensity, of 0.4 to 0.8 difference above placebo treatment for AUC for pain 0 to 72 h using an 11-point pain scale. Therefore, the results will not be clinically meaningful.

A summary of the pivotal studies adapted from Dr. Rigoberto Roca's Deputy Division Director Summary Review found in Appendix B will be presented. The Applicant conducted additional soft tissue surgical models in several general surgical procedures and hysterectomy that will not be discussed.

❖ Pivotal Study BU-002-IM in Arthroscopic Shoulder Surgery

Study BU-002-IM, entitled "An international, randomised, double-blinded, multi-centre, active and placebo-controlled dose response trial to evaluate the efficacy and safety of SABER-Bupivacaine for post-operative pain control in patients following arthroscopic shoulder surgery," was conducted between April 29, 2009 and February 4, 2011. The clinical sites were located in Austria, Denmark, Germany, Latvia, and Sweden.

The objective of the study was to identify the optimal dose of SABER-bupivacaine for postoperative pain control in patients who had undergone a subacromial decompression via an arthroscopic procedure.

Subjects were randomized to one of the following treatment groups (as noted above the SABER-Placebo is the SABER vehicle without bupivacaine):

1. SABER-Bupivacaine
2. SABER-Placebo
3. Bupivacaine HCl

The randomization scheme was in a 2:1:1 ratio, with twice as many subjects being randomized to the SABER-Bupivacaine treatment group.

The protocol-specified primary efficacy endpoints were identified as follows:

- Pain intensity (PI) on movement area-under-the-curve (AUC) over the period from 1 to 72 hours post-surgery, using an 11-point numerical rating scale (NRS) for recording PI. A standardized assessment of pain "on movement" was performed for shoulder flexion to 90 degrees.
- Total use of opioid rescue analgesia 0 to 72 hours post-surgery.

The following table, reproduced from Dr. Roca's review and adapted from Mr. Petullo's Statistical Review (found in Appendix D), depicts the difference in the least square means (LSMEANS) between SABER-Bupivacaine and SABER-Placebo, as well as between` Bupivacaine HCl and SABER-Placebo.

Comparison to SABER-Placebo, Study BU-002-IM

	Difference	95% confidence interval	p-value
SABER-Bupivacaine	-1.1	[-2.1, -0.2]	0.02
Bupivacaine HCl	-0.2	[-1.1, 0.7]	0.1

The Statistical Reviewer's analyses of the results for the second co-primary endpoint, the amount of rescue medication consumed through 72 hours (RES72), indicated a significant treatment effect for SABER-Bupivacaine, but not for Bupivacaine.

Refer to the section below regarding the clinical significance of opioid reduction.

Supportive Studies for the Shoulder Surgical Procedures

The supportive studies conducted in arthroscopic shoulder surgery, Studies CLIN-005-0006 and

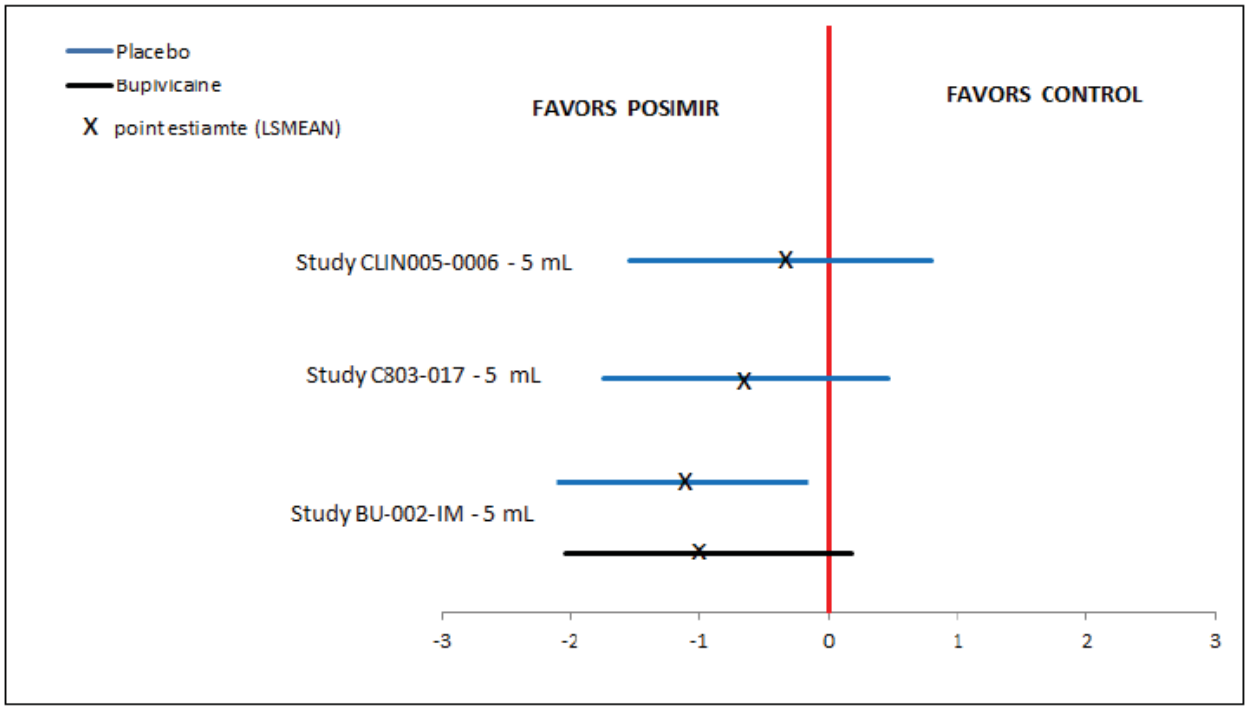
C803-017, were conducted prior to Study BU-002-IM. They are summarized here:

> The first study, CLIN005-0006, was conducted from June 2006 to December 2007 in patients undergoing a variety of shoulder surgeries, including rotator cuff repair, subacromial decompression, glenoid labrum repair or debridement, and biceps tendon repair. The majority of cases were completed arthroscopically, but six cases were completed via a combination of arthroscopic and open techniques. This study failed to demonstrate superiority of SABER-bupivacaine over SABER-placebo. There were no non-SABER comparator treatments evaluated in this study. While it appeared the results of the primary efficacy analyses (pain intensity with movement through 72 hours, AUC_{72M}, and opioid rescue analgesia through 72 hours, RES_{72}) favored SABER-bupivacaine, they failed to reach statistical significance.
>
> The second study, C803-017, was conducted from December 2008 to October 2009 in patients undergoing arthroscopic subacromial decompression; however, a protocol amendment implemented after enrollment of 24 of 60 patients allowed enrollment of patients undergoing an open Mumford procedure (distal clavicle excision) as well. Patients with full-thickness rotator cuff tears were excluded and integrity was confirmed via MRI. This study also failed on the primary efficacy endpoint analyses ($AUC7_{2M}$ and RES_{72}). Similar to the results for Study CLIN005-0006, SABER-bupivacaine treatment was favored over SABER-placebo, but no non-SABER comparator treatments were evaluated.

As noted, these earlier studies in shoulder surgical procedures were conducted in more invasive surgical procedures, such as, open Mumford procedure, rotator cuff repair, and glenoid labrum repair. These procedures involve additional surgical exploration, manipulation, and repair. Therefore, they are more painful than arthroscopic subacromial decompression studied in the pivotal study and may contribute to the lack of statistically significant findings.

Also, the earlier studies did evaluate different techniques for application of SABER-bupivacaine. The earliest study CLIN005-0006 used a combination of subacromial instillation and subcutaneous trailing injection. The subsequent two studies in shoulder surgical procedures limited subacromial instillation of investigational agents.

The figure below, reproduced from Dr. Roca's review and reproduced from Mr. Petullo's review, summarizes the results of AUC72 for the three studies. It illustrates the point estimates and 95% confidence intervals for the difference between SABER-Bupivacaine (identified as Posimir) and SABER-Placebo (identified as placebo), as well as between SABER-Bupivacaine and Bupivacaine HCl (identified as Bupivacaine). The 5 mL dose (represented in blue) is the Applicant's proposed dosage.



The drug development program for SABER-bupivacaine only conducted studies in one orthopedic surgical model. Therefore, we have no data on other orthopedic procedures.

❖ Pivotal Study CLIN803-006-0006 in Inguinal Herniorrhaphy

Study CLIN803-006-0006, entitled "A double-blind, placebo-controlled, pharmacodynamic and pharmacokinetic dose response study of saber-bupivacaine instilled into the wound in patients undergoing open inguinal hernia repair," was conducted between January 18, 2007 and October 17, 2007. The clinical sites were located in Australia and New Zealand.

The primary objective of the study was to assess the dose-response efficacy and pharmacokinetics of SABER-Bupivacaine instilled directly into the wound in subjects undergoing elective open inguinal hernia repair.

Subjects were randomized to one of the following treatment groups:

- Cohort 1: SABER-Bupivacaine 5.0 mL (660 mg of bupivacaine) or SABER-Bupivacaine 2.5 mL (330 mg of bupivacaine) in a 3:1 ratio
- Cohort 2: SABER-Bupivacaine 5.0 mL (660 mg of bupivacaine) or SABER-Placebo 5.0 mL in a 3:1 ratio

The protocol-specified primary efficacy endpoints were:

- Mean pain intensity on movement normalized AUC over the time period 1 to 72 hours post-surgery
- Proportion of patients receiving opioid rescue medication during the study.

The following, reproduced from Dr. Roca's review and adapted from Mr. Petullo's review, depicts the difference in the least square means (LSMEANS) of the two doses of SABER-Bupivacaine compared to SABER-Placebo.

Comparison of SABER-Bupivacaine to SABER-Placebo, Study CLIN803-006-0006

	Difference	95% confidence interval	p-value
SABER-Bupivacaine 330 mg	-0.8	[-1.6, -0.5]	0.1
SABER-Bupivacaine 660 mg	-1.4	[-2.1, 0.6]	0.001

The second co-primary endpoint had been pre-specified to be the proportion of subjects receiving opioid rescue medication through Day 15. The Applicant performed a post-action analysis for the time period of 0 to 72 hours, using the rationale that this was the same time period used for the pain intensity co-primary endpoint. The review team evaluated both time periods. In addition to comparing the proportions when the rescue medication was coded as "rescue," Mr. Petullo, the statistical reviewer, also compared the proportions of subjects who used any opioids, regardless of the coded designation. Regardless of which time period was evaluated, there was a significant difference noted between the higher dose of SABER-Bupivacaine (660 mg) and SABER-Placebo only when the opioids coded as rescue were analyzed. When the analysis considered all opioids, regardless of the coded designation, there was no longer a significant treatment effect.

Refer to the section below regarding the clinical significance of opioid reduction.

Supportive Studies for the Inguinal Herniorrhaphy

A supportive study conducted in inguinal herniorrhaphy, Study CLIN005-0010, was a multicohort study conducted prior to Study CLIN803-006-0006 that failed to meet the primary endpoint of mean pain intensity (PI) on movement normalized AUC over the time period 1 to 72 hours post-surgery. This study differed from Study CLIN803-006-0006 in the treatment arms as well as in the manner in which the treatment drug was administered into the wound area, i.e., subcutaneously or into the subaponeurotic space. The primary endpoints were initially pain intensity at rest and on movement, and pain control, as assessed by the subject.

Clinical significance of opioid reduction in BU-001-IM and CLIN803-006-0006

The Anesthetic and Analgesic Drug Products Advisory Committee convened on November 15, 2018, to discuss the assessment of opioid analgesic sparing outcomes in clinical trials for acute pain. The Division concurs with the opinions of the Advisory Committee that a "statistically significant difference alone has no significance as it is unknown how the results translate to clinical outcomes." The committee felt that there are other criteria that may be important clinically, such as, time to mobilization or an integrated global measure of pain management and recovery from surgery. The discussion and opinions of the Advisory Committee from November 15, 2018 may be found at the following link:
https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-15-2018-meeting-anesthetic-and-analgesic-drug-products-advisory-committee-meeting

Safety Original NDA Submission

The safety of SABER-bupivacaine is related to both its active and inactive components. While the safety of bupivacaine, in concentrations up to 0.75%, infiltrated into surgical incision sites has been established, the safety of bupivacaine 12%, benzyl alcohol (BA) 22%, and sucrose acetate isobutyrate (SAIB) 66% instilled into surgical wounds has not been previously evaluated.

The safety database was derived form a total of 13 clinical studies that were conducted with the to-be-marketed formulation. A total of 1075 patients or healthy subjects were exposed to study drug. Of this group, 547 subjects were exposed to the 5 mL dose of SABER-bupivacaine.

The identified safety issues for this product were related to the following:

- risks associated with systemic exposure to bupivacaine, SAIB, and benzyl alcohol
- local toxicity related to each of these components of SABER-bupivacaine

Dr. Simone, the Primary Clinical Reviewer, determined that there were no data to indicate that there was bupivacaine systemic toxicity with the 5 mL dose when administered by various techniques following a variety of surgical procedures. In addition, there was also no evidence to suggest that dose dumping occurs with SABER-bupivacaine.

➢ Neurologic Adverse Events

The formulation's polymer contains benzyl alcohol, which might contribute to the neurological adverse events reported. The benzyl alcohol from the SAIB is absorbed over a period of 12-24 hours according to the Applicant. This represents a 1.1 g exposure over a 24-hour period, which far exceeds the exposure currently experienced by adult patients receiving intravenous medications that use benzyl alcohol as a preservative. The toxic reactions that might occur following intravenous benzyl alcohol have only been described for neonates. Based on the reaction of neonates to benzyl alcohol, the most common presenting symptoms and signs include metabolic acidosis, central nervous system depression, thrombocytopenia, hypotension, and respiratory distress.

The frequency of adverse events associated with central nervous system (CNS) involvement were more frequent in the SABER-containing treatment groups, SABER-bupivacaine and SABER-placebo. These events are summarized in the table below.

Frequency of CNS-Related Adverse Events, by Treatment Group and Dose

System Organ Class	Preferred Term	SABER-Bupivacaine 2.5 mL N = 50		SABER-Bupivacaine 5 mL N = 542		SABER-Placebo N = 268		Bupivacaine HCl N = 124	
		n	%	n	%	n	%	n	%
Ear and Labyrinth Disorders	Tinnitus	3	6	34	6	19	7	3	2
Nervous System Disorders	Dizziness	15	30	133	25	79	29	11	9
	Dysgeusia	6	12	37	7	29	11	1	1
	Headache	17	34	102	19	48	18	11	9
	Hypoesthesia	4	8	29	5	23	9	1	1
	Paresthesia	10	20	42	8	23	9	3	2
	Somnolence	21	42	140	26	100	37	7	6

The Applicant did not measure plasma or urine levels of benzyl alcohol, making an assessment of possible risk difficult, but it is noteworthy that somnolence occurred in over 25% of subjects receiving SABER-containing treatments but in only 6% of subjects treated with bupivacaine HCl. Similarly, dizziness occurs in 25% or more of subjects treated with SABER-containing products but only in 9% of bupivacaine HCl treated subjects. The alternative cause would include bupivacaine toxicity, however, there were fewer subjects with neurologically reported symptoms in the bupivacaine HCL group. In addition, bupivacaine toxicity would not explain the findings occurring in the SABER-placebo treated subjects and would not be supported by the Cmax values reported for the majority of the subjects receiving SABER-bupivacaine.

➢ Local Toxicity Related to SAIB Exposure

The pharmacology toxicology team provided the following summary regarding the animal study finding from the original NDA review cycle (verbatim).

> Based on the original NDA review, there were no nonclinical deficiencies that would preclude approval; however, there were some concerns for local toxicity with SABER-bupivacaine. The nonclinical data included an acceptable systemic safety profile demonstrating that subcutaneous administration studies of SABER-bupivacaine in rats and rabbits provided exposures that, in the absence of clear nonclinical systemic toxicity, exceed those achieved in the clinical trials. Studies that addressed inadvertent release of bupivacaine demonstrated that there was no dose-dumping and bupivacaine in SABER-bupivacaine is released over 3 days. However, there were some concerns of local toxicity associated with the vehicle and the resulting formation of the depot along with its persistence in tissues. In a single subcutaneous injection study of SABER-bupivacaine in rodents and rabbits, there were local toxicity findings (i.e., swelling,

discoloration, and a significant to mild-to-marked inflammation of the subcutaneous tissues) associated with cyst formation in rats and a granulomatous inflammation around vacant spaces thought to represent the SAIB depot in rabbits and the SAIB depot vehicle was found to be essentially unchanged and still present 12 months after injection described as viscous materials. In wound healing studies in rats and minipigs, microscopic evidence of inflammation, cysts, and mild dermal gap were observed in rats and slightly less advanced re-epithelialization, more inflammation (moderate in severity), giant cells, and clear vacuoles thought to contain SAIB.

In summary, the nonclinical program demonstrated that the product has the potential for local toxicity with a depot-provoked foreign body reaction and the severity of which should be generally related to the volume of SABER-bupivacaine instilled to the area of a particular site. While bupivacaine in SABER-bupivacaine is released over 3 days, the SAIB depot is expected to remain at injection sites for a year or longer.

Dr. Simone identified in his review that the frequency of adverse events identified as application site discoloration (which included hematomas), localized pruritus, contusion, incision site hemorrhage, wound dehiscence, and wound secretion was higher in the SABER-bupivacaine treatment group compared to the bupivacaine HCl treatment group. Application site discoloration, contusion, wound secretion, and pruritus were also more frequent in the SABER-placebo treatment group compared to the Bupivacaine HCl treatment group, suggestive that it was the SABER component that may have been playing a role in these adverse events.

The frequencies of these events are summarized in the table below, reproduced from Dr. Simone's review. Of note, in the table below, a patient may have had more than one type of adverse event, and multiple occurrences of one type of adverse event were counted only once.

Skin related adverse events by treatment group

Adverse Event	SABER-Bupivacaine 2.5 mL	Saber-Bupivacaine 5 mL	SABER-bupivacaine* with Bupivacaine HCl	SABER-Placebo	Bupivacaine HCl
	N=50	N=547	N=82	N=268	N=124
Pruritus	14 (28%)	108 (20%)	5 (6%)	64 (24%)	6 (5%)
Hematomas and Suffusions	13 (26)	86 (16%)	23 (28%)	34 (13%)	3 (2%)
suffusions†		24 (4%)		7 (3%)	
hematomas†	13 (26)	62 (11%)	23 (28%)	27 (10%)	3 (2%)
Bruising	12 (24%)	67 (12%)	82 (100%)	15 (6%)	8 (6%)
Erythema	7 (14%)	42 (8%)	8 (10%)	16 (6%)	2 (2%)
Ecchymosis		42 (8%)		20 (7%)	1 (1%)
Discoloration		41 (7%)		26 (10%)	4 (3%)
Dehiscence		20 (4%)		5 (2%)	
Bleeding	1 (2%)	31 (6%)		7 (3%)	
Infection		22 (4%)	2 (2%)	7 (3%)	5 (4%)
Total	47 (94%)	459 (84%)	120 (146%)	194 (72%)	29 (23%)

* 71 with 7.5 mL of SABER-bupivacaine and 11 with 5 mL
† Suffusion was the term used to describe hematoma in trial.

The data in the table indicate that SABER-bupivacaine, and in some instances SABER-placebo, are associated with an increased incidence in adverse events at the surgical incision site compared to bupivacaine HCl. While most of the AEs resolved spontaneously, there were some instances where one AE led to another, e.g., a hematoma becoming infected, that compounds the risk to the patient.

The table below, reproduced from Dr. Roca's review, summarizes the frequency of dehiscence reported for each treatment group, organized by study and procedure.

Frequency of Dehiscence, by Procedure and Treatment Group

Study ID	Procedure	SABER-Bupivacaine 5 mL	SABER-Placebo	Bupivacaine HCl
BU-001-IM	Hysterectomy	2 (3%)	0	0
BU-002-IM	Arthroscopic Shoulder	2 (4%)	0	0
C803-025	Abdominal procedures (all)	22 (12%)	10 (13%)	0
	Laparotomy	6 (23%)	NA	0
	Laparoscopic Cholecystectomy	2 (7%)	NA	0
	Laparoscopically-assisted colectomy	14 (11%)	10 (13%)	NA
C803-027	Abdominal procedures	10 (100%)	NA	NA

- **Local Toxicity at the Shoulder Joint and Surrounding Tissues**

Dr. Simone identified three reports of adverse events related to the shoulder joint and surrounding tissues, that may represent chondrolysis, in the patients who had undergone arthroscopic surgery. One of the cases had been identified as a serious adverse event.

The Division conveyed via a Discipline Review letter, on January 14, 2014 and teleconference held on January 27, 2014, the concern that, even though efficacy had been demonstrated in the clinical trials involving arthroscopic shoulder surgery, the occurrence of these three cases raised safety concerns. The Applicant responded to the letter and teleconference, on February 3, 2014, by submitting additional information to support the contention that the three cases did not meet the pre-specified definition of chondrolysis, because they did not have the radiographic findings stipulated in the case definition.

After reviewing the additional information, Dr. Simone conceded that the cases did not meet the case definition, but still noted that the cases represented some type of chondropathy. It is not clear if these findings may represent a safety signal or natural progression of the disease process in these patients. However, there weren't any bupivacaine-only treated patients with enough long-term follow-up that could serve as a control.

The overall assessment of the Division was that the Applicant had provided sufficient data to demonstrate the efficacy of Posimir with respect to post-operative analgesia in inguinal herniorrhaphy and arthroscopic subacromial decompression. However, the Applicant had not provided sufficient data to demonstrate that Posimir is safe when used as directed in the Applicant's proposed labeling.

Complete Response Action for Original NDA review cycle

The application received a Complete Response on February 14, 2014 (Appendix E) and the Applicant was advised that the application did not contain sufficient information to demonstrate that Posimir was safe when use in the manner described in the proposed label. The following safety deficiencies were identified:

a. There were adverse events related to the shoulder joint and surrounding tissues in subjects who underwent follow-up assessments at 18 months, after their arthroscopic subacromial decompression surgery.

b. The risk of bruising, hematoma, pruritus, and dehiscence occurred following administration of SABER-containing products (SABER-bupivacaine and SABER-placebo) substantially more often than following administration of bupivacaine HCL.

c. There was a marked increased risk of neurologically related adverse events, i.e., dizziness, dysgeusia, headache, hypoesthesia, paresthesia, and somnolence, which

occurred with substantially greater frequency following administration of SABER-containing products compared to bupivacaine HCl.

The applicant was advised to conduct additional studies to adequately characterize the risk profile of SABER-bupivacaine to address the deficiencies listed above. Specifically, the following types of studies need to be conducted:

a. A safety study evaluating the occurrence of adverse reactions associated with the shoulder joint and the surrounding tissues, including the skin, following arthroscopic subacromial decompression. Safety assessments need to be performed at appropriate intervals following the administration of study drug to capture the onset and duration of the reactions and need to be carried out for an appropriate period of time to capture late-onset events.

   The treatments need to include SABER-bupivacaine and either bupivacaine HCL or a non-SABER containing placebo (or both). The study needs to be randomized and double-blinded in design and needs to include enough subjects to detect reactions with an incidence rate of ≥ 1%. Efficacy data must be collected during the study to allow the safety data to be placed in clinical context when the benefit:risk analysis is performed.

b. A safety study evaluating the occurrence of adverse reactions associated with the skin and underlying tissues. Safety assessments need to be performed at appropriate time intervals following administration of study drug to capture the onset and duration of the reactions and to be carried out until complete healing of the surgical wound has occurred. The protocol needs to incorporate standardized definitions for the reactions observed thus far in the clinical development program, e.g., hematoma, ecchymosis, dehiscence, to assure uniform classification of the reactions among investigators.

   The treatments need to include SABER-bupivacaine and either bupivacaine HCL or a non-SABER containing placebo (or both). The study needs to be randomized and double-blinded. The study must evaluate subjects undergoing each of the surgical procedures studied to date, with the numbers of subjects undergoing each of the procedures evenly distributed. Efficacy data must be collected during the study to allow the safety data to be placed in clinical context when the benefit:risk analysis is performed.

c. A safety study evaluating the occurrence of adverse reactions associated with neurotoxicity. Safety assessments need to be performed at appropriate time intervals following administration of study drug to capture the onset and duration of the reactions and to be carried out for the duration of systemic exposure to benzyl alcohol. The clinical impact of the adverse reactions needs to be captured, e.g., delayed discharge due to somnolence; delayed time to ambulation due to dizziness.

The treatments need to include SABER-bupivacaine and either bupivacaine HCL or a non-SABER containing placebo (or both). The study needs to be randomized and double-blinded in design. The study must evaluate subjects undergoing each of the surgical procedures studied to date, with the numbers of subjects undergoing each of the procedures evenly distributed. Efficacy data must be collected during the study to allow the safety data to be placed in clinical context when the benefit:risk analysis is performed.

It was strongly recommended that the Applicant discuss the design of this study with the Division prior to implementation.

Applicant Formal Dispute Resolution Request

The Applicant submitted a formal dispute resolution request (FDRR) on November 21, 2014 to appeal the February 12, 2014 Complete Response letter. However, because the Applicant requested a determination of both safety *and* efficacy in their FDRR, an additional review of the efficacy data was conducted by Dr. Mary (Parks) Thanh Hai. The full details of Dr. Thanh Hai's review can be found in the FDRR Appeal Denied letter issued on January 15, 2015 (Appendix F).

Dr. Thanh Hai concluded the following (verbatim)

> In reviewing your FDRR and additional materials cited earlier, I believe efficacy is present with Posimir, but it is modest and inconsistent across different surgical procedures. My conclusion on efficacy precludes complete dismissal of the safety concerns raised by the Division.
>
> By your own admission, you did not present data in an 'unambiguous' manner and 'unclear descriptions' may have contributed to the CR action. While I would concur with you that your NDA submission and some of your data presentations in the FDRR lacked clarity, I do believe you have made a reasonable attempt to address the deficiencies in the CR letter through reanalysis of current trial data and by providing more extensive explanations of specific cases and new long-term safety data. However, I am unable to consider your re-analyses and new long-term safety data in the determination of efficacy and safety of Posimir, as requested in your FDRR…Consequently, the new long-term safety data and re-analyses must first be reviewed by the Division to determine if they adequately address the deficiencies in your program. I would caution that such re-analyses and follow-up data may not fully address the deficiencies because they were not prospectively planned and can, therefore, generate a degree of skepticism on their validity. For this reason, I recommend two potential pathways for you to address the deficiencies identified in the CR letter:
>
> 1. Plan and discuss with the Division a prospective trial that will specifically assess the safety concerns related to surrounding tissues of the joint, surgical incision sites, and potential complications of acute exposure to high doses of benzyl alcohol, *or*

2. Prepare for resubmission the materials, re-analyses, and data presentation proposed in your End-of-Review briefing materials. This resubmission will be classified as a Class 2 resubmission as it will, at a minimum, include additional long-term data on patients not previously reviewed in the NDA. You are encouraged to discuss with the Division your proposed resubmission, which will be subject to a 6-month review cycle and may also be presented before a public advisory committee meeting should the Division deem it necessary to seek outside expert opinion on your application.

Interactions with the Applicant after Formal Dispute Resolution Denial

From February 15, 2015 (End of Review Meeting) to March 10, 2017 (submission of the final protocol amendment #5 for Study C803-028) there were ongoing interactions with the Applicant regarding the recommendation related to the design of the new prospective trial to assess both safety and efficacy to support the approval of Posimir. These interactions are discussed further in the detailed Regulatory Summary that can be found in Appendix A. In addition, there is a timeline at the end of the Regulatory Summary that describes the interactions between the Applicant and the Agency between February 15, 2015 and March 10, 2017 regarding the planning and design of the new Phase 3 study.

The primary issues discussed during this time frame were the surgical model and the need for an active comparator and a placebo comparator. Inclusion of both comparators was recommended to better characterize the findings related to the local toxicity in surgical wounds and the systemic CNS symptoms thought to be related to benzyl alcohol in the SAIB formulation. Of note, in the clinical trials submitted to support the original NDA submission, SABER-placebo was extensively used as the primary comparator, such that, it was difficult to distinguish the local toxicity and systemic effects of the formulation.

NDA Complete Response Resubmission

Overview of NDA CR submission

As previously discussed, the original NDA received a CRL based on the risk-benefit analysis, such that the safety profile for SABER-bupivacaine was unacceptable when administered into post-operative wounds. Specifically, there were concerns regarding the shoulder joint, surrounding tissue, and skin in patients receiving SABER-bupivacaine during arthroscopic shoulder surgery, the incidence of adverse events which could be attributed to systemic benzyl alcohol exposure, and the incidence of wound-related adverse events after administration of either SABER-bupivacaine or SABER-placebo in patients undergoing soft tissue surgeries.

The Applicant proposed to address the identified safety concerns outlined in the CRL in the following ways:

- The PERSIST study was conducted to address the safety (and efficacy, as discussed during the FDRR process) issues, in the following manner:

  - Serial wound examinations out to study day 60, outlined in Protocol Amendment 5
  - Non-vehicle and active control groups
  - Patients questioned daily for the presence of 10 symptoms of interest

- Analyzed follow-up safety data from previously completed studies, including the arthroscopic shoulder procedures.
  - Regarding wound-related adverse events –
    - Written follow-up survey of investigators in Study C803-025 to determine whether additional cases of dehiscence had been observed beyond the 2-week study
    - Reanalyzed wound complication data to decrease potential influences from treatment groups, surgical procedures, and patient populations
  - Regarding neurological adverse events –
    - Reanalyzed solicited and spontaneously-reported potential benzyl alcohol-induced neurological adverse events
    - Vital sign analysis during T_{max} for benzyl alcohol
  - Regarding chondropathy –
    - Evaluated baseline and 18-month post-surgical MRIs for patients in Study C803-017/C803-017e
    - Surveyed investigators in Study CLIN005-006, regarding reported outcomes over the 10 years since study completion
    - Reanalyzed safety data from Study BU-002-IM, including baseline and 6-month post-operative MRIs, functional assessments, and wound healing assessments

❖ New Clinical Study: PERSIST Study C803-028, Laparoscopic cholecystectomy to evaluate safety and efficacy of Posimir

Study Design, Objectives, and Endpoints

The Applicant conducted a new soft tissue study in laparoscopic cholecystectomy that will be discussed below entitled, A **P**lacebo-controlled trial of SAB**ER**®-Bupivacaine for the management of po**S**toperat**I**ve pain following laparoscopic cholecys**T**ectomy (**PERSIST**) to evaluated safety and safety. This study was conducted between November 11, 2015 and August 16, 2017 in 22 sites in the United States.

The details of the study are described in Dr. Petit-Scott's clinical review and Ms. Meaker's statistical review.

The major aspects of the study design are summarized here. It was a randomized, parallel-group, double-blind, placebo-controlled (Part 1) and active-controlled (Part 2) multicenter trial evaluating the safety and efficacy of SABER-Bupivacaine 5 mL in patients undergoing elective

outpatient laparoscopic cholecystectomy.

The objective of the study changed based upon the two parts.

- Part 1: To evaluate the safety and efficacy of SABER-Bupivacaine for alleviating postoperative pain on movement compared with saline placebo in patients undergoing laparoscopic cholecystectomy.
- Part 2: To evaluate the safety and efficacy of SABER-Bupivacaine for alleviating postoperative pain on movement compared with bupivacaine HCl in patients undergoing laparoscopic cholecystectomy.

The need for an additional study and the recommendation of the addition of an active comparator arm, bupivacaine, was first recommended September 23, 2014 at the End-of-Review-Cycle meeting. After the full protocol was submitted on October 22, 2015, the addition of the active comparator was discussed at the following interactions:

- January 11, 2016 advice letter
- April 5, 2016 teleconference

With submission of the Amendment 3, on June 6, 2016, the Applicant discontinued the placebo control arm of the study and added an active comparator, bupivacaine. The discontinuation of the placebo control arm of the study was not a recommendation proposed by the Agency.

Subjects were randomized 1:1 and stratified by sex in both parts of the study. The treatments for each part are describe below:

- Part 1: subjects were randomized to receive one of the two treatments
    - SABER-bupivacaine 5 mL (660 mg of bupivacaine base) by direct instillation into the four surgical incision sites (4-ports)
    - Saline placebo 5 mL was administered by direct instillation into the surgical incisions.
- Part 2: subjects were randomized to receive one of the two treatments.
    - SABER-bupivacaine 5 mL (660 mg of bupivacaine base) by direct instillation into the four surgical incisions (4-ports)
    - Bupivacaine HCl plane (75 mg) was infiltrated into the 4 incision sites.

Each part of the study was a standalone study, even though the Applicant chose to name them Part 1 and Part 2.

The protocol-specified efficacy endpoints were identified as follows:

> *Primary efficacy endpoints*
> Part 1: Pain intensity on movement measured at scheduled time points from 0 to 72 hours following test drug administration, adjusted for prior rescue medication use and analyzed by a mixed effect ANOVA model of repeated measures (MMRM).

Part 2: Pain intensity on movement measured at scheduled time points from 0 to 48 hours following test drug administration, adjusted for prior rescue medication use and analyzed by a mixed effect ANOVA model of repeated measures (MMRM).

Key secondary efficacy endpoints

Part 1: Total IV morphine-equivalent dose of rescue opioids used during 0-72 hours following test drug administration.

Part 2: Pain intensity on movement measured at scheduled time points from 0 to 72 hours following test drug administration, adjusted for prior rescue medication use.

Subject enrollment in Part 1 was initiated in November 11, 2015 in 17 sites in the United States. Part 1 was discontinued, after 92 subjects (46/group) had been randomized and treated, to incorporate an active control.

Subject enrollment in Part 2 was initiated in August 2016. A total of 296 subjects were randomized and treated (148/group). The study was completed on August 16, 2017.

Efficacy results of Protocol C803-028

The following table, reproduced from the Applicants complete study report for Protocol C803-028, summarize the results of the primary endpoints for Part 1 and 2.

Primary Outcomes by Study Part: Pain Intensity on Movement from 0 to 72 Hours Post-treatment (Part 1) and from 0 to 48 Hours Post-treatment (Part 2) (mITT Population)

	Part 1		Part 2	
	SABER-Bupivacaine (N=46)	Saline Placebo (N=46)	SABER-Bupivacaine (N=148)	Bupivacaine HCl (N=148)
Pain intensity on movement 0 to 72 hours				
Mean (SE)	4.38 (0.091)	5.17 (0.107)		
95% CI	(4.21, 4.56)	(4.96, 5.38)		
Pain intensity on movement 0 to 48 hours				
Mean (SE)			5.55 (0.065)	5.87 (0.059)
95% CI			(5.42, 5.67)	(5.76, 5.99)
SABER-Bupivacaine versus comparator [1]				
LS Mean Difference (SE)	-0.785 (0.432)		-0.371 (0.2412)	
95% CI	(-1.631, 0.062)		(-0.844, 0.101)	
p-value	—		0.1235	

CI = confidence interval; mITT = modified intent-to-treat; SAP = Statistical Analysis Plan; SE = standard error; WOCF = worst observation carried forward

Note: For each subject, all pain scores up to the first scheduled pain score taken after the elapsed time from study treatment equaled 72 hours (Part 1) or 48 hours (Part 2) were included in this analysis.

Note: Pain measurements were adjusted for the use of rescue medications by the half-life substitution method.

Note: For subjects who dropped out prior to 72 hours post-treatment due to an adverse event or lack of efficacy, missing scheduled measurements were imputed by the WOCF method. For all other subjects, missing values were imputed by multiple imputation using the Markov Chain Monte Carlo method.

[1] Estimates and p-value presented here are combined estimates from 5 multiple imputation replicates of a mixed effects repeated measures model with fixed effects for study site, sex, treatment and two-way interactions, study subject as a random effects and time as a repeated factor. Standard error estimates include a contribution for variability between replicates. For details on covariance model selection, see Section 7.1 of the SAP (Appendix 16.1.9).

Of note, neither Part 1 or Part 2 of Protocol C803-028 showed a statistically significant difference to the relevant comparator arm.

Ms. Meaker notes that Part 1 stopped after only 30% of the planned sample had been treated, but the observed results were consistent with the anticipated treatment difference of 0.8 units. The lack of sufficient evidence to detect a statically significant difference can be attributed to the lack of power for efficacy.

The Applicant contends that Part 2 should not be considered an adequate and well-controlled study in the overall assessment of efficacy of SABER-bupivacaine is related to the change from saline placebo to bupivacaine HCl control treatment for following study reasons:

- the change was not prospectively planned, therefore, bias was not minimized
- numerous changes at “behest of FDA introduced bias and increased variability beyond acceptable experimental limits”
- no concurrent placebo control, lack of assay sensitivity
- primary efficacy endpoint was 0 to 48 h versus 0 to 72 h, therefore results cannot be integrated with results from other studies

- inappropriate pooling of Part 1 and Part 2 SABER-bupivacaine data for secondary endpoints

The Agency does not agree with the Applicant because the PERSIST Part 2 was planned as an adequate and well-controlled study intended to show superiority vs. bupivacaine HCl for treatment of pain on movement after surgery.

Safety results in Protocol C803-028

➢ Overview

This study in patients undergoing laparoscopic cholecystectomy included more intensive and longer duration evaluations and assessments for concerning neurological symptoms, both solicited and spontaneously reported, and complications related to wound healing. In addition, the PERSIST protocol allowed better characterization of the formulation because the study comparators were non-SABER-placebo (saline) or bupivacaine. In addition, the study allowed differentiation of neurologic symptoms related to the formulation or to bupivacaine.

There were no deaths reported and 14 patients reported 15 serious adverse events (SAEs) during the trial. Of the 15 reported SAE, 9 of the subjects were randomized and dosed subjects in the PERSIST trial of which, 6 SAEs were related to SABER-bupivacaine and 3 to bupivacaine HCl. The majority of the SAE's were related to underlying gallbladder disease or post-operative complications unrelated to the study drug treatment.

During the course of the study, 99.0% of all subjects (384/388 subjects) reported at least one TEAE. The overall incidences of TEAEs were similar among the treatment groups and study parts. The incidence of spontaneously reported TEAEs was also similar between treatment groups and study parts.

The majority of spontaneously-solicited TEAEs were mild in severity. Nineteen patients reported at least one severe TEAE. In Part 1, there were six patients with severe TEAEs in the SABER-bupivacaine treatment group, including five with peri-incisional bruising and one with pruritis. There were no severe spontaneously-reported TEAEs in the saline group. All five cases of bruising were reported as related to study drug and all resolved without treatment. In Part 2, there were nine patients in the SABER-bupivacaine group and four in the bupivacaine HCl group with one or more severe TEAEs. The TEAEs resolved by the end of the study period.

➢ Neurologic Adverse Events

There was an increase in CNS AEs in both parts of the study summarized here:

- An increased incidence of dysgeusia in the SABER-bupivacaine treatment groups in both Part 1 and Part 2 of the study compared to the respective controls.
- In Part 2 of the study, there was an increased incidence of headache and dizziness in the SABER-bupivacaine treatment group compared to the bupivacaine HCl treatment group.

The majority of the spontaneously-solicited TEAEs were mild in severity and resolved by the

end of the study period.

The Agency requested ten solicited symptoms of interest during the study. The symptoms included somnolence, nausea, dizziness, headache, vomiting, constipation, pruritus, dysgeusia, paresthesia, and hypoesthesia were collected via a LogPad. The LogPad automatically queried patients at regular time intervals, with the 6 and 10-hour entries specifically intended to capture potential benzyl alcohol exposure and toxicity. The incidence of solicited adverse events was higher in both treatment groups in Part 2 of the study when compared to Part 1. The solicited TEAEs that occurred with increased frequency (> 5% disparity between treatment groups) in the SABER-bupivacaine group in Part 1 included somnolence, headache, and dysgeusia. Those that occurred with increased frequency in the saline group included nausea and pruritus. The solicited TEAEs that occurred with increased frequency in the SABER-bupivacaine group in Part 2 included somnolence and dysgeusia. Those that occurred with increased frequency in the bupivacaine group included nausea and vomiting.

Because benzyl alcohol has a T_{max} of one hour, a half-life is 4.7 hours, and can be measured in the plasma up to 12 hours' after administration, the incidence of the 10 symptoms of interest early in the post-operative course is likely more clinically relevant. Therefore, Dr. Petit-Scott requested the following table of the solicited symptoms occurring within 6 hours of administration in response to an Information Request.

Incidence of LogPad Solicited Adverse Events Within 6 hours Post-Treatment (Safety Population)

	Part 1		Part 2		Parts 1 & 2	
Dictionary-Derived Term (Verbatim LogPad Term)	**SABER-Bupivacaine (N=45)**	**Saline Placebo (N=47)**	**SABER-Bupivacaine (N=148)**	**Bupivacaine HCl (N=148)**	**SABER-Bupivacaine (N=193)**	**Study Total (N=388)**
Subjects reporting at least one solicited adverse event [1], n (%)	25 (55.6%)	29 (61.7%)	103 (69.6%)	97 (65.5%)	128 (66.3%)	254 (65.5%)
Somnolence (Drowsiness)	18 (40.0%)	16 (34.0%)	60 (40.5%)	48 (32.4%)	78 (40.4%)	142 (36.6%)
Nausea (Nausea)	9 (20.0%)	13 (27.7%)	48 (32.4%)	57 (38.5%)	57 (29.5%)	127 (32.7%)
Dizziness (Dizziness)	3 (6.7%)	3 (6.4%)	28 (18.9%)	31 (20.9%)	31 (16.1%)	65 (16.8%)
Headache (Headache)	5 (11.1%)	4 (8.5%)	23 (15.5%)	18 (12.2%)	28 (14.5%)	50 (12.9%)
Vomiting (Vomiting)	2 (4.4%)	3 (6.4%)	10 (6.8%)	15 (10.1%)	12 (6.2%)	30 (7.7%)
Constipation (Constipation)	0 (0.0%)	4 (8.5%)	9 (6.1%)	10 (6.8%)	9 (4.7%)	23 (5.9%)
Pruritus (Itching)	1 (2.2%)	1 (2.1%)	6 (4.1%)	5 (3.4%)	7 (3.6%)	13 (3.4%)
Events Added with Amendment 2, n (%)	**(N=23)**	**(N=22)**	**(N=148)**	**(N=148)**	**(N=171)**	**(N=341)**
Dysgeusia (Metallic Taste in Mouth)	3 (13.0%)	2 (9.1%)	26 (17.6%)	22 (14.9%)	29 (17.0%)	53 (15.5%)
Paraesthesia (Tingling)	0 (0.0%)	0 (0.0%)	2 (1.4%)	6 (4.1%)	2 (1.2%)	8 (2.3%)
Hypoaesthesia (Numbness)	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)	1 (0.6%)	2 (0.6%)

Note: Solicited events were reported on the Adverse Events CRF, based on subject-reported symptoms collected on the LogPad electronic diary.

Note: Dizziness, Somnolence, Constipation, Nausea, Vomiting, Pruritus, and Headache were solicited on the LogPad electronic diary from all treated subjects. Dysgeusia, Paraesthesia, and Hypoaesthesia were solicited on the LogPad electronic diary only from subjects treated under Protocol Amendment 2 (April 2016) and later.

Note: For each symptom, subjects reporting more than one symptom are counted only once.

Note: Table is sorted by descending total subjects reporting each adverse event.

[1] This line includes all 10 LogPad-solicited events reported by subjects both pre- and post-Amendment 2.

Source: Response to Information Request, October 11, 2019, NDA 204803.

The table indicates that patients treated with a SABER product had an increased incidence of somnolence, headache, pruritus, and dysgeusia when compared to patients treated with saline placebo or bupivacaine HCl within 6 hours of administration. Because somnolence, headache, dysgeusia, and pruritus were observed with greater frequency in SABER-treated patients in the clinical studies evaluated during the original NDA review, it is very likely that systemic BA may be the cause.

➢ Local Toxicity Related to SAIB Exposure

The surgical sites were evaluated by trained medical personnel in blinded fashion, with particular focus on six prespecified wound-related adverse events, which included peri-incisional bruising, wound hematoma, wound dehiscence, surgical site infection, surgical site bleeding, and drainage from the surgical incision. Each of the prespecified wound-related adverse events will be discussed briefly below.

Bruising

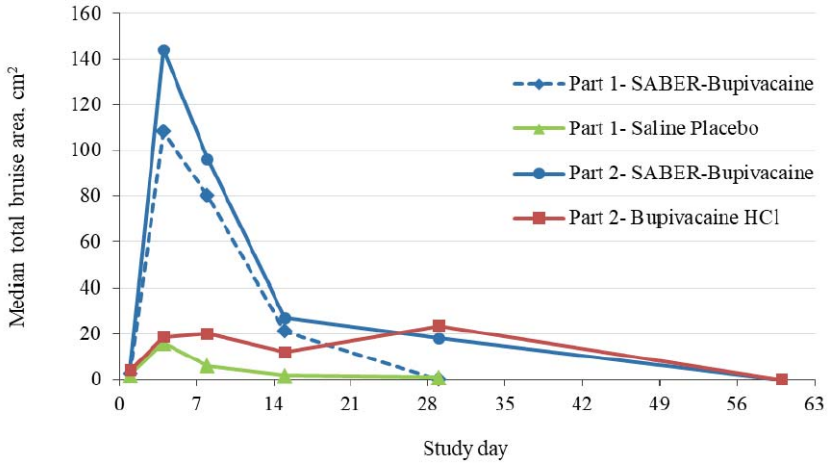
There was a higher incidence of related TEAEs among the SABER-Bupivacaine treatment groups than the control groups in both parts of the trial, primarily because there was a higher incidence of peri-incisional bruising among SABER-Bupivacaine-treated subjects.

During the study, 99% of the treated patients reported at least one treat-emergent adverse event (TEAE) Overall, peri-incisional bruising was more prevalent in the SABER-bupivacaine treated subjects:

- Part 1: 91.1% SABER-bupivacaine vs. 70.2% saline placebo
- Part 2: 95.9% SABER-bupivacaine vs. 70.9% bupivacaine HCl

The prevalence of bruising was greatest on Day 4 and the SABER-bupivacaine bruises were larger than the control arm bruises. Most bruising had resolved by Day 28. The following graph reproduced from the CSR on page 131, shows that subjects treated with SABER-bupivacaine had a greater total area than the control subjects.

Total Area of Bruising by Study Day



Note: Bruise area calculated as a rectangle (length × width) based on length and width recorded in the CRF.
Source: Table 14.3.1.10.2

There were consistent differences in the incidence of spontaneously-reported adverse events. Specifically, the adverse events reported more frequently in the SABER-bupivacaine groups compared to the control groups in both parts of the study included post-procedural contusion and incision site hemorrhage. In Part 2, incision site erythema and hematoma were both reported with a higher frequency than in the bupivacaine HCl group.

Surgical Site Bleeding

Surgical site bleeding was rated as spotting of the dressing, soaking of the dressing, or continuous bleeding throughout the study. In Part 1, there was a slightly higher incidence of surgical site bleeding reported in patients treated with SABER-bupivacaine than those treated with saline; 49% versus 43%, respectively. In Part 2 of the study, the incidence was higher in patients treated with bupivacaine HCl compared to those treated with SABER-bupivacaine; 16% versus 13%, respectively. Furthermore, there is a higher incidence of bleeding through day 8 (POD 7) in patients treated with SABER-bupivacaine in both parts of the study.

Drainage from the Surgical Incision

There was not a higher incidence of drainage from the wound treated with SABER-bupivacaine.

Wound Hematoma

There were no wound hematomas reported in either treatment group in Part 1 of the study. In Part 2 of the study, the incidence of post-operative wound hematoma was higher in the SABER-bupivacaine treatment group compared to the bupivacaine HCl treatment group. Specifically, the incidence of wound hematoma was 4% versus 1%, respectively. Almost all hematomas occurred on days 4 or 8 at the umbilical incision. Two patients in the SABER-bupivacaine group and one patient in the bupivacaine HCl group had more than one wound hematoma. The

Applicant stated that all but one hematoma was reported by two investigative sites, suggesting that potentially those sites over-called any swelling of the wound a hematoma. This hypothesis is not based on verifiable data.

Wound Dehiscence

There were five cases of wound dehiscence in Part 2 of the study; two in the SABER-bupivacaine treatment group and three in the bupivacaine HCl treatment group. These events were described as superficial with small wound separation at the edges. Most involved the umbilical or epigastric incisions and appeared most commonly on day 4 or 8. None required treatment, and all resolved.

Surgical Site Infection (SSI)

There were seven cases of surgical site infection; five in patients treated with SABER-bupivacaine and two in a patient treated with bupivacaine HCl. The umbilical incision was involved in most cases. They were considered superficial and resolved within 28 days with oral antibiotics.

The Applicant has stated that the overall incidence of surgical site infections is consistent with reports in the published literature, ranging from 0.8 to 4.1%, and all cases resolved with oral antibiotic treatment and no additional complications were observed. Even though, the incidence of surgical site infections may not be unexpectedly high and there were no subsequent complications, surgical site infections are still concerning with administration of SABER-bupivacaine in soft tissue surgical wounds. Any post-operative antibiotic treatment is a concern and not benign in and of itself and this increased incidence in combination with other wound-related adverse events in patients treated with SABER-bupivacaine negatively impacts the benefit-risk profile of this drug product.

Abnormal Wound Healing

All cases of abnormal healing were resolved by Study Day 29, except for a single patient in the bupivacaine HCl treatment group who developed an umbilical hernia requiring surgical correction.

Retained SAIB Formulation in the Wound

The long-term impact of residual SAIB formulation in the wound is unknown. Specifically, nonclinical data suggest components of the SAIB formulation persist in the wound up to one year after administration, which could increase the development of scar or fibrotic tissue in the wound. An increase in fibrotic tissue could in turn result in adverse events such as development of adhesions and bowel obstruction after intra-abdominal procedures. Additionally, increased fibrotic tissue could may surgical re-exploration challenging with increased risk of surgical complications.

The Applicant's Post-Action Analysis of Additional Study Safety Data to Address the Deficiencies in the Complete Response Letter

This section will focus on whether the previously identified clinical deficiencies have been adequately addressed.

In the End-of-Review Meeting Package, submitted Aug. 15, 2014, the Applicant presented additional information from a post-action analyses of data from the original NDA, and included supportive published literature articles where needed to address the three safety concerns identified in the CRL. This information was included in the Complete Response NDA resubmission.

Analysis of Follow-up Safety Data for Adverse Events Related to the Shoulder Joint and Surrounding Tissues

The two most concerning adverse events in patients with a history of shoulder injury requiring surgical intervention are glenohumeral chondrolysis and adhesive capsulitis (AC), commonly referred to as frozen shoulder. Glenohumeral chondrolysis generally presents with profound pain, decreased range of motion, and radiographic evidence of loss of cartilage. AC is a painful condition of the shoulder that involves progressive loss of both passive and active glenohumeral joint range of motion. In general, significant loss of function is defined as more than 25% loss of normal shoulder range of motion in at least two directions, most commonly abduction and external rotation. Chondropathy is not synonymous with, nor a precursor for, chondrolysis. It refers to a variety of joint diseases, including arthritic conditions, and is not related to administration of local anesthetics.

The Applicant conducted four additional evaluations in patients undergoing shoulder surgery in their clinical studies, including re-reading MRIs concerning for joint changes or chondropathy, re-reading all MRIs in study C80-017 and Study C803-017e, follow-up physical examinations, and long-term follow-up for patients in Study BU-002-IM and Study CLIN005-0006 which will be discussed briefly below.

The first additional evaluation involved two independent orthopedic surgeons re-reading baseline and 18-month follow-up MRIs, in a blinded fashion, for the three patients from Study C803-017e with a reported SAE or concerning MRI findings for post-arthroscopic glenohumeral chondrolysis (PAGCL) or chondropathy. The surgeons concluded that there were no signs of chondrolysis or chondropathy in any patient, even after the concerns identified by the Division were presented.

The second additional evaluation involved a radiologist re-reading, in a blinded fashion, the baseline and 18-month follow-up MRIs from "as many MRI images as possible" from Study C803-017 and Study C803-017e. Of the 45 follow-up MRIs completed at 18 months, 43 (96%) were available for re-read.

Once the MRIs were read by the radiologist, an orthopedic surgeon with experience in shoulder surgery reviewed the images with the radiologist to assess the clinical relevance of any radiological findings. Their finding in the staged reading process were summarized in a report. The verbatim conclusion of their report, from the Complete Response re-submission ISS (verbatim from the ISS, page 35):

- *No unexpected injuries or findings*
- *Prevalent findings that did not show change on the post-operative [images]*
- *All changes noted on the images were characterized as related to surgery or to natural progression of an underlying disease or condition*
    - *Majority were related to the acromio-clavicular joint and bursitis*
    - *In a limited number of cases, there were changes in the rotator cuff that were related to surgical debridement*
    - *In particular, there were no cartilage or bone lesions identified that would be of concern*

The third additional evaluation involved follow-up physical examinations of patients treated in Study C803-017 by still blinded investigators 18 months post-operatively. These results indicate that there were no concerning surgical site healing or local tissue conditions observed at the 18-month follow-up visit. In addition, the results of the shoulder examination were consistent with reports in the published literature regarding post-operative functional changes and physical examination findings.

And fourth, the Applicant evaluated long-term follow-up data from patients who completed Study BU-002-IM and Study CLIN005-0006 in shoulder surgery.

Study BU-002-IM
Most treated patients in all treatment groups had either improvement or no change at the six-month follow-up exam. There were no reports of cartilage thinning in the glenohumeral joint and no evidence that administration of SABER-bupivacaine resulted in abnormal healing or the shoulder joint or surrounding tissue.

Study CLIN005-0006
The Applicant sent each investigator in the study a letter and a survey CRF listing each of the treated patients at their site. The investigators were asked to review the clinical records and indicate on the CRF whether chondrolysis was reported. All but one investigator responded and reported no cases of chondrolysis. The single investigator who did not respond to the written survey request had responded to the earlier telephone survey and indicated no patient had developed chondrolysis subsequent to the study.

The additional information submitted for the safety issue related to the shoulder joint and associated tissues was adequate to address the shoulder related safety deficiencies in the CR letter. However, it should be noted that SABER-bupivacaine was administered into the subacromial space rather than in the surgical site which may have had an impact on wound-

related adverse events.

Analysis of Follow-up Safety Data for Local Toxicity to SAIB Exposure

The wound-related adverse events of interest, as described in the CRL, included bruising, hematoma, pruritis, and dehiscence. To address these issues, the Applicant evaluated follow-up data from the following studies:

- C803-25 (3 cohorts: laparotomy, laparoscopic cholecystectomy, and laparoscopic assisted colectomy)
- CLIN803-006-0006 (inguinal herniorrhaphy)
- BU-001-IM (abdominal hysterectomy)
- BU-002-IM (arthroscopic shoulder surgery) and
- C803-017e(arthroscopic shoulder surgery)

It appeared that this post-action assessment of the above studies did not identify any abnormalities in wound healing or long-term adverse events.

In addition, the Applicant enlisted Dr. James M. Anderson, M.D., Ph.D., an expert on biocompatible injectable and implant materials and foreign body reactions to biomaterials to review the two nonclinical studies, one in rats and one in rabbits, that demonstrated foreign body reactions to SABER-bupivacaine. He concluded the following:

> *"These findings are similar and equivalent for both studies and demonstrate the normal resolution of the inflammatory and healing responses with the expected foreign body reaction at the implant/tissue interface. Overall, these findings indicate that these formulations are biocompatible in both rats and rabbits and no untoward pathology findings were found in either species."* (ISS, p. 64, PDF, Applicant's submission, NDA 204803)

The additional information included in the complete response resubmission for the wound related safety issues is a post-action analysis conducted by the Applicant instead a prospective unbiased collection of data. The PERSIST study indicates ongoing wound related safety issues with SABER-bupivacaine, specifically wound hematoma and dehiscence. There is a concern that these adverse events may mask an early surgical infection or create an environment conducive to surgical site infections.

Analysis of Follow-up Safety Data for Neurologically Related Adverse Events

As described in the CRL, the Division noted an imbalance in the incidence of nervous system adverse events, potentially related to benzyl alcohol exposure, specifically somnolence, dizziness, and dysgeusia, between patients treated with a SABER product and those treated with bupivacaine HCl. The Applicant provided a rationale for this imbalance, indicating it was due to the varied methods for adverse event collection; specifically, whether adverse events were spontaneously reported or queried. The Applicant has stated that when the adverse events were analyzed from studies using the same collection methods, headache was the only

adverse event reported with an increased frequency in patients treated with a SABER product, and none resulted in more serious adverse events or delayed time to discharge from the PACU.

This represents another post-action analysis of data conducted by the Applicant instead of a prospective unbiased collection of data. Furthermore, the PERSIST study identifies ongoing concerns related to adverse events related to benzyl alcohol.

Clinical Pharmacology Review of the Submitted Data

DURECT Corporation submitted a New Drug Application (NDA) for Posimir™ (*notated as Posimir or 'SABER-Bupivacaine' throughout this study; they are interchangeably used in the review*) under Section 505(b)(2) of the Food, Drug, and Cosmetic Act. The Applicant has developed Posimir [660 mg bupivacaine/5 mL (132 mg bupivacaine/mL; 13.2%)] for post-surgical analgesia as injection/infiltration/instillation (e.g., as a trailing subcutaneous injection administered along each side of the incision; as a wound infiltration; or instillation directly into the wound) into the wound before closure. Posimir is claimed by the Applicant as bupivacaine extended-release (ER) sterile solution. The Applicant proposed Marcaine® (NDA 16964) as the listed drug, and, appropriately the Applicant conducted a relative bioavailability study between Posimir and Marcaine® (Study BU-001-IM).

The Applicant claimed that Posimir was administered once per surgery and deliver bupivacaine over, at least, 72 hours. As such, Posimir was considered as single dose use only. The total Posimir dose proposed is 5 mL per surgery. Since Posimir is administered at the local site(s) as a local acting product, the critical clinical pharmacology aspect of this NDA was to focus on the bupivacaine systemic exposure from the systemic safety purpose. The systemic bupivacaine exposure from the proposed Posimir formulation can be significantly influenced by the tissue properties at the site of administration, which may differ in their degree of vascularization and presence of different types of tissue at or near the wound.

Table 1 contains the studies provided by the Applicant. Except as indicated in the table below (SABER01-01), all the studies submitted in the clinical pharmacology section were reviewed from the clinical pharmacology perspective. It is noted that BU-002-IM and CLIN803-006-0006 were identified as 'pivotal' efficacy trials. Most of the bupivacaine exposure information came from the studies conducted with the final formulation.

Table 1 Studies submitted under Clinical pharmacology section

Study	P	Surgery	Study Drug (Dose)	Type of Administration	Clinical Pharm review
SABER01-01	I	Healthy Subjects	(b) (4)		**No**; not a to-be-marketed formulation, and it is not in patients under surgery
CLIN005-0008	I	Healthy Subjects **-abdomen**	SABER-Bup 5.0 mL Bupivacaine HCl IV Infusion (20 mL)	Two 2.5 mL Trailing SC Inj.[a]	Y; not an absolute BA study
CLIN004-0001	IIa	Hernia Repair Under general anesthetic	SABER-Bup (2.5, 5.0, 7.5 mL) Bup HCl (15 – 17.5 mL) SABER-Placebo	2 trailing SC inj.	Y
CLIN004-0009	IIa	Hernia Repair With local anesthetic (Marcaine);	SABER-Bup (5.0, 7.5 mL) Bup HCl (5.0, 7.5 mL)	Infiltration + trailing inj.	Y; Use of local anesthetic.

CLIN005-0007	II	PILOT study Hernia Repair	SABER-Bup (5.0 mL)	Instillation	**Cursory review:** Posimir 'seeped' out from the wound.' Per Applicant
CLIN803-006-0006	II	Hernia Repair	SABER-Bup (2.5, 5.0 mL) SABER-Placebo	Instillation	Y; linearity information
CLIN005-0006 (06-07)	II	Subacromial Decompression	SABER-Bup (5.0 mL) SABER-Placebo	Subacromial Inj. + SC trailing inj. Subacromial Inj.	Y
BU-002-IM (09-2010)	II	Subacromial Decompression	SABER-Bup (5.0, 7.5 mL) SABER-Placebo Bup HCl 50 mg (20 mL)	Subacromial Inj.	Y; "SABER-Bup fluid leaked"
CLIN005-0002	II	Appendectomy	SABER-Bup (5.0 mL) SABER-Placebo	Trailing Inj.Only Infiltration + trailing inj.	Y
BU-001-IM	II	Hysterectomy	SABER-Bup (5.0 mL) SABER-Placebo Bup HCl 100 mg (40 mL)	Instillation /Infiltration	Y; relative BA
C803-025	III	Laparotomy procedures[b]	SABER-Bup (5.0 mL) SABER-Placebo Bup HCl 30 mL	Instillation /Infiltration	Y

a. Trailing inj. - advancing a needle into the SC space and inject continuously as the needle was withdrawn.
b. Laparotomy, Laparoscopic Cholecystectomy, Laparoscopically Assisted Colectomy

Out of the many studies conducted, the following surgical procedures are proposed in the Label and the studies which the pertinent PK exposure information is available (Table 2).

Table 2 Proposed indications in the Label and the PK studies which pharmacokinetic information is available

Proposed Label incision type or surgical procedure	Proposed Administration	Study report presenting the PK information
Open (Linear) Incisions	After closure of the fascial layer (if applicable) and immediately prior to skin closure, POSIMIR should be distributed within the entire length of the incision using a bare (needle-free) syringe tip or, for greater precision, a short blunt-tipped cannula (e.g., 14-gauge IV catheter) attached to the syringe tip. For long incisions, an irrigation catheter may be placed into the incision above the fascial layer, followed by closure of the cutaneous layer over the catheter. POSIMIR may then be administered through the irrigation catheter while the catheter is gradually withdrawn from the incision.	**BU-001-IM** **C803-025, Cohort 1** **C803-025, Cohort 3**
Laparoscopic or Endoscopic Port Incisions	After removing the trocars and (if applicable) desufflating the abdomen, POSIMIR should be instilled directly into the port incisions using either a bare (needle-free) syringe tip or, for greater precision, a short blunt-tipped cannula (e.g., 14-gauge IV catheter) attached to the syringe tip. The 5 mL drug volume should be divided among the port incisions to provide coverage of all the incisions.	**C803-025, Cohort 2**

Inguinal Hernia Repair Surgery	One half (2.5 mL) of the 5 mL dose of POSIMIR should be instilled into the floor of the inguinal canal and the other half (2.5 mL) should be instilled into the subcutaneous space or endoscopic port incisions just prior to closure of the skin.	**CLIN803-006-0006**
Arthroscopic Subacromial Decompression Surgery	At the close of surgery, the entire 5 mL dose of POSIMIR should be instilled into the subacromial space using an 18 gauge or larger-bore needle. The needle may be inserted through an existing arthroscopic port or through intact skin to reach the subacromial space. Correct placement of the needle tip within the subacromial space should be confirmed by direct visualization with the arthroscope. POSIMIR should not be instilled into the intra-articular space.	**CLIN005-0006 BU-002-IM**

Source: Response to Information Request, Sequence Number 0031, 10/4/19

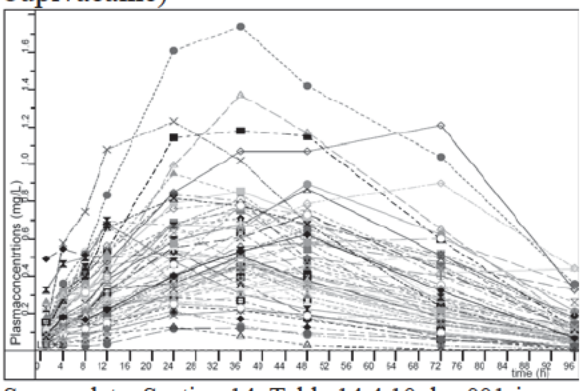
Below is a discussion of the conduct and results of the Applicant's surgical procedure studies assessing the bioavailability and pharmacokinetics of bupivacaine. Bupivacaine was analyzed via the liquid chromatography mass spectrometry (LC-MS/MS) method.

1. Open (Linear) Incisions Procedure

Study BU-001-IM was a Phase 2, randomized, multi-center, double-blind, parallel group, placebo- and active-controlled study in women undergoing primary elective open non-malignant abdominal hysterectomy. The relative bioavailability result in this study was used to establish the "link" between the proposed product and Marcaine®.

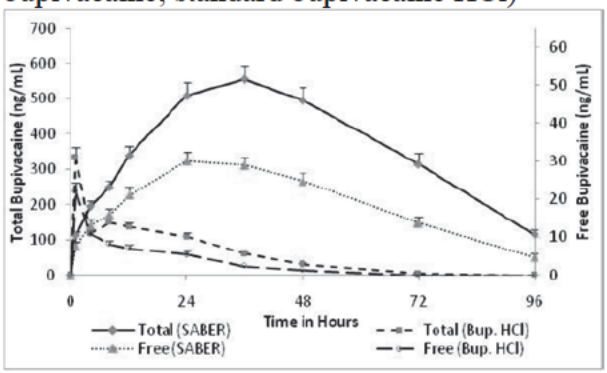
The individual and mean (SEM) patient plasma concentrations by-time profiles following instillation of 5 mL SABER-Bupivacaine (660 mg bupivacaine) are presented in Figures 1 and 2, respectively.

Figure 1 Individual total bupivacaine plasma concentrations following administration of 5 mL SABER-Bupivacaine (660 mg bupivacaine)



Source data: Section 14, Table 14.4.10; bu-001-im-report-body.pdf (p.96/603)

Figure 2 Mean (SEM) total and free bupivacaine plasma concentrations following administration of SABER-Bupivacaine (660 mg bupivacaine) or Marcaine® (100 mg bupivacaine; standard bupivacaine HCl)

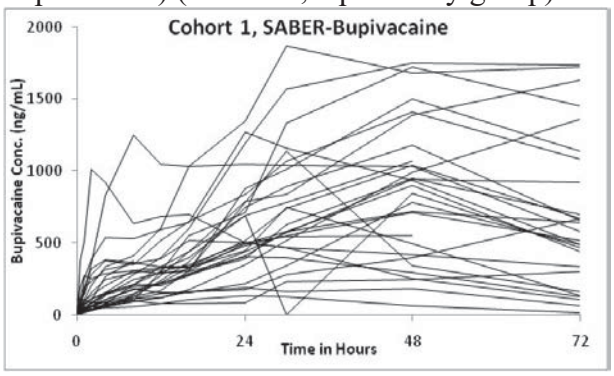


Source: summary-clin-pharm.pdf (p.48/80)

Study C803-025 was a Phase 3, multi-center, randomized, double-blind, active- and placebo-controlled trial evaluating the safety, efficacy, effectiveness and pharmacokinetics of SABER-Bupivacaine 5.0 mL, in patients undergoing laparotomy related surgical procedures with various wound sizes. The surgical procedures (or cohorts) are as follows:
1) Cohort 1 – Laparotomy; 2) Cohort 2 - Laparoscopic cholecystectomy; and, 3) Cohort 3 - Laparoscopically-assisted colectomy.

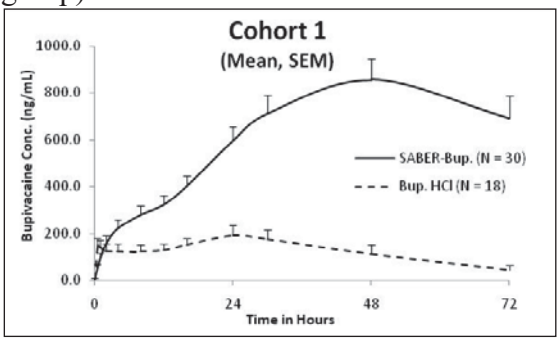
The individual and mean (SEM) patient plasma concentrations by-time profiles for Cohort 1, laparotomy group, are presented in Figures 3 and 4, respectively.

Figure 3 Individual Bupivacaine Plasma Concentration Following Administration of 5 mL of SABER-Bupivacaine (660 mg bupivacaine) (Cohort 1, laparotomy group)



Source: c803-025-report-body.pdf (p.111/2215)

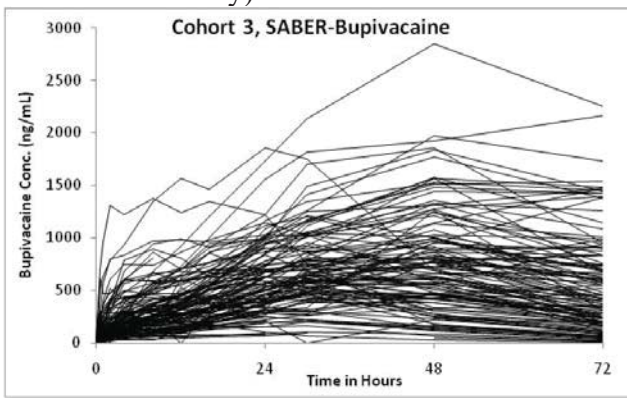
Figure 4 Mean (SEM) Bupivacaine Plasma Concentration Following Administration of 5 mL SABER-Bupivacaine (660 mg bupivacaine) or 150 mg Sensorcaine (Bupivacaine HCl) (Cohort 1, laparotomy group)



Source: c803-025-report-body.pdf (p.112/2215)

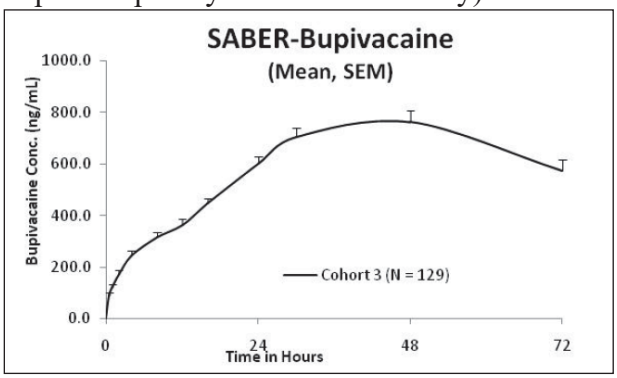
The individual and mean (SEM) patient plasma concentrations by-time profiles for Cohort 3, Laparoscopically-assisted colectomy group, are presented in Figures 5 and 6, respectively.

Figure 5 Individual Bupivacaine Plasma Concentration Following Administration of 5 mL of SABER-Bupivacaine (660 mg bupivacaine) (Cohort 3, Laparoscopically-assisted colectomy)



Source: c803-025-report-body.pdf (p.117/2215)

Figure 6 Mean (SEM) Bupivacaine Plasma Concentration Following Administration of 5 mL SABER-Bupivacaine (660 mg bupivacaine) only (Cohort 3, Laparoscopically-assisted colectomy)



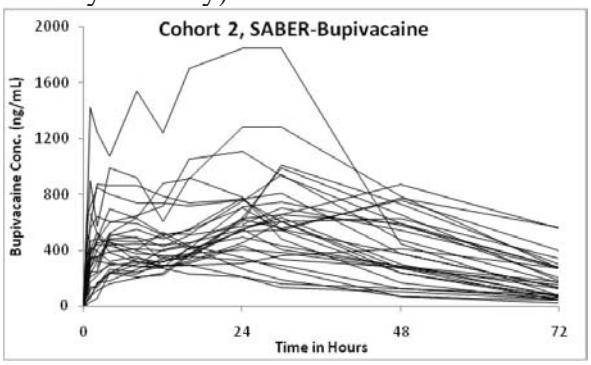
Source: c803-025-report-body.pdf (p.117/2215)

2. Laparoscopic or Endoscopic Port Incisions Procedure

Cohort 2 of Study C803-025 evaluated the safety, efficacy, effectiveness and pharmacokinetics of SABER-Bupivacaine 5.0 mL, in patients undergoing laparoscopic cholecystectomy.

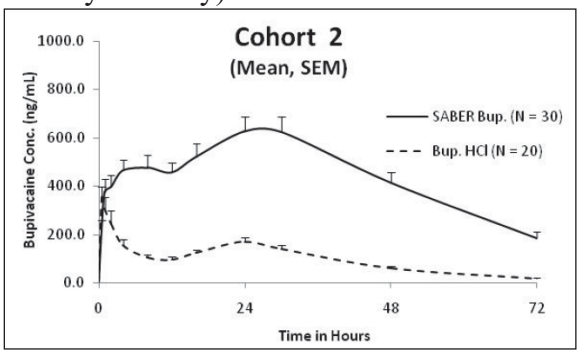
The individual and mean (SEM) patient plasma concentrations by-time profiles for Cohort 2, Laparoscopic cholecystectomy group, are presented in Figures 7 and 8, respectively.

Figure 7 Individual Bupivacaine Plasma Concentration Following Administration of 5 mL of SABER-Bupivacaine (660 mg bupivacaine) (Cohort 2, Laparoscopic cholecystectomy)



Source: c803-025-report-body.pdf (p.114/2215)

Figure 8 Mean (SEM) Bupivacaine Plasma Concentration Following Administration of 5 mL SABER-Bupivacaine (660 mg bupivacaine) or 150 mg Sensorcaine (Bupivacaine HCl) (Cohort 2, Laparoscopic cholecystectomy)



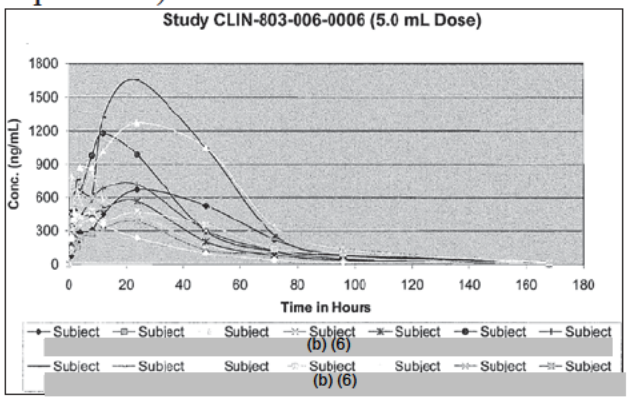
Source: c803-025-report-body.pdf (p.115/2215)

3. Inguinal Hernia Repair Surgery Procedure

Study CLIN-803-006-0006 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-response, Phase II study to examine the efficacy, pharmacokinetics, and safety of SABER-Bupivacaine instilled directly into the wound in patients undergoing elective open unilateral tension-free inguinal hernia repair.

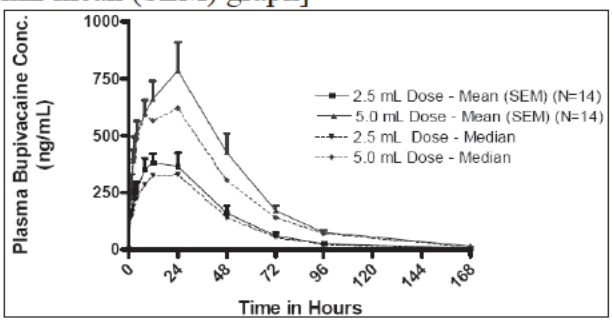
The individual and mean (SEM) patient plasma concentrations by-time profiles following instillation of 5 mL SABER-Bupivacaine (660 mg bupivacaine) are presented in Figures 9 and 10, respectively.

Figure 9 Individual Bupivacaine Plasma Concentration Following Administration of 5 mL of SABER-Bupivacaine (660 mg bupivacaine)



Source: clin-803-006-0006-csr.pdf (p. 1209/3611)

Figure 10 Mean (SEM) Bupivacaine Plasma Concentration Following Administration of 5 mL SABER-Bupivacaine (660 mg bupivacaine) [this figure also displays 2.5 mL mean (SEM) graph]



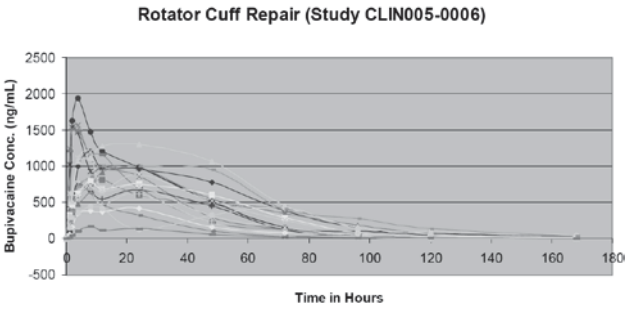
Source: clin-803-006-0006-csr.pdf (p. 87/3611)

4. Arthroscopic Subacromial Decompression Surgery Procedure

Study CLIN005-0006 was a randomized, double-blind, placebo-controlled, Phase 2 study to examine the efficacy and safety of SABER-Bupivacaine administered subcutaneously or into the subacromial space in subjects undergoing elective arthroscopic shoulder surgery. The study was conducted in 2 separate and sequential cohorts, Cohort 1 and Cohort 2, with various dosing schemes, e.g., in Cohort 1, SABER-Bupivacaine injection was administered as either 'prior to wound closure' or 'after wound closure' as trailing subcutaneous injections along each side of the incision line; in Cohort 2, SABER-Bupivacaine injection was administered into the subacromial space during the wound closure. For bupivacaine exposure assessment, SABER-Bupivacaine 5.0 mL (660 mg bupivacaine) administered in the subacromial space during the wound closure was analyzed.

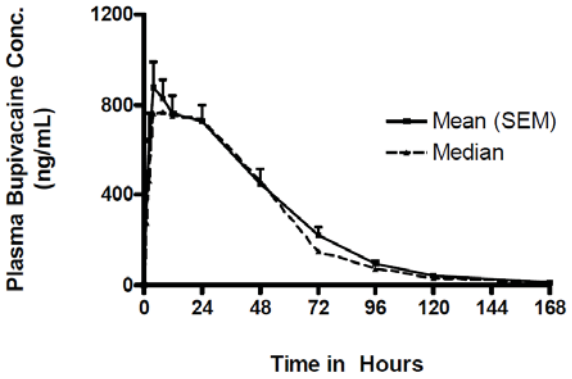
The individual and mean (SEM) patient plasma concentrations by-time profiles following administration of 5 mL SABER-Bupivacaine (660 mg bupivacaine) are presented in Figures 11 and 12, respectively.

Figure 11 Individual plots of bupivacaine concentrations following rotator cuff repair surgery with 5 mL SABER-Bupivacaine (660 mg bupivacaine)



Source: clin005-0006-csrb.pdf (p. 675/2237)

Figure 12 Mean (SEM) plots of bupivacaine concentrations following rotator cuff repair surgery with 5 mL SABER-Bupivacaine (660 mg bupivacaine)



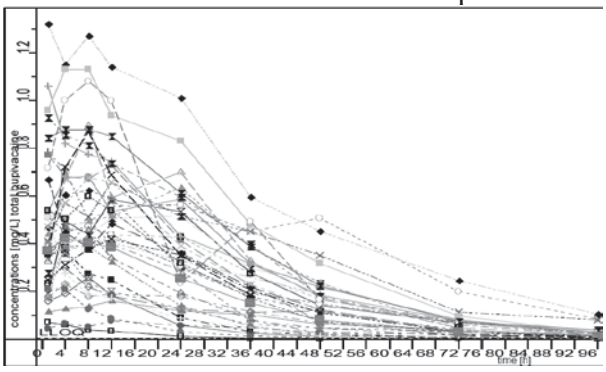
Source: clin005-0006-csrb.pdf (p. 669/2237)

Study BU-002-IM was a parallel group, randomized, double-blinded, active- and placebo-controlled, dose response trial of SABER-Bupivacaine with post-operative assessments of pain intensity, PK, safety, and health economics in patients undergoing elective arthroscopic shoulder surgery.

The individual and mean (SEM) patient plasma concentrations by-time profiles following administration of 5 mL SABER-Bupivacaine (660 mg bupivacaine) are presented in Figures 13 and 14, respectively.

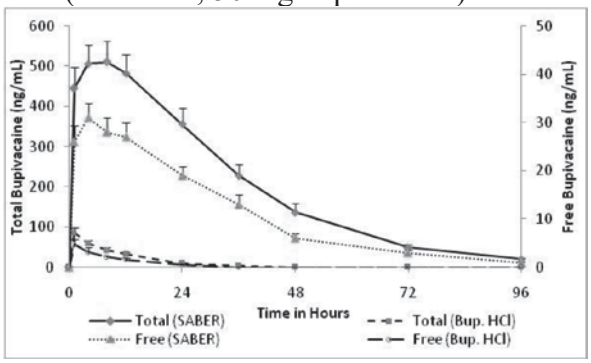
Individual bupivacaine plasma concentrations profiles are shown in Figures 25 and 26 from 5 mL SABER-Bupivacaine and Marcaine, Cohorts a and c, respectively.

Figure 13 Individual bupivacaine plasma concentration profiles following 5 mL SABER-Bupivacaine (660 mg bupivacaine) administered into the subacromial space



Source: bu-002-im-report-body.pdf (p. 651/706)

Figure 14 Total and free bupivacaine plasma concentrations following administration of 5 mL SABER-Bupivacaine (660 mg bupivacaine) or 20 mL standard bupivacaine HCl (Marcaine; 50 mg bupivacaine)



Source: summary-clin-pharm.pdf (p. 39/80)

Clinical Pharmacology Summary

The bupivacaine exposure information from the proposed surgical procedures are presented in Table 3.

Table 3: Overall Bupivacaine Pharmacokinetic information by Surgical Site or Procedure

Surgical Site or Procedure	POSIMIR dose	Cmax (ng/mL)	AUC0-t (h*ng/mL)[a]	AUC0-inf (h*ng/mL)	Tmax (h)	T1/2 (h)
Open (Linear) Incisions	660 mg (5.0 mL)					
BU-001-IM Abdominal hysterectomy	N	59	59	54	59	54
	Mean	625	35232	36830*	36.0#	19.5*
	SD	310	18719	21060*	-	4.67*
	Minimum	119	4421	4474*	4.0	11.3
	Maximum	1740	105324	122170*	95.9	58.1
C803-025 Cohort 1 Laparotomy	N	30	30	Insufficient data to compute	30	Insufficient data to compute
	Mean	956	41942		48.1#	
	SD	484	24344		-	
	Minimum	133	635		2.2	
	Maximum	1870	96625		72.8	
C803-025 Cohort 3 Colectomy	N	129	129	Insufficient data to compute	129	Insufficient data to compute
	Mean	850	39602		46.6#	
	SD	478	24049		-	
	Minimum	92	1626		1.1	
	Maximum	2850	136309		73.8	
Laparoscopic or Endoscopic Port Incisions	660 mg (5.0 mL)					
C803-025 Cohort 2 Laparoscopic cholecystectomy	N	30	30	Insufficient data to compute	30	Insufficient data to compute
	Mean	752	30997		24.3#	
	SD	307	12680		-	
	Minimum	357	11100		1.0	
	Maximum	1850	68108		48.6	
Inguinal Hernia Surgery	660 mg (5.0 mL)					
CLIN803-006-0006 Open inguinal hernia repair	N	14	14	14	14	14
	Mean	867	40823	41461	24.0#	28.6
	SD	427	20312	20221	-	13.4
	Minimum	383	15338	18089	4.0	20.9
	Maximum	1650	78602	78909	24.1	73.3

Arthroscopic Subacromial Decompression Surgery	660 mg (5.0 mL)					
BU-002-IM Arthroscopic subacromial decompression	N	36	36	36	36	36
	Mean	593	19395	19963	5.9#	16.4
	SD	299	12056	12587	-	5.1
	Minimum	70	1028	1051	1.0 [b]	8.4
	Maximum	1320	55369	58966	24.0	28.9
CLIN005-0006 Arthroscopic subacromial decompression	N	18	18	18	18	18
	Mean	1006	47015	47649	8.0#^	26.1
	SD	454	20040	20116	-	8.2
	Minimum	172	7247	7346	2.1	16.6
	Maximum	1940	85980	86448	26.9	50.8

[a] t = last
[b] The BU-002-IM minimum value for Tmax was incorrectly reported as "0.0" in the original NDA but has been corrected here (see BU-002-IM CSR, Section 11.4.2.2 for details).
#Median;
^Source: summary-clin-pharm.pdf (p.35/80)
*BU-001-IM Abdominal hysterectomy: Subjects (b) (6); extrapolation of AUCt-inf exceeds 20%, and value not used in descriptive statistics; Source: bu-001-im-report-body.pdf (p.531/603)
Source: Response to Information Request, Sequence Number 0031, 10/4/19

Overall, the individual and mean plasma concentration-time profiles of bupivacaine after administration of Posimir show that bupivacaine was measurable at least up to 72 hours, with most of the bupivacaine Tmax (median) occurring at 10 – 48 hours post Posimir administration.

Based on the observed bupivacaine systemic profile, Posimir exhibits the characteristics of delayed Tmax. However, Posimir is a locally administered drug and exerts its action locally. The bupivacaine systemic exposure from Posimir should only be used as supportive evidence to determine if Posimir can be categorized as an extended release product. Whether Posimir can be categorized as an extended release product should also rely on other aspects (e.g. in vitro release profile, especially whether Posimir could reduce the dosing frequency clinically compared to IR formulation of bupivacaine, etc.)

Comparison of mean Cmax and AUC values obtained from Study BU-002-IM with Study CLIN005-0006, in both the SABER-Bupivacaine and standard bupivacaine HCl groups, showed that Cmax and AUC values from Study BU-002-IM were about 50% lower than Study CLIN005-0006. The Applicant suspected leakage/seepage of SABER-Bupivacaine of various volumes of the administered dose from the wound between the time of drug administration and closure of the wound (arthroscopic portals).

It appears that there is no correlation between bupivacaine Cmax or AUC and incision lengths. That is, increase in incision lengths does not necessarily increase bupivacaine Cmax or AUC. This observation is reasonable since the entire 5 mL-volume of Posimir was administered at the surgical site.

Regarding the relative bioavailability of Posimir compared to Marcaine, bupivacaine mean Cmax value from Posimir (660 mg bupivacaine) was 625 ng/mL compared to 342 ng/mL with Marcaine

(100 mg). Bupivacaine mean AUC value Posimir (660 mg bupivacaine) was 36830 ng.h/mL compared to 5740 ng.h/mL with Marcaine (100 mg). Bupivacaine Cmax and AUC values from the 2.5 and 5.0 mL Posimir exhibited linear pharmacokinetics.

Regulatory Summary

Posimir is formulated as a 12% solution (132 mg bupivacaine/mL) with a maximum administration volume of 5 mL allowing for 660 mg of bupivacaine to be instilled within a site. Posimir contains two principal excipients, benzyl alcohol ((BA) 22% (220 mg/mL)) to provide for reducing viscosity on initial instillation and sucrose acetate isobutyrate ((SAIB) 66% (725 mg/mL)) for the formation of a depot matrix for the extended release of bupivacaine.

DURECT Corporation opened IND 066086 on October 23, 2002. The original formulation of their drug product included (b) (4) a compound with carcinogenic potential. In the nonclinical studies conducted by the Applicant, tissue inflammation and necrosis were observed and the Division advised the Applicant to change the formulation based on these findings prior to initiating studies in humans. The IND was withdrawn and clinical studies were conducted outside the United States. The product was subsequently reformulated using BA and the (b) (4) was removed. The IND was reopened on December 23, 2005, with Phase 2 study protocols.

The following table summarizes the interactions between DURECT Corporation and the Division.

Meeting / Communication / Date	Event / Key Clinical Issues
IND 066086 opened / Oct. 23, 2002	Formulation contained (b) (4) a solvent with carcinogenic potential. The Division advised the Sponsor to change the formulation to address the clinical concerns. The Sponsor withdrew the IND before a clinical hold was instituted and conducted a clinical study outside the U.S., which did not demonstrate analgesia. A new formulation was developed, which contained benzyl alcohol in place of (b) (4) and the IND was reopened on Dec. 23, 2005, with two Phase 2 study protocols.
IND 0066086 partial clinical hold / Nov. 3, 2006	Safety concerns for systemic toxicity after administration of SABER-bupivacaine 7.5 mL. The Sponsor was advised to monitor for toxicity for up to 48 hours after administration.
December 27, 2006	The Sponsor proposed to conduct two Phase 3 studies in support of NDA submission. The Sponsor was advised that the NDA would need 400 patient exposures to local wound infiltration and 500 for a novel route of administration, including intra-articular.
End-of-Phase 2 Meeting / Sept. 14, 2007	The following key clinical advice was provided: - Foreign clinical sites are acceptable, but a justification will be needed for the applicability of the data to the U.S. population. - Indications based on limited development programs are not recommended; however, a narrow indication may be possible based on SABER-bupivacaine's novel route of administration. - An indication limited to inguinal hernia surgery would require the demonstration of safety and efficacy in two adequate and well-controlled studies. - Inadequate evaluation of ECG data during Phase 2 studies,

Meeting / Communication / Date	Event / Key Clinical Issues
	therefore, the Phase 3 studies need systematic evaluations of the cardiovascular and neurological effects of SABER-bupivacaine beyond the time of maximum plasma concentration (T_{max}) and throughout the duration of analgesic action. - The NDA will need to demonstrate safety of the benzyl alcohol and SAIB components of the to-be-marketed product.
Request for a Special Protocol Assessment (SPA) / August 1, 2008	The Sponsor submitted a SPA for a study evaluating patients undergoing arthroscopic shoulder surgery. The request was denied. The Sponsor did not resubmit the protocol but opted to conduct the study as a Phase 2.
SPA / No Agreement / Sept. 18, 2008	The key clinical advice provided regarding the proposed arthroscopic shoulder surgical model is as follows: - Provide a rationale as to how administered bupivacaine will not enter the joint capsule - Opioid-sparing is not an indication - A non-SABER placebo should be included in the clinical evaluations - Safety assessments must include neurotoxicity evaluations, prolonged exposure evaluations, and opioid adverse events and should extend through T_{max} - A broad postsurgical indication must include a wide range of evaluated surgical procedures.
Pre-NDA Meeting / July 31, 2012	The following key clinical advice was provided: - Only one adequate and well-controlled study may be acceptable if the results were adequately robust and able to withstand sensitivity analyses - The single study must provide evidence of efficacy and safety of SABER-bupivacaine when administered during a variety of surgical procedures - The single study must allow a determination of the adequacy of the dosing paradigm to be used with SABER-bupivacaine - Wound discoloration needs to be further evaluated - SABER-bupivacaine effect on the QTc interval needs to be characterized.
NDA 204803 received / April 12, 2013	NDA filed on June 17, 2013.
Discipline Review Letter (DRL) / Jan. 14, 2014	The risk of chondrolysis and select adverse events, and efficacy issues were included in the DRL (refer to the text following this table for additional information).
Response to Discipline Review Letter / Feb. 3, 2014	The Applicant provided responses to the clinical deficiencies identified in the DRL, including adequate evidence of efficacy for SABER-bupivacaine following both arthroscopic subacromial decompression and inguinal herniorrhaphy. The Applicant provided supportive information for the safe administration of SABER-bupivacaine during arthroscopic shoulder surgery, such that chondrolysis was no longer a safety concern included in the CRL.

Meeting / Communication / Date	Event / Key Clinical Issues
Complete Response Letter / Feb. 12, 2014	Clinical CR issues identified: - Insufficient data to fully characterize adverse events reported in patients who received SABER-bupivacaine during arthroscopic shoulder surgery - Wound-related adverse events, particularly bruising, hematoma, pruritus, and dehiscence, occurred more frequently in patients treated with SABER products - Increased incidence of neurologically-related adverse events in patients treated with SABER products.
End-of-Review-Cycle Meeting / Sept. 23, 2014	This meeting was held to discuss the deficiencies identified in the CRL and determine a path toward approval. The discussion focused on the following key issues: - An additional study in a soft tissue model would be needed to support a broad post-surgical indication - Bupivacaine should be included as an active comparator treatment - Physician education and post-market pharmacovigilance monitoring regarding the risk of chondrolysis after administration of SABER-bupivacaine will not replace the required data to support safe use - Post-surgical bruising had not been adequately addressed - Safety database was inadequate to fully characterize the safety profile of SABER-bupivacaine for the following reasons: • Nonclinical data suggesting the SAIB component of the drug product persists for months after administration and can generate foreign body reactions • Systemic exposure to benzyl alcohol • Limited data on the risks of bruising, hematoma, pruritus, and dehiscence after administration of SABER-bupivacaine compared to bupivacaine HCl - Adverse events of interest to be evaluated in new clinical study were discussed - The increase incidence in neurologically-related adverse events in SABER-bupivacaine-treated patients may have been due to the adverse event reporting method - Time to PACU discharge may be an acceptable clinical outcome to determine the impact of neurological-related adverse events after administration of SABER-bupivacaine - The Applicant no longer plans to pursue a post-arthroscopic shoulder indication.
Formal Dispute Resolution Request (FDRR) / Nov. 21, 2014	Based on the issues identified in the CRL and the disagreement on how to adequately address the issues, the Applicant submitted a FDRR.
FDRR Meeting / Dec. 16, 2014	Key issues discussed included End-of-Review meeting minutes, safety of SABER-bupivacaine, efficacy in surgical models evaluated, DURECT's response to the DRL, wound healing questionnaire, risk/benefit of SABER-bupivacaine, and potential neurotoxicity. Final determination on the Applicant's FDRR will be made by Jan. 15, 2015.
FDRR Appeal Denial Letter / Jan. 15, 2015	FDRR appeal denied based on safety and efficacy concerns. Dr. Thanh Hai proposed two paths forward for the Applicant:

Meeting / Communication / Date	Event / Key Clinical Issues
	- Conduct an additional clinical study to better characterize the risk-benefit profile of SABER-bupivacaine - Include all information provided in the EOR background materials in a resubmission with a justification as to why this additional information is supportive of a favorable risk-benefit profile for SABER-bupivacaine.
Phase 3 protocol synopsis received / Feb. 22, 2015	Sponsor proposed to evaluate the safety and efficacy of SABER-bupivacaine in patients undergoing laparoscopic cholecystectomy.
Advice Letter / June 15, 2015	Division provided feedback for proposed Phase 3 study.
Phase 3 protocol received / Aug. 31, 2015; Protocol Amendment 1 received / Oct. 22, 2015	Comments send to the Sponsor in an Advice Letter, dated Jan. 11, 2016, and included the following: - Adverse event-based stopping criteria must be included in the protocol - Vital sign monitoring must be around the time of T_{max} for benzyl alcohol - All laboratory data must be included in NDA resubmission - Pulse oximetry must be included in the safety monitoring - The adverse events of dysgeusia, paresthesia, and hypoesthesia must be included as solicited adverse events - Strong recommendation for bupivacaine to be included as an active comparator - Opioid conversion method needed.
Advice Letter / Jan. 11, 2016	The Division provided advice on the proposed safety monitoring and recommended bupivacaine as an active comparator.
Protocol Amendment 2 received / Feb. 23, 2016	This amendment addressed some the previously identified safety concerns but not an active comparator.
Teleconference / April 5, 2016	The need for an active control group was discussed.
Advice Letter Issued / May 16, 2016	Outlined unresolved safety and statistical concerns.
Protocol Amendment 3 Received / June 6, 2016	This amendment incorporated an active control, bupivacaine HCl, and some previously recommended safety monitoring.
Advice Letter Issued / Sept. 19, 2016	Recommendations regarding the dose of bupivacaine HCl and unresolved safety concerns outlined, including inadequate stopping criteria, duration of monitoring for benzyl alcohol toxicity, removal wound-related adverse events, and the use of anticoagulant and antiplatelet medications post-operatively.
Protocol Amendment 4 received / Jan. 19, 2017	This amendment addressed the proposed dose of bupivacaine HCl, measurement of wound-healing issues, and use of post-operative anticoagulant and antiplatelet medications.
Teleconference / Feb. 7, 2017	Discussion focused on ongoing safety concerns, including wound-related serious adverse events, cardiac and neurological serious adverse events, stopping criteria, benzyl alcohol safety monitoring, and exclusion criteria.
Protocol Amendment 5 received /	There were no further safety concerns and the protocol was allowed to

Meeting / Communication / Date	Event / Key Clinical Issues
March 10, 2017	proceed.
NDA 204803 Resubmission received / June 27, 2019	Initial review determined the submission was a Complete Response to the identified deficiencies noted in the CRL dated Feb. 21, 2014.

The Applicant submitted NDA 204803 on April 12, 2013, pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Upon completion of the initial NDA review, Dr. Arthur Simone identified the following two clinical deficiencies that were communicated to the Applicant in a Discipline Review Letter (DRL), dated January 14, 2014, and in a teleconference held on January 17, 2014:

> *"For arthroscopic acromial decompression surgery (trials CLIN005-0006, C-803-017, and BU-002-IM) you have adequately demonstrated the efficacy of SABER-bupivacaine. However, the risk of chondrolysis, based on the incident observed with SABER-bupivacaine treatment, outweighs the benefit of SABER-bupivacaine for this surgical procedure and prevents its approval for this indication.*
>
> *For the other surgical procedures studied, you have not adequately demonstrated the efficacy of SABER-bupivacaine. In addition, the incidence of somnolence, dizziness, dysgeusia, hematoma, bruising, dehiscence, and pruritus were greater with SABER-bupivacaine and SABER-placebo treatments than with bupivacaine HCl. Therefore, the risks of SABER-bupivacaine have outweighed the benefits for the non-arthroscopic procedures studied to date."*

In response to the DRL, the Applicant submitted additional information to support the efficacy of SABER-bupivacaine. After review of the Applicant's responses to the deficiencies identified in the DRL, Dr. Simone concluded that adequate evidence of efficacy for use of SABER-bupivacaine over SABER-placebo following both arthroscopic subacromial decompression and inguinal herniorrhaphy had been provided and that efficacy concerns would not be included in the pending Complete Response Letter. He did, however, continue to have the following three concerns regarding the safe administration of SABER-bupivacaine, which were communicated to the Applicant in the Complete Response Letter, dated February 12, 2014:

> *"There were adverse events related to the shoulder joint and surrounding tissues in subjects who underwent follow-up assessments at 18 months, after their arthroscopic subacromial decompression surgery. There were insufficient data due to the limited number of subjects and the lack of an appropriate comparator to permit a determination of whether SABER-bupivacaine causes adverse reactions affecting the joint or the surrounding structures to a clinically relevant greater extent than either bupivacaine HCl or a non-SABER containing placebo.*
>
> *The risk of bruising, hematoma, pruritus, and dehiscence occurred following administration of SABER-containing products (SABER-bupivacaine and SABER-placebo) substantially more often than following administration of bupivacaine HCL. There were insufficient data to determine whether the risk is greater with SABER-bupivacaine than for either bupivacaine HCl or a non- SABER containing placebo following the surgical*

procedures studied and whether the risk was greater with only certain surgical procedures.

There was a marked increased risk of neurologically related adverse events, i.e., dizziness, dysgeusia, headache, hypoesthesia, paresthesia, and somnolence, which occurred with substantially greater frequency following administration of SABER-containing products compared to bupivacaine HCl. There were insufficient data to determine whether the risk is greater with SABER-bupivacaine than for either bupivacaine HCl or a non-SABER containing placebo following each of the surgical procedures studied and clinical impact of these reactions, e.g., whether they delayed discharge from the post-anesthesia care unit or affected time to ambulation."

Information needed to resolve these deficiencies included the following (from the CRL):

Conduct additional studies to adequately characterize the risk profile of SABER-bupivacaine. Specifically, the following types of studies need to be conducted:

- A safety study evaluating the occurrence of adverse reactions associated with the shoulder joint and the surrounding tissues, including the skin, following arthroscopic subacromial decompression. Safety assessments need to be performed at appropriate intervals following the administration of study drug to capture the onset and duration of the reactions and need to be carried out for an appropriate period of time to capture late-onset events. Input should be solicited from expert consultants to help design the study, particularly with respect to appropriate assessments, their frequency and the duration of follow-up.
  The treatments need to include SABER-bupivacaine and either bupivacaine HCL or a non-SABER containing placebo (or both). The study needs to be randomized and double-blinded in design and needs to include enough subjects to detect reactions with an incidence rate of ≥ 1%. Efficacy data must be collected during the study to allow the safety data to be placed in clinical context when the benefit:risk analysis is performed.

- A safety study evaluating the occurrence of adverse reactions associated with the skin and underlying tissues. Safety assessments need to be performed at appropriate time intervals following administration of study drug to capture the onset and duration of the reactions and to be carried out until complete healing of the surgical wound has occurred. The protocol needs to incorporate standardized definitions for the reactions observed thus far in the clinical development program, e.g., hematoma, ecchymosis, dehiscence, to assure uniform classification of the reactions among investigators.
  The treatments need to include SABER-bupivacaine and either bupivacaine HCL or a non-SABER containing placebo (or both). The study needs to be randomized and double-blinded. The study must evaluate subjects undergoing each of the surgical procedures studied to date, with the numbers of subjects undergoing each of the procedures evenly distributed. Efficacy data must be collected during the study to allow the safety data to be placed in clinical context when the benefit:risk analysis is performed.

- A safety study evaluating the occurrence of adverse reactions associated with

neurotoxicity. Safety assessments need to be performed at appropriate time intervals following administration of study drug to capture the onset and duration of the reactions and to be carried out for the duration of systemic exposure to benzyl alcohol. The clinical impact of the adverse reactions needs to be captured, e.g., delayed discharge due to somnolence; delayed time to ambulation due to dizziness. The treatments need to include SABER-bupivacaine and either bupivacaine HCL or a non-SABER containing placebo (or both). The study needs to be randomized and double-blinded in design. The study must evaluate subjects undergoing each of the surgical procedures studied to date, with the numbers of subjects undergoing each of the procedures evenly distributed. Efficacy data must be collected during the study to allow the safety data to be placed in clinical context when the benefit:risk analysis is performed.

The Division strongly recommended that the Applicant discuss the design of the studies with the Division prior to implementation.

In response to the CRL, the Applicant requested a formal dispute resolution, which was addressed by Dr. Mary Thanh Hai, Deputy Director in the Office of Drug Evaluation II (ODE II) at the time. After review of the Applicant's request, the additional data submitted, and the reviews completed by the Division, the appeal was denied. Dr. Thanh Hai proposed the following two paths forward for the Applicant: a) conduct an additional clinical study to better characterize the risk-benefit profile of SABER-bupivacaine *or* b) submit all the information provided in the End-of-Review background materials with justification as to why it is supportive of a favorable risk-benefit profile for SABER-bupivacaine. Because this additional information was not included in the original NDA submission, it could not be reviewed for purposes of modifying the CR regulatory decision.

The Applicant has completed the following additional evaluations to support the safety (and effectiveness) of SABER-bupivacaine when administered into surgical wounds:

- Conducted an additional Phase 3 clinical study evaluating the safety and effectiveness of SABER-bupivacaine in patients undergoing laparoscopic cholecystectomy (lap chole).
- Conducted additional evaluations of the safety of SABER-bupivacaine, including re-analysis of the safety data presented from previously conducted clinical studies.
- Conducted additional evaluations of the effectiveness of SABER-bupivacaine, including reanalysis of the efficacy data presented from previously conducted clinical studies.

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	February 12, 2014
From	Rigoberto Roca, M.D.
Subject	Deputy Division Director Summary Review
NDA/Supplement No.	204803 / 000
Applicant Name	Durect Corporation
Date of Submission	April 12, 2013
PDUFA Goal Date	February 12, 2014
Proprietary Name / Established (USAN) Name	Posimir / (bupivacaine solution)
Dosage Forms / Strength	660 mg bupivacaine/ 5mL 13.2% w/v% solution for instillation
Proposed Indication(s)	Post-surgical analgesia
Action	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Arthur Simone, MD, PhD
CDTL Review	Christopher Breder, MD, PhD
Statistical Review	David Petullo, MS / Janice Derr, PhD
Pharmacology Toxicology Review	Gary Bond, PhD / Adam Wasserman, PhD
ONDQA Review	Edwin Jao, PhD / Julia Pinto, PhD / Prasad Peri, PhD
ONDQA Microbiology Review	Neal Sweeney, PhD / Brian Riley, PhD
Clinical Pharmacology Review	David Lee, PhD / Yun Xu, PhD
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CDTL = Cross-Discipline Team Leader
DGCPC = Division of Good Clinical Practice Compliance
DGMPA = Division of Good Manufacturing Practice Assessment
DMEPA = Division of Medication Error Prevention and Analysis
DRISK = Division of Risk Management
NDMAB = New Drug Manufacturing Assessment Branch
OMP = Office of Medical Policy
OMPQ = Office of Manufacturing and Product Quality
OND = Office of New Drugs
ONDQA = Office of New Drug Quality Assessment
OPDP = Office of Professional Drug Promotion
OSE = Office of Surveillance and Epidemiology
OSI = Office of Scientific Investigations

1. Introduction

Durect Corporation, the Applicant, has submitted a 505(b)(2) new drug application (NDA) for a new formulation of bupivacaine. The reference product is Marcaine NDA 016964. The intent of the new formulation is to allow gradual release of bupivacaine into a surgical site; the indication being sought is post-operative analgesia

This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application and the labeling requested by the Applicant.

2. Background

Posimir® (also referred to as SABER-Bupivacaine in this document) consists of a new formulation of bupivacaine, a currently approved marketed product. Posimir is formulated as a 12% w/w solution (132 mg bupivacaine/mL), which is equivalent to 13.2% w/v due to the fact that the density of SABER-Bupivacaine is 1.1 g/mL at 25ºC. The proposed maximum administration volume that is to be administered to a surgical site is 5 mL, equivalent to 660 mg of bupivacaine.

The purpose of formulating the bupivacaine within a sucrose-based biodegradable matrix (sucrose acetate isobutyrate, also known as SAIB), is in order for the SAIB to form a depot that will allow the bupivacaine to be released into the adjacent tissues over the course of 72 hours.

The Applicant is seeking the following indication: post-surgical analgesia, to be accomplished by administration of Posimir by instillation into the surgical incision such that the product is fully contained within the surgical wound following wound closure.

The various meetings and advice communicated to the Applicant during this drug's development are well-documented by Dr. Simone and Dr. Breder in their respective reviews. The following are the major milestone meetings and issues that were discussed:

1. Communication of Dec 27, 2006:
   The Division communicated the need for a safety database that would consist of at least 400 patients involving administration via local wound infiltration, and at least 500 patients for a novel route, such as intra-articular.

2. End-of-Phase 2 Meeting (September 14, 2007):
   a. Phase 3 trials could be conducted using clinical sites outside the U.S. However, the Sponsor would be required to articulate how the findings from those sites could be extrapolated to the U.S. population. In particular, they would have to provide evidence that the surgical and clinical management of patients in those countries was similar to standard U.S. practices.
   b. In general, indications based on limited development programs are not recommended. However, a narrow indication for SABER Bupivacaine may be

possible due to its relatively novel route of administration, and if there is evidence of substantial safety concerns that result in an acceptable risk-benefit analysis only in a limited condition of use.

c. If the Sponsor wished to pursue an indication limited to inguinal hernia surgery alone, it would require demonstration of efficacy in at least two adequate and well-controlled trials.
d. The Sponsor's Phase 2 evaluation of ECG data to date was inadequate; therefore, Phase 3 trials needed systematic evaluations of the cardiovascular and neurological effects of SABER-bupivacaine beyond T_{max} and throughout the anticipated duration of analgesic effect.
e. The NDA application should address the safety of the novel use of both benzyl alcohol and SAIB in this product.

3. Communication of March 10, 2008
   a. The Division notified the Sponsor that their analysis of the ECG data for QT evaluation from the studies utilizing the 2.5-mL and 5.0-mL doses of SABER-bupivacaine were not adequate because the timing of the ECG relative to pharmacokinetic (PK) sampling had not been provided.
   b. A QT analysis based on ECGs recorded at C_{max} for the 5 ml dose was required.
   c. The Division also stated that there were concerns regarding the central nervous system and the cardiovascular adverse events reported following the administration of the 5 mL dose of SABER-bupivacaine. The Sponsor needed to provide evidence that these adverse events were either not the result of toxicity from the product or that they were not clinically relevant.

4. Request for SPA (August 1, 2008)
   The request was denied, and the Division provided extensive comments and recommendations for revising the protocol so as to come to an agreement on it. The key elements included:
   a. It was noted that the protocol included a number of safeguards to avoid having SABER-bupivacaine gain access into the joint capsule and putting the subject at risk for chondrolysis, e.g., limiting the surgical procedures following which the product can be injected and injecting the product under direct visualization. However, the Division expressed that they still had concern that bupivacaine may enter the joint through seepage or by diffusion when the drug product is in contact with the capsule. Therefore, the Sponsor was to provide either evidence or a rationale that this would not happen.
   b. The Division did not consider opioid sparing or opioid side-effect reduction as indications; rather, they are viewed as evidence that the drug product is efficacious and they provide clinicians with important information regarding the degree of efficacy and the need for analgesic supplementation.
   c. The use of SABER-placebo as a comparator allows the identification of adverse events related only to bupivacaine; a full assessment of safety requires the ability to discern adverse events related to use of the drug product. Therefore, either an additional arm should be added to the trial (either a non-SABER placebo or an

active comparator) or the SABER-placebo should be replaced with either a non-SABER placebo or an active comparator.

d. Safety assessments must include evaluation for signs of bupivacaine related neurotoxicity. These assessments needed to be made proactively and specified in the protocol.
e. Follow-up safety assessments needed to be conducted over a sufficiently long period such that adverse events related to prolonged exposure to either bupivacaine (e.g., post-arthroscopic glenohumeral chondrolysis) or the SABER component of the product would be captured.
f. Opioid-induced adverse events that needed to be captured to describe a reduction in such events included not only constipation, drowsiness and dizziness, but nausea, vomiting, respiratory depression and urinary retention as well.
g. The use of a composite endpoint to assess opiod-related adverse events was acceptable; however, all the major opioid-related adverse events needed to be included, each with appropriate clinically relevant gradations and each with a weighting that puts them into a clinically meaningful order of importance. The protocol would need to specify how each of the adverse events was to be assessed, e.g., how the level of drowsiness is to be ascertained, to minimize variability between assessors and clinical sites. The gradations and weighting for each of the adverse events would require, at a minimum, a clinically-based rationale; further validation may be required.
h. The proposed endpoints for assessing pain relief and opioid use were acceptable; however, the design of the trial may confound the interpretation of the data collected. Specifically, the study permitted analgesics to be administered for pain at rest; however, it requires the assessment of pain with arm movement at specified times. This situation could result in subjects receiving analgesics shortly before a scheduled assessment and, thus, confound interpretation of the primary efficacy data.
i. A major concern for this pivotal study, as well as the entire development program was that the patient populations evaluated are limited in terms of the surgical procedures studied and the overall health of the patients enrolled. While the results from some surgical procedures may be extrapolated to others (e.g., efficacy for hernia repair may imply efficacy for superficial biopsies or wound repairs), a broad indication required evaluation following a wide range of surgical procedures. Data from hernia repair procedures, limited types of shoulder surgery and appendectomy were the only types available.
j. Assessments for neurological and cardiovascular toxicity made at T_{max} would be a key component of the benefit-risk analysis.
k. It was necessary to identify those surgical procedures for which SABER-bupivacaine would be unlikely to provide clinically meaningful analgesia.
l. The patient population from which subjects had been drawn thus far in the clinical development plan had been relatively healthy. It was necessary to evaluate the use of SABER-bupivacaine in the full range of patients in whom the product can be reasonably expected to be used if it is approved for marketing.

5. Pre-NDA meeting (July 31, 2012):
    a. Only one adequate and well-controlled trial would be acceptable if the results of the trial were robust and able to withstand sensitivity analyses.
    b. The purpose of the single trial would be to provide evidence of efficacy and safety for multiple surgical procedures and to allow a determination of the adequacy of the dosing paradigm to be used with SABER-bupivacaine.
    c. The finding of wound discoloration following the administration of SABER-bupivacaine raised safety concerns that needed to be addressed before a benefit risk analysis could be performed. Specifically, the following questions needed to be resolved:
        i. What is the etiology of the discoloration, i.e., infectious, mechanical, chemical, immunological?
        ii. Can anything be done to prevent the discoloration, e.g., change in formulation, dose, or method of administration?
        iii. To what extent does the discoloration limit a surgeon's ability to assess the wound for infection, adequate hemostasis and potential dehiscence?
        iv. Is it possible to identify particular patient populations that are at greater risks for this event?

For the purposes of the 505(b)(2) requirements, the Applicant has identified Marcaine (NDA 016964) as the reference drug which they intend to use for reliance on Agency findings of safety and effectiveness. The Applicant also has also submitted the results of several clinical trials in support of the application.

3. Chemistry, Manufacturing, and Controls (CMC)

(b) (4)

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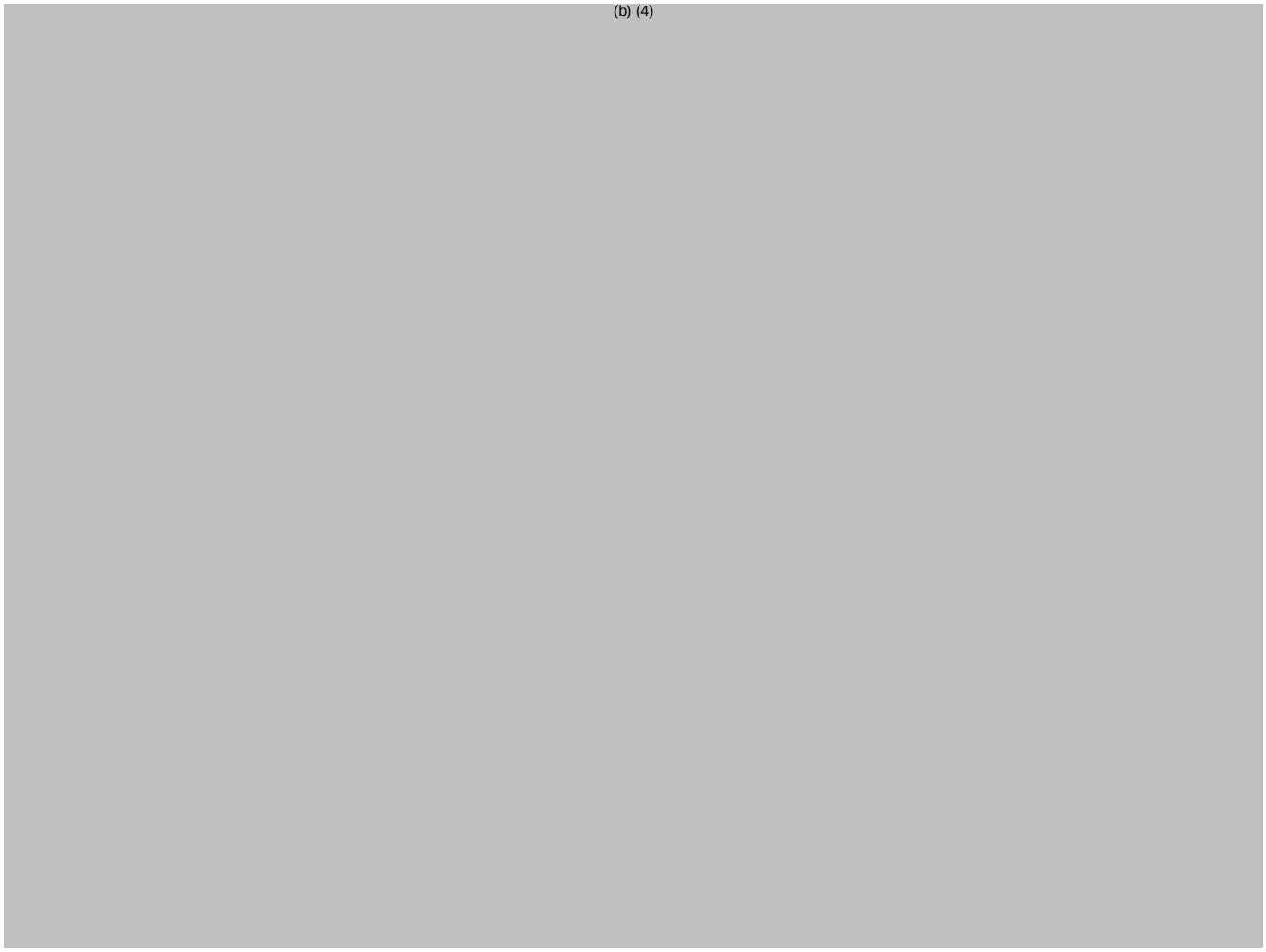


6. Nonclinical Pharmacology/Toxicology

General Considerations

As noted above, the Applicant has identified Marcaine (NDA 016964) as the reference drug for this application, relying on the Agency's prior finding of safety and effectiveness of the active pharmaceutical ingredient, bupivacaine hydrochloride.

The nonclinical program that was conducted by the Applicant in support of this NDA is well described in Dr. Bond's review. As noted in Dr. Wasserman's supervisory memo, the nonclinical issues that were of particular interest for this product were:

- Systemic exposure to bupivacaine
- Potential for dose-dumping
- Excipients
- Drug product specifications with respect to degradants
- Local toxicity - with respect to potential implications for wound healing
- Alternative routes of administration

These will be discussed in further detail below.

Carcinogenicity
As noted in Dr. Bond's review, for the pharmacological active ingredient, bupivacaine, the Applicant made reference to the label of the listed drug (Marcaine, NDA 016964). No carcinogenicity studies were conducted with this product by the Applicant. An evaluation of the carcinogenic potential of the product is not required because it is not intended for chronic administration.

Genotoxicity
Dr. Bond noted that the Applicant conducted an in vitro Ames and chromosomal aberration assays with (b) (4) and the degradants (b) (4) (b) (4) as well as an in vivo micronucleus assay for SABER-Bupivacaine and SABER-Placebo. All results were negative.

Reproductive Toxicology
The Applicant referenced the label for Marcaine for reproductive and developmental toxicology data for the active ingredient in Posimir (i.e., bupivacaine). The Applicant conducted an embryofetal development study in rats to evaluate the SABER component. The overall conclusion was that there was no increase in embryo lethality, no effect on fetal body weight, and no fetal alterations attributed to SABER at any dose tested.

Other Nonclinical Evaluations of Interest
Systemic Exposure to Bupivacaine
Clinical manifestations of toxicities due to bupivacaine are generally seen when plasma concentrations exceed 1000 ng/mL, therefore, the nonclinical program needed to assess the potential exposure that could be seen with the new formulation, in order to support the clinical program.

The Applicant submitted the results of studies in rats and rabbits which demonstrated that the exposure after a single subcutaneous dose provided adequate safety margins for the proposed clinical trials.

Potential for Dose-dumping
Related to the issue of exposure to bupivacaine, the possibility of dose-dumping from the SABER matrix was also evaluated in the nonclinical program; it was not observed.

Excipients
There were two major excipients identified by the review team: sucrose acetate isobutyrate (SAIB) and benzyl alcohol.

The SAIB component has been previously evaluated and is considered Generally Recognized as Safe (GRAS) by the Agency when used by the oral route. However, the amount proposed in this formulation exceeds the amount that has been established as an Acceptable Daily Intake (20 mg/kg) and, in addition, use in this product represents a novel route for this excipient. Because it degrades slowly over time, the exposure is not expected to cause systemic toxicities due to daily

exposure, but there is the concern of local toxicity, which is primarily manifested as a foreign body reaction.

As noted by Dr. Wasserman, benzyl alcohol is used extensively in the industrial settings, in the cosmetic industry, and as a food additive. The Acceptable Daily Intake, based on the World Health Organization's recommendation, is 5 mg/kg. The amount present in 5 mL of Posimir, and which is expected to be release in the first 24 hours is 1,210 mg. Dr. Wasserman noted that there is an approved product that also has significant levels of benzyl alcohol in its formulation (~1,000 mg), fulvestrant. However, fulvestrant (Faslodex, NDA 021344) is indicated for the treatment of hormone receptor positive metastatic breast cancer in post-menopausal women with disease progression following anti-estrogen therapy.

The potential clinical implications of these two excipients are further discussed below in the safety section of this review.

Impurities and Degradants
There were no impurities identified in the drug substance that required qualification. As noted in Dr. Bond's review, four degradants were identified that required safety qualification: (b) (4) (b) (4) All were appropriately qualified and the specifications proposed by the Applicant were deemed acceptable.

Extractables and Leachables
Dr. Bond evaluated the results of the extractable and leachable studies and concluded that all compounds were within the general limits identified by the Agency as not needing additional qualification.

Local toxicity
The potential effects on local tissues were evaluated in two series of studies by the Applicant. The first was in wound healing models in rats and minipigs, and the second was in a single-dose subcutaneous administration model in rats and rabbits.

The results of the wound healing study in the rat indicated that, at 7 days after the incision and subsequent suture of the site, there was no difference in the pressure needed to produce failure of the wound closure. However, there were microscopic changes of inflammation, granulation, angiogenesis and a minimal to mild gap observed in the dermis of rats treated with SABER-Bupivacaine that were not seen in the animals that just had the incisions sutured. There were no SABER-Placebo or bupivacaine treatment groups included in the study.

The results of the wound healing study in the minipigs were limited to histological examinations, which were performed on Day 15. There were no macroscopic differences noted between the three treatment groups (SABER-Bupivacaine, SABER-Placebo, and 5% carboxymethylcellulose gel, instilled as a negative control solution). Microscopically, there was a tendency to less advanced re-epithelialisation and more inflammation and clear vacuoles in the SABER-treated animals.

The single-dose subcutaneous administration studies conducted in the rats and rabbits were similar in that a sacrifice and evaluation was done either on Day 15 or Day 43. It was unclear why these days were chosen by the Applicant, particularly since a previously conducted study with an earlier formulation of the drug product had demonstrated necrosis at an earlier time point (Day 4) and other findings had been reduced by Day 15. Neither study included a bupivacaine-only treatment arm as a control, and the rabbit study also lacked a saline-only negative control.

Alternative Routes of Administration

There was no in vivo evaluation of the adverse effects of inadvertent intravenous or intra-arterial administration, as it was felt that, due to the physical properties of the drug product, such administration would result in profound toxicity due to occlusion of the vessels as the benzyl alcohol rapidly leaves the matrix.

A study evaluating the effects of intra-articular administration in rabbits resulted in microscopic findings of minimal to moderate synovial hyperplasia, fatty degeneration, inflammation, fibrosis and osseous metaplasia present two weeks after administration, and were still present six weeks after injection. The changes were slightly worse with the SABER-Bupivacaine than with SABER-Placebo, but were not present in saline treated joints or in contralateral joints. A similar study done in dogs resulted in similar findings, with the addition of subchondral bone fibrosis and cartilage necrosis.

The rabbit model was used to assess the impact of perineural administration. As noted in Dr. Wasserman's memo, the microscopic examination of the perineural area revealed increased neuronal inflammation and axonal degeneration in SABER-Placebo treated animals. It was somewhat worse with the additional bupivacaine in SABER-bupivacaine and was absent from the bupivacaine and saline-treated animals.

The overall assessment of these findings is well-summarized in Dr. Wasserman's memorandum, and a portion is reproduced here:

> The risks of the product identified in the nonclinical program principally relate to local toxicity associated with the vehicle and the resulting formation of the depot along with its persistence in tissues. This is noted in the single-dose subcutaneous administration studies in rodent and rabbit in which administration produces (by Study Day 14) swelling, discoloration, and a significant mild-to-marked inflammation of the subcutaneous tissue associated with, in rats, cyst formation while in rabbits this appeared as a granulomatous inflammation around vacant spaces thought to represent the SAIB depot. Other findings included dermal evidence of damage which may or may not be secondary to scratching of the administration site by the animals. Inflammation was slowly resolving over 6 weeks post-administration. Notably, the acute effects of the drug product at the site were not evaluated and therefore there may be significant toxicity, such as the necrosis observed with an earlier SAIB (b) (4) version of the product, which would not be observed with the delayed initial histologic assessment. Furthermore, appropriate negative (saline) and immediate-release bupivacaine control groups were not consistently included for distinguishing the effects of bupivacaine from vehicle and to a certain extent the vehicle itself from the injection procedure.
>
> More pertinent to the proposed indication of surgical site instillation were studies in wound healing models conducted with a near-final version of SABER bupivacaine in rat and minipig.

> Microscopic evidence of inflammation, cysts, and mild dermal gap was noted in rats with instillation of SABER-bupivacaine. Cysts were not apparent in an incision only (sham surgery) control group 7 days post- wounding and there was no gap in the dermal layer. Nevertheless, there was no evidence of reduced wound repair strength in the SABER-bupivacaine animals compared to sham surgery animals when tested at this single time-point. A more complete time-course with longer follow-up (to at least 14 days) to observe the full course of wound repair would have been ideal but was not conducted. A study in the minipig in which wounds were treated on SD1 and evaluated on SD15 identified slightly less advanced re-epithelialisation, more inflammation (moderate in severity), giant cells, and clear vacuoles thought to contain SAIB when compared to a control group administered a viscous carboxymethylcellulose solution. Additionally, visual inspection of the wounds suggested a transient delay in healing in SABER-bupivacaine animals which appears no different than carboxymethylcellulose control by 15-days post wounding. Again it is notable that acute evaluation of the wound site was not incorporated into the study design and the carboxymethylcellulose solution was not previously established to be equivalent to a negative (saline) control; therefore, the short-term impact of SABER-bupivacaine on wound healing in this animal model may be underestimated.

The above assessment notwithstanding, Dr. Wasserman's final conclusion was that additional nonclinical studies were not warranted, as the data obtained would be unlikely to alter his recommendation.

Outstanding or Unresolved Issues
As noted by Dr. Wasserman, some of the nonclinical studies that evaluated the extent of the local toxicity could have potentially benefited from the inclusion of additional control arms, and/or evaluations at earlier time points than what were conducted. However, I concur with Dr. Wasserman's final conclusion that additional nonclinical investigations will most likely not yield any significant information. The nonclinical program has demonstrated that the product has the potential for local toxicity, and the variables that impact the toxicity include the amount, location and skill of the practitioner, therefore, it is most likely that the assessment of this risk is going to have to be through clinical assessments.

I concur with the conclusions reached by Drs. Bond and Wasserman that there are no deficiencies in the nonclinical development program that would preclude approval of this supplement.

7. Clinical Pharmacology/Biopharmaceutics

General Considerations.
The Applicant intends to reference the Marcaine label for information on the, distribution, metabolism, and elimination about the active ingredient, bupivacaine. The Applicant assessed the relative bioavailability of Posimir compared to Marcaine in Study BU-001-IM.

Dr. Lee's review summarized the major clinical pharmacology findings that were specific to this product.

Relative bioavailability
The mean C_{max} value for bupivacaine after an administration of Posimir (660 mg bupivacaine) was 625 ng/mL compared to 342 ng/mL with Marcaine (100 mg). The bupivacaine mean AUC

value Posimir (660 mg bupivacaine) was 36830 ng·h/mL compared to 5740 ng·h/mL with Marcaine (100 mg).

Dose Linearity
Based on the results from Study CLIN-803-006-0006, the bupivacaine C_{max} and AUC values from the 2.5 and 5.0 mL Posimir doses exhibited linear pharmacokinetics.

Exposure-Response Relationship
Since the systemic levels of bupiovacaine do not reflect the local concentrations at the surgical site, it is not possible to evaluate a dose-response relationship in the traditional sense.

Incision Length
The data submitted did not demonstrate a correlation between the incision length and bupivacaine's C_{max} and AUC. This is not surprising since the administration instructions in the clinical trials were for the practitioner to administer the entire 5 mL dose regardless of the size of the incision.

Bupivacaine Exposure Relative to the Type of Surgery
The C_{max} and AUC values for bupivacaine were evaluated across several studies. The following were Dr. Lee's conclusions (reproduced from his review):

1. The systemic bupivacaine concentrations were, at least, observed for 72 hours post administration when 5 mL Posimir was administered in all of the surgical procedures; additionally, no dose-dumping was observed;
2. Observed bupivacaine C_{max} and AUC values were not too drastically different in abdominal, shoulder and hernia procedures for the same Posimir dose;
3. Observed bupivacaine C_{max} and AUC values were not too drastically different when 5 mL Posimir was administered as subcutaneous, infiltration and instillation routes of administration;
4. No correlation was observed between bupivacaine C_{max} and AUC and surgical incision lengths, as all 5 mL Posimir was administered in all surgical procedures;
5. No dosage adjustment may be warranted due to weight, age, gender, and race since it is a locally acting product.

<u>*Special Populations*</u>
Dr. Lee noted that there were no specific studies conducted to evaluate the pharmacokinetics of the product in special populations, such as patients with hepatic or renal impairment. Prior knowledge of bupivacaine's metabolism and excretion profile would indicate that Posimir should be used with caution in patients with either of these organ impairments.

Age:
Results from Study C803-025 indicated that C_{max} and AUC values were lower in younger patients (<45 years of age) than older patients (45 to 65, and > 65 years of age). The T_{max} was also noted to be earlier in the younger patients. However, Dr. Lee noted that the degree of difference did not warrant any dose adjustment.

Body Mass Index
Results from Study C803-025 indicated that patients with a body mass index (BMI) <18.5 kg/m^2 had a lower C_{max} and AUC values than patients with a BMI >18.5 kg/m^2. However, Dr. Lee noted that since the product is locally acting, and the observed difference had some variability, with overlapping values between male and female patients, no dose adjustment was warranted.

Thorough QT Study
The Applicant did not conduct a thorough QT study. Instead, the Applicant evaluated electrocardiographic tracings of patients in three of the clinical trials with SABER-Placebo and Bupivacaine HCl control arms. Electrocardiograms were performed in triplicate and read at a central location. The final assessment of the ECG data was that no clinically relevant cardiac electromorphologic changes were likely to occur with the proposed administration of 5 mL of Posimir.

Drug-drug Interactions
There were no drug-drug interactions studies conducted by the Applicant. The Applicant intends to rely on the Marcaine label for this information.

Assessment of Extended-Release Characteristics:
Dr. Lee noted that, based on the observed bupivacaine systemic profile, Posimir exhibited the characteristics of a delayed T_{max}. He also noted, however, that Posimir is a locally administered drug with localized activity, and that characterization of Posimir as an extended-release product should assess other aspects of its performance (e.g., in vitro release profile, and whether Posimir has an impact the dosing frequency compared to an immediate-release formulation).

Outstanding or Unresolved Issues
I concur with the conclusions reached by the clinical pharmacology team that, there are no outstanding or unresolved clinical pharmacology issues that would preclude approval.

6. Clinical Microbiology

Posimir is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application. A product quality microbiology review was performed by Dr. Sweeney; his conclusions are described above in the CMC section.

I concur with the conclusions reached by Dr. Sweeney that there are no outstanding sterility issues that preclude approval.

7. Clinical/Statistical – Efficacy

As noted by Dr. Simone and Mr. Petullo in their respective reviews, the clinical program submitted in support of the efficacy of Posimir consisted of seven trials, as they used the to-be-marketed formulation and methods of administration consistent with their propose labeling. The studies were intended to demonstrate the efficacy of Posimir in two different types of procedures – orthopedic and soft tissue surgeries. The control treatment groups for these studies consisted of SABER-placebo (also referred to by the review team as "placebo") which consisted of the

SABER component without bupivacaine, and bupivacaine hydrochloride (referred to by the review team as the "active' control). The studies are summarized in the table below. The numbers of subjects identified in the table are the number of subjects randomized and treated, with the treatment drug administered in the same manner as proposed by the Applicant.

Study	Phase	Number of Subjects Randomized and Treated	Control	Treatment Arms
Arthroscopic Shoulder Procedure				
CLIN-005-0006	2	45	Placebo	SABER-Bupivacaine, 5 mL SABER-Placebo
C803-017	2b	60	Placebo	SABER-Bupivacaine, 5mL SABER-Placebo
BU-002-IM*	2	107	Active and Placebo	SABER-Bupivacaine, 5 mL SABER-Placebo Bupivacaine HCl
Inguinal Herniorrahaphy				
CLIN-005-0010	2	43	Placebo	SABER-Bupivacaine, 5 mL SABER-Placebo
CLIN-803-006-0006*	2	123	Placebo	SABER-Bupivacaine, 2.5 mL SABER-Bupivacaine, 5 mL SABER-Placebo
Major Abdominal/Hysterectomy				
BU-001-IM	2	114	Active and Placebo	SABER-Bupivacaine, 5mL Bupivacaine HCl SABER-Placebo
C803-025	3	305	Active and Placebo	SABER-Bupivacaine, 5mL Bupivacaine HCl

*Pivotal studies

The Applicant identified Study BU-002-IM and Study CLIN803-006-0006 as pivotal studies, and the remaining five were considered by the Applicant to be supportive studies.

Arthroscopic Surgery

Study BU-002-IM, entitled "An international, randomised, double-blinded, multi-centre, active- and placebo-controlled dose response trial to evaluate the efficacy and safety of SABER-Bupivacaine for post-operative pain control in patients following arthroscopic shoulder surgery," was conducted between April 29, 2009 and February 4, 2011. The clinical sites were located in Austria, Denmark, Germany, Latvia, and Sweden.

The details of the study are described very well in Dr. Simone's and Mr. Petullo's reviews, and will only be briefly summarized here.

The objective of the study was to identify the optimal dose of SABER-bupivacaine for post-operative pain control in patients who had undergone a subacromial decompression via an arthroscopic procedure. The key inclusion criteria stipulated that subjects had to be older than 18 years of age, have the diagnosis of subacromial impingement syndrome, and an intact rotator

cuff (by MRI). The key exclusion criteria stipulated that, in addition to not having any clinically significant systemic abnormalities or concurrent uncontrolled serious illnesses, the subjects should be free of any known major joint trauma, infection, avascular necrosis, chronic dislocation, inflammatory or degenerative glenohumeral arthropathy, glenohumeral arthritis, frozen shoulder or previous surgery of the affected shoulder.

Subjects were randomized to one of the following treatment groups:

1. SABER-Bupivacaine
2. SABER-Placebo
3. Bupivacaine HCl

The randomization scheme was in a 2:1:1 ratio, with twice as many subjects being randomized to the SABER-Bupivacaine treatment group.

The protocol-specified primary efficacy endpoints were identified as follows:

- Pain intensity (PI) on movement area-under-the-curve (AUC) over the period from 1 to 72 hours post-surgery, using an 11-point numerical rating scale (NRS) for recording PI. A standardized assessment of pain "on movement" was performed for shoulder flexion to 90 degrees.
- Total use of opioid rescue analgesia 0 to 72 hours post-surgery.

Secondary endpoints included

- Time to first opioid use
- Opioid-Related Symptom Distress Scale (OR-SDS) score Days 0 to 7
- PI at rest AUC over the period 1 to 72 hours post-surgery
- Patient's pain treatment satisfaction score on Day 4
- The proportion of patients who were dischargeable (on the basis of PADS) on Days 1, 2, 3, 4 and 7
- The proportion of patients who had returned to work by Day 14.

It is noted that the study was described as a double-blind study; however, due to the physical appearance of the SABER containing products compared to bupivacaine hydrochloride, it was not possible to blind the individual applying the treatment. The efficacy assessments were made by someone blinded to the treatment group, so it would be more appropriate to call this study "assessor-blinded" rather than double-blind.

The Applicant screened 126 subjects and 115 subjects were enrolled and randomized. Eight of the randomized patients were discontinued prior to treatment. The following table, adapted from Mr. Petullo's review, summarizes the demographic information of the 107 subjects who were randomized and treated.

Demographic Data, Study BU-002-IM

	Treatment Group		
	SABER-Placebo	**SABER-Bupivacaine**	**Bupivacaine HCl**
Number of Subjects	25	53*	29
Age (in years)			
Mean (SD)	49 (10)	50 (9.5)	52 (11)
Median	52	49	52
[range]	[24, 63]	[28, 70]	[21, 70]
Gender, n (%)			
Female	14 (56)	33 (62)	17 (59)
Male	11 (44)	20 (38)	12 (41)
Race, n (%)			
Caucasian	24 (96)	50 (98)	29 (100)
Black	-	-	-
Asian	1 (4)	1 (2)	-
Other	-	-	-

*2 subjects missing a response for race

There weren't any subjects who withdrew from the study; therefore, the populations that are used for most of the analyses, i.e., the Randomized Population, the Safety Population, and the Intent-to-treat Population, were equivalent.

Efficacy Results

The analysis by the review team for the first of the two primary endpoints identified a significant treatment effect in favor of SABER-Bupivacaine. This is summarized in the following two tables. The first table, adapted from Mr. Petullo's review, depicts the normalized AUC_{72} for the three treatment groups, as calculated by the Applicant compared to by Mr. Petullo's calculations; the two results were consistent with each other.

Results from Analysis of Normalized AUC, Study BU-002-IM

	Normalized AUC_{72} (PI) Mean (SEM)		
	SABER-Placebo N = 25	**SABER-Bupivacaine N = 53**	**Bupivacaine HCl N = 29**
Applicant	6.3 (0.4)	5.0 (0.3)	5.0 (0.4)
Reviewer	6.4 (0.4)	5.3 (0.3)	5.5 (0.4)

The second table, adapted from Mr. Petullo's review, depicts the difference in the least square means (LSMEANS) between SABER-Bupivacaine and SABER-Placebo, as well as between` Bupivacaine HCl and SABER-Placebo.

Comparison to SABER-Placebo, Study BU-002-IM

	Difference	**95% confidence interval**	**p-value**
SABER-Bupivacaine	-1.1	[-2.1, -0.2]	0.02
Bupivacaine HCl	-0.2	[-1.1, 0.7]	0.1

Mr. Petullo's analyses of the results for the second co-primary endpoint, the amount of rescue medication consumed through 72 hours (RES_{72}), indicated a significant treatment effect for

SABER-Bupivacaine, but not for Bupivacaine. The results are summarized in the table below, adapted from Mr. Petullo's review.

Amount of Rescue Medication Consumed, 72 hours, Study BU-002-IM

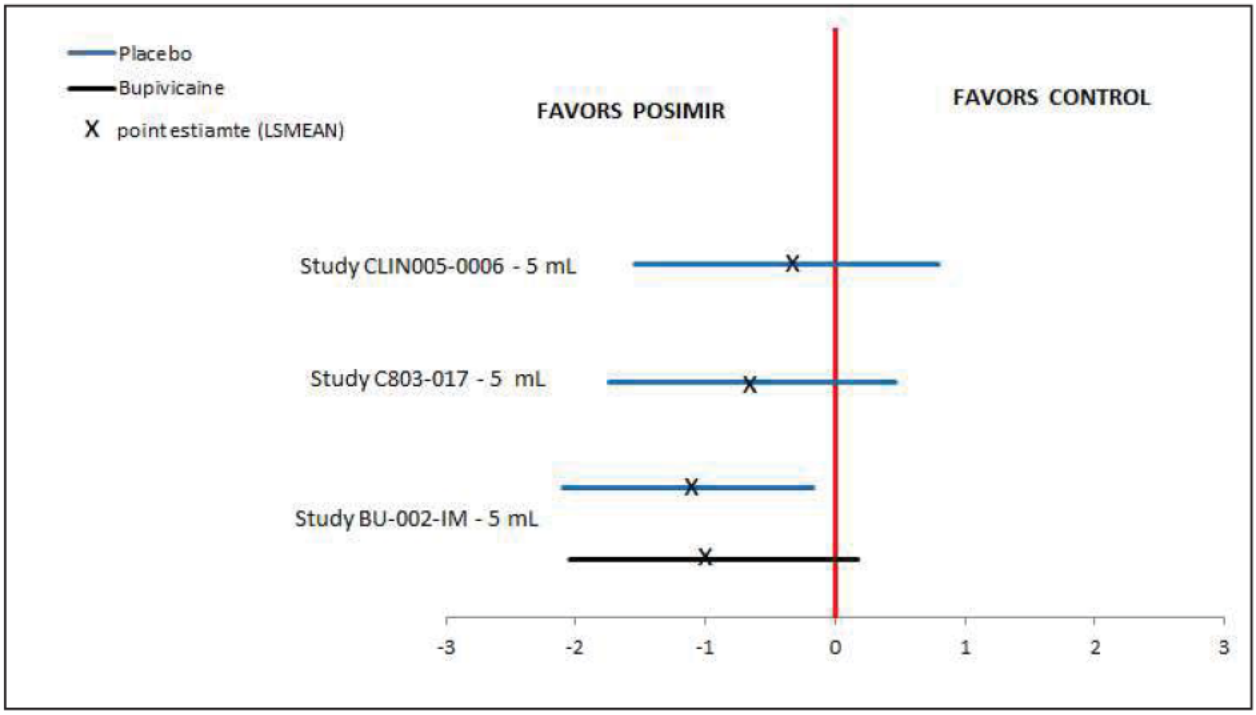
Treatment Group	Morphine Equivalent (mg) mean (stdev)	p-value
SABER-Placebo	22.8 (25.8)	-
SABER-Bupivacaine	13.7 (29.1)	0.01
Bupivacaine HCl	12.3 (17.6)	0.07

The final conclusion by Mr. Petullo was that Study BU-002-IM demonstrated the efficacy of SABER-Bupivacaine in this procedure, as indicated by the analyses of the pre-specified primary endpoints, AUC_{72} and RES_{72}. In addition, this conclusion was supported by the results of the analyses of time to first use of rescue medication.

Efficacy Results from Supportive Studies for this Procedure

Studies CLIN-005-0006 and C803-017 were conducted prior to Study BU-002-IM. Although the general designs of the studies differed in certain components, e.g., in the method of administration, the overall assessment of efficacy included the assessment of pain intensity over a period of days and the use of supplemental analgesia. The studies failed to demonstrate a statistical significance, but the results trended in the right direction.

The figure below, reproduced from Mr. Petullo's review, summarizes the results of AUC_{72} for the three studies. It illustrates the point estimates and 95% confidence intervals for the difference between SABER-Bupivacaine (identified as Posimir) and SABER-Placebo (identified as placebo), as well as between SABER-Bupivacaine and Bupivacaine HCl (identified as Bupivacaine). The 5 mL dose is the Applicant's proposed dosage.



Inguinal Herniorrhaphy

Study CLIN803-006-0006, entitled "A double-blind, placebo-controlled, pharmacodynamic and pharmacokinetic dose response study of saber-bupivacaine instilled into the wound in patients undergoing open inguinal hernia repair," was conducted between January 18, 2007 and October 17, 2007. The clinical sites were located in Australia and New Zealand.

As before, only the major aspects will be summarized here, as the details of the study are well described in Dr. Simone's and Mr. Petullo's reviews.

The primary objective of the study was to assess the dose-response efficacy and pharmacokinetics of SABER-Bupivacaine instilled directly into the wound in subjects undergoing elective open inguinal hernia repair.

The key inclusion criteria stipulated that subjects had to older than 18 years of age (but younger than 65), and scheduled to undergo an elective open unilateral tension-free Lichtenstein-type repair of an inguinal hernia. The key exclusion criteria stipulated that, in addition to not having any clinically significant systemic abnormalities, the subjects were to not have had any previous abdominal surgery with scar tissue formation, or any connective tissue disorder.

Subjects were randomized to one of the following treatment groups:

1. SABER-Bupivacaine 5.0 mL (660 mg of bupivacaine)
2. SABER-Bupivacaine 2.5 mL (330 mg of bupivacaine)
3. SABER-Placebo 5.0 mL
4. SABER-Placebo 2.5 mL

The randomization scheme was in a 3:1 ratio, in favor of the SABER-Bupivacaine treatment group.

The protocol-specified primary efficacy endpoints were:

- Mean pain intensity on movement normalized AUC over the time period 1 to 72 hours post-surgery
- Proportion of patients receiving opioid rescue medication during the study.

There were several secondary endpoints proposed, including mean pain intensity normalized AUC over the time period 1 to 48 hours after surgery, overall treatment satisfaction, and mean total opioid dose used for rescue analgesia.

The Applicant screened 135 subjects and 124 were enrolled and randomized. One subject was randomized but not treated. The following table, adapted from Mr. Petullo's review, summarizes the subjects' demographic information for all randomized and treated subjects.

Demographic Data, Study CLIN803-006-0006

	Treatment Group		
	SABER-Placebo	**SABER-Bupivacaine 330 mg***	**SABER-Bupivacaine 660 mg**
Number of Subjects	32	44	47
Age (in years)			
Mean (SD)	50 (9)	46 (12)	49 (13)
Median	52	48	50
[range]	[28, 65]	[20, 68]	[21, 79]
Gender, n (%)			
Female	-	2 (5)	2 (4)
Male	32 (100)	42 (95)	45 (96)
Race, n (%)			
Caucasian	30 (94)	41 (95)	46 (98)
Black	1 (3)	-	-
Asian	1 (3)	2 (5)	-
Other	-	-	1 (2)

*Race was not documented for one subject

Of the subjects that were randomized and treated, 4 subjects did not complete the study. The following table, adapted from Mr. Petullo review, summarizes the reasons for discontinuation.

Subject Disposition, Study CLIN803-006-0006

Reason for Discontinuation	**SABER-Placebo**	**SABER-Bupivacaine 330 mg**	**SABER-Bupivacaine 660 mg**
Multiple surgeries	-	1	-
Patient's best interest	-	1	-
Underwent surgery for pre-existing condition	1	-	-
Non-allowed concomitant medication	-	1	-

Efficacy Results

The analysis by the review team for the first of the two primary endpoints identified a significant treatment effect in favor of SABER-Bupivacaine. This is summarized in the following two tables. The first table, adapted from Mr. Petullo's review, depicts the normalized AUC_{72} for the three treatment groups, as calculated by the Applicant compared to by Mr. Petullo's calculations; the two results were consistent with each other.

Results from Analysis of Normalized AUC, Study CLIN803-006-0006

	Normalized AUC_{72} (PI) Mean (SEM)		
	SABER-Placebo N = 32	**SABER-Bupivacaine 330 mg N = 43**	**SABER-Bupivacaine 660 mg N = 47**
Applicant	3.6 (0.3)	3.1 (0.3)	2.5 (0.2)
Reviewer	4.0 (0.3)	3.3 (0.3)	2.7 (0.2)

The second table, also adapted from Mr. Petullo's review, depicts the difference in the least square means (LSMEANS) of the two doses of SABER-Bupivacaine compared to SABER-Placebo.

Comparison of SABER-Bupivacaine to SABER-Placebo, Study CLIN803-006-0006

	Difference	95% confidence interval	p-value
SABER-Bupivacaine 330 mg	-0.8	[-1.6, -0.5]	0.1
SABER-Bupivacaine 660 mg	-1.4	[-2.1, 0.6]	0.001

The second co-primary endpoint had been specified to be the proportion of subjects receiving opioid rescue medication through Day 15. The Applicant performed a post-hoc analysis utilizing the time period of 72 hours, with the rationale that this was the same time period used for the other primary endpoint.

The review team evaluated both time periods. In addition to comparing the proportions when the rescue medication was coded as "rescue," Mr. Petullo also compared the proportions of subjects who used any opioids, regardless of the coded designation. The results are summarized in the two tables that follow, adapted from Mr. Petullo's review.

Percent of Subjects Using Opioid Rescue Medication, through Day 15, Study CLIN803-006-0006

Treatment Group	Number of Subjects	Percent of Subjects	
		Opioids Coded as Rescue	All Opioids
SABER-Placebo	32	72	72
SABER-Bupivacaine, 330 mg	43	65	74
SABER-Bupivacaine, 660 mg	47	49*	53

*p-value = 0.04

Percent of Subjects Using Opioid Rescue Medication, through Day 3, Study CLIN803-006-0006

Treatment Group	Number of Subjects	Percent of Subjects	
		Opioids Coded as Rescue	All Opioids
SABER-Placebo	32	72	72
SABER-Bupivacaine, 330 mg	43	63	74
SABER-Bupivacaine, 660 mg	47	49*	51

*p-value = 0.04

As noted in Mr. Petullo's review, regardless of which time period was evaluated, there was a significant difference noted between the higher dose of SABER-Bupivacaine (660 mg) and SABER-Placebo when only the opioids coded as rescue were analyzed. When the analysis considered all opioids, regardless of the coded designation, there was no longer a significant treatment effect.

When Mr. Petullo evaluated the amount of rescue medication used through the first 72 hours after surgery, RES_{72}, he found a significant difference for the comparison of SABER-Placebo and the higher dose of SABER-Bupivacaine (660 mg). This result is summarized in the table below, adapted from Mr. Petullo's review.

Amount of Rescue Medication Consumed, 72 hours, Study CLIN803-006-0006

Treatment Group	Number of Subjects	Morphine Equivalent (mg) mean (stdev)	p-value
SABER-Placebo	32	29.9 (57.6)	-
SABER-Bupivacaine, 330 mg	43	13.1 (14.1)	0.05
SABER-Bupivacaine, 660 mg	47	10.4 (13.1)	<0.01

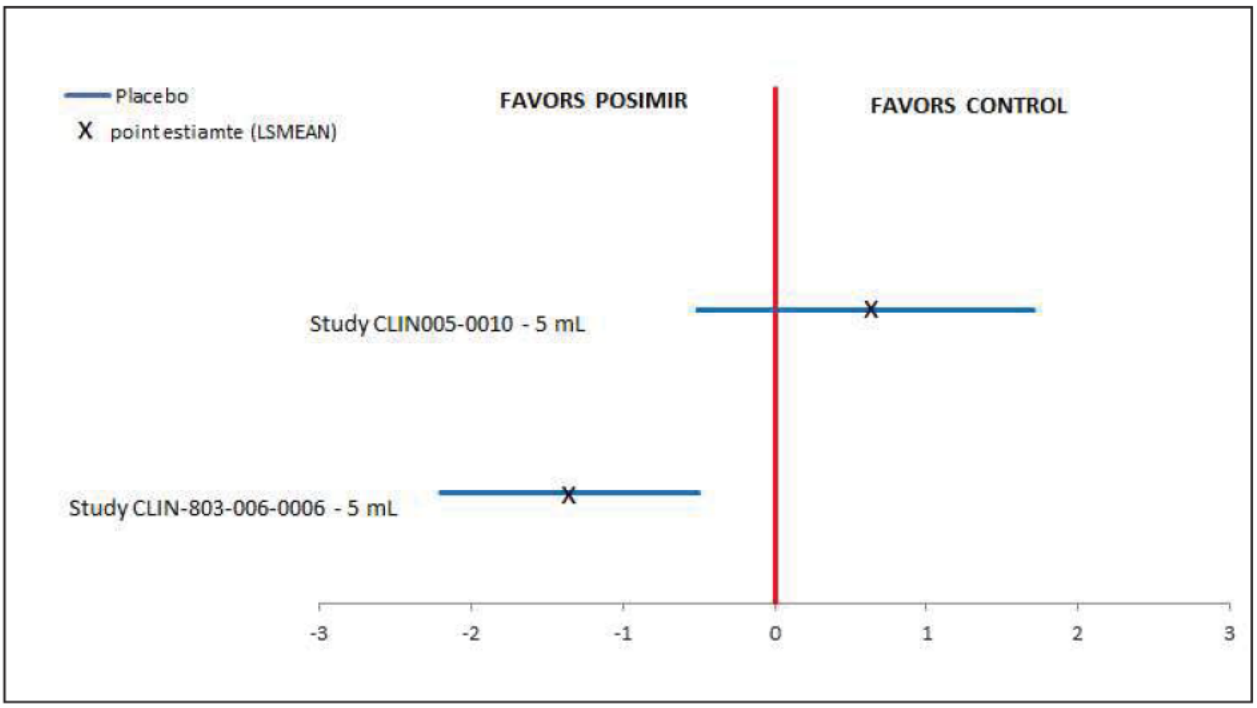
Mr. Petullo also conducted analyses of several secondary endpoints, as well as exploratory analyses to evaluate the extent of the treatment effect. The final conclusion by Mr. Petullo regarding Study CLIN803-006-0006 was as follows, reproduced from his review:

> In summary, in this study there was a significance difference noted between placebo and Posimir 660 mg for the first primary endpoint, AUC_{72}. This difference was supported when I examined the mean PI scores by time, Figure 1. However, the magnitude of the separation between the curves for placebo and Posimir is diminished after 24 hours. There was no difference noted between Posimir 330 mg and placebo for AUC_{72}. For the second primary endpoint, proportion of subjects using rescue medication, when I examined all rescue medication, not just medication coded as rescue, there was not a significant difference between placebo and either dose of Posimir although numerically the numbers were in favor of Posimir. When I examined the amount of rescue medication consumed, RES_{72}, there was a significant difference noted in favor of Posimir 660 mg versus placebo but not Posimir 330 mg. This was supported by my analysis of time to first use of rescue medication. Subjects treated with Posimir 660 mg, on average reported less post-surgical pain, required less rescue medication, and waited longer to request it.

Efficacy Results from Supportive Studies for this Procedure

Study CLIN005-0010 was conducted prior to Study CLIN-803-006-0006. It was conducted in seven clinical sites throughout the United States, and one site in New Zealand. It differed from Study CLIN-803-006-0006 in the treatment arms as well as in manner in which the treatment drug was administered into the wound area. The primary endpoints were initially pain intensity at rest and on movement, and pain control, as assessed by the subject. A protocol amendment changed the primary endpoint to a normalized AUC of the pain intensity scores at rest, and on movement, at 120 hours post-surgery.

The figure below, reproduced from Mr. Petullo's review, depicts the point estimates and 95% confidence interval for the differences between SABER-Bupivacaine and SABER-Placebo for AUC_{72}. The 5 mL dose identified in the graph is equivalent to 660 mg of SABER-Bupivacaine.



Other Studies in Surgeries Involving Soft Tissue

Two additional studies were submitted in support of SABER-Bupivacaine's treatment effect after soft-tissue surgeries. Study BU-IM-001 was in female patients undergoing a hysterectomy, and Study C803-025 was in patients undergoing a colectomy, laparotomy, or laparoscopic cholecystectomy. The studies' descriptions, primary endpoint, analyses, and results are well-detailed in Mr. Petullo's review, and are reproduced below (note: in the reproduced text, "Placebo" is the same as SABER-Placebo, "Posimir" is the same as SABER-Bupivacaine, and "Bupivacaine" is the same as Bupivacaine hydrochloride):

> Study BU-IM-001: This was a randomized, double-blind, dose-ranging, active- and placebo-controlled phase 2 study that evaluated Posimir in female subjects undergoing a hysterectomy. Subjects were enrolled at 13 sites in 5 countries; France, Germany, Hungary, Latvia, and Sweden. This study was to be conducted in two separate cohorts where Cohort 1 received 5.0 mL of study drug and Cohort 2 received 7.5 mL of study drug. However, Cohort 2 was not conducted. In Cohort 1, subjects were randomized 2:1:1 to either Posimir 5.0 mL, placebo, of 40 mL of bupivacaine. Placebo and Posimir were instilled into the surgery site prior to wound closure. Bupivacaine was injected into the muscle, distal layer and subcutaneously around the surgery site.
>
> The primary efficacy variables were AUC_{72} on movement and RES_{72}. Missing pain scores between two non-missing pain scores were not imputed. This is analogous to linear interpolation. Missing pain scores due to discontinuations were imputed using LOCF. The analysis population was defined as all randomized and treated patients. For AUC_{72}, the applicant tested NI of Posimir 660 mg to placebo using ANOVA model with treatment and pooled site as factors. If the upper bound of the 95% CI for the difference was less than or equal to 0.5, NI was established. This is equivalent to using a NI margin of 0.5. If NI was established, superiority was tested. RES_{72} was computed for each subject by converting amount of rescue medication to morphine equivalent doses. If a subject discontinued prior to 72 hours, the Res_{72} will be calculated as amount of rescue used per hour times 72. Results were compared between placebo and Posimir using an ANOVA model with treatment and pooled site.

Of the 115 subjects that were randomized and 114 were treated, 60 Posimir, 27 placebo, and 27 bupivacaine, 113completed the study. One subject in the Posimir arm withdrew consent and one subject in the placebo arm withdrew due to an adverse event. All subjects were female Caucasians with an average age of 46 years old. In the analysis of AUC_{72}, NI was claimed as the 95% CI for the difference of Posimir and placebo was [-0.89, 0.35]. The 95% CI for the difference between Posimir and bupivacaine was [-0.68, 0.47]. However, superiority was not established for either comparison, p-value > 0.05. This analysis did not account for use of rescue medication. Additionally, superiority of Posimir 660 mg over placebo for RES_{72} was not established. Placebo subjects, on average used 26.3 mg morphine equivalent units compared to 22.8 mg for the Posimir 660 mg. Bupivacaine treated subjects used an average of 23.9 mg over 72 hours.

Study C803-025: This was a randomized, double-blind, placebo- and active-controlled phase 3 trial that was conducted in three separate cohorts. Cohort 1 randomized subjects undergoing a laparotomy and Cohort 2 randomized subjects undergoing a laparoscopic cholecystectomy. In Cohorts 1 and 2, subjects were randomized 3:2 to Posimir 660 mg or bupivacaine. Cohort 3 was placebo controlled and evaluated subjects receiving a colectomy. Subjects were randomized 3:2 to Posimir 660 mg or placebo. In all cohorts study drug was instilled into the surgery site prior to wound closure. This study was conducted at nine sites in the United States and two sites in Australia.

The primary efficacy variables were AUC_{72} and RES_{72}. The analysis population was defined as all randomized subjects that received study drug. An ANCOVA model with treatment, pooled site and incision length as a covariate was used to compare results for both endpoints. Since the results of RES_{72} violated the normality assumptions a non-parametric analysis, WRS, was used. Missing pain scores were handled as follows. If a subject dropped out prior to 72 hours due to an adverse event, the subjects' baseline observation was carried forward. If a subject dropped out for any other reason or had intermittent missing data, a multiple imputation approach was used. The Hochberg approach was utilized to account for two primary endpoints. If the largest p-value was less than 0.05, then both endpoints were declared significant. If the largest p-value was greater than 0.05, the other endpoint will be tested at 0.025. The applicant states that data from Cohorts 1 and 2 will be pooled and summarized but would be non-inferential. The data from Cohort 3 was of interest and would be inferential.

A total of 393 subjects were screened in order to randomize 331 subjects, of which 305 received treatment, 26 did not receive study drug. Cohort 1 randomized 30 subjects to Posimir and 18 subjects to bupivacaine, Cohort 2 randomized 30 subjects to Posimir and 20 subjects to bupivacaine, and Cohort 3 randomized 129 to Posimir and 78 subjects to placebo. Of all randomized and treated subjects, 11 did not complete the study. Six subjects withdrew consent, four in the Posimir arms, one in the bupivacaine arm, and one in the placebo arm. Two subjects, one subject in the Posimir arm and one in the bupivacaine arm discontinued due to an adverse event. The other three reasons were lost to follow-up, investigator decision, and other. The average age of all subjects was 56 years old with a range of 22 to 87. Overall the study enrolled approximately equal numbers of males and females, 48% and 52%, respectively. The applicants' results the primary analysis are shown in Table 20.

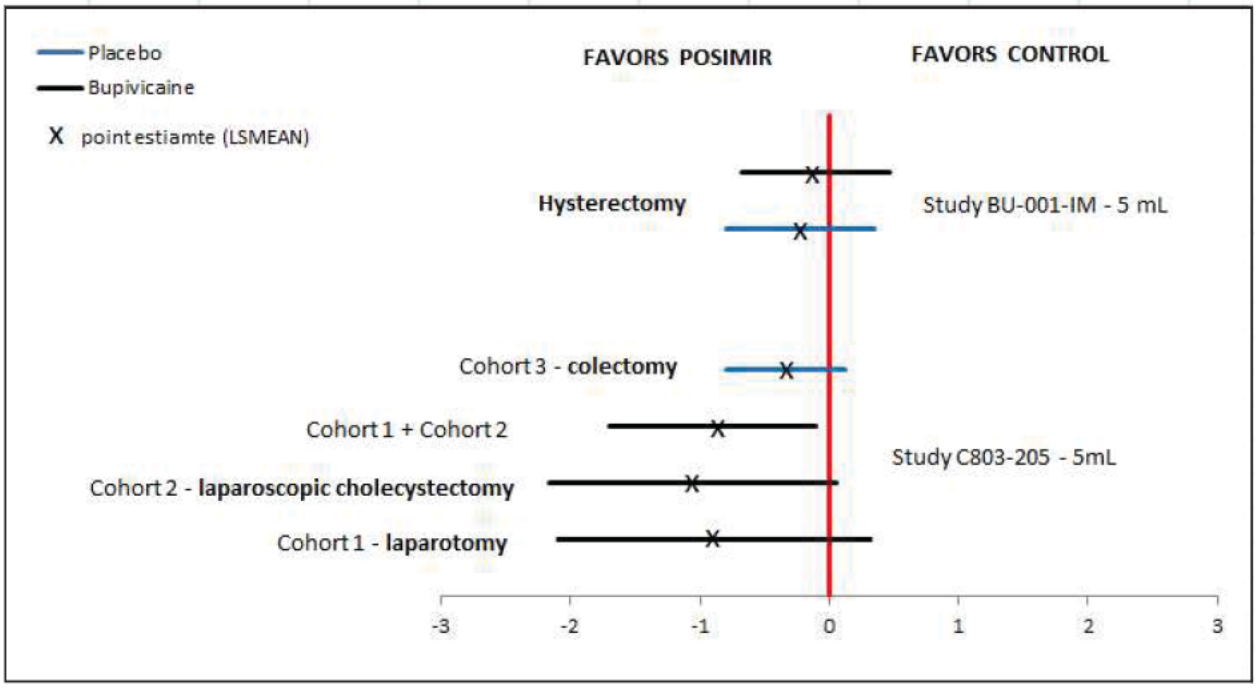
Table 20. Results of applicants' primary analysis from Study C803-025

Cohort	normalized AUC72 (pi)			p-value
	Control	Posimir 5 mL	Difference (95% CI)	
1	5.8	4.9	-0.9 (-2.1, 0.3)	0.15
2	3.9	2.8	-1.1 (-2.2, 0.05)	0.06
3	5.1	4.8	0.34 (-0.8, 0.12)	0.15

Source: Table 15 from applicants CSR

It was noted that the only analysis that a significant difference in the treatment effect was noted was when Cohort 1 and Cohort 2 were pooled by the Applicant. The review team felt that it was not appropriate to pool the data from these two procedures because they were clinically very different procedures.

The figure below depicts the point estimates and the 95% confidence intervals for the differences between SABER-Bupivacaine and control, for AUC_{72}. As Mr. Petullo noted in his review, while a significant treatment effect was not demonstrated, the point estimate was in favor of SABER-Bupivacaine in all cases. The results of the analysis that pooled Cohort 1 and Cohort 2 are also depicted.



Outstanding or Unresolved Issues

Dr. Simone and Mr. Petullo each noted in their respective reviews that the Applicant had provided substantial evidence of efficacy for Posimir in the setting of post-surgical pain associated with shoulder surgery, but not for the setting of inguinal herniorrhaphy. Dr. Breder, in his Cross-Discipline Team Leader review concluded that the Applicant had replicated evidence of a post-operative analgesic effect, but noted that the treatment effect was small.

There were several observations noted by the review team about the drug development program that appeared to be different from other development programs, e.g., that, of the seven clinical trials submitted in support of the application, only one was a Phase 3 study; that, within each of the surgical procedures, the clinical trials evaluating that particular procedure differed in design with respect to the control groups and/or the way Posimir was to be administered; that several of the trials had numerous amendments to the protocol while the trial was in progress; and that the

two trials with statistically significant treatment effects were conducted outside of the United States, while the results of trials that enrolled sites in the United States were not statistically significant.

All of the above are true observations, however, their significance may be overemphasized. Although it is true that most NDA submissions contain more than one Phase 3 trial supporting the requested indication, it is not unheard of for a Phase 2 trial to be considered as a pivotal trial, provided that they are adequately designed, conducted, and achieve a statistically significant result for their pre-specified primary endpoint. The fact that the trials in a particular procedure may have differed from each other is reflective of the fact that they were Phase 2 trials, which by their nature, may be exploring different endpoints and, in the case of Posimir, different methods of administration. This is consistent with the concept that the replicated evidence does not necessarily mean that the trials providing such evidence need to be identical; in fact, there are some potential benefits to having the replicated evidence be derived from trials that are not identical, since that may result in a better assessment of different aspects of a particular drug product.

With respect to the observation that the protocol had multiple amendments: clinical trials often have amendments made to the protocol while the trial is in progress. These usually do not raise any concerns provided they are implemented prior to the unblinding of the database. Lastly, the observation that all the trials in the United States were negative is true, but it is noted that, of those trials which failed to reach a statistically significant difference, the results were trending in favor of the Posimir treatment group. Furthermore, there is no reason to expect that the data generated from the foreign clinical sites be not applicable to the United States population. The medical care and facilities from New Zealand, Australia, and Western Europe are comparable to those in the United States. Lastly, although there may be cultural differences that could theoretically impact the reported pain relief by subjects in the trial, the randomized, controlled design of the clinical trials should obviate that variable.

Subsequently, I believe that, with respect to the indication sought by the Applicant, i.e., post-operative analgesia, the Applicant has submitted substantial evidence of efficacy, by virtue of having two clinical trials that had statistically significant result for the pre-specified protocol endpoints.

That being said, I also believe it is appropriate to look beyond the results of the pre-specified primary endpoint. This would include evaluation of any secondary endpoints that were pre-specified in the protocol, as well as conducting other analyses that are commonly referred to as "sensitivity analyses." These analyses can include performing the analysis of the primary endpoint on different patient populations (e.g., Intent-to-treat population, Per-protocol population); utilization of different imputation schemes for missing data; or evaluation of an endpoint, such as the use of rescue medications, by noting whether the results change based on how the variables were coded in the database. All of these analyses would be performed not only to assess the robustness of the results (i.e., whether the overall trial results hinge on the results from a few subjects), but to also try to get a fuller picture of the treatment effect. Due to the specific aspects of the way Posimir is being proposed to be used, some of the analyses would not be applicable to the clinical trials with Posimir.

With respect to this NDA, I don't think that any of these analyses should be used to determine whether the Applicant has submitted sufficient evidence to demonstrate the efficacy of Posimir in post-operative analgesia, but to help inform the risk benefit analysis that would determine Posimir's approvability. This will be addressed further below.

4. Safety

As noted by Dr. Simone and Dr. Breder, the safety database was derived from a total of 13 studies that were conducted with the to-be-marketed formulation. A total of 1075 patients or healthy subjects were exposed to study drug. The table below, adapted from Dr. Simone's review, summarizes the number of individuals that were exposed to the different treatment groups, and the amount of exposure.

Number of Subjects by Treatment Group and Dose

SABER-Bupivacaine Alone †			SABER-Bupivacaine (S-B) and Bupivacaine HCl				SABER-Placebo		Bupivacaine HCl Alone			
N	Vol. (mL)	Dose (mg)	N	Vol. S-B (mL)	Bup HCl Dose (mg)	Total Bup Dose (mg)	N	Vol. (mL)	N	Vol. (mL)	Conc (%)	Dose (mg)
50	2.5	330	5	5	50	710	16	2.5	1	5	0.25	12.5*
547	5	660	6	5	75	735	218	5	9	7.5	0.25	18.8*
4	7.5	990	45	7.5	50	1040	4	7.5	5	15	0.5	75
			26	7.5	75	1065	30	10	15	17.5	0.5	87.5
									29	20	0.25	50
									38	30	0.5	150
									27	40	0.25	100
601			**82**				**268**		**124**			

†Five subjects in study CLIN005-0008 were put under the 'SABER-Bupivacaine Alone' although they had been previously exposed to a bupivacaine patch as part of the cross-over study. For all safety summaries, they were included under the combination arm.

*These subjects also received bupivacaine HCl (75 mg) pre-operatively as local anesthesia for their procedure.

As noted by Dr. Simone, a total of 547 subjects were exposed to the 5 mL dose of SABER-Bupivacaine, which is the Applicant's proposed dosing regimen.

Deaths

There was one death reported for the entire clinical development program. It occurred on Post-operative Day 40, which was beyond the protocol-specified reporting period. The cause was identified as post-operative complications related to his laparascopic hemicolectomy. The narrative indicated that the patient was an 82-year-old male with significant comorbid conditions, and the cause of death was considered to most likely be due to complications from his underlying Parkinson's disease.

Non-fatal Serious Adverse Events
As noted by Dr. Simone in his review, there were 74 treatment-emergent serious adverse events reported in the safety database. The breakdown with respect to when they occurred is as follows: approximately 11% of these events occurred during the first hour after surgery, 20% occurred in the time period from 1 to 72 hours after treatment, and the remaining 69% occurred >72 hours after treatment.

The system organ classes that were primarily associated with the serious adverse events were Gastrointestinal Disorders, Procedural Complications, Nervous System Disorders, and Administration Site Conditions.

A substantial number of subjects who experience a serious adverse event also had the results of blood samples available. The median value for the C_{max} of bupivacaine was reported to be 730 ng/ml (range: 52 to 1870 ng/mL). Eleven of the cases had a C_{max} value of 1000 ng/mL, but the adverse event occurred well after the expected T_{max}. Thus, the review team concluded that plasma bupivacaine levels were unlikely to play a role in the reported adverse event.

Dr. Simone noted in his review that several of the serious adverse events were associated with the anatomical area involved with the surgical procedure, specifically, a scrotal hematoma following an inguinal repair, a vaginal hematoma following a hysterectomy, and three cases of wound dehiscence. It was also noted that none of the subjects treated with bupivacaine HCl experienced these types of serious adverse events.

Early Discontinuations
The studies consisted of an intra-operative administration of a single dose; therefore, it was not possible for a subject to discontinue treatment due to an adverse event. The Applicant did report that 3 subjects withdrew from the study shortly after surgery due to an adverse event. These were described in Dr. Simone's review as follows:

1. Subject (b) (6) in the BU-001-IM trial was treated with SABER-Placebo and was withdrawn on study Day 1, because of severe abdominal pain.
2. Subject (b) (6) in the C803-025 trial, was treated with bupivacaine HCl and was withdrawn on study Day 3, because of dyspnea, hypoxia associated with pneumonia.
3. Subject (b) (6) in the C803-025 trial, was treated with SABER-Bupivacaine and was withdrawn on study Day 1 because of atelectasis.

In addition, there were an additional 37 subjects who withdrew from the studies. The reasons cited were loss to follow-up, subject's decision, physician's decision, protocol violations, and "other" reasons. The distribution among the different treatment groups was comparable, and the review team concluded that the safety findings would not be impacted by these discontinuations.

Common Adverse Events
The Applicant provided a table of adverse events that were reported at a frequency of > 5%. Dr. Simone created a table that summarized the type of adverse events that occurred in >1% of the subjects treated with SABER-Bupivacaine, but were higher than those reported for the SABER-Placebo and Bupivacaine HCl treatment groups or were no more than a 1% difference in the

incidence between the SABER-Bupivacaine and both Bupivacaine HCl and SABER-Placebo treatments.

The System Organ Classes that were involved mirrored what was seen with the serious adverse events. They were primarily Gastrointestinal Disorders, Administration Site Conditions, Procedural Complications, and Nervous System Disorders.

Other significant Adverse Events

Local toxicity

Dr. Simone noted in his review that frequency of adverse events identified as application site discoloration (which included hematomas), localized pruritus, contusion, incision site hemorrhage, wound dehiscence, and wound secretion was higher in the SABER-Bupivacaine treatment group compared to the Bupivacaine HCl treatment group. Application site discoloration, contusion, wound secretion and pruritus were also more frequent in the SABER-Placebo treatment group compared to the Bupivacaine HCl treatment group, suggestive that it was the SABER component that may have been playing a role in these adverse events.

The frequencies of these events are summarized in the table below, adapted from a table generated by Dr. Simone. It is noted that, in the table below, a patient may have had more than one type of adverse event, and multiple occurrences of one type of adverse event were counted only once.

Adverse Events Associated with Site of Administration, by Treatment Group and Dose

Adverse Event	**SABER-Bupivacaine 2.5 mL** **N = 50**	**SABER-Bupivacaine 5 mL** **N = 547**	**SABER-Bupivacaine with Bupivacaine HCl** **N = 82**	**SABER-Placebo** **N = 268**	**Bupivacaine HCl** **N = 124**
Pruritus	14 (28%)	108 (20%)	5 (6%)	64 (24%)	6 (5%)
Hematomas and Suffusions	13 (26%)	86 (16%)	23 (28%)	34 (13%)	3 (2%)
Suffusions		24 (4%)		7 (3%)	
Hematomas	13 (26%)	62 (11%)	23 (28%)	27 (10%)	3 (2%)
Bruising	12 (24%)	67 (12%)	82 (100%)	15 (6%)	8 (6%)
Erythema	7 (14%)	42 (8%)	8 (10%)	16 (6%)	2 (2%)
Ecchymosis		42 (8%)		20 (7%)	1 (1%)
Discoloration		41 (7%)		26 (10%)	4 (3%)
Dehiscence		20 (4%)		5 (2%)	
Bleeding	1 (2%)	31 (6%)		7 (3%)	
Infection		22 (4%)	2 (2%)	7 (3%)	5 (4%)
Total	47	459	120	194	29

The table below summarizes the frequency of dehiscence reported for each treatment group, organized by study and procedure.

Frequency of Dehiscence, by Procedure and Treatment Group

Study ID	Procedure	SABER-Bupivacaine 5 mL	SABER-Placebo	Bupivacaine HCl
BU-001-IM	Hysterectomy	2 (3%)	0	0
BU-002-IM	Arthroscopic Shoulder	2 (4%)	0	0
C803-025	Abdominal procedures (all)	22 (12%)	10 (13%)	0
	Laparotomy	6 (23%)	NA	0
	Laparoscopic Cholecystectomy	2 (7%)	NA	0
	Laparoscopically-assisted colectomy	14 (11%)	10 (13%)	NA
C803-027	Abdominal procedures	10 (100%)	NA	NA

In Study BU-001-IM, which enrolled women who underwent a hysterectomy, the imbalance in the frequency of hematomas between the treatment groups was more apparent. The frequency of adverse events is summarized in the table below, categorized by System Organ Class and Preferred Term.

Frequency of Hematoma, by Treatment Group, Study BU-001-IM

Primary SOC Preferred term	**SABER-Bupivacaine N = 60**		**SABER-Placebo N = 27**		**Bupivacaine HCl N = 27**		**Total N =114**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Injury, Poisoning, and Procedural Complications	38	(63.3)	9	(33.3)	0	0	47	(41.2)
Post-procedural hematoma	36	(60)	9	(33.3)	0	0	45	(39.5)
Wound Complication	1	(1.7)	0	0	0	0	1	(0.9)

Local toxicities consistent with a foreign body reaction was observed in the nonclinical studies, therefore, it is not unreasonable to suspect that something comparable was occurring in the clinical trials.

CNS Adverse Events

The frequency of adverse events associated with CNS involvement was more frequent in the SABER-containing treatment groups. These events are summarized in the table below.

Frequency of CNS-Related Adverse Events, by Treatment Group and Dose

System Organ Class	**Preferred Term**	**SABER-Bupivacaine 2.5 mL N = 50**		**SABER-Bupivacaine 5 mL N = 542**		**SABER-Placebo N = 268**		**Bupivacaine HCl N = 124**	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Ear and Labyrinth Disorders	Tinnitus	3	6	34	6	19	7	3	2
Nervous System Disorders	Dizziness	15	30	133	25	79	29	11	9
	Dysgeusia	6	12	37	7	29	11	1	1
	Headache	17	34	102	19	48	18	11	9
	Hypoesthesia	4	8	29	5	23	9	1	1

System Organ Class	Preferred Term	SABER-Bupivacaine 2.5 mL N = 50		SABER-Bupivacaine 5 mL N = 542		SABER-Placebo N = 268		Bupivacaine HCl N = 124	
		n	%	n	%	n	%	n	%
	Paresthesia	10	20	42	8	23	9	3	2
	Somnolence	21	42	140	26	100	37	7	6

It is unclear whether the benzyl alcohol may have been involved, since the clinical trials did not assess the plasma or urine for benzyl alcohol levels. However, the lower frequency observed in the patients treated with bupivacaine makes it less likely for bupivacaine to be playing a role in this adverse event.

Chondropathy

At the conclusion of his review, Dr. Simone had identified three reports of chondrolysis in the patients who had undergone arthroscopic surgery. One of the cases had been identified as a serious adverse event. The Applicant had previously been made aware of the Division's concern about the possibility that the administration of the product in the area of a joint could result in chondrolysis.

The Division conveyed via a Discipline Review letter the concern that, even though efficacy had been demonstrated in the clinical trials involving arthroscopic surgery, the occurrence of these three cases raised concerns. The Applicant responded to the letter by submitting additional information to support the contention that the three cases did not meet the pre-specified definition of chondrolysis, because they did not have the radiographic findings stipulated in the case definition.

After reviewing the additional information, Dr. Simone conceded that the cases did not meet the case definition, but still noted that the cases represented some type of chondropathy. Unfortunately, it is very difficult to state one way or the other whether these cases represent a safety signal or simply is a reflection of the natural progression of the disease process in these patients. This was also confounded by the fact that there weren't any Bupivacaine-only treated patients with enough long-term follow-up that could serve as a control.

Outstanding or Unresolved Issues

The overall assessment of the review team with regard to the clinical safety database was that there was no evidence of dose-dumping of the bupivacaine, and that there were no concerns about systemic toxicities due to exposure to the bupivacaine in Posimir.

I concur with the review team that there are a several adverse events of concern, however, primarily the events relating to the CNS, adverse events related to the local site of administration, and events associated with the shoulder surgery. For several of the adverse events, the lack of a treatment group that was not exposed to the SABER component makes it difficult to interpret the significance of the imbalance observed.

4. Advisory Committee Meeting

An advisory committee meeting was not convened for this supplemental application, as there were no issues in this supplemental application that required presentation or discussion at an advisory committee meeting.

10. Pediatrics

The Applicant has requested a waiver be granted from the requirement to study pediatric patients younger than 3 years of age, due to the concerns about benzyl alcohol toxicity in pre-term and term newborns, and concerns about systemic accumulation of bupivacaine due to the diminished clearance in patients younger than 3 years of age.

The Applicant is requesting a deferral for the other age groups, and has proposed a plan for sequential evaluation of patients in the 3 to 18 year age group. They proposed a randomized, double-blind, placebo-controlled study to assess the pharmacokinetics, efficacy, and safety in the 12 to 18 age group, extrapolating data from the adult studies to help guide the design. This would be followed by a similar study in the 6 to 11 age group, utilizing data from the adolescent age group to help guide the design. Lastly, a third study will be conducted in the 3 to 5 year age group, utilizing the data from the 6 to 11 age group to help guide the design.

11. Other Relevant Regulatory Issues

Consultations were obtained from the Office of Scientific Investigations (OSI), the Office of Professional Drug Promotion (OPDP), and the Division of Medication Error Prevention and Analysis (DMEPA). The recommendations made by OPDP and DMEPA were reviewed and incorporated in the appropriate sections in the labeling.

OSI / Division of Good Clinical Practice Compliance (DGCPC) Audits

Two clinical sites from Study CLIN-803-006-0006 were selected for inspection, based on the number of subjects enrolled at these sites. They were Site 001 (Dr. Douglas Nicholson, Australia) and Site 005 (Dr. Richard Turner, Australia). Based on the findings from the inspections, the data were deemed reliable. The classifications for the inspections were No Action Indicated (NAI).

Financial Disclosure

The Applicant certified that there was no financial arrangement with the study investigators whereby the value of compensation to the investigators could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant also certified that no listed investigator was the recipient of significant payments of sorts as defined in 21 CFR 54.2 (f). The Applicant also indicated that the clinical investigators were required to disclose to the Applicant whether the investigator had a proprietary interest in the product or a significant equity in the Applicant, as defined in 21 CFR 54.2(b).

Outstanding or Unresolved Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

In addition to the review disciplines mentioned above, representatives from the Division of Medication Error Prevention and Analysis and the Office of Prescription Drug Promotion were also consulted and their recommendations were incorporated during the discussion of the label.

The labeling will be discussed with the Applicant during a subsequent review cycle.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

Complete Response.

Risk:Benefit Assessment

I believe the Applicant has provided sufficient data to demonstrate the efficacy of Posimir with respect to post-operative analgesia. However, the Applicant has not provided sufficient data to demonstrate that Posimir is safe when used as directed in the Applicant's proposed labeling.

Adverse events regarding the central nervous system, the site of the surgical procedure, and joint chondropathy were reported in the safety database. The possibility of Posimir contributing to the development of a chondropathy in the treated joint, inherently, is a concern, but the reports of the other events are also quite unsettling.

For example, the neurologically-related adverse events reported, such as dizziness, dysgeusia, headache, hypoesthesia, paresthesia, and somnolence occurred with substantially greater frequency in patients in the treatment groups that received SABER-containing products, compared to the patients in the Bupivacaine HCl. In some of these patients, the severity of the event was moderate and protracted (lasting as long as 24 hours).

As for the events related to the site of administration, such as hematoma and dehiscence, they were also reported more often in the patients treated with the SABER component (either SABER-Bupivacaine or SABER-Placebo) compared to the patients treated with Bupivacaine HCl. These events are also concerning because several were considered to be a serious adverse event. Furthermore, adverse events that might reflect a potential interference with wound healing have particular implications for a product that is intended to be administered into a surgical wound.

The significance of these adverse events could not be adequately assessed due to various reasons, including the lack of an appropriate control arm in the some of the clinical trials, the timing of the follow-up assessments, and the number of subjects that had an adequate duration of follow-up.

The inability to determine whether Posimir is safe when used as directed resulted in a risk:benefit assessment that does not support the approval of this NDA at this time.

In order to address these concerns, the Applicant will need to provide additional data from clinical trials that demonstrate that Posimir is safe when used as directed. These data would need to be generated from clinical trials that are designed with the appropriate control treatment group(s), with appropriate evaluations performed at appropriate intervals, and with a follow-up period of an appropriate duration to evaluate the safety concerns.

With respect to the manner in which the potential for joint chondropathy should be evaluated, our current understanding of this phenomenon is not at the point where we know what the appropriate methods, frequency, and duration of evaluations should be. Recent experience indicated that, depending on the drug class, the patient population, and the indication being evaluated, the number of patients that need to be enrolled in such a trial can be in the order of thousands. The Applicant will need to consult with experts in the field and submit a proposal of how they intend to evaluate this issue. These experts will not only need to be able to advise on the natural progression of the chondropathy, but the expected progression of the chondropathy in someone who has had a surgical procedure performed on the joint in question.

Recommendation for Postmarketing Risk Management Activities

None.

Recommendation for other Postmarketing Study Commitments

None.

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/s/

RIGOBERTO A ROCA
02/12/2014

CLINICAL REVIEW

Application Type	New Drug Application
Application Number(s)	204803
Priority or Standard	Standard
Submit Date(s)	April 12, 2013
Received Date(s)	April 12, 2013
PDUFA Goal Date	February 12, 2014
Division / Office	DAAAP / ODE 2
Reviewer Name(s)	Arthur Simone, MD, PhD
Review Completion Date	January 8, 2014
Established Name	SABER-Bupivacaine
(Proposed) Trade Name	Posimir
Therapeutic Class	Local Anesthetic
Applicant	Durect Corporation
Formulation(s)	Solution
Dosing Regimen	Single administration by instillation of 5 mL directly into the surgical incision(s).
Indication(s)	For administration into the surgical incision to produce post-surgical analgesia
Intended Population(s)	Post-surgical adult patients

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

A Complete Response action is recommended based on the failure of the Applicant to demonstrate that a 5 mL dose of SABER-bupivacaine is superior to a placebo or an active comparator in providing postoperative analgesia for a surgical procedure where the risks of SABER-bupivacaine do not outweigh its benefits.

It is recommended that the following deficiencies be conveyed to the Applicant along with the requirements to address them:

Deficiency 1
For arthroscopic acromial decompression surgery (trials CLIN005-0006, C-803-017, and BU-002-IM) you have adequately demonstrated the efficacy of SABER-bupivacaine. However, the risk of chondrolysis, based on the incident observed with SABER-bupivacaine treatment, outweighs the benefit of SABER-bupivacaine for this surgical procedure and prevents its approval for this indication.

Requirements to Address the Deficiency
Provide evidence or a rationale that this event was not related to SABER-bupivacaine treatment. Then conduct another trial comparing SABER-bupivacaine to a non-SABER placebo or active comparator to demonstrate the validity of that evidence or rationale.

Deficiency 2
For the other surgical procedures studied, you have not adequately demonstrated the efficacy of SABER-bupivacaine. In addition, the incidence of somnolence, dizziness, dysgeusia, hematoma, bruising, dehiscence, and pruritus were greater with SABER-bupivacaine and SABER-placebo treatments than with bupivacaine HCl. Therefore, the risks of SABER-bupivacaine have outweighed the benefits for the non-arthroscopic procedures studied to date.

Requirements to Address the Deficiency
Adequately demonstrate the efficacy of SABER-bupivacaine by either repeating the trials for non-arthroscopic procedures already assessed but using a higher dose or revised formulation of SABER-bupivacaine and comparing it to a placebo that does not contain the SABER component. Alternatively, you may evaluate the use of SABER-bupivacaine in heretofore unstudied surgical procedures comparing it to a non-SABER placebo. In addition, from the surgical procedure in which you are able to demonstrate the efficacy of SABER-bupivacaine, you will need to identify the procedures where the

adverse reactions currently observed with SABER containing products occur at a frequency similar to that of bupivacaine HCl. These may be procedures that require small incisions and lower doses of SABER-bupivacaine. Alternatively, the product may be reformulated to decrease or eliminate these risks and re-evaluated to demonstrate efficacy and safety.

1.2 Risk Benefit Assessment

The benefits and risks of SABER-bupivacaine were weighed separately for each of the surgical groupings the Applicant evaluated during clinical development.

Arthroscopic Shoulder Surgery
The Applicant conducted three Phase 2 clinical trials involving arthroscopic subacromial decompression surgeries:

1. CLIN005-0006 failed to demonstrate SABER-bupivacaine was superior to SABER-placebo. For the primary endpoint, the least-squares means of the pain intensity AUC_{0-72}, the difference between treatment groups favored SABER-bupivacaine.
2. C-803-017 failed to demonstrate SABER-bupivacaine was superior to SABER-placebo. For the primary endpoint, the least-squares means of the pain intensity AUC0-72, the difference between treatment groups favored SABER-bupivacaine.
3. BU-002-IM demonstrated SABER-bupivacaine to be superior to SABER-placebo but not to bupivacaine HCl. The differences in the primary endpoint, the least-squares means of the pain intensity AUC0-72, for SABER-bupivacaine and bupivacaine HCl favored SABER-bupivacaine treatment.

For this procedure, the Applicant was able to demonstrate the superiority of SABER-bupivacaine in one of three studies which all utilized the same dose, the same method of administration, and the same comparator, i.e., SABER-placebo. One of the studies also demonstrated that SABER-bupivacaine was not significantly more efficacious than bupivacaine HCl. Based on the finding of superiority in a single trial and the favorable trending of the primary efficacy results across all the studies, SABER-bupivacaine was considered efficacious for this surgical procedure.

The safety findings reported in these trials included a small number of reactions at the incision sites, but most importantly, there was a single case of chondrolysis that was reported at 15 months following surgery and SABER-bupivacaine administration, confirmed by biopsy and MRI scan, and that required additional surgery for resolution. This serious adverse event occurred despite efforts by the Investigators to assure the study drug was not injected into the intra-articular space, and there was no evidence to suggest that it was. Only two of the studies had the long-term follow-up evaluation necessary to detect chondrolysis, and one of those studies performed the evaluation at

6 months after study drug administration, which may have been too early to detect all cases. Thus, it is not certain what the true incidence of this AE was; however, it occurred once in 31 subjects treated with SABER-bupivacaine who were followed for 18 months and did not occur in the 16 subjects treated with SABER-placebo who were followed for the same duration.

Based on the single event of chondrolysis, the risk associated with SABER-bupivacaine outweighs its benefits.

Inguinal Herniorrhaphy

The Applicant conducted two Phase 2 studies involving inguinal hernia repair surgery:

1. CLIN-005-0010 (non-US trial) failed to demonstrate that SABER-bupivacaine was superior to SABER-placebo. The differences in the efficacy endpoint least-squares means of the pain intensity AUC0-72 for SABER-bupivacaine and SABER-placebo favored SABER-placebo treatment.
2. CLIN-803-006-0006 (US trial) demonstrated that SABER-bupivacaine was superior to SABER-placebo.

For both trials, the Applicant utilized the same dose, the same method of administration, the same comparator, and essentially the same patient population in terms of demographic parameters. The only identifiable difference between the trials was that trial which succeeded was conducted outside the U.S., i.e., New Zealand and Australia; whereas the trial which failed was conducted in the U.S. with the exception of one (of seven) sites which was in New Zealand. The repair was specified as a Lichtenstein repair for the non-US trial but not for the US trial. However, in the U.S., the Lichtenstein repair is the most commonly performed repair.

The safety findings for these studies, and the others involving skin incisions longer than those required for a laparoscope or arthroscope, indicated higher incidences of hematoma, dehiscence, bruising, ecchymosis, erythema and pruritus following treatment with SABER-bupivacaine compared to bupivacaine HCl. Some of these adverse reactions also occurred more frequently with SABER-placebo indicating the reactions may be more likely due to a component of SABER rather than bupivacaine.

Based on the mixed efficacy findings with a more favorable efficacy finding for SABER-placebo in the US population and the greater frequency with which reactions occur at the incision site following SABER-bupivacaine that bupivacaine HCl, the risks associated with SABER-bupivacaine outweigh the benefits.

Surgeries Involving the Abdominal and Pelvic Cavities

The Applicant conducted a Phase 2 study involving subjects undergoing hysterectomy and a Phase 3 study involving subjects undergoing one of three types of abdominal procedures:

1. BU-001 failed to demonstrate the superiority of SABER-bupivacaine either over SABER-placebo or bupivacaine HCl. The differences in the primary endpoint, the least-squares means of the pain intensity AUC0-72, for SABER-bupivacaine and both of the control treatments favored SABER-bupivacaine treatment.
2. C803-025 consisted of three surgical cohorts:
    a. Cohort 1 involved patients undergoing laparotomies for a variety of indications. In this cohort, SABER-bupivacaine was not shown to be superior to bupivacaine HCl; however, the differences in the primary endpoint, the least-squares means of the pain intensity AUC0-72, favored treatment with SABER-bupivacaine.
    b. Cohort 2 involved patients undergoing laparoscopic cholecystectomy. In this cohort, SABER-bupivacaine was not shown to be superior to bupivacaine HCl; however, the differences in the primary endpoint, the least-squares means of the pain intensity AUC0-72, favored treatment with SABER-bupivacaine.
    c. Cohort 3 involved patients undergoing laparoscopic assisted colectomy. In this cohort, SABER-bupivacaine was not shown to be superior to SABER-placebo; however, the differences in the primary endpoint, the least-squares means of the pain intensity AUC0-72, favored treatment with SABER-bupivacaine.

    The Applicant reported that the combined data from Cohort 1 and Cohort 2 demonstrated that SABER-bupivacaine was superior to bupivacaine HCl; however, the differences between the surgical procedures, the types of incisions required for the procedures, and the nature and extent of the postoperative pain associated with both procedures do not justify combining the efficacy results. Therefore, for the purposes of this review, each of the three cohorts was considered separately for evaluating efficacy.

The safety findings for these studies, in conjunction with those for the hernia repair studies, indicated higher incidences of hematoma, dehiscence, bruising, ecchymosis, erythema and pruritus following treatment with SABER-bupivacaine as noted above for the herniorrhaphy trials.

Based on the failure to demonstrate the superiority of SABER-bupivacaine in any of the cohorts and the greater frequency with which reactions occur at the incision site following SABER-bupivacaine compared to bupivacaine HCl, the risks associated with SABER-bupivacaine outweigh the benefits for all four of these surgical procedures.

<u>Other Safety Concerns Related to the Use of SABER-Bupivacaine</u>

1. The risk associated with systemic exposure to benzyl alcohol (BA) was not characterized as part of the Applicant's development program as required by the Division. Adult exposures to the amount of BA released by SABER products

have not been determined, but the 1.1 grams of BA released over 12-24 hours is many times the dose to which patients would be exposed with currently approved injectables that utilize BA as a preservative. While this concern was shared with the Applicant during early development, the level of the concern is elevated by some of the safety findings observed for both SABER-bupivacaine and SABER-placebo but no bupivacaine HCl, e.g., increased incidence of somnolence, dizziness and dysgeusia.

2. The risk associated with the sucrose acetate isobutyrate (SAIB) component of SABER has not been fully characterized. The substance has been found present at the injection sites in animals up to a year later, and where it was associated with a foreign body reaction and fibrosis. SAIB was not found to alter the animals' behavior regarding the injection site beyond the first weeks following SABER injection, and the gross appearance of the injection sites was within normal limits at one year following the injection. The long-term follow-up data from the clinical trials suggest SAIB is not associated with untoward reactions; however, those assessments included too few non-white subjects to determine whether there are any local adverse reactions that are related to a patient's skin color. Specifically, individuals with darker colored skin are at increased risk for hypertrophic scarring or keloid formation. Whether there is a risk for an increase in incidence or severity of this reaction with SABER-bupivacaine is not known.

Lastly, it is worth noting that the clinical trials conducted to evaluate the efficacy of SABER-bupivacaine resulted in findings similar to those conducted to evaluate the efficacy Exparel, a liposomal injectable that provides extended release of bupivacaine for postoperative analgesia. Clinical trials comparing Exparel to bupivacaine HCl, failed to demonstrate the superiority of Exparel; rather, they showed the two products to be similar in the magnitude and duration of their effects. However, Exparel was demonstrated to be superior to normal saline placebo for two surgical procedures (bunionectomy and hemorrhoidectomy), its safety profile was demonstrated to be similar to bupivacaine HCl for those procedures, and there was no evidence of a safety risk associated with the liposomes, which are resorbed over the course of 6-12 weeks. Based on those findings, Exparel was approved, but only for use following those two procedures because the manner in which it was administered was unique for each procedure and it was not possible to extrapolate a dose or method of administration that would be safe and efficacious for other surgical procedures.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

At this time, there are no recommendations for postmarketing risk evaluation and mitigation strategies

1.4 Recommendations for Postmarket Requirements and Commitments

At this time, there are no recommendations for postmarketing risk evaluation and mitigation strategies

2 Introduction and Regulatory Background

2.1 Product Information

SABER-Bupivacaine consists of a solution of 12% bupivacaine in 22% benzyl alcohol (BA) and 66% sucrose acetate isobutyrate (SAIB) on a weight/weight (w/w) basis. The solution is instilled directly into a surgical incision, which is then closed with sutures. The benzyl alcohol component of the formulation then rapidly diffuses into the surrounding tissue and is cleared from the circulation over a 12-24 hour period. This leaves a viscous subcutaneous depot of bupivacaine in SAIB. SAIB, which is a high viscosity, biodegradable, hydrophobic, fully esterified sucrose derivative, controls the rate of release of bupivacaine from the formulation into the surgical site where it exerts its effects as a local anesthetic.

The combination of SAIB and BA with bupivacaine provides the product's key attributes:

- extended-release of bupivacaine (up to 72 hours)
- product stability at room temperature
- a high concentration of bupivacaine in a small volume sufficient for administration into surgical incisions
- a solution that can be instilled though a needle free syringe or large bore needle or cannula

The formulation contains 0.242 mg/mL of benzyl alcohol as a solvent, which permits the product to drawn up and instilled using a syringe with or without a large bore needle. After the product is administered into the wound, the benzyl alcohol diffuses out of the matrix, leaving behind the viscous SAIB matrix containing bupivacaine. Bupivacaine diffuses from the matrix into the surrounding tissues where it exerts its analgesic effects for up to 72 hours. The SAIB matrix remains in the surgical wound for an unknown period that is a minimum of several months' duration.

2.2 Currently Available Treatments for Proposed Indications

There are a number of local anesthetic products that are indicated for providing postoperative analgesia; however, there are only three bupivacaine-containing products:

1. Bupivacaine HCl (RLD: Marcaine - NDA16964) without epinephrine is an injectable that can be used for infiltration, regional nerve blocks and neuraxial anesthesia.

2. Bupivacaine HCl (RLD: Marcaine - NDA16964) with epinephrine is an injectable that can also be used for infiltration, regional nerve blocks and neuraxial anesthesia
3. Exparel (NDA022496) is a liposome injection of bupivacaine, an amide-type local anesthetic, indicated for administration into the surgical site to produce postsurgical analgesia. Exparel is only labeled for use following hemorrhoidectomy and bunionectomy.

2.3 Availability of Proposed Active Ingredient in the United States

There are two supplies of bupivacaine that the Applicant will be relying on for their drug substance: (b) (4) There is no known limitation to the bupivacaine supply for either of these manufacturers.

2.4 Important Safety Issues with Consideration to Related Drugs

The more important safety issues related to the use of local anesthetics generally arise from systemic exposure and include the following:

1. Central nervous system reactions. These range from CNS excitation with lightheadedness, dizziness, paresthesias and acute anxiety at lower plasma levels to generalized tonic-clonic seizure activity, depression of conscious activity and respiratory arrest with profound depression of the medullary respiratory center at higher plasma concentrations.
2. Cardiac reactions. These include dose-dependent depression of myocyte activity with associated decreases in myocardial contractility beginning at doses that achieve sodium-channel blockade. Life-threatening arrhythmias and cardiovascular collapse can occur at higher systemic exposures. These toxicities are related, in large part, to agent-specific kinetics of sodium channel blockade.
3. Allergic-type responses. These can range from contact hypersensitivity to anaphylactoid and anaphylactic reactions. Para-aminobenzoic acid (PABA), a metabolite of the local anesthetics, which have an ester linkage between the aromatic nucleus and the amino or piperidine group, is commonly found in the environment and therefore, may serve as a significant source of allergic reactions as many patients present already sensitized to this compound. [Exparel is an amide type of local anesthetic, which are not metabolized to PABA as they have an amide linkage between the aromatic nucleus and the amino or piperidine group.] In addition, the preservatives, methylparaben and metabisulfite, commonly used in multidose local anesthetic preparations may, independently of the local anesthetic, trigger an allergic reaction.

For Exparel, there is an additional concern, the potential for dose dumping. The release of excessive quantities of bupivacaine from the liposomes in Exparel, due to causes such as compression of the product in the surgical wound or variations in local tissue vascularity and blood flow, was a risk factor that the Applicant had to assess for each surgical procedure in which they evaluated the product. This concern is partly addressed by the recommendations in the product labeling that it not be used for surgical procedures other them hemorrhoidectomy and bunionectomy.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Sponsor (now Applicant) elected not to request a preIND meeting for this product. Instead, they opened IND 066086 on October 23, 2002. At that time, the formulation contained (b) (4) a compound with carcinogenic potential, and animal studies conducted with the formulation showed inflammation and necrosis at injection sites. The Sponsor was advised the formulation should be changed to address these concerns and that the Division considered the product unsafe for study in humans. Rather than reformulate the product, the Sponsor withdrew the IND before a clinical hold was instituted and proceeded to conduct the study outside of the U.S. According to the Sponsor, it was due to efficacy related issues that they reformulated the product replacing (b) (4) with benzyl alcohol (BA).

The IND was reopened on December 23, 2005, with protocols for two Phase 2 trials.

On November 3, 2006, the IND was placed on partial clinical hold out of safety concerns for systemic toxicity with the 7.5 mL dose of SABER-bupivacaine, which lacked nonclinical data to support its use in human subjects. Rather than conduct the studies required to support the 7.5 mL dose, the Sponsor abandoned the use of it in the clinical trials. At that time the Sponsor was also advised to monitor subjects for signs and symptoms of cardiac and neurological toxicity for up to 48 hours following study drug administration.

On December 27, 2006, the sponsor was advised that the safety database required for an NDA would need to include 400 subjects for administration of SABER-bupivacaine via local wound infiltration and 500 subjects for a novel route of administration such as intra-articularly. The Sponsor proposed to conduct two Phase 3 studies in support of an NDA submission and to provide the required safety data.

An End-of-Phase 2 meeting was held on September 14, 2007. At that time, the following advice was provided by the Division to the Sponsor:

1. Phase 3 trials could be conducted using clinical sites outside the U.S. However, the Sponsor would be required to articulate how the findings from those sites could be extrapolated to the U.S. population. In particular, they would have to

provide evidence that the surgical and clinical management of patients in those countries was similar to standard U.S. practices.

2. In general, indications based on limited development programs are not recommended. However, a narrow indication for SABER Bupivacaine may be possible due to its relatively novel route of administration, and if there is evidence of substantial safety concerns that result in an acceptable risk-benefit analysis only in a limited condition of use.
3. If the Sponsor wished to pursue an indication limited to inguinal hernia surgery alone, it would require demonstration of efficacy in at least two adequate and well-controlled trials.
4. The Sponsor's Phase 2 evaluation of ECG data to date was inadequate; therefore, Phase 3 trials needed systematic evaluations of the cardiovascular and neurological effects of SABER-bupivacaine beyond Tmax and throughout the anticipated duration of analgesic effect.
5. The NDA application should address the safety of the novel use of both benzyl alcohol and SAIB in this product.

On March 10, 2008, the Division notified the Sponsor that their analysis of the ECG data for QT evaluation from the studies utilizing the 2.5-mL and 5.0-mL doses of SABER-bupivacaine were not adequate because the timing of the ECG relative to pharmacokinetic (PK) sampling had not been provided. A QT analysis based on ECGs recorded at Cmax for the 5 ml dose was required. The Division also stated that there were concerns regarding the central nervous system and the cardiovascular adverse events reported following the administration of the 5 mL dose of SABER-bupivacaine. The Sponsor needed to provide evidence that these adverse events were either not the result of toxicity from the product or that they were not clinically relevant.

The Sponsor submitted a request for a Special Protocol Assessment (SPA) on August 1, 2008, for a trial involving arthroscopic shoulder surgery. The request was denied, and the Division provided extensive comments and recommendations for revising the protocol so as to come to an agreement on it. The key elements included:

1. It was noted that the protocol included a number of safeguards to avoid having SABER-bupivacaine gain access into the joint capsule and putting the subject at risk for chondrolysis, e.g., limiting the surgical procedures following which the product can be injected and injecting the product under direct visualization. However, the Division expressed that they still had concern that bupivacaine may enter the joint through seepage or by diffusion when the drug product is in contact with the capsule. Therefore, the Sponsor was to provide either evidence or a rationale that this would not happen.
2. The Division did not consider opioid sparing or opioid side-effect reduction as indications; rather, they are viewed as evidence that the drug product is efficacious and they provide clinicians with important information regarding the degree of efficacy and the need for analgesic supplementation.

3. The use of SABER-placebo as a comparator allows the identification of adverse events related only to bupivacaine; a full assessment of safety requires the ability to discern adverse events related to use of the drug product. Therefore, either an additional arm should be added to the trial (either a non-SABER placebo or an active comparator) or the SABER-placebo should be replaced with either a non-SABER placebo or an active comparator.
4. Safety assessments must include evaluation for signs of bupivacaine related neurotoxicity. These assessments needed to be made proactively and specified in the protocol.
5. Follow-up safety assessments needed to be conducted over a sufficiently long period such that adverse events related to prolonged exposure to either bupivacaine (e.g., post-arthroscopic glenohumeral chondrolysis) or the SABER component of the product would be captured.
6. Opioid-induced adverse events that needed to be captured to describe a reduction in such events included not only constipation, drowsiness and dizziness, but nausea, vomiting, respiratory depression and urinary retention as well.
7. The use of a composite endpoint to assess opiod-related adverse events was acceptable; however, all the major opioid-related adverse events needed to be included, each with appropriate clinically relevant gradations and each with a weighting that puts them into a clinically meaningful order of importance. The protocol would need to specify how each of the adverse events was to be assessed, e.g., how the level of drowsiness is to be ascertained, to minimize variability between assessors and clinical sites. The gradations and weighting for each of the adverse events would require, at a minimum, a clinically-based rationale; further validation may be required.
8. The proposed endpoints for assessing pain relief and opioid use were acceptable; however, the design of the trial may confound the interpretation of the data collected. Specifically, the study permitted analgesics to be administered for pain at rest; however, it requires the assessment of pain with arm movement at specified times. This situation could result in subjects receiving analgesics shortly before a scheduled assessment and, thus, confound interpretation of the primary efficacy data.
9. A major concern for this pivotal study, as well as the entire development program was that the patient populations evaluated are limited in terms of the surgical procedures studied and the overall health of the patients enrolled. While the results from some surgical procedures may be extrapolated to others (e.g., efficacy for hernia repair may imply efficacy for superficial biopsies or wound repairs), a broad indication required evaluation following a wide range of surgical procedures. Data from hernia repair procedures, limited types of shoulder surgery and appendectomy were the only types available.
10. Assessments for neurological and cardiovascular toxicity made at Tmax would be a key component of the benefit-risk analysis.

11. It was necessary to identify those surgical procedures for which SABER-bupivacaine would be unlikely to provide clinically meaningful analgesia.
12. The patient population from which subjects had been drawn thus far in the clinical development plan had been relatively healthy. It was necessary to evaluate the use of SABER-bupivacaine in the full range of patients in whom the product can be reasonably expected to be used if it is approved for marketing.

The Sponsor did not resubmit the protocol for an SPA; however, they modified the protocol incorporating some of the Division's requirements and recommendations and conducted it as a Phase 2 trial.

At the preNDA meeting held on July 31, 2012, the following key points were discussed:

1. Only one adequate and well-controlled trial would be acceptable if the results of the trial were robust and able to withstand sensitivity analyses.
2. The purpose of the single trial would be to provide evidence of efficacy and safety for multiple surgical procedures and to allow a determination of the adequacy of the dosing paradigm to be used with SABER-bupivacaine.
3. The finding of wound discoloration following the administration of SABER-bupivacaine raised safety concerns that needed to be addressed before a benefit risk analysis could be performed. Specifically, the following questions needed to be resolved:
    a. What is the etiology of the discoloration, i.e., infectious, mechanical, chemical, immunological?
    b. Can anything be done to prevent the discoloration, e.g., change in formulation, dose, or method of administration?
    c. To what extent does the discoloration limit a surgeon's ability to assess the wound for infection, adequate hemostasis and potential dehiscence?
    d. Is it possible to identify particular patient populations that are at greater risks for this event?

2.6 Other Relevant Background Information

SABER-bupivacaine has not been approved for use and has not been marketed outside the United States. Therefore, the data from the Applicant's clinical development program are the only human data available for determining efficacy and characterizing the risk profile for this product.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of adequate quality and well enough organized with complete datasets to allow meaningful review. The various sections of the NDA and supporting documents were consistently arranged according to eCTD standards with functional links to appropriate references.

3.2 Compliance with Good Clinical Practices

For each of the seven key trials used for the evaluation of efficacy and safety, the Applicant asserted:

> All clinical trials have been conducted in accordance with the ethical principles of the Declaration of Helsinki and the principles of Good Clinical Practice (GCP) set forth in the International Conference on Harmonization (ICH) Good Clinical Practice, the US Code of Federal Regulations (CFR Title 21), the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and any local requirements.

3.3 Financial Disclosures

The Applicant certified the following for each of the Investigators involved with the seven key trials that served as the basis for assessing efficacy and safety:

> As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was

the recipient of significant payments of other sorts as defined in 21CFR 54.2(1).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Drs. Edwin Jao and Prasad Peri recommended the product be approved pending the final recommendation from the Office of Compliance regarding site inspections. They had no recommendations for postmarketing commitments or agreements.

The Biopharmaceutics team of Drs. Okpo Eradiri and Elsbeth Chikhale also recommended the approval of the product.

4.2 Clinical Microbiology

The Clinical Microbiology team, Drs. Neal Sweeney and Bryan Riley, recommend that the product be approved and have no recommendations for postmarketing commitments or agreements.

4.3 Preclinical Pharmacology/Toxicology

At the time of this review, Drs. Gary Bond and Adam Wasserman from the Pharmacology-Toxicology team had not finalized their review but indicated that they had no outstanding issues that precluded them from recommending the approval of this application.

4.4 Clinical Pharmacology

At the time of this review, Drs. David Lee and Yun Xu from the Clinical Pharmacology team had no outstanding issues that precluded them from recommending the approval of this application and no recommendations for postmarketing studies.

4.4.1 Mechanism of Action

Sucrose acetate isobutyrate extended release (SABER)-Bupivacaine is a sterile, slow-release formulation designed to release bupivacaine after direct application on to the surgical. The active ingredient, bupivacaine, is contained within a viscous sucrose acetate isobutyrate (SAIB) matrix and solvent (benzyl alcohol). When SABER-Bupivacaine is administered, the solvent diffuses away leaving a depot of SAIB matrix and bupivacaine in-situ which delivers the bupivacaine at the rate of 10 to 20 mg/hour during the first 72 hours. Bupivacaine is delivered over a maximum of 120 hours after one administration of 5.0mL (660 mg [132 mg/mL]) with the majority of the active component, bupivacaine, being delivered in the first 72 hours.

4.4.2 Pharmacodynamics

The onset of effect for SABER-bupivacaine appears to be within 3 hours of its administration, regardless of the surgical site. Its duration of action, based on comparison to SABER-placebo is about 24 hours; although plasma levels are detected for substantially longer periods of time.

4.4.3 Pharmacokinetics

The pharmacokinetics of SABER-bupivacaine varied depending on how and where on the body it was administered. The Clinical Pharmacology team summarized the pharmacokinetic profile of SABER-bupivacaine as follows (verbatim from pp 8-9 of Dr. Lee's review:

1. The systemic bupivacaine concentrations were, at least, observed for 72 hours post administration when 5 mL Posimir was administered in all of the surgical procedures; additionally, no dose-dumping was observed;
2. Observed bupivacaine Cmax and AUC values were not too drastically different in abdominal, shoulder and hernia procedures for the same Posimir dose;
3. Observed bupivacaine Cmax and AUC values were not too drastically different when 5 mL Posimir was administered as subcutaneous, infiltration and instillation routes of administration;
4. No correlation was observed between bupivacaine Cmax and AUC and surgical incision lengths, as all 5 mL Posimir was administered in all surgical procedures;
5. No dosage adjustment may be warranted due to weight, age, gender, and race since it is a locally acting product.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Applicant conducted 15 clinical trials in support of this NDA. Table 1 provides listing of the trials and descriptive information.

Table 1. Listing of Clinical Trials (Based on Table 5.2.1, pp. 1-4, Section 5.2 of NDA)

Trial	Type	Surgical Procedure(s) (N)	Phase	Pivotal (Y/N)	To-be-marketed Formulation (Y/N)
SABER01-01[1]	Double-Blind, Placebo-Controlled followed by a Single-Blind Ropivacaine and Bupivacaine Comparator to Assess the Safety, Tolerability, Sensory Effects, and PK	Normal Subjects (12)	1	N	N
CLIN005-0008	Pharmacokinetic Study	Normal Subjects (5)	1	N	Y
CLIN005-0007[2]	Pilot Study of the Pharmacokinetics	Open Inguinal Hernia Repair (12)	2	N	Y
CLIN-803-006-0006[3]	Double-Blind, Placebo Controlled, PK/PD Dose Response	Open Inguinal Hernia Repair (123)	2	Y	Y
BU-002-IM[3]	randomized, double blinded, active- and placebo-controlled dose response	arthroscopic shoulder surgery (107)	2	Y	Y
C803-025[3]	randomized, double-blind, active- and placebo-controlled, parallel-group	variety of general surgical procedures (305)	3	N	Y
C803-017[3]	Double-Blind, placebo-controlled	Arthroscopic Shoulder Surgery (60)	2b	N	Y
CLIN005-0006[3]	Double-Blind, Placebo Controlled, PK/PD, Dose Response	Open Inguinal Hernia Repair (106)	2	N	Y
CLIN005-0010[3]	Randomized, Double-Blind, Placebo-Controlled	Open Inguinal Hernia Repair (89)	2	N	Y
BU-001-IM[3]	randomized, double-blinded, active- and placebo-controlled dose response	abdominal hysterectomy (114)	2	N	Y

Trial	Type	Surgical Procedure(s) (N)	Phase	Pivotal (Y/N)	To-be-marketed Formulation (Y/N)
C803-027[2]	Open-label, uncontrolled, histological evaluation	laparotomy or laparoscopical-ly assisted colectomy (10)	2	N	Y
CLIN004-0001[2]	PK/PD active-controlled dose escalation	Open Inguinal Hernia Repair (81)	2a	N	Y
CLIN004-0009[2]	PK/PD active-controlled	Open Inguinal Hernia Repair (42)	2a	N	Y
CLIN005-0002[2]	Double-blind, placebo-controlled PK/PD pilot trial	Appendectomy (21)	2	N	Y
C803-017e	Prospective, observational, safety follow-up of subjects in C803-017	Arthroscopic Shoulder Surgery (47)	2b	N	Y

[1] Trial was conducted with a formulation other than the to-be-marketed product.
[2] Trials involving surgical procedures but not included by the Applicant in the ISE due to design or method of study drug administration.
[3] Trials included in the ISE as they were randomized, controlled, parallel design surgical trials of SABER-Bupivacaine using the administration technique and dose proposed for marketing.

5.2 Review Strategy

This review takes into consideration all the clinical trials conducted by the Applicant and the 120-Day Safety Update for evaluating the safety and efficacy of SABER-bupivacaine and for performing the benefit risk analysis that served as the basis for the recommendation for regulatory action. Relevant information pertaining to safety from the chemistry, preclinical and clinical pharmacology sections of the NDA submission were also taken into consideration along with input from members of each of the respective review teams. The expertise of the statistical reviewers was also relied upon for the analysis of the efficacy data contained in those trials assessing efficacy whether or not they were considered by the Applicant to be pivotal.

The evaluation of efficacy was based primarily upon whether treatment with SABER-bupivacaine resulted in superior analgesia versus the comparator treatment as assessed by the primary endpoints in each of the efficacy studies. In those studies where SABER-bupivacaine was demonstrated to be superior to the comparator, based on the primary endpoints, efficacy and clinical utility were further assessed by evaluating the results for the secondary efficacy endpoints. Specifically, the secondary endpoints were evaluated as to whether or not the outcomes trended in the same direction as those of the primary outcomes.

The focus of the safety evaluation was on three aspects of SABER-bupivacaine therapy:

1. The short-term local effects of the product on:
    a. The surgical incision, e.g., erythema, edema, infection
    b. Surgically implanted foreign materials, e.g., breast implants
    c. Surgical wound healing
2. The long-term local effects of the product on:
    a. The surgical incision site due to the persistence of the SAIB component extending to one year in animal studies.
    b. The risk for chondrolysis related to the extended exposure to bupivacaine when the product was injected into the intraarticular space.
3. The risk of systemic exposure to either SABER-bupivacaine or the bupivacaine released by it with emphasis on:
    a. Neurotoxicity
    b. Cardiotoxicity

The efficacy trials are described in Section 9.4 below along with a detailed discussion of the efficacy and key safety findings for each. Summary findings of efficacy are provided in Section 6 below; the analyses and summary findings for safety are provided in Section 7.

5.3 Discussion of Individual Studies/Clinical Trials

Details of the individual trials supporting efficacy are provided in Section 9.4 below. The Applicant conducted trials of the use of SABER-bupivacaine following a variety of surgical procedures. The trials were similar in overall design but differed in terms of the comparator, i.e., placebo versus active or a combination of the two.

6 Review of Efficacy

Efficacy Summary

SABER-bupivacaine was developed by the Applicant as a means of providing postoperative analgesia in a similar fashion to the way bupivacaine HCl is currently used in clinical practice. The benefit of SABER-bupivacaine over bupivacaine HCl was to be a longer duration of analgesia as the bupivacaine diffuses out of the sucrose acetate isobutyrate (SAIB) component of the SABER over a period of 72 hours.

From the clinical development program, the Applicant has identified seven trials that utilized the to-be-marketed formulation and the methods of administration consistent with that proposed in the labeling. These included six Phase 2 trials and a single Phase 3 trial. The Applicant has identified two of the Phase 2 trials as pivotal for the demonstration of efficacy. These seven trials are listed in Table 2 below

Table 2. Summary of clinical trials supporting efficacy

Trial Number	Dates of Conduct	Surgical Procedure(s) Evaluated	Treatments[4]				
			SABER-bupivacaine 2.5 mL	SABER-bupivacaine 5 mL	SABER-bupivacaine 7.5 mL	Bupivacaine HCl	SABER-placebo All doses
CLIN-005-0010[2]	3/06-3/07	inguinal hernia		21	1		21
CLIN005-0006[2]	6/06-12/07	arthroscopic shoulder		21	3		28
CLIN-803-006-0006[1,2]	1/07-10/07	inguinal hernia	42	47			32
C803-017[2]	12/08-10/09	arthroscopic shoulder		40			20
BU-002-IM[1,2]	4/09-2/11	arthroscopic shoulder		53			25
BU-001-IM[2]	5/09-6/10	hysterectomy		60		27	
C803-025[3]	12/09-9/11	laparotomy		26		17	
		laparoscopic cholecystectomy		30		20	
		lap-assisted colectomy		125			77
Totals			42	423	3	64	203

[1] Pivotal trial
[2] Phase 2 trial
[3] Phase 3 trial
[4] Numbers represent the modified Intent-to-Treat (mITT) populations and include only subjects for whom study drug was administered according to the methods in the proposed labeling.

The Applicant has divided the efficacy trials into three groups based on the surgical procedure. These included:

1. Inguinal hernia repair
2. Arthroscopic subacromial decompression
3. Abdominal and pelvic procedures

The efficacy findings for each of these groups is summarized below; details of the study design and results for each of the trials are contained in Section 9.4 of this review.

Inguinal Hernia Repair

The Applicant conducted two Phase 2 trials assessing the efficacy of a 5 mL dose of SABER-bupivacaine when about half of the dose is instilled into the floor of the inguinal canal after the reinforcing mesh is sutured in place and the other half is instilled into the subcutaneous space following suturing of the external oblique but before final closure of the skin. The comparator for both trials was SABER-placebo.

The first trial, CLIN-005-0010 was conducted at seven sites in the U.S. and a single site in New Zealand. It failed to demonstrate SABER-bupivacaine as superior to SABER-placebo. In fact, the efficacy endpoint, the difference of the least-squares mean of pain intensity $AUC_{0\text{-}72\ hours}$ for the two treatment groups favored treatment with SABER-placebo. The secondary endpoints failed to support the SABER-bupivacaine treatment over SABER-placebo. The only secondary endpoint that significantly differed for the two treatments was pain intensity on movement $AUC_{0\text{-}120}$; however, that difference favored the SABER-placebo.

The Applicant then conducted a second trial, CLIN-803-006-0006, using the same method of administration and dose, and with the same patient population demographics. In this trial, SABER-bupivacaine was found to be superior to SABER-placebo and was also found to result in significantly prolonged time to first opioid use. There were no significant differences between treatments for any of the other secondary endpoints.

The results from these trials, despite their similarities, are disparate. The only identifiable difference between the two is the location of the study sites. The successful trial was conducted outside the U.S.; the failed trial was conducted primarily within the U.S. The U.S. trial did not specify the method of hernia repair to be utilized; the non-U.S. study required a Lichtenstein repair be performed, the same repair that is most commonly performed in the U.S. As it is unlikely that the difference could be explained by an innate difference in the patient populations or the skills of the surgeons, it is possible that the 5 mL dose or the attributes of SABER-bupivacaine are not adequate for this procedure. This possibility is supported by the small differences in the pain intensity AUCs for the treatment, less than 2 units on a 10-unit scale, and the dose effect observed in CLIN-803-006-0006 in which the 2.5 mL dose of SABER-bupivacaine was not significantly different from SABER-placebo while the 5 mL dose was.

Arthroscopic Subacromial Decompression

The Applicant conducted three trials to assess the efficacy of 5 mL of SABER-bupivacaine following this procedure when it was instilled into the subacromial space using a large bore needle attached to a 5 mL hypodermic syringe containing the product. The needle was inserted through an existing arthroscopic portal or through intact skin and placed within the subacromial space under direct vision with an arthroscope to assure the product was not instilled into the intra-articular space..

The first trial conducted was CLIN-005-0006 which failed to demonstrate the superiority of SABER-bupivacaine over SABER-placebo; however, the primary endpoints favored treatment with SABER-bupivacaine.

The second trial conducted was C-803-017. It too failed to demonstrate a difference between SABER-bupivacaine and SABER-placebo, but the trends for the primary endpoints both favored SABER-bupivacaine.

The third trial conducted was BU-002-IM. In this trial SABER-bupivacaine was compared to SABER-placebo and bupivacaine HCl. In this trial, SABER-bupivacaine was found to be superior to SABER-placebo for both the mean pain intensity on movement $AUC_{1\text{-}72}$ and for the amount of opioid rescue required. The SABER-bupivacaine was not superior to bupivacaine HCl, but the trend for the primary endpoints favored SABER-bupivacaine treatment. It was noted that SABER-bupivacaine differed substantially from bupivacaine HCl during the first 24 hours after surgery, but the two treatments appeared identical for pain intensity on movement following that time point. Both treatments were substantially more effective than SABER-placebo through 72 hours after surgery.

The results of these three trials, considered together, demonstrated SABER-bupivacaine to be effective at providing postoperative analgesia following arthroscopic subacromial decompression surgery.

Abdominal and Pelvic Procedures

The Applicant conducted two trials to assess the efficacy of SABER-bupivacaine when used following hysterectomy, BU-001-IM (Phase 2), and when used following laparotomy, laparoscopic cholecystectomy and laparoscopic assisted colectomy, C803-025 (Phase 3).

In BU-001-IM, SABER-bupivacaine was compared to both SABER-placebo and bupivacaine HCl. There was no difference between any of the treatments for the primary endpoint, but the trends favored SABER-bupivacaine treatment. However, the treatment effect was less than 0.5 units on the 10 unit pain intensity on movement score.

The only Phase 3 trial conducted in the development program contained three cohorts. Each cohort evaluated a different abdominal surgical procedure and had a single comparator treatment.

Cohorts 1 and 2 evaluated efficacy for patients undergoing laparotomy and laparoscopic cholecystectomy, respectively, with bupivacaine HCl as a comparator. Both cohorts failed to demonstrate a difference between the treatments, but the trend for both cohorts favored SABER-bupivacaine. When the results for these two cohorts were combined, there was a significant difference in the treatments; however, the differences in the procedures, the surgical incisions utilized, and nature of the postoperative pain (extent of incisional versus visceral) preclude this combination of cohorts from being clinically relevant.

Cohort 3 provided a comparison of SABER-bupivacaine to SABER-placebo for providing analgesia following laparoscopic assisted colectomy. There was no difference between the primary endpoints for the two treatments. Interestingly, the treatment effect favored SABER-bupivacaine, but it was much smaller of an effect than was observed with the bupivacaine HCl treatments for the other two cohorts. That may reflect the differences in the nature of the pain for the colectomy compared to laparotomy and laparoscopic cholecystectomy, or it may reflect a greater inadequacy in the dosing for the colectomy.

Conclusion

Overall, the seven efficacy trials conducted by the Applicant demonstrated convincing efficacy only for the use of a 5 mL dose of SABER-bupivacaine following arthroscopic subacromial decompression surgery.

6.1 Indication

The Applicant proposes the following wording as the indication for SABER-bupivacaine (Trade name: Posimir):

> Posimir is an extended-release bupivacaine, an amide-type local anesthetic indicated for administration into the surgical incision to produce post-surgical analgesia

The Applicant has included language in the Dosage and Administration section describing how the product is to be administered in the following specific surgical settings:

1. Linear incisions in abdominal surgery
2. Abdominal laparoscopic surgery portals
3. Inguinal hernia surgery
4. Arthroscopic subacromial decompression surgery

6.1.1 Methods

There were a total of seven trials that systematically evaluated the efficacy of SABER-bupivacaine and that the Applicant appropriately chose to incorporate into the integrated summary of efficacy. These trials shared the following characteristics:

1. used the to-be-marketed formulation
2. randomized
3. double-blinded
4. controlled (SABER-placebo, and/or bupivacaine HCl)
5. parallel design
6. used instillation as the administration technique, the proposed method of administration in the product labeling
7. used the 5 mL dose of SABER-bupivacaine proposed in the product labeling
8. evaluated pain intensity over time and, in some trials, analgesic use over time as well

The use of a placebo control was made ethically acceptable by allowing the use of rescue medication for pain in all of the studies.

In the trials that had a bupivacaine HCl as a control, all postoperative efficacy and safety assessments were to have been done by treatment-blinded personnel who had not participated in study drug administration.

All subjects were to have received a single dose of study drug so the durations of the trials were determined by the need for post-treatment follow-up for the assessments of efficacy and safety. For most of the trials, this was generally for 14 days. Trial C803-025 also included a telephone follow-up at 30 days to assess wound healing status, and four trials had long-term follow-up visits to examine the surgical sites for healing:

- CLIN-803-006-0006: 3 and 6 months
- BU-001-IM: 6 months
- BU-002-IM, 6 months
- C803-017e, 18 months

All seven of the controlled trials used the same method of assessing postoperative pain, i.e., a numerical rating scale from 0 (no pain) to 10 (worst pain imaginable) at rest while supine in bed and then after movement such as sitting up in bed or elevating the arm in the case of shoulder surgery. Pain intensity on movement was used for the primary pain endpoint because it is related to the patient's ability to ambulate and function. The initial pain assessments were made as soon as practical after emergence from anesthesia and were repeated at scheduled intervals over at least 72 hours after surgery. No effort was made to record baseline pain pre-operatively as some of the operations performed were not associated with pre-operative pain and the effects of SABER-bupivacaine are predominantly on surgical incision pain.

The use of rescue analgesia was also to have been recorded for at least 72 hours after surgery in all seven efficacy trials. Two trials, BU-001-IM and BU-002-IM, required therapy with acetaminophen at a dose of 2 or 4 g/day, based on the subject's weight, as background analgesia for all subjects. Any use of opioid rescue was to have been documented, and for most trials, pain intensity prior to opioid administration was also to have been documented. A common set of conversion factors was used to convert the opioid doses to intravenous (IV) morphine equivalents for subsequent statistical analysis. The use of non-opioid analgesics was likewise to have been recorded on case report forms, and was described descriptively, since, as the Applicant states, the rules regarding the use of NSAIDs and acetaminophen varied from trial to trial, making the data too heterogeneous to analyze.

All seven trials used essentially the same pre-specified primary pain endpoint, the time-normalized area under curve (AUC) for the pain intensity on movement assessments. Usually, the AUC was integrated from 0 or 1 to 72 hours after study drug administration, i.e., $AUC_{0\text{-}72}$. The total area under the pain intensity versus time curve (AUC_{total}) was also determined.

Two trials (CLIN005-0006 and CLIN005-0010) integrated pain intensity from 0 to 120 hours. All of the studies used an analysis of variance (ANOVA) or an analysis of covariance (ANCOVA) model to analyze the AUC data. A common primary pain endpoint of $AUC_{0\text{-}72}$ was chosen by the Applicant for the ISE. The Applicant also explored a number of covariates, but none were included in the model, as the linear

relationships of the covariates to AUC_{0-72} had slopes that were not significantly different from zero.

The seven trials evaluating efficacy are listed in Table 3 below.

Table 3. Summary of trials evaluating efficacy

Trial Number	Phase	Comparator(s)	Pivotal? (Y/N)
CLIN-803-006-0006	2	SABER-placebo	Y
CLIN005-0010	2	SABER-placebo	N
CLIN005-0006	2	SABER-placebo	N
C803-017	2b	SABER-placebo	N
C803-025 Cohort 3	3	SABER-placebo	N
C803-025 Cohorts 1 and 2	3	Bupivacaine HCl	N
BU-001	2	SABER-placebo and Bupivacaine HCl	N
BU-002	2	SABER-placebo and Bupivacaine HCl	Y

The Applicant chose to divide the trials into three subgroups for the purposes of analyzing and integrating efficacy findings. The groups included trials involving surgery on soft tissues (Table 4), trials involving orthopedic surgeries (Table 5), and trials involving bupivacaine HCl as a comparator (Table 6).

Table 4. Trials involving surgery on soft tissues (Table 11, p. 43 of Section 5.3.5.3 of the NDA)

Protocol Number	Study Drug / Doses	# of mITT Subjects
CLIN-803-006-0006 Hernia	SABER-Bupivacaine (5 mL, 660 mg) SABER-Placebo	47 32
CLIN005-0010 Hernia	SABER-Bupivacaine (5 mL, 660 mg) SABER-Placebo	21 21
BU-001-IM Hysterectomy	SABER-Bupivacaine (5 mL, 660 mg) SABER-Placebo	60 27
C803-025 Laparoscopically-Assisted Colectomy	SABER-Bupivacaine (5 mL, 660 mg) SABER-Placebo	125 77

Table 5. Trials involving orthopedic surgeries (Table 26, p. 57 of Section 5.3.5.3 of the NDA)

Protocol Number	Surgery	Study Drug / Doses	# of mITT Subjects
BU-002-IM	Subacromial Decompression	SABER-Bupivacaine (5mL, 660 mg) SABER-Placebo	53 25
C803-017	Subacromial Decompression	SABER-Bupivacaine (5 mL, 660 mg) SABER-Placebo	40 20
CLIN005-0006	Subacromial Decompression	SABER-Bupivacaine (5 mL, 660 mg) SABER-Placebo	21 28

Table 6. Trials involving bupivacaine HCl as the comparator (Table 41, p. 71 of Section 5.3.5.3 of the NDA)

Protocol Number	Surgery	Study Drug / Doses	# of mITT Subjects
BU-002-IM	Subacromial Decompression	SABER-Bupivacaine (5 mL, 660 mg) Bupivacaine HCl 20 mL (50 mg)	53 29
BU-001-IM	Hysterectomy	SABER-Bupivacaine (5 mL, 660 mg) Bupivacaine HCl 40 mL (100 mg)	60 27
C803-025	Cohort 1: Laparotomy	SABER-Bupivacaine (5 mL, 660 mg) Bupivacaine HCl 30 mL (150 mg)	26 17
	Cohort 2: Laparoscopic Cholecystectomy	SABER-Bupivacaine (5 mL, 660 mg) Bupivacaine HCl 30 mL (150 mg)	30 20

The Applicant's decision to evaluate efficacy by the subgroups chosen above is helpful for putting the findings into context; however, there are substantial limitations to their utility in interpreting the overall findings for the development program. For example, no basis has been provided for considering inguinal herniorrhaphy, hysterectomy, and laparoscopic colectomy as equivalent surgical procedures for the amount of local anesthetic required or the method of its administration.

It must be noted that the Phase 2 protocol were frequently modified, sometimes in ways that could affect outcomes. For example, BU-001-IM was modified during conduct of the trial to restrict the use of paracetamol to Day 0 to Day 2 instead of the initially permitted Day 0 to Day 7. In BU-002-IM, the protocol was modified during the trial to allow the use of paracetamol from Day 3 to Day 7. Such changes can alter the pain scores and need for rescue opioids and thereby affect the outcome. Similarly, C803-017 was modified to allow an additional type of shoulder procedure to be included in the trial. This amendment was made after 24 of 60 subjects had been enrolled and could, depending on a number of other factors, affect the outcome. While such modifications

are not inappropriate, particularly for Phase 2 trials, they can confound the analysis of efficacy when those Phase 2 trials are the primary source of efficacy data.

6.1.2 Demographics

The choice of patient population was, in part, dictated by the surgical procedure(s) that was under study in the trial. Therefore, the hysterectomy trial had an entirely female population, whereas the hernia repair trials had predominantly male populations. The type of surgery under study also impacted the age range of the patient population. Most of the trials required eligible patients to be in good health and excluded patients with co-morbidity based on concerns for potential neurotoxicity and cardiac toxicity related to elevated systemic exposures to bupivacaine. The C803-025 trial, the only Phase 3 study conducted in the development program, involved subjects undergoing abdominal surgery and did not exclude patients with co-morbidities; it also did not restrict enrollment ages and, therefore, contributed the majority of patients >65 years to the safety and efficacy databases.

Table 7. Summary of subject demographics for trials involving soft tissue surgeries (Table 13, p. 45 in Section 5.3.5.3 of the NDA)

Demographic	SABER-Bupivacaine 5 mL (N=253)	SABER-Placebo (N=157)
Age (years)		
Mean (SE)	54.0 (0.83)	54.0 (1.04)
Standard Deviation	13.26	13.08
Median	54.0	53.0
Min, Max	21, 87	25, 89
≤65	203 (80.2%)	124 (79.0%)
>65	50 (19.8%)	33 (21.0%)
Sex		
Male	121 (47.8%)	96 (61.1%)
Female	132 (52.2%)	61 (38.9%)
Race		
White	242 (95.7%)	146 (93.0%)
Non-White	11 (4.3%)	11 (7.0%)
BMI (kg/m^2)		
≤25	70 (27.8%)	55 (35.0%)
>25	182 (72.2%)	102 (65.0%)
Incision Length (cm)		
Mean (SE)	9.7 (0.25)	8.7 (0.28)
Standard Deviation	3.96	3.53
Median	9.0	7.5
Min, Max	3.5, 24.0	3.0, 20.0

Table 8 Summary of subject demographics for trials involving orthopedic surgeries (Table 28, p. 59 in Section 5.3.5.3 of the NDA)

Demographic	SABER-Bupivacaine 5 mL N=114	SABER-Placebo N=73
Age (years)		
Mean (SE)	49.9 (0.89)	50.6 (1.34)
Standard Deviation	9.50	11.42
Median	49.0	51.0
Min, Max	27, 72	24, 82
≤65	107 (93.9%)	67 (91.8%)
>65	7 (6.1%)	6 (8.2%)
Gender		
Male	46 (40.4%)	38 (52.1%)
Female	68 (59.6%)	35 (47.9%)
Race		
N	112	73
White	107 (95.5%)	70 (95.9%)
Non-White	5 (4.5%)	3 (4.1%)
BMI (kg/m^2)		
≤25	40 (35.1%)	22 (30.1%)
>25	74 (64.9%)	51 (69.9%)

Table 9. Summary of subject demographics for trials involving bupivacaine as a comparator (Table 43, p. 73 in Section 5.3.5.3 of the NDA)

Demographic	SABER-Bupivacaine 5 mL N=169	Bupivacaine HCl N=93
Age (years)		
Mean (SE)	48.8 (0.83)	47.5 (1.39)
Standard Deviation	10.77	13.40
Median	48.0	47.0
Min, Max	23, 85	21, 87
≤65	155 (91.7%)	85 (91.4%)
>65	14 (8.3%)	8 (8.6%)
Gender		
Male	47 (27.8%)	27 (29.0%)
Female	122 (72.2%)	66 (71.0%)
Race		
N	167	93

Demographic	SABER-Bupivacaine 5 mL N=169	Bupivacaine HCl N=93
White	162 (97.0%)	90 (96.8%)
Non-White	5 (3.0%)	3 (3.2%)
BMI (kg/m^2)		
≤25	54 (32.0%)	32 (34.4%)
>25	115 (68.0%)	61 (65.6%)

The demographic distributions were, as expected, influenced by the surgical procedure. However, within each subgroup, there is a reasonable balance between treatment arms for each of the demographic parameters. While most of the subjects were Caucasian, ≤65 years of age, and obese, there is no basis to suspect the treatments would produce different efficacy, or safety, findings in other demographics, especially for other races, which was the demographic that least represented the overall population of patients likely to be treated with SABER-bupivacaine if it were approved in the United States.

6.1.3 Subject Disposition

As with demographics, the Applicant divided the efficacy population into three subgroups: soft tissue surgery, orthopedic surgery, and bupivacaine HCl comparator trials. The subject dispositions for each group are summarized in Table 10,

Table 11, and Table 12 below. As would be expected when a study drug is administered only once and in a controlled setting such as the operating room, over 97% of the subjects completed the trials. There were very few discontinuations, which were evenly distributed between treatment arms, indicating the efficacy findings are not likely to have been affected by either the number of discontinuations or the treatment arms in which they occurred.

Table 10. Summary of subject disposition for trials involving soft tissue surgeries (Table 12, p. 44 in Section 5.3.5.3 of the NDA)

	SABER-Bupivacaine 5 mL	**SABER-Placebo**
Subjects Enrolled	267	165
mITT Population[1]	253 (100%)	157 (100%)
Completed Study		
Yes	248 (98.0%)	152 (96.8%)
No	5 (2.0%)	5 (3.2%)
Primary Reason for Discontinuation		
Subject Decision	3 (1.2%)	1 (0.6%)
Lost to Follow-up	2 (0.8%)	1 (0.6%)
Adverse Events	0	1 (0.6%)
Investigator Decision	0	1 (0.6%)
Other	0	1 (0.6%)

Note: Percentages were based on the number of subjects in the mITT population.
[1] All subjects who were randomized, received any amount of study drug, and had at least one scheduled pain score assessment post-dose. Subjects were analyzed based on the planned treatment.

Table 11. Summary of subject disposition for trials involving orthopedic surgeries (Table 12, p. 44 in Section 5.3.5.3 of the NDA)

	SABER-Bupivacaine 5 mL	SABER-Placebo
Subjects Enrolled	118	74
mITT Population[1]	114	73
Completed Study		
Yes	114 (100.0%)	71 (97.3%)
No	0	2 (2.7%)
Primary Reason for Discontinuation		
Subject Decision	0	2 (2.7%)

Note: Percentages were based on the number of subjects in the mITT population.
[1] All subjects who were randomized, received any amount of study drug, and had at least one scheduled pain score assessment post-dose. Subjects were analyzed based on the planned treatment.

Table 12. Summary of subject disposition for trials involving bupivacaine HCl as a comparator (Table 42, p. 72 in Section 5.3.5.3 of the NDA)

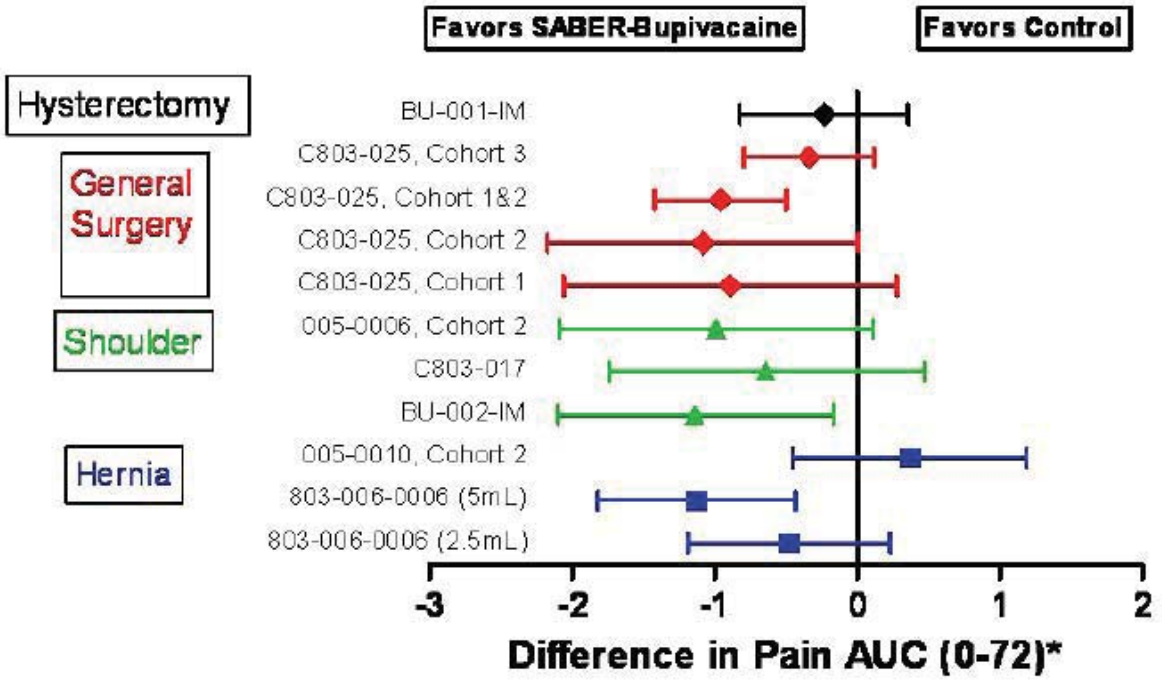
	SABER-Bupivacaine 5 mL	Bupivacaine HCl
Subjects Enrolled	172	98
mITT Population[1]	169 (100.0%)	93 (100.0%)
Completed Study		
Yes	168 (99.4%)	91 (97.8%)
No	1 (0.6%)	2 (2.2%)
Primary Reason for Discontinuation		
Subject Decision	1 (0.6%)	1 (1.1%)
Adverse Event	0	1 (1.1%)

Note: Percentages were based on the number of subjects in the mITT population.
[1] All subjects who were randomized, received any amount of study drug, and had at least one scheduled pain score assessment post-dose. Subjects were analyzed based on the planned treatment.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoints evaluated in the efficacy studies were the $AUC_{0\text{-}72\ hours}$ for normalized pain intensity and the amount of opioid rescue medication administered over the 72 hours following study drug administration. Although the use of rescue analgesia was recorded for all seven trials for at least 72 hours after surgery and designated as a primary endpoint in some of the trials, the Applicant chose, for reasons not given, to not include opioid rescue pain scores in the primary endpoint analyses for the ISE. However the rescue pain scores were included in the sensitivity analyses performed by the Applicant to examine the possible confounding effects of rescue opioids.

The Applicant provided a summary of the trial findings for normalized pain intensity AUCs using a Forest plot, which is contained in Figure 1 below.



*$AUC_{0\text{-}120\ hours}$ were used for Clin005-0006 and Clin005-0010

Figure 1. Forest plot of the differences in normalized pain $AUC_{0\text{-}72}$ between SABER-bupivacaine and the control treatment for the randomized, double-blind, controlled trials

The Applicant used three efficacy subgroups: soft tissue surgery, orthopedic surgery, and bupivacaine HCl as a comparator, for the purposes of integrating and analyzing the

efficacy findings. Each subgroup is considered separately for the normalized pain intensity AUC_{0-72} analyses.

Soft Tissue Surgical Procedures

For the primary endpoint, AUC_{0-72} for pain intensity on movement, the mean and median pain intensity were lower in the SABER-Bupivacaine group than in the SABER-Placebo group and the least-squares (LS) mean difference was statistically significant, favoring SABER-Bupivacaine over SABER-Placebo as shown in Table 13 below.

The results of the sensitivity analysis for pain intensity on movement AUC_{0-72} with opioid pain score data were consistent with those for the primary efficacy endpoint. Over the 72 hour period, mean and median pain intensity was lower in the SABER-Bupivacaine group than the SABER-Placebo group; the LS mean difference in pain intensity between these two treatment groups reached statistical significance favoring SABER-Bupivacaine over SABER-Placebo.

Table 13. Pain on movement AUC results in the soft tissue surgery group (Table 14, p. 46 of section 5.3.5.3 of the NDA)

AUC (0-72 Hours)	SABER-Bupivacaine 5 mL N=253	SABER-Placebo N=157
Mean (SE)	4.1 (0.13)	4.5 (0.16)
Standard Deviation	2.05	1.97
Median	3.8	4.3
Min, Max	0.3, 10.0	0.5, 9.7
LS Mean (SE)[1]	3.8 (0.13)	4.3 (0.16)
95% CI[1]	(3.6, 4.1)	(4.0, 4.6)
LS Mean Difference (SE)[1]	-0.5 (0.19)	
95% CI[1]	(-0.88, - 0.12)	
p-value[1]	0.0099	

[1] Based on an ANOVA model with study and treatment groups as factors.

Table 14. Sensitivity analysis for AUC with opioids in the soft tissue surgery group (Table 15, p. 47 of Section 5.3.5.3 of the NDA)

AUC (0-72)	SABER-Bupivacaine N=253	SABER-Placebo N=157
Mean (SE)	4.2 (0.12)	4.6 (0.14)
Standard Deviation	1.92	1.77
Median	4.0	4.5
Min, Max	0.3, 9.5	0.5, 9.7

AUC (0-72)	SABER-Bupivacaine N=253	SABER-Placebo N=157
LS Mean (SE)[1]	4.0 (0.12)	4.4 (0.14)
95% CI[1]	3.7, 4.2	4.1, 4.6
LS Mean Difference (SE)[1]	-0.4, (0.20)	
95% CI[1]	(-0.75, - 0.06)	
p-value[1]	0.0210	

[1] Based on an ANOVA model with study and treatment groups as factors.

The mean and median values for total morphine-equivalent doses were lower in the SABER-bupivacaine group than in the SABER-placebo group; however, the median difference between the two treatment groups was not statistically significant as indicated in Table 15 below.

Table 15. Total morphine equivalent opioid medication use from 0-72 hours (Table 18, p. 51 of Section 5.3.5.3 of the NDA)

Total Morphine Equivalent Dose	SABER-Bupivacaine N=253	SABER-Placebo N=157
Mean (SE)	40.5 (2.78)	48.0 (4.51)
Standard Deviation	44.15	56.52
Median	26.0	31.0
Q1, Q3	10.0, 59.0	14.0, 68.0
Min, Max	0.0, 292.0	0.0, 447.0
W-statistic[1]	0.81	0.69
p-value[1]	<0.0001	<0.0001
Wilcoxon Rank Sum Test		
Median Difference[2]	-5.0	
95% CI[2]	(-10.0, 0.2)	
p-value	0.0987	

Reviewer's Comments
The decision by the Applicant to combine trials to come up with a soft tissue surgery grouping may not be appropriate for the types of surgical procedures that were included in the clinical trials. The nature and intensity of pain are not similar across the procedures. For example, herniorrhaphy is associated with myofascial and incisional pain whereas colectomy is associated with both of these types of pain and visceral pain as well. Without appropriate adjustments for the types of pain or for the numbers and sizes of the different trials, it is possible that the results for one type of surgical procedure could dominate and affect the outcome. The issue is confounded further by

the failure to include the other soft tissue surgeries (hysterectomy, laparotomy and laparoscopic cholecystectomy) only because a different comparator was used.

Assuming that it is appropriate to combine the results for the different surgical procedures, the AUC for pain on movement results do indicate that there is a statistical difference between the treatment groups; however, the differences are less than half a unit indicating they are not likely to be clinically relevant. The lack of a difference in the use of opioid rescue suggests that the differences in pain intensity for the first 72 hours are not clinically significant for the two treatment groups.

Orthopedic Surgical Procedures

The mean and median pain intensity scores were lower in the SABER-bupivacaine group than in the SABER-placebo group and the LS mean of the difference between the two treatment groups was statistically significant, favoring SABER-Bupivacaine over SABER-Placebo. The values are summarized in Table 16 below.

The sensitivity analysis for AUC_{0-72} for the mean pain intensity scores on movement with opioid pain score data are presented in Table 17. The Applicant states that the results of the sensitivity analysis are practically identical to the primary analysis indicating that any confounding due to rescue opioid administration is minimal.

Table 16. Pain on movement AUC results in the orthopedic surgery group (Table 29, p. 60 of Section 5.3.5.3 of the NDA)

AUC (0-72 Hours)	**SABER-Bupivacaine 5 mL N=114**	**SABER-Placebo N=73**
Mean (SE)	5.3 (0.19)	5.9 (0.25)
Standard Deviation	1.98	2.15
Median	5.3	6.0
Min, Max	1.3, 9.8	0.2, 10.0
LS Mean (SE)[1]	5.2 (0.20)	5.9 (0.24)
95% CI[1]	(4.8, 5.6)	(5.5, 6.4)
LS Mean Difference (SE)[1]	-0.7 (0.32)	
95% CI[1]	(-1.36, -0.11)	
p-value[1]	0.0205	

[1] Based on an ANOVA model with study and treatment groups as factors.

Table 17. Sensitivity analysis for AUC with opioids in the orthopedic surgery group (Table 30, p. 60 of Section 5.3.5.3 of the NDA)

AUC (0-72)	**SABER-Bupivacaine 5mL N=114**	**SABER-Placebo N=73**
Mean (SE)	5.3 (0.18)	6.0 (0.24)
Standard Deviation	1.97	2.04
Median	5.5	6.3
Min, Max	1.1, 9.8	0.6, 10.0
LS Mean (SE)[1]	5.3 (0.20)	6.0 (0.24)
95% CI[1]	(4.9, 5.7)	(5.6, 6.5)
LS Mean Difference (SE)[1]	-0.7 (0.30)	
95% CI[1]	(-1.33, -0.12)	
p-value[1]	0.0195	

[1] Based on an ANOVA model with study and treatment groups as factors.

The differences in the morphine-equivalent rescue medication (Table 18) were considered by the Applicant to be an additional indicator of the efficacy of SABER-bupivacaine in this clinical setting.

Table 18. Total morphine equivalent opioid medication use from 0-72 hours (Table 33, p. 65 of Section 5.3.5.3 of the NDA)

Total Morphine Equivalent Dose	**SABER-Bupivacaine 5 mL N=114**	**SABER-Placebo N=73**
Mean (SE)	31.8 (3.14)	48.1 (4.97)
Standard Deviation	33.55	42.50
Median	21.5	40.0
Q1, Q3	4.0, 54.3	16.3, 63.1
Min, Max	0.0, 176.0	0.0, 224.3
W-statistic1	0.86	0.86
p-value1	<0.0001	<0.0001
Wilcoxon Rank Sum Test		
Median Difference2	-12.4	
95% CI2	(-23.0, -4.7)	
p-value	0.0025	

[1] Shapiro-Wilk test for Normality Assumption
[2] Hodges-Lehmann estimates for median difference

Reviewer's Comments
The combining of results for the shoulder surgery studies are more clinically relevant than so doing for the soft tissue surgeries. The exclusion of the bupivacaine HCl treatment arm for BU0002-IM is reasonable given that the SABER-placebo treatment arm comparison was included.

While the findings were statistically significant, the differences in mean pain scores were small, i.e., less than 1 unit on the 10-point numeric rating scale. The differences in the rescue requirements, however, suggest that the pain intensity differences are clinically relevant.

Bupivacaine HCl as the Comparator
The Applicant summarized the pain intensity on movement AUC_{0-72} findings for this subgroup as shown in Table 19 below. They noted that the therapeutic effect of SABER-bupivacaine compared to bupivacaine HCl was approximately the same as the therapeutic effect compared to SABER-placebo. The effect was statistically significant (p=0.04).

The Applicant performed a sensitivity analysis of pain intensity on movement AUC_{0-72} with opioid pain score data. The results, shown in Table 20, were, according to the Applicant, consistent with those for the primary efficacy endpoint in that over the 72 hour period, mean, median, and least square (LS) mean pain intensity were lower in the SABER-Bupivacaine group than in the bupivacaine HCl group; however, the LS mean difference between the treatment groups significant.

Table 19. Pain on movement AUC results in the bupivacaine HCl as a comparator group (Table 44, p. 74 of section 5.3.5.3 of the NDA)

AUC (0-72 Hours)	**SABER-Bupivacaine 5 mL N=169**	**Bupivacaine HCl N=93**
Mean (SE)	4.3 (0.16)	4.9 (0.23)
Standard Deviation	2.06	2.21
Median	4.2	4.7
Min, Max	0.0, 9.8	0.7, 10.0
LS Mean (SE)[1]	4.3 (0.16)	4.9 (0.22)
95% CI[1]	(4.0, 4.6)	(4.5, 5.3)
LS Mean Difference (SE)[1]	-0.6 (0.27)	
95% CI[1]	(-1.08, -0.03)	
p-value[1]	0.0401	

[1] Based on an ANOVA model with study and treatment groups as factors.

Table 20. Sensitivity analysis for AUC with opioids in the bupivacaine HCl as a comparator group (Table 45, p. 74 of Section 5.3.5.3 of the NDA)

AUC (0-72)	SABER-Bupivacaine 5 mL N=169	Bupivacaine HCl N=93
Mean (SE)	4.4 (0.15)	4.9 (0.22)
Standard Deviation	2.01	2.12
Median	4.3	4.8
Min, Max	0.0, 9.8	0.7, 9.7
LS Mean (SE)[1]	4.5 (0.16)	4.9 (0.21)
95% CI 1	(4.1, 4.8)	(4.5, 5.3)
LS Mean Difference (SE)[1]	-0.5 (0.30)	
95% CI[1]	(-0.98, 0.05)	
p-value[1]	0.0762	

[1] Based on an ANOVA model with study and treatment groups as factors.

The findings for the use of rescue opioid medications during the first 72 hours following surgery and study drug administration are summarized in Table 21 below. No difference was observed between treatment groups.

Table 21. Total morphine equivalent opioid medication use from 0-72 hours (Table 48, p. 79 of Section 5.3.5.3 of the NDA)

Total Morphine Equivalent Dose	SABER-Bupivacaine 5mL N=169	Bupivacaine HCl N=93
Mean (SE)	32.1 (3.78)	39.2 (7.41)
Standard Deviation	49.10	71.42
Median	16.0	18.0
Q1, Q3	4.0, 35.0	8.0, 36.0
Min, Max	0.0, 289.0	0.0, 437.2
W-statistic[1]	0.63	0.50
p-value[1]	<0.0001	<0.0001
Wilcoxon Rank Sum Test		
Median Difference[2]	-2.0	
95% CI[2]	(-7.0, 2.0)	
p-value	0.3077	

[1] Shapiro-Wilk test for Normality Assumption
[2] Hodges-Lehmann estimates for median difference

Reviewer's Comments
Although the Applicant has found a statistical difference between SABER-bupivacaine and bupivacaine HCl in this subgroup analysis, several points need to be taken into consideration:

1. Different doses of bupivacaine HCl were used in the different trials that compose this subgroup. If the highest dose of bupivacaine HCl, i.e., 40 mL, were used in the trials, it is possible the results would have favored treatment with bupivacaine HCl.
2. The differences observed between treatment groups are small, less than 1 unit on the pain scale, indicating the clinical significance of the findings is small, if one exists at all.
3. The benefit of SABER-bupivacaine over bupivacaine HCl is lost when the use of opioids is taken into consideration.
4. There was no difference in opioid use during the first 72 hours following surgery

The efficacy data for this subgroup do not indicate a clinical benefit from SABER-bupivacaine that is superior to bupivacaine HCl

Additional Analyses of the Primary Endpoint
The Applicant evaluated several covariates including cumulative incision length (soft tissue trials only), age, and body mass index (BMI). These were explored in linear relationship to the 72-hour AUC; none was found to have a slope significantly different from zero, and therefore, they were not included in the ISE.

Applicant's Conclusions Regarding the Primary Endpoints
The Applicant made the following conclusions based on the efficacy results from the seven randomized, double-blind, controlled trials using a 5 mL dose of the final formulation of SABER-Bupivacaine and using the instillation method of administration:

1. SABER-bupivacaine causes a statistically significant reduction in pain intensity on movement and reduced need for opioids over a 72 hour period after surgery.
2. Two of the seven trials (CLIN-803-006-0006 and BU-002-IM) show statistically significant reduction in the pre-specified primary endpoint of reduction in pain on movement AUC_{0-72} compared to SABER-Placebo and are considered the pivotal efficacy studies.
    a. The primary pain endpoints of both trials stand up to sensitivity analysis accounting for possible confounding by rescue opioid doses.
    b. In addition, using the common endpoint of IV morphine equivalents of total opioid use over 0-72 hours, both trials showed a statistically significant and clinically important reduction in the need for postoperative opioids.
3. All seven of the trials used a common method of assessing pain intensity and opioid use so that efficacy results could be pooled and statistically analyzed using common primary endpoints.

4. The efficacy results of the pooled analyses of the primary pain endpoint by surgery type were also statistically significant compared to placebo and provide consistent supportive evidence for the two pivotal trials.
5. A pooled analysis of the primary pain endpoint for the three trials that included a bupivacaine HCL control showed statistical superiority for SABER-Bupivacaine over bupivacaine HCl.
6. A wide variety of surgical procedures were studied, including inguinal hernia repair, subacromial decompression shoulder surgery, abdominal hysterectomy, open laparotomy, laparoscopic cholecystectomy, and laparoscopic colectomy. The incision lengths ranged from a few centimeters for laparoscopic cholecystectomy to up to 35 cm for open laparotomy. The seriousness of the surgery ranged from ambulatory procedures such as hernia repair to major abdominal surgery requiring hospitalization for a week. Thus, the breadth of surgical experience with SABER-Bupivacaine should allow extrapolation of the results to other types of surgery.

Reviewer's Comments

The normalized pain intensity score $AUC_{0\text{-}72\ hours}$ data provided by the Applicant were analyzed by Dr. David Petullo from the Office of Biostatistics. Using that data and limiting the AUC time period to 72 hours, he generated a Forest plot for the efficacy trials comparing SABER-bupivacaine AUCs to the two comparators, SABER-placebo and bupivacaine HCl. Figure 2 contains his plots for the two pivotal trials and the other trials involving the same surgical procedures. Figure 3 contains the plots generated for the trials involving surgical procedures other than herniorrhaphy and subacromial shoulder decompression.

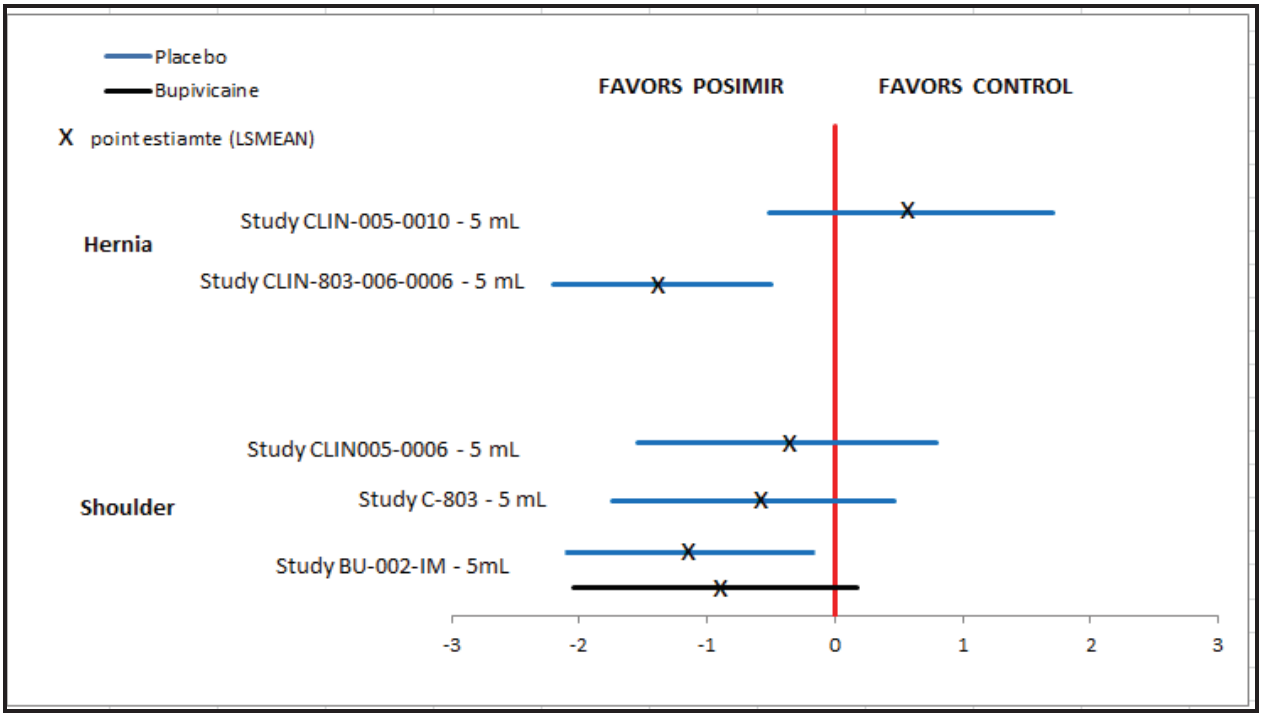


Figure 2. Forest plot of AUC_{0-72} for pain intensity scores for trials involving subjects undergoing either herniorrhaphy or arthroscopic subacromial decompression (combined Figure 5, p 19, and Figure 8, p. 29, from the statistical review)

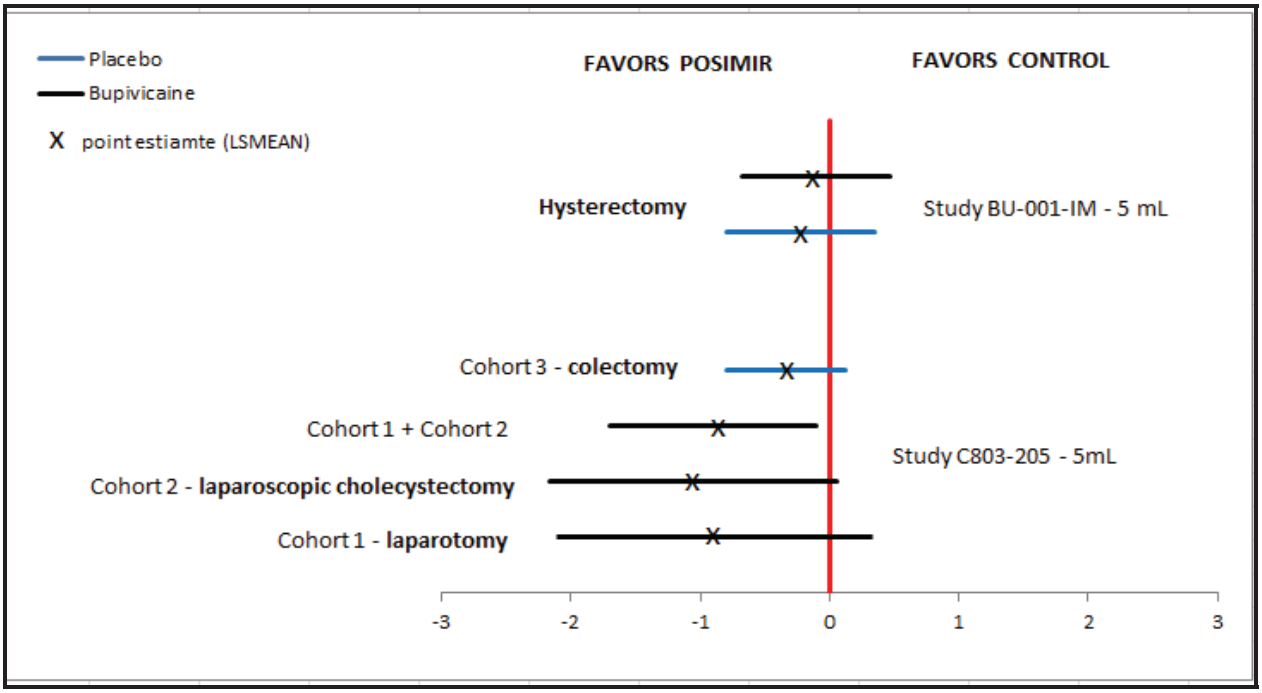


Figure 3. Forest plot of AUC0-72 for pain intensity scores for trials involving subjects undergoing surgery other than herniorrhaphy or subacromial decompression (Figure 9, p. 32 of the statistical review)

The plots indicate that there were three trials for which SABER-bupivacaine was superior to either SABER-placebo or bupivacaine HCl: hernia trial CLIN-803-006-0006, shoulder repair trial BU-002 and the combine Cohort1 and Cohort2 data from C803-205. It is noteworthy that SABER-bupivacaine was not superior to either SABER-placebo or bupivacaine HCl for the other trials involving either herniorrhaphy or shoulder repair surgery despite the similarities in study design and doses of study drugs. For the shoulder surgery trials that failed, the primary endpoint trended in the direction favorable to SABER-bupivacaine; however, for the failed herniorrhaphy trial, the primary endpoint trended in the direction favoring SABER-placebo. The findings for the herniorrhaphy trials and Study C803-205 are discussed below.

The discrepancy in the findings of the two herniorrhaphy trials warrants further consideration. The protocols were reviewed to determine whether there was a difference in the patient populations or methods of administering the study drug that could potentially explain the difference in the outcomes. There were no significant differences in the enrollment criteria. The most notable difference was that CLIN-803-006-0006 limited the age range from 18-65 years whereas CLIN-005-0010 imposed no upper age limit; however, the demographics for the enrollees were similar between treatment groups and between the two trials. Both protocols required identical administration of study drug, i.e., during wound closure, the study drug was to be "instilled gradually throughout the inguinal canal and the abdominal wall layers to cover all raw surfaces of the wound, filling up subaponeurotic and subcutaneous spaces." The only major difference was where the two trials were conducted. CLIN-803-006-0006 (SABER-bupivacaine was superior to SABER-placebo) was conducted at one site in New Zealand and at four sites in Australia; CLIN-005-0010 (SABER-bupivacaine was inferior to SABER-placebo) was conducted at seven sites in the United States and one site in New Zealand. If there was a difference in surgical technique between countries, it was not apparent from the study reports. Lichtenstein or tension-free repairs are commonly performed in each of the three countries; it was an entry criterion in CLIN-803-006-0006 but not in CLIN-005-0010. The two trials are described in detail in Section 9.4 of this review.

An alternative explanation for the findings in the herniorrhaphy trials might be that the treatment effect is so small that a trial with a negative outcome for SABER-bupivacaine would not be unexpected. This explanation would be supported by the small differences observed in pain scores between the two treatment groups and by the number of trials that failed to show a significant difference between SABER-bupivacaine and SABER-placebo but trended in favor of SABER-bupivacaine treatment. The Applicant made no comment about the discrepancy in the findings for the two trials but accurately reported the findings.

6.1.5 Analysis of Secondary Endpoints(s)

Using the same three efficacy population subgroups for the analyses of secondary endpoints as they did for the primary endpoints, the Applicant analyzed the following secondary efficacy endpoints:

- Mean pain intensity on movement AUC (time normalized area under the curve) during the period 0 to 72 hours post-dose SABER-Bupivacaine vs. Bupivacaine HCl
- Normalized AUC0-24, AUC24-48 and AUC48-72 of pain intensity on movement
- Mean total IV morphine-equivalent dose during the period 0 to 72 hours post-dose
- Total IV morphine equivalent opioid use by each 24 hour window
- Time to first opioid use
- Mean pain intensity at rest AUC (time normalized area under the curve) during the period 0 to 72 hours post-dose

Soft Tissue Surgical Procedures

In their pain intensity on movement intermediate AUCs analyses, the Applicant found that the LS mean pain intensity differences was lower in the SABER-Bupivacaine group than in the SABER-Placebo group, and the LS mean difference between these treatment groups was statistically significant for the 0-24 hour interval, favoring SABER-Bupivacaine over SABER-Placebo. Beyond the first hours, there was no significant difference between the treatments. These scores are summarized in Table 22 below.

Table 22. Least square mean pain scores by day (based on Table 17, p. 50 of Section 5.3.5.3 of the NDA)

AUC time range	SABER-bupivacaine N=253 LS Mean (SE)	SABER-placebo N=157 LS Mean (SE)
0-24 hours	4.3 (0.14)	5.1 (0.17)
24-48 hours	4.0 (0.15)	4.3 (0.18)
48-72 hours	3.1 (0.15)	3.5 (0.18)

The mean and median total morphine-equivalent doses were lower in the SABER-Bupivacaine group than in the SABER-Placebo group on each of the 3 days analyzed, but they were not significantly different on any of the three days.

Reviewer's Comments

At none of the 24-hour time periods did the LS mean pain scores differ by a single unit or more suggesting that the differences between the treatments, while statistically significant for the first 24 hours after surgery, are not likely clinically significant. The

lack of a significant difference in opioid rescue also suggests that there is not a clinically relevant difference between SABER-bupivacaine and SABER-placebo.

Orthopedic Surgical Procedures

In their pain intensity on movement intermediate AUCs analyses, the Applicant found that the LS mean pain intensity differences was lower in the SABER-Bupivacaine group than in the SABER-Placebo group, and the LS mean difference between these treatment groups was statistically significant for the 0-24 hour interval, favoring SABER-Bupivacaine over SABER-Placebo. Beyond the first 24 hours, there was no significant difference between the treatments. These scores are summarized in Table 23 below.

Table 23. Least square mean pain scores by day (based on Table 32, p. 64 of Section 5.3.5.3 of the NDA)

AUC time range	SABER-bupivacaine N=114 LS Mean (SE)	SABER-placebo N=73 LS Mean (SE)
0-24 hours	5.3 (0.23)	6.6 (0.27)
24-48 hours	5.4 (0.22)	5.9 (0.26)
48-72 hours	4.7 (0.21)	5.2 (0.26)

[1] Based on an ANOVA model with study and treatment groups as factors.

The mean and median total morphine-equivalent doses were lower in the SABER-Bupivacaine group than in the SABER-Placebo group on each of the 3 days analyzed, and were significantly different on the first two days as shown in Table 24.

Table 24. Total morphine-equivalent use by day (based on Table 34, p. 66 of Section 5.3.5.3 of the NDA)

AUC time range	SABER-bupivacaine N=114		SABER-placebo N=73	
	Mean (SE)	Median	Mean (SE)	Median
0-24 hours	19.4 (1.69)	16.0	32.8 (3.22)	28.0
24-48 hours	7.5 (1.30)	3.2	9.9 (1.32)	8.0
48-72 hours	4.9 (0.83)	0.0	5.6 (1.22)	0.0

Reviewer's Comments

The secondary endpoint data for both the pain score AUC and opioid rescue totals support the primary endpoint findings. It is interesting to note that the differences in mean pain intensity AUCs are greater than a single unit for the first 24 hours, the only time period for which the difference is significant. The magnitude of the difference in combination with a significant difference in opioid use over the same time period suggests that the difference is clinically relevant. The significant difference in opioid rescue totals for the period of 24-48 hours after surgery suggests that SABER-

bupivacaine is still having an effect although the mean pain intensity AUCs do not differ during the same period.

Bupivacaine HCl as the Comparator

In their pain intensity on movement intermediate AUCs analyses, the Applicant found that the LS mean differences between the SABER-bupivacaine and bupivacaine HCl treatment groups were approximately the same, but significantly different favoring SABER-bupivacaine, for the 0-24 hour interval and the 24-48 hour interval, but by the third day (hours 48-72) both groups had declined to a "mild pain score" with a non-significant difference between treatments. These scores are summarized in Table 25 below.

Table 25. Least square mean pain scores by day (based on Table 47, p. 78 of Section 5.3.5.3 of the NDA)

AUC time range	SABER-bupivacaine N=169 LS Mean (SE)	Bupivacaine HCl N=93 LS Mean (SE)
0-24 hours	5.0 (0.16)	5.9 (0.22)
24-48 hours	4.3 (0.18)	5.0 (0.25)
48-72 hours	3.6 (0.18)	3.7 (0.24)

The Applicant also reported that there was no difference in total morphine-equivalent opioid medication use for the two treatment groups in any of the first three days following study drug administration.

Reviewer's Comments

The AUC data suggest there is a difference, albeit small and not likely clinically relevant, between SABER-bupivacaine and bupivacaine HCl during the first 48 hours following surgery. However, the small benefit observed with SABER-bupivacaine for pain on movement is not observed with opioid use over the same time period. As was the case for the primary endpoint, accounting for the use of opioid rescue medication during the first 72 hours would likely eliminate any differences between treatment groups. The use of a range of doses of bupivacaine HCl also needs to be considered. It is possible that uniform use of 40 mL of bupivacaine HCL, rather than 20 mL or 30 mL doses used in some of the trials, may have resulted in SABER-bupivacaine appearing to be less efficacious than bupivacaine HCl.

6.1.6 Other Endpoints

None of the other secondary endpoints, e.g., patient satisfaction scores, modified brief pain inventories, function scores, demonstrated a difference between treatment groups.

These endpoints and the results associated with them are discussed in detail in the reviews of the individual studies that are found in Section 9.4 of this review.

6.1.7 Subpopulations

The Applicant states that none of the subgroup analyses they conducted for the pooled analyses indicated that SABER-Bupivacaine is ineffective in any particular subgroup of patients. They acknowledged that, based on the pharmacokinetics of bupivacaine, the elderly have a reduced clearance and higher plasma levels. Therefore, they contend that it would be reasonable to advise caution for the use of SABER-bupivacaine in elderly or frail patients.

Reviewer's Comments
There did not appear to be any subgroups for which efficacy varied in a substantial way. It should be noted that the populations requiring some of the surgical procedures were limited by the nature of the procedure itself, e.g., hysterectomies were performed on middle-aged women, inguinal herniorrhaphies were more commonly performed in younger and middle-aged men.

While the Applicant's comment about the need for caution when using bupivacaine in elderly patients is not unwarranted, they have made no recommendations as to how the caution should manifest itself in the clinical setting. The use of lower doses of SABER-bupivacaine has not been demonstrated to be effective; given the limited amount of efficacy, there is a real possibility that lower doses would not be effective. Therefore, the alternatives are to demonstrate safety in the elderly before approving the product for use in that population or to not recommend its use in the elderly due to the potential risk. The data currently available do not indicate a clear increase in risk for the few elderly subjects who participated in the clinical trials.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant states that the 5 mL dose of SABER-bupivacaine has been demonstrated to have similar efficacy in incisions ranging from a few centimeters, e.g., for laparoscopic procedures, up to 35 cm, e.g., for laparotomy incisions. Therefore, they contend there is no evidence to suggest that more SABER-bupivacaine is needed for longer incisions or that lower amounts should be used for shorter incisions.

Reviewer's Comments
Given the limited efficacy that was observed in the clinical studies conducted to date, there is a real possibility that an increase in the dose of SABER-bupivacaine following

some surgical procedures may enhance its efficacy. The Applicant has not conducted any dose-controlled studies to more precisely determine the dose necessary for any surgical procedure.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

SABER-bupivacaine is intended for one-time use following a surgical procedure; therefore, persistence of efficacy and tolerance are not issues relevant to this product.

It should be noted that repeat dosing was not evaluated by the Applicant and was not recommended by the Division.

6.1.10 Additional Efficacy Issues/Analyses

There were no additional efficacy issues or analyses.

7 Review of Safety

Safety Summary

The safety of SABER-bupivacaine is related to both its active and inactive components. While the safety of bupivacaine, in concentrations up to 0.75%, infiltrated into surgical incision sites has been established, the safety of bupivacaine 12%, benzyl alcohol (BA) 22%, and sucrose acetate isobutyrate (SAIB) 66% instilled into surgical wounds has not been heretofore evaluated.

In the clinical trials, a total of 683 subjects were treated with the to-be-marketed formulation of SABER-bupivacaine; 268 subjects were treated with SABER-placebo; and 124 subjects were treated with bupivacaine HCl.

The risks associated with the administration can be broadly characterized as system or local reactions. The Applicant was advised to evaluate both, and in particular, to evaluate the risks associated with each of the three components of SABER-bupivacaine, not the effects of the bupivacaine alone. As the systemic effects of benzyl alcohol and the local effects of the SAIB were not fully evaluated, the risk profile of SABER-bupivacaine has not been fully characterized. In the subsections that follow, the risks associated with each of the components are described to the extent possible with the data available.

Risks Associated with Systemic Exposures

The Applicant did a thorough evaluation of the risks for toxicity related to systemic exposure following administration of SABER-bupivacaine. These included proactive assessments for signs and symptoms of neurotoxicity and extensive cardiac monitoring that was combined with plasma bupivacaine measurements provide a pharmacokinetic context for interpreting the data. There were no safety signals suggesting that SABER-bupivacaine posed an increased risk of cardiac or neurological toxicity compared to either SBER-placebo or bupivacaine HCl treatments.

SAIB has been demonstrated to remain intact in the instillation site for months following its administration. Therefore, the risk of systemic toxicity associated with this component of SABER is likely to be low.

Benzyl alcohol is absorbed into the circulation during the 12-24 hours following the administration of SABER-bupivacaine. The 5 mL dose of SABER-bupivacaine results in a 1.1 gm exposure to benzyl alcohol. It is not known what the systemic effects, if any, this exposure may have. There were a number of adverse events suggesting neurotoxicity that were observed in the clinical trials, e.g., somnolence, dizziness, dysgeusia, raising the concern that they were due to bupivacaine exposures. However, they occurred in both the SABER-bupivacaine and the SABER-placebo treatment

groups, and to a substantially lesser extent, if at all, in the bupivacaine HCL treatment group. This indicates that the SABER is likely putting patients at risk, and the benzyl alcohol would be the component systemically available to do so.

Risks Associated with Local Exposure

The assessment of local toxicity was complicated by the lack of a non-SABER placebo treatment arm in any of the clinical trials. Therefore, local toxicity assessments depend on comparisons to bupivacaine HCl treatment to discern the risks associated with SABER and on the comparison of SABER-bupivacaine to SABER-placebo to discern the risks associated with bupivacaine.

Overall, there were no substantial differences in the risks profiles between SABER-placebo and SABER-bupivacaine. There were substantial differences in local reactions between the SABER treatments and bupivacaine HCl treatment with the greater risk being posed by the SABER treatments. The incidence of hematomas, erythema, ecchymosis, dehiscence, bleeding, bruising, and pruritus at the incision sites was substantially increased with the use of the SABER treatments. Based on these differences, the safety profile for SABER-bupivacaine is inferior to that of bupivacaine HCl for local tissue toxicity.

Lastly, the local tissue effects of SABER-bupivacaine were evaluated predominantly on white subjects. There are substantial differences in healing between individuals with white and individuals with darker skin. Specifically, darker skin is associated with increased risk of hypertrophic scarring. Given the types of adverse reactions at the instillation site associated with SABER-bupivacaine and the persistence of SAIB at the site, it is important that the product be more thoroughly evaluated in non-white populations to determine the nature and extent of the risk SABER-bupivacaine may pose.

Summary

Overall, the systemic and local toxicity of SABER-bupivacaine has been demonstrated to be greater than that of bupivacaine HCl for general surgical procedures. Much of that risk is likely attributable to the SABER component of the product.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

A prototype formulation of SABER-Bupivacaine was used in a single clinical trial (SABER01-01) conducted in 2003. The formulation contained (b) (4) (b) (4) on a % w/w basis. The product was administered by (b) (4) (b) (4) The study findings indicated that the product did not produce any consistent analgesia; therefore, a new formulation was developed. The new formulation contained a higher amount of bupivacaine base (12% w/w) and the solvent was changed to benzyl alcohol (22% w/w); the amount of SAIB was slightly reduced (66% w/w). This formulation was used in all subsequent clinical trials and is proposed as the formulation for marketing.

A total of 13 clinical trials have been conducted with the to-be-marketed formulation of the drug product, and these serve as the basis for the evaluation of the product's safety. These trials are listed in the table below. For these trials, a total of 1109 subjects were randomized; the 1075 subjects who received any study drug were included in the safety database.

Table 26 includes all of the clinical trials used to evaluate the two formulations of SABER-bupivacaine; the methods of administration used; the surgical procedures, if any, that were performed; and the number of subjects who were included in the safety database.

Table 26. Summary of trials used to assess safety (based on Table 1 on pp.14-15 of Section 5.3.5.3 of the NDA)

Protocol Number	Phase	Surgery	Type of Administration	Number of Safety Subjects
SABER01-01[A]	1	N/A Healthy Subjects	Subcutaneous (SC) Trailing Injections	12
CLIN005-0008	1	N/A Healthy Subjects	IV Infusion, Patch, or SC trailing injection	5
CLIN004-0001	2	Inguinal Hernia Repair	SC Trailing Injections + infiltrate	81
CLIN004-0009	2	Inguinal Hernia Repair	SC trailing injections Only or Infiltration + SC trailing injections	42
CLIN005-0002	2	Appendectomy	SC trailing injections or Infiltration + SC trailing injections	21
CLIN005-0006	2	Subacromial Decompression	Subacromial Instillation + SC trailing injections or Subacromial Instillation only	106
CLIN005-0007	2	Inguinal Hernia Repair	Instillation	12
CLIN005-0010	2	Inguinal Hernia Repair	Infiltration + SC trailing injections or Instillation	89
CLIN803-006-0006	2	Inguinal Hernia Repair	Instillation	123
BU-001-IM	2	Hysterectomy	Instillation or Infiltration	114
BU-002-IM	2	Subacromial Decompression	Subacromial Instillation	107
C803-017	2	Subacromial Decompression	Subacromial Instillation	60

Protocol Number	Phase	Surgery	Type of Administration	Number of Safety Subjects
C803-017e[B]	2	N/A, Follow-up to 803-017	N/A	47
C803-025	3	Laparotomy, Laparoscopic Cholecystectomy, Laparoscopically assisted Colectomy	Instillation 12or Infiltration	305
C803-027	2	Laparotomy, Laparoscopically assisted Colectomy	Instillation	10

[A] These subjects were not included in the pooled analyses because the formulation used was not the same as the to-be-marketed formulation.
[B] These subjects were all enrolled in trial C803-017and were not counted twice in determining the total number of safety subjects.

The Applicant's rationale for which studies should be used to assess safety is appropriate. Therefore, for the purposes of this review, safety data from all of the clinical studies, except SABER01-01, were considered for evaluation of the risks associated with the to-be-marketed formulation of SABER-bupivacaine.

7.1.2 Categorization of Adverse Events

The Applicant used MedDRA version 13.0 to code the adverse events (AEs) reported in the integrated safety database. All of the AEs reported in the safety database were treatment emergent, defined as those AEs that occurred during and after dosing and those existing AEs that worsened during the trial. Additionally, AEs that occurred on the day of surgery, but prior to dosing, that had a causality of "related" were included as TEAEs.

Pain that was evaluated as part of efficacy endpoints was not considered an adverse event unless explicitly reported as an adverse event on the Adverse Event Case Report Form (CRF).

In the long-term follow-up trials, an adverse event was considered as occurring during the follow-up phase based on the following criteria:

- Trials BU-001-IM and BU-002-IM: any AE occurring greater than 18 days after the dose date

- Trial C803-017e: any AE that was reported on C803-17e Adverse Event CRF
- Trial CLIN-803-006-0006: any AE that was reported on the follow-up Adverse Event CRF.

An adverse event that continued over the treatment and follow-up phase was counted only once in the period during which the event started unless the event had a new onset or worsened in intensity in the long-term follow-up phase.

The adverse event database was evaluated for the appropriateness and consistency of the categorization of AEs by system organ class (SOC) and the coding of AEs to preferred terms. The AEs were consistently assigned to the appropriate SOC. Coding of the verbatim terms for the AEs to preferred terms was consistent within the database, with the following exceptions:

- Numbness and/or tingling were classified as either “hypoaesthesia” or “paraesthesia.”
- Hematomas, bruises, discoloration, ecchymosis, erythema, suffusion, redness and associated with the surgical incision site were all coded as “Application site discolouration.”
- Wound infections were split into “postoperative wound infection,” and “incision site infection.”
- Bleeding at the operative site was split into “wound haemorrhage” and “incision site haemorrhage”

Overall, the categorization of AEs by the Applicant was consistent and appropriate. The Applicant stated that grouping multiple terms into the category “application site discolouration” was consistent with MedDRA dictionary used for the conversion of verbatim descriptions of the AEs to preferred terms. The basis for determining whether an infection should be classified as postoperative wound infection or incision site infection was not provided; neither was the basis for splitting bleeding AEs at the operative site. For the purposes of this review, the infection and bleeding AEs are treated only as incision site infection and hemorrhage, respectively, and the “application site discolouration” will be considered as is and as hemoatomas, suffusions, erythemas (redness and erythema) and discoloration (bruises, discoloration, ecchymosis).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence of Adverse Events

The Applicant did not pool the safety data from the Phase 1 trial, SABER01-01, because the trial did not use the final formulation of SABER-Bupivacaine. The to-be-marketed formulation was used in all subsequent trials. The formulation studied in SABER01-01 contained a different solvent, (b) (4)

(b) (4) therefore, the decision to not pool the data was appropriate, and the safety data from that trial will be considered separately in this review as well.

The Applicant grouped the safety data from the remaining studies as follows:

- Pooled Group A (Treatment Period): These included 10 randomized, double-blind, controlled, Phase 2 and 3 trials involving three types of surgical procedures: orthopedic, inguinal hernia repair, or abdominal surgery. These trials provided comparisons of SABER-bupivacaine with SABER-placebo or bupivacaine HCl. The trials included in this group were the following:
  - Orthopedic: CLIN005-0006, BU-002-IM, C803-017
  - Inguinal Hernia Repair: CLIN004-0001, CLIN004-0009, CLIN005-0010, CLIN-803-006-0006
  - Abdominal Surgery: CLIN005-0002, BU-001-IM, C803-025

- Pooled Group B (Long Term Follow-Up Period): This group is a subset of Group A and includes four double-blind trials with a long-term safety follow-up that assessed the long-term local effects of SABER-bupivacaine, i.e., the impact of SABER-bupivacaine on wound healing and local tissue conditions. The trials included:
  - C803-017e
  - CLIN-803-006-0006
  - BU-001-IM
  - BU-002-IM

  A subject was considered to be “enrolled” in the long-term follow-up phase if any one of the following criteria for each trial was met:
  - Trial C803-017e: any subject enrolled in C803-017e
  - Trial CLIN-803-006-0006: any subject who reported any adverse event or collected any wound healing data on the follow-up period CRF
  - Trials BU-001-IM and BU-002-IM: any subject who reported any adverse event that started 18 days after the first dose date or collected any wound healing data in the follow-up visits.

  Disposition, demographics, and baseline characteristics were not separately summarized for Pooled Group B, since it is a subset of the Pooled Group A patients with long-term follow-up data.

- Pooled Group C (All trials using the final formulation): This group included all 13 trials conducted with the final formulation of SABER-Bupivacaine whether blinded or open-label in design. For this pooled group, the Applicant provided only disposition, demographics and adverse event summaries. [The open-label studies included: CLIN005-0007, CLIN005-0008, and C803-027.]

The Applicant's approach to pooling the safety data was appropriate. For the purposes of this review, the Pooled Groups A and B were evaluated separately to determine the "immediate" and "delayed" risks, respectively, associated with the proposed use of SABER-bupivacaine; while the combination of these two sets, i.e., Pooled Group C was used to assess overall risk of the product.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 1075 patients or healthy subjects comprised the safety population of the ISS database. Each subject was exposed to study drug. Table 27 below summarizes the extent of study drug exposures for the ISS safety population. A total of 547 subjects were exposed to the 5 mL dose of SABER-bupivacaine, which is the proposed dose for product labelling. Eleven subjects were also exposed to the labeled dose, but in conjunction with bupivacaine HCL that was administered by infiltration after surgery to provide "immediate analgesia."

Table 27. Overall exposures to study drugs (based on Table 11 on p. 31 of Section 5.3.5.3 of the NDA submission)

Saber-Bupivacaine Alone†			**Saber-Bupivacaine (S-B)+ Bupivacaine HCl**				**Saber-Placebo**		**Bupivacaine HCl Alone**			
No. of Pts.	Vol. (mL)	Dose (mg)	No. of Pts.	Vol. S-B (mL)	Bupiv. HCl Dose (mg)	Total Bupiv. Dose (mg)	No. of Pts.	Vol. (mL)	No. of Pts.	Vol. (mL)	Conc. (%)	Dose (mg)
50	2.5	330	5	5	50	710	16	2.5	1	5	0.25	12.5*
547	5	660	6	5	75	735	218	5	9	7.5	0.25	18.8*
4	7.5	990	45	7.5	50	1040	4	7.5	5	15	0.5	75
			26	7.5	75	1065	30	10	15	17.5	0.5	87.5
									29	20	0.25	50
									38	30	0.5	150
									27	40	0.25	100
Total			Total				Total		Total			
601			82				268		124			

† Five subjects in study CLIN005-0008 were put under the 'SABER-Bupivacaine Alone' although they had been previously exposed to a bupivacaine patch as part of the cross-over study. For all safety summaries, they were included under the combination arm.

* These subjects also received bupivacaine HCl (75 mg) pre-operatively as local anesthesia for their procedure.

The Applicant summarized the demographic information for subjects in all clinical studies involving the to-be-marketed formulation of SABER-bupivacaine in tabular form, which is presented in Table 28 below. The table indicates that the subjects exposed to the proposed 5 mL dose were mostly white, not Hispanic, and 65 years of age or less. These subjects were evenly divided by gender; half the subjects underwent abdominal

surgical procedures while the other half was nearly evenly split between those undergoing inguinal hernia repairs and those undergoing orthopedic procedures.

Table 28. Summary of demographic information for the subjects exposed to the final formulation of SABER-bupivacaine (based on Table 7 on p. 25 of Section 5.3.5.3 of the NDA submission)

Demographic	SABER- Bupivacaine 2.5 mL (N=50)	SABER-Bupivacaine 5 mL (N=542)	SABER-Bupivacaine/ Bupivacaine HCl (N=91)	All SABER-Bupivacaine (N=683)	SABER-Placebo (N=268)	Bupivacaine HCl (N=124)
Age (years)						
n	50	542	91	683	268	124
Mean (SE)	45.3 (1.68)	51.6 (0.56)	44.2 (1.42)	50.1 (0.51)	51.9 (0.81)	46.9 (1.20)
Standard Deviation	11.89	13.10	13.51	13.36	13.32	13.34
Median	47.5	51.0	45.0	51.0	52.0	47.0
Min, Max	20, 68	19, 87	18, 69	18, 87	18, 89	21, 87
≤ 65	49 (98.0%)	465 (85.8%)	87 (95.6%)	601 (88.0%)	225 (84.0%)	116 (93.5%)
<45	23 (46.0%)	160 (29.5%)	43 (47.3%)	226 (33.1%)	83 (31.0%)	51 (41.1%)
45 - 65	26 (52.0%)	305 (56.3%)	44 (48.4%)	375 (54.9%)	142 (53.0%)	65 (52.4%)
>65	1 (2.0%)	77 (14.2%)	4 (4.4%)	82 (12.0%)	43 (16.0%)	8 (6.5%)
>75	0	17 (3.1%)	0	17 (2.5%)	11 (4.1%)	2 (1.6%)
Sex	(n=50)	(n=542)	(n=91)	(n=683)	(n=268)	(n=124)
Male	46 (92.0%)	275 (50.7%)	85 (93.4%)	406 (59.4%)	161 (60.1%)	56 (45.2%)
Female	4 (8.0%)	267 (49.3%)	6 (6.6%)	277 (40.6%)	107 (39.9%)	68 (54.8%)
Ethnicity	(n=1)	(n=313)	(n=9)	(n=323)	(n=157)	(n=38)
Hispanic or Latino	1 (100.0%)	43 (13.7%)	1 (11.1%)	45 (13.9%)	12 (7.6%)	10 (26.3%)
Not Hispanic or Latino	0	270 (86.3%)	8 (88.9%)	278 (86.1%)	145 (92.4%)	28 (73.7%)
Race	(n=49)	(n=540)	(n=91)	(n=680)	(n=268)	(n=124)
White	47 (95.9%)	501 (92.8%)	88 (96.7%)	636 (93.5%)	250 (93.3%)	119 (96.0%)
Non-White	2 (4.1%)	39 (7.2%)	3 (3.3%)	44 (6.5%)	18 (6.7%)	5 (4.0%)
BMI (kg/m2)	(n=50)	(n=540)	(n=91)	(n=681)	(n=268)	124
>30	5 (10.0%)	152 (28.1%)	13 (14.3%)	170 (25.0%)	73 (27.2%)	32 (25.8%)
Surgery Type	(n=50)	(n=542)	(N=91)	(n=683)	(n=268)	(n=124)
Orthopedic	0	152 (28.0%)	3 (3.3%)	155 (22.7%)	89 (33.2%)	29 (23.4%)
Inguinal Hernia Repair	50 (100.0%)	117 (21.6%)	83 (91.2%)	250 (36.6%)	67 (25.0%)	30 (24.2%)
Abdominal Surgery	0	273 (50.4%)	0	273 (40.0%)	112 (41.8%)	65 (52.4%)
None	0	0	5 (5.5%)	5 (0.7%)	0	0

The 547 exposures to SABER-bupivacaine at the proposed 5 mL dose occurred primarily in Caucasians less than 65 years of age. Changes in wound healing and skin can occur with advancing age, and these changes may alter the safety of SABER-bupivacaine in older patients; however, 94 subjects over the age of 65 years, of whom 17 were over the age of 75 years, were treated with the 5 mL dose of SABER-bupivacaine, which should be adequate to assess the risk of toxicity at the instillation site. This same set of subjects would also likely be adequate to determine whether there is a clinically significant increase in the risk of systemic exposure, if there is one. Thus, the safety data should be adequate to characterize the risk profile in the adult "white" population.

For non-whites, there were only 39 exposures to the 5 mL dose of SABER-bupivacaine, 18 exposures to SABER-placebo, and 5 exposures to bupivacaine. These numbers are too small to evaluate the safety of SABER-bupivacaine for a significant portion of the US patient population, an issue not considered by the Applicant. The reason for concern with this patient group is their greater tendency for hypertrophic scar (i.e., keloid) formation at incision sites at 4-8 weeks following surgery. In the development program, most of the follow-up evaluations occurred at 2 weeks after surgery further limiting the likelihood of detecting whether there is a risk for this adverse event. In the non-white population there were 74 skin related adverse events, or 8% of the 926 AEs that were reported. There were no reported cases of hypertrophic scarring, but this was not unexpected given the limited follow-up. The incidence for skin related adverse events is summarized in Table 29 below.

Table 29. Incidence of adverse events by race

Treatments	Race	N (%)	Skin Related Adverse Events* (n=926)	Skin Related SAEs* (n=14)	Skin Related Severe AEs* (n=14)
SABER-bupivacaine 5 mL	White	501(93%)	464 (93%)	7 (1%)	8 (2%)
	Non-white	39 (7%)	39 (100%)	0	0
SABER-placebo	White	250 (93%)	180 (72%)	4 (2%)	4 (2%)
	Non-white	18 (7%)	27 (150%)	0	0
Bupivacaine HCl	White	119 (96%)	37# (31%)	0	1 (1%)
	Non-white	5 (4%)	2 (40%)	0	0

* Percentages are based on the number of subjects in the treated race group.
# This number includes 7 subjects who received SABER-bupivacaine in addition to the bupivacaine HCl. Excluding these subjects reduces the incidence to 25%.

The data are too limited to draw conclusions about the risk of SABER products based on race, but they do suggest that adverse events are less likely to occur with bupivacaine HCl than a SABER-containing product and that non-whites tend to experience AEs with greater frequency than whites.

7.2.2 Explorations for Dose Response

The Applicant states that the bupivacaine dose incorporated into SABER-bupivacaine was predicated on the published reports of the infusion of bupivacaine into surgical wounds using elastomeric pumps. Their review of the literature led them to believe this is a well-established model bupivacaine infusion and that a 10-20 mg/h infusion rate into a surgical wound could be used to provide analgesia for a period of up to 72 hours. Based on this information, they selected a bupivacaine dose of 660 mg for use in the formulation as that dose would deliver approximately 10 mg/h of bupivacaine over a 72 hour period.

In addition to the dose of bupivacaine to be incorporated into the formulation, the amount of formulation to be instilled into the surgical wound needed to be considered. The Applicant considered a 5 mL volume of SABER-Bupivacaine solution to be the most practical volume to both keep bupivacaine in solution during storage and rapidly form an extended-release depot when instilled into a surgical wound. They felt that this dose of SABER-bupivacaine would permit adequate analgesia over the range of incision lengths that has been shown to be amenable to bupivacaine infusion using a catheter and an elastomeric pump. The incision lengths treated with SABER-Bupivacaine during clinical development ranged from a few centimeters in the arthroscopic subacromial decompression studies to 20-30 centimeters for midline incisions in open laparotomy surgeries. The Applicant states that the data from Cohorts 1 and 2 of Trial C803-025 provide evidence that the 5 mL volume of SABER-Bupivacaine provided similar efficacy for both long midline laparotomy incisions (Cohort 1) and small laparoscopic portals (Cohort 2). Based on these efficacy data, the Applicant believes the use of the 5 mL dose of SABER-Bupivacaine can be used in surgical incisions ranging from laparoscopic or arthroscopic portals to midline abdominal incisions up to 35 cm in length.

The Applicant states that “SABER-Bupivacaine has shown similar efficacy in incisions ranging from a few centimeters in laparoscopic cholecystectomy to laparotomy incisions up to 35 cm. Hence, there is no evidence to suggest that more drug is needed for longer incisions. Likewise, there is no evidence to suggest that lower amounts should be used for shorter incisions.” [Section 3.3.3.1 of the ISE] However, there is very little data to support their statements. A total of 44 subjects had a 2.5 mL dose of SABER-bupivacaine instilled into their surgical wounds, and only 4 subjects had a 7.5 mL dose of SABER-bupivacaine (alone) instilled into their surgical wound. All other uses of these doses involved a method of administration other than instillation. In addition, the efficacy findings suggest, as discussed in Section 6 of this review, that only for arthroscopic shoulder surgery has efficacy been clearly demonstrated; for the other procedures, SABER-bupivacaine did not significantly differ from SABER-placebo or bupivacaine HCl, with the exception of one hernia study that had results which were contrary to a similar study using the same patient population, dosing, and method of administration. The data available to date suggest that SABER-bupivacaine has an

analgesic effect, but the appropriate dose (or possibly, the appropriate formulation) for surgical procedures other than shoulder arthroscopy has not been identified.

7.2.3 Special Animal and/or In Vitro Testing

Special testing of SABER-bupivacaine in animals was conducted by the Applicant to address four safety concerns:

1. The duration and risks associated with the Sucrose Acetate Isobutyrate (SAIB) component of the product after injection in the tissues
2. The impact of SABER-bupivacaine on wound healing
3. The cause and risk associated with the change in color that occurs with the product over the course of its shelf life.
4. The effect of SABER-bupivacaine and SABER-placebo in and around joints.

Studies of the Safety of SAIB

The potential for local and systemic toxicity after subcutaneous administration of the SABER-bupivacaine formulation was assessed in two extended single-dose and one repeated-dose toxicity studies using rats and rabbits. The safety of SAIB (and benzyl alcohol) as inactive ingredients was established in these studies. The local administration of SABER-bupivacaine resulted in a chronic granulomatous inflammation, i.e., foreign body granuloma. All examined sites in the control (SABER-placebo) and all dose groups demonstrated similar histopathological patterns of a chronic subcutaneous inflammation. Despite these findings and that the studies lacked a true placebo control, i.e., all of the treatment arms contained SAIB, the Applicant concluded that the safety of the excipients SAIB and benzyl alcohol as inactive ingredients was affirmed and the safety of the complete formulation was established.

In Study WIL-434007, rabbits were given a single subcutaneous injection of SABER-bupivacaine (with (b) (4) in place of benzyl alcohol as the solvent) or SABER-placebo. SAIB was present in the tissues at 12 months following the injection; however, the amount was not quantified. The Applicant noted that “single doses of SABER Bupivacaine did not result in test article-related injection site reactions up to 52 weeks post-injection.” However, in their conclusions they state that “macroscopic and microscopic effects indicative of inflammation at the injection sites were attributed to the injection procedure and/or the placebo and were typical of a normal reaction to a foreign body and subsequent wound healing.” The macroscopic findings included white patches and viscous contents in both SABER-bupivacaine and SABER-placebo treated animals. The microscopic findings included variably sized, discrete ovoid spaces, thought to be the site of study drug deposition. The spaces were surrounded by thin bands of fibrous connective tissue, which thickened over time, and variable numbers of inflammatory cells. Minimal to moderate degeneration and regeneration of the

panniculus muscle adjacent to the ovoid spaces were present in some animals through the 6-week post-injection and in one animal at the 52-week post-injection evaluation. These findings contrasted with those of studies 7116-1109, 12-11-803-R-SC-AD, and B167-05 in which radiolabeled product was injected. In these studies, 40-60% of the radioactivity was present at 6 weeks post-dosing; however, by 10 weeks post-dosing, there was no radioactivity present. It is possible that SAIB was still in the tissues of these animal studies.

These animal findings raise the concern that SAIB will persist substantially longer in the body tissues than any analgesic effects of the product and may be associated with a foreign body response in humans as well. The long-term follow-up evaluations in subjects as they relate to these risks are discussed in Section 7.4.5 below.

Studies on the Effects on Wound Healing

The Applicant conducted two studies to assess the effects of SABER-bupivacaine on wound healing: DUR2 (a rat study) and 60111 (a minipig study).
In study DUR2, SABER-bupivacaine was compared to SABER-placebo, and in vivo biomechanical testing was performed 7 days following treatment. The Applicant reports that, with the exception of one group involving subcutaneous administration of the SABER-placebo, the measured parameter of in-vivo wound strength revealed there were no significant differences between the groups at 7 Days post-wounding. In addition, there were no differences observed in mechanical wound strength between study groups with materials administered directly into the wound prior to incision closure, or by paired subcutaneous trailing injection immediately following wound closure.

In study 60111, SABER-bupivacaine was compared to the vehicle alone and to 5% carboxymethyl cellulose (CMC). The Applicant concluded from that study SABER Bupivacaine caused no adverse macroscopic effects in the wound tissue in comparison with the vehicle-treated wounds but slightly less wound contraction. Microscopically, a slight tendency towards less advanced re-epithelialization, more inflammation, higher numbers of giant cells and clear vacuoles were noted in the SABER-bupivacaine treated wounds compared to the CMC-treated wounds. Despite these findings, the Applicant concluded that SABER-bupivacaine had no significant adverse effects on the wound healing.

These studies suggest that wound healing is not adversely affected by SABER-bupivacaine. The clinical findings related to this issue are considered in Section 7.4.5 below.

Studies on the Safety Implications of the Color Changes

SABER-bupivacaine has a light yellow solution when it is first manufactured; it gradually darkens on storage such that by 6 months, it has reached or exceeded the limits of the brown-yellow European Pharmacopeia Standards (see Figure 4).

Multiple attempts by the Applicant to determine the compound(s) responsible for this color change were not successful; therefore, they made the decision to test a highly colored lot of the drug product in a repeated dose toxicity study (BR1265). In this repeated-dose toxicity study an aged and deeply colored SABER-Bupivacaine formulation was subcutaneously injected in rats once per week for 4 weeks at 102 or 240 mg/kg of bupivacaine. The end of study stability analysis confirmed that the color of the SABER-bupivacaine tested was a dark brown color. The high dose (240 mg/kg) tested was the NOAEL for systemic effects and represented a 4-fold safety factor relative to the maximum recommended human dose based on a body surface area extrapolation. Therefore, the Applicant concluded that the dark brown discoloration did not cause adverse systemic effects in rats, supporting the safety of the SABER-bupivacaine.

Figure 4. Range of product color as observed at release and on stability over the next 36 months (Figure 30 on p. 140 of Section 2.3.P of the NDA)

The inability of the Applicant to identify the cause for the change of color occurring over time is disconcerting. Although the animal safety findings are reassuring, there are no human data to substantiate those findings, and the safety database contains no information related to the color of the product administered to subjects.

Study on the Effects of SABER on and near Joints

A study of the effects of a single intra-articular dose of SABER containing products was conducted in dogs. Pathology was evaluated at 14 and 42 days after dosing. The following test groups were evaluated:

- SABER-Bupivacaine (3 doses)
- SABER placebo
- saline control
- undosed stifle joints.

Gross examinations of the unopened stifle joint and histopathology evaluations were conducted. The following key findings were reported, per Dr. Bond of the Pharmacology-Toxicology review team:

- Hyperplasia, fatty degeneration, inflammation, fibrosis, and a fibrinous exudate of the synovium, necrosis and fibrosis of the joint cartilage, and fibrosis of the subchondral bone were the microscopic lesions observed in the stifle joints of dogs treated with SABER-placebo or SABER-bupivacaine. Both treatments resulted in comparable joint effects. Except for the fibrinous exudate on days 14 and 42, synovial lesions in the low and mid dose test article groups were similar in incidence, but less severe than those in the SABER-placebo and high dose groups. In addition, no microscopic lesions were present in the right stifle joint (non-injected) of any dogs except for the high dose group which was explained as due to shift in weight bearing resulting from dosed joint compensation.
- At day 14, joint cartilage necrosis was present in one SABER-placebo animal (moderate) and one high dose SABER-bupivacaine treated animal (marked), but not in the other two test article groups. Joint cartilage necrosis of marked severity was observed in all SABER-placebo and high dose SABER-bupivacaine dogs at 42 days after dosing.

7.2.4 Routine Clinical Testing

In most of the trials, clinical laboratory assessments were performed at baseline and at the end of the trial (usually study day 14); however, in trials BU-001-IM and BU-002-IM, laboratory assessments were also performed on postoperative Days 1, 2, and 3 in an effort to evaluate acute changes in blood chemistry, hematology.

Vital signs were the safety parameter most intensively monitored by the Applicant. Hourly measurements for up to 8 hours postoperatively, then daily on postoperative days 1-3, and at the end of study was the routine followed in most of the trials.

Three trials collected electrocardiography (ECG) data that were included in an integrated analysis of electrocardiographic parameters: Trials BU-001-IM, BU-002-IM, and C803-025. Each of these trials had the same three dose groups, collected electrocardiograms at defined time points, and had the electrocardiographic parameters analyzed at central ECG laboratories. For all three trials, the baseline ECG was taken pre-operatively (either pre-surgery or at the screening visit). The ECGs were done in triplicate and were done at frequent intervals over a 3 day period to cover the period of maximal systemic exposure to bupivacaine. Immediately after each of the scheduled ECGs, blood samples were collected and analyzed for bupivacaine. Trial C803-025

used continuous Holter monitoring to not only capture ECGs at the specified time points, but also to detect any arrhythmic events occurring between ECG recordings.

Given the long history of use of bupivacaine in the perioperative setting and the persistence of the SAIB moiety in the wound, the laboratory, vital sign and ECG assessments were adequate for evaluating the systemic safety of these components of the product, but only up to 6 months following its administration. The risks associated with the benzyl alcohol in the product can only be considered by comparing the findings for SABER-bupivacaine and SABER-placebo to those of treatment with bupivacaine HCl alone; however, the data for such comparisons is very limited.

Table 30 summarizes the safety parameters that were evaluated in each of the clinical trials.

Table 30. Summary of the safety assessments made in the clinical trials (Table 2, p. 11 of Section 2.7.4 of the NDA)

Trial	AEs	Concomitant Medication	Clinical Laboratory Evaluations	Vital Signs	Physical Exam	Wound Healing	ECGs	PK	Specific AEs Collected by Direct Questioning	Long-Term Follow-up	Other Assessments
CLIN005-0008	X	X	X	X	X		X	X			
CLIN004-0001	X	X	X	X	X	X		X			Bowel function
CLIN004-0009	X	X	X	X	X	X		X			Bowel function
CLIN005-0002	X	X	X	X	X	X	X	X	X[2]		Bowel function
CLIN005-0006	X	X	X	X	X	X		X	X[2]		Bowel function
CLIN005-0007	X	X	X	X	X	X		X	X[2]		Bowel function
CLIN005-0010	X	X	X	X	X	X			X[2]		Bowel function
CLIN-803-006-0006	X	X	X	X	X	X	X	X	X[2]	X	Bowel function
BU-001-IM	X	X	X	X	X	X	X[1]		X[3]	X	MRI
BU-002-IM	X	X	X	X	X	X	X[1]		X[3]	X	MRI
C803-017	X	X	X	X	X	X	X		X[4]		MRI
C803-017e	X	X				X	X			X	MRI
C803-025	X	X	X	X	X	X	X[1]				
C803-027	X	X	X	X	X	X	X	X			Punch biopsy and histopath-ology

[1] Trials that included more extensive investigations of cardiac safety, including triplicate ECGs for assessment of QTc, at fixed time points as described in the ISS.

[2] Trials that used the modified Brief Pain Inventory (mBPI) to elicit opioid-related AEs (nausea, vomiting, drowsiness, itching, constipation, dizziness, tinnitus, dysgeusia, and paresthesia)

[3] Trials that used direct questioning to elicit bupivacaine-related AEs (numbness of the tongue and mouth, light-headedness, tinnitus, visual disturbance, slurring of speech, muscular twitching, and irrational conversation)

[4] Trials used direct questioning to elicit bupivacaine-related AEs (ringing in the ears, metallic taste in the mouth, and numbness or tingling) and opioid-related adverse events (constipation, drowsiness, dizziness, nausea, vomiting, respiratory depression, and urinary retention)

7.2.5 Metabolic, Clearance, and Interaction Workup

The Applicant did not assess the metabolism, clearance, or drug-drug interactions for SABER-bupivacaine or any of its components. Although the metabolism, clearance and potential for drug-drug interactions of bupivacaine are well understood, no information was provided in the NDA for the benzyl alcohol, which is reported to rapidly diffuse from the drug product into the surrounding tissues, or for the SAIB, which based on animal studies persists for months, if not indefinitely, in the tissues.

The acute use of SABER-bupivacaine limits the exposure to benzyl alcohol such that the safety assessments performed by the Applicant will likely capture any untoward effects this component may have following one-time use of the product.

The persistence of SAIB in animal wounds for periods of up to 12 months raises the potential for safety issues in humans. Although histological changes consistent with a foreign body reaction occurred in the animals, there was no evidence of behavioral changes, macroscopic abnormalities, or defects in the healing processes. Therefore, the findings from the long-term, follow-up evaluations in the clinical trials, described and discussed in Section 7.3.5 below, take on greater weight in characterizing the risk profile for SABER-bupivacaine.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The adverse events of greatest concern for local anesthetics are related to the systemic exposure and include cardiac and central nervous system toxicity. The Applicant actively monitored patients for changes in cardiac rhythm during the 72 hours following administration of SABER-bupivacaine in an effort to characterize the cardiac risks. The Applicant was advised to proactively assess subjects for signs of neurotoxicity and to incorporate these assessments into study protocols; this advice was incorporated into several of the protocols by having subjects respond to a list of relevant questions in electronic diaries. Therefore, the safety data for neurotoxicity are derived from patient reported reactions and those reactions that were observed and recorded by the investigative staff. This approach would likely capture most of the neurotoxic reactions.

7.3 Major Safety Results

7.3.1 Deaths

The Applicant indicated that there were no deaths reported within the protocol-specified reporting periods; however, one subject died on postoperative Day 40 from surgical complications related to his laparoscopic hemicolectomy. The Applicant did not consider the death to be related to the study drug, SABER-bupivacaine.

The subject was an 82-year-old male patient (Patient (b) (6) in Trial C803-025), with a past medical history of Parkinson's disease, megacolon and constipation, who was treated with SABER-Bupivacaine 5 mL following a laparoscopic assisted colectomy (b) (6)) performed for "mega colon inversion." Postoperatively, the subject developed prolonged postoperative ileus and experienced a prolonged hospital course that was complicated by thrombophlebitis of the upper extremities, atrial fibrillation, renal failure, "neurological" deterioration, anemia, malnutrition, hyponatremia, hypocalcemia, metabolic acidosis, and hypotension. He died 40 days after surgery. The patient had a medical history significant for Parkinson's disease. The Investigator regarded the death as unrelated to study drug, and considered the outcome as most likely due to an intestinal motility disorder associated with Parkinson's disease.

Based on the information provided, the Applicant's conclusion that the death was unrelated to the study drug is supported and appropriate.

7.3.2 Nonfatal Serious Adverse Events

There were 74 treatment-emergent serious adverse events (SAEs), which are summarized in Table 31 below. The Applicant reported that, overall, the incidence of SAEs was about the same between the All SABER-Bupivacaine group and the two control groups and that most of the SAEs appeared to be related to complications of surgery, anesthesia, analgesics, or co-morbidity. About 11% of the SAEs occurred during the first hour after surgery, about 20% occurred from 1-72 hours after treatment, and the remaining 69% occurred >72 hours after treatment. Thus, they conclude that relatively few of the SAEs occurred during the Tmax of SABER-Bupivacaine. Their review of the SAEs occurring within 72 hours of SABER-bupivacaine led them to conclude that none of the cases appeared to be due to bupivacaine toxicity.

Over 50 of the SABER-Bupivacaine or bupivacaine HCl patients reporting SAEs also had PK measurements during the trial. The Applicant indicated that the Cmax data for

the treatment emergent SAE cases showed that the median Cmax was 730 [range: 52-1870] ng/mL. Eleven of the SAE cases had Cmax >1000 ng/mL, however all but one of the cases occurred well after the Tmax.

The SAE of chondropathy was reported in the follow-up shoulder surgery trial C803-017e. The diagnosis of degenerative cartilage disease was made by glenoid biopsy at a second surgery for revision acromioplasty about 15 months after the original surgery and treatment with SABER-bupivacaine. Three months later at the scheduled 18 month MRI, the chondral surfaces were described as unremarkable with no evidence of chondrolysis. This SAE is noteworthy because the Applicant reported that the drug product was not injected into the intra-articular space suggesting that seepage or diffusion of bupivacaine through the joint capsule may have occurred, if not an inadvertent intra-articular injection. The Applicant provided no alternative explanation for this SAE or a rationale for considering it to be unrelated to the SABER-bupivacaine. They did note that the event was an "unexpected medically important event of mild severity, with a possible relationship to SABER™–Bupivacaine."

Also of note among the SAEs are the occurrences of five cardiac SAEs in subjects treated with SABER-containing products compared to a single instance of supraventricular tachycardia that occurred in a subject treated with bupivacaine HCL. There were similar findings for SAEs potentially indicative of neurotoxicity, or possibly cardiac toxicity: five events of presyncopy, syncopy or unresponsiveness occurred with SABER-bupivacaine treatments; no such events occurred with bupivacaine HCL. A review of the narratives for these events indicated that the Applicant's rationale for these events not being related to the study drug were generally well supported, e.g., the availability of plasma bupivacaine levels less than 400 mcg/mL for two of the cases of syncope, and the spontaneous recovery from the other events moments after they began, while plasma bupivacaine levels would not have changed significantly. In all cases of syncope, cardiac etiology was ruled out, and none of the subjects had an ongoing cardiac ischemia or arrhythmia that would have reduced cardiac output causing the loss or near loss of consciousness. The spontaneous recoveries would also support the unlikely role of SABER-bupivacaine having a neurotoxic effect causing these episodes.

Lastly, it is worth noting the occurrence of SAEs associated with the area involved with the surgical procedures, specifically, the occurrence of the scrotal hematoma following inguinal hernia repair with SABER-bupivacaine (2.5 mL), the vaginal hematoma following SABER-bupivacaine (5 mL), the three cases of wound dehiscence – two following SABER-bupivacaine (5 mL) and one following SABER-placebo, and the single case of wound infection following SABER-bupivacaine (5 mL). While the incidence of each of these in the total population may appear low, when taken in the context of the individual procedure, it rises significantly, e.g., the vaginal hematoma incidence rises from < 1% to > 2%. More importantly from a safety perspective is that none of the subjects treated with bupivacaine HCl experienced one of these SAEs.

Table 31. Table of Serious Adverse Events (Based on Table 8.2, pp. 804-808 of ISS in the NDA)

System Organ Class /Preferred Term	SABER-Bupivacaine 2.5 mL (N=50)		SABER-Bupivacaine 5 mL (N=542)		SABER-Bupivacaine/ Bupivacaine HCl (N=91)		All SABER-Bupivacaine (N=683)		SABER-Placebo (N=268)		Bupivacaine HCl (N=124)	
	Subjects[1]	Events	Subjects[1]	Events	Subjects[1]	Events	Subjects[1]	Events	Subjects[1]	Events	Subjects[1]	Events
Subjects Reporting at Least One Adverse Event	6 (12%)	7	41 (8%)	47	2 (2%)	2	49 (7%)	56	18 (7%)	23	10 (8%)	14
Gastrointestinal disorders	1 (2%)	1	14 (3%)	14	0	0	15 (2%)	15	3 (1%)	4	1 (<1%)	2
Injury, poisoning and procedural complications	1 (2%)	2	5 (<1%)	6	0	0	6 (<1%)	8	3 (1%)	3	1 (<1%)	1
Wound dehiscence	0	0	2 (<1%)	2	0	0	2 (<1%)	2	1 (<1%)	1	0	0
Scrotal haematoma	1 (2%)	2	0	0	0	0	1 (<1%)	2	0	0	0	0
Nervous system disorders	1 (2%)	1	3 (<1%)	3	1 (1%)	1	5 (<1%)	5	2 (<1%)	2	1 (<1%)	1
Presyncope	1 (2%)	1	1 (<1%)	1	0	0	2 (<1%)	2	1 (<1%)	1	0	0
Syncope	0	0	2 (<1%)	2	0	0	2 (<1%)	2	1 (<1%)	1	0	0
Unresponsive to stimuli	0	0	0	0	1 (1%)	1	1 (<1%)	1	0	0	0	0
Tongue paralysis	0	0	0	0	0	0	0	0	0	0	1 (<1%)	1
General disorders and administration site conditions	0	0	3 (<1%)	3	1 (1%)	1	4 (<1%)	4	2 (<1%)	2	0	0
Application site discolouration	0	0	0	0	1 (1%)	1	1 (<1%)	1	1 (<1%)	1	0	0
Respiratory, thoracic and mediastinal disorders	0	0	4 (<1%)	5	0	0	4 (<1%)	5	0	0	3 (2%)	3
Infections and infestations	0	0	3 (<1%)	4	0	0	3 (<1%)	4	3 (1%)	3	4 (3%)	4
Postoperative wound infection	0	0	1 (<1%)	1	0	0	1 (<1%)	1	0	0	0	0

System Organ Class /Preferred Term	SABER-Bupivacaine 2.5 mL (N=50)		SABER-Bupivacaine 5 mL (N=542)		SABER-Bupivacaine/ Bupivacaine HCl (N=91)		All SABER-Bupivacaine (N=683)		SABER-Placebo (N=268)		Bupivacaine HCl (N=124)	
	Subjects[1]	Events	Subjects[1]	Events	Subjects[1]	Events	Subjects[1]	Events	Subjects[1]	Events	Subjects[1]	Events
Investigations	0	0	3 (<1%)	3	0	0	3 (<1%)	3	1 (<1%)	1	0	0
Electrocardiogram change	0	0	2 (<1%)	2	0	0	2 (<1%)	2	0	0	0	0
Electrocardiogram QT prolonged	0	0	1 (<1%)	1	0	0	1 (<1%)	1	0	0	0	0
Cardiac disorders	1 (2%)	1	1 (<1%)	1	0	0	2 (<1%)	2	4 (1%)	4	1 (<1%)	1
Acute coronary syndrome	1 (2%)	1	0	0	0	0	1 (<1%)	1	0	0	0	0
Acute myocardial infarction	0	0	1 (<1%)	1	0	0	1 (<1%)	1	0	0	0	0
Atrial fibrillation	0	0	0	0	0	0	0	0	1 (<1%)	1	0	0
Atrial flutter	0	0	0	0	0	0	0	0	1 (<1%)	1	0	0
Myocardial infarction	0	0	0	0	0	0	0	0	1 (<1%)	1	0	0
Myocardial ischaemia	0	0	0	0	0	0	0	0	1 (<1%)	1	0	0
Supraventricular tachycardia	0	0	0	0	0	0	0	0	0	0	1 (<1%)	1
Neoplasms benign, malignant and unspecified	1 (2%)	1	1 (<1%)	1	0	0	2 (<1%)	2	0	0	0	0
Reproductive system and breast disorders	0	0	2 (<1%)	2	0	0	2 (<1%)	2	1 (<1%)	1	0	0
Vaginal haematoma	0	0	2 (<1%)	2	0	0	2 (<1%)	2	0	0	0	0
Blood and lymphatic system disorders	0	0	1 (<1%)	1	0	0	1 (<1%)	1	1 (<1%)	1	0	0
Congenital, familial and genetic disorders	1 (2%)	1	0	0	0	0	1 (<1%)	1	0	0	0	0

System Organ Class /Preferred Term	SABER-Bupivacaine 2.5 mL (N=50)		SABER-Bupivacaine 5 mL (N=542)		SABER-Bupivacaine/ Bupivacaine HCl (N=91)		All SABER-Bupivacaine (N=683)		SABER-Placebo (N=268)		Bupivacaine HCl (N=124)	
	Subjects[1]	Events	Subjects[1]	Events	Subjects[1]	Events	Subjects[1]	Events	Subjects[1]	Events	Subjects[1]	Events
Musculoskeletal and connective tissue disorders	0	0	1 (<1%)	1	0	0	1 (<1%)	1	0	0	0	0
Chondropathy	0	0	1 (<1%)	1	0	0	1 (<1%)	1	0	0	0	0
Pregnancy, puerperium and perinatal conditions	0	0	1 (<1%)	1	0	0	1 (<1%)	1	0	0	1 (<1%)	1
Renal and urinary disorders	0	0	1 (<1%)	1	0	0	1 (<1%)	1	0	0	0	0
Vascular disorders	0	0	1 (<1%)	1	0	0	1 (<1%)	1	2 (<1%)	2	0	0
Psychiatric disorders	0	0	0	0	0	0	0	0	0	0	1 (<1%)	1

All SABER-Bupivacaine treatment group includes SABER-Bupivacaine 2.5 mL, SABER-Bupivacaine 5 mL and SABER-Bupivacaine/Bupivacaine HCl treatment groups

Table is sorted by descending total incidence of each system organ class in All SABER-Bupivacaine then by descending total incidence of each preferred term within each system organ class in All SABER-Bupivacaine.

[1] At each level of summation (overall, system organ class, preferred term), subjects reporting more than one adverse event are counted only once.

7.3.3 Dropouts and/or Discontinuations

The single-dose, intraoperative administration of the study drug precluded the discontinuation of study treatment due to an adverse event. However, three subjects withdrew from the study shortly after surgery due to adverse events:

1. Subject (b) (6) in the BU-001-IM trial was treated with SABER-Placebo and was withdrawn on study Day 1, because of severe abdominal pain.
2. Subject (b) (6) in the C803-025 trial, was treated with bupivacaine HCl and was withdrawn on study Day 3, because of dyspnea, hypoxia associated with pneumonia.
3. Subject (b) (6) in the C803-025 trial, was treated with SABER-Bupivacaine and was withdrawn on study Day 1 because of atelectasis.

All three cases were considered by the Investigators and Applicant to be unrelated to study drug.

In addition to the discontinuations due to adverse events, subjects discontinued the trials due to physicians' decisions, protocol violations, loss of follow-up, subjects' decisions, and "other" reasons. These subjects' dispositions are summarized in Table 32 below.

Table 32. Subject disposition for the safety population (Table 6, p. 24 of the ISS)

	SABER-Bupivacaine 2.5 mL	**SABER-Bupivacaine 5 mL**	**SABER-Bupivacaine/ Bupivacaine HCl**	**All SABER-Bupivacaine**	**SABER-Placebo**	**Bupivacaine HCl**
Subjects Randomized	51	560	91	702	277	130
Safety Population	50 (98.0%)	542 (96.8%)	91 (100.0%)	683 (97.3%)	268 (96.8%)	124 (95.4%)
Completed Trial						
Yes	48 (96.0%)	532 (98.2%)	89 (97.8%)	669 (98.0%)	261 (97.4%)	122 (98.4%)
No	2 (4.0%)	10 (1.8%)	2 (2.2%)	14 (2.0%)	7 (2.6%)	2 (1.6%)
Primary Reason for Discontinuation						
Adverse Event	0	1 (0.2%)	0	1 (0.1%)	1 (0.4%)	1 (0.8%)
Lost to Follow-up	0	4 (0.7%)	0	4 (0.6%)	1 (0.4%)	0
Physician Decision	0	0	0	0	1 (0.4%)	0
Protocol Violation	2 (4.0%)	0	1 (1.1%)	3 (0.4%)	0	0
Withdrawal by Subject	0	4 (0.7%)	1 (1.1%)	5 (0.7%)	3 (1.1%)	1 (0.8%)
Other	0	1 (0.2%)	0	1 (0.1%)	1 (0.4%)	0

Review's Comments
In total, 98% of the subjects completed the trials in which they participated. The 23 subjects that did not complete the trials were evenly distributed among treatment groups and among the reasons for discontinuation. Therefore, subject disposition did not suggest the safety findings would be biased or limited based on discontinuations from the trials.

7.3.4 Significant Adverse Events

Two other adverse events of importance were noted by the Applicant and warrant consideration. The following information provided verbatim from p. 33 of the final study report for C803-017e:

Chondrolysis was suspected on MRIs in two subjects ((b) (6) and (b) (6)). However, these events were not deemed AEs by the Investigators.

> Subject (b) (6), who received 5.0 mL SABER™-Bupivacaine in the C803-017 trial, on the Month 18 MRI (17 Dec 2010) had shown a full thickness tear of the supraspinatus tendon, superior labral tear, with no progression of chondral loss from the baseline exam. These were deemed not clinically significant by the investigator.
>
> Subject (b) (6), who received SABER™-Placebo in the C803-017 trial, underwent revision surgery between trials on (b) (6) due to lack of relief from Subacromial Impingement Syndrome. The original operation included bursectomy, debridement of labrum, glenhumeral joint inspection, removal of subcromial spurs, resection of coracoacromial ligament, and subacromial decompression. No additional injury had occurred following the original surgery and the repeat operation was considered unlikely related to SABER™-Placebo administered during the previous C803-017 trial. The Month 18 MRI (02 Apr 2011) showed evidence of repeat surgery with placement of 2 microscrews, partial thickness tear of the supraspinatus tendon, minor subacromial bursitis, humeral chondral defect with subchondral oedema, lateral subacromial spurring with narrowing of subacromial space. MRI findings, including suspected chondrolysis, were consistent with clinical observations of reduced passive range of motion, positive impingement sign, and pain.

Reviewer's Comments
These two events raise the concern that SABER may have a deleterious effect on connective tissues surrounding the joint capsule. Such a finding does not appear to be inconsistent with the findings in the dog study described in Section 7.2.3 above.

7.3.5 Submission Specific Primary Safety Concerns

The safety focus for this NDA was on two areas:

- risks associated with systemic exposure to bupivacaine, SAIB, and benzyl alcohol
- local toxicity related to each of these components of SABER-bupivacaine.

The Applicant did not specifically address the risks associated with SAIB or the benzyl alcohol, but did rigorously evaluate the risks for neurological and cardiac toxicity related to systemic bupivacaine exposure following the use of SABER-bupivacaine. There were no data to indicate that such toxicity occurred with the 5 mL dose when administered by various techniques following a variety of surgical procedures. There was also no evidence to suggest that dose dumping occurs with SABER-bupivacaine following its use in the same clinical settings.

The nonclinical data and some of the human subject data indicate that the SAIB remains intact where it was deposited for months following its administration. As such, its effects would likely occur only locally, and further concern for systemic toxicity is not warranted.

The benzyl alcohol from the SABER is absorbed over a period of 12-24 hours according to the Applicant. This represents a 1.1 g exposure over a 24 hour period, which far exceeds the exposure currently experienced by adult patients receiving intravenous medications that use benzyl alcohol as a preservative. The toxic reactions that might occur following intravenous benzyl alcohol have only been described for neonates, in whom toxicity is documented for exposures exceeding 100 mg/kg/d. For a 70 kg adult, the exposure to benzyl alcohol would be approximately 16 mg/kg/d; whether dose dumping would change the threshold is uncertain. Little is reported in the literature about the toxicity of benzyl alcohol in adults. That which is reported relates to contact reactions with cosmetics and pulmonary reactions related to the inhalation of benzyl alcohol containing saline solutions during nebulizer treatments. Based on the reaction of neonates to benzyl alcohol, the most common presenting symptoms and signs include metabolic acidosis, central nervous system depression, thrombocytopenia, hypotension, and respiratory distress.

The Applicant did not measure plasma or urine levels of benzyl alcohol, making an assessment of possible risk difficult, but it is striking that somnolence occurred in over

25% of subjects receiving SABER containing treatments but in only 6% of subjects treated with bupivacaine HCl. Similarly, dizziness occurs in 25% or more of subjects treated with SABER containing products but only in 9% of bupivacaine HCl treated subjects. The alternative causes would include bupivacaine toxicity, but that would not explain the findings occurring in the SABER-placebo treated subjects and would not be supported by the Cmax values reported for the majority of the subjects receiving SABER-bupivacaine. This risk bears further evaluation in future studies.

The local tissue effects of SABER-containing products and SABER-bupivacaine in particular were explored. The Applicant had combined a number of adverse events under the preferred term "application site discolouration," e.g., hematomas, suffusions (often used to describe hematomas), bruising, and erythema. For the purposes of this portion of the safety review, these events separated out for analysis.

The ISS database was reviewed and, in a treatment-blinded manner, any verbatim-term adverse events that were related to skin and that might possibly be related to study drug (in this reviewer's opinion) were identified and used to create a database for the analyses that follow. This database consisted of 925 adverse events from eight system organ classes. It consisted of adverse events that occurred during both the "main treatment" and "follow up" phases of the individual trials. Table 33 summarizes the AEs by treatment group.

Table 33. Skin related adverse events by treatment group

Adverse Event	SABER-Bupivacaine 2.5 mL	Saber-Bupivacaine 5 mL	SABER-bupivacaine* with Bupivacaine HCl	SABER-Placebo	Bupivacaine HCl
	N=50	N=547	N=82	N=268	N=124
Pruritus	14 (28%)	108 (20%)	5 (6%)	64 (24%)	6 (5%)
Hematomas and Suffusions	13 (26)	86 (16%)	23 (28%)	34 (13%)	3 (2%)
suffusions†		24 (4%)		7 (3%)	
hematomas†	13 (26)	62 (11%)	23 (28%)	27 (10%)	3 (2%)
Bruising	12 (24%)	67 (12%)	82 (100%)	15 (6%)	8 (6%)
Erythema	7 (14%)	42 (8%)	8 (10%)	16 (6%)	2 (2%)
Ecchymosis		42 (8%)		20 (7%)	1 (1%)
Discoloration		41 (7%)		26 (10%)	4 (3%)
Dehiscence		20 (4%)		5 (2%)	
Bleeding	1 (2%)	31 (6%)		7 (3%)	
Infection		22 (4%)	2 (2%)	7 (3%)	5 (4%)
Total	47 (94%)	459 (84%)	120 (146%)	194 (72%)	29 (23%)

* 71 with 7.5 mL of SABER-bupivacaine and 11 with 5 mL
† Suffusion was the term used to describe hematoma in trial.

The data in the table indicate that SABER-bupivacaine, and in some instances SABER-placebo, are associated with an increased incidence in adverse events at the surgical incision site compared to bupivacaine HCl. While most of the AEs resolved spontaneously, there were some instances where one AE led to another, e.g., a hematoma becoming infected, that compound the risk to the patient.

It is worth noting that some of the adverse events were reported more frequently following one surgical procedure compared to others. An example is hematomas. They occurred with greater frequency following hysterectomy than the arthroscopic shoulder surgeries, and as indicated in Table 34 below, the occurrence with the two SABER products is more striking than it is in the Table 33 where the AEs are lumped across trials.

Table 34. Hematoma adverse events following hysterectomy

Primary SOC / **Preferred term**	**SABER-bupivacaine N=60**		**SABER-placebo N=27**		**Bupivacaine HCL N=27**		**Total N=114**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Injury, Poisoning and Procedural Complications	38	(63.3)	9	(33.3)	0	0.0	47	(41.2)
Post-procedural hematoma	36	(60.0)	9	(33.3)	0	0.0	45	(39.5)
Wound complication	1	(1.7)	0	0.0	0	0.0	1	(0.9)

These data indicate that SABER-bupivacaine, and to a similar degree, SABER-placebo are associated with adverse reactions at the surgical site that put patients at increased risk for more serious complications, e.g., infection, and which can have a deleterious effect on the surgical outcome, e.g., need for surgical intervention to repair dehiscence or abnormal healing. As these events were seen to a lesser extent, if at all, with bupivacaine HCl treatment, they substantially affect the benefit:risk ratio in a negative manner.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

An adverse event table was created from the ISS dataset by first selecting those AEs that occurred in more than 1% of the population treated with SABER-bupivacaine 5 mL and by then eliminating those AEs where the incidence was lower for SABER-bupivacaine than for both bupivacaine HCl and SABER-placebo treatments or where there was no more than a 1% difference in the incidences between the SABER-bupivacaine and both bupivacaine HCl and SABER-placebo treatments. The results are listed in Table 35 below. The results are similar to those of the Applicant; however, they elected to use a 5% incidence for their cutoff.

Reviewer's Comments
This table highlights the safety concerns regarding adverse reactions involving the incision site. Specifically, the greater frequency with which application site discoloration (which includes hematomas), localized pruritus, contusion, incision site hemorrhage, wound dehiscence, and wound secretion occurred with SABER-bupivacaine treatment compared to bupivacaine HCl. Some of these events occurred more frequently with SABER-placebo treatment compared to bupivacaine treatment suggesting the SABER component plays a role in these reactions, i.e., application site discoloration, contusion, wound secretion, and pruritus.

The findings also highlight the need to better characterize the safety of the benzyl alcohol contained in SABER-bupivacaine as discussed in Section 7. Above.
Little is reported in the literature about the toxicity of benzyl alcohol in adults. That which is reported relates to contact reactions with cosmetics and pulmonary reactions related to the inhalation of benzyl alcohol containing saline solutions during nebulizer treatments. Based on the reaction of neonates to benzyl alcohol, the most common presenting symptoms and signs include metabolic acidosis, central nervous system depression, thrombocytopenia, hypotension, and respiratory distress.

The Applicant did not measure plasma or urine levels of benzyl alcohol, making an assessment of possible risk difficult, but it is striking that somnolence occurred in over 25% of subjects receiving SABER containing treatments but in only 6% of subjects treated with bupivacaine HCl. Similarly, dizziness occurs in 25% or more of subjects treated with SABER containing products but only in 9% of bupivacaine HCl treated subjects. The alternative causes would include bupivacaine toxicity, but that would not explain the findings occurring in the SABER-placebo treated subjects and would not be supported by the Cmax values reported for the majority of the subjects receiving SABER-bupivacaine. This risk bears further evaluation in future studies.

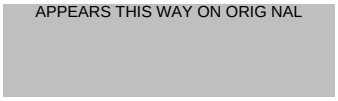

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Table 35. Adverse events with an incidence >1% with SABER-bupivacaine treatment and that exceed those with SABER-placebo and Bupivacaine HCl treatments by more than 1%

System Organ Class	Preferred Term	SABER-bupivacaine 2.5 mL (n=50)		SABER-bupivacaine 5 mL (n=542)		SABER-placebo (n=268)		Bupivacaine HCl (n=124)	
		n	%	n	%	n	%	n	%
Blood and lymphatic system disorders	Anemia	0	0%	28	5%	11	4%	4	3%
Cardiac disorders	Tachycardia	1	2%	20	4%	4	1%	8	6%
Ear and labyrinth disorders	Tinnitus	3	6%	34	6%	19	7%	3	2%
Gastrointestinal disorders	Abdominal pain	1	2%	23	4%	5	2%	2	2%
	Constipation	17	34%	140	26%	80	30%	15	12%
	Dyspepsia	1	2%	19	4%	8	3%	2	2%
	Gastro-esophageal reflux disease	1	2%	11	2%	1	0%	3	2%
	Nausea	18	36%	275	51%	141	53%	47	38%
	Vomiting	5	10%	106	20%	45	17%	18	15%
General disorders and administration site conditions	Application site discoloration	17	34%	221	41%	87	32%	15	12%
	Fatigue	0	0%	12	2%	5	2%	5	4%
Infections and infestations	Postoperative wound infection	2	4%	18	3%	2	1%	4	3%
Injury, poisoning and procedural complications	Contusion	2	4%	15	3%	1	0%	0	0%
	Incision site haemorrhage	0	0%	27	5%	4	1%	0	0%
	Wound dehiscence	0	0%	18	3%	4	1%	0	0%
	Wound secretion	2	4%	23	4%	10	4%	3	2%

System Organ Class	Preferred Term	SABER-bupivacaine 2.5 mL (n=50)		SABER-bupivacaine 5 mL (n=542)		SABER-placebo (n=268)		Bupivacaine HCl (n=124)	
		n	%	n	%	n	%	n	%
Metabolism and nutrition disorders	Hypokalemia	0	0%	25	5%	14	5%	2	2%
Nervous system disorders	Dizziness	15	30%	133	25%	79	29%	11	9%
	Dysgeusia	6	12%	37	7%	29	11%	1	1%
	Headache	17	34%	102	19%	48	18%	11	9%
	Hypoesthesia	4	8%	29	5%	23	9%	1	1%
	Paresthesia	10	20%	42	8%	23	9%	3	2%
	Somnolence	21	42%	140	26%	100	37%	7	6%
Psychiatric disorders	Insomnia	1	2%	26	5%	9	3%	6	5%
Renal and urinary disorders	Dysuria	0	0%	15	3%	7	3%	0	0%
	Urinary retention	1	2%	17	3%	7	3%	1	1%
Respiratory, thoracic and mediastinal disorders	Dyspnea	0	0%	14	3%	2	1%	6	5%
	Oropharyngeal pain	0	0%	17	3%	4	1%	1	1%
Skin and subcutaneous tissue disorders	Pruritus	14	28%	93	17%	57	21%	4	3%
	Pruritus generalized	0	0%	9	2%	1	0%	1	1%
Vascular disorders	Hypotension	3	6%	22	4%	12	4%	2	2%

7.4.2 Laboratory Findings

Hematology
For most of the trials, hematology assessments were performed at baseline and at the end of the trial, usually study day 14. In trials BU-001-IM and BU-002-IM, hematology measurements were also made on postoperative Days 1, 2, and 3, providing some data for acute changes.

In Pooled Group A, i.e., the initial treatment period, the Applicant reported that the expected acute (i.e., days 1-3) postoperative changes from baseline in hematologic parameters occurred in all study groups, with no consistent differences between treatment groups. The changes included:

1. An acute reactive leukocytosis that was mostly due to an increase in neutrophils.
2. A small acute decrease in lymphocytes, but little change in monocytes, eosinophils or basophils.
3. An acute decrease in platelet count on postoperative Days 1-3, but by the end of the trial there was an increase over baseline, with no difference between treatment groups.
4. All of the red cell parameters showed an acute drop on postoperative Days 1-3, with no consistent differences between treatment groups.
5. The mean hematocrit (HCT) decreased acutely by about 3 percentage points, whereas the mean hemoglobin (HgB) decreased acutely by about 1 g/dL. By the final measurement, the acute drop had recovered by about 50%, but was still below baseline.
6. There was a mean decrease in hemoglobin levels of about 1g/dL after surgery, and there were outliers in all treatment groups with a decrease from baseline of 3 to 4 g/dL.
7. A total of 19 patients received one or more transfusions of packed red blood cells (RBC) in either the BU-001-IM hysterectomy trial or the C803-025 abdominal surgery trial. About half of the transfusions were for preexisting anemia and five transfusions were given prior to treatment with study drug. The other transfusions were for surgical blood loss or postoperative anemia. There did not appear to be any imbalance in transfusions between treatment groups. RBC transfusions were given to 5 patients in the bupivacaine HCl group(4.0%), to 11 patients in the All SABER-Bupivacaine group (1.7%), and to 3 patients in the SABER-Placebo group (1.1%).

The Applicant noted that the shifts from baseline generally mirrored the changes noted above with little difference between treatment groups.

Reviewer's Comments
Based on a review of the data, the Applicant has accurately described the results. There did not appear to be any clinically relevant changes to hematology parameters

associated with the use of SABER-bupivacaine. Hemolysis was not reported for any of the SABER treatment groups; a concern based on in vitro mixing of SABER-bupivacaine and blood. It should be noted that the acute changes, i.e., those base on postoperative days 1-3, were derived from a safety database that consisted of 121 subjects treated with SABER-bupivacaine, 52 subjects treated with SABER-placebo, and 56 subjects treated with bupivacaine HCl, which may limit the ability to discern treatment-related differences in the laboratory parameters.

Chemistry

The Applicant reported that a number of chemistry parameters showed the acute changes, but the changes were about the same across treatment groups, and there was no indication of toxicity from bupivacaine or the SABER formulation. They attributed the changes to the stress, blood loss, and reduced nutrition of the immediate postoperative period. Specifically, they reported the following findings:

1. There were acute decreases in BUN, potassium, total cholesterol, and triglycerides in the first three post-operative days. Many of the acute changes had normalized by the end of the trial.
2. Albumin had decreased by 0.2 g/dL at the end of the trial, with little difference between treatment groups.
3. There were no consistent increases in ALT, AST, Bilirubin, creatine, LDH, CK, or uric acid indicative of treatment-related organ injury.
4. With the exception of acute decreases in potassium of about -0.3 mEq/L in all groups, all other electrolytes did not change appreciably in the postoperative period. Glucose increased acutely by about 13 – 20 mg/dL, but by the end of the trial the glucose had normalized. About 14% of patients had abnormally elevated glucose at the baseline determination. Two of the trials (BU-001-IM and BU-002-IM) included the measurement of C-reactive protein (CRP). The levels rose acutely on postoperative Days 1 and 2 and then rapidly returned to normal by the end of the trial. This is the expected pattern and timing of CRP increase and decline after surgery (Cole et al 2008). A review of the laboratory SAS file (ADLB) revealed treatment emergent clinically significant outliers in most of the analytes. The outliers were almost all from the major abdominal surgery trial C803-025 with no apparent imbalance between treatment groups. The outliers were appropriately documented as TEAE in the Investigations SOC. Two patients had significant treatment emergent liver function test abnormalities at the final visit. Patient (b) (6) in the CLIN005-0010 hernia trial had elevated AST, ALT, and LDH (1116, 1083, and 700 U/L) which were considered not treatment related and had all normalized one month later. Patient (b) (6) in the C803-027 abdominal surgery trial had elevated ALT, AST, and Alkaline Phosphatase (660, 308, 203 U/L). Other laboratory tests were normal and no apparent etiology was established. Three patients had creatinine values between 2.0 and 2.3 mg/dL at trial entry. Patient (b) (6) in the C803-025 trial had an increase in creatinine from 0.8 to 2.0 mg/dL at the final visit.

Reviewer's Comments
There did not appear to be any clinically relevant differences between SABER-placebo and SABER-bupivacaine treatments suggesting adverse reactions related to bupivacaine release from the product or between SABER-bupivacaine and bupivacaine HCl suggesting adverse reactions related to a component of SABER, i.e., the SAIB or the benzyl alcohol.

7.4.3 Vital Signs

Vital signs were the safety parameter most frequently monitored by the Applicant, with hourly measurements up to 8 hours following the surgical procedure, then daily on Days 1-3, and at the end of study, usually on Day 14.

The Applicant reports that the systolic blood pressure (SBP) was highly variable at baseline, with values ranging from 70 to 198 mmHg, and that, in general, SBP increased by around 5-15 mmHg in the first few hours after surgery. However, there were also some hypotensive values and a few values in excess of 200 mmHg. By Days 1-3 after surgery, the min-max values were less extreme and the median changes from baseline were in the range of -4 to 11 mmHg. SABER-Placebo often had the higher increases from baseline and bupivacaine HCl had the lowest increases in SBP.

The Applicant noted that the diastolic blood pressure (DBP) tended to mirror the SBP. At baseline there were a few extreme values ranging from 23 to 118 mmHg. In the first few hours after surgery, the DBP increased about 0-10 mmHg. By postoperative Days 1-3, the median increase from baseline was only a few mmHg, often with SABER-Placebo having the highest increase and bupivacaine HCl having the lowest increase from baseline.

Heart rate (HR) at baseline had a few extreme values ranging from 41 to 120 beats per minute (bpm). Extreme values in HR were recorded throughout the observation period, but during the first few hours after surgery there was a small increase of a few bpm among the treatment groups. On postoperative Days 1-3 the increase in HR compared to baseline ranged from 3-8 bpm often with bupivacaine HCl having a somewhat lower change from baseline. The lowest HR was measured in a subject treated with 2.5 mL SABER-Bupivacaine in the pivotal hernia trial. There was no mention of bradycardia and the subject was not reported to have had any cardiac or vascular adverse events. The highest HR was from a subject who was treated with bupivacaine HCl in the C808-025 trial. He had an episode of apnea and supraventricular tachycardia that were considered by the Applicant as likely due to a Dilaudid overdose. After treatment with naloxone, he recovered without further episodes of tachycardia.

The baseline respiratory rate ranged from 4-55 breaths per minute; however, fewer extreme values were recorded postoperatively. In the first hours following surgery, there was a small increase in respiratory rate of about 1-2 breaths per minute; by postoperative Days 1-3, the increase in respiratory rate was about 0-2 breaths per minute, with no evidence of, what the Applicant termed, "extreme" hyperpnea. In the immediate post-dose period there was a minimum respiration rate of 0 reported in a subject treated with SABER-Bupivacaine 5 mL (subject # (b) (6). It was noted that the subject had normal respiratory rate thereafter, and did not have any respiratory system adverse events. In the SABER-Placebo group, there was a minimum respiratory rate of 3 in the immediate post-dose period (subject # (b) (6) (b) (6)) in a subject who had normal respiratory rate thereafter and did not have any respiratory system adverse events. The Applicant noted that the two subjects who did report AEs of apnea (# (b) (6) treated with bupivacaine HCl, and (b) (6) treated with SABER-bupivacaine 5 mL) both had minimum respiratory rates of 8 at the time of the event.

Body temperature at baseline ranged from 30.9 to 38.1°C. There were few extreme changes from baseline during the early postoperative hours, but by postoperative Days 1-3 there were a few maximum temperatures ranging from 38.3 to 40.0°C, with median increases in temperature ranging from 0.1 to 0.9°C. The Applicant indicated that there were no obvious differences across treatment groups.

Reviewer's Comments
As suggested by the Applicant's reporting of the vital sign findings, there did not appear to be any safety signals based on the protocol mandated vital sign assessments. It is interesting to note that the increases in blood pressure observed with SABER-placebo suggest a lack of efficacy for the study drug -- as would be expected. The postoperative decreases in blood pressure, suggesting less pain during the period, were observed with bupivacaine HCl more so than SABER-bupivacaine, suggesting bupivacaine HCl is the more efficacious of the two products.

7.4.4 Electrocardiograms (ECGs)

The Division emphasized the need to adequately assess the cardiac risks associated with systemic exposures to bupivacaine following the administration of SABER-bupivacaine. The Applicant made the following assessments to evaluate and characterize those risks.

The three trials with SABER-placebo and bupivacaine HCl control arms were used in the integrated ECG analysis. This resulted in a 526 subject database. All ECGs were done in triplicate and were done at multiple intervals over a 3 day period to cover the

period of Tmax. Immediately after each of the scheduled ECGs, blood samples were collected to determine plasma bupivacaine concentrations for the purpose of concentration-effect modeling. All electrocardiograms were read centrally. In addition, trial C803-025 used continuous Holter monitoring to detect any pro-arrhythmic events. The dose and method of administration of the SABER-Bupivacaine, i.e., instillation directly into the surgical wound, proposed for marketing were used in these studies. Supra-therapeutic doses were not assessed, but the plasma concentrations attained were considered by the Applicant as representative of those expected in clinical practice and included values over 2000 ng/mL. The incisions studied ranged from a few centimeters in the arthroscopic and laparoscopic procedures to over 30 cm in open laparotomy thereby assessing the risk for SABER-bupivacaine use in a variety of incisions with differing vascularity producing a range of Tmax and Cmax values. The data obtained provide an assessment of the effects of SABER-bupivacaine on heart rate, cardiac conduction, and repolarization.

The mean ECG parameters were comparable between the three treatment groups. Most of the mean parameters were reported by the Applicant to be within the normal range, although the QRS interval in the SABER-Bupivacaine group was slightly longer than the normal range, 101 msec. For all three treatment groups, heart rate increased with mean values of 6 bpm for the SABER treatments and 3 bpm for bupivacaine HCl treatment over the 72 hours following surgery. The RR and PR intervals showed a reciprocal decrease from baseline with little difference between the treatment groups. There was little change in the QRS interval from baseline values. The QT interval decreased, the QTcF was unchanged, and the QTcB intervals increased from baseline which was reported to be consistent with the increased heart rate.

All treatment groups were reported to have a double-digit increase in ΔQTcF in the immediate postoperative recovery period (1 to 4 hours), which was followed by a sustained decrease over the next 72 hours, resulting in a time-averaged ΔQTcF close to zero. The initial increase in ΔQTcF in the first few hours after surgery was attributed by the Applicant to the autonomic effects of surgery and anesthesia, as it was observed with all three treatments.

The placebo-corrected change in QTcF from baseline (ΔΔQTcF) was determined using data from the time points common to all three pooled trials. Based on the analysis, the Applicant concluded that there was no signal of QTcF prolongation at any time point, and that no upper 90% confidence interval (UCI) exceeded 10 msec.

An analysis of ECG outliers in the three pooled trials was conducted by the Applicant. The results are summarized in Table 44.
There is a greater incidence of tachycardia outliers than bradycardia outliers during the postoperative period, with the SABER-Bupivacaine group having a higher incidence of tachycardia, whereas bupivacaine HCl had a higher incidence of bradycardia; a finding that was consistent with the overall increase in heart rate from baseline. Outliers for

increased PR or QRS intervals were uncommon and showed little relationship to treatment group. About 2% of the patient population had QT intervals that exceeded 500 msec, and no relation to treatment group was apparent. There were four patients in the SABER-Bupivacaine group and one in the bupivacaine HCl group with one or more QTcF measurements >500 msec. All of the QTcF outliers >500 msec occurred within the first 4 hours post-dosing and the corresponding bupivacaine plasma concentrations ranged from 49 to 412 ng/mL. It was observed that all of the patients with QTcF >500 msec also had abnormally high baseline QTcF, ranging from 448 to 484 msec. The proportion of patients who had an increase in QTcF of >60 msec from baseline was higher in the SABER-Bupivacaine and the SABER-Placebo groups compared to the bupivacaine HCl group.

The pooled PK data for trials BU-001-IM, BU-002-IM, and C803-025 were used to statistically model the relationship between bupivacaine plasma concentration and ΔQTcF. Common slope analyses were performed to confirm if the slope was comparable across studies. A linear mixed effect model with a random intercept and slope including time-matched bupivacaine plasma concentration as a fixed effect and subject as a random effect was used. It was found that only trials C803-025 and BU-001-IM had a common slope, so trial BU-002-IM was modeled separately. The modeling data for the pooled trials C803-025 and BU-001-IM showed a small negative slope for the SABER-Bupivacaine group and a small positive slope for the bupivacaine HCl group, both of which were significantly different from zero indicating that the change in QTcF decreases when the plasma bupivacaine concentration is higher for the SABER-Bupivacaine group. For the individually modeled trial (BU-002-IM) the slope for the SABER-Bupivacaine group was slightly positive, but not substantially different from zero indicating that the QTc change does not depend on the bupivacaine concentration. The slope for the bupivacaine HCl group was significantly positive. The overall result was that the estimated QTcF changes at Cmax for SABER-bupivacaine were -9 msec and -4 msec for trails C803-025/BU-001 and BU-002, respectively. The estimated QTcF changes at Cmax for bupivacaine HCl were 7 msec and 5 msec for trails C803-025/BU-001 and BU-002, respectively.

In addition to the standard analyses of pooled ECG data, the Applicant collected Holter monitoring data in trial C803-025. The data were analyzed for the presence of pro-arrhythmic events using standard diagnostic software. Comparison of the baseline data taken while the subject was at rest in the supine position with the on-treatment data was reported by the Applicant to show no clear evidence of clinically significant induction of supraventricular or ventricular arrhythmias.

Reviewer's Comments
Overall, the ECG data indicated that no clinically relevant cardiac morphological changes were likely to occur with the proposed instillation of 5 mL of SABER-bupivacaine based on the lack of clinically relevant differences observed when the changes were compared to those of SABER-placebo and bupivacaine HCl.

7.4.5 Special Safety Studies/Clinical Trials

Study C803-027, "Open-Label, Histological Evaluation of Surgical Wounds in Subjects Treated with SABER®-Bupivacaine," was conducted to characterize the surgical wound healing, appearance, and histology of peri-incisional discoloration that followed administration of SABER-Bupivacaine in 10 subjects undergoing general abdominal surgery. In this study, the entire 5 mL dose was instilled into the incision, i.e., none into the laparoscopic port wounds.

Application site discoloration was observed in all 10 subjects, although the discoloration for one subject was inadvertently not recorded as an AE. No intervention was required and all cases of discoloration completely resolved over a period of several weeks with no sequelae. It was noted that all subjects were treated with antithrombotic agents for DVT prophylaxis and it is possible that inhibition of hemostasis by these agents may have contributed to the postoperative bruising that most likely underlies the wound discoloration. [Note: The aPTT values were, per the Applicant, "generally within the normal range and as expected did not show any prolongation due to treatment with enoxaparin." One subject was noted to have an increase from 31.7 sec preoperatively to 41.1 sec on postoperative day 1.

Mild, self-limited bleeding from the incision(s) was reported in five subjects. No action other than dressing changes was needed. Cutaneous wound dehiscence was reported in 5/10 subjects (all four of the open laparotomy subjects and one laparoscopy subject). Most of the cases of dehiscence occurred late (post-operative days 12-36) and were due to stitches pulling out of the skin at the inferior end of the incision. No surgical repair was necessary and local wound care allowed all of the cases of dehiscence to heal normally. No surgical wound infections were reported.

From the Structured Wound Healing Questionnaire administered on Day 30, it was found most of the incisional pain had resolved, but three subjects still had limitations due to incisional discomfort. One subject still had a small amount of bruising around the incision, 4 subjects had dehiscence, and 4 subjects had some drainage from the incision. There were no ER visits, hospitalizations, or surgical procedures required for wound complications.

Histological examination of punch biopsy specimens obtained from the area of maximal discoloration did not show any pathological findings.

Without a comparator treatment arm and with only 10 subjects, it is difficult to draw safety conclusions from this study. It is interesting to note that the rate of dehiscence in this study was similar to that in its predecessor, C803-025, and exceeded rates cited in the literature for gastroenterological procedures. This study reinforced the findings of

C803-025 for postoperative wound drainage and dehiscence. While these adverse events did not appear to negatively affect the subjects' recovery, they do raise concern for the risks associated with incomplete closure of the incision and with drainage of serosanguinous fluids, in particular, the risk for wound infection. This study is reviewed in more detail in Section 9.4.9 below.

7.4.6 Immunogenicity

SABER-bupivacaine is a small molecule drug product and would not be expected to be immunogenic. No immunogenicity issues related to the use of SABER-bupivacaine were identified during the nonclinical and the clinical development programs.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The clinical development program included trials that had 2.5 and 7.5 mL doses of SABER-bupivacaine administered to subjects. The Applicant ceased using the 7.5 mL doses when the Division expressed concern over the lack of nonclinical data to support the use of this dose. At that point, 4 subjects had been exposed to that volume of SABER-bupivacaine alone; 71 subjects had been exposed to the 7.5 mL dose of SABER-bupivacaine but in conjunction with 50 or 75 mg doses of bupivacaine HCl. A total of 50 subjects were exposed to the 2.5 mL dose of SABER-bupivacaine. Given the limited exposures to both a lower and higher dose, it is not possible to evaluate any of the adverse events for dose dependency. The Applicant made no statements regarding dose dependence for the treatment emergent adverse events observed in the clinical trials.

7.5.2 Time Dependency for Adverse Events

The adverse events were monitored over two different periods: immediate, i.e., from time of study drug administration to the “end of the trial,” generally 14 days, and long-term, i.e., a one- or two-time follow-up visit with the last visit at 6 or 18 months following surgery. Most of the AEs occurred within the first few days of study drug administration, as would be expected based on the duration of release of bupivacaine and benzyl alcohol. AEs related to the persistence of SAIB at the instillation site or to slowly developing reactions to bupivacaine, e.g., chondrolysis, can take weeks to months to develop. The 6-month follow-up was possibly too soon to pick up some reactions, notably, chondrolysis, but the 18-month follow-up should have been adequate. The limited number of subjects who underwent long-term follow-up is a short coming the clinical development program, but it does provide some valuable information.

7.5.3 Drug-Demographic Interactions

The Applicant performed subgroup analyses on the Pooled Group A and B safety data. Treatment-Emergent Adverse Events (TEAEs) during the main treatment and follow-up periods were summarized by age, gender, race, Body Mass Index (BMI), surgery type, and geographical region (US vs. Ex-US). The results of the analyses are summarized in Table 36 below.

Table 36. Summary of treatment emergent adverse events by subgroups (Table 31, p. 70 of the ISS)

Subgroup	All SABER-Bupivacaine (N=652)		SABER-Placebo (N=268)		Bupivacaine HCl (N=124)	
	N	n (%)	N	n (%)	N	n (%)
≤65 years	573	506 (88%)	225	205 (91%)	116	94 (81%)
>65 years	79	76 (96%)	43	40 (93%)	8	7 (88%)
Male	388	355 (91%)	161	147 (91%)	56	47 (84%)
Female	264	227 (86%)	107	98 (92%)	68	54 (79%)
White	606	540 (89%)	250	227 (91%)	119	96 (81%)
Non-White	43	40 (93%)	18	18 (100%)	5	5 (100%)
BMI ≤25	199	177 (89%)	86	79 (92%)	40	31 (78%)
BMI >25	451	404 (90%)	182	166 (91%)	84	70 (83%)
Orthopedic	152	113 (74%)	89	73 (82%)	29	11 (38%)
Hernia	237	221 (93%)	67	65 (97%)	30	29 (97%)
Abdominal	263	248 (94%)	112	107 (96%)	65	61 (94%)
US Sites	244	238 (98%)	133	132 (99%)	29	28 (97%)
Ex-US Sites	408	344 (84%)	135	113 (84%)	95	73 (77%)

The >65 year subgroup had a consistently higher TEAE frequency than the ≤65 year subgroup. The Applicant did not include that bupivacaine HCl treatment group in this analysis due to the small number of subjects > 65 years old. For many of the system organ class (SOC) categories, the >65 year subgroup has a higher frequency of AE compared to the ≤65 year subgroup. The Applicant attributed this to several factors:

- More of the older patients underwent major abdominal surgery.
- The older patients have less physiological reserve for surgical stress.
- Older patients have a higher burden of co-morbidity.

In the Nervous system SOC, the >65 year subgroup had a lower incidence than the ≤65 year subgroup. This was attributed to the two shoulder studies (C803-017 and CLIN005-0006) where the majority of the patients was under 65 years and had reported a relatively high rate of Nervous system AEs perhaps more readily captured by AE checklists that were used. There was not a great disparity between the subgroups for the Cardiac disorders. It was noted that the older subjects tended to have higher bupivacaine concentrations, attributed to reduced clearance, but the Applicant noted that most of the increased AEs for the subgroup did not appear to be related to bupivacaine.

The consistently lower TEAE frequency in the Ex-US sites compared to US sites, was considered by the Applicant as possibly due to a cultural reluctance of patients to report AEs.

The Applicant's rationale for the differences in TEAEs based on age has merit. It is not clear that the differences in US and ex-US can be so readily explained. Perhaps more importantly, it should be noted that for the both age groups, both genders, both BMI groups, white race, and ex-US sites, there was a slightly lower incidence of TEAEs with bupivacaine HCl treatment than with either SABER-bupivacaine or SABER-placebo treatments. There was no difference among the treatments for non-white race, US sites and surgical procedure with the exception of orthopedic, i.e., arthroscopic shoulder surgeries, where the incidence of TEAEs was half that of the two SABER products. These data suggest an overall increase in risk for a TEAE with a SABER treatment compared to bupivacaine HCl.

Also worth noting is that the difference in TEAEs between arthroscopic shoulder surgery and the other types was due to differences in the rates of application site discoloration, wound secretion, incision site hemorrhage, dehiscence, infection, bradycardia, tachycardia, hypokalemia, and anemia. The anemia and hypokalemia were associated with the abdominal procedures and were not unexpected. All but one case of bradycardia occurred with herniorrhaphy, and most of the cases of tachycardia occurred with abdominal procedures. The preponderance of incision site TEAEs occurring with the non-arthroscopic procedures is likely due to the differences in incision lengths.

7.5.4 Drug-Disease Interactions

The Applicant performed no analysis of possible drug-disease interactions for SABER-bupivacaine. In their proposed labeling, the use the same wording as found in the Marcaine label for use in patients with hepatic and renal impairment.

As most of the patients who were enrolled in the clinical trials were relatively healthy, the impact of any given disease or comorbidity on the risks associated with SABER-bupivacaine, and vice versa, are not known. It is appropriate to note the potential risks related to renal and hepatic impairment and emphasize the greater systemic exposures to bupivacaine that occur with SABER-bupivacaine compare to bupivacaine HCl formulations.

7.5.5 Drug-Drug Interactions

There were no formal drug-drug interaction (DDI) studies conducted with SABER-Bupivacaine.

The Applicant noted that the labeling for approved bupivacaine HCl products warns against the use of bupivacaine in combination with:

- other local anesthetics because of the possibility of additive pharmacodynamic effects
- certain antiarrhythmic drugs due to possible additive effects on cardiac ion channels

The Applicant also noted that some of the labeled DDI precautions are for epinephrine-containing formulations, which they state will not apply to SABER-bupivacaine because it is not formulated with any epinephrine, and there is no need to use epinephrine with it due to it long acting effects related to the SAIB excipient..

The Applicant also noted that there have been published studies of the pharmacokinetic DDI with bupivacaine. These included the effects of cimetidine, a weak CYP3A4 inhibitor, on bupivacaine plasma concentration, which have produced conflicting results, i.e., either no effect or a small increase in bupivacaine AUC. The azole-antifungal drugs are much more potent inhibitors of CYP3A4, the main route of bupivacaine metabolism, but these have not been demonstrated to have DDI with other medications used in hospitalized patients, and therefore, the Applicant postulates, would not likely have a significant impact on plasma bupivacaine levels following SABER-bupivacaine administration.

Reviewer's Comments
Given the lack of formal DDI studies involving SABER-bupivacaine and the substantially higher systemic levels of bupivacaine that it produced in the clinical trials, compared to bupivacaine HCl, the labeling for SABER-bupivacaine, if it is approved, should reflect the DDI found in similar bupivacaine products, most notably Exparel. Specifically, along with the cautionary statement that DDIs may occur, the label should inform clinicians that the higher exposures to bupivacaine with SABER-bupivacaine, compared to bupivacaine HCl, may put subjects at increased risk for the occurrence and severity of these interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

SABER-bupivacaine is intended as an acute use product; therefore, evaluation of its carcinogenicity potential was not required and is not necessary to fully assess the product's safety.

7.6.2 Human Reproduction and Pregnancy Data

Exparel was not evaluated for use in pregnant subjects, and at present, its use in this population cannot be recommended. Until further information is available, the Pregnancy Category section of the SABER-bupivacaine label should be the same as that for bupivacaine HCl.

7.6.3 Pediatrics and Assessment of Effects on Growth

SABER-bupivacaine was not administered to pediatric subjects during the clinical development program. Based on the proposed acute indication for SABER-bupivacaine, it is not anticipated that it would have an adverse effect on growth.

The Applicant has requested that a waiver be granted for the study of SABER-bupivacaine in pre-term and term newborn infants up to 3 years of age due to the concerns for benzyl alcohol toxicity and a waiver for children up to 3 years of age due to risk of systemic accumulation of bupivacaine due to its diminished clearance.

Regarding the risk for benzyl alcohol toxicity, SABER-bupivacaine contains 242 mg/mL of benzyl alcohol as a solvent for the bupivacaine base and to reduce the viscosity of SAIB to allow its instillation into surgical wounds. In adults, the benzyl alcohol in the SABER-bupivacaine formulation rapidly diffuses into the surrounding tissues and is systemically absorbed and cleared from plasma over a 12-24 hour period. One of the clinical trials indicated that instillation of SABER-bupivacaine in surgical wounds following hysterectomy resulted in maximum concentrations of benzyl alcohol occurring in an hour or less. The mean Cmax was 0.39 (minimum-maximum: 0.06-1.1) mg/L. The rapid release of benzyl alcohol from SABER-Bupivacaine is not expected to differ between adults and children; however, its clearance and that of its metabolite, benzoic acid, has been shown to be greatly reduced in the neonate due to reduced hepatic

functioning that cannot conjugate benzoic acid with glycine to produce hippuric acid, which is excreted by the kidney. The result is an accumulation of benzoic acid that can lead to gasping syndrome and death.

The Applicant also noted that the European Commission guidelines on excipient labelling for products which can deliver 90 mg/kg/day of benzyl alcohol states that such products "must not be given to premature babies or neonates. Due to the risk of fatal toxic reactions arising from exposure to benzyl alcohol in excess of 90 mg/kg/day, this product should not be used in infants and children up to 3 years old." [European Commission, Vol. 3B, Guidelines, Excipients in the label and package leaflet of medicinal products for human use, 2003; pages 6-7.]

Regarding the risk for systemic accumulation of bupivacaine due to reduced clearance, there is evidence in the literature for reduced plasma protein binding and reduced hepatic metabolism of bupivacaine for pediatric patients less than a year of age compared to adults and older children. The evidence, however, is limited in terms of the numbers of studies conducted and the number of subjects evaluated in the studies, and the data are not sufficient to indicate an age at which pediatric subjects would be able to safely tolerate exposures to bupivacaine that would likely occur with SABER-bupivacaine treatment.

Reviewer's comments
The Applicant's rationale for not evaluating the safety or efficacy of SABER-bupivacaine in pediatric subjects less than 3 years of age is well founded. It is, therefore, recommended that this waiver be granted and that the label be modified to reflect this safety concern, i.e., the product should be contraindicated for use in patients less than 3 years of age out of concern for benzyl alcohol toxicity and the risk of toxicity from systemic accumulation of bupivacaine.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The potential for overdose with SABER-bupivacaine exists if the drug is administered intravascularly, if more than 5 mL of the product is instilled in the surgical sites evaluated in the clinical development program, and potentially, if the product is instilled in surgical sites not evaluated in the clinical development program if the release of bupivacaine from the product is increased due to the environmental conditions (e.g., temperature, pH, and vascularity of the surrounding tissues) at those sites.

Bupivacaine, the active ingredient of SABER-bupivacaine, is not associated with any abuse potential; therefore, the risk of abuse with SABER-bupivacaine is expected to be equally as low.

SABER-bupivacaine is intended for single dose application; therefore, withdrawal and rebound are not issues of concern for the product.

7.7 Additional Submissions / Safety Issues

There are no additional safety issues.

The Applicant submitted a 120-day safety update at th.

8 Postmarket Experience

SABER-bupivacaine is not currently marketed in the United States or elsewhere in the world.

9 Appendices

9.1 Literature Review/References

The Applicant did not submit a comprehensive literature review as part of this NDA. Such a review was not requested or required by the Division. Publications cited by the Applicant in their Clinical Overview, Clinical Summary, and final study report background sections were included in the NDA submission.

9.2 Labeling Recommendations

At the time of this review, the product has not been shown to provide benefits that outweigh risks for any of the surgical procedures that have been studied in the clinical trials. Therefore, there are no labeling recommendations at this time.

9.3 Advisory Committee Meeting

An Advisory Committee was not convened to review data or provide input regarding any issue related to this application; there were no issues identified that warranted such input.

9.4 Review of Efficacy Trials

9.4.1 BU-002-IM (Phase 2, Pivotal Trial – Shoulder Arthroscopy)

Title: An international, randomised, double-blinded, multi-centre, active- and placebo-controlled dose response trial to evaluate the efficacy and safety of SABER-Bupivacaine for post-operative pain control in patients following arthroscopic shoulder surgery

Study Dates: April 29, 2009 to February 4, 2011

Objectives
The objective was to identify the optimal dose of SABER-bupivacaine for post-operative pain control administered into the subacromial space in patients undergoing elective arthroscopic shoulder surgery on the basis of PK, efficacy, and safety evaluations

Efficacy Endpoints
Primary endpoints:

- Pain intensity (PI) on movement AUC over the period 1 to 72 hours post-surgery using an 11-point NRS for recording PI. A standardized assessment of pain "on movement" was performed for shoulder flexion to 90 degrees.
- Total use of opioid rescue analgesia 0 to 72 hours post-surgery.

Secondary endpoints:

- Time to first opioid use
- Opioid-Related Symptom Distress Scale (OR-SDS) score Days 0 to 7
- PI at rest AUC over the period 1 to 72 hours post-surgery
- Patient's pain treatment satisfaction score on Day 4
- The proportion of patients who were dischargeable (on the basis of PADS) on Days 1, 2, 3, 4 and 7
- The proportion of patients who had returned to work by Day 14.

Inclusion Criteria (verbatim from p. 35 of final study report)

1. Written informed consent was obtained according to local regulations before any trial-related activities. A trial-related activity was any procedure that would not have been performed during the routine management of the patient

2. Subacromial impingement syndrome, diagnosed by a positive subacromial impingement test, full passive range of motion and exclusion of shoulder instability
3. MRI with intact rotator cuff as judged by radiologist
4. Age 18 years of age and above
5. Patients suitable for general anaesthesia
6. Willing to refrain from strenuous activities and avoid modifications to prescribed physiotherapy/exercise levels throughout the course of the trial
7. Ability to read, understand, communicate and voluntarily sign the approved informed consent form prior to the performance of any trial specific procedures.

For female patients of childbearing potential:

8. A negative urine pregnancy test at screening
9. Use of adequate contraception (contraceptive pill, contraceptive injection, contraceptive implant or intrauterine device) throughout the trial period and for 1 week after the trial was completed, according to local law.

Exclusion Criteria (verbatim from pp. 35-36 of final study report)

1. Participation in another clinical trial with an investigational drug or device within 30 days before inclusion in this trial
2. Previous participation in this trial
3. Known serious / important reactions in previous anaesthesia procedures with local anaesthetics
4. Known major joint trauma, infection, avascular necrosis, chronic dislocation, inflammatory or degenerative glenohumeral arthropathy, glenohumeral arthritis, frozen shoulder or previous surgery of the affected shoulder
5. Known clinically significant hepatic, gastrointestinal, renal, haematological, urologic, neurological, respiratory, endocrine or cardiovascular system abnormalities
6. Known serious uncontrolled illness: cancer, psychiatric or metabolic disturbances. History of cured localised malignancies was allowed (i.e. basal or squamous cell skin carcinoma, breast carcinoma or cervical carcinoma)
7. Abnormal electrocardiogram (ECG) (interpretation of ECG must have been done by physician). Abnormalities such as sinus tachycardia, right bundle branch block, ectopic atrial rhythm or premature atrial contractions were not necessarily reason for exclusion (interpretation by physician)
8. Prolonged QT syndrome (QT greater 450 milliseconds [msec] for males, greater than 470 msec for females) or family history of long QT syndrome (interpretation of ECG must have been done by physician)
9. Current or regular use of analgesic medication for other indication(s)
10. Conditions contraindicated for use of opioids, including paralytic ileus, acute or severe bronchial asthma or hypercarbia
11. Current or regular use of anticonvulsants or antiepileptics

12. Connective tissue disorders (systemic lupus erythematosus, scleroderma, mixed connective tissue disease)
13. Current or regular use of antidepressants, monoamine oxidase inhibitors, or medication known to be associated with QT prolongation
14. Known or suspected alcohol abuse or illicit drug use within the 6 months prior to trial enrolment
15. Known sensitivity to bupivacaine (or similar local anaesthetics), benzyl alcohol or other trial drugs (paracetamol, morphine) or their constituents
16. Unwillingness or inability to comply with the trial visit schedule
17. Breast feeding
18. Situated in an institution due to regulatory order or judicial direction.

Surgical Requirements (verbatim from p. 36 of final study report)

1. Arthroscopic subacromial decompression which may also have included the following procedures: distal clavicle excision (DCE), bursectomy, synovectomy, removal of loose body, resection of coracoacromial ligament and subacromial spurs, and minor debridement of articular cartilage
2. No shoulder instability procedures and biceps tenodesis, or biceptal tentomy
3. No open shoulder surgery.

If placements of sutures or suture anchors were deemed necessary during surgery, these patients were considered randomisation failures. For these patients randomisation to treatment was cancelled, and following surgery they were withdrawn from further participation in the trial.

Anesthesia Requirements (verbatim from pp. 36-37 of final study report)

1. No use of strong opioids during the screening period or pre-operatively (other analgesics were allowed during the screening period but not on day of surgery for treatment of shoulder pain)
2. The surgery was performed under general anaesthesia
3. No use of local anaesthetics for wound perfusion or nerve blocks during the shoulder surgery
4. No use of NSAIDs, as a pre-emptive medication or during the shoulder surgery
5. The time when the anaesthetic gas was closed and the continuous opioid (sulfentanil) infusion was stopped was recorded
6. All the medication used during the anaesthesia was recorded
7. Epinephrine could be used in perfusion solution for reduction of bleeding
8. No administration of IV opioids at end of surgery for pain prophylaxis.

Summary of Methodology

This trial was designed as a phase 2, randomized, double-blinded, active- and placebo-controlled, parallel-group, dose-response study in patients undergoing elective arthroscopic shoulder surgery. The trial was to two cohorts, 5 mL of SABER-bupivacaine and 7.5 mL SABER-bupivacaine, which were to be evaluated sequentially. For each cohort there were to be three treatment arms: SABER-bupivacaine, an equal volume of SABER-placebo, and 20 mL of 2.5% bupivacaine HCl. All study drugs were to be administered into the subacromial space.

Based on efficacy, PK, and safety results from cohort 1 the Data Review Committee (DRC) was to recommend whether to continue the trial and recruit patients for the cohort 2

A total of 115 subjects were randomized in cohort 1. After screening, the subjects were randomized in a 2:1:1 fashion to SABER-bupivacaine, SABER-placebo, and bupivacaine HCl treatments, respectively. The study schematic and schedule that follow provide detailed information on the flow of the trial and the specific assessments made.

All patients received paracetamol as post-operative background treatment. If the combination of study drug and paracetamol did not provide adequate pain relief, subjects were allowed rescue medication in the form of morphine administered intravenously or orally. Rescue medication was to be documented by the subject in an electronic diary (eDiary).

To evaluate the long-term clinical effects of the SAIB component of the SABER-bupivacaine, the following evaluations were to have been performed at 6 months following the surgical procedure:

1. Clinical assessment of the wound healing and local tissue conditions
2. Constant-Murley functionality assessment
3. MRI imaging of shoulder

MRI was selected by the Applicant for the imaging assessment for its purported higher sensitivity and specificity compared to ultrasound or computer tomography (CT) for evaluating bone, cartilage and soft tissue. The images were assessed centrally by independent reviewers for changes from the preoperative baseline.

The trial was conducted in nine centers in 5 countries. Upon completion of the first cohort, the DRC recommended against continuing the study with the second cohort because they believed the increase to the 7.5 mL dose, i.e., an increase in dose of 50%, would provide a clinically significant improvement in the efficacy over an appropriate time period (at least 24 hours) compared to bupivacaine HCL.

Amendments

The protocol was amended 5 times. Amendment 1 was made prior to the trial initiation date; the remaining amendments were made after enrollment had begun. The main reasons for each amendment are listed below:

1. (August 21, 2008): The dosage of oral morphine rescue medication was changed to the short-acting 10 mg tablet formulation due to unavailability of 15 mg oral morphine tablets in some of the countries where the study was being conducted. The amendment also clarified that rescue medication could be given until Day 7. Furthermore, if analgesics were needed for any indication, including post-operative pain from Day 7 to EOT, this was to be recorded as concomitant medication.

   It was not required that patients were hospitalized on Days 3, 4, and 7, but some of the assessments on these days used for evaluation of home readiness via PADS had to be done by the investigator or other health care personnel possibly twice a day. The procedures were therefore changed so the PADS assessments were only done morning and afternoon on Day 1 and 2, i.e., while patient was still in hospital, followed by once daily on Days 3, 4, 7, to be more convenient for the patient if they were already discharged.

   The text for administration of paracetamol four times daily was clarified to state that on day of surgery the first dose was administered as soon as possible following completion of surgery, then every 6 hours daily until midnight (24:00h), and that for subsequent days the patients would be prompted by the eDiary at the required time points.

2. (January 23, 2009): The number of subjects enrolled at the time of this amendment was 23. With the amendment, the number of planned trial sites, which was originally 5 to 7, was changed to 5 to 10. In order to investigate the long-term safety of SABER-bupivacaine, the follow-up visit 6 months after surgery was added. There were also some changes to unblinding as a result of introduction of the 6-month visit. Unblinding of blinded sponsor's staff was to be carried out after all patients had completed the Day 14/EOT visit. At this point the efficacy data and the safety data of the immediate post-operative period were analyzed. Unblinding of the patients and of the blinded site staff was not carried out until after all patients had completed the long-term follow-up visit at 6 months.

   Since at enrolment it was not feasible to define what criteria should be fulfilled for a patient to be evaluable, all decisions regarding evaluability were to be made after the trial had ended.

   Post-operative pain was optimized by including IV morphine 2 mg (allowed at 5 minutes intervals until pain relief) for patients with difficulties swallowing.

The selection criteria to exclude someone situated in an institution due to regulatory order or judicial direction was added.

Instead of confirming administration in the eDiary, patients were to receive a reminder to take their paracetamol.

There was also clarification that current or regular use of analgesic medication other than described under rescue medication and background treatment were not allowed during this trial.

More flexibility with regards to PK sampling time points was introduced.

Additionally the volume of blood to be collected for PK and laboratory tests was increased from 120 mL to 130 mL.

Causality classification for AEs was changed to related and not related (previously it had been probable, possible and unlikely).

Supplementary safety information regarding safety of benzyl alcohol was added.

3. (July 13, 2009) This amendment was made after 93 subjects had been enrolled. With the amendment, the required treatment period with paracetamol was shortened to 3 days (72 hours) post-surgery. This was because a high level of patient non-compliance with the 7-day regime was observed due to lack of pain with increasing time from day of surgery. A change was also made to state that study drugs were to be repacked with other syringes in order to minimize the risk of administering more study drug than intended according to the protocol procedures. There was also clarification of the text to make sure the exact amount of SABER-Bupivacaine was dispensed from the vials. In addition, blood sampling at baseline was removed because “it was clinically and scientifically unnecessary and was compromising patient comfort” according to the Applicant. The antiemetic treatment was clarified and was altered to enable the possibility of using fentanyl in case sufentanil was not available. Lastly, there was a clarification to indicate the appointment of a designated physician as Data Monitoring Physician with the responsibility for ongoing safety monitoring.

4. (December 11, 2009) This amendment was made after 107 subjects had been enrolled in the trial. The number of sites increased to 20. The procedures for collection of PK samples were modified to decrease the number of patients having blood samples taken for PK and clarifying that a blood sample for PK analysis should be taken in case of any cardiac or CNS events.

5. (February 25, 2010) This amendment was made after 126 subjects had been enrolled. The amendment addressed an issue with wording of the 3rd

amendment concerning paracetamol, i.e., stopping use of paracetamol after three days, which unintentionally resulted in not allowing for other analgesics other than rescue morphine from Days 3 to 7 when the subject had minimal pain that would likely respond to a non-narcotic analgesic. Therefore, the use of paracetamol was reinstated on an as needed basis for the period from 72 hours to 7 days post-surgery. There was also a clarification of the use of ondansetron as antiemetic treatment, despite its being listed among the drug products disallowed during the study.

The source data at a number of trial sites indicated that the number of morphine tablets dispensed did not correspond with the eDiary entries made by some patients. The discrepancies noted fall into two categories: 1) Oral morphine rescue medication was not entered in the eDiary due to patient oversight. 2) Erroneous recording of oral morphine rescue medication in the eDiary resulting in too high a number of tablets being recorded, e.g. paracetamol entered where oral morphine rescue medication should have been entered. In order to ensure that the correct data in relation to consumption of oral morphine rescue medication were captured, the missing data, i.e., oral morphine tablets taken by patients, but not entered in the eDiary by patients, were entered in the concomitant medication pages of the eCRF. After unblinding, it was discovered that these data were not correctly represented in the tables and listings. When programming the data for these patients, it was not taken into account that the data in the eCRF was in a different format from the data in the eDiary, i.e., entered as dosage in mg and frequency, rather than number of tablets. Consequently SAS programs and corresponding tables and listings for morphine rescue medication were updated. In addition, a process was set up to document and correct the incorrect data by making changes in the eDiary. In addition to this problem, the morphine equivalent dosage for subject (b) (6) was not accurate due to an inconsistency in the process for resolving queries on eDiary data, one eDiary entry for patient (b) (6) was overlooked when cleaning the data in accordance with the procedure described above. As a consequence, an additional analysis of the total morphine equivalent dosage was performed with morphine equivalent dosage for subject (b) (6) on 07-Dec-2009 set to 0 and an additional table “Total Morphine Equivalent Dosage, amended to include 0 usage for patient (b) (6) ” was created.

There was also one change to the planned analysis. The pair-wise comparison of placebo versus standard bupivacaine HCl for opioid consumption was excluded.

The multiple changes in the use of analgesics at the various stages of the trial raise concern over the validity of any findings regarding the impact of SABER-bupivacaine on opioid use. The other changes to the protocol were not likely to have a major impact on the overall efficacy or safety findings of the trial.

Schematic

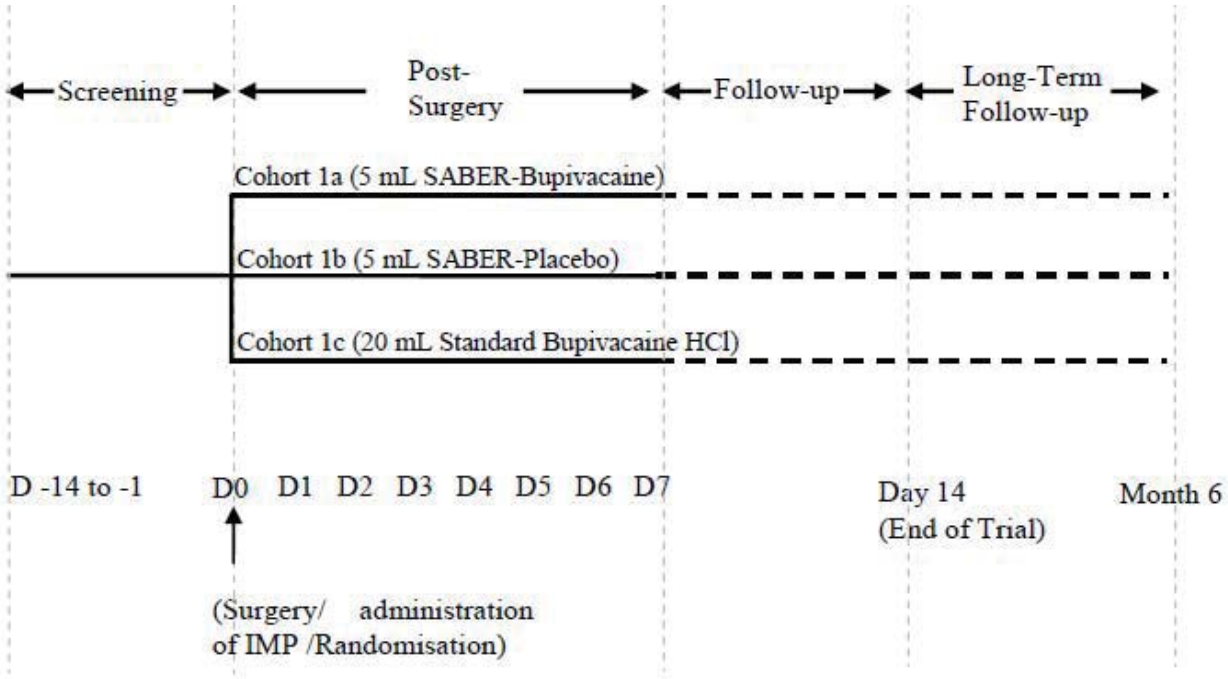


Figure 5. Study schematic (Figure 9-1, p.32 of the final study report)

Schedule (based on Table 9-3, pp. 42-43 of final study report)

Visit	Screening	Day of Surgery						End of Trial	Long-term Follow-up
Day	-14 to -1	0	1	2	3	4	7 ± 1 day	14 ± 4 days	6 ± 1 month
Procedure									
Informed consent	X								
Demographics	X								
Medical history	X								
Inclusion/exclusion criteria	X	X							
Physical examination	X								
Constant Functionality Score	X								X
Urine pregnancy test	X	X						X	
Return to work assessment	X							X	
Vital signs[1]	X	X	X	X	X	X	X		
ECG recording[2]	X	X	X	X	X				
Laboratory: blood sampling[3]	X		X	X	X			X	
Concomitant illness	X								
Concomitant medication[4]	X	X	X	X	X	X	X	X	
Randomisation[5]		X							
PK blood sampling[6]		X	X	X	X	X			
Hand-out & Training in eDiary	X	X							
Background pain treatment[4] treatment[7]		X	X	X					
Rescue medication administration and recording eDiary[8]		X	X	X	X				
Rescue medication and recording in eCRF (concomitant medication form)					X	X	X		
Pain intensity assessment (NRS) eDiary[9]	X	X	X	X	X	X	X		
OR-SDS scoring eDiary[10]		X	X	X	X	X	X		
Home readiness evaluation[11]		X	X	X	X	X	X		
Patient's pain treatment expectations/satisfaction	X					X			

Visit	Screening	Day of Surgery						End of Trial	Long-term Follow-up
Day	-14 to -1	0	1	2	3	4	7 ± 1 day	14 ± 4 days	6 ± 1 month
Procedure									
Rescue and background treatment accountability			X	X	X	X		X	
Recording of adverse events including CNS side effects		X	X	X	X	X	X	X	
Surgical wound healing							X	X	X
MRI of shoulder	X								X
End of Trial								X	

[1] Vital signs: Heart rate and blood pressure on Day 0 in the afternoon; on Days 1 and 2, morning and afternoon; on Days 3, 4 and 7 once daily.
[2] ECG: At screening and baseline. Baseline ECG was done in the interval from the evening before surgery and up to start of surgery. Post-surgery at 1, 4, 8, 12, 24, 36, 48 and 72 hours.
[3] Laboratory blood sampling: the screening laboratory sample was taken anytime from the screening visit to 1 day prior to surgery.
[4] Concomitant medication: at screening, day of surgery, Days 1, 2, 3, 4 and 7, and EOT.
[5] Randomization: patients were randomized 24 hours prior to day of surgery.
[6] Pharmacokinetic blood sampling: pre-surgery, and 1, 4, 8, 12, 24, 36, 48, 72 and 96 hours post-surgery, taken in connection with ECG recording. This applied only for the first 58 patients randomized in the trial.
[7] Background pain treatment: Paracetamol four times daily 0-72 hours post-surgery. NB dose was according to weight.
[8] Rescue medication recording eDiary: eDiary to prompt recording four times each day. From 0 to 72 hours post-surgery.
[9] Pain assessment: On Day 0 at 1, 2, 4, 6, 8, 12 hours post-surgery. On Days 1 to 7 approximately at 08:00, 12:00, 16:00 and 20:00.
[10] OR-SDS: Daily in the evening, including on Days 5 and 6.
[11] Home readiness evaluation: As vital signs: on Day 0 in the afternoon; on Days 1 and 2, morning and afternoon; on Days 3, 4 and 7 once daily.

Subject Disposition

A total of 126 subjects were screened for the study in an effort to assure 100 evaluable subjects for the first cohort. Table 37 provides a summary of subject disposition. A total of 23 subjects were excluded from the per protocol (PP) population due to protocol deviations (8 randomized to the SABER-bupivacaine group, 7 from the SABER-placebo group, and 8 from the bupivacaine HCl group). The most frequent reason for exclusion from the PP population was disallowed medications, which affected 12 subjects. Three of the 12 subjects (one from each treatment group) had disallowed medications during surgery. Six subjects were excluded due to the incorrect anesthetic being used during surgery (3 subjects in both the SABER-bupivacaine and bupivacaine HCL groups). The other reasons for exclusion included: all procedures were no performed arthroscopically, disallowed surgical procedure, and disallowed condition related to the operative shoulder.

Table 37. Disposition of subjects (based on Table 10-1, p. 69 of the final study report)

Subject Status	**SABER-bupivacaine. 5 mL n (%)**	**SABER-placebo 5 mL n (%)**	**Bupivacaine HCl (0.25%) 20 mL n (%)**	**Total n (%)**
Total (screened) population				126
Randomized	53 (42)	25 (20)	29 (23)	107 (85)
Safety population	53 (100)	25 (100)	29 (100)	107 (100)
ITT population	53 (100)	25 (100)	29 (100)	107 (100)
Withdrawn	0	0	0	0

Reported Efficacy Findings

The mean pain intensity (PI) on movement AUC over the time period 1 to 72 hours post-surgery (ITT population) for the SABER-bupivacaine group was 5.16 (SD: ± 1.94). The corresponding mean PIs on movement AUC for the SABER-placebo and bupivacaine HCl groups were 6.43 (SD: ± 1.77) and 5.16 (SD: ± 2.38), respectively. Thus, SABER-bupivacaine was superior to SABER-placebo but not to bupivacaine HCl for this primary endpoint. The total mean use of rescue analgesia, i.e., the morphine equivalent dosage (mg) for the ITT population, from 0 to 72 hours for the SABER-bupivacaine group was 14.15 mg (± 29.15 mg). The corresponding total morphine equivalent dosages for the SABER-placebo and bupivacaine HCl groups were 22.85 mg (± 25.17 mg) and 13.31 mg (± 18.69 mg), respectively. Pair-wise comparisons using ANOVA did not show statistical superiority of SABER-bupivacaine over either SABER-placebo or bupivacaine HCl for the 0 to 72 hour period; the p-values were 0.075 and 0.837, respectively. However, using the non-parametric Friedman test resulted in a finding of superiority of SABER-bupivacaine to SABER-placebo with a p-value of 0.013. Figure 6 and Figure 7 show the mean PI on movement and mean total opioid usage over various intervals of the study.

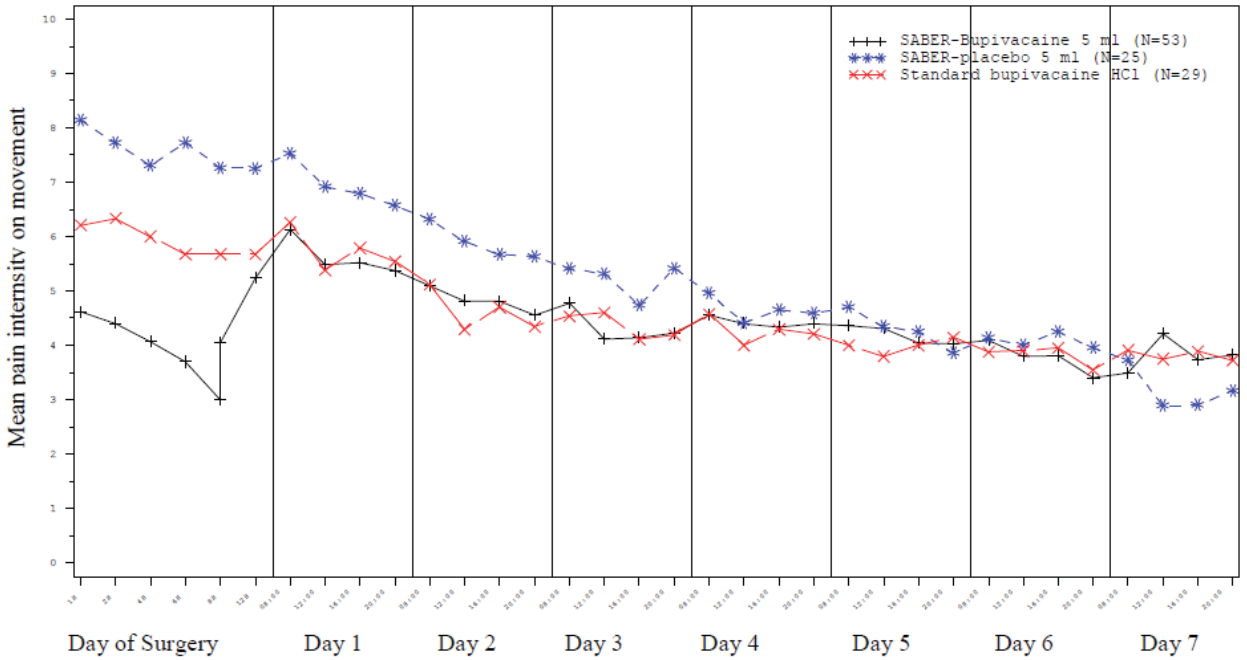


Figure 6. Pain intensity on movement over time in the ITT population (Figure 11-1, p. 80 of the final study report)

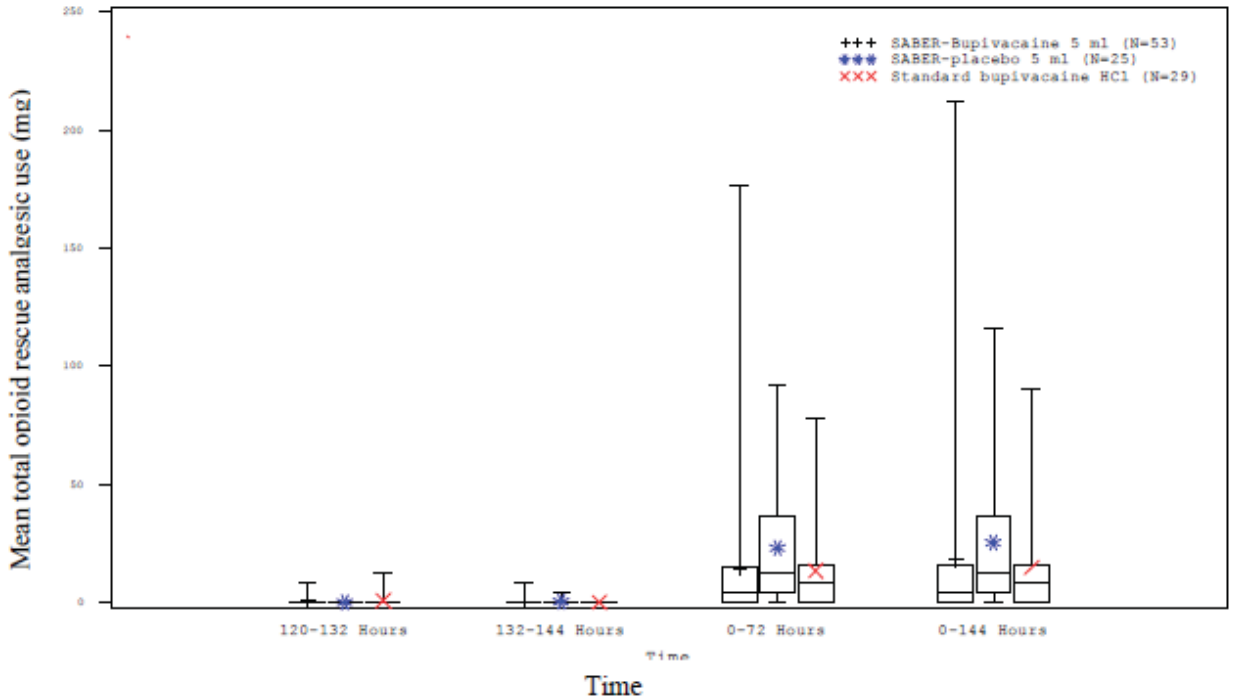


Figure 7. Mean total opioid rescue over time in the ITT population (Figure 11-2, p. 85 of the final study report)

The Applicant noted the following findings for the secondary efficacy endpoints:

1. There were no statistically significant differences between groups for time (hours) to first opioid rescue medication.
2. The comparison of the Opioid-Related Symptom Distress Scale (OR-SDS) scores for Day 0 to Day 7 did not reveal any statistically significant differences between treatment groups.
3. The mean PI at rest AUC from 1 to 72 hours post-surgery (ITT population) for the SABER-bupivacaine, SABER-placebo and bupivacaine HCl groups were 2.50 (SD: ± 1.34), 3.43 (SD: ± 2.05) and 2.33 (SD:± 1.76), respectively. SABER-bupivacaine was superior to SABER-placebo, but not to bupivacaine HCl, which was also superior to SABER-placebo.
4. On Day 4, after surgery had been performed, there were no statistically significant differences in the patients‟ pain satisfaction score between the treatment groups; SABER-Bupivacaine against SABER-placebo (p-value: 0.995) and SABER-Bupivacaine against standard bupivacaine HCl (p-value: 0.699).
5. There were no statistically significant differences between the treatment groups in the patients “home-readiness,” based on PADS, on Days 1, 2, 3, 4 or 7.
6. There were no statistically significant differences between the treatment groups in the number of patients who had returned to work after 14 days.

Summary of Reported Safety Findings

The Applicant summarized the treatment-emergent adverse events (TEAEs) by an overall summary by treatment group (Table 38), by actual AEs (Table 39), and by relationship to study drug (Table 40). They noted that the majority of the 65 reported TEAEs were of mild or moderate intensity, and that only 9 of the 37 subjects who reported TEAEs experienced events that were considered to be treatment related. They concluded that there were no notable differences being between treatment groups.

Table 38. Summary of TEAEs by treatment group (safety population) p. 122

Patients with	SABER-Bupivacaine 5 mL N 53			SABER-Placebo 5 mL N 25			Bupivacaine HCl N 29			Total N 107		
	n	(%)	n’	n	(%)	n’	n	(%)	n’	n	(%)	n’
TEAEs	16	(30.2)	28	10	(40.0)	19	11	(37.9)	18	37	(34.6)	65
Deaths	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
SAEs	1	(1.9)	1	1	(4.0)	1	4	(13.8)	4*	6	(5.6)	6
Related TEAEs	5	(9.4)	6	2	(8.0)	2	2	(6.9)	2	9	(8.4)	10

Patients with	SABER-Bupivacaine 5 mL N 53			SABER-Placebo 5 mL N 25			Bupivacaine HCl N 29			Total N 107		
	n	(%)	n'	n	(%)	n'	n	(%)	n'	n	(%)	n'
TEAEs leading to discontinuation	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
TEAEs not yet known to be recovered**	4	(7.5)	6	2	(8.0)	2	4	(13.8)	5	10	(9.3)	13
TEAEs leading to change in concentration of medication	5	(9.4)	7	5	(20.0)	6	4	(13.8)	4	14	(13.1)	17

SAE = serious adverse event; TEAE = treatment-emergent adverse event; N = number of patients in a treatment group; n = number of patients with at least one event in the category; % = percentage of patients with at least one event in the category based on N; n' = number of events in a specified category.
*One pregnancy case was reported as an SAE
**At the EOT visit

Table 39. Summary of TEAEs with SOC rates > 2% total (based on Table 12-2, p. 124 of final study report)

Primary SOC Preferred term	SABER-Bupivacaine 5 mL N 53			SABER-Placebo 5 mL N 25			Bupivacaine HCl N 29			Total N 107		
	n	%	n'	n	%	n'	n	%	n'	n	%	n'
All TEAEs	16	30.2	28	10	40.0	19	11	37.9	18	37	34.6	65
Nervous system disorders	5	9.4	7	2	8.0	3	4	13.8	5	11	10.3	15
Headache	3	5.7	4	1	4.0	2	1	3.4	1	5	4.7	7
Investigations	5	9.4	5	2	8.0	2	2	6.9	2	9	8.4	9
Alanine aminotransferase increased	1	1.9	1	2	8.0	2	0	0.0	0	3	2.8	3
Gastrointestinal disorders	2	3.8	3	3	12.0	3	1	3.4	1	6	5.6	7
Nausea	1	1.9	1	3	12.0	3	1	3.4	1	5	4.7	5
Cardiac disorders	1	1.9	1	2	8.0	2	3	10.3	3	6	5.6	6
Musculoskeletal and connective tissue disorders	3	5.7	3	1	4.0	1	2	6.9	2	6	5.6	6
Musculoskeletal pain	2	3.8	2	1	4.0	1	2	6.9	2	5	4.7	5
Skin and subcutaneous	2	3.8	2	2	8.0	2	2	6.9	2	6	5.6	6

tissue disorders												
Injury, poisoning and procedural complications	3	5.7	3	1	4.0	1	0	0.0	0	4	3.7	4
General disorders and administration site conditions	1	1.9	1	2	8.0	2	0	0.0	0	3	2.8	3
Respiratory, thoracic and mediastinal disorders	1	1.9	1	0	0.0	0	2	6.9	2	3	2.8	3

Primary SOCs are presented in descending frequency.
Preferred terms are sorted within primary SOC in descending total frequency, based on MedDRA. A patient with multiple occurrences of a TEAE under one treatment was counted only once in the preferred term for that treatment. A patient with multiple TEAEs within a primary SOC was counted only once in the total row.
N = number of patients in a treatment group; n = number of patients with at least one event in the category; % = percentage of patients with at least one event in the category based on N; n' = number of events in a specified category; SOC = system organ class; TEAE = treatment-emergent adverse event.

Table 40. Summary of TEAEs Related with suspected relationship to trial medication (based on Table 12-3, p. 126 of final study report

Primary SOC Preferred term	**SABER-Bupivacaine 5 mL N 53**		**SABER-Placebo 5 mL N 25**		**Bupivacaine HCl N 29**		**Total N 107**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**%**
All Related TEAEs	5	(9.4)	2	(8.0)	2	(6.9)	9	(8.4)
Investigations	2	(3.8)	1	(4.0)	1	(3.4)	4	(3.7)
Alanine aminotransferase increased	0	0.0	1	(4.0)	0	0.0	1	(0.9)
ECG T-wave abnormal	1	(1.9)	0	0.0	0	0.0	1	(0.9)
ECG T- wave inversion	1	(1.9)	0	0.0	0	0.0	1	(0.9)
ECG QT prolonged	0	0.0	0	0.0	1	(3.4)	1	(0.9)
Cardiac disorders	1	(1.9)	1	(4.0)	1	(3.4)	3	(2.8)
Angina unstable	1	(1.9)	0	0.0	0	0.0	1	(0.9)
Atrial fibrillation	0	0.0	1	(4.0)	0	0.0	1	(0.9)
Sinus bradycardia	0	0.0	0	0.0	1	(3.4)	1	(0.9)
Musculoskeletal and connective tissue disorders	2	(3.8)	0	0.0	0	0.0	2	(1.9)
Musculoskeletal pain	2	(3.8)	0	0.0	0	0.0	2	(1.9)
Respiratory, thoracic and mediastinal disorders	1	(1.9)	0	0.0	0	0.0	1	(0.9)
Pulmonary arterial hypertension	1	(1.9)	0	0.0	0	0.0	1	(0.9)

Primary SOCs are presented in descending frequency. Preferred terms are sorted within primary SOC in descending total frequency, based on MedDRA. A patient with multiple occurrences of a TEAE under one treatment was counted only once in the preferred term for that treatment. A patient with multiple TEAEs within a primary SOC was counted only once in the total row. ECG = Electrocardiogram; N = number of

patients in a treatment group; n = number of patients with at least one event in the category; % = percentage of patients with at least one event in the category based on N; SOC = system organ class; TEAE = treatment-emergent adverse event.

The Applicant noted that of the 6 SAEs, which were reported in six patients; four occurred in the standard bupivacaine HCl group (one pregnancy case was reported as an SAE), and one each in both the SABER-bupivacaine and SABER-placebo groups. Only one SAE was considered by them to be related to trial drug: the severe pulmonary arterial hypertension experienced by the patient in the SABER-bupivacaine group.

Changes to the ECG

The Applicant indicated that changes in ECG morphology were rare; in all groups, the main observation was an increase in the incidence of either T wave flattening or T wave inversion in post-surgery recorded ECGs. They stated that "this may have been due to the surgical procedure." They reported that, overall, no signal indicating an increased cardiac risk for patients exposed to either SABER-Bupivacaine or bupivacaine HCL was observed. While the ECGs were assessed for morphological changes by a central laboratory, the Investigators assessed subjects' ECGs at various time points following study drug administration, as well as at screening and baseline, and identified those that they considered to be "clinically significant abnormal ECGs." Their findings are summarized in Table 41 below.

Table 41. Summary of in the occurrence of clinically significant ECGs per Investigators (Table 12-9, p. 140 of final study report)

Time	SABER-bupivacaine 5 mL N=53		SABER-placebo 5 mL N=25		Bupivacaine HCL N=29	
	n	%	n	%	n	%
Screening	0	0.0	0	0.0	0	0.0
Baseline	0	0.0	0	0.0	0	0.0
1 hour	3	(5.7)	0	0.0	1	(3.4)
4 hours	1	(1.9)	0	0.0	0	0.0
8 hours	2	(3.8)	0	0.0	0	0.0
12 hours	0	0.0	0	0.0	0	0.0
24 hours	2	(3.8)	0	0.0	0	0.0
36 hours	1	(1.9)	0	0.0	0	0.0
48 hours	1	(1.9)	0	0.0	1	(3.4)
72 hours	2	(3.8)	1	(4.0)	0	0.0

N = Number of patients in treatment group; n = number of patients with data available; % = percentage based on N.

Neurological Adverse Events
In the period Day 0-3, three patients in the safety population reported a total of six CNS side effects. Numbness of the tongue and mouth was reported four times by the same patient in the standard bupivacaine HCl group. Lightheadedness and muscular twitching were each reported once by one patient in the standard bupivacaine HCl group and one patient in the SABER-Bupivacaine group, respectively. No CNS side effects were reported by patients in the SABER-placebo group. There were no CNS related SAEs reported.

Overall, no CNS side effects occurred for ≥ 1% of patients (safety population). CNS side effects occurring during the interval Day 0 to 3 and Day 0 to 7 were similar; there were only three additional CNS side effect events were reported between Day 4 and Day 7: slurring of speech (one event) and two additional events of numbness of the tongue and mouth (reported by the same patient who reported it previously), all occurring in the standard bupivacaine HCl group.

6-Month Follow-up Evaluations
At the 6-month follow-up visit, the Applicant reported that there were no subjects whose surgical site healing or local conditions were "not as expected." This same finding was also observed at the Day 7 and Day 14 (end of trial) evaluations.

Constant-Murley Functionality Testing
The functional assessment of the shoulder utilized the Constant-Murley functionality test that was carried out at Screening and at the 6 month follow-up visit. The score included both the sum of the scores for the questions on pain, work, recreation/sport, and sleep, as well as the hand level with outstretched arm, which were added to the scores for the objective dimension questions on forward elevation, lateral elevation, internal rotation, and external rotation at the shoulder. A higher score indicated better ability to perform the activities. The Applicants-reported findings are summarized in Table 9 below.

Table 42. Constant Functionality Scores before and at 6 months after surgery

Constant Functionality Score Timepoint	SABER-bupivacaine	SABER-placebo	Bupivacaine HCl
Screening	44.7 (± 12.5)	41.7 (± 11.7)	42.0 (± 11.3)
6-month Follow-up	61.6 (± 15.2)	63.2 (± 12.4)	65.6 (± 6.8)

The Applicant reported that there were no notable differences in the change in Constant functionality from screening between the treatment groups, i.e. all showed similar levels of improvement post-operatively.

Magnetic Resonance Imaging (MRI) Evaluations
MRI studies were performed on 126 at screening; there were 101 performed at the 6-month follow-up assessment. The Applicant summarized the finds as follows:

1. Mild or moderate changes were observed in 11.8% of patients, with no differences between the SABER-Bupivacaine and standard bupivacaine groups.
2. Minimal changes were observed in the shoulder joint, e.g., synovitis, fibrosis and necrosis pathology (treatment groups not specified).
3. Single localized pocket of minimal effusion or vehicle was observed in 20% of the patients who received either SABER-bupivacaine or SABER-placebo.
4. Generalized joint effusion was observed in 5% of the patients (treatment groups not specified).

The Applicant reported that no safety concerns were raised based on these MRI findings. However, the MRI report also included an assessment of subjects with lower shoulder functionality than expected, based on the non-SABER group. The findings and comments of the radiologist are listed in Table 43 below. The radiologist concluded that, overall, the decreases in Constant-Murley scores cannot be explained by the evaluation of the MRIs. The subacromial decompression is an unreliable surgery, and this result is not unusual.

Table 43. MRI findings of patients treated with SABER products who had decreases in functionality after 6 months. (based on unlabeled table, p. 32 of final study report Appendix 16.1.11)

Unique Subject Identifier	Actual Treatment	Constant-Murley Scores			Lars Engebretsen (radiologist) comments
		Follow-up	Screening	Difference	
(b) (6)	SABER-Bupivacaine	46	56	-10	No MRI finding to explain this
	SABER-Bupivacaine	6	19	-13	No MRI finding to explain this
	SABER-placebo	41	52	-11	Mild sub deltoid inflammation at follow up
	SABER-Bupivacaine	40	45	-5	No change to explain this
	SABER-Bupivacaine	21	23	-2	Osteoarthritis in the acromio-clavicular joint can explain this
	SABER-Bupivacaine	32	37	-5	No explanation on MRI for this change
	SABER-placebo	36	44	-8	No explanation on MRI for this change

Pharmacokinetic Findings
The Applicant reported individual bupivacaine plasma concentrations out to 96 hours following the administration of SABER-bupivacaine and bupivacaine HCL. The plots of

bupivacaine concentration as a function of time for individual subjects receiving these two treatments are shown below.

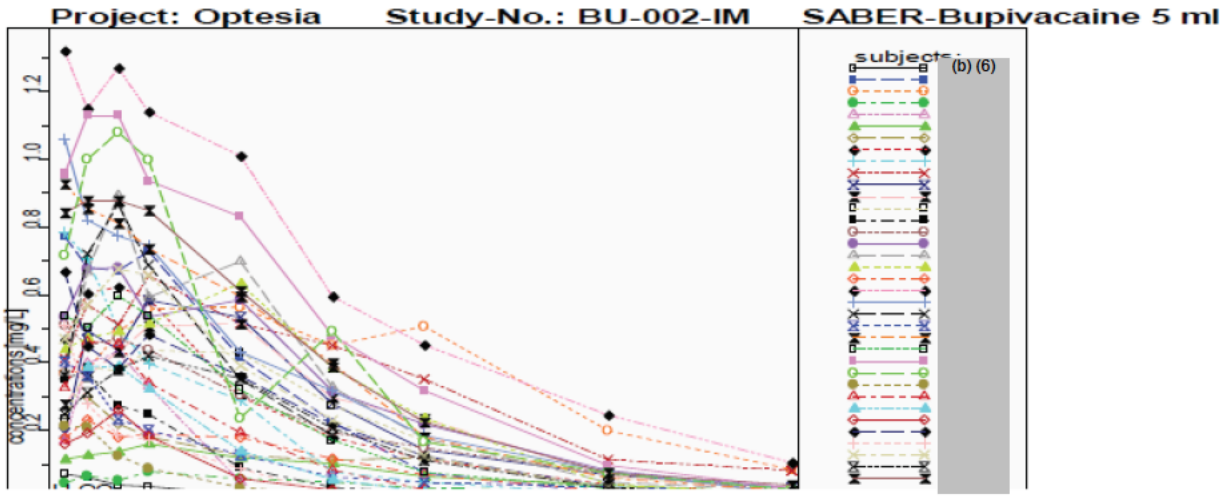


Figure 8. Individual total bupivacaine plasma concentrations following SABER-bupivacaine (Figure 11-3, p 105 of final study report)

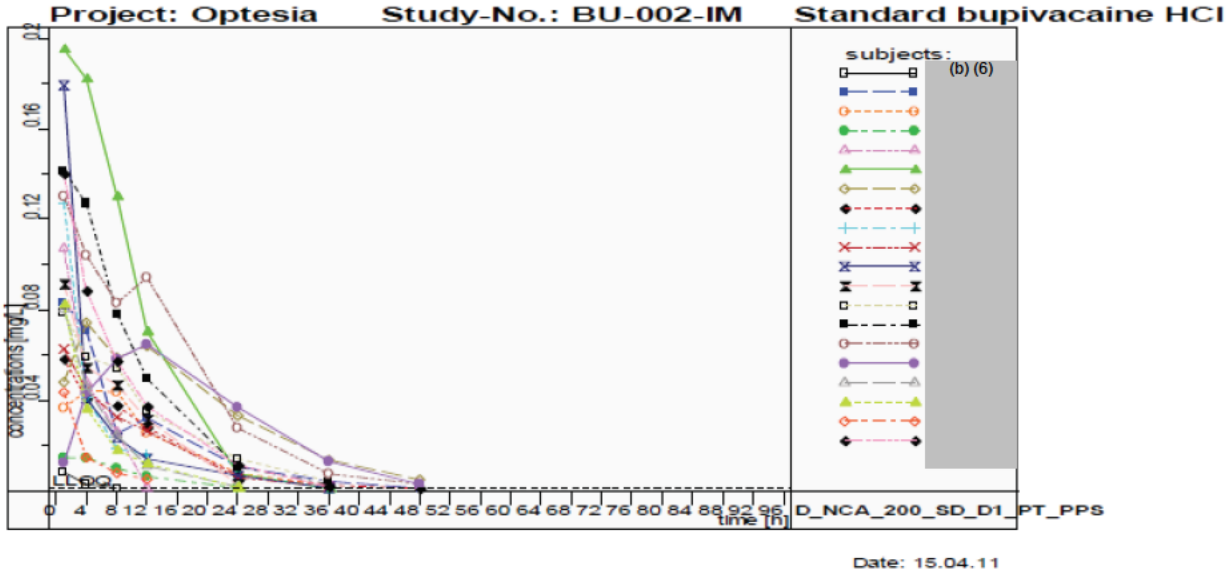


Figure 9. Individual total bupivacaine plasma concentrations following bupivacaine HCl (Figure 11-4, p 105 of final study report)

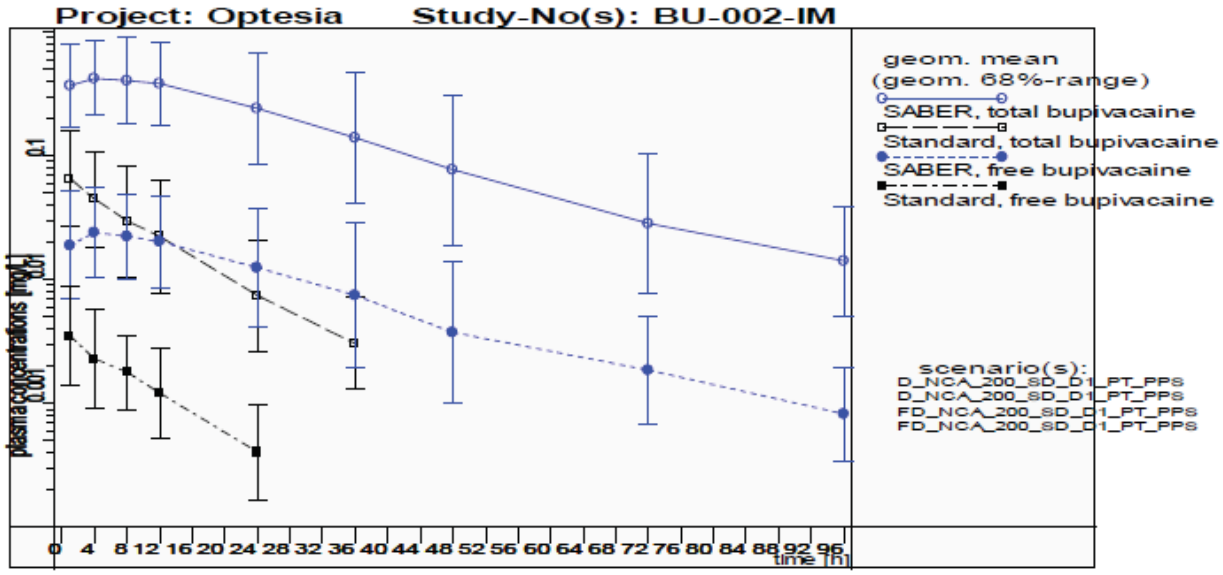


Figure 10. Geometric mean total and free bupivacaine plasma concentrations following SABER-bupivacaine and bupivacaine HCl administration (Figure 11-5, p. 106 of final study report)

Discussion

The Applicant only conducted the first cohort of this study. They reported that the Data Review Committee (DRC) did not recommend to proceed with Cohort 2 (i.e., the 7.5 mL dose) as it was not expected that an increase of 50% would provide a clinically significant improvement in the efficacy over an appropriate time period (at least 24 hours) compared to standard bupivacaine. The Applicant also reported that the DRC did not see any safety concerns for increasing the dose to 7.5 mL based on the available safety information.

With this trial, SABER-bupivacaine was demonstrated to be superior to SABER-placebo for its ability to reduce pain intensity during the first 72 hours following arthroscopic surgery for the treatment of subacromial impingement syndrome. During the first 24 hours following surgery, SABER-bupivacaine provided a substantial amount of pain relief compared to bupivacaine HCl; however, from the first post-operative day through Day 7, the PI scores for SABER-bupivacaine and bupivacaine HCL were indistinguishable from each other although through the end of Day 3, both were substantially more effective than SABER-placebo.

The assessments of the use of opioids during the trial were possibly affected by the background use of paracetamol and the multiple changes regarding its use that were made at varying points into the trial. In the end, the mean total use of rescue analgesia (morphine equivalent) between 0 and 72 hours in the SABER-Bupivacaine group was lower compared to the SABER-placebo group for both the ITT and PP groups. Pair-

wise comparisons for the 0 to 72 hour post-surgery period did not show statistical superiority of SABER-Bupivacaine over either SABER-placebo or standard bupivacaine HCl for both the ITT and PP populations. Furthermore, the reduction in use of opioids associated with SABER-bupivacaine treatment was not accompanied by any reduction in opioid symptoms as measured by the OR-SDS suggesting the amount of reduction was not clinically meaningful.

SABER-bupivacaine failed to distinguish itself from SABER-placebo in any of the secondary efficacy endpoints other than PI at rest AUC from 1 to 72 hours following surgery; however, it was no better than bupivacaine HCl for this metric, and bupivacaine HCl was also found to be significantly better than SABER-placebo.

Overall, SABER-bupivacaine was demonstrated to be superior to SABER-placebo at reducing postoperative pain, both at rest and with movement, during the first 72 hours following arthroscopic surgery of the shoulder. It was also demonstrated to reduce the consumption of opioids during the same time period. However, bupivacaine HCl was similarly efficacious for the endpoints evaluated; although it did not appear to offer as much pain relief during the first 24 hours following surgery.

The safety findings from this trial, in conjunction with the PK findings, raise some concerns over the risks that were observed and that are likely to occur in the general population:

1. Based on the PK data, there is a nearly 10 fold greater systemic exposure to bupivacaine with SABER-bupivacaine compared to bupivacaine HCl. The highest C_{max} for free bupivacaine following SABER-bupivacaine administration was 0.0739 mg/L (73.9 mg/mL). The systemic bupivacaine exposures persist for 96 hours with SABER-bupivacaine compared to 48 hours with bupivacaine HCl. The combination of high systemic bupivacaine concentrations that persist for > 12 hours, indicate that the risk of cardiac and neurological toxicity are greater with SABER-bupivacaine than bupivacaine HCl for the doses studied and this particular surgical procedure. and the variability of C_{max} between subjects

2. The ECG data in Table 41 indicate that there is a difference between treatment groups for clinically significant changes to the ECG during the 72 hours following treatment, with SABER-bupivacaine associated with more abnormalities than both bupivacaine HCL and SABER-placebo. While the incidence of adverse events (Table 40) did not differ substantially between treatment groups, the findings for SABER-bupivacaine suggest it has a greater potential for adverse outcomes. The small number of subjects in the safety population, combined with the variability in the PK data, suggests that a greater number of subjects would need to be evaluated to adequately characterize the risk of cardiac toxicity.

3. The risk of neurotoxicity did not appear to be different between the treatment arms; however, that cannot be used to allay concerns of cardiac toxicity as bupivacaine has been reported to produce life-threatening cardiac arrhythmias in the absence of prodromal neurotoxicity.

4. The persistence of SABER in the surgical wound, based on animal data indicating the substance to remain for at least a year in surgical wounds in rabbits with an accompanying foreign body reaction, was part of the basis for having the Applicant perform a long-term follow-up evaluation of the subjects. The MRI findings suggest the substance may be persistent in the shoulder. The Applicant acknowledged "at 6 months, some effusion of remaining vehicle in the subacromial joints was observed." Whether this component of the product is inducing some of the unexplained changes observed in the MRI scans and some of the untoward changes in the functionality testing is uncertain. It appears longer follow-up, and perhaps a larger safety population, are necessary to discern if there is a real risk associated with SABER.

5. The risk of chondrolysis was another reason for the Applicant to perform long-term follow-ups of the safety population. In 2009, the FDA issued a Drug Safety Communication for Healthcare Professionals (See Section 9.5 of this review) that reported cases of chondrolysis occurring in patients who were administered local anesthetics in the intra-articular space following orthopedic surgeries. Bupivacaine was the most frequently cited agent associated with these adverse events and it was generally administered as an infusion over a 48-72 hour period. The shoulder was most commonly affected primarily at the glenohumeral joint. The symptoms of chondrolysis occurred as early as 2 months after the infusions, but the median time to diagnosis was 8.5 months. In more than half of the reports, the patients required additional surgery, including arthroscopy or arthroplasty. It is not clear from the reports which factor or combination of factors contributed to this serious adverse event, but it was noted that it had not been reported following single injections of local anesthetics.

   Based on the MRI findings and the functionality testing results, the possibility that chondrolysis could be occurring with SABER-bupivacaine treatment needs to be considered. However, it is likely that the Applicant has not followed subjects sufficiently long to discern this adverse event. It is also possible that the small number of subjects exposed to SABER-bupivacaine is inadequate to determine whether the risk of chondrolysis exists for the product.

Conclusions

1. SABER-bupivacaine has been demonstrated to be superior to SABER-placebo as an analgesic following arthroscopic shoulder surgery; however it appears to be no better than bupivacaine HCl.

2. Compared to the placebo and bupivacaine HCl, SABER-bupivacaine is associated with increased incidence of ECG abnormalities.
3. The magnitude and duration of systemic bupivacaine exposures following administration of SABER-bupivacaine greatly exceed those of bupivacaine HCl, and are such that the risks of cardiac and neurological toxicity are likely increased; although the safety population was not likely large enough to address this concern.
4. There are possible safety signals related to the persistence of SABER and to the effects of prolonged exposure to bupivacaine within the subacromial space, which have not been observed with single injections of bupivacaine HCl, that were not adequately addressed by this study.

The findings of this study do not demonstrate that the benefits of SBAER-bupivacaine outweigh its risks and suggest that bupivacaine HCl would be a similarly effective and possibly safer alternative treatment.

9.4.2 CLIN-803-006-0006 (Phase 2, Pivotal Trial – Inguinal Herniorrhaphy)

Title: A double-blind, placebo-controlled, pharmacodynamic and pharmacokinetic dose response study of saber-bupivacaine instilled into the wound in patients undergoing open inguinal hernia repair

Study Dates: January 18, 2007, to October 17, 2007

Objectives

Primary objectives were to assess the dose-response efficacy and pharmacokinetics of SABER-bupivacaine instilled directly into the wound in patients undergoing elective open inguinal hernia repair.

The secondary objectives were to examine the safety and tolerability of SABER-bupivacaine instilled directly into the wound in patients undergoing elective open inguinal hernia repair.

Efficacy Endpoints

Primary endpoints:

1. Mean pain intensity on movement normalized AUC over the time period 1 to 72 hours post-surgery
2. Proportion of patients receiving opioid rescue medication during the study.

Secondary endpoints:

1. Mean pain intensity normalized AUC over the time period of 1 to 48 hours;
2. Overall treatment satisfaction;
3. Mean total opioid dose for analgesia rescue during the study; and
4. Mean function activities (Days 1 through 5).
5. The modified Brief Pain Inventory.
6. An overall assessment of treatment satisfaction was made using a 6-point verbal rating scale (very dissatisfied, dissatisfied, slightly dissatisfied, slightly satisfied, satisfied, very satisfied).
7. Data on worst and least pain in the past 24 hours were collected using a 0 to 10 NRS with scores ranging from 0 (no pain) to 10 (worst pain possible).
8. Data on the extent the pain has interfered with normal function (getting out of bed, walk, interact with visitors, fall asleep, stay asleep, eat, deep breath/post-operative exercises, cough) were collected on a 0 to 10 NRS with scores ranging from 0 (does not interfere) to 10 (completely interferes).

9. Worst pain and least pain were summarized using an AUC from Day 1 to Day 5, normalizing by dividing by the time interval. The data were summarized by treatment group and compared between groups

Inclusion Criteria (verbatim from p. 43 of final study report)

1. Male and female patients, 18 to 65 years of age, who planned to undergo elective open unilateral tension-free Lichtenstein-type inguinal hernia repair;
2. Determined to be in good health prior to study participation based on a medical history, physical examination, 12-lead ECG, and laboratory tests;
3. Systolic BP no greater than 160 mmHg and diastolic BP no greater than 95 mmHg;
4. A requirement that men and women agreed to use a medically acceptable method of contraception throughout the study period and for 1 week after the study is completed for all patients. Acceptable methods were abstinence, birth control pills/patches, diaphragm with spermicide, intrauterine device (coil), condom and foam, surgical sterilization, and progestin implant or injection;
5. A requirement to refrain from strenuous activities throughout the study period and avoid modifications to prescribed exercise levels throughout the course of the study;
6. Ability to read, understand, communicate, and voluntarily sign the approved informed consent form prior to the performance of any study specific procedures.

Exclusion Criteria (verbatim from pp. 43-44 of final study report)

1. Pregnancy or lactating;
2. Presence of previous abdominal surgery with scar tissue that would limit patients' ability to participate;
3. Evidence of clinically significant hepatic, gastrointestinal, renal, hematologic, urologic, neurologic, respiratory, endocrine, or cardiovascular system abnormalities, psychiatric disorders, or acute infection unrelated to the disease under study;
4. Connective tissue disorders (systemic lupus erythematosus, scleroderma, mixed connective tissue disease);
5. Known or suspected alcohol abuse within the 6 months prior to study enrollment or illicit drug use;
6. Current or regular use of analgesic medication for other indication(s);
7. Current or regular use at screening of tryptyline or imipramine antidepressants or monoamine oxidase inhibitors;
8. Use of any prescription drugs or over the counter medication starting within 7 days before treatment and throughout the study (except for birth control medications) that may interfere with the conduct or interpretation of the study results;
9. Participation in another clinical study concurrent or within 30 days of enrollment;

10. Known sensitivity to bupivacaine, BA, or other treatments or their constituents;
11. Patient unwilling or unable to comply with the study procedures.

Summary of Methodology

Prior to surgery, subjects were randomly assigned to receive one of the following treatments:

1. SABER-bupivacaine 5.0 mL (660 mg of bupivacaine)
2. SABER-bupivacaine 2.5 mL (330 mg of bupivacaine)
3. SABER-placebo 5.0 mL
4. SABER-placebo 2.5 mL

Subjects were randomized 3:1 in favor of the SABER-bupivacaine treatments. The SABER-placebo groups were to be pooled to increase the statistical power. The study was divided into 2 cohorts of 60 subjects each with Cohort 1 consisting of the 2.5 mL treatment groups and Cohort 2 consisting of the 5 mL treatment groups.

The inguinal hernia surgery was performed according to standard local practice under general anesthesia. The study drug was administered during wound closure, and was to be instilled gradually throughout the inguinal canal and the abdominal wall layers to cover all raw surfaces of the wound, filling the subaponeurotic and subcutaneous spaces.

The study schematic and schedule below provide the detail for the assessments made and their timing.

Amendments

There were three amendments made to the protocol. The first amendment was made prior to subject enrollment; the others occurred 2 and 4 months into this 9 month long study.

1. (November 16, 2006) This amendment altered the design of the study by:
   a. removing the 7.5 mL dose of treatment such that the study became a 2 Cohort dose-finding examining only a 2.5 mL and a 5.0 mL dose of SABER-bupivacaine
   b. modifying the first primary endpoint to be Mean Pain Intensity AUC over the time period 1 to 72 hours post-surgery to include in the Mean Pain Intensity AUC of the earliest time point where Pain Intensity was collected post-surgery
   c. modifying the secondary endpoints to include mean pain intensity AUC over the time period 1 to 48 hours post-surgery, opioid usage, functional activity, and treatment satisfaction
   d. including an interim analysis after 50% of the patients completed the study and the ongoing blinded data and safety monitoring throughout the study to

ensure safety, pharmacokinetic, and pharmacodynamic trends remained acceptable

e. reducing the number of pharmacokinetic profiles required to a minimum of 32 complete profiles to be consistent with the removal of the 7.5 mL Cohort while ensuring adequate data collection within Cohorts 1 and 2
f. collecting pain intensity data at 12:00 separate from the collection of modified Brief Pain Inventory data to allow consistent and logical data collection with the e-diary
g. increasing the potential number of participating sites to 8 to ensure acceptable patient enrollment

2. (March 12, 2007) This amendment altered the protocol by:
    a. adding two follow-up visits to assess safety, local tissue reaction, and surgical wound healing following administration of SABER-Bupivacaine and SABER-Placebo at 3 and 6 months following their administration
    b. deleting the interim analysis after 50% completion of the trial to assess safety, pharmacokinetics, and pharmacodynamics of the 2 cohorts, to allow consideration of treatment at a higher dose under a further protocol amendment
    c. deleting the analysis of the pharmacodynamic data after 50% of the patients had completed the trial

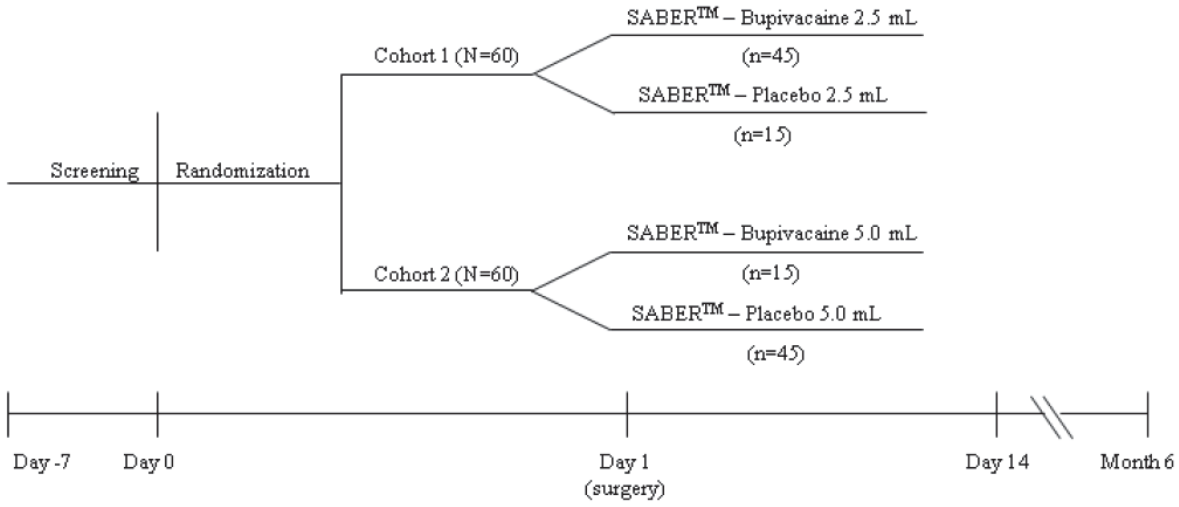
3. (May 21, 2007) This amendment clarified the data management procedures for the evaluation of inguinal hernia repair wound healing follow-up study and described the collection and processing of ECG data at 2 selected sites, which implemented continuous cardiac monitoring during the course of the double-blind phase. The amendment noted the following:
    a. The clinical databases corresponding to the double-blind treatment phase and the follow-up wound evaluation study were structured according to the following plan:
        i. The database was locked upon completion of the double-blind treatment phase of the study and unblinded in accordance with the approved Data Management Plan. The unblinded (double-blind) portion of the data was summarized and analyzed in accordance with the approved Statistical Analysis Plan for the double-blind phase. The CSR was signed off upon completion of the double-blind study.
        ii. A second clinical database was created for the follow-up study in order to capture the required data for patients participating in this part of the protocol. This database was locked when all data was obtained in accordance with the amended Data Management Plan. The data was summarized and analyzed in accordance with a specific Statistical Analysis Plan for the follow-up extension. The

wound healing follow-up study has been written up as an appendix to the final CSR.

b. At two clinical sites, participating in continuous cardiac monitoring, the following procedure was implemented:
    i. Continuous ECG monitoring was initiated as soon as practical after the surgical procedure and continued for 24 hours. Parameters were set as per standard routine practice for the hospital. In the event of an alarm, a 12-lead ECG was performed if clinically indicated (e.g., bradycardia episodes). During Surgery/Treatment Day 0 or any Follow-up Days 1, 2, 3, 4, and 5, a 12-lead ECG was performed only if clinically indicated. The ECG was evaluated and documented in the study data collection forms (electronic CRF).
    ii. There was no change to the study protocol requirement of performing ECGs if clinically indicated during Surgery/Treatment Day 0 or any subsequent study follow-up day.
    iii. Copies of ECG traces generated during the conduct of the study at these sites were transferred to the sponsor in a de-identified manner (name and date of birth replaced with patient initials and study identification number).
    iv. A review of the baseline ECGs compared to all subsequent ECGs was performed centrally by an independent cardiologist and summarized as an appendix to the final clinical study report.

The first amendment was not expected to impact the trial findings, as it was instituted prior to enrollment of any subjects. The changes instituted with the second amendment occurred after enrollment had begun; however, the amendment only extended the trial for follow-up evaluations. Provided the subjects enrolled to date were included in the follow-up evaluations, the amendment would not be expected to impact the trial findings. The third amendment occurred nearly half way through the study. Whether continuous ECG monitoring of subjects already enrolled and treated would have altered the safety findings of the study cannot be determined.

Schematic (Figure 1, p. 41 of final study report)



Schedule (based on Table 1, p. 49 of final study report)

Study Phase	Screening	Treatment	Follow-Up			Study Completion	Long-Term Follow-Up	
Visit Name		**Day 0 ***	**Days 1-3**	**Days 4-5**	**Days 6-13**	**Day 14**	**Month 3**	**Month 6**
Informed consent	x							
Inclusion/exclusion criteria	x							
Medical history	x							
Demographics	x							
Physical examination	x					x	x	x
Safety Labs: chemistry, hematology, urinalysis	x					x		
Pregnancy test	x							
12-lead ECG	x†	x†	x†	x†				
Concomitant medications	x	x	x	x	x	x	x	x
Vital signs	x	x‡	x			x		
Screen fail patient	x§	x						
Evaluate to enter treatment		x						
Assign patient randomization number		x						
Undergo hernia repair surgical procedure		x						
Instill specified volume of treatment		x						
Pharmacokinetic plasma sample collection		x	x	x#	x**			
Pain intensity evaluations		x	x	x				
Modified brief pain inventory evaluations			x	x				
Dispense/review patient e-diary		x	x	x#		x		
Rescue analgesia pain intensity evaluations		x	x	x	x	x		
Discharge patient following site visit		x††	x	x#		x		
Adverse event evaluation		x	x	x	x	x	x	x
Evaluation of surgical site healing and local tissue conditions			x	x	x	x	x	x

† Screening baseline ECG and then as indicated; 2 study centers performed continuous ECG monitoring for 24 hours as soon as practical after the surgical procedure and, if clinically indicated, a 12-lead ECG.
‡ Vital signs collection times: pretreatment, and post-treatment (hourly for the first 8 hours or until discharge if earlier).
§ If screening laboratory assays or ECG show a clinically significant abnormal result, screen fail patient.
|| Assign patient randomization number after successful completion of all screening procedures and evaluation to enter treatment at Day 0.
* Pharmacokinetic plasma sampling in the first 32 patients ONLY. Refer to Appendices 2, 3, and 4 of the protocol in Appendix 16.1.1 for specific timings of evaluations.
# Day 4 only.
** Day 7 only.
†† According to local practice.

Subject Disposition

A total of 135 patients were assessed for eligibility to enroll in the trial. The Applicant reported the disposition of the 124 subjects who were ultimately randomized as indicated in Table 44 below.

Table 44. Subject disposition (based on Table 3, p. 67 of the final study report)

	SABER-Bupivacaine 2.5 mL	**SABER-Bupivacaine 5.0 mL**	**SABER-Placebo**
Patients randomized, N	45	47	32
Patients who discontinued the study, n (% randomized)	3 (6.7)	0	1 (3.1)
Reason for discontinuation , n (% randomized)			
Multiple surgeries	1 (2.2)	0	0
Patient's best interest	1 (2.2)	0	0
Underwent surgery for preexisting condition	0	0	1 (3.1)
Non-allowed concomitant medications	1 (2.2)	0	0

The Applicant noted the following, related to the extension of the trial by the second amendment: a total of 104 of the 124 randomized subjects were evaluated at 3- and/or 6-month follow-up assessments. There were 102 patients assessed at Month 3 (SABER-Bupivacaine 2.5 mL, N=34; SABER-Bupivacaine 5.0 mL, N=42; placebo, N=26) and 94 patients assessed at Month 6 (SABER-Bupivacaine 2.5 mL, N=32; SABER-Bupivacaine 5.0 mL, N=38; placebo, N=24); 2 patients assessed at Month 6 were not assessed at Month 3. All patients who did not complete the long-term follow-up phase of the study were lost to follow up. Throughout the study, no patients discontinued because of AEs

There were a total of 76 protocol deviations: 25 for the SABER-bupivacaine 2.5 mL treatment; 30 for SABER-bupivacaine 5 mL treatment; and 21 for the combined SABER-placebo treatments. The types of deviations and their distribution among treatment arms did not suggest that there were any irregularities in the conduct of the trial or that the results of the trial would be adversely affected by their occurrence.

Reported Efficacy Findings

Based on the findings summarized in Table 45, the Applicant concluded that for both the ITT and efficacy evaluable populations, the normalized AUC for mean pain intensity on movement from 1 to 72 hours was significantly improved in the SABER-Bupivacaine 5.0-mL group versus the SABER-placebo group; furthermore, no significant differences were observed between the SABER-bupivacaine 2.5-mL group and the SABER-placebo group.

Table 45. Normalized AUC for Pain Intensity on movement from 1-72 hours (based on Table 7. P. 58 of final study report)

AUC Parameter	SABER-Bupivacaine 2.5 mL N=42	SABER-Bupivacaine 5.0 mL N=47	SABER-Placebo N=31
ITT Population			
Mean (SEM)	3.11 (0.25) *	2.47 (0.19) †	3.60 (0.30)
Median (95% CI)	2.73 (2.29, 3.28)	2.42 (1.85, 3.05)	3.77 (2.94, 4.13)
Efficacy Evaluable Population			
Mean (SEM)	3.11 (0.26) ‡	2.47 (0.19) §	3.61 (0.31)
Median (95% CI)	2.72 (2.28, 3.28)	2.42 (1.85, 3.05)	3.80 (2.94, 4.14)

* p=0.1574 versus SABER-placebo
† p=0.0033 versus SABER- placebo
‡ p=0.1733 versus SABER-placebo
§ p=0.0036 versus SABER-placebo

For the second primary endpoint, supplemental opioid rescue medication after surgery, the Applicant reported that smaller amounts were required by subjects treated with SABER-bupivacaine 5.0-mL group than those in the SABER-bupivacaine 2.5-mL group or placebo group; however the differences were not significant for either SABER-bupivacaine treatment compared to SABER-placebo. These results are summarized in Table 46 below.

Table 46. Post-operative analgesic requirements (based on Table 8, p.74 of the final study report)

Pain Parameter	SABER-Bupivacaine 2.5 mL *	SABER-Bupivacaine 5.0 mL †	SABER-Placebo
ITT Population			
Supplemental analgesic taken n (%) [95% CI]	31 (72.1) [56.3, 84.7]	25 (53.2) [38.1, 67.9]	23 (71.9) [53.3, 86.3]
No supplemental analgesic taken n (%)	12 (27.9)	22 (46.8)	9 (28.1)
Efficacy Evaluable Population			
Supplemental analgesic taken n (%) [95% CI]	30 (71.4) [55.4, 84.3]	25 (53.2) [38.1, 67.9]	22 (71.0) [52.0, 85.8]
No supplemental analgesic taken n (%)	12 (28.6)	22 (46.8)	9 (29.0)

* 2.5 mL versus SABER-placebo; p=0.9952
† 5.0 mL versus SABER-placebo; p=0.0909
‡ 2.5 mL versus SABER-placebo; p=0.8963
§ 5.0 mL versus SABER-placebo; p=0.1145

The Applicant reported the following findings for the secondary efficacy endpoints (based on data tables included in the final study report when the result was not explicitly reported by the Applicant):

1. Mean pain intensity normalized AUC over the time period of 1 to 48 hours: In both the ITT and efficacy evaluable populations, the mean pain intensity on movement normalized AUC from 1 to 48 hours was improved with SABER-bupivacaine versus placebo, with a statistically significant difference observed between SABER-bupivacaine 5.0 mL and placebo and a trend toward statistical significance between SABER-bupivacaine 2.5 mL and placebo. The mean pain intensity at rest normalized AUC from 1 to 48 hours approached a statistically significant difference between SABER-bupivacaine 5.0 mL and placebo, while there were no statistically significant between-group differences between SABER-Bupivacaine 2.5 mL and placebo.
2. Time to first use of rescue analgesic (not included in the protocol specified endpoints): In the ITT population, the time-to-first use of opioid medication was greatest in the SABER-bupivacaine 5.0-mL group (median, 131.8 hours; 95% CI: 31.9, not defined), followed by the SABER-bupivacaine 2.5-mL group (median, 10.8 hours; 95% CI: 1.1, 52.7), and the placebo group (median, 2.7 hours; 95% CI: 1.1, 25.3); the difference between the SABER-bupivacaine 5.0-mL group and placebo was statistically significant (p=0.0174).
3. Overall treatment satisfaction: The values were not reported.
4. Mean total opioid dose for analgesia rescue during the study: There were no differences in the supplemental analgesic requirements between any of the treatments.
5. Mean function activities (Days 1 through 5): The data were not reported.
6. The modified Brief Pain Inventory: There were no apparent differences between treatment groups.
7. An overall assessment of treatment satisfaction: The data were not reported.
8. Worst and least pain in the past 24 hours were collected using a 0 to 10 NRS with scores ranging from 0 (no pain) to 10 (worst pain possible): The findings were not reported.
9. Data on the extent the pain has interfered with normal function (getting out of bed, walk, interact with visitors, fall asleep, stay asleep, eat, deep breath/post-operative exercises, cough: the findings were not reported.
10. Worst pain and least pain from Day 1 to Day 5: There were no significant differences between treatment groups.

The Applicant made the following conclusions regarding the efficacy findings from the trial:

1. The use of SABER-bupivacaine 5.0 mL (660 mg) instilled directly into the wound effectively managed pain in patients who underwent elective, open, unilateral, tension-free, inguinal hernia repair.

2. SABER-bupivacaine 5.0 mL (660 mg) significantly improved the mean pain intensity on movement normalized AUC compared with SABER-placebo post-surgery for 48 and 72 hours.
3. Patients treated with SABER-bupivacaine 5.0 mL (660 mg) required significantly less opioid rescue medication post-surgery compared with SABER-Placebo for 48 and 72 hours.
4. Over the study period, SABER-Bupivacaine 5.0 mL (660 mg) significantly prolonged the time to first opioid use compared with SABER-Placebo.
5. Efficacy endpoints in the SABER-Bupivacaine 2.5 mL (330 mg) group were not statistically significantly different from SABER-Placebo; however, a trend toward a significant difference versus SABER-Placebo was observed with the mean pain intensity on movement normalized AUC from 1 to 48 hours and MEDD taken on Day 2.
6. Patient satisfaction with overall pain treatment was observed in each treatment group and persisted throughout the duration of the study.
7. Functional activity improved over time in all treatment groups.

Summary of Reported Safety Findings

The Applicant reported serious adverse events (SAEs) in 11 subjects during the treatment phase and the 6-month follow-up phase; the 6 patients that reported an SAE during the treatment phase included 3 who were treated with SABER-Bupivacaine 2.5 mL, 2 who were treated with SABER-Bupivacaine 5.0 mL, and 1 who was treated with placebo. Only one event (vasovagal syncope) was considered possibly related to treatment. [Reviewer comment: subject (b) (6) experienced hypotension, bradycardia and 14 seconds of asystole on post-operative day 1 that were considered study drug related; he received SABER-bupivacaine 5 mL. However, after unblinding, the Applicant noted that the plasma bupivacaine levels were "below toxic levels" and that the subject had been treated with atenolol 25 mg for hypertension. The Applicant and Investigators revised the causality to "unlikely related" based on this information.]

The Applicant reported adverse events (AEs)for the safety population by system organ class (Table 47) and by preferred terms (Table 48); however, only those AEs occurring in >10% of subjects in any treatment group were reported in the preferred term summary (

Table 47. Summary of adverse events by system organ class (based on Table 20, p. 91 of the final study report)

System Organ Class	SABER-Bupivacaine 2.5 mL [N=44] n (%)	SABER-Bupivacaine 5.0 mL [N=47] n (%)	Placebo [N=32] n (%)
Nervous system disorders	29 (65.9)	25 (53.2)	23 (71.9)
Gastrointestinal disorders	24 (54.5)	16 (34.0)	22 (68.8)

System Organ Class	SABER-Bupivacaine 2.5 mL [N=44] n (%)	SABER-Bupivacaine 5.0 mL [N=47] n (%)	Placebo [N=32] n (%)
Injury, poisoning, and procedural complications	16 (36.4)	original: 16 (34.0) ad-hoc: 15 (31.9)	8 (25.0)
Cardiac disorders	10 (22.7)	15 (31.9)	7 (21.9)
Skin and subcutaneous tissue disorders	12 (27.3)	11 (23.4)	7 (21.9)
Vascular disorders	5 (11.4)	5 (10.6)	3 (9.4)
Ear and labyrinth disorders	2 (4.5)	5 (10.6)	5 (15.6)
Musculoskeletal and connective tissue disorders	4 (9.1)	3 (6.4)	2 (6.3)
General disorders and administration site conditions	2 (4.5)	2 (4.3)	3 (9.4)
Infections and infestations	1 (2.3)	1 (2.1)	3 (9.4)
Renal and Urinary Disorders	2 (4.5)	1 (2.1)	1 (3.1)
Respiratory, thoracic, and mediastinal disorders	0	2 (4.3)	2 (6.3)
Metabolism and nutrition disorders	2 (4.5)	1 (2.1)	0
Psychiatric disorders	1 (2.3)	0	1 (3.1)
Investigations	0	0	2 (6.3)

Table 48. Summary of most common adverse events (based on Table 22, p. 93 of the final study report)

Preferred Term	SABER-Bupivacaine 2.5 mL [N=44] N (%)	SABER-Bupivacaine 5.0 mL [N=47] N (%)	Placebo [N=32] N (%)
Somnolence	17 (38.6)	13 (27.7)	15 (46.9)
Constipation	16 (36.4)	10 (21.3)	17 (53.1)
Dizziness	13 (29.5)	9 (19.1)	9 (28.1)
Nausea	13 (29.5)	8 (17.0)	9 (28.1)
Pruritus	12 (27.3)	9 (19.1)	7 (21.9)
Bradycardia	9 (20.5)	12 (25.5)	7 (21.9)
Headache	11 (25.0)	9 (19.1)	7 (21.9)
Postprocedural hemorrhage	8 (18.2)	12 (25.5)	5 (15.6)
Postoperative wound	9 (20.5)	7 (14.9)	3 (9.4)

complication			
Dysgeusia	5 (11.4)	5 (10.6)	4 (12.5)
Paresthesia	8 (18.2)	2 (4.3)	2 (6.3)
Tinnitus	2 (4.5)	5 (10.6)	5 (15.6)

The Applicant noted that most nervous system AEs were mild or moderate in severity. Severe AEs reported in the original safety analysis included headache (n=1) and migraine (n=1) in the SABER-bupivacaine 2.5-mL group; headache (n=1) and syncope vasovagal (n=1) in the SABER-Bupivacaine 5.0-mL group; and no severe AEs in the placebo group. Severe AEs reported in the ad-hoc analysis, which imputed missing severity data as "severe" rather than "mild," included somnolence (n=6), dizziness (n=4), paresthesia (n=3), dysgeusia (n=1), headache (n=1), and migraine (n=1) in the SABER-Bupivacaine 2.5-mL group; dizziness (n=3), somnolence (n=3), headache (n=1), and syncope vasovagal (n=1) in the SABER-Bupivacaine 5.0-mL group; and dizziness (n=2), dysgeusia (n=2), and somnolence (n=5) in the placebo group.

The Applicant described the AE data at the 6-month follow-up only by severity and relationship to study drug (Table 49). They noted that at the 6 months' follow up, the only AE that occurred at an incidence of >10% in any treatment group was postoperative wound complication, which occurred in 19% (7/36) of patients treated with SABER-bupivacaine 2.5 mL and 12% (3/26) of patients treated with placebo.

Table 49. Summary of 6-month follow-up AEs (Table 21, p. 77 of final study report)

	SABER-Bupivacaine 2.5 mL (N=36)	**SABER-Bupivacaine 5.0 mL (N=42)**	**SABER-Placebo (N=26)**
Patients with ≥1 adverse event, n (%)	21 (58.3)	15 (35.7)	11 (42.3)
Maximal severity			
Mild	13 (36.1)	8 (19.0)	5 (19.2)
Moderate	5 (13.9)	7 (16.7)	5 (19.2)
Severe	3 (8.3)	0 (0.0)	1 (3.8)
Strongest relationship to treatment			
Unrelated	11 (30.6)	11 (26.2)	6 (23.1)
Unlikely	8 (22.2)	4 (9.5)	4 (15.4)
Probably/possibly	2 (5.6)	0 (0.0)	1 (3.8)
Patients with ≥1 serious adverse event	4 (11.1)	0 (0.0)	2 (7.7)

The Applicant summarized adverse events considered probably or possibly related to study drug as shown in Table 50 below.

Table 50. Adverse events probably or possibly related to study drug administration (based on Table 27, p. 97 of the final study report)

System Organ Class/Preferred Term	SABER-Bupivacaine 2.5 mL [N=44] n (%)	SABER-Bupivacaine 5.0 mL [N=47] n (%)	SABER-Placebo [N=32] n (%)
Patients with adverse events, n (%)	8 (18.2)	13 (27.7)	9 (28.1)
Nervous System Disorders	**6 (13.6)**	**5 (10.6)**	**4 (12.5)**
Dizziness	4 (9.1)	0	0
Dysgeusia	2 (4.5)	2 (4.3)	1 (3.1)
Headache	0	1 (2.1) †	1 (3.1)
Paresthesia	3 (6.8)	1 (2.1)	2 (6.3)
Somnolence	3 (6.8)	3 (6.4)	1 (3.1)
Gastrointestinal Disorders	**3 (6.8)**	**2 (4.3)**	**4 (12.5)**
Constipation	2 (4.5)	2 (4.3)	3 (9.4)
Nausea	1 (2.3)	0	2 (6.3)
Injury, Poisoning and Procedural Complications	**1 (2.3)**	**4 (8.5)**	**0**
Postprocedural Hemorrhage	0	4 (8.5) ‡	0
Postoperative Wound Complication	1 (2.3)	0	0
Cardiac Disorders	**2 (4.5)**	**3 (6.4)**	**2 (6.3)**
Bradycardia	2 (4.5) §	3 (6.4)	2 (6.3)
Skin and Subcutaneous Tissue Disorders	**3 (6.8)**	**4 (8.5)**	**2 (6.3)**
Pruritus	3 (6.8)	4 (8.5)	2 (6.3)
Ear and Labyrinth Disorders	**0**	**1 (2.1)**	**2 (6.3)**
Tinnitus	0	1 (2.1)	2 (6.3)

Overall, the most common AEs, i.e., those with an incidence >10% in at least 1 treatment group, included somnolence, constipation, dizziness, pruritus, bradycardia, headache, post-procedural hemorrhage, postoperative wound complication, nausea, and dysgeusia. Adverse events from the modified Brief Pain Inventory (i.e., nausea/vomiting, drowsiness, itching, constipation, dizziness, ringing ears, metallic taste, and numbness or tingling of the toes or fingers) were reported in each treatment group. The incidence of all AEs probably or possibly related to treatment was 18.2% (8/44) in the SABER-bupivacaine 2.5 mL group, 27.7% (13/47) in the SABER-bupivacaine 5.0 mL group, and 28.1% (9/32) in the SABER-placebo group, and were mild or moderate in severity.

Nervous system adverse events were reported in 29 (66%), 25 (53%), and 23 (72%) of SABER-bupivacaine 2.5-mL, SABER-Bupivacaine 5.0-mL, and SABER-placebo treatments, respectively. Cardiac adverse events were experienced by 10 (23%), 15 (32%), and 7 (22%) patients treated with SABER-Bupivacaine 2.5 mL, SABER-Bupivacaine 5.0 mL, and placebo, respectively. There were 5 vasovagal syncopal episodes during recovery from general anesthesia among patients from all dose groups, including placebo; however, cardiovascular causes of syncope were ruled out.

The Applicant reported that ECG analyses revealed that SABER-Bupivacaine did not result in any clinically relevant changes in HR, PR, QRS, and QT interval, when corrected for HR. The QTcF result in the regular set of 12-lead ECGs showed a mean changes from baseline which would not indicate any signal that SABER-Bupivacaine affected cardiac depolarization or repolarization. They also noted that in the telemetry set of ECGs, showed a non-dose related increase in QTcF duration, likely due to lack of power, concomitant general anesthesia, and large spontaneous variability in QTc durations rather than a direct effect of SABER-bupivacaine.

Postoperative wound complication was the only AE reported in >10% of patients during the 6-month follow-up. This AE occurred in 7 (19.4%) subjects in the SABER-bupivacaine 2.5 mL group and 3 (11.5%) of subjects in the SABER-placebo group. Surgical site healing and local tissue conditions were reported as expected or normal in all patients at 6 months.

Discussion

The trial demonstrated that the 5 mL dose, but not the 2.5 mL dose, of SABER-bupivacaine was superior to SABER-placebo. The difference between the mean AUC values for SABER-bupivacaine 5 mL and SABER-placebo was just over 1 unit on the 10 unit pain scale. The clinical relevance of the difference is not readily discernible. Despite the significantly longer delay to first opioid rescue with SABER-bupivacaine 5 mL compared to SABER-placebo, there was no significant difference in opioid use over the first 72 hours.

Table 51 below summarizes the AEs related to the surgical incision. There was a substantial difference between SABER-placebo and the SABER-bupivacaine treatments only for “application site discoloration,” which was an Applicant-defined composite preferred term used to describe any peri-incisional skin color changes that developed in the postoperative period that included, among other AEs, bruising, ecchymosis, erythema, redness, and hematoma.

Table 51. Adverse events related to the surgical incision

Preferred Term	**SABER-Placebo (n=31)**		**SABER-Bupivacaine 2.5 mL (n=42)**		**SABER-Bupivacaine 5 mL (n=47)**	
Application site discolouration	7	23%	15	36%	16	34%
Application site pustules	0	0%	0	0%	1	2%
Haematoma	0	0%	1	2%	0	0%
Incision site complication	0	0%	2	5%	0	0%
Incision site hypoaesthesia	0	0%	1	2%	0	0%
Incision site infection	4	13%	0	0%	0	0%

Preferred Term	SABER-Placebo (n=31)		SABER-Bupivacaine 2.5 mL (n=42)		SABER-Bupivacaine 5 mL (n=47)	
Incision site oedema	2	6%	4	10%	2	4%
Incision site pain	1	3%	1	2%	1	2%
Local swelling	0	0%	0	0%	1	2%
Postoperative wound infection	0	0%	2	5%	2	4%
Scrotal haematoma	0	0%	5	12%	0	0%
Skin laceration	1	3%	0	0%	0	0%
Suture related complication	0	0%	4	10%	0	0%
Wound secretion	0	0%	2	5%	1	2%
Total	**15**	**48%**	**37**	**88%**	**24**	**51%**

Review of the verbatim terms indicated there were 5 cases of hematoma: 3 (7%) with SABER-bupivacaine 2.5 mL and 2 (4%) with SABER-bupivacaine 5 mL treatment.

The only cardiac adverse event that occurred more frequently than 5% was bradycardia, which occurred in 51%, 43%, and 45% of subjects treated with SABER-bupivacaine 5 mL, SABER-bupivacaine 2.5 mL, and SABER-placebo (both doses combined), respectively.

Table 52 provides key PK parameters from measurements made during the trial. The Cmax values were within the 2 mcg/ml threshold generally cited for toxicity.

Table 52. Summary PK information for bupivacaine (from Table 18, p.88 of the final study report)

Pharmacokinetic Parameters	SABER-Bupivacaine 2.5 mL	SABER-Bupivacaine 5.0 mL
Cmax (ng/mL), mean (SEM)	466.79 (60.48)	866.57 (114.02)
Tmax (hr), median (range)	12.0 (2.9-24.10)	23.95 (4.0-24.10)
T1/2 (hr) median (range)	23.50 (13.02–46.5)	25.41 (20.87–73.33)

Conclusions
This trial demonstrated the efficacy of the 5-ml dose of SABER-bupivacaine for providing postoperative analgesia following inguinal herniorrhaphy. The 5 mL dose of SABER-bupivacaine was significantly better than SABER-placebo and trended in the direction of being superior to SABER-placebo. The differences in mean pain intensity AUCs were small, just over 1 unit (out of 10) for the 5 mL dose and just under 1 unit for the 2.5 mL dose. There was no difference in the opioid rescue requirements (the second of the primary endpoints); however, there was a delay to the first opioid rescue with the 5 mL dose compared to the two other treatments.

There were no signs of cardiac or neurological toxicity that appeared to be dose related. There were differences in the incision sites that were worse with SABER-bupivacaine treatments than SABER-placebo. Whether the wound “discolouration” that occurred in the 23% of subjects in the SABER-placebo group was related to the SABER components, cannot be determined from the study, but the overall incidence appears to be substantially greater than that observed in clinical practice. However, there appeared to be no long-term problems associated with the use of any of the SABER products.

9.4.3 BU-001-IM (Phase 2, Controlled Trial – Abdominal Hysterectomy)

Title: An international, randomised, double-blinded, multi-centre, active- and placebo-controlled dose response trial to evaluate the efficacy and safety of SABER-Bupivacaine for post-operative pain control in patients undergoing primary, elective, open, abdominal hysterectomy

Study Dates: May 26, 2009, to June 1, 2010

Objectives
The objective was to identify the optimal dose of instilled SABER-Bupivacaine for post-operative pain control in abdominal hysterectomy for a non-malignant indication on the basis of efficacy, safety and PK evaluations.

Efficacy Endpoints
Primary endpoints:

- Pain intensity (PI) on movement area under the curve (AUC) over the time period 1 to 72 hours post-surgery
- Total use of opioid rescue analgesia 0 to 72 hours after surgery.

Secondary endpoints:

- Time to first opioid rescue medication usage
- OR-SDS score Day 0 to Day 7
- PI “at rest” 1 to 72 hours post-surgery AUC
- Patient’s pain treatment satisfaction score on Day 4
- Proportion of patients who were dischargeable (according to PADS) post-surgery Days 0, 1, 2, 3, 4 and 7

Inclusion Criteria (verbatim from pp. 30-31 of final study report)

1. Written informed consent was obtained according to local regulations before any trial-related activities. A trial-related activity was any procedure that would not have been performed during the routine management of the patient
2. Females 18 years of age and above
3. A planned elective, open abdominal hysterectomy for a non-malignant indication that required a Pfannenstiel incision. Surgery could be either supravaginal hysterectomy or a total abdominal hysterectomy (with or without salpingo-oophorectomy)
4. Patients suitable for general anaesthesia
5. Body Mass Index (BMI) no more than 35 kg/m^2

6. A requirement to refrain from strenuous activities throughout the trial period and to avoid modifications to prescribed exercise levels throughout the course of the trial
7. Ability to read, understand, communicate and voluntarily sign the approved informed consent form prior to the performance of any trial specific procedures.

Exclusion Criteria (verbatim from pp. 31-32 of final study report)

1. Participation in another clinical trial with an investigational drug or device within 30 days before inclusion in this trial
2. Previous enrolment into this trial
3. Known serious / important reactions in previous anaesthesia procedures with local anaesthetics
4. Known clinically significant hepatic, gastrointestinal, renal, haematological, urologic, neurological, respiratory, endocrine or cardiovascular system abnormalities
5. Known serious uncontrolled illness: cancer, psychiatric or metabolic disturbances. History of cured localised malignancies was allowed (i.e. basal or squamous cell skin carcinoma, breast carcinoma or cervical carcinoma)
6. Abnormal electrocardiogram (ECG) (interpretation of ECG must have been done by physician). Abnormalities such as sinus tachycardia, right bundle branch block, ectopic atrial rhythm or premature atrial contractions were not necessarily reason for exclusion (interpretation by physician)
7. Prolonged QT syndrome (QT higher than 470 milliseconds [msec]) or family history of long QT syndrome (interpretation of ECG must have been done by physician)
8. Current or regular use of analgesic medication for other indication(s)
9. Current or regular use of antidepressants, monoamine oxidase inhibitors, or medication known to be associated with QT prolongation (according to Appendix 1 of the Clinical Trial Protocol)
10. Conditions contraindicated for use of opioids, including paralytic ileus, acute or severe bronchial asthma or hypercarbia
11. Current or regular use of anticonvulsants or antiepileptics
12. Connective tissue disorders (systemic lupus erythematosus, scleroderma, mixed connective tissue disease)
13. Known or suspected alcohol abuse or illicit drug use within the 6 months prior to trial enrolment
14. Known sensitivity to bupivacaine (or similar local anaesthetics), benzyl alcohol or other trial drugs (paracetamol, morphine) or their constituents
15. Unwillingness or inability to comply with the trial visit
16. Situated in an institution due to regulatory order or judicial direction

Summary of Methodology

This trial was designed as a phase 2, randomized, multi-center, double-blinded, parallel-group, placebo- and active-controlled study in female adult patients undergoing primary, elective, open, abdominal hysterectomy for non-malignant conditions. The trial was to have two cohorts, 5 mL of SABER-bupivacaine and 7.5 mL SABER-bupivacaine, which were to be studied sequentially. For each cohort, an equal volume of SABER-placebo was to be administered as a placebo comparator and 40 mL of 0.25% bupivacaine HCL (100 mg of bupivacaine) was to be administered as an active control.

After the data for cohort 1 were analyzed, a decision was to be made, based on the efficacy, safety and pharmacokinetic results, regarding whether the second cohort would be initiated.

Each cohort consisted of a screening period beginning up to 14 days prior to the; a 7-day post-surgical period; an End of Trial (EOT) visit on post-operative Day 14; and a follow-up visit six months following surgery.

A total of 115 patients were randomized in cohort 1. After screening, the subjects were randomized 2:1:1 to the treatment groups: instillation of 5 mL of SABER-Bupivacaine (660 mg bupivacaine); instillation of 5 mL of SABER-placebo; infiltration of 40 mL of 2.5% bupivacaine hydrochloride (HCl) (100 mg bupivacaine).

All patients received paracetamol as post-operative background treatment. If this did not provide adequate pain relief, patients were to be given morphine intravenously or orally. Rescue medication was to be documented by the patient in the patient's electronic diary (eDiary/eCRF).

The trial was conducted in 13 centers in five countries. Upon completion of the first cohort, unblinded safety and efficacy data were analyzed. Based on the efficacy, safety and PK results, a recommendation was received from the Data Review Committee not to continue the trial with cohort 2.

Amendments

Four amendments were made to the protocol; the first three were made prior to the enrollment of any subjects. The amendments included the following:

1. August 25, 2008: Due to the unavailability of a 15 mg morphine tablet dose in some of the participating countries, 10 mg tablets were used to ensure that all countries were adhering to the same rescue medication regimen. This amendment also clarified the timings for the evaluation of home readiness using the Post Anesthetic Discharge Scoring (PADS).
2. January 20, 2009: This amendment added the long-term safety visit to assess the effects of SAIB component of SABER on the surgical wound, allowed paracetamol on Day 0 of the trial, allowed supplemental intravenous morphine in

addition to that administered by PCA, clarified the recording of background treatment in the eCRF not the eDiary, allowed flexibility regarding the taking of PK blood samples, allowed the use of alternative anesthesia during surgery, clarified the definition of "at rest," for pain assessments.

3. March 25, 2009: This amendment incorporated MRI scans as part of the long-term follow-up and benzyl alcohol plasma concentrations as part of the PK analyses at selected sites. MRI of the hysterectomy scar was to allow evaluation for the presence and the degree of inflammation, edema, scarring irregularities, fibrosis, and scar thickness between treatment arms.
4. July 13, 2009: this amendment restricted the use of paracetamol only to Day 0 to Day 2 (72 hours) instead of Day 0 to Day 7; allowed intravenous paracetamol beginning immediately after surgery to ensure that there was sufficient pain relief from background medication and subsequent adherence to the protocol. The amendment also required that alternative syringes were packed with the study drug to avoid application of the incorrect volume of the treatment following surgery.

Only 34 of the 115 subjects were randomized according to the final version of the protocol, i.e., were treated in accordance with the 4th amendment. The incorporation of the 4th amendment after more than half the subjects had been evaluated may have had an impact on the study findings, depending on how the last 34 subjects were randomized.

Schematic

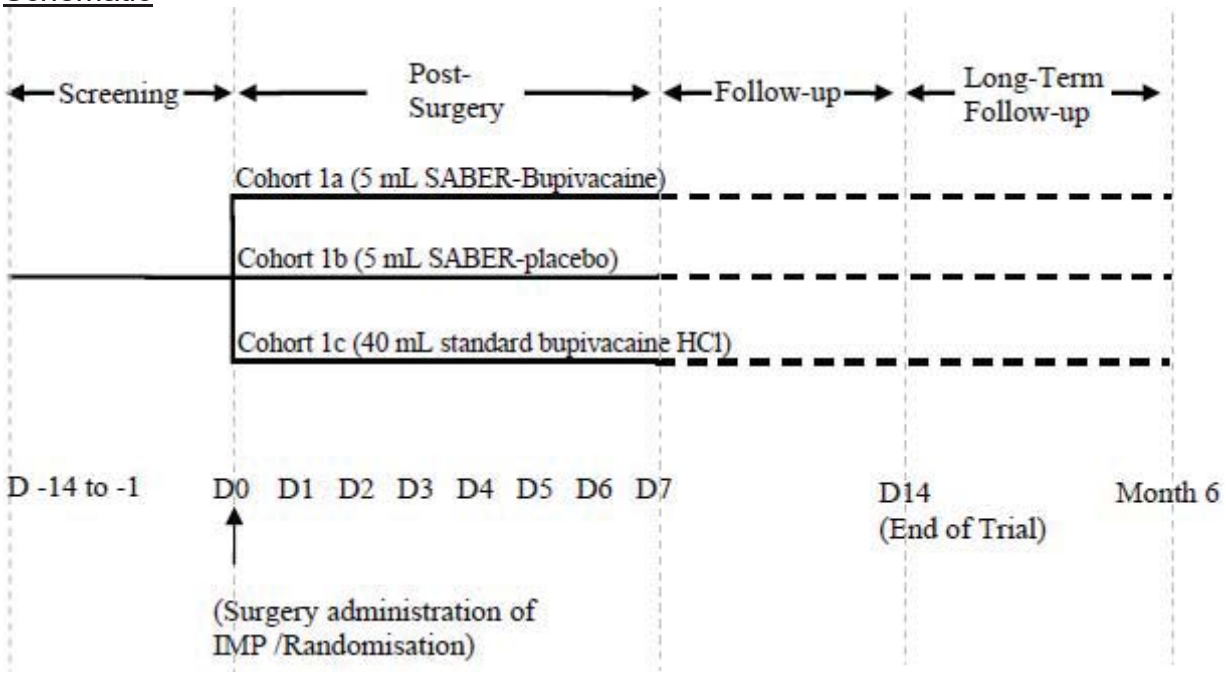


Figure 11. Study schematic (Figure 9-1 on p. 28 of the final study report)

Schedule (based on Table 9-2 on p. 37-38 of final study report)

Visit	Screening	Day of Surgery						EOT	Long-Term Follow-Up
Day	-14 to -1	0	1	2	3	4	7 (± 1)	14 (± 1)	6 mo. (± 1 mo.)
Procedure									
Informed consent	X								
Demographics	X								
Medical history	X								
Inclusion/exclusion criteria	X	X							
Physical examination"	X								
Vital signs[1]	X	X	X	X	X	X	X		
"ECG recording[2]	X	X	X	X	X			X	
Laboratory: blood sampling[3]"	X		X	X	X			X	
Concomitant illness	X	X							
Concomitant medication	X	X	X	X	X	X	X	X	
"Randomisation		X							
PK blood sampling[4]		X	X	X	X	X			
"eDiary hand-out and training	X	X							
Background pain treatment[5]		X	X	X					
Rescue medication administration and recording eDiary[6]		X	X	X	X	X	X		
Pain intensity assessment (NRS) eDiary[7]	X	X	X	X	X	X	X		
OR-SDS scoring eDiary[8]		X	X	X	X	X	X		
Home readiness evaluation[9]		X	X	X	X	X	X		
Patient's pain treatment expectations/satisfaction	X					X			
Rescue medication accountability			X	X	X	X	X	X	
Recording of AEs including CNS side effects		X	X	X	X	X	X	X	
Surgical wound healing							X	X	X
MRI[10]									X
EOT								X	

1. Heart rate and blood pressure performed on Day 0 in the afternoon, on Day 1 and 2 in the morning and afternoon and on Day 3, 4, and 7; once/day.

2. Baseline ECG was completed between the evening before surgery to the time of the surgery. Post-surgery ECGs were performed at 1, 4, 8, 12, 24, 36, 48 and 72 hours.
3. Screening laboratory samples were taken anytime between the screening visit and 1 day prior to surgery.
4. At pre-surgery and 1, 4, 8, 12, 24, 36, 48 and 72 hours post-surgery, blood was taken at the same time the ECG was performed. Additionally, a PK sample was taken 96 hours post-surgery.
5. Background treatment: Paracetamol 4 times daily on Day 0 to 2 (both days included [72 hours]); dose according to weight.
6. Day of surgery automatic recording of rescue medication via PCA device, Days 1 to 7 eDiary prompt four times/day.
7. On Day 0, at 1, 2, 4, 6, 8 and 12 hours post-surgery. On Days 1 to 7 at approximately 08:00 hours, 12:00 hours, 16:00 hours and 20:00 hours.
8. Daily in the evening, also performed on Day 5 and Day 6 (not shown on schedule)
9. Home readiness based on PADS, performed on Day 0 in the afternoon, Day 1 and 2 in the morning and afternoon and on Days 3, 4 and 7 once/day
10. MRI will be performed at selected sites

Subject Disposition

Of the 119 patients who were enrolled, 115 patients were randomized, 114 were dosed and 113 completed the study. One subject, randomized to the SABER-bupivacaine group, withdrew consent prior to surgery, and one subject in the SABER-placebo group withdrew consent after surgery due to a treatment-emergent adverse event (TEAE). The table below summarizes subject disposition by treatment.

Table 53. Subject disposition (based on Table 10-1, p. 61 and Table 11-1, p. 64 of final study report)

Subject Status	SABER-bupivacaine n (%)	SABER-placebo n (%)	Bupivacaine HCl n (%)	Total n (%)
Enrolled				119
Randomized	61 (51)	27 (23)	27 (23)	115 (97)
Completed	60 (98)	26 (96)	27 (100)	113 (98)
Withdrawn	1 (2)	1 (4)	0 (0)	2 (2)
Intent-to-treat (ITT)	61 (100)	27 (100)	27 (100)	115 (100)
Per-Protocol (PP)	46 (75)	22 (82)	22 (82)	90 (78)

Percentages for the randomized population are based upon the total set. All other percentages are based on the randomized population.

Protocol deviations leading to exclusion from the per protocol (PP) population occurred in a total of 25 subjects: 15 from the SABER-Bupivacaine group, 5 from the SABER-placebo group, and 5 from bupivacaine HCl group. The reasons for exclusion from the PP population included:

- Incorrect anesthetic used during surgery: 19 subjects
  - 11 from the SABER-bupivacaine group
  - 4 from the SABER-placebo group
  - 4 from standard bupivacaine HCl group)
- Dose of study drug outside the specified range: 2 subjects (both treated with SABER-bupivacaine); however, for one of these subjects the dosage had been entered incorrectly into the CRF (as 55% of dose) when she had actually received the correct dose of dosage (100% of dose)
- Use of a disallowed medication: 3 subjects, 1 from each treatment group
- Missing pain intensity on movement: 1 subject from SABER-bupivacaine group

Reported Efficacy Findings

The mean pain intensity (PI) on movement AUC from Day 0 through Day 7 for subjects in the intent-to-treat (ITT) population are shown in the figure below.

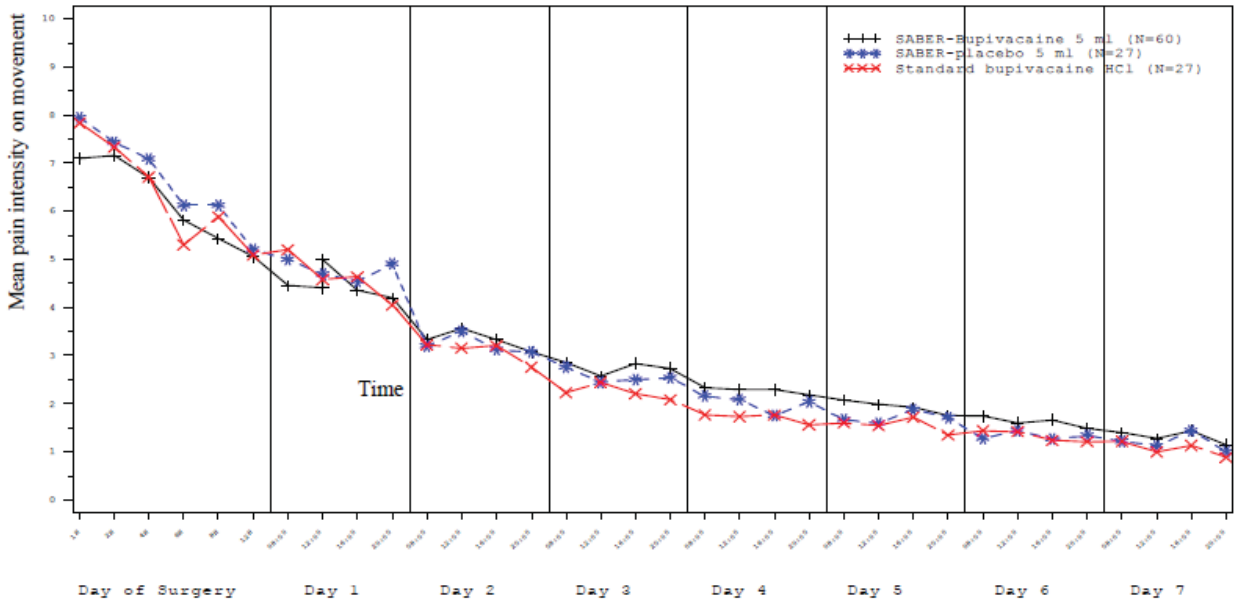


Figure 12. Mean pain intensity on movement over time for the ITT population (Figure 11-1, p. 73 of the final study report)

The Applicant indicated that between 1 and 72 hours after surgery, the mean AUC for PI on movement was similar across the three treatment groups, and the criterion for non-inferiority of SABER-Bupivacaine against SABER-placebo was met for the ITT population. In the subsequent superiority testing, they determined that SABER-Bupivacaine was not significantly superior to SABER-placebo. They reported similar results for the PP population. They performed the same analyses against bupivacaine HCl treatment and found similar results for both the ITT and PP populations. They concluded that, “from a clinical point of view, the pain levels in the three treatment groups were very similar.”

The second primary efficacy endpoint was the total use of opioid rescue analgesia from 0 to 72 hours after surgery. The findings are illustrated in the figure below.

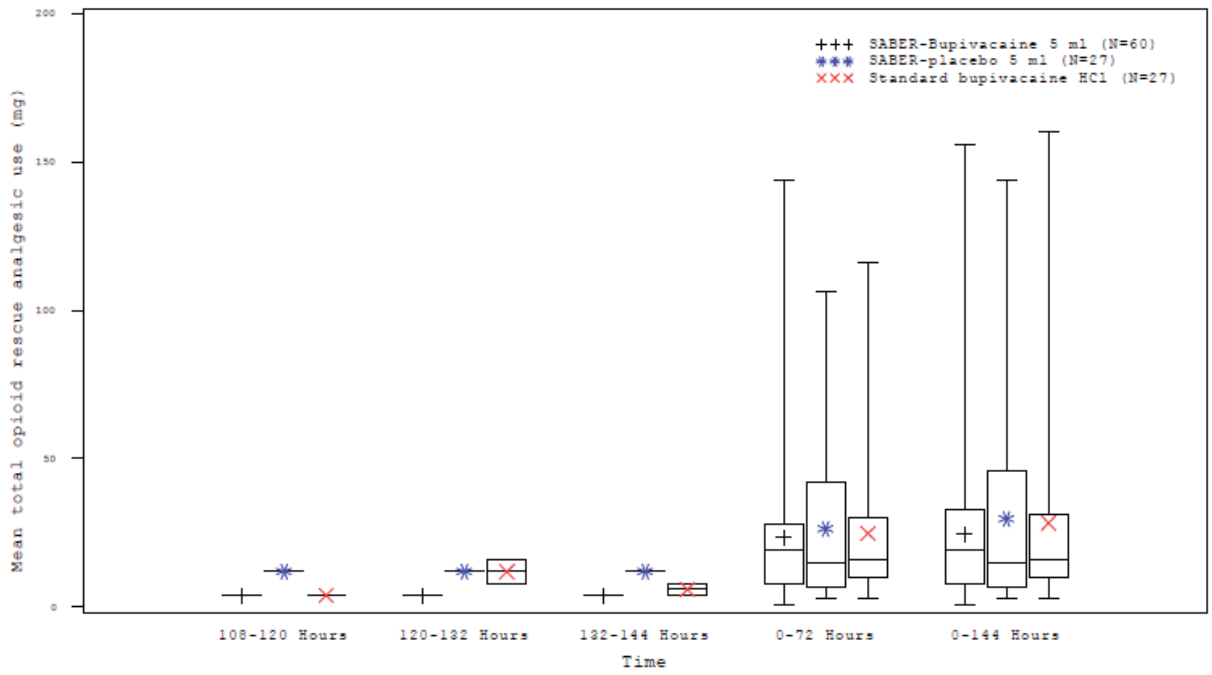


Figure 13. Mean total opioid rescue over time in the ITT population (Figure 3.3, p. 448 of the final study report)

The Applicant reported that the mean use of rescue analgesia (morphine equivalent dosages) was not statistically superior for SABER-bupivacaine over SABER-placebo or bupivacaine HCl for subjects in the PP population and the ITT population. This finding occurred not only for the 0-72 hours following surgery but for Day 4, Day 5, Day 6 and the total usage between Day 0 and Day 6 of the study.

The findings reported by the Applicant for the secondary efficacy endpoints were similar to those reported for the primary endpoints, i.e., SABER-Bupivacaine were not demonstrated to be superior to either SABER-placebo or bupivacaine HCl. The following results are verbatim from the final study report:

- The median time to first opioid rescue medication was similar across all treatment groups. No statistically significant differences were shown.
- Comparison of the opioid-related symptom distress scale (OR-SDS) scores on Day 0 to Day 7 did not reveal any statistically significant differences between treatment groups with the exception of the OR-SDS score on Day 0 which was significantly lower in the SABER-Bupivacaine group than in the SABER-placebo group. Overall, 114 patients (99.1% of patients in the ITT population) experienced an opioid-related side effect as reported via the OR-SDS.
- Non-inferiority of SABER-Bupivacaine against SABER-placebo from 1 to 72 hours regarding the mean PI at rest AUC from 1 to 72 hours post-surgery (ITT population) was not shown. Non-inferiority of SABER-Bupivacaine against standard bupivacaine HCl at 1 to 72 hours post-surgery was shown but the

SABER-Bupivacaine group was not shown to be statistically superior over the standard bupivacaine HCl group.

- On Day 4 the majority of patients were either satisfied or very satisfied with the pain treatment they had received for their surgery. The odds ratio for the pairwise comparisons of SABER-Bupivacaine against SABER-placebo and SABER-Bupivacaine against standard bupivacaine HCl confirmed that there were no statistical differences between the groups analysed.
- There were no statistical differences in the patients' home readiness on Day 1, Day 2 or Day 3 based on the PADS system.

Summary of Reported Safety Findings

The Applicant summarized the treatment-emergent adverse events (TEAEs) as shown in Table 54 below.

Table 54. Summary of TEAEs by treatment group (based on Table 12-1, p. 119 of final study report)

Patients with	SABER-Bupivacaine N 60			SABER-placebo N 27			Bupivacaine HCl N 27			Total N 114		
	n	%	n'	n	%	n'	n	%	n'	n	%	n'
TEAEs	50	83	144	24	89	54	24	89	55	98	86	253
Deaths	0	0	0	0	0	0	0	0	0	0	0	0
SAEs	7	12	8	0	0	0	0	0	0	7	6	8
Related TEAEs	39	65	50	11	41	13	2	7	2	52	46	65
TEAEs leading to discontinuation	0	0	0	1	4	1	0	0	0	1	1	1
TEAEs not yet known to be recovered*	15	25	19	7	26	8	2	7	5	24	21	32
TEAEs leading to change in concentration of medication	24	40	41	13	48	18	18	67	28	55	48	87

SAE = serious adverse event; TEAE = treatment-emergent adverse event; N = number of patient in a treatment group; n = number of patients with at least one event in the category; % = percentage of patients with at least one event in the category based on N, n' = number of events in a specified category.
*At the EOT visit

The Applicant indicated that there were no notable differences between treatment groups with regard to total TEAEs experienced. Of the 52 subjects who reported at least one TEAE that was considered to be related to treatment, 39 (65%) occurred in the SABER-Bupivacaine group compared to 11 (40.7%) in the SABER-placebo group and 2 (7.4%) in the standard bupivacaine HCl group. Only one TEAE (abdominal pain) lead to patient discontinuation from the study; that event was reported for a subject in the SABER-placebo group.

Seven subjects (6%) experienced a total of 8 SAEs, all patients reporting SAEs were in the SABER-Bupivacaine group). The Applicant considered 6 of the SAEs to be unrelated to treatment; two (abnormal ECG and ECG QT prolongation) were considered related to treatment. The other 6 SAEs included 2 instances of hematoma infection and a single instance of bronchospasm, laryngeal edema. and renal neoplasm. The Applicant summarized the TEAEs that were considered to be related to study drug as shown in Table 55 below.

Table 55. Summary of TEAEs considered related to study drug (based on Table 12-3, p. 123 of final study report)

Primary SOC **Preferred term**	**SABER-bupivacaine N=60**		**SABER-placebo N=27**		**Bupivacaine HCL N=27**		**Total N=114**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
All Related TEAEs	39	(65.0)	11	(40.7)	2	(7.4)	52	(45.6)
Injury, Poisoning and Procedural Complications	38	(63.3)	9	(33.3)	0	0.0	47	(41.2)
Post-procedural hematoma	36	(60.0)	9	(33.3)	0	0.0	45	(39.5)
Operative haemorrhage	2	(3.3)	0	0.0	0	0.0	2	(1.8)
Wound complication	1	(1.7)	0	0.0	0	0.0	1	(0.9)
Overdose	1	(1.7)	0	0.0	0	0.0	1	(0.9)
Nervous system disorders	4	(6.7)	2	(7.4)	1	(3.7)	7	(6.1)
Dizziness	4	(6.7)	2	(7.4)	1	(3.7)	7	(6.1)
Investigations	2	(3.3)	1	(3.7)	0	0.0	3	(2.6)
WBC count increased	0	0.0	1	(3.7)	0	0.0	1	(0.9)
ECG abnormal	1	(1.7)	0	0.0	0	0.0	1	(0.9)
ECG QT prolonged	1	(1.7)	0	0.0	0	0.0	1	(0.9)
General disorders and administration	2	(3.3)	0	0.0	0	0.0	2	(1.8)
Pyrexia	1	(1.7)	0	0.0	0	0.0	1	(0.9)
Inflammation of wound	1	(1.7)	0	0.0	0	0.0	1	(0.9)
Vascular disorders	1	(1.7)	1	(3.7)	0	0.0	2	(1.8)
Wound haemorrhage	1	(1.7)	1	(3.7)	0	0.0	2	(1.8)
Gastrointestinal disorders	0	0.0	0	0.0	1	(3.7)	1	(0.9)
Abdominal pain	0	0.0	0	0.0	1	(3.7)	1	(0.9)

Primary SOCs are presented in descending frequency.
Preferred terms are sorted within primary SOC in descending total frequency, based on MedDRA. A patient with multiple occurrences of a TEAE under one treatment was counted only once in the preferred term for that treatment. A patient with multiple TEAEs within a primary SOC was counted only once in the total row.
ECG = electrocardiogram; MedDRA = Medical dictionary for regulatory activities; N = number of patient in a treatment group; n = number of patients with at least one event in the category; % = percentage of patients with at least one event in the category based on N; SOC = system organ class; TEAE = treatment-emergent adverse event; WBC = white blood cell.

Adverse Events of Special Interest

Due to the high concentration of bupivacaine in SABER-bupivacaine and the potential for toxic systemic exposures, the Applicant was charged with evaluating the risk for cardiac and neurological toxicity.

To monitor for cardiac toxicity, ECGs were recorded at predetermined times and evaluated for changes in morphology with special consideration given to the PR, QRS, and QT intervals, heart rate, and the occurrence of QTcF prolongation. Altogether, 1344 study ECGs were available from 115 patients assigned to the three different treatment groups according to the study protocol. ECG interval data and interpretation findings were analyzed at a central ECG laboratory where baseline recordings were compared to recordings made at different treatment time points from 1 hour up to 72 hours after surgery. Three patients experienced ECG abnormalities: QTc prolongation, inverted T waves without Q waves, and non-specific ST-T changes. These patients all belonged to the SABER-bupivacaine group. The changes were all classified as SAEs and were experienced at: 4, 6, 8 (worsening QTcF prolongation from that measured at 4 hours), and at 72 hours following study drug administration. Aside from the SAEs, the Applicant reported that the frequencies of ECG interpretation findings were low in all treatment groups. The main observation was an increase of T wave flattening and transient decreases in heart rate in post-surgery ECGs. They indicated that the observations were found in all three treatment groups, and no correlation was found between ECG measurements and bupivacaine plasma concentrations.

The only sign of neurotoxicity, based on TEAEs considered related to study drug was dizziness, which occurred more often in subjects treated with SABER-placebo than in the other two treatment groups. However, somnolence was also observed in > 5% of SABER-bupivacaine treated subjects. It was reported for 8% of subjects treated with SABER-bupivacaine and 7% of subjects treated with bupivacaine HCl, but not reported for any SABER-placebo treated subjects.

Because the SAIB component of SABER-bupivacaine, and SABER-placebo, were found to persist unaltered in animal tissues for at least a year, the effects, if any, of this substance in the surgical wound was to be evaluated. To this end, the Applicant had the surgical site evaluated for healing and local tissue conditions at the 6-month follow-up visit and evaluated the scar in a subset of subjects using MRI.

Based on the physical examination, the surgical site healing and local tissue conditions were as expected in 73 (64%) patients at Day 7, in 99 (87%) patients at end of treatment (EOT = Day 14) and in 108 (95%) patients at the 6 months follow-up visit. There was, however, a notable difference between treatment groups. All subjects in the bupivacaine HCl group had healed and had local tissue conditions as expected by Day 7, whereas 32 (53%) subjects and 8 (30%) subjects had not healed or did not have local tissue conditions as expected in the SABER-Bupivacaine and SABER-placebo groups, respectively. By EOT, 50 (83%) subjects in the SABER-Bupivacaine group and 22

(82%) in the SABER-placebo group had healed and had local tissue conditions that were considered to be normal at that point of recovery. At the 6 months follow-up visit the majority of patients had surgical site healing/local tissue conditions as expected with no notable differences between treatment groups.

The Applicant reported that the MRI scans indicated the mean scar thickness after 6 months was 12.5 mm for the SABER-Bupivacaine group compared with 11.5 mm for both the SABER-placebo and bupivacaine HCl groups. Small focal edema was reported for 3 out of 10 subjects in the SABER-bupivacaine group, 3 out of 5 subjects in the SABER-placebo group, and 0 out of 6 subjects in the bupivacaine HCl group. These were described as a diffuse fluid signal detected by the scanner, without cavities, and with no vehicle and no foreign body reaction. There no findings of fibrosis with the MRIs. The edema was not considered to be pathological and the changes observed with the MRI were not detected in the clinical evaluation of local tissue condition and wound healing at 6 months. In addition, the Applicant noted that there was no correlation between the MRI findings and the reports of post procedural hematoma during the first two weeks post-surgery. Overall, the findings from the MRIs were considered by the external wound healing expert to be of limited clinical relevance.

Summary of Pharmacokinetics Results

The Applicant reported the following findings based on the PK assessments made during the study:

1. With the SABER-formulation, bupivacaine plasma concentrations increased slowly and for extended durations both total and free bupivacaine were observed.
2. The geometric mean C_{max} of bupivacaine was 0.548 mg/L and was observed at a median t_{max} of 36 hours.
3. Ninety-six (96) hours post dose there were still measureable plasma concentrations of bupivacaine in all patients of the SABER-Bupivacaine group.
4. C_{max} values following SABER-bupivacaine treatment were highly variable. In contrast, bupivacaine plasma concentrations following bupivacaine HCl showed a geometric mean C_{max} of 0.313 mg/L at a median t_{max} of 1 h post dose. Bupivacaine plasma concentrations were lower than in the SABER-Bupivacaine group by 4 hours post dose and beyond.
5. The geometric mean apparent $t_{1/2}$ of bupivacaine was approximately 18 hours for SABER-Bupivacaine and 8.5 hours for bupivacaine HCl, respectively.
6. Both values were influenced (prolonged) by flip-flop pharmacokinetics.
7. The average plasma protein binding of bupivacaine was approximately 5%, free bupivacaine plasma concentrations generally paralleled those of total bupivacaine. There was a large interindividual variability of C_{max} of both total and free bupivacaine.
8. The highest individual Cmax-values of total and free bupivacaine were 1.74 mg/L and 0.099 mg/L, respectively. The probability of C_{max} of free plasma bupivacaine

for 5.0 mL (7.5 mL) SABER-Bupivacaine to exceed 0.100 mg/L (0.150 mg/L) was approximately 1%.

9. Benzyl alcohol plasma concentrations were highest at 1 hour post dose, followed by a rapid decrease. The apparent $t_{1/2}$ of benzyl alcohol was 4.7 hours and may also have been influenced by flip-flop kinetics. Benzyl alcohol plasma concentrations were below the limit of quantification well before C_{max} of bupivacaine was reached.
10. Alpha-1-acid glycoprotein (AAG) plasma concentrations increased by approximately 50% until 72 hours post-surgery. AAG and % free bupivacaine showed a slight reciprocal relationship with a decrease of the % free fraction of bupivacaine with increasing AAG.
11. There was no apparent influence of either total or free bupivacaine on any cardiovascular parameters (QTcF, QTcB, and QRS) even at the highest observed bupivacaine plasma concentrations. The few reported CNS side effects did not correlate with either C_{max} or t_{max} of free bupivacaine.

Discussion

This trial failed to demonstrate that SABER-bupivacaine was superior to either SABER-placebo or bupivacaine HCL. The failure of bupivacaine to differ from SABER-placebo suggests that the dosing was inadequate or that the pain associated with the procedure is more related to visceral than superficial trauma. Based on the 40 mL dose of bupivacaine HCl 0.25%, the more likely reason for the failure is the greater intensity of the visceral pain.

The safety evaluations demonstrated that SABER-bupivacaine and SABER-placebo are both associated with a substantial amount of hematoma formation, 60% and 33%, respectively, while bupivacaine HCl was not associated with any instances of this adverse event. Two of the hematomas became infected, which were considered SAEs. Subject (b) (6) and (b) (6) experienced infected hematomas in the vagina that were considered unrelated to study drug and treated medically. In addition to the hematomas, all of the other incision related AEs were related to SABER-containing treatments. These included wound hemorrhage (2 cases with SABER-bupivacaine and 2 cases with SABER-placebo) and inflammation. There was a single case of dehiscence, which occurred with SABER-bupivacaine treatment.

The only ECG TEAEs to occur were all serious and occurred with SABER-bupivacaine treatment. These included, “abnormal ECG” and prolonged QT interval (512 msec), focal anterior lead changes without Q waves, and marked nonspecific changes. The first and last events were considered related to study drug and required follow-up care and resolved. The focal anterior lead changes were not resolved by the end of the treatment period.

The MRI findings at 6 months after surgery indicated that SABER is still present in the surgical wound; however, the physical examination findings indicated there were no adverse effects associated with its presence.

Conclusions

This trial demonstrated that, for patients undergoing hysterectomy, SABER-bupivacaine was not superior to either SABER-placebo or bupivacaine HCl. From a clinical perspective, there was no apparent difference in pain control on movement for any of the treatments. SABER-bupivacaine was associated with a substantial number of adverse events and SAEs, some of which were observed in subjects treated with SABER-placebo but not observed in any subjects treated with bupivacaine HCl.

This study demonstrated no benefit for SABER-bupivacaine but showed substantial risk with the product compared to SABER-placebo and bupivacaine HCl when used for incisional analgesia following hysterectomy.

9.4.4 CLIN-005-0010 (Phase 2, Controlled Trial – Inguinal Herniorrhaphy)

Title: A Randomized, Double-blind, Placebo-controlled Study of the Efficacy and Safety of Subcutaneous or Subaponeurotic SABER™-Bupivacaine in Patients Undergoing Open Inguinal Hernia Repair

Study Dates: March 30, 2006 to March 22, 2007

Objectives

Primary objective: to determine the efficacy of SABER-bupivacaine administered subcutaneously or into the subaponeurotic space in subjects undergoing elective open inguinal hernia repair.

Secondary objectives: to determine the safety and tolerability of SABER-bupivacaine administered subcutaneously or into the subaponeurotic space in subjects undergoing elective open inguinal hernia repair.

Efficacy Endpoints

Primary Efficacy Endpoints:

1. Pain intensity (PI) during movement and PI while at rest, assessed using the time-weight average scores (AUCs) for the PP Population (0=no pain, 10=worst pain possible) for 120 hours following study drug administration.
2. Pain control by study day and treatment, assessed using the numerical score for the PP Population (1=Poor, 5=Excellent) for each of the 5 days following study drug administration.

Secondary Endpoints:

1. The Modified Brief Pain Inventory evaluation of worst and least pain, assessed using the time-weighted average and daily numerical scores for the per protocol population
2. Rescue medication analgesics, assessed using the opioid rescue analgesia cumulative morphine equivalent dose for the per protocol population
3. Function scores and hours sitting and walking, assessed by the individual function scores
4. Overall treatment satisfaction scores, assessed using the individual subject scores (1=very dissatisfied; 6=very satisfied)
5. Pain intensity over time scores

Inclusion Criteria (verbatim from p. 36 of the final study report)

1. Males and females, 18 years of age or above, who planned to undergo ambulatory open repair of inguinal hernia, requiring an incision of 4 to 6 cm in length.
2. Determined to be in good health prior to study participation based on a medical history, physical examination, electrocardiogram (ECG), and laboratory tests.
3. Body Mass Index (BMI) 13 through 35 kg/m^2.
4. Systolic blood pressure no greater than 160 mmHg and diastolic blood pressure no greater than 95 mmHg.
5. A requirement that males and females must agree to use a medically acceptable method of contraception throughout the study period and for 1 week after the study was completed for all subjects. Acceptable methods that may have been used were abstinence, birth control pills/patches, diaphragm with spermicide, intra-uterine device (coil), condom and foam, surgical sterilization, and progestin implant or injection.
6. A requirement to refrain from strenuous activities throughout the study period and avoid modifications to prescribed physiotherapy and exercise levels throughout the course of the study.
7. Ability to read, understand, communicate, and voluntarily sign the approved informed consent form prior to the performance of any study specific procedures.

Exclusion Criteria (verbatim from pp. 36-37 of the final study report)

1. Pregnancy or lactation.
2. Presence of abdominal surgery with scar tissue that would have limited subjects' ability to participate.
3. Evidence of clinically significant hepatic, gastrointestinal, renal, hematologic, urologic, neurologic, respiratory, endocrine, reproductive, or cardiovascular system abnormalities, psychiatric disorders, or acute infection.
4. Connective tissue disorders (systemic lupus erythematosus, scleroderma, mixed connective tissue disease).
5. Current or regular use at screening of triptyline or imipramine antidepressants, monoamine oxidase inhibitors.
6. Known or suspected alcohol abuse within the 6 months prior to study enrollment or illicit drug use.
7. Use of any prescription drugs or over-the-counter medication starting within 7 days before treatment and throughout the study (except for birth control medications) that may have interfered with the conduct or interpretation of the study results (Note: subjects taking regular analgesic medications for other indications were excluded from the study).
8. Participation in another clinical study concurrent or within 30 days of enrollment.
9. Known sensitivity to bupivacaine, BA, or other study drugs or their constituents.
10. Subjects unwilling or unable to comply with the study visit schedule.

Summary of Methodology

This trial was designed as a randomized, double-blind, placebo-controlled, Phase 2 study that examined the efficacy of SABER-Bupivacaine instilled throughout the subaponeurotic and subcutaneous spaces, administered to subjects undergoing elective open inguinal hernia repair by one of two methods:

1. injection into the subaponeurotic space
2. subcutaneously

The trial was conducted in 2 separate and sequential cohorts (Cohort 1 and Cohort 2) each of which evaluated a single method of administration. Approximately equal numbers of subjects were to be enrolled, in sequence, to each cohort.

The trial included a screening period, admission to the clinic and surgery on Day 0, postoperative evaluations, discharge from clinic, and follow-up evaluations extending to Day 14.

Post-operative evaluations took place on Days 1, 2, 4, and 5 by telephone and an in-clinic evaluation on Days 3 and 14 (follow-up). Subjects were to have recorded pain intensity (PI), concomitant medications, adverse events (AEs), and use of rescue analgesia on diary cards from Days 0 through 5. Subjects also were to have recorded AEs and concomitant medications through Day 14.

The protocol specified treatments for each of the cohorts are described below.

Cohort 1:
Immediately prior to surgery, the first 45 subjects were randomly assigned in a 1:1:1 ratio to receive 1 of the following treatments:

- Treatment Group 1: Prior to wound closure, 5.0 mL of SABER-Placebo was to have been injected into the superior, medial, and inferior subaponeurotic spaces. After wound closure, SABER-bupivacaine was to have been administered as two trailing subcutaneous injections along each side of the incision line (expected to be 4 to 6 cm). The total delivered volume of SABER-bupivacaine was 5.0 mL.
- Treatment Group 2: Prior to wound closure, 5.0 mL of SABER-bupivacaine was to have been injected into the superior, medial, and inferior subaponeurotic spaces. After wound closure, SABER-placebo was administered as 2 trailing subcutaneous injections along each side of the incision line (expected to be 4 to 6 cm). The total delivered volume of SABER-placebo was 5.0 mL.
- Treatment Group 3: Prior to wound closure, 5.0 mL of SABER-placebo was injected into the superior, medial, and inferior subaponeurotic spaces. After wound closure, SABER-placebo was administered as two trailing subcutaneous injections along each side of the incision line (expected to be 4 to 6 cm). The total subcutaneously delivered volume of SABER-placebo was 5.0 mL. The total delivered volume of SABER-placebo was 10.0 mL.

Cohort 2:
Immediately prior to surgery, the second group of 45 subjects was randomly assigned in a 1:1 enrollment ratio to receive 1 of the following treatments:

- Treatment Group 4: During the wound closure, 5.0 mL of SABER-placebo was instilled gradually throughout the inguinal canal and the abdominal wall layers to cover all raw surfaces of the wound, filling up subaponeurotic and subcutaneous spaces.
- Treatment Group 5: During the wound closure, 5.0 mL of SABER-bupivacaine was instilled gradually throughout the inguinal canal and the abdominal wall layers to cover all raw surfaces of the wound, filling up subaponeurotic and subcutaneous spaces (7.5 mL specified for Cohort 2a comprising Treatment 5a).

Note: Protocol Amendment 04, dated 14 November 2006, changed the amount of drug to be administered in Cohort 2 from 7.5 mL to 5.0 mL. However, one subject was administered Treatment 5a (7.5 mL) before this amendment was put into effect. No subjects received 7.5 mL of placebo.

The trial was conducted at seven sites in the United States and one site in New Zealand.

Amendments

1. (March 9, 2006) modified the protocol to:
    a. Clarify SAE reporting.
    b. Clarify that follow-up visits on Days 1, 2, 4 and 5 will be conducted by telephone and the follow-up visit on Day 3 will be conducted in the clinic.
    c. Clarify the method of assigning subject numbers and randomization numbers.

    This amendment was implemented prior to any subject enrollment.

2. The purpose of Protocol Amendment 02, dated 09 (June 2, 2006) modified the protocol to:
    a. Clarify that a central laboratory will be used for the clinical laboratory evaluations.
    b. Clarify that only subjects with a BMI of 13 through 35 kg/m2 will be included.
    c. Clarify that epinephrine should only be used during the first infusion during the surgical procedure.
    d. Clarify that pre-operative and intra-operative bupivacaine should not be used.
    e. Clarify that combination analgesics (eg, Vicodin, Lortab) should not be used.
    f. Clarify the surgical procedure.

One study site had enrolled subjects prior to the implementation of this amendment.

3. (September 19, 2006) modified the protocol to:
    a. Change the treatments to be administered in this study.
    b. The original protocol was designated as Cohort 1, and compared the effectiveness of an injection of SABER-bupivacaine with SABER-placebo injected into the superior, medial, and inferior subaponeurotic spaces or as 2 trailing subcutaneous injections along each side of the incision line according to a specific randomization scheme.
    c. Cohort 2 was added and was designed to compare the effectiveness of direct in-the-wound instillation (no needle injections) of SABER-bupivacaine to SABER-placebo. During wound closure, SABER-Bupivacaine or SABER-placebo was to be instilled gradually throughout the inguinal canal and the abdominal wall layers to cover all raw surfaces of the wound, filling up subaponeurotic and subcutaneous spaces according to a specific randomization scheme.
    d. Allowed for a direct comparison of a SABER-bupivacaine to SABER-placebo injection administration technique to that of SABER-bupivacaine versus SABER-placebo instillation within the same study and within the same investigative sites.
    e. Modified the inclusion criterion for age; the inclusion criterion was changed from “18 to 65 years of age” to “18 years of age or above”.

4. (November 14, 2006) modified the protocol to clarify the following for Cohort 2:
    a. Changed the amount of SABER-placebo to be used during the wound closure from 7.5 mL to 5.0 mL in Treatment Group 4 (the Applicant states that this change resulted from an FDA recommendation that additional safety data be collected on the 7.5-mL dose before its use in clinical trials).
    b. Changed the amount of SABER-bupivacaine to be used during the wound closure from 7.5 mL to 5.0 mL in Treatment Group 5 (the Applicant states that this change resulted from an FDA recommendation that additional safety data be collected on the 7.5-mL dose before its use in clinical trials).
    c. A drug screen test for opiates, opioid receptor antagonists, and cocaine was to be performed at screening for Cohort 2.
    d. During surgery, incision length was to be documented for all subjects.
    e. No additional bupivacaine or other amide local anesthetic could be used at the surgical site.
    f. New sponsor contacts.
    g. New labels for the study drug syringe were to be used for Cohort 2.

Schedule (Table 9.1, p. 43 of the final study report)

Study Phase	Screening	Treatment	Follow-up			Study Completion
Visit Name		Day 0[a]	Days 1-3	Days 4-5	Days 6-13	Day 14
Informed consent	X					
Inclusion/Exclusion criteria	X					
Medical history	X					
Demographics	X					
Physical examination	X					X
Safety labs: chemistry, hematology, urinalysis	X					X
Urine drug toxicology screen	X[b]					
Pregnancy test	X					
12-lead ECG	X[c]	X[c]	X[c]	X[c]		
Concomitant medications	X	X	X	X	X	X
Vital signs	X	X[d]	X			X
Screen fail subject	X[e]	X				
Evaluate to enter treatment		X				
Assign subject number	X[f]					
Undergo hernia repair surgical procedure		X				
Inject study drugs 1 and 2		X				
PI evaluations[g]		X	X	X		
Modified Brief Pain Inventory evaluations[g]			X	X		
Dispense/Review subject diary card		X	X	X[h]		X
Rescue analgesia PI evaluations		X	X	X	X	X
Discharge subject following site visit		X[i]	X			X
AE evaluation		X	X	X	X	X

[a] Treatment to occur within 7 days of Screening.
[b] For Cohort 2 only.
[c] Screening baseline ECG and then as indicated.
[d] Vital signs collection times: pretreatment, post-treatment: monitored hourly for the first 8 hours or until discharge if earlier.
[e] If screening laboratory assays or ECG showed a clinically significant abnormal result, subject screen failed.
[f] Subject randomization number assigned after successful completion of all screening procedures.
[g] Refer to Appendices 2, 3, and 4 of the protocol for evaluation times.
[h] Telephone review of diary card.
[i] According to local practice.

Subject Disposition (Table 14.1.1, p. 104 of the final study report)

Disposition	Treatment 1 (N 13)	Treatment 2 (N 18)	Treatment 5 (N 22)	Treatment 5a (N 1)	SABER-BUP (N 40)	Pooled Placebo (N 35)	All Subjects (N 89)
Number of subjects randomized	13	18	22	1	40	35	89
Number of subjects completing study	13 (100.0%)	18 (100.0%)	20 (90.9%)	1 (100.0%)	38 (95.0%)	34 (97.1%)	86 (96.6%)
Number of subjects who prematurely withdrew	0 (0.0%)	0 (0.0%)	2 (9.1%)	0 (0.0%)	2 (5.0%)	1 (2.9%)	3 (3.4%)
Reasons for Subject Withdrawal:							
Adverse event	0 (0.0)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Protocol violation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Noncompliance	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to follow up	0 (0.0%)	0 (0.0%)	2 (9.1%)	0 (0.0%)	2 (5.0%)	1 (2.9%)	3 (3.4%)
Withdrew consent	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other (Specify)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Analysis Population							
Safety	13	18	22	1	40	35	89
Intent to Treat (ITT)	13	18	22	1	40	35	89
Per Protocol (PP)	11	18	22	1	40	34	86

Treatments (5mL): 1 = SABER-Bupivacaine subcutaneous, 2= SABER-Bupivacaine subaponeurotic, 3= SABER-Placebo, 4= SABER-Placebo, 5=SABER-Bupivacaine subaponeurotic and subcutaneous spaces . Treatments 4a and 5a are as 4 and 5, but 7.5 mL. SABER-BUP = Treatments 2 and 5. Pooled Placebo=Treatments 3, 4a, and 4.

Reported Efficacy Findings

For the assessments of pain intensity with movement, which are summarized in Table 56 below, the Applicant reported that the mean values in the SABER-bupivacaine treatment groups were 2.82, 2.53, and 4.05 for Treatments 1, 2, and 5, respectively, compared to 3.02 in the Pooled Placebo group. Treatment 2 had the lowest mean value (least pain). Compared to the Pooled Placebo group, Treatment 2 was numerically lower (treatment difference = -0.49, 95% CI = -1.50 to 0.51), although the difference did not reach statistical significance (P=0.332). The only statistically significant difference represented a higher PI AUC value, which occurred in Treatment 5 compared to Pooled Placebo (P=0.035). Similar results were observed for PI at rest, which are summarized in Table 57 below, where the only statistically significant difference for PI AUC at rest represented a higher PI AUC value in Treatment 5 than in Pooled Placebo (P=0.014).

Table 56. Summary of $AUC_{0\text{-}120\ hours}$ pain intensity on movement results (Table 11.1, p. 65 of the final study report)

Treatment	n	Mean (SD)	Comparison to Pooled Placebo	
			Mean Difference (95% CI)	*P*-value
Treatment 1	11	2.82 (2.418)	-0.21 (-1.40 - 0.99)	0.734
Treatment 2	18	2.53 (1.236)	-0.49 (-1.50 - 0.51)	0.332
Treatment 5	21	4.05 (1.824)	1.03 (0.07 - 1.99)	0.035
SABER-BUP	39	3.35 (1.740)	0.27 (-0.54 - 1.08)	0.512
Pooled Placebo	34	3.02 (1.651)		

Treatments:
1 = SABER-Bupivacaine subcutaneous (5.0 mL)
2 = SABER-Bupivacaine subaponeurotic (5.0 mL)
5 = SABER-Bupivacaine subaponeurotic and subcutaneous spaces (5.0 mL)
SABER-BUP =Treatments 2 and 5
Pooled Placebo = Treatments 3 and 4 (both SABER-placebo)

Table 57. Summary of $AUC_{0\text{-}120\ hours}$ pain intensity at rest results (Table 11.2, p. 65 of the final study report)

Treatment	n	Mean (SD)	Comparison to Pooled Placebo	
			Mean Difference (95% CI)	*P*-value
Treatment 1	11	1.53 (1.440)	-0.01 (-0.89 - 0.88)	0.991
Treatment 2	18	1.40 (0.961)	-0.13 (-0.87 - 0.62)	0.733
Treatment 5	21	2.42 (1.632)	0.89 (0.18 - 1.60)	0.014
SABER-BUP	39	1.95 (1.443)	0.38 (-0.22 – 0.98)	0.209
Pooled Placebo	34	1.53 (1.136)		

Treatments:
1 = SABER-Bupivacaine subcutaneous (5.0 mL)
2 = SABER-Bupivacaine subaponeurotic (5.0 mL)
5 = SABER-Bupivacaine subaponeurotic and subcutaneous spaces (5.0 mL)
SABER-BUP =Treatments 2 and 5
Pooled Placebo = Treatments 3 and 4 (both SABER-placebo)

The other primary efficacy variable was pain control by study day and treatment, assessed using the numerical score for the PP Population (1=Poor, 5=Excellent). These results are summarized in the Table 58 below. The mean values in the SABER-bupivacaine treatment groups were 3.7, 4.0, and 3.2 for Treatments 1, 2, and 5, respectively, compared to 3.8 in the Pooled Placebo group. Treatment 1 on Days 1 through 4 and Treatment 2 on Day 5 had the highest mean values, i.e., the best pain control. The Applicant limited the statistical comparisons to the SABER-BUP versus Pooled Placebo groups. There were no statistically significant differences in pain control between the two groups during the study, i.e., Days 1 through 5.

Table 58. Pain control for Day 1 through Day 5 (Table 11.3 p. 66 of the final study report)

Treatment Group	Mean Pain Control by Day				
	Day 1	Day 2	Day 3	Day 4	Day 5
Treatment 1	3.8	3.8	4.0	4.2	3.7
Treatment 2	3.7	3.6	3.9	3.9	4.0
Treatment 5	3.0	3.0	3.5	3.4	3.2
SABER-BUP	3.4	3.3	3.7	3.6	3.6
Pooled Placebo	3.0	3.2	3.4	3.6	3.8

Treatments:
1= SABER-Bupivacaine Subcutaneous (5.0 mL)
2= SABER-Bupivacaine Subaponeurotic (5.0 mL)
5=SABER-Bupivacaine (5.0 mL)
SABER-BUP=Treatments 2 and 5
Pooled Placebo=Treatments 3 and 4

The findings for the secondary efficacy endpoints modified brief pain inventory, rescue analgesic medication, function scores and hours sitting and walking, overall treatment satisfaction, and pain intensity over time, there were no significant differences between treatment groups. Subjects who received Treatment 5 fared worse than those who received SABER-placebo for each of these endpoints with the exception of rescue analgesic medication.

Summary of Reported Safety Findings

The overall frequency of AEs was similar between treatment groups. The most commonly reported treatment-emergent AEs were nausea (46 events total), dizziness (42 events total), constipation (40 events total), and somnolence (38 events total) and the majority of treatment-emergent AEs were of mild or moderate severity. There were no deaths or discontinuations due to AEs. Three SAEs occurred (syncope vasovagal, orthostatic hypotension, and oliguria); all of these events were moderate in intensity and none were considered related to study drug by the investigator.

Nausea, somnolence, dizziness, and constipation were reported by approximately 50% of subjects over all treatment groups. Vomiting, tinnitus, pruritus, dysgeusia, and paresthesia also occurred with high frequency. Vomiting, dysgeusia, and paresthesia all tended to have a lower frequency of occurrence in the SABER-BUP group compared to the Pooled Placebo treatment group.

Analyses of specific safety evaluations of interest showed a decreased incidence of opioid-related side effects with SABER-bupivacaine treatment in Cohort 1. The frequency of the nervous system disorders of dizziness and somnolence was less in the SABER-bupivacaine treatment groups (Treatment 1 and Treatment 2) compared to placebo (Treatment 3). Specifically, the frequency of dizziness was 64.3% in the placebo group, 27.8% in the SABER-bupivacaine subaponeurotic treatment group (Treatment 2), and 30.8% in the SABER-bupivacaine subcutaneous treatment group (Treatment 1). The frequency of somnolence was 50% in the placebo group, 11.1% in the SABER-bupivacaine subaponeurotic treatment group (Treatment 2), and 30.8% in the SABER-bupivacaine subcutaneous treatment group (Treatment 1). This decreased incidence in opioid-related side effects correlates with a reduction in opioid use in the SABER-bupivacaine treatment group compared to placebo.

Overall, the higher incidence of early signs of CNS toxicity (paresthesia, dysgeusia, tinnitus) and opioid-related side effects could be attributed to general anesthesia and active daily solicitation of presence or absence of these symptoms from the patients as part of the Adapted Modified Brief Pain Inventory questionnaire. Exposure to SABER-bupivacaine did not result in higher frequency of CNS and cardiovascular events as compared to placebo. These symptoms can be associated with local anesthetic overdose. Therefore, investigated 5.0 mL SABER-bupivacaine dose demonstrated adequate systemic safety profile.

With regard to local safety, direct needle-free in-wound deposition of SABER-bupivacaine was associated with lower frequency of surgical site hemorrhage (4.5%) as compared to subaponeurotic injections (11.1%). Overall, rates of procedural complications across all treatment groups including placebo were comparable. Administration of SABER-bupivacaine was well tolerated, demonstrating no signs of abnormal wound healing or unexpected findings.

Discussion

The trial failed to show efficacy of SABER-bupivacaine, compared to SABER-placebo, for providing significant analgesia in the postoperative period following open, inguinal hernia repair surgery. Of the treatments evaluated, Treatment 5 was designed and added to the protocol because it reflects the manner of administration the Applicant is proposing for product labeling. However, Treatment 5 was the only treatment to be demonstrated to be less effective than placebo treatment for all efficacy endpoints except rescue analgesic requirements. It is not clear from the conduct of the study as to why this result occurred and the Applicant did not address the issue in the final study report.

In terms of the safety of the study drugs, there did not appear to be any differences between treatments relative to the signs and symptoms of neurological or cardiac toxicity. The effects of the treatments related to the incision sites and to skin overall are summarized in Table 59 below. The only toxicity that stands out are the edema and swelling associated with the incision site following Treatment 5. There appears to be no clinical significance for this finding based on the lack of findings reported at the 14 day follow-up examination.

Table 59. Adverse events related to the surgical site and skin

Preferred term	Treatment 1	Treatment 2	Treatment 3 and Treatment 4	Treatment 5	Treatment 5a
	SABER-Placebo 5 mL+SABER-Bupivacaine 5 mL (n=11)	SABER-Bupivacaine 5 mL+SABER-Placebo 5 mL (n=18)	SABER-Placebo 5 mL+SABER-Placebo 5mL and SABER-Placebo 5 mL (n=35)	SABER-Bupivacaine 5 mL (n=21)	SABER-Bupivacaine 7_5 mL (n=1)
Application site discoloration	1 (9%)	2 (11%)	1 (3%)	1 (5%)	0
Contusion	0	0	0	1 (5%)	0
Erythema	0	1 (6%)	0	0	0
Genital injury	0	2 (11%)	0	0	0
Incision site blister	0	0	0	1 (5%)	0
Incision site complication	0	0	2	0	0
Incision site erythema	0	0	1 (3%)	0	0
Incision site hemorrhage	0	0	1 (3%)	0	0
Incision site edema	0	0	0	4 (19%)	0
Incision site pain	0	1 (6%)	3 (9%)	0	0
Incision site pruritus	1 (9%)	0	4 (11%)	1 (5%)	0
Inflammation	0	1 (6%)	0	0	0

Preferred term	Treatment 1	Treatment 2	Treatment 3 and Treatment 4	Treatment 5	Treatment 5a
	SABER-Placebo 5 mL+SABER-Bupivacaine 5 mL (n=11)	SABER-Bupivacaine 5 mL+SABER-Placebo 5 mL (n=18)	SABER-Placebo 5 mL+SABER-Placebo 5mL and SABER-Placebo 5 mL (n=35)	SABER-Bupivacaine 5 mL (n=21)	SABER-Bupivacaine 7_5 mL (n=1)
Infusion site hemorrhage	0	0	0	0	0
Local swelling	0	0	0	1 (5%)	0
Edema peripheral	0	0	0	0	1 (100%)
Pruritus	5 (45%)	4 (22%)	6 (17%)	0	0
Pruritus generalised	0	0	0	5 (24%)	0
Rash generalised	0	0	1 (3%)	1 (5%)	0
Skin laceration	0	1 (6%)	0	0	0

Conclusions

The results of this trial indicate that the Applicant-proposed administration technique and dosing of SABER-bupivacaine following inguinal herniorrhaphy provide less analgesia postoperatively than SABER-placebo. The trial also showed that the combination of SABER-bupivacaine and SABER-placebo tended to provide better analgesia than the SABER-bupivacaine alone.

The trial did not identify any safety concern for SABER-bupivacaine when used as the Applicant proposes.

Given the inferior efficacy of SABER-bupivacaine compared to SABER-placebo, the benefits of SABER-bupivacaine do not outweigh the minimal risks that were observed in the trial.

9.4.5 C803-025 (Phase 3, Non-Pivotal Trial - Abdominal Procedures)

Title: Bupivacaine Effectiveness and Safety in SABER® Trial (BESST)

Study Dates: December 21, 2009 to September 30, 2011

Objectives

1. to evaluate effectiveness of SABER-Bupivacaine against an active comparator (Bupivacaine HCl in Cohorts 1 and 2) and efficacy of SABER-Bupivacaine against
2. to assess wound healing and systemic safety, including effect on corrected QT interval (QTc), of 5 mL SABER-Bupivacaine instilled directly into the surgical wound(s) against SABER-Placebo and against Bupivacaine HCl (150 mg)
3. to characterize PK in the general surgical population with wound sizes ranging from laparoscopic portals to open laparotomies

Efficacy Endpoints

The 2 co-primary efficacy endpoints were:

- mean pain intensity on movement AUC (time-normalized AUC) during the period 0 to 72 hours post-dose
- mean total morphine-equivalent opioid dose for supplemental analgesia during the period 0 to 72 hours post-dose

The secondary efficacy endpoints included:

- mean pain intensity on movement normalized AUC during the period 0 to 48 hours post-dose
- mean total morphine-equivalent dose during the period 0 to 48 hours post-dose
- proportion of patients who had evidence of a wound infection as assessed by an Investigator at Visits 3 (Day 7) and 4 (Day 14)
- time to first use of opioid rescue medication after extubation
- incidence of opioid-related AEs, defined as any of the following preferred terms: Constipation, Drowsiness or Somnolence, Dizziness, Nausea, Vomiting, Respiratory depression, or Urinary retention
- mean pain intensity at rest normalized AUC during the period 0 to 72 hours post-dose
- mean pain intensity at rest normalized AUC during the period 0 to 48 hours post-dose

Other efficacy endpoints of interest identified in the SAP were:

- mean scores on the RI-49 postoperative functional subscales (emotional functioning, physical functioning, bowel symptoms, general symptoms, and appetite) and opioid-related distress at each timepoint
- modified Post-Anesthesia Discharge Scoring System (mPADSS) score at each timepoint
- Treatment Satisfaction at each timepoint

Exploratory efficacy endpoints identified in the SAP were:

- proportion of patients experiencing a wound infection during the period 0 to 30 days post-dose as reported on the AE eCRF. Wound infection was defined as any of the following preferred terms: Wound infection, Incision site cellulitis, Incision site infection, Postoperative wound infection, Wound infection fungal, and Wound infection staphylococcal.
- proportion of patients experiencing a wound infection as reported on the Wound Healing Structured Questionnaire eCRF at the 1-Month Follow-up Call
- time to first wound infection
- mean pain intensity on movement normalized AUC during the periods 0 to 24 and 0 to 36 hours post-dose
- mean total morphine-equivalent dose during the periods 0 to 24 and 0 to 36 hours post-dose
- mean pain intensity at rest normalized AUC during the periods 0 to 24 and 0 to 36 hours post-dose
- proportion of patients who did not use opioids during the periods 0 to 24, 0 to 36, 0 to 48, and 0 to 72 hours post-dose

Inclusion Criteria (verbatim from pp. 20-21 of the final study report)

1. Patients must have provided written consent to participate in the trial prior to any trial procedures and understood that they were free to withdraw from the trial at any time
2. Patients must have been able to read and understand the consent form, complete trial-related procedures, and communicate with the trial staff
3. Males and females, 18 years of age and older
4. Patients must have been scheduled to undergo elective general surgical procedures according to the surgical requirements (see Section 9.1)
5. ASA (American Society of Anesthesiologists) Physical Status I to III (equivalent to P1 to P3, defined in Protocol Appendix 2)
6. Body mass index (BMI) < 45 kg/m^2
7. Patients must have had electrocardiogram (ECG) wave form within normal limits or nonspecific ST-T changes, heart rate of 45 to 100 beats per minute (bpm), PR up to 220 ms (PR is the duration from onset of atrial depolarization until onset of ventricular depolarization, measured from the beginning of the P wave to the beginning of the QRS complex), QRS up to 110 ms (QRS is part of

electrocardiographic wave representing ventricular depolarization), and a Bazett formula-corrected QT interval (QTcB) of < 450 ms

8. Female and male patients must have agreed to use a medically acceptable method of contraception throughout the patient's entire trial participation period and for 1 week after the trial participation was completed. Medically acceptable methods of contraception that could be used by the patient and/or the partner included oral contraception or patches (consistently for 3 months prior to trial dosing), NuvaRing (etonogestrel/ethinyl estradiol vaginal ring), diaphragm with vaginal spermicide, intrauterine device (coil), condom and vaginal spermicide, surgical sterilization (6 months post surgery), postmenopausal patient (had not experienced a menstrual period for a minimum of 2 years), and progestin implant or injection (used consistently for 3 months prior to trial dosing)

Exclusion Criteria (verbatim from pp. 21-22 of the final study report)

1. Patients who were pregnant or lactating
2. Undergoing emergency surgery (unless full consent could be obtained and all screening procedures could be completed prior to surgery)
3. Significant concomitant surgical procedure
4. History of multiple prior laparotomy procedures
5. Cancer with known metastases pre-operatively, which were suspected to affect post-operative recovery and postoperative pain
6. Planned formation of stoma during surgery or plans to undergo another laparotomy procedure within 30 days postoperatively
7. Pre-operative evidence of sepsis or septic shock
8. Pre-operative evaluation that suggested a surgery that may have precluded full closure of the incision(s)
9. Patients with current or regular use of systemic steroids, anticonvulsants, antiepileptics, antidepressants, or monoamine oxidase inhibitors who could not be withdrawn from these medications as described in Section 9.4.7.1
10. Patients with current or regular use of drugs known to significantly prolong the QTc interval within a period at least 5 times the drug's half-life before Day 0
11. Patients with known hypersensitivity to local anesthetic agents of the amide type (e.g., lidocaine or bupivacaine)
12. Patients with known hypersensitivity to morphine
13. Patients with conditions contraindicated for use of opioids, including paralytic ileus, acute or severe bronchial asthma, or hypercarbia
14. Patients with atrial fibrillation/flutter or other non-sinus rhythm (including paced rhythm); left bundle branch block; or the following conditions: right bundle branch block in presence of a cardiac disease, clinically significant cardiomyopathy, or myocardial infarction within last 6 months.
15. Patients with a serum creatinine level two times more than the local laboratory normal limit

16. Patients who had received greater than 600 mg morphine-equivalent daily dose for 3 or more days per week in the month prior to the surgical procedure
17. Patients who were currently being treated with methadone, or had history of methadone use within the previous 6 months
18. Patients with known or suspected abuse of opioids or other illicit drugs
19. Patients with known or suspected alcohol abuse
20. Patients participating in any other trial with an investigational drug or device concurrently or within 30 days prior to Day 0 of this trial
21. Patients who, in the Investigator's opinion, should not have participated in the trial or may not have been capable of following the trial schedule for any reason

Summary of Methodology

This was a Phase 3, international, multicenter, randomized, double-blind, parallel-group active- and placebo-controlled trial evaluating the safety, efficacy, effectiveness, and PK of SABER-Bupivacaine 5 mL in patients undergoing a variety of general surgical procedures with various wound sizes. All surgical procedures were elective, non-urgent.

Approximately 304 eligible patients were to have received 1 of 3 treatments administered to the surgical wound(s):

- SABER-bupivacaine 5 mL
- Bupivacaine HCl 0.5% solution 30 mL
- SABER-placebo 5 mL

The allocation ratio of active (Cohort 1) vs. active control (Cohort 2) or active vs. placebo (Cohort 3) was 3 to 2. The ratio was to meet two criteria: one was to have adequate sample size on SABER-Bupivacaine 5 mL for safety evaluation; and the other was to have optimal power to detect efficacy in Cohort 3. Randomization was to have been stratified by surgical procedure (cohort) and by clinical site. The cohorts were as follows:

- Cohort 1: Laparotomy. Approximately 50 patients were to have been randomized to receive either SABER-Bupivacaine 5 mL or Bupivacaine HCl 30 mL 0.5% solution in a 3:2 ratio, respectively. This cohort included patients undergoing open laparotomy for resection of liver, small bowel, stomach, spleen, gall bladder, or colon. There were no restrictions on laparotomy incision length, closure of stoma, or anatomical placement of the incision.

- Cohort 2: Laparoscopic cholecystectomy. Approximately 50 patients were to be randomized to receive either SABER-Bupivacaine 5 mL or Bupivacaine HCl 30 mL 0.5% solution in a 3:2 ratio, respectively. There were no restrictions on the number of laparoscopic portals or conditions encountered during the operation to require conversion into open surgery.

- Cohort 3: Laparoscopically-assisted colectomy. Approximately 204 patients were to have been randomized to receive either SABER-Bupivacaine 5 mL or SABER-Placebo 5 mL in a 3:2 ratio, respectively. This cohort included patients undergoing laparoscopically-assisted colectomy without planned formation or closure of stoma for colon cancer, diverticulitis, or polyps. A pneumoperitoneal and an intracorporeal approach was to be used to explore the abdomen, mobilize the colon, identify critical structures, and ligate the vascular pedicle for left-sided and sigmoid colectomies. The bowel could be exteriorized through a small incision for resection and anastomosis. Allowed minor concomitant procedures included appendectomy, cholecystectomy, and liver biopsy/wedge resection. Conversion from laparoscopically-assisted to open surgery with an incision length of up to 15 cm was allowed at the surgeon's discretion for the patient's safety and technical difficulties, such as presence of associated conditions, findings of advanced disease, or inadequate oncologic margins. Patients were not to be dosed with the investigational product if extensive concomitant surgical procedures were performed and/or conversion to open surgery required an incision greater than 15 cm.

All patients received medical care given under normal circumstances for the specified elective surgical procedures.

Patient participation lasted for up to 61 days, consisting of a screening period for up to 30 days before surgery, at least 72-hour (3-day) hospital stay following surgery and administration of the single dose of investigational product, a follow-up visit on Day 7 ± 1 day, a final clinic visit on Day 14 ± 3 days, and a 1-Month Follow-up Call on Day 30 ± 3 days.

Technique of Study Drug Administration:

Bupivacaine HCl: In the active comparator treatment groups (Cohorts 1 and 2); 30 mL of Bupivacaine HCl 0.5% solution was administered by infiltration with a hypodermic needle into the peri-incisional tissues.

SABER-Containing Products: For the SABER-Bupivacaine and SABER-Placebo treatment groups, investigational product was drawn up and administered using a NORM-JECT® 5-mL Luer Lock syringe connected to a Tunneltip™ irrigation catheter with a Luer Lock fitting. The supplied Tunneltip irrigation catheter was flexible, 15 cm long, 2 mm in diameter, with smooth rounded tip and graduated centimeter markings for wound length measurement and control of instillation. To account for the dead space in the catheter, sites were instructed to draw 5.5 mL of investigational product in the syringe with the provided 16 gauge needle. Sites were instructed to purge excess air and investigational product from the syringe and catheter once connected to ensure administration of 5 mL of

investigational product. The syringes, needles, and catheters were supplied sterile and individually packaged.

For laparoscopic portals, the investigational product was administered directly into the open port incision through an irrigation catheter and/or by the syringe tip. The port incision was then closed with a suture after dosing.

For linear incisions, after closure of the peritoneum and securing hemostasis in the subcutaneous space, the irrigation catheter was placed into the wound and the cutaneous layer was closed over the catheter with subcuticular stitches. The syringe containing the test drug was then attached to the catheter and test drug was gradually injected while slowly withdrawing the catheter. In this way, the SABER formulation was evenly distributed along the length of the incision with minimal leakage of the drug. A final stitch was used to close the space where the catheter was withdrawn. The volume delivered per centimeter of wound length was calculated based on incision length measured using the centimeter marking on the irrigation catheter.

In Cohort 1, the entire 5 mL dose of SABER-Bupivacaine was evenly distributed within the laparotomy incision. In Cohort2, the larger port incisions received a larger volume of test drug than did the smaller port incisions. In Cohort 3, there was generally a 5-10 cm linear incision for exteriorizing the colon for resection and anastomosis (the hand port). Approximately 80-90% of the SABER-Bupivacaine was instilled into the hand port using the irrigation catheter method. The remaining 10-20% of test drug was directly instilled into the laparoscopic port incisions.

To avoid seepage of the product from the wound, instillation was performed after a tight closure of the skin with subcuticular stitches (no staples) and Steri-Strips. No drains were placed in the area of investigational product placement.

The prepared SABER-Bupivacaine, SABER-Placebo, and Bupivacaine HCl were to be administered within 1 hour of being drawn up into the syringe. The time of investigational product administration was defined as completion of drug deposition into the surgical wound(s). The patient number, patient identifier, vial number, date, and time of when the investigational product was drawn up and administered were recorded on the appropriate source document.

One blinded interim analysis was planned when approximately 50% of Cohort 3 patients had completed the trial. An adaptive feature of the trial allowed for a pooled and blinded onetime sample size re-estimation for Cohort 3

A periodic evaluation of AEs, including systemic and local reactions, was performed by reviews of pooled and blinded data from the clinical database by the Steering Committee and DURECT's medical monitor.

The trial was conducted at 15 sites in the US, 3 sites in Australia, and 1 site in New Zealand. Six sites (5 in the US and 1 in Australia) were each assigned 2 site numbers one number was assigned for patients in Cohort 1 and another number was assigned for patients in Cohort 3.

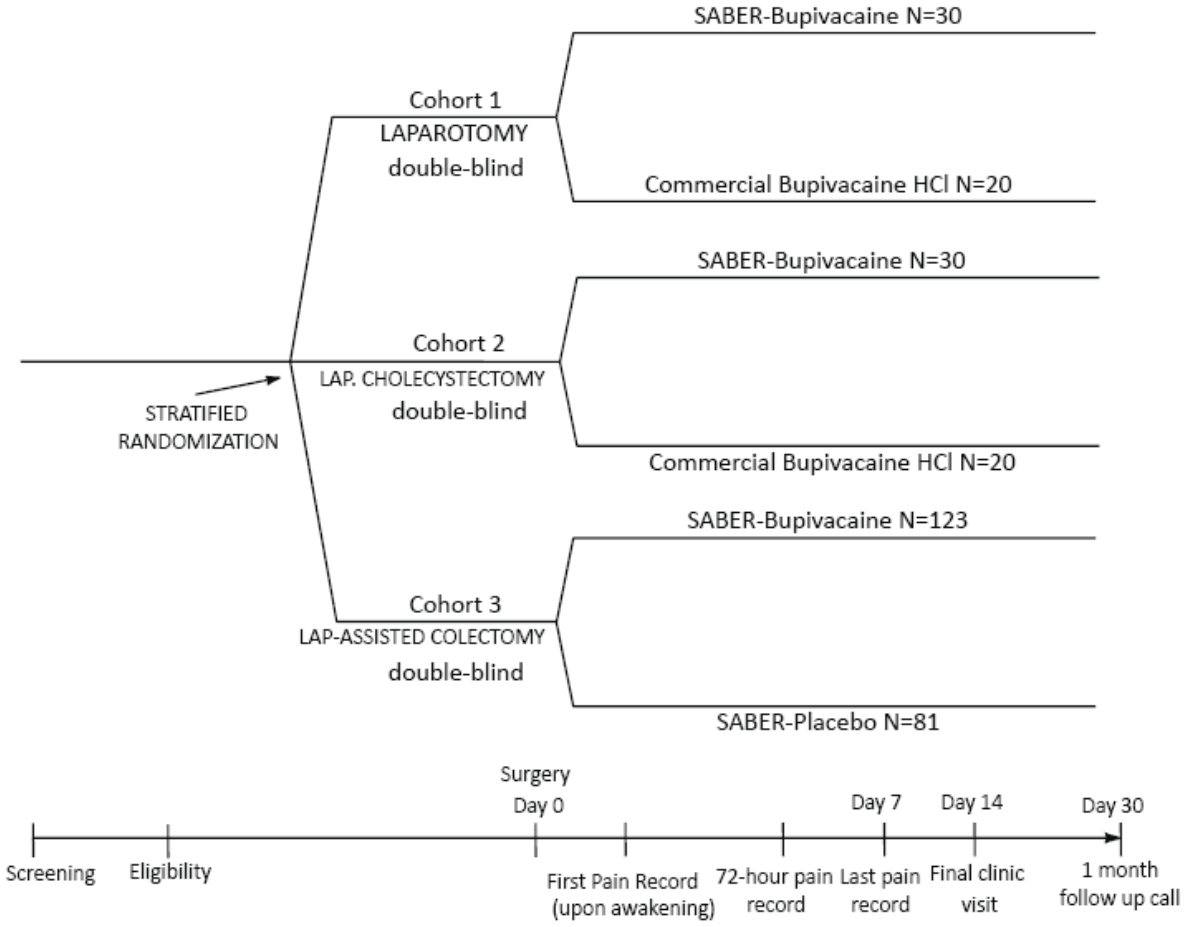
Amendments
The protocol was amended twice:

1. (July 27, 2010): included the following changes:
    a. Increased the number of clinical centers in Cohorts 1 and 3
    b. Clarified the distinction between primary and secondary efficacy endpoints, surgical requirements, and postoperative pain management instructions
    c. Revised the inclusion criterion regarding ECGs to a heart rate of 45 to 100 bpm to include the upper end of normal rate while still excluding tachycardia
    d. Revised the inclusion criterion regarding contraception to ensure male patients also used a medically acceptable method of birth control.
    e. Revised the exclusion criterion regarding cancer to allow common non-extensive metastasis, which would not affect postoperative recovery and pain.
    f. Clarified the exclusion criteria regarding restricted medications.
    g. Clarified the exclusion criterion regarding ECGs to include normal clinically insignificant changes that were not expected to affect analysis
    h. Added the use of a paper diary for pain intensity records in cases of LogPad malfunction
    i. Clarified where safety laboratory tests were conducted
    j. Clarified that the Hochberg adjustment was intended for co-primary endpoint analysis
    k. Clarified PK sample storage conditions

2. (May 3, 2011) included the following changes:
    a. Planned last patient, last visit timeline update
    b. Added secondary endpoints of a 48-hour version of the primary endpoints (0 to 72 hours) to support a 48-hour SABER-Bupivacaine benefit
    c. Added the category of "other endpoints of interest" to minimize the number of secondary endpoints
    d. Clarified that enrollment in Cohort 3 would be up to approximately 35 patients per site (no minimum or maximum per site)

e. Added that digital pictures of surgical wounds might be acquired at selected clinical sites to facilitate tracking of wound healing progress and support the description of observations around surgical incisions, with no planned systematic or standardized analysis of images
f. Added descriptions of endpoint analyses for mean pain intensity on movement AUC (normalized) and at rest during the period 0-48 hours post-dose, mean total morphine-equivalent dose, and proportion of patients who experience a wound infection during postsurgical period

Schematic (Figure 1, p. 18 of the final study report)



Schedule (Table 1, pp. 30-31 of the final study report)

Trial Procedures	Visit 1 Screening	Visit 2 Treatment				Visit 3 Follow Up	Visit 4 Final Visit/Early Term	1 Month Follow Up Call
	Day -30 to Day-1	Day 0	Day 1	Day 2	Day 3	Day 7 (± 1 day)	Day 14 (± 3 days)	Day 30 (+ 3 days)
Informed Consent (prior to any trial procedures)	√							
Demographics	√							
Medical History	√							
Physical Examination	√						√	
Height and Weight	√						√[1]	
Inclusion / Exclusion Criteria	√	√[2]						
Safety Labs (Chemistry, Hematology, Urinalysis)	√						√	
Pregnancy Test	√[3]	√[4]						
12-lead electrocardiogram (ECG)	√						√	
Vital Signs[5] (BP, Heart Rate, Respiratory Rate, Temperature)	√	←[6]→				√	√	
Adverse Events (AEs)[7]	←	→						
Concomitant Medications	←	→						
IVRS Randomization		√						
Surgery		√						
Holter Monitoring[8]	√	←	→					
Pharmacokinetic (PK) Plasma Sample[9]		←	→					
Dosing		√						
Patient Evaluations[10, 11, 12,]		←	→					
Supplemental Analgesia[13]		←	→					
Dispense Paper Diary[14] and LogPad/ Review Instructions		√	√	√	√			
Discharge (at least 72 hours post-dose)					√			
mPADSS[15]		√	√	√		√	√	
Surgical Wound(s) Healing and Local Tissue Conditions Evaluation						√	√	

Trial Procedures	Visit 1 Screening	Visit 2 Treatment				Visit 3 Follow Up	Visit 4 Final Visit/Early Term	1 Month Follow Up Call
	Day -30 to Day-1	Day 0	Day 1	Day 2	Day 3	Day 7 (± 1 day)	Day 14 (± 3 days)	Day 30 (+ 3 days)
Surgical Wound(s) Healing Questionnaire								√
Collect / Review Paper Diary and LogPad						√	√	
Reconcile Unused Supplemental Analgesia							√	

BP = blood pressure, IVRS = interactive voice response system, mPADSS = modified Post-Anesthesia Discharge Scoring System, Term = termination

[1] Weight only
[2] Inclusion/exclusion criteria reviewed to confirm patient was still eligible
[3] Serum pregnancy test for females of childbearing potential
[4] Urine pregnancy test for females of childbearing potential
[5] Vital signs measured after a10-minute supine rest
[6] Vital signs taken just prior to PK sampling: pre-dose and 0.5, 1, 2, 4, 8, 12, 16, 24, 30, 48, and 72 hours post-dose
[7] AE collection started when the patient signed the consent form and continued through final visit/early termination. Ongoing AEs at the time of completion/early termination were to be followed until resolved or until 30 days after the patient's last trial visit, whichever came first.
[8] A single baseline Holter recording (10-minute supine resting immediately after initiation of the Holter recording) was collected via an ambulatory recording procedure for each patient starting at the end of the Screening Visit. On Day 0 (day of surgery), Holter monitoring was started at least 1 hour prior to induction of general anesthesia.
[9] PK sampling was done pre-dose (prior to induction of general anesthesia) and 0.5, 1, 2, 4, 8, 12, 16, 24, 30, 48, and 72 hours post-dose after 10-minute supine rest and ECG acquisition.
[10] On Day 0 (day of surgery), pain intensity evaluations at rest and on movement were completed upon awakening (or 4 hours post-dose, whichever occurred earlier), and continued at 6, 8, 10, and 12 hours post-dose. On Days 1 to 7, pain intensity evaluations at rest and on movement were completed 4 times a day at 08:00, 12:00, 16:00, and 20:00 hours (clock time).
[11] A Treatment Satisfaction evaluation was completed in the paper diary every evening at 20:00 (clock time).
[12] A Recovery Index – 49 (RI-49) questionnaire was completed in the paper diary on Day 2 at approximately 20:00 (clock time) and at Visit 3.
[13] Moderate to severe pain (Pain Intensity Numeric Rating Scale [PI-NRS] ≥ 4) treated per pain management instructions.
[14] See Sections 9.5.1.2, 9.5.1.3.4, 9.5.1.3.6 of the protocol and Protocol Appendix 4.
[15] mPADSS was collected in the evening on Day 0 (after the surgery), Days 1 and 2 in the morning and afternoon, and once daily at Visit 3 and Visit 4.

Subject Disposition

A total of 393 patients were screened and 331 patients were randomized. There were 26 patients who were randomized but not treated. The reasons for not treating these patients included: conditions encountered during surgery necessitated procedures that did not meet protocol requirements, peri-operative epidural analgesia was administered, the test drug was not available, or the subject withdrew consent. Two patients who were treated with study drug discontinued because of AEs, both of which were considered to be unrelated to study drug. Subject disposition is summarized in Table 60 below.

Table 60. Subject disposition (Table 4, p. 59 of the final study report)

	Cohort 1		Cohort 2		Cohort 3		Cohorts 1&2		
	SABER-Bupivacaine	Bupivacaine HCl	SABER-Bupivacaine	Bupivacaine HCl	SABER-Bupivacaine	SABER-Placebo	SABER-Bupivacaine	Bupivacaine HCl	Total
Patients Randomized	32	23	30 20		140	86 62 43			331
Safety Population [a]	30 (93.8%)	18 (78.3%)	30 (100.0%)	20 (100.0%)	129 (92.1%)	78 (90.7%)	60 (96.8%)	38 (88.4%)	305 (92.1%)
ITT Population [b]	26 (81.3%)	17 (73.9%)	30 (100.0%)	20 (100.0%)	126 (90.0%)	77 (89.5%)	56 (90.3%)	37 (86.0%)	296 (89.4%)
PP Population [c]	25 (78.1%)	16 (69.6%)	30 (100.0%)	20 (100.0%)	119 (85.0%)	68 (79.1%)	55 (88.7%)	36 (83.7%)	278 (84.0%)
Completed Study									
Yes	28 (93.3%)	17 (94.4%)	30 (100.0%)	19 (95.0%)	124 (96.1%)	76 (97.4%)	58 (96.7%)	36 (94.7%)	294 (96.4%)
No	2 (6.7%)	1 (5.6%)	0	1 (5.0%)	5 (3.9%)	2 (2.6%)	2 (3.3%)	2 (5.3%)	11 (3.6%)
Primary Reason for Discontinuation									
Lost to Follow-up	0	0	0 0		1 (0.8%)	0 0 0			1 (0.3%)
Adverse Event	1 (3.3%)	0	0	1 (5.0%)	0	0	1 (1.7%)	1 (2.6%)	2 (0.7%)
Patient Decision	1 (3.3%)	1 (5.6%)	0	0	3 (2.3%)	1 (1.3%)	1 (1.7%)	1 (2.6%)	6 (2.0%)
Investigator Decision	0	0	0 0 0			1 (1.3%)	0 0		1 (0.3%)
Other	0	0	0 0		1 (0.8%)	0 0 0			1 (0.3%)

ITT = Intent-to-treat, PP = Per-protocol
Note: Cohort 1 = Laparotomy; Cohort 2 = Laparoscopic Cholecystectomy; Cohort 3 = Laparoscopically Assisted Colectomy
Note: Denominators for the Safety, ITT, and PP populations were the number of patients randomized. Otherwise, denominators were the number of patients in the Safety population.
[a] All patients who received any amount of study drug
[b] All randomized patients excluding patients from Site 09 (Cohort 1) and Site 31 (Cohort 3), independent of their exposure to investigational product or the success of surgery, who had at least 1 postsurgical pain intensity record
[c] All ITT patients who did not experience any major protocol violations

Reported Efficacy Findings

The primary pain endpoints were defined as the time normalized AUC of pain on movement over 0-72 hours and the total amount of rescue opioids taken over 0-72 hours expressed as IV morphine equivalents.

For Cohorts 1 and 3 (laparotomy and laparoscopic assisted colectomy, respectively), there was about 1.5 to 1.9 fold excess number of opioid rescue pain scores compared to the number of scheduled pain scores. The opposite was true for Cohort 2

(laparoscopic cholecystectomy), where the number of opioid rescue pain scores was less than half the number of scheduled pain scores (only observed scores were counted for these comparisons).

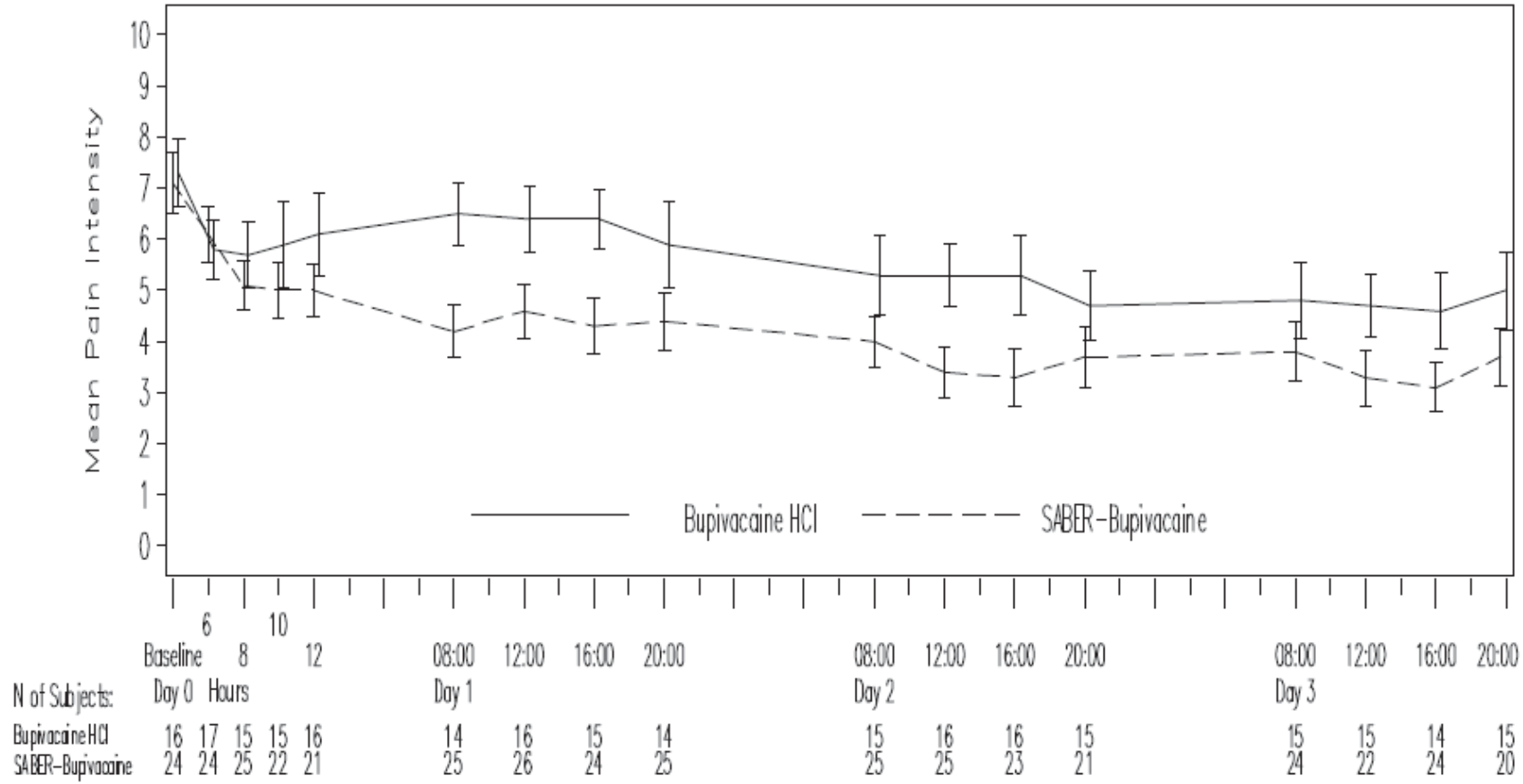
Both Cohorts 1 and 3 had higher pain intensity on movement AUC than Cohort 2, which involved a less extensive surgical procedure. In all 3 cohorts and all treatment groups, there was a 1 or 2-unit reduction in mean pain score (NRS 1-10) AUC over the 3-day observation period, with Cohort 2 reaching mild pain levels by the third day. The changes in mean pain intensity over time for each of the treatments for Cohorts 1, 2, and 3 are shown in Figure 14, Figure 15, and Figure 16, respectively.

In Cohort 1 there was about a 15% reduction in pain intensity on movement AUC 0-72 hours when comparing SABER-Bupivacaine to the active control, and the therapeutic difference increased over the 3-day period. The differences in AUC did not reach statistical significance, and it was noted that opioids were extensively used during this time period.

In Cohort 2, the treatment effect was more consistent with a 24-30% reduction in pain intensity AUC on movement when comparing SABER-Bupivacaine to active control over the 3-day period. The differences in AUC from 0-72 hours for the two treatment groups were not significantly different. The treatment effect was both clinically and statistically significant at the 0-24 and 24-48 hour time intervals, and the secondary endpoint of AUC 0-48 hours also was significant. When Cohorts 1 and 2 were combined, the therapeutic effect was statistically significant.

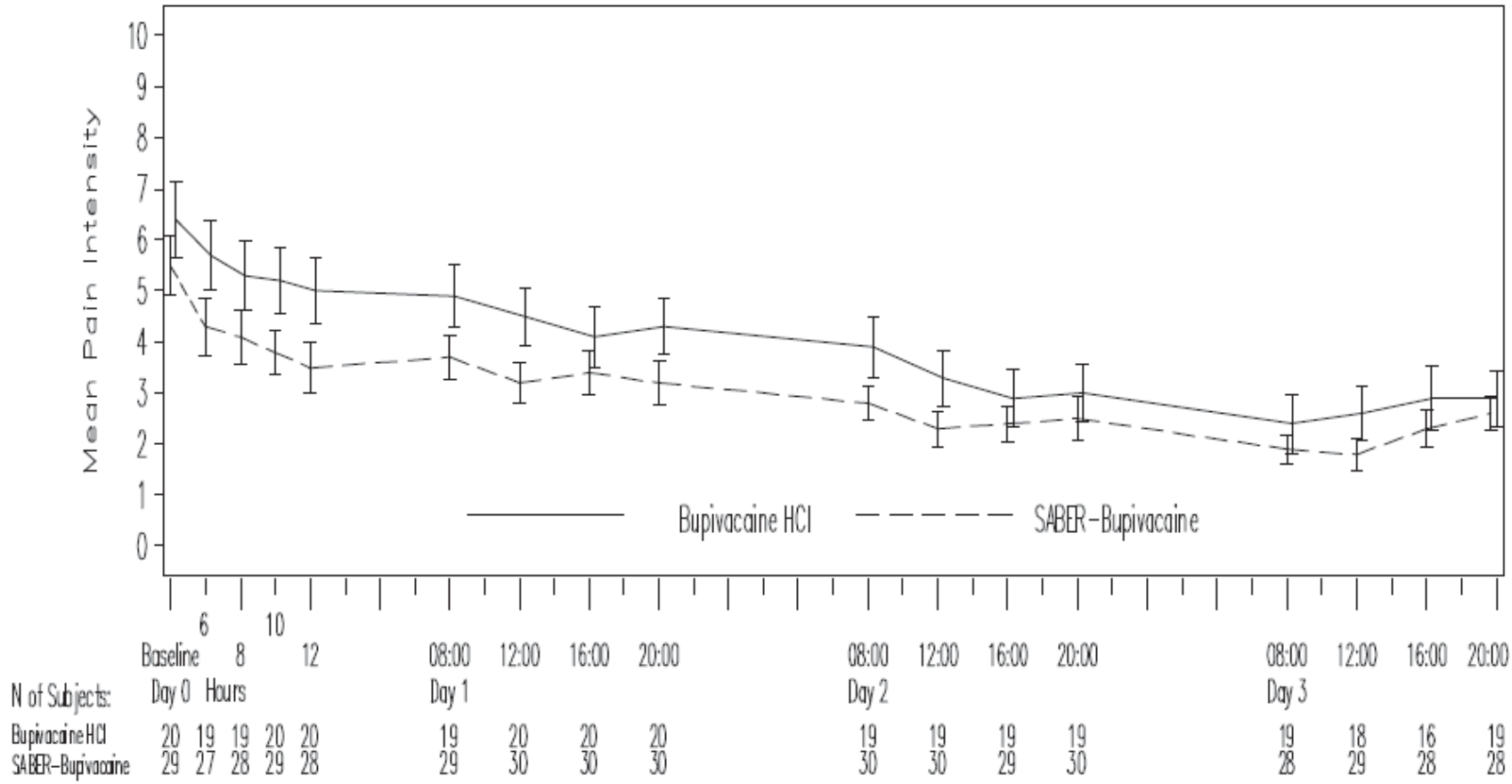
In Cohort 3 there was minimal, but consistent, pain relief compared to placebo over the 3-day period, although statistical significance was not achieved at any time interval. It was noted that there was extensive use of opioids in this treatment group and that the majority of the 5 mL of study drug volume was instilled into the 5–10 cm incision for exteriorizing the colon and only about 1 mL of study drug was instilled into the remaining 3 to 5 laparoscopic ports, which may be a source of undertreated incisional pain.

Figure 14. Mean (±SE) pain intensity on movement over time for Cohort 1 - Laparotomy (Figure 6. p. 85 of final study report)



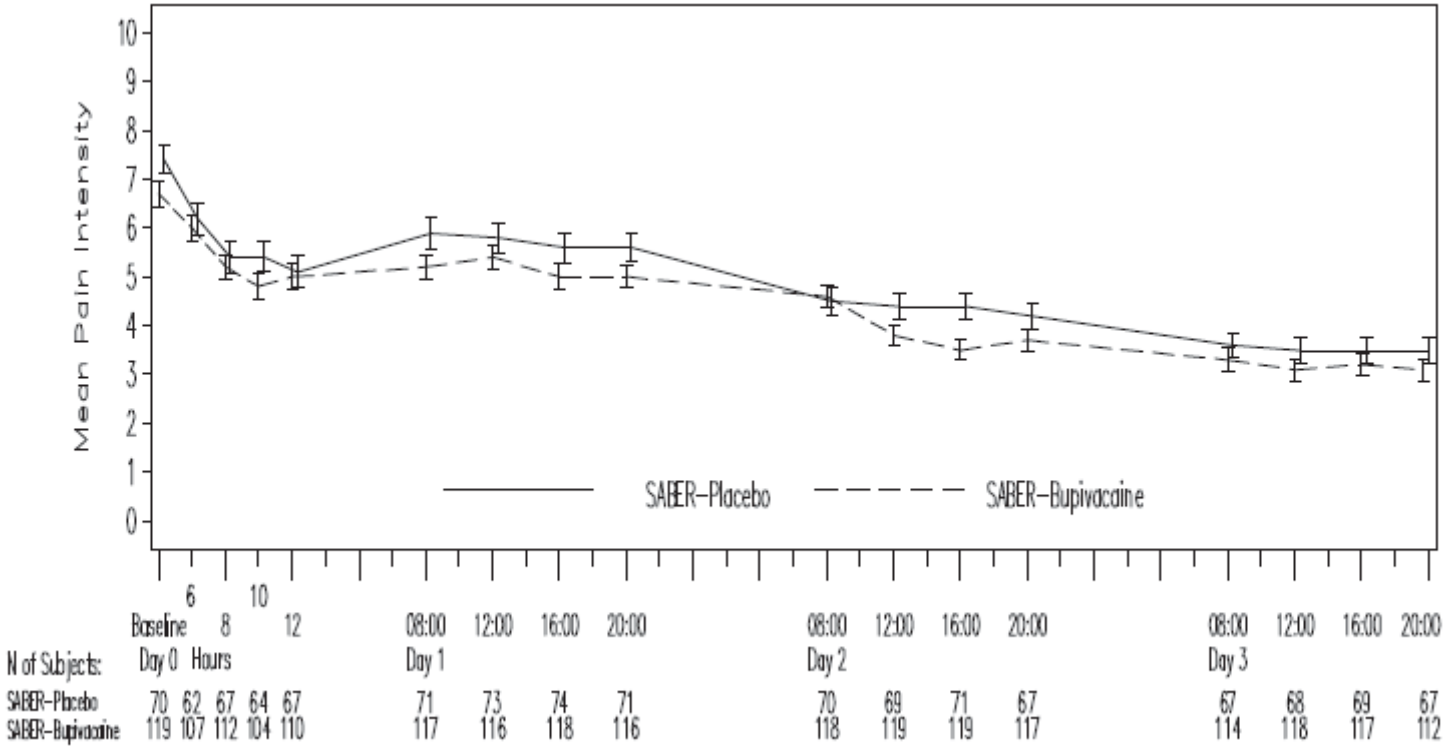
Note: Baseline was the first pain score recorded between end of treatment and 4 hours post-dose. Missing baseline pain scores were imputed with the worst value during first 24 hours.

Figure 15. Mean (±SE) pain intensity on movement over time for Cohort 2 - laparoscopic cholecystectomy (Figure 7, p. 86 of the final study report)



Note: Baseline was the first pain score recorded between end of treatment and 4 hours post-dose. Missing baseline pain scores were imputed with the worst value during first 24 hours.

Figure 16. Mean (±SE) pain intensity on movement over time for Cohort 3 - laparoscopic cholecystectomy (Figure 8, p. 87 of the final study report)



Note: Baseline was the first pain score recorded between end of treatment and 4 hours post-dose. Missing baseline pain scores were imputed with the worst value during first 24 hours.

The second co-primary endpoint was the mean total amount of opioids administered over 0-72 hours, expressed as IV morphine equivalents in milligrams using standard conversion factors to convert different opioids to morphine equivalents. The protocol specified that patients with moderate to severe pain (pain score ≥ 4) could be treated with either an IV morphine bolus of 0.5 to 2 mg with at least 15 min between injections, or oral morphine in 10 to 30 mg doses with at least 1 hour between doses. Oxycodone or fentanyl could be given to patients who did not tolerate morphine. Patient controlled analgesia, long-acting and combination opioids, and NSAIDs were prohibited. These instructions were not always followed and some patients were treated on a pre-emptive basis around the clock when the pain score was < 4.

The open laparotomy patients in Cohort 1 required the greatest amount of opioids over 0-72 hours and opioid use was relatively sustained over 3 days. Cohort 3 also required a substantial amount of opioid over 0-72 hours, but showed some reduction in opioid use over the 3-day observation period. Cohort 2 required comparatively less opioids and used very little medication after the first 24 hours. Cohorts 2 and 3 showed a somewhat lower median opioid use in the SABER-Bupivacaine group compared to control, but the reverse was true for Cohort 1. For all three cohorts, there were no significant differences in opioid use between SABER-Bupivacaine and control groups at any time interval.

Pain intensity at rest AUCs were evaluated for each of the cohorts. For the 0-72 hour time period there were no significant differences among any of the treatment groups. There were statistically significant differences only for Cohort 2 from 0-48 hours and 24-48 hours, and for Cohort 3 from 0-24 hours.

Time to first opioid use was evaluated. There were no statistically significant between-group differences for the individual cohorts but the difference for Cohorts 1&2 combined was statistically significant ($p = 0.0342$).

Recovery Index (RI-49) Subscales assessed at two time points used a patient self-report questionnaire to evaluate the quality of postoperative recovery by responses to 49 questions in the form of a 5-category Likert scale reflecting the severity, frequency or bothersomeness of six subscales: Emotional, Physical Functioning, Bowel Symptoms, General Symptoms, Appetite, and Opioid Side Effects. The questionnaire was administered on postoperative days 2 and 7. Consistent with higher pain intensity and opioid use, Cohort 1 had somewhat higher subscales than Cohort 3, whereas Cohort 2 had the lowest scores, indicating the best quality of recovery compared to Cohorts 1 and 3. In all 3 cohorts, physical function was the subscale category with the highest score. The order of severity of the remaining five subscales was completely different for each cohort. By day 7 most of the subscale scores had declined by an average of 35-40%, indicating some recovery in the various domains. There were no significant differences between treatment groups for any of the subscales at either time point.

Modified post-anesthesia discharge scoring assessed five predictors of dischargeability: vital signs, activity level, nausea and vomiting, pain, and surgical bleeding. There were no significant differences between any of the treatments in any of the cohorts for this assessment.

Summary of Reported Safety Findings

Cardiovascular and neurological TEAE were of special interest as high plasma concentrations of bupivacaine may cause AEs in these body systems. Cardiovascular TEAE were somewhat more frequent in the Bupivacaine HCl control groups in Cohorts 1 and 2, whereas in Cohort 3 the SABER-Bupivacaine group had a greater frequency of cardiovascular TEAEs than the SABER-Placebo control group. There was little difference between treatment groups in the frequency of neurological TEAEs in Cohorts 1 and 2, whereas in Cohort 3, the SABER-Placebo group had approximately twice as many neurological TEAEs as the SABER-Bupivacaine group. Wound infections were most frequent in Cohort 1 and least frequent in Cohort 2, with little imbalance between treatment groups whereas in Cohort 3 there were more infections in the SABER-Bupivacaine group compared to placebo. The incidence of SAEs was in proportion to the seriousness of the surgery, with Cohort 1 having the highest frequency, followed by Cohort 3, and Cohort 2 having only a single SAE. Only two patients discontinued prematurely due to TEAEs and a single patient died on postoperative day 40 due to prolonged ileus unrelated to study drug.

Table 61 below provides a summary of the TEAEs associated with the trial.

Table 61. Summary of treatment emergent adverse events

Cohort	Cohort 1		Cohort 2		Cohort 3	
Treatment	**SABER-Bupivacaine (N=30)**	**Bupivacaine HCl (N=18)**	**SABER-Bupivacaine (N=30)**	**Bupivacaine HCl (N=20)**	**SABER-Bupivacaine (N=129)**	**SABER-Placebo (N=78)**
At Least One TEAE	30 (100%)	17 (94%)	28 (93%)	20 (100%)	126 (98%)	75 (96%)
At Least One Cardiovascular TEAE	4 (13%)	7 (39%)	2 (7%)	2 (10%)	19 (15%)	6 (8%)
At Least One Neurological TEAE	6 (20%)	4 (22%)	17 (57%)	10 (50%)	23 (18%)	29 (37%)
At Least One Wound Infection TEAE	4 (13%)	2 (11%)	1 (3%)	1 (5%)	12 (9%)	2 (3%)
At Least One Non-Opioid TEAE	27 (90%)	17 (94%)	27 (90%)	19 (95%)	124 (96%)	74 (95%)
At Least One Serious TEAE	9 (30%)	4 (22%)	0	1 (5%)	16 (12%)	9 (12%)

Cohort	Cohort 1		Cohort 2		Cohort 3	
Treatment	SABER-Bupivacaine (N=30)	Bupivacaine HCl (N=18)	SABER-Bupivacaine (N=30)	Bupivacaine HCl (N=20)	SABER-Bupivacaine (N=129)	SABER-Placebo (N=78)
At Least One TEAE Leading to Study Discontinuation	1 (3%)		0	(5%)	0	0
Maximum Relationship to Study Drug						
Related[a]	12 (40%)	4 (22%)	17 (57%)	10 (50%)	79 (61%)	47 (60%)
Not Related[b]	18 (60%)	13 (72%)	11 (37%)	10 (50%)	47 (36%)	28 (36%)
Maximum Severity						
Mild	5 (17%)	2 (11%)	4 (13%)	2 (10%)	54 (42%)	29 (37%)
Moderate	16 (53%)	11 (61%)	16 (53%)	13 (65%)	51 (40%)	32 (41%)
Severe	9 (30%)	4 (22%)	8 (27%)	5 (25%)	21 (16%)	14 (18%)
At Least One Severe and Related TEAE	1 (3%)	0	2 (7%)	1 (5%)	0	2 (3%)
At Least One Serious and Related TEAE	1 (3%)	0	0	0	0	1 (1%)
Deaths	0		0		1 (<1%)	0

TEAE = treatment-emergent adverse event
Note: Cohort 1 = Laparotomy; Cohort 2 = Laparoscopic Cholecystectomy; Cohort 3 = Laparoscopically Assisted Colectomy
Note: At each level of summation (overall, system organ class, preferred term), patients reporting more than 1 adverse event were counted only once.
[a] Includes all events reported as "Possible", "Probable", or missing relationship to study drug.
[b] Includes all events reported as "Unlikely" or "Not Related" relationship to study drug.

Most of the SAEs were reported to be “obvious complications of intestinal surgery” and almost all were considered to be unrelated to study drug. With the exception of the fatal case of postoperative ileus, all subjects recovered from the SAE. The median time to onset was on Day 13 (range: -2 to 32) and median time to resolution was 5.5 days (range: 0 to 90 days). As with other measures of postoperative complications, Cohort 1 had the highest incidence of SAEs, whereas Cohort 2 had only a single SAE. There were no consistent or striking imbalances between treatment groups in the total number of subjects with SAEs, but there were a greater number of gastrointestinal SAEs in the SABER-bupivacaine group in Cohort 3. There was a single neurological SAE (presyncope in a SABER-placebo subject) and 3 subjects with cardiac SAEs, including a myocardial infarction in a SABER-bupivacaine patient on Day 29 of the trial. The

subjects with atrial fibrillation/atrial flutter supraventricular tachycardia were both in control groups.
The death occurred in a subject with Parkinson's disease who developed a prolonged postoperative ileus following a laparoscopic hemicolectomy. He had been treated with SABER-bupivacaine. His death occurred 40 days after his surgery and was not considered related to study drug.

The SAEs that were related to the surgical wounds included the following:

- Postoperative wound infection – 1 event with SABER-bupivacaine treatment in Cohort 1
- Wound dehiscence – 2 events with SABER-bupivacaine treatment in Cohort 1 and 1 event with SABER-placebo treatment in Cohort 3
- Application site discoloration (abdominal hematoma at incision site)– 1 event with SABER-placebo treatment in Cohort 3

Among the non-serious adverse events gastrointestinal symptoms were the most frequently reported TEAE and were considered to be most likely due to the effects of anesthesia, bowel surgery and opioid administration. There were no consistent differences between treatment groups for these events. General disorders and administration site conditions were the next most frequently reported SOC, with application site discoloration being the most common TEAE in the SOC. This was a Sponsor-defined composite term comprised of approximately190 verbatim terms describing any aspect of peri-incisional skin color. This TEAE was consistently more common among the SABER-Bupivacaine groups compared to bupivacaine HCl in Cohorts 1 and 2 and similar frequency in the Cohort 3 treatment groups, suggesting that this TEAE was most likely intensified by the SABER formulation.

Among the nervous system SOC adverse events, headache was the most common TEAE, with an apparent imbalance in Cohort 2, occurring in 37% of subjects treated with SABER-bupivacaine compared to 5% of subjects treated with bupivacaine HCl. Although Cohort 2 had the least extensive surgery and the fastest recovery, the incidence of neurological TEAEs was substantially higher in this cohort.

Cardiac system SOC adverse events were similar among treatment groups although there were higher incidence rates for tachycardia in the bupivacaine treatment groups than in the SABER-bupivacaine treatment groups. Holter monitoring of subjects for 3 days after dosing revealed the following:

- Large procedure-related changes of both heart rate and change-from-baseline QT parameters were observed.
- Despite this, very small changes of QT parameters were observed post-dosing of SABER-Bupivacaine when adjusted for by the placebo-response (ΔΔQTcF and ΔΔQTbtb). In the time-matched analysis, occasional mean peak ΔΔQT effects of around 5 msec with an upper bound slightly exceeding 10 msec were observed. The peak effects were not observed at the same post-dosing timepoint for

ΔΔQTcF (24 hours) and ΔΔQTbtb (1 and 16 hours) and not at the time for the observed peak bupivacaine plasma peak levels (48 hours).

- Exposure response analysis of ΔΔQTc and ΔΔQTbtb does not provide evidence of bupivacaine-induced QT prolongation in this setting. Using the concentration effect model, predicted QT effect levels (ΔΔQTcF and ΔΔQTbtb) at observed mean peak plasma levels were all small and clearly below any level of clinical concern with the upper bound of the CI well below 10 msec.
- Based on these observations, the data support that SABER-Bupivacaine in the peri-operative setting at mean plasma levels exceeding 800 ng/mL does not cause QT prolongation.
- SABER-Bupivacaine did not have an effect on cardiac conduction (the PR and QRS interval)

The frequency and nature of AEs was not correlated with bupivacaine plasma concentration as assessed by Cmax. Importantly, there were no differences in the incidence of cardiovascular or neurological AEs with increasing Cmax. There were no AEs suggestive of bupivacaine toxicity in any of the patients in the Cmax >1500 ng/mL subgroup.

Summary of Reported Pharmacokinetic Findings

The PK findings for Cmax and Tmax in each of the cohorts are summarized in Table 62 below.

Table 62. PK summary for the three cohorts (from Tables 19, 20, and 21, on pp. 113, 116, and 118, respectively, in the final study report)

Cohort	PK Parameter	Treatment	
1		SABAER-bupivacaine (n=30)	Bupivaciane HCl (n=18)
	Cmax (ng/mL) Mean (SEM) [Range]	955.6 (88.5) [133 – 1870]	250.6 (44.8) [19 – 551]
	Tmax (hr) Median [range]	48.1 [2-73]	16.3 [1-48]
2		SABAER-bupivacaine (n=30)	Bupivaciane HCl (n=20)
	Cmax (ng/mL) Mean (SEM) [Range]	752.1 (56.0) [357 – 1850]	370.5 (55.0) [101- 1170]
	Tmax (hr) Median [range]	24.3 [1 – 49]	0.9 [1 – 24]
3		SABAER-bupivacaine (n=129)	SABER-placebo
	Cmax (ng/mL) Mean (SEM) [Range]	849.6 (42.1) [92 – 2850]	N/A
	Tmax (hr) Median [range]	46.6 [1 – 74]	N/A

Discussion

In none of the cohorts was SABER-bupivacaine found to be significantly more effective than its comparator. There was a trend favoring the SABER-bupivacaine treatment, and in some of the secondary AUC time blocks, there was a significant difference between treatment arms.

The clinical basis for combining efficacy data from Cohorts 1 and 2 was not provided, and while the increase in the number of subjects and the comparison of the same treatment groups would seem reasonable, the more appropriate combination, if any were appropriate, would be Cohorts 1 and 3 as both involved the same major abdominal surgical procedure, colectomy, and both involved a surgical incision larger than that required for laparoscopic ports. It is not clear how the findings for the combined cohort, the only statistical "win" for the trial, should be interpreted in terms of evaluating the efficacy of SABER-bupivacaine.

The safety findings from the study provide evidence that SABER-bupivacaine is not associated with cardiac or neurological toxicity at the highest systemic exposures. The lumping of many of the local adverse events under the preferred term "application site discolouration" was problematic in that some of the AEs subsumed in the term are key for assessing safety. In an effort to discern the underlying nature of the incision site "discolorations," the adverse event database was reviewed for all adverse events affecting the surgical incisions. A total of 115 events were found; the majority of these fell into the categories listed in Table 63 below. The only adverse event that appeared to be related to the treatment was dehiscence, which, as the Applicant noted, seems to be related to the SABER portion of the product as it occurs consistently in the SABER-containing treatment arms but not at all in the bupivacaine HCl treatment arms.

Table 63. Adverse events associated with the surgical incision

Surgical Site AE	Laparotomy		Laparoscopic Cholecystectomy		Laparoscopically Assisted Colectomy	
	Bupivacaine HCl (n=18)	SABER-bupivacaine (n=30)	Bupivacaine HCl (n=20)	SABER-bupivacaine (n=30)	SABER-placebo (n=78)	SABER-bupivacaine (n=129)
Bleeding	0	4 (13%)	0	0	4 (5%)	18 (14%)
Drainage	1 (6%)	3 (10%)	1 (5%)	1 (3%)	7 (9%)	16 (12%)
Dehiscence	0	3 (10%)	0	2 (7%)	5 (6%)	8 (6%)
Infection	3 (17%)	6 (20%)	1 (5%)	1 (3%)	2 (3%)	13 (10%)
Seroma/hematoma	0	0	0	0	2 (3%)	2 (2%)
Bruising or ecchymosis	0	0	0	0	1 (1%)	7 (5%)

Conclusions

This trial did not demonstrate SABER-bupivacaine to be significantly more efficacious than either bupivacaine HCl or SABER-placebo. Although the SABER-bupivacaine treatments trended in a superior direction versus the comparators, only when efficacy

data from Cohorts 1 and 2 were combined was a statistically significant difference in treatments observed. Given the increase rate of dehiscence observed with SABER treatments and the minimal difference in efficacy observed for each of the cohorts, the benefits of SABER-bupivacaine do not outweigh the associated risks.

9.4.6 CLIN005-0006 (Phase 2, Controlled Trial – Shoulder Arthroscopy)

Title: A Randomized, Double-blind, Placebo-controlled Study of the Efficacy and Safety of Subcutaneous or Subacromial SABER™-Bupivacaine in Patients Undergoing Rotator Cuff Repair

Study Dates: June 12, 2006 – December 10, 2007

Objectives

Primary Efficacy Objective:
To determine the efficacy of SABER-bupivacaine injected into the subacromial space for subjects undergoing elective arthroscopic shoulder surgery involving subacromial decompression.

Secondary Efficacy Objectives:

- To determine the efficacy of SABER-Bupivacaine injected into the subacromial space followed by SABER™-Bupivacaine administered as 2 trailing subcutaneous injections along each side of the incision line for subjects undergoing elective arthroscopic shoulder surgery involving subacromial decompression
- To determine the efficacy of SABER-Bupivacaine injected into the subacromial space for subjects undergoing elective arthroscopic shoulder surgery involving subacromial decompression

Efficacy Endpoints

Primary Endpoints:

- Pain intensity with movement (PImove) and pain intensity at rest (PIrest), assessed using the time-weighted average scores (AUCs) for the per protocol (PP) population over 120 hours
- Pain control by study day and treatment, assessed using the numerical score for the PP Population

Secondary Endpoints:

- Modified Brief Pain Inventory
- time-weighted average scores of worst and least pain
- opioid rescue analgesia cumulative morphine equivalent doses
- function Scores
- Overall treatment satisfaction score
- Pain intensity over time

Inclusion Criteria (verbatim from p. 35 of the final study report)

1. Males and females, 18 years of age and older.
2. Pain indicative of rotator cuff disease and subacromial impingement, necessitating shoulder surgery. Cohort 2 was restricted to arthroscopic surgery only.
3. Need for procedures involving but not limited to subacromial decompression.
4. Determined to be in good health prior to study participation based on a medical history, physical examination, electrocardiogram (ECG), and laboratory tests.
5. Body Mass Index (BMI) 13 through 35 kg/m^2.
6. Systolic blood pressure no greater than 160 mmHg and diastolic blood pressure no greater than 95 mmHg.
7. A requirement that males and females must agree to use a medically acceptable method of contraception throughout the study period and for 1 week after the study was completed for all subjects. Acceptable methods that could be used were abstinence, birth control pills/patches, diaphragm with spermicide, IUD (coil), condom and foam, surgical sterilization, and progestin implant or injection.
8. A requirement to refrain from strenuous activities throughout the study period and avoid modifications to prescribed physiotherapy and exercise levels throughout the course of the study.
9. Ability to read, understand, communicate, and voluntarily sign the approved informed consent form prior to the performance of any study specific procedures.

Exclusion Criteria (verbatim from p. 36 of the final study report)

1. Open or mini-open shoulder surgery procedures. (Note: Per Protocol Amendment 03, this applied to Cohort 2 only.)
2. Pregnancy or lactation.
3. Evidence of major joint trauma, infection, avascular necrosis, chronic dislocation, inflammatory or degenerative glenohumeral arthropathy, frozen shoulder or previous surgery of the affected shoulder.
4. Evidence of clinically significant hepatic, gastrointestinal, renal, hematologic, urologic, neurologic, respiratory, endocrine, reproductive or cardiovascular system abnormalities, psychiatric disorders, or acute infection.
5. Connective tissue disorders (systemic lupus erythematosus, scleroderma, mixed connective tissue disease).
6. Current or regular use at screening of triptyline or imipramine antidepressants, monoamine oxidase inhibitors.
7. Known or suspected alcohol abuse or illicit drug use within the 6 months prior to study enrollment.
8. Use of any prescription drugs or over-the-counter medication starting within 7 days before treatment and throughout the study (except for birth control medications) that may interfere with the conduct or interpretation of the study results (Note: subjects taking regular analgesic medications for indications other

than that related to the rotator cuff injury/disease were to be excluded from the study).
9. Participation in another clinical study concurrent or within 30 days of enrollment.
10. Known sensitivity to bupivacaine, BA, or other study drug constituents.
11. Subjects unwilling or unable to comply with the study visit schedule.

Summary of Methodology

This was a randomized, double-blind, placebo-controlled, Phase 2 study in which the study drug was administered subcutaneously or into the subacromial space in subjects undergoing elective arthroscopic shoulder surgery under local or general anesthesia.

The study was conducted in 2 separate and sequential cohorts (Cohort 1 and Cohort 2). Approximately equal numbers of subjects were to have been enrolled, in sequence, to each cohort. The study duration was up to 21 days comprising screening, admission to clinic and surgery (Day 0), postoperative evaluations, discharge from clinic, and follow-up through Day 14. The subjects were evaluated on Days 1 and 2 in the clinic or at home, on Day 3 in the clinic, and on Days 4 through 7 by telephone following surgery and treatment. Subjects returned on Day 14 for follow-up evaluation and plasma collection. Subjects recorded pain intensity (PI), concomitant medications, adverse events (AEs), and rescue analgesia on diary cards from Day 0 through Day 7. Subjects also recorded AEs and concomitant medications through Day 14.

Cohort 1:
Immediately prior to surgery a maximum of 45 subjects were to have been randomly assigned in a 1:1:1 ratio (Treatment Group 1, Treatment Group 2, Treatment Group 3) to receive 1 of the following treatments:

- Treatment Group 1: Prior to wound closure, 5.0 mL of SABER-Placebo was injected into the subacromial space. After wound closure, a total volume of 5.0 mL of SABER-Bupivacaine was administered as 2 trailing subcutaneous injections along each side of the incision line. The total amount of bupivacaine was 660 mg.
- Treatment Group 2: Prior to wound closure, 5.0 mL of SABER-Bupivacaine was injected into the subacromial space. After wound closure, a total volume of 5.0 mL of SABER-Placebo was administered as 2 trailing subcutaneous injections along each side of the incision line. The total amount of bupivacaine was 660 mg.
- Treatment Group 3: Prior to wound closure, 5.0 mL of SABER-Placebo was injected into the subacromial space. After wound closure, a total volume of 5.0 mL of SABER-Placebo was administered as 2 trailing subcutaneous injections along each side of the incision line. (The total delivered volume of SABER-Placebo was 10.0 mL.)

For all treatment groups, if the procedure was performed arthroscopically, the subcutaneous doses of study drug were administered evenly around all arthroscopic portals.

Cohort 2:
Upon completion of Cohort 1, enrollment of subjects into Cohort 2 was started. Immediately prior to surgery, a minimum of 45 subjects were randomly assigned in a 1:1 enrollment ratio (Treatment Group 4 and Treatment Group 5) to receive 1 of the following treatments:

- Treatment Group 4: During wound closure, 5.0 mL of SABER-Placebo was injected into the subacromial space (7.5 mL specified for Cohort 2a comprising Treatment 4a and Treatment 5a).
- Treatment Group 5: During wound closure, 5.0 mL of SABER-Bupivacaine was injected into the subacromial space (7.5 mL specified for Cohort 2a comprising Treatment 4a and Treatment 5a). For Treatment 5, the total amount of bupivacaine was 660 mg. For Treatment 5a, the total amount of bupivacaine was 990mg. [Note: Protocol Amendment 04, dated 15 November 2006, changed the amount of drug to be administered in Cohort 2 from 7.5 mL to 5.0 mL. However, 4 subjects were administered Treatment 4a (7.5 mL SABER-Placebo) and 3 subjects were administered Treatment 5a (7.5 mL SABER-Bupivacaine) before this amendment was put into effect.

Nine subjects were randomized to receive SABER-Placebo or 5.0 mL SABER-Bupivacaine at 1 participating center in order to obtain PK measurements in the double-blind portion of the study. Of these 9 subjects, 4 received 5.0 mL SABER-Bupivacaine and 5 received SABER-placebo. Upon completion of the double-blind portion of the study, a supplemental PK substudy protocol was implemented to enroll up to 14 additional PK subjects to receive 5.0 mL open-label SABER-Bupivacaine subacromially.

The study was conducted at six sites in the United States and one site in New Zealand.

Amendments

1. (March 29, 2006): This amendment modified the protocol as follows:
    a. Clarify that, for those procedures performed arthroscopically without an “open” incision, the subcutaneous doses of study drug would be administered evenly to all arthroscopic incisions.
    b. Clarify that subjects 18 to 65 years of age would be included.
    c. Clarify that the recommended analgesic was generic oxycodone (5.0 mg).
    d. Clarify the method of assigning subject numbers and randomization numbers.
    e. Clarify the SAE reporting procedures.

2. (May 31, 2006): This amendment made the following modifications to the protocol:
    a. Clarify that a central laboratory would be used for the clinical laboratory evaluations.
    b. Clarify that follow-up visits for Days 1 and 2 could be performed either at home or in the clinic.
    c. Clarify that only subjects with a BMI of 13 through 35 kg/m2 would be included.
    d. Clarify that epinephrine would only be used during the first infusion during the surgical procedure.
    e. Clarify that preoperative and intraoperative bupivacaine would not be used.
    f. Clarify that combination analgesics (eg, Vicodin and Lortab) would not be used.
    g. Clarify the surgical procedure.

3. (September 20, 2006): This amendment modified the protocol as follows:
    a. The protocol was amended to include, as Cohort 2, a design to compare the effectiveness of direct in-the-wound placement of SABER-Bupivacaine versus SABER-Placebo. (No injection into tissues was to be performed as part of the new procedure. A needle was used only to allow administration of the study drug into the subacromial space.) During wound closure, SABER-Bupivacaine or SABER-Placebo was injected into the subacromial space according to a specific randomization scheme. This amendment also allowed for a direct comparison of a SABER-Bupivacaine versus SABER-Placebo injection administration technique to that of SABER-Bupivacaine versus SABER-Placebo in-the-wound placement technique within the same study and within the same investigative sites. [Note: The in-the-wound procedure was added to this study after positive results became available from another study that used this technique.]
    b. Changed the inclusion and exclusion criteria to stipulate that only arthroscopic procedures were to be used in Cohort 2. Therefore, the following additions were made to the inclusion criteria:
        i. Clinical features of pain indicative of rotator cuff disease and subacromial impingement, necessitating arthroscopic shoulder surgery
        ii. Arthroscopic procedures involving but not limited to subacromial decompression
    c. The following was added to the exclusion criteria:
        i. Open or Mini-open shoulder surgery procedures.
    d. Modified the inclusion criterion for age; the inclusion criterion was changed from “18 to 65 years of age” to “18 years of age or older.”

4. (November 15, 2006): This amendment made the following modifications to the protocol for Cohort 2 of the trial:
    a. Change the amount of SABER-Bupivacaine that would be injected into the subacromial space during the wound closure from 7.5 mL to 5.0 mL in Treatment Group 5 (this change resulted from an FDA recommendation that additional safety data be collected on the 7.5-mL dose before its use in clinical trials).
    b. Change the amount of SABER-Placebo that would be injected into the subacromial space during the wound closure from 7.5 mL to 5.0 mL in Treatment Group 4 (this change resulted from an FDA recommendation that additional safety data be collected on the 7.5-mL dose before its use in clinical trials).
    c. A drug screen test for opiates, opioid receptor antagonists, and cocaine would be performed at screening for Cohort 2.
    d. During surgery, incision length would be documented for all subjects.
    e. No additional bupivacaine or other amide local anesthetic would be used at the surgical site.
    f. New sponsor contacts.
    g. New labels for the study drug syringe were used for Cohort 2.

Schedule (Table 9.2, p. 42 of the final study report)

Study Phase	Screening	Treatment	Follow-up			Study Completion
Visit Name		Day 0[a.]	Days 1 to 3	Days 4 to 7	Days 8 to 13	Day 14
Informed consent	X					
Inclusion/Exclusion criteria	X					
Medical history	X					
Demographics	X					
Physical examination	X					X
Safety Labs: chemistry, hematology, urinalysis	X					X
Drug screening (opiates, opioid receptor antagonists, and cocaine)	X[b]					
Pregnancy test	X					
12-lead ECG	X[c]	X[c]	X[c]	X[c]		
Concomitant medications	X	X	X	X	X	X
Vital signs	X	X[d]	X			X
Screen fail subject	X[e]	X				
Evaluate to enter treatment		X				
Assign subject number	X[f]					
Undergo surgical procedure		X				
Inject study drugs 1 and 2		X				
Pain intensity evaluations[g]		X	X	X		
Modified Brief Pain Inventory evaluations[g]			X	X		
Dispense/Review subject diary card		X	X	X[h.]		X
Rescue analgesia pain intensity evaluations	~~X~~ *	X	X	X	X	X
Discharge subject following site visit		X[i]	X			X
Adverse event evaluation		X	X	X	X	X

a. Treatment to occur within 7 days of screening.
b. Cohort 2 only.
c. Screening Baseline ECG, then if clinically indicated postoperatively.
d. Vital signs collection times: pretreatment, post-treatment: monitored hourly for the first 8 hours or until discharge if earlier.
e. If screening laboratory assays or ECG show a clinically significant abnormal result, screen fail subject.
f. Assign subject randomization number after successful completion of all screening procedures.
g. Refer to Appendices 2, 3, and 4 of the protocol for evaluation times postoperatively.
h. Telephone review of diary card.

[i.] According to local practice.
* Note: Rescue analgesia pain intensity evaluations were not performed at screening, this was an error in Appendix 1 of the Protocol and Protocol Amendments (Section 16.1.1) that contradicts the schedule described in the Study Synopsis and Sections 4.0, 14.0, and 15.0 of the Protocol and Protocol Amendments, as well as the Patient Diary, CRF, and Study Reference Manual.

Subject Disposition

The Applicant reported that a total of 92 subjects were randomized and 90 completed the study; two subjects withdrew consent. Subject disposition is summarized in Table 64 below.

Table 64. Subject disposition (Table 10.1, p. 57 of the final study report)

	Treatment 1 (n=14)	Treatment 2 (n=10)	Treatment 5 (n=21)	Treatment 5a (n=3)	SABER-BUP (n=31)	Pooled Placebo (n=44)	All Subjects (N=92)
Number of subjects randomized	14	10	21	3	31	44	92
Number of subjects completing study	14 (100.0%)	10 (100.0%)	21 (100.0%)	2 (66.7%)	31 (100.0%)	43 (97.7%)	90 (97.8%)
Number of subjects who prematurely withdrew	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	1 (2.3%)	2 (2.2%)
Reasons for Subject Withdrawal:							
Withdrew consent	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	1 (2.3%)	2 (2.2%)
Analysis Population							
Safety	14	10	21	3	31	44	92
Intention to Treat (ITT)	14	10	21	3	31	44	92
Per Protocol (PP)	14	9[a.]	21	3	31	44	91

[a.] Subject (b) (6) (Treatment 2) was not included in the Per Protocol Population because the study drug vials were reversed; therefore, SABER-Bupivacaine and Placebo were administered to this subject in the incorrect order.

Treatments (5.0 mL):
1=SABER-Bupivacaine Subcutaneous
2=SABER-Bupivacaine Subacromial
3=SABER-Placebo
4=SABER-Placebo
5=SABER-Bupivacaine
Treatments 4a and 5a are the same as Treatments 4 and 5, but using 7.5 mL
SABER-BUP=Treatments 2 and 5
Pooled Placebo=Treatments 3, 4a, and 4
Treatment 3 (n=16)
Treatment 4a (n=4)
Treatment 4 (n=24)

Reported Efficacy Findings

The average PI scores over the 120 hours following study drug administration (AUC/120 hours) during movement and at rest are summarized by treatment group in Table 65 and Table 66, respectively. Treatment 2 had the lowest mean value (least pain). The comparison to the Pooled Placebo group demonstrates that Treatment 2 was significantly better than Pooled Placebo. The SABER-BUP group was numerically better than Pooled Placebo; however, the difference did not reach statistical significance. For average PI during rest, Treatment 2, Treatment 5, and SABER-BUP were numerically better than Pooled Placebo; however, none of the differences reached statistical significance.

Table 65. Pain on movement AUC results (Table 11.1, p. 64 of the final study report)

		Comparison to Pooled Placebo		
Treatment	**n**	**Mean (SD)**	**Mean Difference (95% CI)**	***P*-value**
Treatment 1	14	5.47 (2.352)	0.25 (-1.13 – 1.62)	0.720
Treatment 2	9	3.27 (1.648)	-1.95 (-3.59 – -0.31)	0.020
Treatment 5	21	5.12 (2.230)	-0.10 (-1.29 – 1.09)	0.866
SABER-BUP	30	4.56 (2.219)	-1.03 (-2.14 – 0.09)	0.072
Pooled Placebo	44	5.22 (2.281)		

Treatments (5.0 mL):
1 = SABER-Bupivacaine Subcutaneous
2 = SABER-Bupivacaine Subacromial
3 = SABER-Placebo
4 = SABER-Placebo
5 = SABER-Bupivacaine
Treatments 4a and 5a are the same as Treatments 4 and 5, but using 7.5 mL
SABER-BUP = Treatments 2 and 5
Pooled Placebo = Treatments 3, 4a, and 4

Table 66. Pain at rest AUC results (Table 11.2, p. 64 of the final study report)

		Comparison to Pooled Placebo		
Treatment	**n**	**Mean (SD)**	**Mean Difference (95% CI)**	***P*-value**
Treatment 1	14	3.53 (2.331)	0.43 (-0.76 – 1.63)	0.473
Treatment 2	9	2.16 (1.496)	-0.95 (-2.37 – 0.48)	0.190
Treatment 5	21	2.58 (1.674)	-0.52 (-1.56 – 0.51)	0.315
SABER-BUP	30	2.45 (1.609)	-0.73 (-1.71 – 0.24)	0.136
Pooled Placebo	44	3.10 (1.995)		

Treatments (5.0 mL):
1 = SABER-Bupivacaine Subcutaneous
2 = SABER-Bupivacaine Subacromial
3 = SABER-Placebo
4 = SABER-Placebo

5 = SABER-Bupivacaine
Treatments 4a and 5a are the same as Treatments 4 and 5, but using 7.5 mL
SABER-BUP = Treatments 2 and 5
Pooled Placebo = Treatments 3, 4a, and 4

The other primary efficacy variable was pain control by study day and treatment, assessed using a numerical score for subjects in the PP Population (1=Poor, 5=Excellent). The average pain control scores for Day 1 through Day 7 are summarized by treatment group in Table 67 below. The Applicant limited the statistical comparisons to the SABER-BUP versus Pooled Placebo groups. The only statistically significant difference observed was on Day 1; no statistically significant differences were observed during the rest of the study (Days 2 through 7) for pain control.

Table 67. Pain control efficacy results (Table 11.3, p. 65 of the final study report)

Treatment Group	Mean Pain Control by Day						
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Treatment 1	3.0	2.7	3.1	3.0	3.2	3.1	3.1
Treatment 2	3.3	3.4	3.2	3.4	3.4	3.7	3.8
Treatment 5	3.3	3.4	3.4	3.7	3.6	3.6	3.7
SABER-BUP	3.3	3.4	3.3	3.6	3.5	3.6	3.7
Pooled Placebo	2.5	3.0	3.4	3.4	3.4	3.4	3.6
p-value (SABER-BUP vs. Pooled Placebo)	0.008	0.111	0.767	0.532	0.608	0.380	0.689

For the secondary endpoints, there were no significant differences between the pooled placebo treatments and any of the SABER-bupivacaine treatments, including the combined SABER-BUP, for worst and least pain, need for rescue analgesia, opioid rescue analgesia requirements, function scores and hours sitting and walking (with the exception of SABER-BUP vs. pooled placebo for deep breath function), overall treatment satisfaction, and pain intensity over time.

Summary of Reported Safety Findings

There was one TEAE that was classified as severe and one that was classified as serious; both occurred in subjects treated with SABER-placebo.

The overall frequency of AEs was similar between treatment groups. The most commonly reported treatment-emergent AEs were nausea (64 events total), somnolence (60 events total), pruritus (57 events total), and constipation (48 events total). The majority of treatment-emergent AEs were of mild or moderate severity. The

one reported severe AE was for post-procedural pain, which was also the only SAE reported.

Among the different SABER-bupivacaine treatment groups, the differences in AEs were negligible with the exception of the patients receiving SABER-bupivacaine subcutaneously These subjects showed a slightly higher frequency of opioid-related AEs while demonstrating lower pain reduction as compared to subacromial injections, which would indicate that this form of treatment provided less effective local pain control.

Among skin reactions, pruritus was the most frequently observed (64% in the pooled placebo group and 58% in the SABER-bupivacaine groups). Its occurrence was attributed to the use of opioids.

Dysgeusia (27% in the pooled placebo group and 23% in the SABER-bupivacaine groups) as well as hypoesthesia and paresthesia observed between 13% and 25% were attributed to general anesthesia as the incidences were similar among all treatment groups.

Discussion

This trial failed to show efficacy for SABER-bupivacaine with the exception of its injection, all 5 mL, into the subacromial space followed by the infiltration of SABER-placebo into the incision lines. For this use, it was superior to placebo only for pain on movement. It is worth noting that the injection of SABER-bupivacaine in both locations, subacromial and along the incision lines, i.e., Treatment 5, was not effective. This suggests the 5 mL dose cannot be split, and raises the issue as to whether the dosing paradigm is appropriate.

Rather than consider a change in dosing, the Applicant performed a subgroup analysis on subjects from both cohorts who had minimal or no glenohumeral pathology. In this subanalysis, those treatment groups using subacromial administration of SABER-bupivacaine (Treatments 2 and 5) had a lower PI on movement compared to placebo (Treatments 3 and 4). Treatment 1, which used subcutaneous administration of SABER-bupivacaine, did not show a reduction in PI on movement compared to placebo. No differences between treatment groups were observed in consumption of opioid supplementation in the subgroup analysis. When differences in surgical procedures between Cohort 1 and Cohort 2 were reviewed, it was discovered that 33% of subjects in Cohort 1 and 51% of subjects in Cohort 2 underwent surgical procedures which involved manipulations of the glenohumeral joint. Overall, subjects with more extensive surgical procedures reported higher postoperative pain scores and responded poorly to SABER-Bupivacaine treatment. Therefore, they thought the higher proportion of subjects with glenohumeral surgery in Cohort 2 may explain the differences observed between the 2 cohorts.

Based on the findings, the Applicant concluded that this trial underlined the importance of proper drug deposition in relation to the area where surgical manipulations were being performed. Because the glenohumeral joint is tightly shielded by rotator cuff muscles from the subacromial area, they postulated that subacromial administration of SABER-bupivacaine in patients with isolated subacromial impingement syndrome will yield better analgesic activity than would be seen in patients with glenohumeral procedures. Further investigation of subacromial deposition of SABER-bupivacaine may require the selection of a patient population limited to subacromial impingement syndrome who undergo arthroscopic subacromial decompression without extensive surgical procedures on rotator cuff muscles and the glenohumeral joint to ensure SABER-bupivacaine contact with pain-producing anatomical structures manipulated during the surgery.

The trial did not identify any safety concerns specific to SABER-bupivacaine, at least, not in comparison to SABER-placebo. There were no over signs of systemic toxicity that could be attributed to bupivacaine exposures. It was interesting to note the extent to which nervous system and skin AEs occurred in all treatment groups. The AEs are summarized in Table 68 below. Although the numbers of exposures are relatively small, the consistency of the AEs suggests that signal is real. The rates of the AEs with SABER-placebo treatment also suggests the AEs are not related to bupivacaine leaving the SABER or one of its components as the causative agent. However, without a true placebo treatment arm, it is not possible to make a definitive statement regarding any of these AEs.

Table 68. Summary of nervous system and skin AEs (from Table 12.3, pp. 82-84 of the final study report)

SOC Preferred Term	Treatment 1 (n=14)	Treatment 2 (n=10)	Treatment 5 (n=21)	Treatment 5a (n=3)	SABER-BUP (n=31)	Pooled Placebo (n=44)
Nervous system disorders	**12 (85.7%)**	**10 (100.0%)**	**17 (81.0%)**	**3 (100.0%)**	**27 (87.1%)**	**43 (97.7%)**
Dizziness	7 (50.0%)	3 (30.0%)	9 (42.9%)	2 (66.7%)	12 (38.7%)	20 (45.5%)
Dysgeusia	5 (35.7%)	2 (20.0%)	5 (23.8%)	1 (33.3%)	7 (22.6%)	12 (27.3%)
Headache	0 (0.0%)	1 (10.0%)	9 (42.9%)	1 (33.3%)	10 (32.3%)	7 (15.9%)
Hypoesthesia	3 (21.4%)	4 (40.0%)	1 (4.8%)	0 (0.0%)	5 (16.1%)	9 (20.5%)
Paresthesia	4 (28.6%)	1 (10.0%)	3 (14.3%)	1 (33.3%)	4 (12.9%)	11 (25.0%)
Somnolence	7 (50%)	8 (80%)	11 (52%)	2 (67%)	19 (61%)	32 (73%)
Skin and subcutaneous tissue disorders	**9 (64.3%)**	**7 (70.0%)**	**12 (57.1%)**	**2 (66.7%)**	**19 (61.3%)**	**28 (63.6%)**
Pruritus	9 (64.3%)	7 (70.0%)	11 (52.4%)	2 (66.7%)	18 (58.1%)	28 (63.6%)

It bears noting that there was no long-term follow-up evaluation of subjects in this trial that would have permitted an assessment of the risk for chondrolysis. Given the concerns the Agency has had related to the infusion of local anesthetics into the intra-articular space, this is an important safety assessment that is lacking from this study. [The Agency's concerns for this safety issue arose after this trial was completed.]

Conclusions

This trial failed to identify an effective dose or method of administration for SABER-bupivacaine following arthroscopic shoulder surgery. The trial did not indicate that there was a risk for systemic toxicity related to bupivacaine release from SABER-bupivacaine, but it did raise a concern for local reactions to the product that may be due to SABER or one of its components.

9.4.7 C803-017 (Phase 2, Controlled Trial – Shoulder Arthroscopy)

Title: A Double-Blind, Multi-Center, Placebo-Controlled Trial of SABER™-Bupivacaine for Post-Operative Pain Control and Opioid Sparing/Opioid-Related Adverse Event Reduction Following Arthroscopic Shoulder Surgery

Study Dates: December 11, 2008 – October 29, 2009

Objectives

1. Explore analgesic effectiveness and characterize the safety profile of 5.0 mL SABER-bupivacaine in an orthopedic surgical model compared to SABER-placebo.
2. Explore the reduction in frequency of opioid-related AEs by 5.0 mL SABER-bupivacaine in an orthopedic surgical model compared to SABER-placebo.

Efficacy Endpoints

Primary Endpoints:

- Mean pain intensity on movement area under the curve (AUC) (time normalized area under the curve) during the period 0 to 72 hours post-dose.
- Mean total morphine-equivalent opioid dose for supplemental analgesia during the period 0 to 72 hours post-dose.

Secondary Endpoints:

- Frequency of subject-reported opioid-related AEs during 0 to 72 hours post-dose and during the trial: constipation, drowsiness, dizziness, nausea, vomiting, respiratory depression, and urinary retention.
- Mean pain intensity on movement AUC (time normalized area under the curve) during the period 0 to 48 hours post-dose.
- Mean total morphine-equivalent opioid dose for supplemental analgesia during the period 0 to 48 hours post-dose.
- Time-to-first use of opioid supplemental medication.
- Severity of subject reported opioid-related AEs during 0 to 72 hours post-dose and during the trial: constipation, drowsiness, dizziness, nausea, vomiting, respiratory depression, and urinary retention.

Inclusion Criteria (verbatim from pp. 24-25 of the final study report)

1. Provided written consent to participate in the trial prior to any trial procedures and understood that they were free to withdraw from the trial at any time.

2. Able to read and understand the consent form, complete trial-related procedures, and communicate with the trial staff.
3. Males and females, 18 to 65 years of age, with clinical syndrome of subacromial impingement (diagnosed by positive subacromial impingement sign, i.e. pain with shoulder elevation, and full passive range of motion) and scheduled for arthroscopic shoulder surgery.
4. American Society of Anesthesiologists (ASA) Physical Status Classification of P1 or P2 prior to trial participation based on medical history, physical exam, 12-lead ECG, and laboratory tests.
5. ECG wave form within normal limits or had nonspecific ST segment and T wave changes and the interval measurements with a heart rate of 45 to 105 beats per minute, PR (duration from onset of atrial depolarization until the onset of ventricular depolarization) up to 220 ms, QRS (part of ECG wave representing ventricular depolarization) up to 110 ms and a QTc (corrected QT interval) of < 450 ms.
6. Systolic blood pressure no greater than 139 mmHg and diastolic blood pressure no greater than 89 mmHg.
7. Male and female subjects agreed to use a medically acceptable method of contraception throughout the entire trial period and for 1 week after the trial was completed. Medically acceptable methods of contraception that could be used by the subject and/or the partner included abstinence, oral contraception or patches (consistently for 3 months prior to trial dosing), NuvaRing (etonogestrel/ethinyl estradiol vaginal ring), diaphragm with vaginal spermicide, intrauterine device (IUD) (coil), condom and vaginal spermicide, surgical sterilization (6 months post-surgery), post-menopausal subject/partner (not experienced a menstrual period for a minimum of two years), and progestin implant or injection (used consistently for 3 months prior to trial dosing).
8. Refrained from strenuous activities throughout the trial period and avoided modifications to prescribed exercise levels throughout the course of the trial.

Exclusion Criteria (verbatim from pp. 25-26 of the final study report)

1. Subjects with glenohumeral arthritis.
2. Subjects with major or full thickness rotator cuff tears diagnosed by MRI.
3. Subjects with previous arthroscopic surgery or open surgery on the study shoulder.
4. Subjects with chronic pain conditions requiring continuous use of corticosteroids for greater than three months.
5. Subjects with fibromyalgia.
6. Subjects with rheumatoid arthritis.
7. Subjects with sero-negative inflammatory arthropathies.
8. Subjects with a calculated creatinine clearance < 30 mL/min.
9. Subjects who were pregnant or lactating.

10. Subjects receiving more than 20 mg of hydrocodone daily (or equivalent narcotic dose) on routine basis (more than three out of seven days per week) within seven days prior to Day 0 (day of surgery).
11. Subjects, who in the Investigator's opinion, had developed opioid tolerance.
12. Subjects who required the use of non-steroidal anti-inflammatory drugs (NSAIDs) within 24 hours prior to the scheduled arthroscopic shoulder surgery.
13. Subjects with regular use of anticonvulsants, antiepileptics, antidepressants, or monoamine oxidase inhibitors at screening.
14. Subjects with regular use of drugs known to significantly prolong the QTc interval within seven days prior to Day 0 or within a period of less than five times the drug's half-life, whichever was longer.
15. Subjects with known hypersensitivity to local anesthetic agents of the amide type (e.g., lidocaine, bupivacaine).
16. Subjects with known hypersensitivity to morphine or other opioids.
17. Subjects with conditions contraindicated for use of opioids, including paralytic ileus, acute or severe bronchial asthma or hypercarbia.
18. Subjects with known or suspected abuse of opioids or other illicit drugs.
19. Subjects with known or suspected alcohol abuse.
20. Subjects participating in any other trial with an investigational drug or device concurrently or within 30 days prior to Day 0 of this trial.
21. Subjects who, in the Investigator's opinion, should not participate in the trial or may not be capable of following the trial schedule for any reason.

Summary of Methodology

This was a randomized, double-blind, multi-center, placebo-controlled, parallel-group trial of a single dose of 5.0 mL SABER-bupivacaine in subjects undergoing arthroscopic shoulder surgery with the index procedure being subacromial decompression under general anesthesia. Eligible subjects were randomly assigned in a 2:1 ratio into one of two treatment groups prior to surgery:

- Treatment 1: 5.0 mL of SABER-bupivacaine injected interstitially into the subacromial space.
- Treatment 2: 5.0 mL of SABER-placebo injected interstitially into the subacromial space.

General anesthesia with propofol induction using IV fentanyl or an equivalent opioid per local practice was used for all subjects.

Supplemental rescue analgesia for moderate to severe post-operative shoulder pain in both treatment groups was provided, if needed, with oral administration of morphine.

Subjects were issued a LogPad, a handheld electronic device that captured efficacy and safety data and transferred it directly into a trial database. The device was provided to

the subject by the clinical site for the duration of the trial and was returned at the end of the trial. After receiving treatment with study drug, the LogPad was used to record:

- Shoulder pain intensity on movement.
- Presence of opioid-related AEs.
- Presence of SABER-bupivacaine related AEs.

Subjects were instructed to transmit from home the data collected in the LogPad device at the end of each day. Subjects were also dispensed a paper diary prior to discharge and were instructed to record the following information in the diary from the time of discharge through trial completion/early termination:

- Supplemental rescue opioid analgesia taken.
- Shoulder pain intensity evaluation on movement prior to taking supplemental analgesia.
- Details of opioid-related AEs.
- Details of SABER™-Bupivacaine related AEs.
- Details of all other AEs.
- Paracetamol/Acetaminophen taken.
- All other concomitant medications taken.

The paper diaries were collected and reviewed by trial staff at each clinic visit.

The trial was conducted at eight sites in Australia and two sites in New Zealand.

Amendments

1. (September 16, 2008): the following modifications to the protocol were made:
    a. Maximum age for study entry set to 65 years.
    b. Blood pressure for study entry changed to < 139 mmHg for systolic and <89 mmHg for diastolic.
    c. Rule for calculated creatinine added for study entry.
    d. Minor corrections and clarifications to text.

    [No subjects had been enrolled at the time of this amendment]

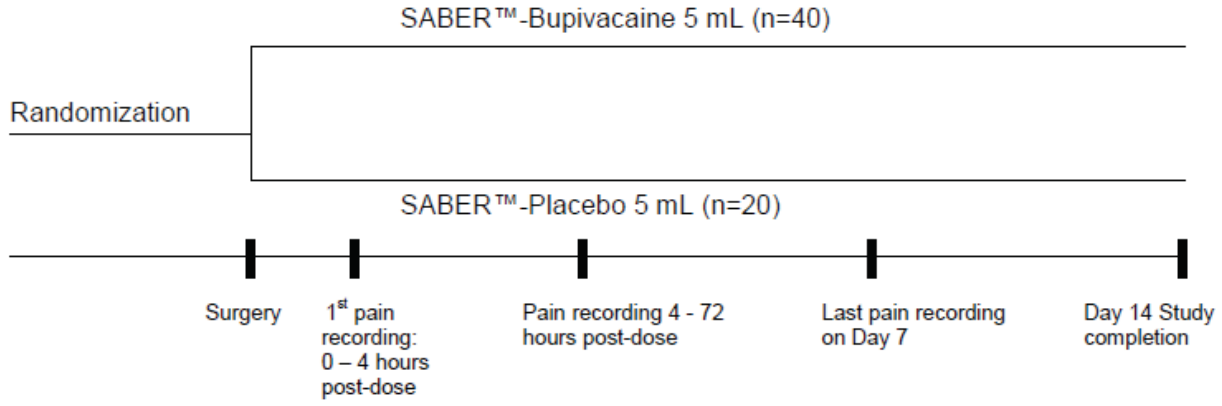
2. (October 9, 2008): the following modifications were made to the protocol:
    a. List of opioid-related AEs expanded to include nausea, vomiting, respiratory depression and urinary retention.
    b. Shoulder pain intensity evaluation amended to occur on movement.
    c. Time for follow up of AEs amended to occur until resolved or until 30 days after the last visit.
    d. Analysis amended to analysis of covariance with age as a covariate, and with Wilcoxon Rank-Sum test.
    e. Additional monitoring for early signs of bupivacaine toxicity.

f. Endpoints, statistical analysis, study schema sections clarified incorporating the Amendment changes.

[No subjects had been enrolled at the time of this amendment]

3. (26 May 29, 2009): the following modifications to the protocol were made: (24 subjects enrolled prior to the amendment):
   a. Addition of text to ensure relevance of Protocol for sites in the US, Australia and New Zealand. [It should be noted that no US sites were activated during the study and as a result no subjects were enrolled in the US for this study.]
   b. Clarifications of surgical requirements:
   c. Specification that subacromonial decompression be performed arthroscopically.
   d. Inclusion of open Mumford procedure to allow variations in surgical procedure, while maintaining uniformity of patient population.
   e. Clarifications of anesthetic requirements:
   f. Specification that short-acting opioids used during general anesthesia were not restricted.
   g. Specification that antiemetic medications used during general anesthesia were not restricted.
   h. Timeframe provided for acceptable historical MRI.
   i. Timeframe for randomization amended for greater flexibility.
   j. Additional method for administration of Investigational Product provided.
   k. Shoulder pain intensity amended to be recorded in the source notes until discharge.

Schematic (Figure 1, p. 17 of the final study report)



Schedule for Screening and Study Completion (Table 1, p. 18 of the final study report)

Trial Procedures	Screening	Trial Completion or Early Term
	Visit 1	Visit 3
	Day –14 to Day –1	Day 14 (± 3 days)
Informed Consent (prior to any trial procedures)	√	
Demographics	√	
Medical History	√	
Physical Examination	√	√
Height and Weight	√	√ [1]
Inclusion / Exclusion Criteria	√	
Magnetic Resonance Imaging (MRI) [2]	√	
Safety Labs (Chemistry, Haematology, Urinalysis)	√	√
Pregnancy Test	√ [3]	
12-lead ECG	√	
Vital Signs [4] (BP, HR, Respiratory Rate, Temperature)	√	√
Dispense LogPad/Review Instructions	√	
Shoulder Pain Intensity Evaluations (LogPad)	√ [5]	
Collected Unused Supplemental Analgesia (Morphine IR)		√
Collect / Review LogPad		√
Collect / Review Paper Diary		√
Surgical Site Healing and Local Tissue Conditions Evaluation		√
Adverse Events [6]	√	√
Concomitant Medications	√	√

1. Weight only
2. Historical MRI of good quality that was not older than three months from screening was acceptable
3. Serum pregnancy test for females of childbearing potential
4. Blood pressure and heart rate were to be measured after the subject had been resting for five minutes
5. Pain intensity on movement was to be done once a day for three days
6. AE collection was to start from the time a subject signed the consent form and was to continue through until study completion/early termination. Ongoing AEs at the time of completion/early termination were to be followed until resolved or until 30 days after the last trial visit, whichever came first.

Schedule for Day 0 of the study (Table 2, p. 19 of the final study report)

Trial Procedures	Visit 2 / Day 0											
	Hours Post-Dose											
	Pre-Dose	0	1	2	3	4	5	6	7	8	10	12
Pregnancy Test [1]	√											
Review Inclusion/Exclusion Criteria	√											
Collect LogPad	√											
Review LogPad Instructions	√											
IVRS Randomization	√											
Arthroscopic Shoulder Surgery	√											
Concomitant Medications	←	—	—	—	—	—	—	—	—	—	—	→
Adverse Events	←	—	—	—	—	—	—	—	—	—	—	→
Vital Signs [2] (BP, HR, Respiratory Rate, Temperature)	√	√ [3]	√	√	√	√	√	√	√	√		
Dosing [4]		√										
Shoulder Pain Intensity on Movement [5]		←	- -	- -	→							
Supplemental Analgesia (Morphine IR) [6]		If needed for moderate to severe pain										
Re-dispense LogPad					←	→						
Shoulder Pain Intensity on Movement (LogPad)						√		√		√	√	√
Opioid-Related Adverse Events (LogPad) [7]										at 20:00 (clock time)		
Bupivacaine-Related Adverse Events [8]										at 20:00 (clock time)		
Dispense Paper Diary / Review Instructions										prior to discharge		

1. Urine pregnancy test for females of childbearing potential
2. Blood pressure and heart rate were to be measured after the subject had been resting for five minutes; monitored hourly throughout the day up to eight hours post-dose or discharge (whichever was first).
3. Immediately following dosing
4. 5.0 mL SABER™-Bupivacaine or 5.0 mL SABER™-Placebo were to be administered into the subacromial space
5. Pain intensity on movement evaluation was to be done upon awakening from surgery
6. Pain intensity on movement evaluation was to be done prior to taking supplemental analgesia
7. Constipation, drowsiness, dizziness, nausea, vomiting, respiratory depression and urinary retention
8. Ringing in the ears, metallic taste in the mouth, numbness or tingling.

Schedule Day 1 and Day 2 of the study (Table 3, p. 20 of the final study report)

Trial Procedures	Days 1 and 2			
	Target Time			
	08:00	12:00	16:00	20:00
Supplemental Analgesia (Morphine IR) [1]	If needed for moderate to severe pain			
Shoulder Pain Intensity on Movement (LogPad)	√	√	√	√
Opioid-Related Adverse Events (LogPad) [3, 4]				√
Bupivacaine-Related Adverse Events [3, 5]				√
Concomitant Medications [3]	←	—	—	→
Adverse Events [3]	←	—	—	→

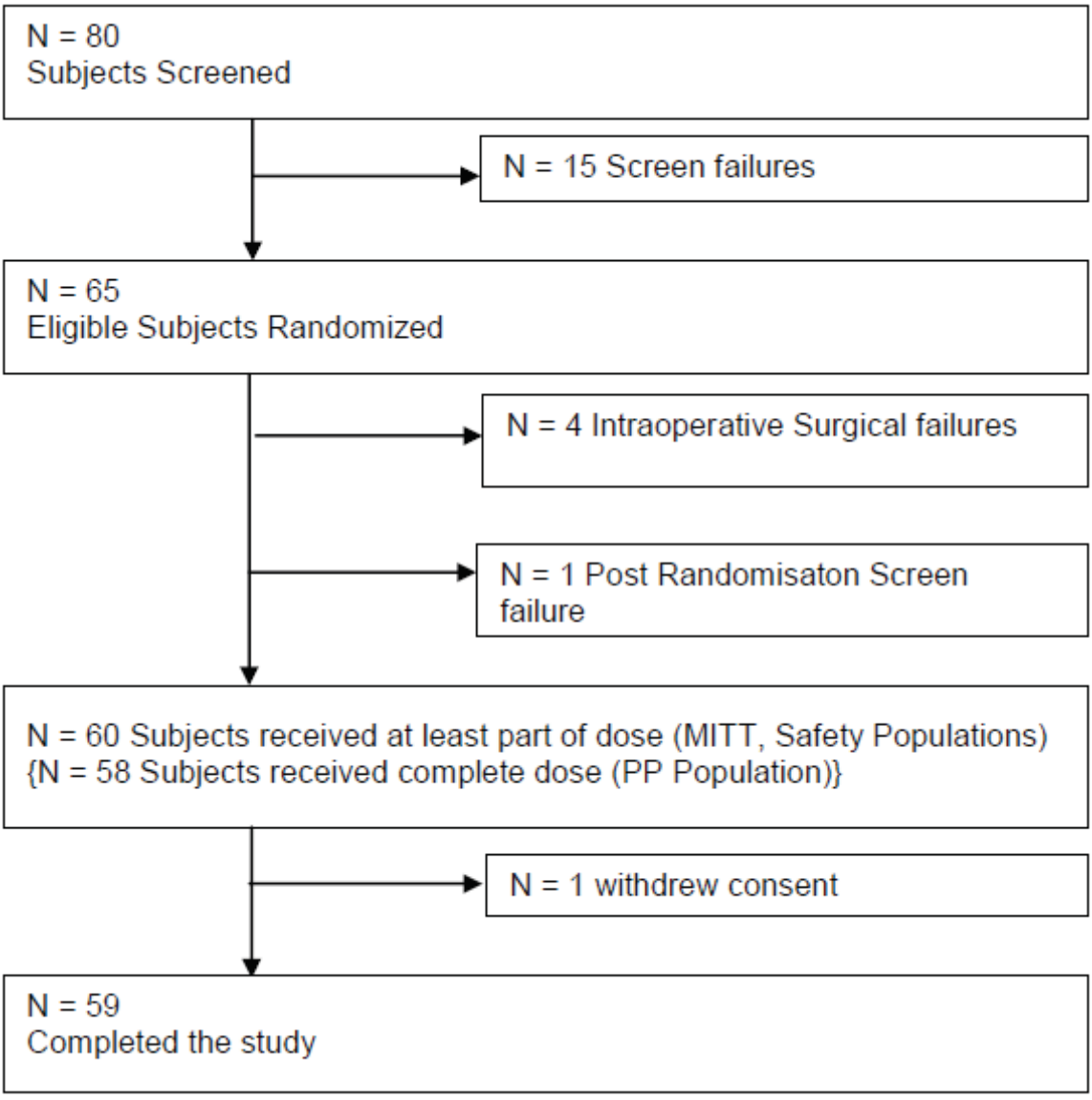
1. Pain intensity on movement evaluation was to be done prior to taking supplemental opioid analgesia and recorded in the paper diary; Supplemental analgesic taken was to be recorded in the paper diary
3. Specific details were to be recorded in the paper diary
4. Constipation, drowsiness, dizziness, nausea, vomiting, respiratory depression and urinary retention
5. Ringing in the ears, metallic taste in the mouth, numbness or tingling.

Schedule Day 3 to Day 13 of the study (Table 4, p. 20 of the final study report)

Trial Procedures	Days 3 to 7				Days 8 to 13
	Target Time				
	08:00	12:00	16:00	20:00	N/A
Supplemental Analgesia (Morphine IR) [1]	If needed for moderate to severe pain				
Supplemental Analgesia (Paracetamol/Acetaminophen) [2]	If needed for mild pain				
Shoulder Pain Intensity on Movement (LogPad)	√	√	√	√	
Opioid-Related Adverse Events (LogPad) [3, 4]				√	
Bupivacaine-Related Adverse Events [3, 5]				√	
Concomitant Medications [3]	←	—	—	—	→
Adverse Events [3]	←	—	—	—	→

1. Pain intensity on movement evaluation was to be done prior to taking supplemental opioid analgesia and recorded in the paper diary; Supplemental analgesic taken was to be recorded in the paper diary
2. Paracetamol/Acetaminophen taken were to be recorded in the paper diary
3. Specific details were to be recorded in the paper diary
4. Constipation, drowsiness, dizziness, nausea, vomiting, respiratory depression and urinary retention
5. Ringing in the ears, metallic taste in the mouth, numbness or tingling.

Subject Disposition (Figure 2, p. 41 of the final study report)



Subject (b) (6) in the SABER™-Placebo group withdrew consent, and did not complete the study. Two subjects did not receive the full 5.0 mL of Investigational Product;

Subject (b) (6) received only 4.0 mL of SABER-placebo and Subject (b) (6) received only 0.5 mL of SABER-bupivacaine. The remaining 58 subjects were included in the per protocol subjects set.

Reported Efficacy Findings

There were two co-primary efficacy endpoints: the pain intensity scores and morphine equivalent dose of rescue analgesics.

Although not statistically significant, there was a trend towards the 5.0 mL SABER-bupivacaine group in pain intensity normalized AUC over 0-72 hours. The least-squares means were 5.33 for the 5.0 mL SABER-bupivacaine group and 5.97 for the SABER-placebo group. The pain scores in the SABER-bupivacaine group were consistently lower than in the SABER-placebo group, the mean difference between the groups being most prominent in the first 6 – 10 hours after surgery.

Cumulative morphine equivalent dose over 0-72 hours was not statistically significant between treatment groups; although, there was a trend towards the 5.0 mL SABER-bupivacaine group in cumulative morphine equivalent dose over 0-72 hours. The least-squares mean were 44.27 for the 5.0 mL SABER-bupivacaine group and 54.51 for the SABER-placebo group.

For the secondary efficacy endpoints of pain intensity on movement, cumulative morphine equivalent dose, and time to first opioid use, there were no significant differences between treatment groups, but there was a trend for each favoring the SABER-bupivacaine treatment.

Summary of Reported Safety Findings

A total of 367 AEs were reported during the study period by 57 (95%) of the subjects. A total of 263 AEs were reported by 38 subjects (95%) in the 5.0 mL SABER-bupivacaine group, and 104 AEs were reported by 19 subjects (95%) in the SABER-placebo group. Only one SAE was reported during the study. The event was pyrexia and was reported by subject (b) (6) who was treated with SABER-bupivacaine. The event was considered to be mild and unlikely to be related to study drug.

Somnolence, nausea, constipation, and dizziness were the most common AEs for both treatment groups. Paresthesia, pruritus, tinnitus, and dysgeusia occurred more often with SABER-bupivacaine treatment. Nine subjects (22.5%) in the SABER-bupivacaine group reported paresthesia compared to two subjects (10%) in the SABER-placebo group. Six subjects (15.0%) in the 5.0 mL SABER-bupivacaine group reported tinnitus, compared to one subject (5.0%) in the SABER-placebo group.

There were no TEAEs suggestive of cardiotoxicity related to systemic exposure to bupivacaine.

Surgical site healing was assessed in all subjects on Day 14; all 60 subjects had surgical site healing "as expected." The local tissue condition was also assessed in all subjects at that time; all 60 subjects had local tissue condition 'as expected'. There was one TEAE of post-operative wound complication, "haemoserous ooze from wound," reported at Day 2 for Subject (b) (6) treated with SABER-bupivacaine, the AE had resolved by the Day 14 assessment.

Discussion

The efficacy data from this trial indicated that SABER-bupivacaine has potential analgesic properties, but the product is either ineffective following arthroscopic shoulder surgery or the dosing used in this trial was inadequate, or the method of administration was not appropriate.

The safety data from this trial did not indicate cardiac toxicity related to SABER-bupivacaine. The increased incidence of tinnitus and paresthesia observed with SABER-bupivacaine are suggestive of neurotoxicity that may be due to elevated systemic bupivacaine levels; however, the low number of subjects in the two treatment groups limits the ability to discern whether this is a real safety signal.

The review of the safety data indicated two additional differences in the treatments: twitching, which occurred in 5 (12.5%) subjects treated with SABER-bupivacaine and no subjects treated with SABER-placebo, and pruritus, which occurred in 9 (22.5%) of subjects treated with SABER-bupivacaine and 2 (10%) subjects treated with SABER-placebo. The clinical relevance of the pruritus relates to patient comfort and, more importantly, the risk of infecting the wound or interfering with the healing process if the patients scratch the surgical site. The two cases reported as severe were from the two subjects treated with SABER-placebo, which suggests the SABER component of the product is an irritant. The clinical significance of the twitching is uncertain, but may be a sign of local toxicity from the bupivacaine.

The study is limited by the lack of a long-term follow-up examination of the subjects to assess the risk of chondrolysis due to the bupivacaine exposures and the risk of prolonged exposure to the SAIB component of the SABER-bupivacaine.

Conclusions

The trial failed to demonstrate that SABER-bupivacaine is more effective than SABER-placebo in reducing postoperative pain following arthroscopic shoulder surgery. The data suggest that an increase in the dose or a change in the method of administration may improve the outcome. The trial did not demonstrate a clear risk for cardiac or

neurological toxicity due to elevated bupivacaine exposures, but the data suggest a possibility of increased neurotoxicity with the SABER-bupivacaine treatment. A major shortcoming of the study was a long-term follow-up evaluation assessing subjects for chondrolysis.

9.4.8 C803-017e

Title: A Multi-Center, Prospective, Observational, Extension Trial Following DURECT Protocol C803-017 to Investigate the Long-term Safety of SABER™-Bupivacaine Following Arthroscopic Shoulder Surgery

Dates: July 5, 2010 to April 18, 2011

Objective
To investigate the long-term safety of SABER-Bupivacaine or SABER-Placebo following arthroscopic shoulder surgery for subjects enrolled in DURECT Protocol C803-017

Efficacy Endpoints
There were no efficacy endpoints evaluated in this study. It was strictly a safety follow-up study.

Inclusion Criteria (verbatim from p. 15 of the final study report)

1. Subject had provided written consent to participate in the trial prior to any trial procedures and understood that they were free to withdraw from the trial at any time.
2. Subject was able to read and understand the consent form, complete trial-related procedures, and communicate with the trial staff.
3. Subject had participated in the DURECT C803-017 trial and received SABER-Bupivacaine or SABER-Placebo approximately 18 months (± 2 weeks) before enrolling in this trial.

Exclusion Criteria (verbatim from p. 15 of the final study report)

1. Subject had participated in any other trial with an investigational drug or device since their participation in the DURECT C803-017 trial.

Summary of Methodology
This trial visit was scheduled to occur at 18-month post-dose from the DURECT C803-017 trial (± 2 weeks). The clinical sites were to contact subjects and ask them to return for an 18 months post-dose clinic visit. The clinical site was to make at least three documented phone call attempts followed by a certified letter to a subject about

participation in this extension trial. If the subject did not respond to any of these attempts, then that subject was to be deemed unable to participate.

The following evaluations were to be made at the time of the follow-up visit:

1. Pain Intensity on Movement Evaluation at Month 18: A shoulder pain intensity evaluation “on movement” was to be done following active assisted shoulder elevation to 90° at the clinic visit. Subjects were to assess their pain intensity using an 11-point Pain Intensity Numeric Rating Scale (PI-NRS), with numerical rating scale (NRS) scores ranging from 0 (no pain) to 10 (pain as bad as you can imagine). If the subject was unable to elevate their shoulder completely to 90° due to severe pain, the pain assessment provided under these circumstances was to be recorded (e.g. if subject could only elevate their shoulder to 45°, then the pain intensity that the subject rated in that position was to be recorded). The subject’s NRS score was to be recorded by clinical site staff on the appropriate source document and CRF.
2. Surgical Site Healing and Local Tissue Evaluation at Month 18: The Investigator or other medically qualified clinical site personnel assessed the surgical site for the presence or absence of infection, bleeding, discoloration, and dehiscence, rated wound healing as “expected” or “unexpected”, and recorded observations on the appropriate CRF and source document. If an abnormal finding was observed, a corresponding AE was to be documented.
3. Shoulder Examination at Month 18: A shoulder examination was to be conducted. Any clinically significant changes from the examination performed on completion of the DURECT C803-017 trial were to be recorded on the AE CRF.
4. MRI at Month 18: An MRI shoulder exam was to be performed with the same settings and parameters as the DURECT C803-017 trial baseline MRI exam. Any clinically significant changes from the DURECT C803-017 trial baseline MRI exam were to be recorded on the AE CRF.
5. Medical History Update at Month 18: Any changes to the subject’s medical history since their completion in the DURECT C803-017 trial were to be recorded by trial staff on the appropriate source document and Medical History CRF.
6. Adverse Events: All AEs from the time the subject signed the informed consent form for this trial through completion of the clinic visit were to be recorded. All AE details including severity and causality were to be recorded by trial staff on the appropriate source document and AE CRF. If a Serious Adverse Event (SAE), related to Investigational Product administration in the DURECT C803-017 trial, occurred between the subject’s completion of the DURECT C803-017 trial and participation in this trial and came to the attention of the Investigator at the Month 18 post-dose clinic visit, then it was to be reported immediately to DURECT in the same way as the SAEs occurring during the trial.

7. Concomitant Medications: Any concomitant medications taken within 30 days of the 18 Month visit, during the Month 18 visit, and for ongoing AEs were to be recorded on the appropriate concomitant medication CRFs.

Subject Disposition

The 60 subjects who received treatment in the DURECT C803-017 trial qualified to participate in this trial. Of these, seven subjects were treated at Site 03, which declined participation in this extension trial, three subjects were lost to follow-up, and three subjects did not meet inclusion/exclusion criteria. Of the 40 subjects treated with SABER-bupivacaine, 31 completed this study; of the 20 subjects treated with SABER-placebo, 16 completed this study.

Reported Safety Results

Four subjects did not undergo the MRI scan as part of this study:

- One subject had had an MRI scan performed approximately 4 weeks earlier and that scan was used in place of the study-mandated MRI scan.
- Two subjects declined the scan, one experienced claustrophobia and the other had an unpleasant experience with the initial MRI scan.
- One subject had an ultrasound done instead of the MRI scan due to an implanted nerve stimulator. This was also done at the time of his original enrollment in C803-017.

Two subjects were considered to have treatment emergent adverse events that were considered possibly related to study drug. These included:

- Subject (b) (6) Mild degenerative cartilage disease - onset date was October 19, 2010 (dosed with SABEDR-bupivacaine on July 28, 2009).
- Subject (b) (6): Mild Partial Rupture biceps tendon right shoulder- onset date was July 26, 2010 (dosed with SABER-placebo on September 17, 2009)

Chondrolysis was suspected on MRIs in two additional subjects ((b) (6) and (b) (6)). However, these events were not deemed as AEs by the Investigators.

Subject (b) (6) who received 5.0 mL SABER-Bupivacaine, was found on the Month-18 MRI to have a full thickness tear of the supraspinatus tendon, superior labral tear, with no progression of chondral loss from the baseline exam. These were deemed not clinically significant by the Investigator.

Subject (b) (6) who received SABER-Placebo, underwent revision surgery between trials, due to lack of relief from Subacromial Impingement Syndrome. The original operation included bursectomy, debridement of labrum, glenohumeral joint inspection, removal of subacromial spurs, resection of coracoacromial ligament, and subacromial

decompression. No additional injury had occurred following the original surgery and the repeat operation was considered unlikely related to SABER-Placebo. The Month-18 MRI showed evidence of repeat surgery with placement of 2 microscrews, partial thickness tear of the supraspinatus tendon, minor subacromial bursitis, humeral chondral defect with subchondral edema, lateral subacromial spurring with narrowing of subacromial space. The MRI findings, including suspected chondrolysis, were consistent with clinical observations of reduced passive range of motion, positive impingement sign, and pain.

The SAE of chondrolysis is described in greater detail in Section 7.3.2 above.

Discussion

The Applicant notes in the study report that, in trial C803-017, SABER-bupivacaine and SABER-placebo injections were performed "extra-articularly (into the subacromial space)." They also noted that at the Month-18 visit, there were no traces of Investigational Product identified on the MRI evaluation. While they noted the "unexpected medically important event" of chondrolysis, they concluded that "5.0 mL SABER™-Bupivacaine was found to be safe and well tolerated at 18 months post-dose." However, the finding of one case of chondrolysis is an important safety signal given the efforts by the Investigators to avoid intra-articular injection of the study drugs and the small number of subjects who were enrolled in the study. The other adverse events related to tendon tears also raise the concern that the SABER component of the study drugs may have an adverse effect on the local tissues. The lack of a placebo that had none of the SABER components would have been helpful in putting these findings into context, but the small numbers of subjects would limit the utility of including the additional treatment arm. Given the risk of chondrolysis that has been associated with intra-articular administration of local anesthetics, especially with bupivacaine administered following shoulder surgery, it would be inappropriate to minimize the findings of this study. If the Applicant can provide a sound rationale for why the findings of this study should be attributed to something other than study drug, a more definitive trial could be conducted to confirm the purported safety of SABER-bupivacaine following shoulder surgery. If such a rationale cannot be provided, the use of SABER-bupivacaine should be contraindicated following shoulder surgery, and consideration should be given to avoid its use near any joint capsule.

Conclusions

This study raises serious concerns for the safety of SABER-bupivacaine following arthroscopic shoulder surgery. These concerns need to be addressed before SABER-bupivacaine is allowed to be used in this clinical setting – either in future trials or in clinical practice.

9.4.9 C803-027 (Phase 2, Open-Label, Safety Study – Abdominal Procedures)

Title: Open-Label, Histological Evaluation of Surgical Wounds in Subjects Treated with SABER®-Bupivacaine

Study Dates: May 16, 2012 – September 19, 2012

Objectives

To characterize the surgical wound healing, appearance and histology of peri-incisional discoloration that may be observed following administration of SABER-Bupivacaine in subjects undergoing general abdominal surgery

Efficacy Endpoints

There were no efficacy endpoints evaluated in this safety study.

Inclusion Criteria

1. Subjects must have provided written consent to participate in the trial prior to any trial procedures and understand that they are free to withdraw from the trial at any time.
2. Subjects must have been able to read and understand the consent form, complete trial-related procedures, and communicate with the trial staff.
3. Males and females, 18 years of age and older.
4. Subjects must have been scheduled to undergo elective open laparotomy or laparoscopically assisted colectomy according to Surgical Requirements (see Protocol, Section 6.2.1).
5. Subjects must have had an ASA Physical Status (American Society of Anesthesiologists) P1 to P3.
6. Subjects must have had a body mass index < 45.
7. Female and male subjects must have agreed to use a medically acceptable method of contraception throughout the subject's entire trial participation period and for 1 week after the trial participation is completed. Medically acceptable methods of contraception that may have been used by the subject and/or the partner include, oral contraception or patches (consistently for 3 months prior to trial dosing), NuvaRing (etonogestrel/ethinyl estradiol vaginal ring), diaphragm with vaginal spermicide, IUD (coil), condom and vaginal spermicide, surgical sterilization (6 months post-surgery), post-menopausal subject (not experienced a menstrual period for a minimum of two years), and progestin implant or injection (used consistently for 3 months prior to trial dosing).

Exclusion Criteria

1. Subjects who were pregnant or lactating.
2. Subjects who were undergoing emergency surgery (unless full consent can be obtained and all screening procedures can be completed prior to surgery).
3. Subjects with significant concomitant surgical procedure.
4. Subjects with known metastatic cancer pre-operatively, which are suspected to impact post-operative recovery and wound-healing.
5. Planned formation of stoma during surgery or plans to undergo another laparotomy procedure within 30 days post-operatively.
6. Subjects with pre-operative evidence of sepsis or septic shock.
7. Subjects with pre-operative evaluation that suggested a surgery that may have precluded full closure of the incision(s).
8. Subjects with a history of or with current coagulopathy.
9. Subjects with known hypersensitivity to local anesthetic agents (e.g. lidocaine, bupivacaine).
10. Subjects with a serum creatinine level two times more than the local laboratory normal limit.
11. Subjects with known or suspected abuse of opioids or other illicit drugs.
12. Subjects with known or suspected alcohol abuse.
13. Subjects participating in any other trial with an investigational drug or device concurrently or within 30 days prior to Day 0 of this trial.
14. Subjects who, in the Investigator's opinion, should not participate in the trial or who may not be capable of following the trial schedule for any reason.

Summary of Methodology

This was a single-center, open-label, Phase 2, surgical wound evaluation of SABER-Bupivacaine in subjects undergoing laparotomy or laparoscopically assisted colectomy. Eligible subjects were those patients who received SABER-Bupivacaine 5 mL administered to the main surgical wound using the same administration technique used in the C803-025 trial:

> The SABER-bupivacaine was drawn up and administered using a NORM-JECT® 5-mL Luer Lock syringe connected to a Tunneltip™ irrigation catheter with a Luer Lock fitting. [Note: The Tunneltip irrigation catheter is flexible, 15 cm long, 2 mm in diameter, with smooth rounded tip and graduated centimeter markings for wound length measurement and control of instillation. To account for the dead space in the catheter, 5.5 mL of SABER-bupivacaine was to be drawn up in the syringe with a 16 gauge needle. Excess air and SABER-bupivacaine were to be purged from the syringe and catheter to ensure administration of 5 mL of SABER-bupivacaine.

> After closure of the peritoneum and securing hemostasis in the subcutaneous space, the irrigation catheter was placed into the wound and the cutaneous layer was closed over the catheter with subcuticular stitches. The syringe containing the SABER-bupivacaine was then attached to the catheter and test drug was gradually injected while slowly withdrawing the catheter. In this way, the SABER-bupivacaine was to have been evenly distributed along the length of the incision with minimal leakage of the drug. A final stitch was used to close the space where the catheter was withdrawn.

Based on the incidence of peri-incisional skin discoloration observed in the C803-025 trial, it was estimated that 20 to 30 treated subjects should yield at least 10 subjects with peri-incisional discoloration. Screening and enrollment were suspended once 10 subjects manifested peri-incisional discoloration. All participating subjects were expected to receive medical care given under normal circumstances for the specified elective surgical procedures.

One 3mm or 4mm punch biopsy was to be obtained from within the anticipated location of maximum peri-incisional discoloration surrounding the surgical wound. If there was no peri-incisional discoloration of the surgical wound by Day 3, a punch biopsy at least 5 cm away from the surgical wound was to be obtained. Biopsy tissue was to be assessed with conventional histologic examination after fixation, sectioning, and staining with hematoxylin and eosin stains.

Subjects with discoloration or bruising greater than 4 cm in diameter surrounding any of the laparoscopic portal entries were to have an additional 3 or 4 mm punch biopsy obtained from within the anticipated location of maximum discoloration on Day 1, 2, or 3. The punch biopsy specimen must have been taken from an area at least 2 cm away from the laparoscopic portal incision. If more than one portal entry has discoloration, only one biopsy from one of the portals was to be obtained. If no discoloration developed, a biopsy was not to be obtained. The laparoscopic portals were not to be treated with SABER-Bupivacaine, and the entire 5 mL was instilled into the main incision.

Digital photographs of the surgical wound (including any peri-incisional discoloration surrounding the surgical wound) and discoloration surrounding any of the laparoscopic portal entries (if applicable) were to be taken throughout the trial until resolution of the discoloration.

Amendments
(December 7, 2011): this modified the protocol as follows:

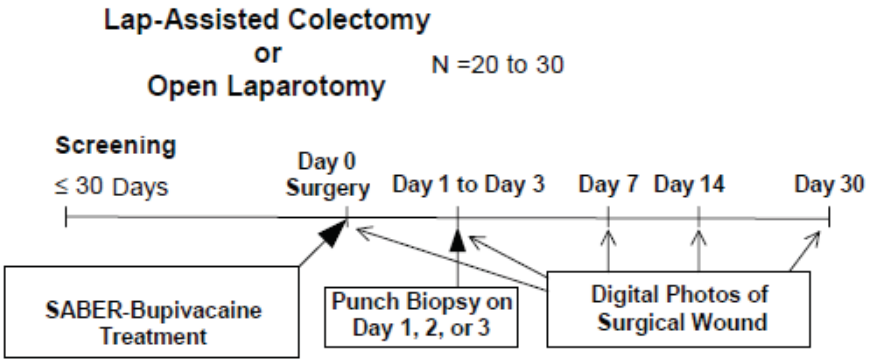
- Updated the medical monitor contact and increased the number of sites from three to four.

(March 26, 2012): the protocol was modified as follows:

- Improved the description of the planned location for biopsy samples and the timing of samplings.
- An additional pain assessment was added in an attempt to discriminate between surface wound pain amenable to local anesthesia and deep visceral pain more amenable to systemic analgesics

Both amendments to the protocol were enacted before the first subject was enrolled.

Schematic (Figure 1, p. 22 of the final study report)



Schedule (Table 1, p.29 of the final study report)

Procedure	Screening	Treatment				Day 7 Follow-Up	Day 14 Follow-Up	Final / Early Term	Additional Follow-Up (if needed)
Visit	1	2				3	4	5	Unscheduled
Day	–30 to –1	0	1	2	3	7 (± 2)	14 (± 3)	30 (+3)	As needed
Informed Consent (prior to any trial procedures)	X								
Demographics	X								
Medical History	X								
Physical Examination	X							X	
Height and Weight	X							X[1]	
12-lead ECG	X							X	
Vital Signs [2] (BP, HR, RR, Temp)	X	X	X	X	X	X	X	X	X
Safety Labs (Chemistry, Hematology, Urinalysis)	X							X	
Complete Blood Count and Coagulation Panel [3]		X	← - -	- - -	- - →				
Pregnancy Test	X[4]	X[5]							
Review Inclusion/Exclusion Criteria	X	X							
Dispense Paper Diary and Review Instructions		X	X	X	X	X	X		
Dosing		X							
Pain Intensity Evaluation [6]		← - -	- - -	- - -	- - -	- - →			
Digital Photographs of Surgical Wound(s)		X[7]	X[8]	X[8]	X[8,9]	X[7]	X[7]	X[7]	X[7]
Punch Biopsies [10]			← - -	- - -	- - →				
Pain at Wound(s) Discoloration [11]			← - -	- - -	- - →	X	X	X	X
Skin Blanching [12]			← - -	- - -	- - →				
Collect and Review Paper Diary			X	X	X	X	X	X	
Surgical Wound(s) Healing and Local Tissue Conditions Evaluation			X	X	X	X	X	X	X
Surgical Wound(s) Healing Questionnaire								X	
Adverse Events [13]	X	← - -	- - -	- - -	- - -	- - -	- - -	- - -	- - →
Concomitant Medications	X	← - -	- - -	- - -	- - -	- - -	- - -	- - -	- - →

1 Weight only
2 Measured seated after the subject is resting for 5 minutes
3 Complete blood count and coagulation panel was done prior to surgery and on the day the punch biopsy is obtained
4 Serum pregnancy test for females of childbearing potential
5 Urine pregnancy test for females of childbearing potential
6 On Day 0 (day of surgery), Pain Intensity Evaluations at rest and on movement were completed upon awakening (or 4 hours post-dose, whichever occurs earlier), and continue at 6, 8, 10, and 12 hours post-dose. On Days 1 to 7, Pain Intensity Evaluations at rest and on movement were completed four times a day at 08:00, 12:00, 16:00, and 20:00 hours (clock time). Evaluations were documented in the paper diary.
7 Six digital photographs of the surgical wound(s) were taken post-surgery: two at a 90º angle to the main surgical wound, two at a +45º angle, and two at a -45º angle.
8 Six digital photographs of the surgical wound(s) were taken before and after obtaining the punch biopsy at matching angles listed above. If a biopsy was not obtained on that day, six digital photographs of the surgical wound(s) were taken at matching angles listed above.
9 If the subject remained in the hospital Day 4 to Day 6, six white-balanced digital photographs of the surgical wound(s) were taken each day at matching angles listed above.
10 One 3 or 4mm punch biopsy was taken within the anticipated location of maximum peri-incisional discoloration surrounding surgical wound on Day 1, 2, or 3. If there was no surgical wound discoloration by Day 3, a punch biopsy at least 5cm away from the surgical wound was obtained. Subjects with discoloration or bruising greater than 4cm in diameter surrounding any of the laparoscopic portal entries had one 3 or 4mm punch biopsy obtained from within the anticipated location of maximum discoloration on Day 1, 2, or 3. The punch biopsy specimen must have been

taken from an area at least 2 cm away from the laparoscopic portal incision. If more than one portal entry had discoloration, only one biopsy from one of the portals will be obtained. If no discoloration develops around the portal(s), a biopsy will not be obtained.

11 If discoloration develops around surgical wound(s), subjects will evaluate the pain intensity in response to a light touch in the location(s) of discoloration. This will be assessed before the biopsy was taken and recorded by site personnel.

12 Performed before biopsy was taken

13 AEs collection started from the time the subject signed the consent form and continued through trial completion/early termination. Ongoing AEs at the time of completion/early termination were followed until resolved or until 30 days after the last trial visit, whichever comes first.

Subject Disposition

Ten subjects were enrolled and completed the study per protocol. There were no discontinuations due to adverse events. All ten subjects were enrolled by a single site. Six subjects underwent laparoscopically assisted colectomy and were discharged 4-6 days after surgery; four subjects underwent open laparotomy and were discharged 4-8 days after surgery.

Reported Efficacy Observations

As there was no control group, the Applicant compared the efficacy assessments to those made in the completed Phase 3 trial (C803-025). They reported the following observations:

1. The initial pain intensity rates were similar, with most subjects experiencing severe incisional pain on movement at 4 hours after surgery.
2. Initial incisional pain tended to be somewhat more intense than deep pain and the laparoscopy portal incisions could be a source of pain.
3. In comparison toC803-025, the AUC_{0-72} tended to be about one point lower, perhaps because the subjects all knew that they were receiving active treatment.
4. The median opioid use over 0-72 hours (24.5 mg of IV morphine equivalents) was considerably less than that used by the subjects in C803-025.
5. The reduced pain intensity and opioid use observed in this trial compared to C803-025 may also be due to use of NSAIDs, which were permitted in this trial but not in C803-025.

Summary of Reported Safety Findings

Two subjects experienced seepage of SABER-Bupivacaine and did not receive the full 5 mL dose. The reported doses for those subjects were 4.7 mL and 4 mL. As the laparoscopic ports were not treated in those subjects who underwent laparoscopic assisted colectomy, the entire 5 mL dose was instilled into the incision, resulting in a relatively high drug exposure per mg/cm for those incisions. The exposure for the open laparotomy subjects was considerably lower per mg/cm, as the incisions were longer.

There were a total of 57 adverse events reported. All but one of the AEs were of mild or moderate intensity and about one fifth of the AEs were considered to be treatment-related. The greatest number of AEs was reported on post-operative day one, and these were mostly related to wound complications or other postoperative complications or symptoms. No cardiac AEs were reported and none of the neurological AEs were suggestive of systemic bupivacaine toxicity. There were no premature discontinuations due to adverse events. Only one subject had two serious adverse events on postoperative day 23 due to a syncopal event and fall while using the toilet, resulting in an orbital fracture and a subdural hematoma (the only AE rated as severe). There were no deaths.

The most common TEAEs were wound discoloration (10 subjects) followed by incision site hemorrhage (5 subjects), and wound dehiscence (5 subjects).

Application site discoloration was observed in all 10 subjects, although the discoloration for one subject was inadvertently not recorded as an AE. No intervention was required and all cases of discoloration completely resolved over a period of several weeks with no sequelae. It was noted that all subjects were treated with antithrombotic agents for DVT prophylaxis and it is possible that inhibition of hemostasis by these agents may have contributed to the postoperative bruising that most likely underlies the wound discoloration. [Note: The aPTT values were, per the Applicant, “generally within the normal range and as expected did not show any prolongation due to treatment with enoxaparin.” One subject was noted to have an increase from 31.7 sec preoperatively to 41.1 sec on postoperative day 1.

Mild, self-limited bleeding from the incision(s) was reported in five subjects. No action other than dressing changes was needed. Minor, cutaneous wound dehiscence was reported in 5/10 subjects (all four of the open laparotomy subjects and one laparoscopy subject). Most of the cases of dehiscence occurred late (post-operative days 12-36) and were due to a few stitches pulling out in the thin skin at the inferior end of the incision. No surgical repair was necessary and local wound care allowed all of the dehiscences to heal normally. The incidence of dehiscence is somewhat higher than has been observed in previous studies of SABER-Bupivacaine, but is consistent with a 41% incidence of minor dehiscence reported in a prospective study of clean orthopedic surgery (Noninfectious Wound Complications in Clean Surgery: Epidemiology, Risk Factors, and Association with Antibiotic Use. Uckay I, Agostinho A, Belaieff W, Toutous-Trellu L, Scherer-Pietramaggiori S, Andres A, Bernard L, Vuagnat H, Hoffmeyer P, and Wyssa B; World J Surg; 35: 973-980; 2011)

No surgical wound infections were reported.

The Structured Wound Healing Questionnaire was administered on the final scheduled study visit on day 30 and provided additional insight into the degree of recovery from surgery and any ongoing problems or complications of wound healing. Most of the

incisional pain had resolved, but three subjects still had limitations due to incisional discomfort. One subject still had a small amount of bruising around the incision, 4 subjects had dehiscence, and 4 subjects had some drainage from the incision. There were no ER visits, hospitalizations, or surgical procedures required for wound complications.

Histological examination of punch biopsy specimens obtained from the area of maximal discoloration did not show any pathological findings.

Discussion

Without a comparator treatment arm and with only 10 subjects, it is difficult to draw safety conclusions from this study. It is interesting to note that the rate of dehiscence in this study was similar to that in its predecessor. It should also be noted that the reference cited by the Applicant for rates of dehiscence dealt with wound complications following orthopedic surgery, including trauma, in a patient population with a median age of 70 years. Dehiscence rates cited elsewhere in the literature for gastroenterological procedures, a more apropos reference, were under 5%.

Conclusions

This study reinforced the findings of C803-025 for postoperative wound drainage and dehiscence. While these adverse events did not appear to negative affect the subjects recovery, they do raise concern for the risks associated with incomplete closure of the incision and the drainage of serosanguinous fluids, in particular, the risk for wound infection.

9.5 Information for Healthcare Professionals: Chondrolysis Reported with Continuously Infused Local Anesthetics (marketed as bupivacaine, chloroprocaine, lidocaine, mepivacaine, procaine and ropivacaine)

[November 13, 2009 Updated: February 16, 2010]: The Food and Drug Administration (FDA) has reviewed 35 reports of chondrolysis (necrosis and destruction of cartilage) in patients given continuous intra-articular infusions of local anesthetics with elastomeric infusion devices to control post-surgical pain. The significance of this injury to otherwise healthy young adults warrants notification to health care professionals.

The local anesthetics (with and without epinephrine) were infused for extended periods of time (48 to 72 hours) directly into the intra-articular space using an elastomeric pump.

Chondrolysis was diagnosed within a median of 8.5 months after the infusion. Almost all of the reported cases of chondrolysis (97%) occurred following shoulder surgeries. Joint pain, stiffness, and loss of motion were reported as early as the second month after receiving the infusion. In more than half of these reports, the patients required additional surgery, including arthroscopy or arthroplasty (joint replacement).

It is not known which specific factor or combination of factors contributed to the development of chondrolysis in these cases. The infused local anesthetic drugs, the device materials, and/or other sources may have resulted in the development of chondrolysis. It is important to note that single intra-articular injections of local anesthetics in orthopedic procedures have been used for many years without any reported occurrence of chondrolysis.

Local anesthetics are approved as injections for the production of local or regional anesthesia or analgesia. Neither local anesthetics nor infusion devicesare approved for an indication of continuous intra-articular infusion.

Health care professionals are encouraged to follow the instructions for use of elastomeric infusion devices, and to not use these devices for continuous intra-articular infusion of local anesthetics after orthopedic surgery.

Based on the reported cases of chondrolysis, following continuous intra-articular infusion with local anesthetics, the FDA is requiring the drug manufacturers to update their product labels to warn healthcare professionals about this potential serious adverse effect. FDA is also exploring possible options for addressing the safety issues with the infusion devices (e.g., labeling changes, etc.).

The FDA is requiring the changes to the drug label under the authorities granted by the Food and Drug Administration Amendments Act (FDAAA) of 2007.

This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA intends to update this sheet when additional information or analyses become available.

To report any unexpected adverse or serious events associated with the use of this drug, please contact the FDA MedWatch program using the information at the bottom of the page.

Considerations for Health Care Professionals

- Understand that both the local anesthetics and the elastomeric infusion devices —or any other type of device used for intra-articular infusions—are not approved or cleared by the FDA for continuous intra-articular infusion.
- Be aware of the possibility for and monitor for the emergence of the signs and symptoms of chondrolysis, such as joint pain, stiffness and loss of motion. The appearance of these symptoms can be variable, but they may begin two or more months after surgery.
- Recognize that patients experiencing chondrolysis may require additional diagnostic and therapeutic procedures and may eventually require arthroplasty (joint replacement).
- Inform patients of the signs and symptoms of chondrolysis so they are aware of and able to notify their healthcare professional if they experience persistent joint pain, stiffness, or a severe decrease or loss of motion in the joint.

Information for Patients

- Discuss with your healthcare professional any questions or concerns you have about your orthopedic surgical procedure and what to expect immediately following surgery, including how to manage postsurgical pain.
- Talk with your healthcare professional about available FDA-approved options to manage postsurgical pain.
- If, after an orthopedic surgical procedure, you have received a prolonged infusion of a local anesthetic into your joint with a disposable elastomeric pump or any other infusion pump, pay attention to symptoms of joint pain, stiffness and a decrease or loss of motion and alert your healthcare professional if these symptoms persist.

Data Summary

Between 2006 and 2008, 35 reports of chondrolysis (primarily in the shoulder) occurring in patients administered continuous intra-articular infusions of local anesthetics with elastomeric infusion devices were reported to the FDA's Adverse Event Reporting System (AERS). Thirty-two (91%) of these patients received bupivacaine (with or without epinephrine) as an intra-articular infusion after having undergone arthroscopic and other surgical procedures.[1] Two of the 32 patients received ropivacaine in addition to bupivacaine. Additionally, two of the 35 patients received bupivacaine as a single injection along with an intra-articular infusion of lidocaine. The

average infusion time in the reported cases was between 48 and 72 hours. The most commonly reported site of infusion was the glenohumeral (glenoid) space (46%).

Sixteen of the 32 (50%) bupivacaine-associated AERS reports included the dose administered, with 10 of 16 patients receiving 500mg over 48 hours or 250mg/day. While this daily intra-articular dose was within the maximum dose listed in the drug label (400mg/day), it is important to note that this maximum labeled daily dose was determined for the approved uses and not for off-label uses such as continuous intra-articular infusions with elastomeric infusion devices.

In the reported cases, symptoms of chondrolysis occurred as early as 2 months after the infusion (median of 5 months) and chondrolysis was diagnosed with a median of 8.5 months after the infusion. The median age of the affected patients was 25 years, with an age range of 16-58 years. Six of the reports involved pediatric patients between 16 and 18 years. In almost all of the reported cases (34/35 or 97%), the location of chondrolysis was in the shoulder joint. The remaining report involved the knee joint.

The FDA received four additional reports of chondrolysis in patients administered continuous intra-articular infusions of lidocaine in the shoulder after the initial 35 bupivicaine-related cases reported from 2006 to 2008. [2] The FDA AERS data is supported by recent literature reports of patients experiencing chondrolysis after bupivacaine infusions and preclinical studies showing chondrolysis after chondrocyte exposure to bupivacaine, lidocaine, and ropivacaine.[3,4,5,6]

The most common manufacturer of elastomeric infusion device mentioned among the 32 infusion-patients was Stryker (n=11). The other companies mentioned in the report were the manufacturers I-Flow and Breg, and the distributor Don Joy (n=14 combined). This finding suggests that the reported cases of chondrolysis are not associated with any single manufacturer of elastomeric infusion devices.

Based on the reported cases of chondrolysis following continuous intra-articular infusion of local anesthetics with elastomeric infusion devices, the FDA is requiring the manufacturers of local anesthetics and of pumps that may be used to infuse local anesthetics to update their product labels to warn healthcare professionals about this potential serious adverse effect. FDA is also exploring possible options for addressing the safety issues with the infusion devices (e.g., labeling changes, etc.). Because the reported cases involved significant injury to otherwise healthy young adults, FDA wants to advise healthcare professionals that elastomeric infusion devices or any other infusion pump are not cleared by FDA to deliver intra-articular infusions of local anesthetics and should not be used for this purpose.

References:

[1]The 35 cases were obtained from an AERS search for *bupivacaine reports* received on or before 7/16/08.

[2] These 4 reports are from an additional AERS search for reports of *local anesthetics other than bupivacaine* received up to 1/22/09.

[3]Bailie DS, Ellenbecker TS. Severe chondrolysis after shoulder arthroscopy: a case series. *J. Shoulder Elbow Surg.* 2009; 18:742-747.

[4]Hansen BP, Beck CL, Beck EP, Townsley RW. Postroscopic glenohumeral chondrolysis. *Am. J. Sports. Med.* 2007; 35:1628-1634.

[5]Dragoo JL, Kortokova T, Kanwar R, Wood B. The effect of local anesthetics administered via pain pump on chondrocyte viability. *Am. J. Sports. Med*. 2008; 36:1484:1488.

[6]Piper SL, Kim HT. Comparison of ropivacaine and bupivacaine toxicity in human articular chondrocytes. *J. Bone Joint Surg*. 2008; 90:986-991.

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/s/

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01/08/2014

CHRISTOPHER D BREDER
01/08/2014
reviewed with comment in my cdtl review

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA Serial Number: 204-803/0000

Drug Name: Posimir (extended release bupivacaine)

Indication(s): Postsurgical analgesia

Applicant: Durect Corporation

Date(s): Received: April 12, 2013
PDUFA: February 12, 2014

Review Priority: Standard – 10 month

Biometrics Division: Division of Biometrics II

Statistical Reviewer: David Petullo, M.S.

Concurring Reviewers: Janice Derr, Ph.D.

Medical Division: Division of Anesthesia, Analgesia, and Addiction Products

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Keywords: clinical studies, NDA review, double-blind, foreign clinical data

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SUMMARY OF REVISIONS

- Page 9. The following sentence regarding subject (b) (6) who was randomized to treatment, Posimir 330 mg, but did not receive study drug was added to the last paragraph. "One subject randomized to Posimir 330 mg did not receive study drug and was excluded from all analysis."

- Page 10. Table 2 was revised. The number of subjects randomized to Posimir 330 mg was 44 not 43. A footnote was added to the table stating that one subject randomized to Posimir 330 mg did not report a value for race.

- Page 11. Corrected a grammatical error in the third paragraph. Sentences 2 and 3 were revised. "Even though LOCF imputation for subjects that discontinued due to an adverse event may not have been appropriate, there were only four subjects that discontinued. This is not an issue." was changed to "Even though LOCF imputation for subjects that discontinued due to an adverse event may not be appropriate, there were only four subjects that discontinued, therefore this was not an issue."

- Page 11. The following two sentences were added to the results and conclusion section. "Note, one subject treated with Posimir 330mg was administered non-allowed rescue medication during surgery and only had one efficacy assessment post-surgery. This subject was excluded from my efficacy analyses."

- Page 15. Corrected a typographical error in the second sentence of the first paragraph. "In Figure 1 there is clear separation between in the curves for both doses of Posimir and placebo out to approximately 24 hours post-surgery." was changed to "In Figure 1 there is clear separation between the curves for both doses of Posimir and placebo out to approximately 24 hours post-surgery."

- Page 15. Corrected a misquoted reference in the third sentence of the first paragraph. "The non-significance of the comparison of Posimir 330 mg to placebo for AUC_{72} was supported by the results observed in Table 6 where nominal statistical significance was only noted out to 12 hours." was changed to "The non-significance of the comparison of Posimir 330 mg to placebo for AUC_{72} was supported by the results observed in Table 7 where nominal statistical significance was only noted out to 12 hours."

- Page 19. The word LSMEANS in the last sentence of the fourth paragraph was changed to LSMEANs

- Page 22. Corrected a typographical error in the second sentence under Statistical Methodologies. "AUC_{72} was to be tested for non-inferiority (NI) to placebo first, it established, superiority of Posimir to placebo would be tested." was revised to "AUC_{72} was to

be tested for non-inferiority (NI) to placebo first, if established, superiority of Posimir to placebo would be tested."

- Page 27. Correct a misquoted value in the second sentence of the first paragraph. The amount of rescue medication used by Posimir was misquoted should have been 13.7 mg not 12.3 mg.

- Page 28. Corrected a typographical error in the last sentence of the second paragraph. "That being said, Posimir was significantly better than placebo for primary endpoints, bupivacaine was not." Was changed to "That being said, Posimir was significantly better than placebo for the primary endpoints, bupivacaine was not."

- Page 29. The sample size for treatment group 5 in Table 18 was misquoted. It should have been 21 not 35.

- Page 29. A typographical error was corrected in the third paragraph. Categorized was misspelled as "catagorized".

- Page 32. In the first sentence of the second paragraph, the sample size for Study BU-001-IM was misquoted. "Of the 119 subjects randomized and treated, 61 Posimir, 27 placebo, and 27 bupivacaine, 117 completed the study." was revised to "Of the 119 subjects enrolled, 114 were randomized and treated, 60 Posimir, 27 placebo, and 27 bupivacaine. Of these 114 subjects, 113 completed the study."

- Page 32-33. In the last paragraph the sample size for Study C803-025 was misquoted. "A total of 393 subjects were screened in order to randomize 331 subjects. Cohort 1 randomized 32 subjects to Posimir and 23 subjects to bupivacaine, Cohort 2 randomized 30 subjects to Posimir and 20 subjects to bupivacaine, and Cohort 3 randomized 140 to Posimir and 86 subjects to placebo." was changed to "A total of 393 subjects were screened in order to randomize 331 subjects. Of these 26 did not receive treatment. Cohort 1 randomized 30 subjects to Posimir and 18 subjects to bupivacaine, Cohort 2 randomized 30 subjects to Posimir and 20 subjects to bupivacaine, and Cohort 3 randomized 129 to Posimir and 78 subjects to placebo."

- Page 33. Corrected a typographical error in the last sentence of the first paragraph. "The applicants' results the primary analysis are shown in Table 20." was changed to "The applicants' results for the primary analysis are shown in Table 20. "

- Page 33. Corrected a typographical error in the third sentence of the second paragraph. "However, the clinical reviewer felt it was inappropriate to pool the data from these two surgical procedures as they clinically different." was changed to "However, the clinical reviewer felt it was inappropriate to pool the data from these two surgical procedures as they were clinically different."

1. EXECUTIVE SUMMARY

Durect Corporation has submitted an application evaluating Posimir, a formulation of bupivacaine that contains an extended-release biodegradable matrix that according to the applicant continuously delivers bupivacaine for 72 hours. Continuous wound perfusion with local anesthetics was developed as a method to extend the duration of action resulting in a reduction of pain and decreased opioid consumption. To support the efficacy of Posimir for treating post-surgical pain, the applicant submitted results from seven clinical trials that evaluated various surgical procedures. Of these seven trials, shown in Table 1, two were identified as pivotal. The applicant claims the analyses of the data from these two studies demonstrated a statistically significant treatment effect in favor of Posimir 660 mg. The other five studies failed to report a statistically significant treatment effect.

Based on my review of the data from the two placebo-controlled clinical trials that were identified as pivotal, CLIN-803-0006-06 (hernia repair surgery) and BU-002-IM (arthroscopic shoulder surgery), there is evidence to support the efficacy of Posimir 660 mg in treating post-surgical pain associated with shoulder surgery. However, I did not find substantial evidence to support the efficacy of Posimir in treating post-surgical pain associated with hernia repair.

In Study BU-002-IM, analyses of the primary efficacy endpoints indicated that subjects treated with Posimir 660 mg on average, had less post-surgical pain and consumed less post-surgical opioid medication than subjects treated with placebo. The evidence of an analgesic effect was further supportive by the analyses of secondary endpoints such as time to first use of rescue medication and amount of opioid rescue medication required during the first 72 hours following surgery. This evidence was further supported by two supportive studies, C803-017 and CLIN005-0006, where results suggested, though not statistically significant, that Posimir 660 mg reduced post-surgical pain associated with shoulder surgery and the amount of post-surgical opioid medication required. However, the clinical benefit beyond 12 hours is unclear. When I examined pain intensity scores by time in Study BU-002-IM, Figure 4, the nominal statistical significance between placebo and Posimir 660 mg was only noted out to approximately 12 hours. This early separation in pain scores could impact the significant difference demonstrated in the comparison of the primary endpoint, AUC_{72}.

The benefit of Posimir in treating post-surgical pain associated with hernia repair surgery is not so clear. In the study identified as pivotal, Study CLIN-803-0006-06, the primary analyses indicated that subjects treated with Posimir 660 mg on average, had less post-surgical pain and consumed less post-surgical opioid medication than subjects treated with placebo. However, this effect was not observed in a study identified as supportive, CLIN005-0010. In this study, on average, subjects treated with Posimir 660 mg reported more pain than the placebo subjects and they required more opioid rescue medication. The only notable difference between these two studies was that the Study CLIN005-0010 was conducted mainly in the United States whereas Study CIN-803-0006-06 was conducted in Australia and New Zealand. Based on these results, I do not think there is substantial evidence to support the applicant's claim that Posimir is effective in treating post-surgical pain associated with hernia repair.

2. INTRODUCTION

2.1 Overview

The applicant states that local anesthetics such as bupivacaine are widely administered as analgesics. However, a significant limitation is their short duration of action, typically 4-6 hours. Continuous wound perfusion with local anesthetics was developed as a method to extend the duration resulting in a reduction of pain and decreased opioid consumption. Posimir is a formulation of bupivacaine that contains an extended-release biodegradable matrix that according to the applicant, continuously releases bupivacaine over 72 hours.

The development program for Posimir was conducted under IND 66,086. The Applicant submitted the results of seven active- and placebo-controlled studies to support efficacy, Table 1. The placebo arm in the below studies refers to the extended-release biodegradable matrix without bupivacaine.

Table 1. Clinical Studies conducted by the applicant

Surgical Procedure	Study	Phase	Control	Pivotal or Supportive	Reviewed in Section
Inguinal hernia	CLIN-803-006-0006	2	placebo	Pivotal	3.2.1
	CLIN005-0010	2	placebo	Supportive	
Arthroscopic shoulder	BU-002-IM	2	active/placebo	Pivotal	3.2.2
	C803-017	2b	placebo	Supportive	
	CLIN005-0006	2	placebo	Supportive	
Major abdominal	803-025	3	active/placebo	Supportive	3.2.3
Hysterectomy	BU-001-IM	2	active/placebo	Supportive	

Source: Reviewer

Study CLIN-803-006-0006 (CLIN-803) and Study BU-002-IM (BU-002) were indicated by the applicant as pivotal studies to establish efficacy. It is unclear why these studies were identified as pivotal other than the fact that they demonstrated a significant treatment effect in favor of Posimir. Study CLIN-803 was conducted from June 2007 to October 2007 at five sites in Australia and New Zealand. Study BU-002 was conducted from April 2009 to February 2011 at nine sites in five countries, Austria, Denmark, Germany, Latvia, Poland, and Sweden. The protocols for these studies were not reviewed by FDA.

Studies 803-025, C803-017, CLIN005-0006, CLIN005-0010, and BU-001-IM were indicated as supportive studies. It appears these studies were indicated as supportive as they failed to show a significant treatment effect for Posimir. The protocols for studies CLIN005-0006 and CLIN005-0010 were reviewed by the clinical team in Jan 2006 but were not reviewed by the statistics team. The results from these supportive studies will be presented and discussed following my review of the pivotal studies.

There were several statistical issues discussed between the applicant and the FDA during the IND stage. During an End-of-Phase 2 meeting held on September 14, 2007, the applicant was informed that area-under-curve (AUC) of pain scores would be acceptable as a primary endpoint. However, the endpoint reduction in opioid use by itself may not have clinical significance unless some additional benefit can be demonstrated, such as fewer opioid-related adverse events. Via a written communication dated March 24, 2009, the applicant was advised that the use of ice

should be standardized and it would not be acceptable to include "use of ice" as a covariate in the primary analyses. The applicant was also informed that missing data should be appropriately accounted for in the statistical analysis plan. A subject that discontinues due to an adverse event should not have a good pain score imputed. Further, the use of rescue medication should be accounted for in the primary efficacy analysis. In a pre-NDA meeting held on July 31, 2012, the applicant was told that whether or not the results from the submitted surgical procedures would support a broad indication would be a review issue and the proposed indication, "extended relief of post-surgical pain," would not be acceptable. Further, it was pointed out that it was not clear that the pivotal studies accounted for the use of rescue medication in the primary efficacy analyses.

2.2 Data Sources

All data was supplied electronically by the Applicant as SAS transport files and can be found at the following location in the CDER electronic document room (EDR):

\\Cdsesub1\EVSPROD\NDA204803\0000\m5\datasets

3. STATISTICAL EVALUATION

Studies CLIN-803 and BU-002 evaluated pain associated with different surgical procedures, hernia repair and arthroscopic shoulder surgery, respectively. These procedures are evaluated separately under Sections 3.2.1 and 3.2.2. Two supportive studies that evaluated pain associated with hysterectomy and major abdominal surgeries are discussed in Section 3.2.3.

3.1 Data and Analysis Quality

The electronic data submitted by the Applicant for the two pivotal studies was of sufficient quality to allow a thorough review of the data. I was able to derive the primary and secondary endpoints for each study. The statistical analyses of my derived endpoints were in agreement with the Applicant's analyses.

The Office of Scientific Investigation did not identify any significant issues during the audits of the sites from two studies identified as pivotal.

3.2 Evaluation of Efficacy

My review focuses on the studies, pivotal and supportive, submitted to support post-surgical pain associated with hernia repair and shoulder surgery. For each procedure, I thoroughly review the pivotal study and then present the results of the failed supportive studies. Following my review of the individual studies, I present the combined results from both the pivotal and supportive studies and then give my overall conclusion for each procedure.

3.2.1 Inguinal Hernia Repair

3.2.1.1 Pivotal Study

In the study indicated as pivotal, CLIN-803, the applicant appropriately addressed my major concern regarding the use of rescue medication and the need to account for its use when deriving

the primary endpoint, AUC of pain scores out to 72 hours post-surgery. The applicant addressed this concern in a sensitivity analysis.

Study Design and Endpoints

Eligible patients that were to undergo an open unilateral tension free Lichtenstein-type inguinal hernia repair were randomized to one of four treatments: Posimir 2.5 mL (330 mg), Posimir 5.0 mL (660 mg), placebo 2.5 mL, or placebo 5.0 mL. This study was conducted in two cohorts. Cohort 1 comprised of the Posimir and placebo administered as 2.5 mL and the second cohort comprised of Posimir and placebo administered as 5.0 mL. Following surgery, a single dose of the study drug was instilled gradually throughout the inguinal canal and the abdominal wall layers to cover all raw surfaces of the wound, filling the subaponeurotic and subcutaneous spaces. Rescue analgesia for break-through pain was allowed upon request. Post-operative efficacy assessments included pain intensity (PI) at rest and during bowel movement, use of rescue medication, time of first bowel movement, post-operative nausea and vomiting, and occurrence of constipation. PI was assessed using an 11-point scale with 0 being no pain and 10 the worst pain and was measured at baseline (prior to surgery), end of general anesthesia, before first dose of rescue medication, and at 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after surgery.

The applicant pre-specified two primary efficacy outcomes; AUC of PI scores out to 72 hours post-surgery (AUC_{72}) and the proportion of subjects receiving opioid rescue medication through Day 15. The primary null hypotheses to be tested by the applicant were no difference between treatment groups in terms of AUC and opioid rescue use. The applicant estimated that a sample size of 120 subjects or 60 per cohort would provide 90% power to detect an effect size 0.67 for the difference in AUC_{72}. Post-hoc, the applicant changed the proportion of subjects using rescue through Day 15 to Day 3 or 72 hours. The rationale for this change was that 72 hours post-surgery was the time frame utilized for the other primary endpoint, AUC_{72}. A pre-specified secondary endpoint was amount of rescue medication used through 72 hours in morphine equivalents, RES_{72}. The time to first use of rescue medication was also evaluated.

Patient Disposition, Demographic and Baseline Characteristics

This study screened 135 subjects in order to randomize 124 eligible subjects; 32 placebo, 45 Posimir 330 mg, and 47 Posimir 660 mg. One subject randomized to Posimir 330 mg did not receive study drug and was excluded from all analysis. Demographics for all randomized and treated patients are shown in Table 2.

Table 2. Demographics for Study CLIN-803

Characteristic	Treatment		
	placebo	Posimir 330 mg*	Posimir 660 mg
Number of Patients (n)	32	44	47
Age in years			
Mean (SD)	50 (9)	46 (12)	49 (13)
Median	52	48	50
[range]	[28, 65]	[20, 68]	[21, 79]
Gender (%)			
Female	-	2 (5)	2 (4)
Male	32 (100)	42 (95)	45 (96)
Race (%)			
Caucasian	30 (94)	41 (95)	46 (98)
Black	1 (3)	-	-
Multiple	1 (3)	2 (5)	-
Other	-	-	1 (2)

*One subject randomized to Posimir 330 mg did not report race.
Source: Reviewer

This study comprised of mostly male Caucasian subjects with a mean age of approximately 50 years old and was evenly distributed between treatment arms. There were four subjects that did not complete the study, three in the Posimir 330 mg arm and one in the placebo arm. Reasons for discontinuation are shown in Table 3.

Table 3. Disposition of subjects in Study CLIN-803

Reason for Discontinuation	Placebo	Posimir 330 mg	Posimir 660 mg
Multiple surgeries	-	1	-
Patients best interest	-	1	-
Underwent surgery for preexisting condition	1	-	-
Non-allowed medication	-	1	-

Source: Reviewer

Even though these subjects discontinued the study, there was efficacy data for these subjects as they discontinued after 72 hours.

Statistical Methodologies

The analysis dataset defined by the applicant was all randomized subjects who successfully underwent the surgical procedure without any major deviations. An AUC, similar to a time-weighted average, was calculated for each patient using PI scores measured at 1, 2, 3, 4, 6, 8, and 12 hours following surgery on Day1 and at 8 AM, 12 PM, 4 PM, and 8 PM on Days 2 and 3. This AUC was normalized for each subject by dividing the AUC by 72 hours. This represents the average PI over 72 hours. Missing PI scores were handled as follows.

- If a patient withdrew from the study prior to 72 hours, the last recorded pain score was carried forward (LOCF)

- If a pain measurement was not recoded for a specific visit, the previous maximum pain score was used for the first missing value and any subsequent missing values.

The applicant conducted a sensitivity analysis to examine use of rescue medication. When a scheduled pain score was assessed within one half-life of the rescue medication and the pain score measured prior to using rescue medication was higher, the scheduled pain score was replaced with the rescue pain score. Any missing rescue pain scores were imputed using the worst observation carried forward (WOCF). Half-lives of 5.5, 2, and 4 hours were assumed for tramadol, morphine, and oxycodone, respectively.

The AUC_{72} for each dose of Posimir was compared to placebo using an analysis of variance (ANOVA) model with treatment and site as main effects. It was pre-specified that the placebo groups would be pooled. Dunnett's adjustment was used to account for two comparisons to placebo. The proportion of subjects using rescue medication through Day 3 and Day 15 were compared between treatment arms using a Cochran Mantel Haenszel (CMH) test. To account for the second primary endpoint, a step-down approach was used. If the comparison of AUC_{72} was statistically significant then the proportion of subjects using rescue was tested. The results for RES_{72} were compared between treatment groups using a Wilcoxon rank-sum (WRS) test. Time to first post-operative use of rescue medication was analyzed using Kaplan-Meier methods. A log-rank test was used to compare the survival curves between both doses of Posimir and placebo, and the median time to first use of rescue medication was reported. To account for the two comparisons of Posimir to placebo, I utilized the Sidak adjustment. The Sidak adjustment is slightly more powerful than the Bonferroni adjustment and assumes the individual tests are independent.

Overall, the statistical methodologies utilized by the Applicant for the analyses of the primary and secondary efficacy outcomes were acceptable. Even though LOCF imputation for subjects that discontinued due to an adverse event may not have been appropriate, there were only four subjects that discontinued, therefore it was not an issue. The hypotheses posed by the applicant seemed to indicate that a statistical win would be required for each primary endpoint, AUC_{72} and proportion of subjects using rescue medication. However, with the sequential testing strategy utilized, AUC_{72} was tested first. This would allow for a win on AUC_{72} but not on proportion of subjects using rescue medication.

Results and Conclusions

A summary of the applicant's primary analysis and mine for AUC_{72} are shown in Table 4. Both analyses account for missing pain scores and rescue medication. Note, one subject treated with Posimir 330mg was administered non-allowed rescue medication during surgery and only had one efficacy assessment post-surgery. This subject was excluded from my efficacy analyses.

Table 4. Results from analysis of normalized AUC in Study CLIN-803

	Normalized AUC_{72} (PI) - mean (SEM)		
	Placebo (n=32)	Posimir 330 mg (n=43)	Posimir 660 mg (n=47)
Applicant	3.6 (0.3)	3.1 (0.3)	2.5 (0.2)
Reviewer	4.0 (0.3)	3.3 (0.3)	2.7 (0.2)

Source: Reviewer

The point estimates for the difference in LSMEANs between the two doses of Posimir and placebo from my analysis are shown in Table 5. I also present the corresponding 95% confidence intervals (CI) for the difference and associated p-values for the comparison to placebo.

Table 5. Comparison of Posimir to placebo in Study CLIN-803

treatment	Difference	95 % CI	p-value
Posimir 330 mg	-0.8	[-1.6, 0.5]	0.1
Posimir 660 mg	-1.4	[-2.1, -0.6]	0.001

Source: Reviewer

Note, the AUCs and p-values in my analyses were slightly different from the applicant, although minor. These differences are most likely due to how I handled the use of rescue medication and missing data. I discuss this below. Regardless, my analysis agrees with the applicant: there was a significant difference noted for Posimir 660 mg versus placebo but not for the 330 mg dose.

As an AUC is cumulative and derived from the PI scores measured at each time point, I examined subject level data for missing pain scores. Based on the electronic data submitted by the Applicant, missing data due to discontinuation was not an issue. This was not unexpected as the study was conducted in an inpatient setting and patients only received a single dose of treatment. However, there were some intermittent missing pain scores. The amount of missing data is shown in Table 6.

Table 6. Missing pain assessments in Study CLIN-803

Time-point (hours post-dose)	Number of missing observations (%)			
	Placebo (n=32)	Posimir 330 mg (n=43)	Posimir 660 mg (n=47)	Combined (n=122)
1	3 (9.4)	1 (2.3)	-	4 (3.3)
2	1 (3.1)	-	1 (2.1)	2 (1.6)
3	-	-	-	-
4	1 (3.1)	1 (2.3)	-	2 (1.6)
6	3 (9.4)	2 (4.7)	2 (4.3)	7 (5.7)
8	2 (6.3)	-	2 (4.3)	4 (3.3)
10	2 (6.3)	1 (2.3)	4 (8.5)	7 (5.7)
12	6 (18.8)	4 (9.3)	2 (4.3)	12 (9.8)
22	4 (12.5)	-	-	4 (3.3)
26	3 (9.4)	1 (2.3)	2 (4.3)	6 (4.9)
30	2 (6.3)	3 (7.0)	-	5 (4.1)
34	2 (6.3)	-	1 (2.1)	3 (2.5)
46	2 (6.3)	2 (4.7)	4 (8.5)	8 (6.6)
50	2 (6.3)	1 (2.3)	4 (8.5)	7 (5.7)
54	4 (12.5)	3 (7.0)	2 (4.3)	9 (7.4)
58	1 (3.1)	2 (4.7)	3 (6.4)	6 (4.9)
70	-	1 (2.3)	2 (4.3)	3 (2.5)

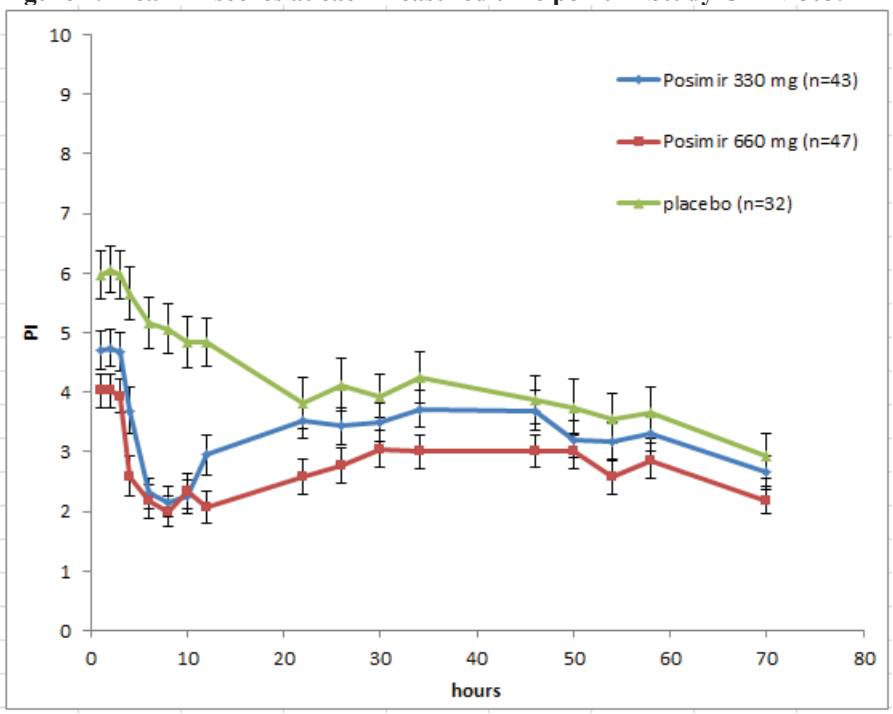
Source: Reviewer

Missing PI scores were less than 10% at all measured time points, with the most missing data being at 12 hours post-surgery. This was not unexpected as it would be the most inconvenient time point to collect. As missing data was fairly low and this was an inpatient study with a single administration of study drug, I decided it was acceptable to use WOCF for missing PI scores when deriving the AUC for each subject. This is in contrast to the applicant who used LOCF.

Next, I accounted for the use of rescue medication. When I only considered medication coded as rescue in the applicant's dataset, there were 511 uses of tramadol and oxycodone. However, when I expanded this to include concomitant medication and surgery medication, there were 714 uses of opioids which included fentanyl, morphine, oxycodone, tramadol, and codeine. In my derivation of AUC_{72} I considered all opioid medication regardless of how classified. If a patient received rescue at time x, for any time point within $x + 4$ hours, the highest score from time 0 up until time x was used. If the PI score for the windowed observation was higher than the worst observed score, it was not replaced. I did not consider 592 uses of APAP, although I did examine its use in an exploratory analysis and did not note any significant differences between treatment groups. I discuss this in more detail below.

Using the above methods for missing PI scores and use of rescue medication, the mean PI scores for each treatment group by time are shown in Figure 1. Error bars indicate the 95% CI of the point estimate.

Figure 1. Mean PI scores at each measured time point in Study CLIN-803.



Source: Reviewer

I compared each dose of Posimir to placebo at each time point using the same ANOVA model utilized in primary analysis. However, as this was exploratory I did not adjust for multiplicity. Results are shown in Table 7.

Table 7. Comparisons of PI scores at assessed time point in Study CLIN-803

	Difference from placebo (PI)					
Time point (hrs)	Posimir 330 mg (n=43)			Posimir 660 mg (n=47)		
	mean	stder	p-value	mean	stder	p-value
1	-1.3	0.5	0.01	-1.9	0.5	< 0.0001
2	-1.3	0.5	0.01	-2.0	0.5	< 0.0001
3	-1.3	0.5	0.01	-2.0	0.5	< 0.0001
4	-2.0	0.5	<0.0001	-2.0	0.5	<0.0001
6	-2.9	0.5	<0.0001	-3.0	0.5	<0.0001
8	-2.9	0.5	<0.0001	-3.0	0.5	<0.0001
10	-2.6	0.5	<0.0001	-2.5	0.5	<0.0001
12	-1.9	0.5	0.0002	-2.8	0.5	<0.0001
22	-0.3	0.5	0.6	-1.2	0.5	0.01
26	-0.7	0.5	0.2	-1.4	0.5	0.007
30	-0.4	0.5	0.4	-0.9	0.5	0.06
34	-0.5	0.5	0.3	-1.3	0.5	0.01
46	-0.2	0.5	0.7	-0.9	0.5	0.07
50	-0.5	0.5	0.3	-0.7	0.5	0.2
54	-0.4	0.5	0.5	-1.0	0.5	0.04
58	-0.4	0.5	0.5	-0.8	0.5	0.1
70	-0.3	0.4	0.5	-0.7	0.4	0.7

Source: Reviewer

The results presented in Figure 1 and Table 7 may help with the clinical interpretation of the effect size observed with the primary endpoint, AUC_{72}. In Figure 1 there is clear separation between the curves for both doses of Posimir and placebo out to approximately 24 hours post-surgery. The non-significance of the comparison of Posimir 330 mg to placebo for AUC_{72} was supported by the results observed in Table 7 where nominal statistical significance was only noted out to 12 hours. On the other hand, nominal significance for Posimir 660 mg versus placebo was noted out to approximately 24 hours and the comparison to placebo for AUC_{72} was statistically significant. It should be noted that for both doses of Posimir, the separation from placebo during hours 24 − 72 was not the same magnitude observed during hours 0 − 24. Hence, the significant difference demonstrated in the comparison of AUC_{72} for the Posimir 660 mg arm may be influenced by the early separation in the pains curves.

The results from the proportion of subjects using rescue medication through Day 3 and Day 15 are shown in Tables 8 and 9.

Table 8. Percent of subjects using opioid rescue medication through Day 15 in Study CLIN-803

Treatment	n	Opioids coded as rescue	All Opioids
Placebo	32	72	72
Posimir 330 mg	43	65	74
Posimir 660 mg	47	49*	53

*p-value=0.04
Source: Reviewer

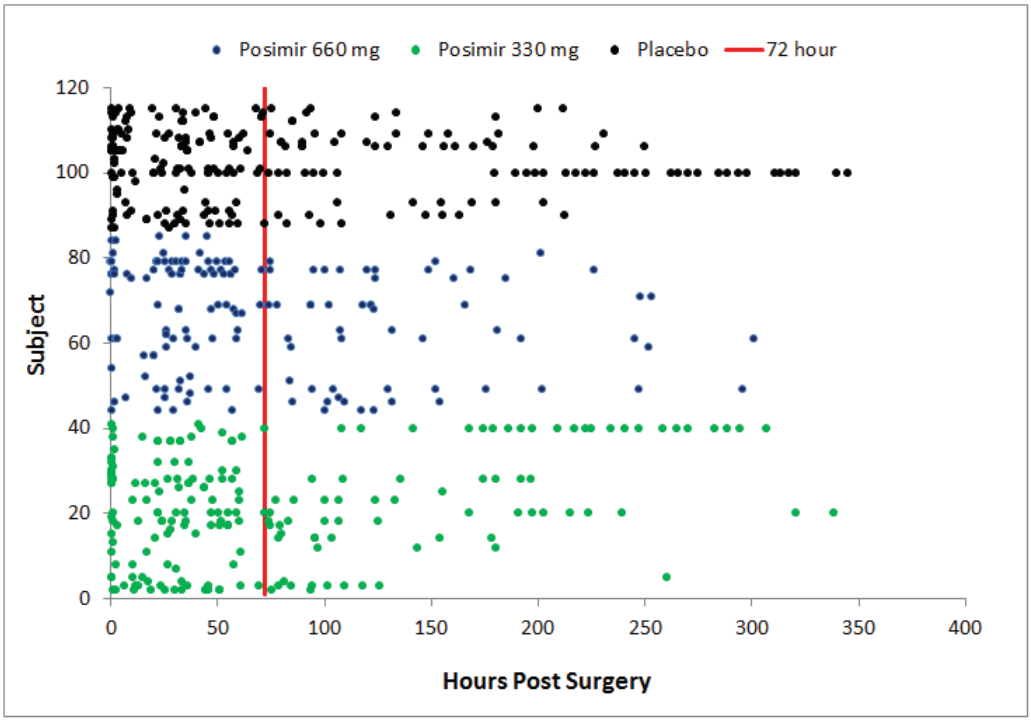
Table 9. Percent of subjects using opioid rescue medication through Day 3 in Study CLIN-803

Treatment	n	Opioids coded as rescue	All Opioids
Placebo	32	72	72
Posimir 330 mg	43	63	72
Posimir 660 mg	47	49*	51

*p-value=0.04
Source: Reviewer

Regardless of duration, Day 3 or Day 15, when I examined only opioids coded as rescue there was a significant difference noted between placebo and Posimir 660 mg for the percentage of subjects using rescue medication, p-value=0.04. However, when I considered all opioids, not just those coded as rescue, there was no longer a significant treatment effect. Further, regardless of how opioids were coded, I noticed there was very little difference in the results from Day 3 versus Day 15. To explore this, I present subject level use of rescue opioids in Figure 2. I present the data for all opioids regardless of classification. The reference line indicates the 72 hour time point.

Figure 2. Subject level use of rescue medication after study drug administration in Study CLIN-803



Source: Reviewer

In Figure 2, if a subject used rescue medication, they used early and often. Hence there was very little difference between the percentages of subjects using through Day 3 versus Day 15.

I also examined the amount of opioid rescue medication (mg morphine equivalent) consumed through 72 hours post-surgery, RES_{72}. While not a pre-specified primary endpoint, I considered RES_{72} to be a clinically relevant endpoint. Further, this was a co-primary endpoint in Study BU-002. Medications were converted to morphine equivalents using the conversion table provided by the applicant. It was pre-specified that results would be compared using an ANOVA model with treatment and site if the assumptions of normality and heterogeneity of variance were met. If these assumptions were violated, a non-parametric test would be used. In my analysis and the applicant's these assumptions were violated. A plot of the residuals indicated the data was left skewed and a test for homogeneity of the variance was rejected, p-value < 0.001. Therefore a non-parametric test, Wilcoxon Rank Sum (WRS) test was utilized. Results are shown in Table 10.

Table 10. Amount of rescue medication consumed through 72 hours post-surgery in Study CLIN-803

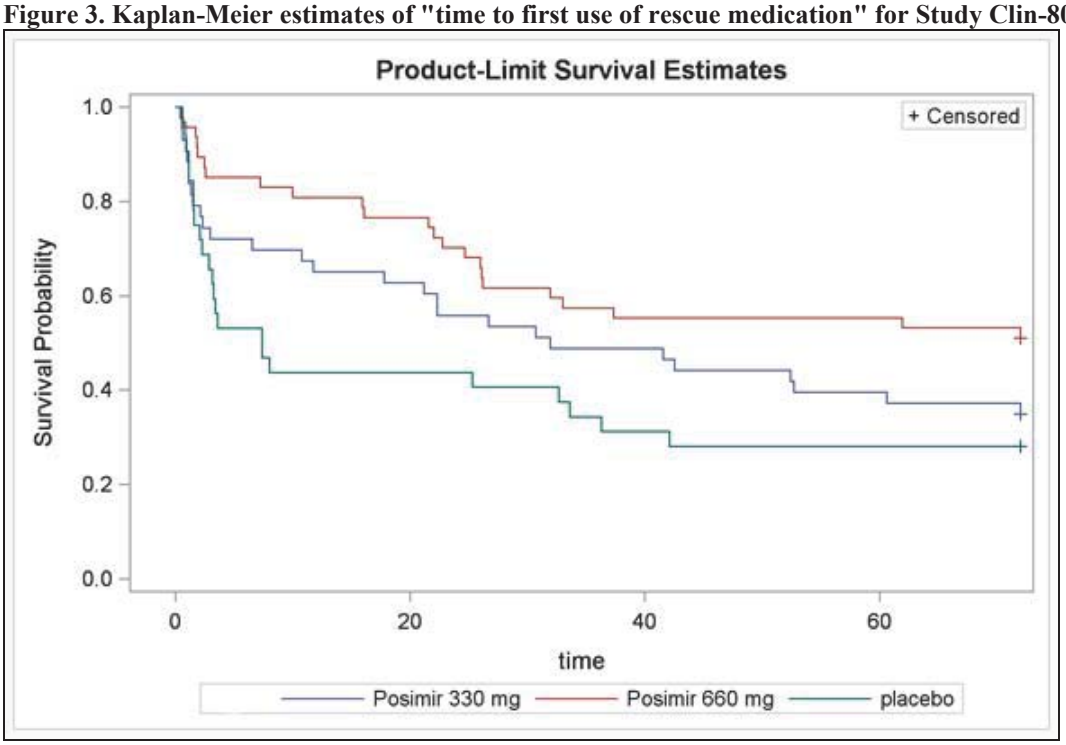
Treatment	Morphine Equivalent (mg) mean (stdev)	p-value
Placebo (n=32)	29.9 (57.6)	-
Posimir 330 mg (n=43)	13.1 (14.1)	0.05
Posimir 660 mg (n=47)	10.4 (13.1)	< 0.01

Source: Reviewer

There was a significant difference noted for the comparison of placebo to Posimir 660 mg, p-value < 0.01. However, the comparison of placebo to Posimir 330 mg was borderline significant at the 0.05 level. Regardless of dose, the use of Posimir reduced the amount of opioid medication consumed.

Next I examined the time to first use of rescue medication. In this analysis I considered all post-operative opioids not just those coded as rescue medication. A subject was considered censored if they did not use rescue medication prior to 72 hours post-surgery. The median time to first use of post-operative rescue medication was 7.4 hour hours in the placebo arm, 31.9 hours in Posimir 330 mg, and 72 hours in the Posimir 660 mg treatment arm. Using Kaplan-Meier methods, the survival curves for time to first use of rescue medication for each treatment arm are shown in Figure 3.

Figure 3. Kaplan-Meier estimates of "time to first use of rescue medication" for Study Clin-803



Source: Reviewer

Based on the log-rank test adjusted for the two comparisons, a significant difference exists in the distributions of time to first use of rescue medication between Posimir 660 mg and placebo, p-value=0.02 However, the was not a significant difference noted between Posimir 330 mg and placebo, p-value=0.7.

Even though my examination for use of rescue medication did not include approximately 600 uses of APAP, I did explore its use. The percentage of subjects using APAP was similar amongst treatment arms. Approximately 78, 77, and 55 percent of subjects used APAP in the placebo, Posimir 330 mg, and Posimir 660 mg arms, respectively. The average amount of APAP consumed during the first 72 hours post-treatment was also similar between treatment arms; 2.9, 2.8, 2.3 grams for the placebo, Posimir 330 mg, and Posimir 660 mg, respectively. Based on this

information, I decided it was acceptable to exclude the use of APAP from my analyses of rescue medication.

During my exploration of the data for use of rescue medication, I also noted that there was considerable use of medication that could be classified as rescue medication prior to study drug administration. The majority of medication used was fentanyl and morphine and most subjects were involved. In fact only three subjects did not use; two in the placebo arm and one in the Posimir 330 mg arm. The amount of medication in morphine equivalent daily doses was 4.2 mg, 3.1 mg, and 3.4 mg, in the placebo, Posimir 330 mg, and Posimir 660 mg arms, respectively. There were no significant differences noted. Even though pre-treatment use of rescue type medication was not considered in determining the percentage of subjects who used post-treatment rescue medication or amount of post-operative rescue medication, I did consider it when deriving AUC_{72} as it could have influenced the 1 and 2 hour pain assessments. There did not appear to be a difference between treatment arms in the frequency or amount of "rescue" medication used pre-treatment. Further, based on discussions with the medical officer, this use of rescue medication is typical for this type of surgery.

In summary, in this study there was a significance difference noted between placebo and Posimir 660 mg for the first primary endpoint, AUC_{72}. This difference was supported when I examined the mean PI scores by time, Figure 1. However, the magnitude of the separation between the curves for placebo and Posimir is diminished after 24 hours. There was no difference noted between Posimir 330 mg and placebo for AUC_{72}. For the second primary endpoint, proportion of subjects using rescue medication, when I examined all rescue medication, not just medication coded as rescue, there was not a significant difference between placebo and either dose of Posimir although numerically the numbers were in favor of Posimir. When I examined the amount of rescue medication consumed, RES_{72}, there was a significant difference noted in favor of Posimir 660 mg versus placebo but not Posimir 330 mg. This was supported by my analysis of time to first use of rescue medication. Subjects treated with Posimir 660 mg, on average reported less post-surgical pain, required less rescue medication, and waited longer to request it.

3.2.1.1 Supportive Studies

The Applicant submitted the results of a phase 2 trial that evaluated Posimir in subjects undergoing hernia repair surgery, Study CLIN005-0010. The study design and results are presented below. This study failed to show a significant treatment benefit of Posimir in treating post-surgical pain associated with hernia repair surgery.

This was a randomized double-blind, placebo-controlled phase 2 study that evaluated Posimir administered subcutaneous and subaponeurotic to subjects following open hernia repair surgery and was conducted in two cohorts. Subjects were enrolled at seven sites in the United States (California, New York, Pennsylvania, Utah, and Wisconsin) and one site in New Zealand. In Cohort 1, subjects were randomized to one of three treatment arms. In treatment arm 1, placebo was injected into the subaponeurotic space and Posimir 660 mg was administered subcutaneously along the incision line after wound closure. In treatment arm 2, Posimir 660 mg was administered into the subaponeurotic space and placebo was administered subcutaneously along the incision line. In treatment arm 3, placebo was administered in both locations. For Cohort 2, placebo or Posimir 660 mg was instilled into the surgery site prior to wound closure,

treatment arms 4 and 5, respectively. One subject in treatment arm 5 was administered 7.5 mL Posimir (990 mg).

The primary efficacy endpoints were PI at rest and on movement and pain control as assessed by the subject. PI was assessed using an 11-point NRS and pain control was evaluated using a 5-point scale. For pain control subjects were asked "How would you rate your overall pain control in the last 24 hours?" Responses were poor, fair, good, very good, or excellent. The pre-specified primary endpoints were PI and pain control on Days 0 through 7. For subjects that required supplemental analgesia, pain scores on movement were recoded prior to use. Via a protocol amendment, the primary endpoint was changed to a normalized AUC of PI scores for at rest and on movement at 120 hours post-surgery and were compared between treatment arms using an ANOVA model where the comparison of interest was treatment arm 5 versus pooled placebo, treatment arms 3 and 4. Missing data was imputed using LOCF for monotonic missingness and intermittent missing scores used the average of adjacent scores. The applicant also conducted a sensitivity analysis where pain scores prior to using rescue medication was used in the derivation of the AUC.

The analysis population consisted of all randomized and treated subjects. The number of subjects per treatment arm is shown in Table 11.

Table 11. Number of subjects per treatment arm in Study CLIN005-0010

Treatment Number	Description	Number of subjects randomized and treated
1	Placebo subaponeurotic 5 ml + Posimir SC 5 mL	14
2	Placebo SC 5 mL + Posimir subaponeurotic 5 mL	13
3	Placebo SC 5 mL + Placebo subaponeurotic 5 mL	18
4	Placebo subaponeurotic 5 mL	21
5	Posimir subaponeurotic 5 mL	22
5a	Posimir subacromial 7.5 mL	1

SC=subcutaneous
Source: Reviewer

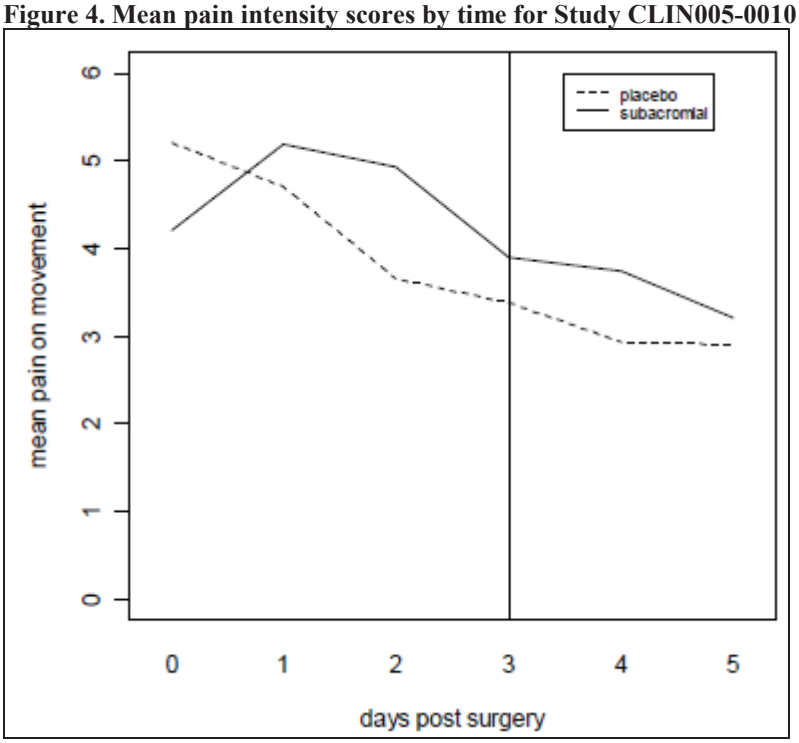
Of the 89 subjects that were randomized and treated, 86 completed the study. There were three subjects that were lost to follow-up, two on active drug and one on placebo. This study mostly evaluated male Caucasian subjects. There were five female subjects randomized, two Asian subjects, one African American subject, and four classified as other. The average age in years was 48 with a range of 21 to 89. The analysis population consisted of all randomized and treated subjects.

The only comparison that demonstrated statistical significance in favor of Posimir was treatment group 5 versus pooled placebo. However, AUC at 120 hours post-surgery was not the endpoint examined in the pivotal study, CLIN-803-006-0006 and the two placebo groups received different volumes of study drug. To compare the results of this study to the pivotal study, I compared mean AUC_{72} for treatment groups 4 and 5 as these treatment arms received the same volume of study drug administered in the pivotal study. The LSMEANs were 4.1 and 4.8 for placebo and Posimir, respectively. The 95% CI for the difference between Posimir and placebo

was [-0.5, 0.8]. The point estimate 0.6, while not significant, was in favor of placebo. This analysis accounted for the use of rescue medication by incorporating pain scores measure prior to using rescue medication when deriving the AUC. Even though this study used LOCF for discontinuations due to AE's they were only two dropouts and none were attributable to an AE.

I next examined the PI scores that were used to generate the AUC's reported above. The pain intensity scores by time are shown in Figure 4. The solid vertical line indicates the 72 hour time point. The solid line in the figure represents Posimir 660 mg, indicated as subacromial in the legend. Note, there is no subacromial space in the abdominal cavity.

Figure 4. Mean pain intensity scores by time for Study CLIN005-0010



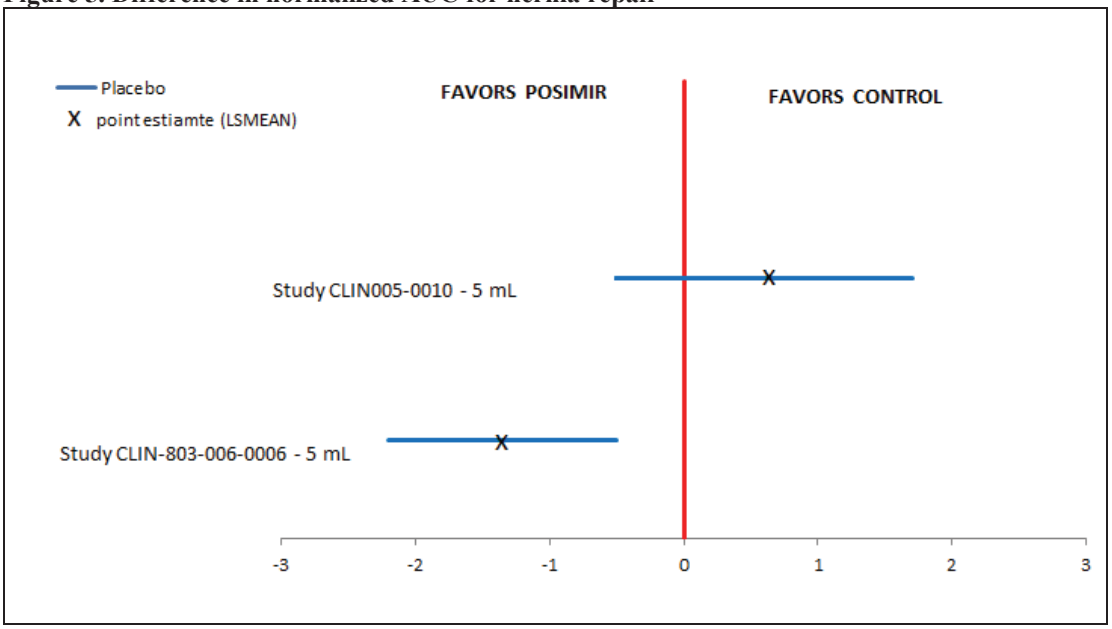
Source: Figure 3 from applicant's CSR

Clearly, the mean pain scores for the Posimir 660 mg treatment arm increased during the first 24 hours. This effect was not observed in the placebo arm. The clinical rationale for this effect is unknown.

Since the point estimate for the difference in AUC_{72} was in the wrong direction, I examined the amount of rescue medication consumed through 72 hours for treatment arms 4 and 5. Results, even though not significant, indicate that subjects in the placebo arm, on average used less rescue medication than subjects in the Posimir 660 mg arm. It seems for this study, placebo subjects had less post-surgical pain and used less rescue medication. There were no differences in the demographics between studies except that this study was mainly conducted in the United States, whereas the successful study was conducted in Australia and New Zealand.
Further examination of these results by site location, United States versus Australia and New Zealand, did not reveal any significant findings. In general the mean AUC_{72} for the Posimir treatment arm was higher than the placebo arm.

I summarize the results of AUC_{72} for the two studies that evaluated post-surgical pain associated with hernia repair surgery. Figure 5 shows the point estimates and 95% CI for difference from placebo for AUC_{72}. Note, the 5 mL dose is equal to 660 mg of Posimir.

Figure 5. Difference in normalized AUC for hernia repair



Source: Reviewer

I consider these results to be inconclusive. It seems that for the failed supportive study, placebo subjects had less post-surgical pain and used less rescue medication. The only notable difference in demographics between these two studies was the location. The failed study was mainly conducted in the United States, whereas the successful study was conducted in Australia and New Zealand.

3.2.2 Arthroscopic Shoulder Surgery

3.2.2.1 Pivotal Study

Study BU-002 was identified as pivotal by the applicant. Of the statistical issues identified during IND stage, the applicant addressed my concern regarding use of rescue medication and accounting for it the primary analysis. The applicant conducted a sensitivity analysis where use of rescue medication was accounted for in analysis.

Based on the results of a previous trial in subjects undergoing hernia repair surgery, the applicant estimated 25 placebo subjects and 50 Posimir 660 mg subjects would provide 80% power to detect a significant difference in morphine equivalent doses of 0.6 mg. Additionally, 25 subjects on standard release Bupivacaine were included.

Study Design and Endpoints

Eligible patients that were to undergo arthroscopic shoulder surgery were randomized to placebo, Posimir 660 mg, or bupivacaine in a 1:2:1 fashion. Following surgery, a single dose of the study drug was administered into the subacromial space. Subjects remained in the hospital at least 48 hours following surgery. Allowed rescue medication during the first 72 hours following surgery was oral morphine and if needed, IV morphine. Since standard bupivacaine and Posimir are different in appearance, dosed at different volumes, and administered differently, a non-blinded surgery team performed the procedure and administered study drug. All other staff involved in post-treatment assessments were blinded. PI was measured (11-point NRS) at 1, 2, 4, 6, 8, and 12 hours post-treatment (Day 0) and at 8:00, 12:00, 16:00, 20:00 on Days 1-7. Subjects were *not* instructed to measure PI scores prior to using rescue medication.

Patient Disposition, Demographic and Baseline Characteristics

Overall, 126 subjects were screened and 115 were randomized. Eight randomized subjects discontinued prior to surgery and did not receive treatment. Demographics for randomized and treated subjects are shown in Table 12.

Table 12. Patient demographics for Study BU-002

Characteristic	Treatment		
	placebo	Posimir 660 mg	bupivacaine
Number of Patients	25	53*	29
Age in years			
Mean (SD)	49 (10)	50 (9.5)	52 (11)
Median	52	49	52
[range]	[24, 63]	[28, 70]	[21, 70]
Gender, n (%)			
Female	14 (56)	33 (62)	17 (59)
Male	11 (44)	20 (38)	12 (41)
Race, n (%)			
Caucasian	24 (96)	50 (98)	29 (100)
Black	-	-	-
Asian	1 (4)	1 (2)	-
Other	-	-	-

*2 subjects missing response for race
Source: Reviewer

There were slightly more females than males which was consistent amongst the three treatment arms. The study mainly evaluated Caucasian subjects and as expected, there were no subjects that discontinued from the study.

Statistical Methodologies

The applicant identified two primary endpoints, AUC_{72} and the amount of opioid rescue medication in morphine equivalent doses used through 72 hours, RES_{72}. AUC_{72} was to be tested for non-inferiority (NI) to placebo first, if established, superiority of Posimir to placebo would be tested. The rationale given was that the use of rescue medication may dilute the treatment effect and superiority may not be established. NI was to be declared if the upper limit (UL) for the 95% confidence interval (CI) for the difference between the AUC_{72} for Posimir and placebo was less than or equal to 0.5. Superiority would be tested using an ANOVA model with treatment and pooled country as factors. Rescue medication consumed during the first 72 hours following

treatment was converted to morphine equivalent doses (mg) using the conversion table provided by the sponsor. Results for RES_{72} would be compared between placebo and Posimir using an ANOVA model with treatment and site as effects. If the assumptions of normality and homogeneous variance were not met, a non-parametric test would be used. There would be no formal comparison between Posimir and standard bupivacaine; hence no adjustments for multiplicity were incorporated into the analysis.

This study did not instruct subjects to measure pain scores prior to using rescue medication. To account for this, the applicant proposed a post-hoc sensitivity analysis based on FDA's advice. In this analysis, if a subject used rescue medication on or before a scheduled assessment, within one half-life of the rescue drug, the rescue pain score was considered to be the worst pain score observed prior to its use. This is analogous to worst observation carried forward (WOCF). I took a slightly different approach. Instead of using WOCF when subject used rescue medication, I randomly assigned each subject a moderate pain score, a score 5, 6, or 7. If a subject used rescue medication within 4 hours of a schedule pain assessment, this pain score was used if it larger than the recorded pain score. I used a 4 hour window regardless of the rescue medication used.

The applicant's dataset that contained the pain scores recorded following surgery did not contain the time of assessment. I utilized their derived dataset that contain the time of assessment. Per the applicant's explanation, pain was assessed at pre-specified time points post-surgery and the actual time of assessment was not recorded.

Results and Conclusions

The results of the applicant's primary analysis and mine when testing for superiority of Posimir to placebo for AUC_{72} are shown in Tables 13 and 14. The applicant's results presented below were from the sensitivity analysis that accounted for the use of rescue medication. My results are consistent with the applicant. There was a significant treatment effect in favor of Posimir.

Table 13. Results from analysis of normalized AUC in Study BU-002

	Normalized AUC_{72} (PI) - mean (SEM)		
	Placebo (n=25)	Posimir 660 mg (n=53)	Bupivacaine (n=29)
Applicant	6.3 (0.4)	5.0 (0.3)	5.0 (0.4)
Reviewer	6.4 (0.4)	5.3 (0.3)	5.5 (0.4)

Source: Reviewer

The point estimates for the difference in LSMEANs between the Posimir 660 mg and placebo from my analysis are shown in Table 14. I also present the corresponding 95% CI for the difference and the p-values for the comparison to placebo. For interest, I also present the comparison of placebo to bupivacaine.

Table 14. Comparison of Posimir to placebo in Study BU-002

	Difference	95% CI	p-value
Posimir 660 mg	-1.1	[-2.1, -0.2]	0.02
Bupivacaine	-0.2	[-1.1, 0.7]	0.1

Source: Reviewer

While not used for inferential value, I did compare bupivacaine to Posimir, results not shown. A significant difference was not noted, p-value of 0.7. As the applicant used LOCF, included pooled country in their ANOVA model, and used different windows for the adjustment of rescue medication, my derivation of the mean AUC for each treatment arm differ slightly as I used BOCF and a constant 4 hour window when considering use of rescue medication. The applicant's pre-specified statistical analysis plan indicated they would test for NI of Posimir to placebo first. If NI was established, superiority would be tested. Even though NI was established as indicated by the 95% CI shown in Table 14, there is no clinical interpretation of establishing NI to placebo as a rationale for a NI margin was not established. Regardless, superiority was demonstrated.

As an AUC is cumulative and derived from the PI scores measured at each time point, I examined subject level data for missing PI scores. Similar to Study ClIN-803, monotonic missing data was not an issue as subjects were hospitalized following surgery and none withdrew prior to 72 hours. However, there were some intermittent missing data. The amount of data missing at each time point post-surgery is shown in Table 15.

Table 15. Missing pain assessments in Study BU-002

Time-point (hours post-dose)	Number of missing observations (%)			
	Placebo (n=25)	Posimir 660 mg (n=53)	Bupivacaine (n=29)	Combined (n=107)
1	-	-	-	-
2	7 (28.0)	8 (15.1)	5 (17.2)	20 (18.7)
4	2 (8.0)	7 (13.2)	6 (20.7)	15 (14.0)
6	2 (8.0)	7 (13.2)	4 (13.8)	13 (12.1)
8	2 (8.0)	4 (7.5)	1 (3.4)	7 (6.5)
12	1 (4.0)	-	1 (3.4)	2 (1.9)
22	4 (16.0)	8 (15.1)	5 (17.2)	17 (15.9)
26	2 (8.0)	5 (9.4)	3 (10.3)	10 (9.3)
30	1 (4.0)	5 (9.4)	5 (17.2)	11 (10.3)
34	1 (4.0)	3 (5.7)	3 (10.3)	7 (6.5)
46	3 (12.0)	8 (15.1)	3 (10.3)	14 (13.1)
50	3 (12.0)	3 (5.7)	2 (6.9)	8 (7.5)
54	1 (4.0)	6 (11.3)	2 (6.9)	9 (8.4)
58	3 (12.0)	4 (7.5)	3 (10.3)	10 (9.3)
70	3 (12.0)	5 (9.4)	4 (13.8)	12 (11.2)
72	2 (2.0)	9 (17.0)	4 (13.8)	15 (14.0)

Source: Reviewer

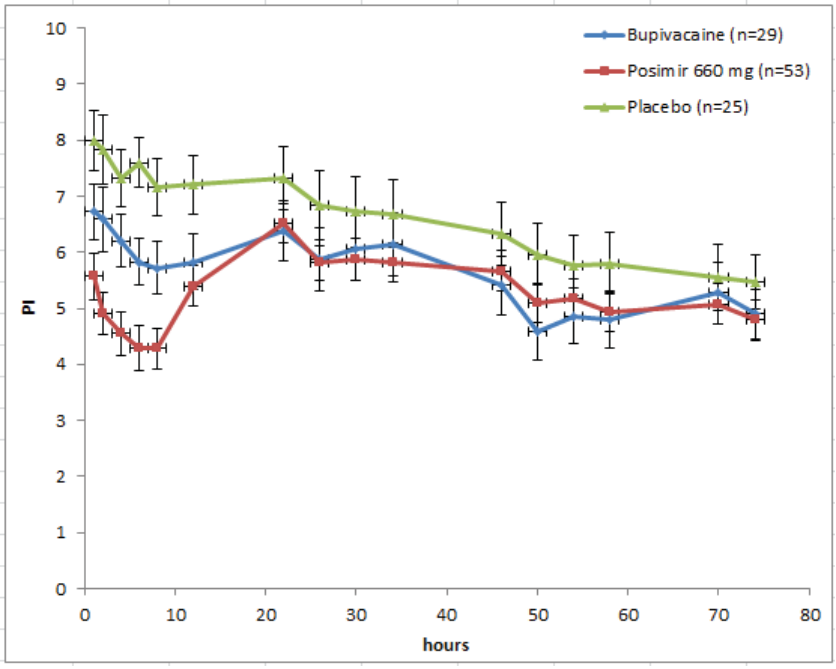
There were more missing PI assessments in this study than in pivotal hernia repair study, CLIN-803. However, in all cases it was less than 20% with the most missing data at the 2, 22, and 72 hour post-treatment time point. Since there were no patterns or trends noted with the missing data and this was an inpatient study with a single administration of study drug, I was not concerned and used WOCF to impute missing pain scores. The applicant used LOCF.

Next, I accounted for the use of rescue medication. When I only considered medication coded as rescue, there were 427 uses of morphine. When I expanded this to include concomitant medication, general anesthesia, and IV medication; there were 697 uses of opioids which

included fentanyl, midazolam, morphine, oxycodone, propofol, and tramadol. In my analysis of PI scores I considered all opioid medication regardless of how classified. As with Study CLIN-803, I did not consider 609 uses of APAP. If a patient received rescue at time *x*, for any time point within *x* + 4 hours, the assigned rescue pain score was used. If the PI score for the windowed observation was higher than the rescue pain score, it was not replaced.

The mean PI scores for each treatment group at each assessed time point are shown in Figure 6. Error bars indicate the 95% CI of the point estimate. This display of the PI scores that were used to generate AUC_s may help with the clinical interpretation of the effect size observed with the primary endpoint, AUC_{72}.

Figure 6. Mean PI scores at each measured time point in Study BU-002-IM



Source: Reviewer

The above figure demonstrates separation in the curves for Posimir and bupivacaine from placebo out 72 hours. However, the magnitude of the separation from approximately 24 − 72 hours is not the same magnitude observed for hours 1 − 24. This was also observed in Study CLIN-803. It should be noted that regardless of treatment, most subjects had moderate pain throughout the study. Moderate pain is defined as a score between 4 and 7.

Exploring the data that generated the curves above, I compared the mean PI scores of Posimir and bupivacaine to placebo at each time point. As this was exploratory, I did not adjust for multiplicity. Results are shown in Table 16.

Table 16. Comparison of PI scores by time in Study BU-002

Time point (hrs)	Difference from placebo (PI)					
	Posimir 660 mg (n=53)			Bupivacaine (n=29)		
	LSMEAN	stder	p-value	LSMEAN	stder	p-value
1	-2.4	0.7	0.0003	-1.3	0.7	0.09
2	-2.9	0.6	<0.0001	-1.3	0.7	0.08
4	-2.8	0.6	< 0.0001	-1.1	0.7	0.13
6	-3.3	0.6	<0.0001	-1.7	0.7	0.01
8	-2.8	0.6	<0.0001	-1.4	0.7	0.03
12	-1.8	0.6	0.004	-1.4	0.7	0.05
22	-0.8	0.6	0.19	-0.9	0.7	0.18
26	-1.0	0.6	0.09	-1.0	0.7	0.16
30	-0.9	0.7	0.19	-0.7	0.9	0.38
34	-0.8	0.6	0.18	-0.5	0.7	0.47
46	-0.7	0.6	0.29	-0.9	0.7	0.20
50	-0.9	0.6	0.16	-1.4	0.7	0.05
54	-0.6	0.6	0.34	-0.9	0.7	0.20
58	-0.9	0.6	0.16	-1.0	0.7	0.15
70	-0.5	0.6	0.45	-0.3	0.7	0.69
72	-0.7	0.6	0.25	-0.6	0.7	0.39

Source: Reviewer

From Table 16, the difference between Posimir and placebo is nominally significant out to 12 hours post-surgery. This indicates that the significant difference noted in the comparison of AUC_{72} may be influenced by the early separation in the curves. There were no significant differences noted between bupivacaine and placebo. Based on the information in Figure 6 and Table 16, the clinical benefit of Posimir 660 mg in reducing post-surgical pain associated with shoulder repair surgery after 12 hours post-surgery is unclear.

Next I examined the second co-primary efficacy endpoint, amount of opioid rescue medication consumed through 72 hours, RES_{72}. I considered all opioids used regardless of how the applicant classified the use. It was pre-specified that results would be compared using an analysis of variance (ANOVA) model with treatment and site if the assumptions of normality and heterogeneity of variance were met. If these assumptions were violated, a non-parametric test would be used. In my analysis and the applicant's these assumptions were violated. A plot of the residuals indicated the data was left skewed and a test for homogeneity of variance was rejected, p-value < 0.001. Therefore a non-parametric test, Wilcoxon Rank Sum (WRS), was utilized. Results are shown in Table 17.

Table 17. Amount of rescue medication consumed through 72 hours post-surgery in Study BU-002

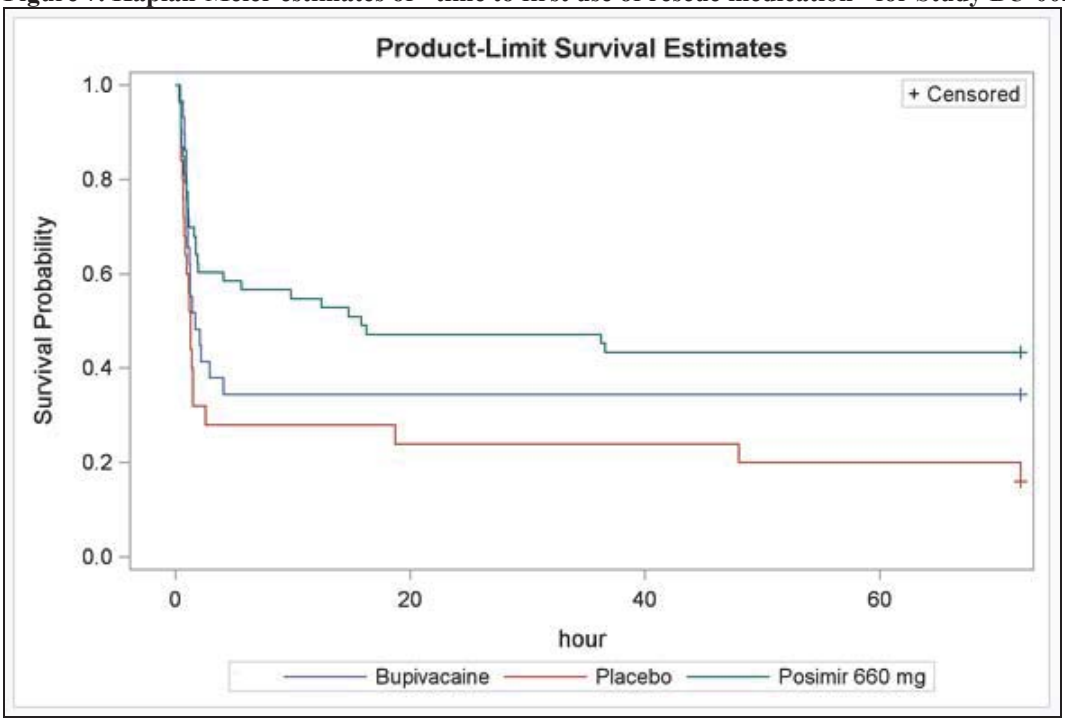
Treatment	Morphine Equivalent (mg) mean (stdev)	p-value
Placebo (n=25)	22.8 (25.8)	-
Posimir 660 mg (n=53)	13.7 (29.1)	0.01
Bupivacaine (n=29)	12.3 (17.6)	0.07

Source: Reviewer

There was a significant treatment effect noted for Posimir 660 mg but not for bupivacaine. Subjects treated with Posimir 660 mg, on average used less rescue medication than placebo subjects, 13.7 mg versus 22.8 mg, respectively.

Next I examined time to first use of rescue medication. The median time to first use of post-operative rescue medication was 1.3 hours in placebo subjects, 15.8 hours in Posimir 660 mg treated subjects, and 1.7 hours in subjects treated with bupivacaine. Using Kaplan-Meier methods, the survival curves for time to first use of rescue medication for each treatment arm are shown in Figure 7. In this analysis I considered all post-operative opioids not just those coded as rescue medication. A subject was considered censored if they did not use rescue medication prior to 72 hours post-surgery.

Figure 7. Kaplan-Meier estimates of "time to first use of rescue medication" for Study BU-002



Source: Reviewer

Based on the log-rank test, a significant difference exists in the distributions of time to first use of rescue medication between Posimir 660 mg and placebo, p-value=0.01. However, there was not a significant difference between placebo and bupivacaine.

Even though my examination of rescue medication usage did not include 609 uses of APAP, I did explore its use. Every subject regardless of treatment took APAP at some point post-surgery. The average amount of APAP consumed during the first 72 hours post-treatment was also similar between treatment arms; 9.2, 9.8, 9.8 grams for the placebo, Posimir 660 mg, and bupivacaine, respectively. Based on this information, I decided it was acceptable not to include the use of APAP in my analyses of rescue medication.

As in Study CLIN-803 there were some subjects that used rescue medication prior to surgery, 40% in placebo arm, 34% in the Posimir arm, and 38% in the bupivacaine arm. Rescue medication used was mostly fentanyl or morphine. Again, as the clinical team felt this usage was appropriate, I did not include this use when determining the amount of rescue medication consumed through 72 hours. However, as done with Study CLIN-803, I did account for it when deriving AUCs as it could influence early pain scores.

In summary, this study did demonstrate the efficacy of Posimir in treating post-surgical pain associated with shoulder repair. There was a significant difference in favor of Posimir when I examined the pre-specified primary endpoints, AUC_{72} and RES_{72}. This was supported by the analysis of secondary endpoints such as pain scores at each time point and time to first use of rescue medication. However, the clinical benefit of Posimir 660 mg in reducing post-surgical pain associated with shoulder repair surgery after 12 hours post-surgery is unclear. Although the study did not demonstrate that it was any better than standard bupivacaine, it was not designed to do so. That being said, Posimir was significantly better than placebo for the primary endpoints, bupivacaine was not.

3.2.2.2 Supportive Studies

Two studies, CLIN803-017 and CLIN005-0006, that failed to demonstrate a statistically significant treatment benefit of Posimir in treating post-surgical pain associated with shoulder repair surgery were indicated as supportive by the applicant and are discussed below. Based on the applicants clinical study reports, these studies were conducted prior to the pivotal study. Study CLIN005-0006 was conducted from 2006 to 2007. Study C803-017 was conducted from 2008 to 2009. It is my impression that the applicant conducted these studies in a chronological order until a significant study was obtained.

Study CLIN005-0006: This was a randomized, double-blind, placebo-controlled phase 2 study conducted at six sites in Utah, Georgia, Pennsylvania, California, and Texas and one site in New Zealand. This study was conducted in two cohorts. In cohort 1, eligible subjects were randomized equally to one of three treatment arms. In treatment arm 1, prior to wound closure, 5 mL of placebo was injected into the subacromial space. After wound closure 5 mL of Posimir was administered as two trailing subcutaneous injections along each side of the incision line. In treatment arm 2, prior to wound closure 5 mL of Posimir was injected into the subacromial space. After wound closure 5 mL of placebo was injected along the incision line. In treatment arm 3, placebo was injected into the subacromial space and along the incision line. In cohort 2, subjects were randomized equally to either placebo, treatment arm 4, or Posimir 7.5 mL, treatment arm 5. In Cohort 2 study drug was only injected into the subacromial space. Via a protocol amendment the dose for Cohort 2 was changed from 7.5 mL to 5.0 mL. There were four subjects in treatment arm 4 and three subjects in treatment arm 5 that received the 7.5 mL dose. These treatment arms are referred to as 4a and 5a, respectively. The 5 mL dose of Posimir corresponds to 660 mg active product and the 7.5 mL dose corresponds to 990 mg.

Efficacy was assessed using the subjects' evaluation of pain intensity on movement and at rest and pain control collected via the subjects' diary. PI was assessed using an 11-point NRS and pain control was evaluated using a 5-point scale. Subjects were asked "How would you rate your overall pain control in the last 24 hours?" Responses were poor, fair, good, very good, or

excellent. The pre-specified primary endpoints were PI and pain control on Days 0 through 7. For subjects that required supplemental analgesia, pain scores on movement were recoded prior to use. Via a protocol amendment, the primary endpoint was changed to a normalized AUC of PI scores for at rest and on movement at 120 hours post-surgery and were compared between treatment arms using an ANOVA model where the comparison of interest was treatment arm 5 versus pooled placebo, treatment arms 3 and 4. Missing data was imputed using LOCF for monotonic missingness and intermittent missing scores used the average of adjacent scores. The applicant also conducted a sensitivity analysis where pain scores prior to using rescue medication was used in the derivation of the AUC. Post-hoc the applicant examined AUC_{72} and RES_{72}.

The analysis population consisted of all randomized and treated subjects. The number of subjects per treatment arm is shown in Table 18.

Table 18. Number of subjects per treatment arm in Study CLIN005-0006

Treatment Number	Description	Number of subjects randomized and treated
1	Placebo subacromial 5 ml + Posimir SC 5 mL	14
2	Placebo SC 5 mL + Posimir subacromial 5 mL	10
3	Placebo SC 5 mL + Placebo subacromial 5 mL	16
4	Placebo subacromial 5 mL	24
5	Posimir subacromial 5 mL	21
4a	Placebo subacromial 7.5 mL	4
5a	Posimir subacromial 7.5 mL	3

SC=subcutaneous
Source: Reviewer

Overall, there were slightly more male subjects than female, 59% versus 41%, respectively. The average age of subjects was 54 years old with a range of 22 to 82 years old. The majority of subjects were Caucasian with the exception of 7 African American subjects, 2 Asian, and 3 subjects categorized as other. Of the 92 subjects that were randomized and treated, 90 completed the study. Two subjects withdrew consent, one in the active arm and one in the placebo.

This study failed to show a significant difference between placebo and Posimir for AUC of PI scores out to 120 hours post-surgery. In a post-hoc analysis there was a significant difference noted in the AUC_{72} for subjects that received Posimir via a subacromial injection and the pooled placebo group. However the placebo subjects in treatment group 3 received 10 mL of study drug and the placebo subjects in treatment arm 4 received 5 mL of study drug. A more relevant comparison would be treatment groups 4 and 5 as these treatment arms received 5 mL of study drug which was the volume administered in the pivotal study, BU-002-IM. The LSMEANs for AUC_{72} were 5.6 and 5.2 for placebo and Posimir, respectively. The corresponding 95% CI for the difference between Posimir and placebo was [-1.7, 0.5] and failed to show a significant difference. This analysis did account for the use of rescue medication by using the pain scores that were measured prior to using rescue when deriving the AUCs.

Study C803-017: This was a randomized, double-blind, multi-center, placebo-controlled phase 2b study conducted at 8 sites in Australia and 2 sites in New Zealand. Eligible subjects were randomized to receive either placebo or Posimir 660 mg injected interstitially into the

subacromial space upon completion of the procedure. Assessment of efficacy was based on shoulder PI on movement and use of supplemental opioid analgesia. For subjects that required supplemental analgesia, pain scores on movement were recoded prior to use. Two primary efficacy endpoints were identified, normalized AUC_{72} and RES_{72} as measured by morphine equivalent units. The primary null hypotheses were that there were no differences between treatment groups in terms of AUC_{72} and RES_{72}.

The analysis population consisted of 20 placebo subjects and 40 Posimir 660 mg subjects which constitute all randomized and treated subjects. A normalized AUC_{72} was calculated for each subject using the standard trapezoidal rule and were compared between treatment groups using an ANCOVA model with treatment, site, and age as factors. Missing data was imputed using BOCF for subjects that discontinued due to an adverse event and LOCF for discontinuations due to any other reason. Intermittent missing data was replaced by using the mean of the values before and after. The mean total opioid dose was computed for each subject and compared between treatment groups using the same ANCOVA model. In case the normality assumption was violated, the applicant also conducted a non-parametric WRS test. To account for two primary endpoints the applicant utilized the Hochberg approach.

Of the 60 subjects randomized to treatment, 59 completed the study. One subject in the placebo withdrew consent. The majority of these subjects were Caucasian; 100% in placebo arm and 93% in the Posimir arm. There was one Aborigine, one Asian, and one other in the Posimir treatment arm. While the placebo arm enrolled equal numbers of male and female subjects, the Posimir treatment arm had slightly more female subjects than male subjects; 58% versus 42%, respectively. Results of the applicant's primary analysis are presented in Table 19. Even though the pain scores we measured prior to using rescue analgesia, the applicant did not utilize them in deriving the AUC_{72}.

Table 19. Applicant's results for the primary analysis in Study C803-017

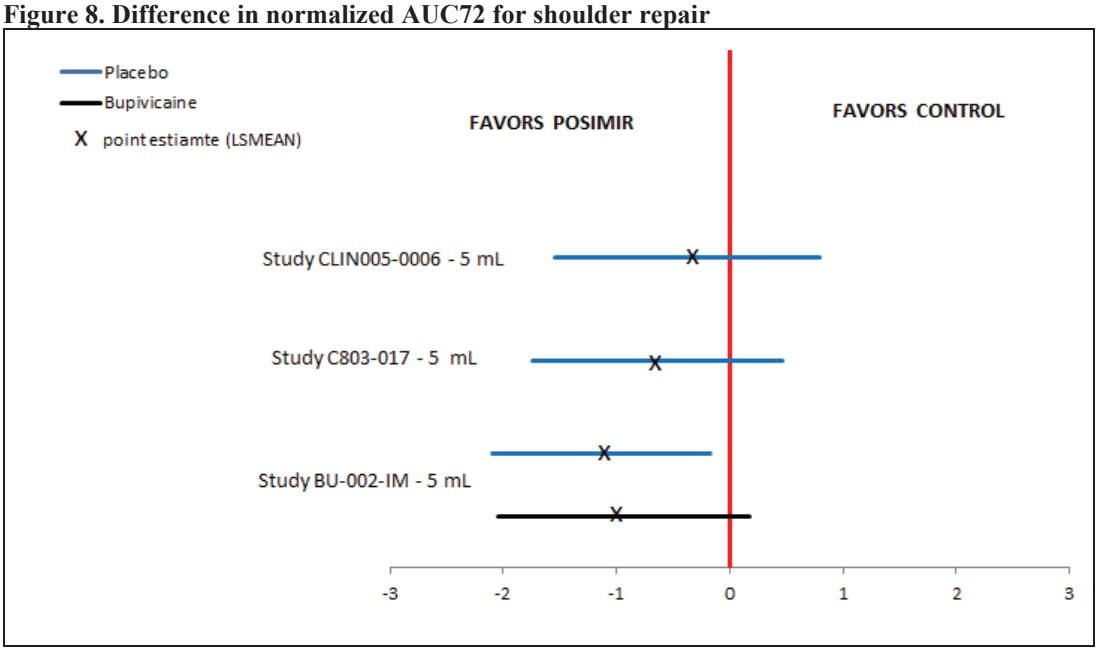
Endpoint	Placebo (n=20)	Posimir 5 mL (n=40)	Difference (95% CI)	p-value
AUC_{72} (pi)	5.8	5.4	-0.64 [-1.7, 0.47]	0.3
RES_{72} (mg)	49.9	44.5	-10.7 (-30.0, 9.6)	0.3

Source: Tables 14.1.8.1 and 14.1.9.1 from applicant's CSR

A significant treatment effect was not observed for either endpoint.

I summarize the results of AUC_{72} for the three studies that evaluated post-surgical pain associated with shoulder repair surgery. Figure 8 shows the point estimates and 95% CI for difference from placebo for AUC_{72}. The 5 mL dose is equal to 660 mg of Posimir.

Figure 8. Difference in normalized AUC72 for shoulder repair



Source: Reviewer

Unlike the studies that evaluated post-surgical pain associated with hernia repair, all supportive studies, while not significant, supported the treatment benefit of Posimir. The point estimate for AUC_{72} was in the right direction. The comparison of Posimir to bupivacaine in Study BU-002-IM, while not significant, did favor Posimir. Of interest, in this study bupivacaine was not significantly different from placebo in the analyses of the primary and secondary efficacy endpoints.

3.2.3 Other Surgical Procedures

The results from two additional studies evaluated post-surgical pain associated with a hysterectomy and major abdominal surgery. Study BU-001-IM was conducted in female subjects undergoing a hysterectomy and Study C803-025 evaluated subjects undergoing a colectomy, laparotomy, or laparoscopic cholecystectomy. Each study is discussed briefly and the applicants' analyses are presented.

Study BU-IM-001: This was a randomized, double-blind, dose-ranging, active- and placebo-controlled phase 2 study that evaluated Posimir in female subjects undergoing a hysterectomy. Subjects were enrolled at 13 sites in 5 countries; France, Germany, Hungary, Latvia, and Sweden. This study was to be conducted in two separate cohorts where Cohort 1 received 5.0 mL of study drug and Cohort 2 received 7.5 mL of study drug. However, Cohort 2 was not conducted. In Cohort 1, subjects were randomized 2:1:1 to either Posimir 5.0 mL, placebo, of 40 mL of bupivacaine. Placebo and Posimir were instilled into the surgery site prior to wound closure. Bupivacaine was injected into the muscle, distal layer and subcutaneously around the surgery site.

The primary efficacy variables were AUC_{72} on movement and RES_{72}. Missing pain scores between two non-missing pain scores were not imputed. This is analogous to linear

interpolation. Missing pain scores due to discontinuations were imputed using LOCF. The analysis population was defined as all randomized and treated patients. For $AUC_{72,}$ the applicant tested NI of Posimir 660 mg to placebo using ANOVA model with treatment and pooled site as factors. If the upper bound of the 95% CI for the difference was less than or equal to 0.5, NI was established. This is equivalent to using a NI margin of 0.5. If NI was established, superiority was tested. RES_{72} was computed for each subject by converting amount of rescue medication to morphine equivalent doses. If a subject discontinued prior to 72 hours, the Res_{72} will be calculated as amount of rescue used per hour times 72. Results were compared between placebo and Posimir using an ANOVA model with treatment and pooled site.

Of the 119 subjects enrolled, 114 were randomized and treated, 60 Posimir, 27 placebo, and 27 bupivacaine. Of these 114 subjects, 113 completed the study. One subject in the Posimir arm withdrew consent and one subject in the placebo arm withdrew due to an adverse event. All subjects were female Caucasians with an average age of 46 years old. In the analysis of AUC_{72}, NI was claimed as the 95% CI for the difference of Posimir and placebo was [-0.89, 0.35]. The 95% CI for the difference between Posimir and bupivacaine was [-0.68, 0.47]. However, superiority was not established for either comparison, p-value > 0.05. This analysis did not account for use of rescue medication. Additionally, superiority of Posimir 660 mg over placebo for RES_{72} was not established. Placebo subjects, on average used 26.3 mg morphine equivalent units compared to 22.8 mg for the Posimir 660 mg. Bupivacaine treated subjects used an average of 23.9 mg over 72 hours.

Study C803-025: This was a randomized, double-blind, placebo- and active-controlled phase 3 trial that was conducted in three separate cohorts. Cohort 1 randomized subjects undergoing a laparotomy and Cohort 2 randomized subjects undergoing a laparoscopic cholecystectomy. In Cohorts 1 and 2, subjects were randomized 3:2 to Posimir 660 mg or bupivacaine. Cohort 3 was placebo controlled and evaluated subjects receiving a colectomy. Subjects were randomized 3:2 to Posimir 660 mg or placebo. In all cohorts study drug was instilled into the surgery site prior to wound closure. This study was conducted at nine sites in the United States and two sites in Australia.

The primary efficacy variables were AUC_{72} and RES_{72}. The analysis population was defined as all randomized subjects that received study drug. An ANCOVA model with treatment, pooled site and incision length as a covariate was used to compare results for both endpoints. Since the results of RES_{72} violated the normality assumptions a non-parametric analysis, WRS, was used. Missing pain scores were handled as follows. If a subject dropped out prior to 72 hours due to an adverse event, the subjects' baseline observation was carried forward. If a subject dropped out for any other reason or had intermittent missing data, a multiple imputation approach was used. The Hochberg approach was utilized to account for two primary endpoints. If the largest p-value was less than 0.05, then both endpoints were declared significant. If the largest p-value was greater than 0.05, the other endpoint will be tested at 0.025. The applicant states that data from Cohorts 1 and 2 will be pooled and summarized but would be non-inferential. The data from Cohort 3 was of interest and would be inferential.

A total of 393 subjects were screened in order to randomize 331 subjects. Of these 26 did not receive treatment. Cohort 1 randomized 30 subjects to Posimir and 18 subjects to bupivacaine,

Cohort 2 randomized 30 subjects to Posimir and 20 subjects to bupivacaine, and Cohort 3 randomized 129 to Posimir and 78 subjects to placebo. Of all randomized subjects, 11 did not complete the study. Six subjects withdrew consent, four in the Posimir arms, one in the bupivacaine arm, and one in the placebo arm. Two subjects, one subject in the Posimir arm and one in the bupivacaine arm discontinued due to an adverse event. The other three reasons were lost to follow-up, investigator decision, and other. The average age of all subjects was 56 years old with a range of 22 to 87. Overall the study enrolled approximately equal numbers of males and females, 48% and 52%, respectively. The applicants' results for the primary analysis are shown in Table 20.

Table 20. Results of applicants' primary analysis from Study C803-025

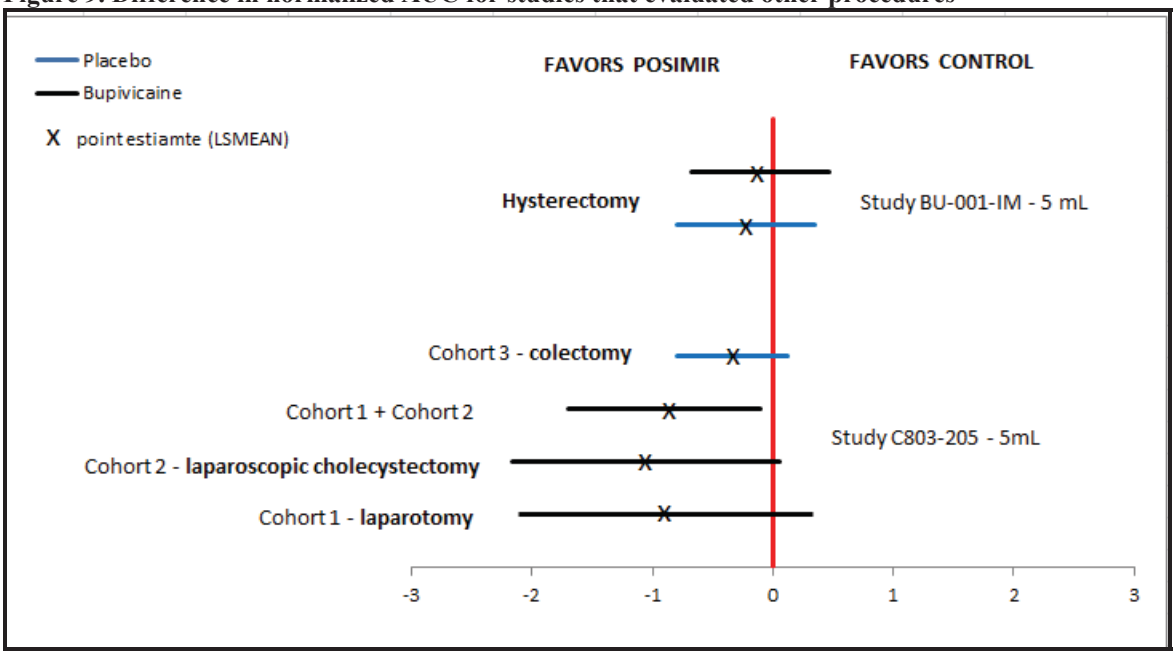
Cohort	normalized AUC_{72} (pi)			p-value
	Control	Posimir 5 mL	Difference (95% CI)	
1	5.8	4.9	-0.9 (-2.1, 0.3)	0.15
2	3.9	2.8	-1.1 (-2.2, 0.05)	0.06
3	5.1	4.8	0.34 (-0.8, 0.12)	0.15

Source: Table 15 from applicants CSR

The only significant difference noted was when the applicant pooled Cohorts 1 and 2. Superiority of Posimir over bupivacaine was noted, results not shown. However, the clinical reviewer felt it was inappropriate to pool the data from these two surgical procedures as they were clinically different. Further, there were no significant differences noted for the comparison of Posimir to control for RES_{72}, results not shown.

Figure 9 shows the point estimates and the 95% CI for the difference of Posimir from control for AUC_{72}. I included the two studies that evaluated post-surgical pain associated with hysterectomy, colectomy, laparoscopic cholecystectomy, and laparotomy. While there was not a significant treatment effect noted, in all cases, the point estimate was in favor of Posimir. I included the results from the pooled analysis in Study C803-025 although clinically, it was inappropriate to pool these two procedures.

Figure 9. Difference in normalized AUC for studies that evaluated other procedures



Source: Reviewer

Results from these two supportive studies, while not significant, indicated numerically that Posimir was better than placebo.

3.3 Evaluation of Safety

The primary medical officer, Dr. Arthur Simone, reviewed the safety data for this application.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The Applicant examined the primary efficacy endpoint, AUC_{72}, in Study BU-002 for differences due to age or gender. As this study was conducted mainly in Caucasian subjects, differences due to racial subgroups were not examined. Age was categorized as less than 45 years old or 45 years or older. Since I could not locate a subgroup analysis for CLIN-803 in the applicant's clinical study report, I conducted my own analysis. However, this study was included in a pooled analyses located in the integrated summary of efficacy. Each study will be discussed separately below.

Study CLIN-803

Since the majority of these subjects were male Caucasians, gender and racial subgroups were not examined. I examined the primary endpoint, AUC_{72} for any differences due to age using an ANOVA model with treatment and age. The results for my subgroup analysis for gender are shown in Table 21.

Table 21. Subgroup analysis for age, gender, and country in Study CLIN-803

Subgroup		AUC_{72} LSMEAN (PI)		Difference	95% CI
		placebo	Posimir 660 mg		
Age (years)	< 45 (n=)	5.6	3.4	-2.2	[-3.4, 0]
	≥ 45 (n=)	3.4	2.2	-1.2	[-2.8, 0]

Source: Reviewer

There was not a significant treatment interaction with age when I examined AUC_{72} in Posimir 660 mg and placebo. While not significant, the point estimates were in the right direction.

Study BU-002

The applicant examined AUC_{72} for any treatment interactions with age and gender using an ANOVA model with treatment, site, age, and gender. The 95% CI for the difference of Posimir 660 mg from placebo were presented. The applicant tested for NI and superiority to placebo. The results using my analyses are shown in Table 22.

Table 22. Subgroup analysis for age and gender in Study BU-002

Subgroup		AUC_{72} LSMEAN (PI)		Difference	95% CI
		placebo	Posimir 660 mg		
Gender	female (n=47)	6.3	5.4	-0.9	[-2.2, 0.5]
	male (n=33)	6.7	5.2	-1.5	[-3.1, 0.0]
Age (years)	< 45 (n=22)	6.7	5.2	-1.5	[-3.3, 0.3]
	≥ 45 (n=55)	6.3	5.4	-1.0	[-2.1, 0.2]

Source: Reviewer

There was not a significant treatment interaction with age or gender and all point estimates, while not significant, were in favor of Posimir. Region of conduct for the seven studies submitted to support efficacy is shown in Table 23.

Table 23. Geographic location of clinical studies

Study	Region	Phase	Type of control	Surgical Procedure
CLIN-803-006-0006	Oceania	2	placebo	Inguinal hernia
CLIN005-0010	USA/New Zealand	2	placebo	Inguinal hernia
BU-002-IM	Europe	2	active/placebo	Arthroscopic shoulder
C803-017	Oceania	2b	placebo	Arthroscopic shoulder
CLIN005-0006	USA/New Zealand	2	placebo	Arthroscopic Shoulder
803-025	Oceania	3	active/placebo	Major abdominal
BU-001-IM	Europe	2	active/placebo	Hysterectomy

Source: Reviewer

Most of these studies were conducted outside of the United States so I did not examine results for difference in geographic locations. However, the applicant should indicate why they believe these results are applicable to the population in the United States.

4.2 Other Special/Subgroup Populations

There were no other subgroups of interest that were identified or analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In the three studies that evaluated Posimir 660 mg in treating post-surgical pain associated with arthroscopic shoulder repair, only the pivotal study, BU-002-IM, demonstrated a statistically significant treatment effect in favor of Posimir. The two supportive studies provided additional evidence. Although not statistically significant, results favored Posimir. However, when I examined mean PI scores by time there did not seem to be a clinically relevant difference between Posimir 660 mg and placebo beyond 12 hours. Furthermore, since the pivotal study was conducted entirely in Europe, the Applicant should provide evidence that the surgical procedures in Europe are similar to those conducted in the United States.

In the two studies that evaluated Posimir in treating post-surgical pain associated with hernia repair, only the pivotal study, CLIN-803-006-0006, demonstrated a statistically significant treatment effect in favor of Posimir. The supportive study demonstrated, while not significant, a point estimate that was in the wrong direction. It favored placebo. The only notable difference in the two studies was that the failed study was conducted mainly in the United States whereas the successful study was conducted in Australia and New Zealand.

The three supportive studies that evaluated Posimir in other procedures, while not significant, numerically favored Posimir 660 mg when I examined the primary endpoint AUC_{72}.

5.2 Conclusions and Recommendations

In Study BU-002-IM, the analyses of the AUC_{72} and RES_{72} yielded significant differences between Posimir 660 mg and placebo for treating post-surgical pain associated with shoulder surgery. This was supported by various secondary endpoints. Although an AUC is acceptable as the primary efficacy endpoint, differences in AUCs have little clinical interpretation when considering treatment effect size. One can examine the pain scores that make up an AUC to aid in the clinical interpretation. Figure 4 is a graph of the mean PI scores by time that supports the statistical significance of the primary efficacy endpoint, AUC_{72}. The clinical significance of the treatment beyond 12 hours is unclear. There were no concerns regarding the analysis populations, statistical analyses, or imputation of missing data that could not be addressed. The approach to handling rescue medication in the analysis was appropriate.

In Study CLIN-803-0006-06, the analysis of the primary efficacy endpoints, AUC_{72} and RES_{72} demonstrated a significant treatment effect in favor of Posimir 660 mg. This was supported by the analyses of various secondary endpoints such PI scores by time and time to first use of rescue medication. However, Study CLIN005-0010, did not support this conclusion. Based these results and lack of any rationale as to why one study worked and one study failed and the fact that the failed was conducted mainly in the United States, I do not believe the results from the two studies support an indication for treating post-surgical pain associated with hernia repair.

In conclusion, the efficacy of Posimir 660 mg was demonstrated in treating post-surgical pain associated with shoulder repair surgery as indicated by the significance of the pre-specified primary endpoints and was supported by the significance of various secondary endpoints.

Evidence was also provided in two supportive secondary studies. The applicant should provide evidence that these results are applicable to the population in the United States. In my opinion there was not substantial evidence to support the efficacy of Posimir in treated post-surgical pain associated with hernia repair.

5.3 Label Review

Using the label provided in the submission, I have the following comments regarding Section 14. My comments and suggestions follow the Applicant's proposed wording and are italicized. It may be beneficial to include the graph of mean PI scores by time, Figure 4, in the label.

The efficacy of TRADENAME was evaluated in two multicenter, randomized, double-blind, placebo-controlled clinical trials. One trial evaluated the treatment of patients undergoing inguinal hernia surgery; the other trial evaluated the treatment in patients undergoing shoulder subacromial decompression surgery.

There is not sufficient evidence to make the claim of efficacy for hernia repair. Thus, I recommend deletion of that information from the label.

14.1 Inguinal Hernia Repair

A randomized, multicenter, double-blind, placebo-controlled, dose response study of 122 patients undergoing open unilateral tension-free inguinal hernia repair evaluated TRADENAME, 2.5 mL and 5 mL. The mean age of patients was 48 years (range 20 to 79 years).

Study medication was instilled directly into the wound at the conclusion of the surgery, prior to wound closure (as described in section 2.1). Pain intensity was rated by the patients on a 0 to 10 numeric rating scale (NRS). Postoperatively, patients were allowed rescue medication (Tramadol 50-100 mg IV or orally, or equivalent, as needed for moderate to severe pain (maximum 400 mg daily) and acetaminophen 1 g at 6 hour intervals, as needed for mild to moderate pain). The primary outcome measure for pain intensity was the normalized area under the curve (nAUC) of the NRS pain intensity on movement scores collected over the first 72 hour period.

In this clinical study, TRADENAME 5 mL demonstrated a significant reduction of pain intensity compared to placebo (1.1 point mean nAUC reduction [31%] in pain intensity, p= 0.0031) for 72 hours. There was also an attendant significant decrease in opioid consumption over 0-72 hours for patients treated with TRADENAME 5 mL compared to patients treated with placebo (80% reduction in median morphine equivalents, p= 0.0085). The clinical benefit of this reduced opioid consumption was not demonstrated in this clinical study.

I did not recommend labeling for hernia repair. I recommend deletion of this section from the label.

14.2 Shoulder Subacromial Decompression

A randomized, multicenter, double-blind, placebo-controlled study of TRADENAME 5 mL (660 mg) compared to Placebo 5 mL, and to bupivacaine HCl, 20 mL of 0.25% solution (50 mg), was

conducted in 107 patients that underwent arthroscopic subacromial decompression. The mean age of patients was 50 years (range 21 to 70 years).

The above information is consistent with the study report. However, there are no claims supported for the comparison of Posimir to bupivacaine. I recommend removing that statement from the first sentence.

Study medication was instilled directly into the wound at the conclusion of the surgery, prior to wound closure (as described in section 2.1). Pain intensity was rated by the patients on a 0 to 10 numeric rating scale (NRS). Postoperatively, patients were allowed rescue medication (background pain treatment was acetaminophen [500 or 1000 mg depending on patient weight] 4 times a day starting immediately after surgery, patients also had access to morphine as rescue medication, as needed, via 10 mg short acting oral morphine, at a minimum of 1 hour intervals or IV administration of morphine 2 mg, at 5 minute intervals). The primary outcome measure for pain intensity was the normalized area under the curve (nAUC) of the NRS pain intensity on movement scores collected over the first 72 hour period.

The above information is consistent with the study report.

In this clinical study, TRADENAME 5 mL demonstrated a significant reduction of pain intensity compared to placebo (1.3 point mean nAUC reduction [21%] in pain intensity, p= 0.0122) for 72 hours.

I recommend deletion of p-values. Since an AUC may not be readily interpretable, a statement such as "Patients randomized to Posimir experienced less post-surgical pain compared to patients randomized to placebo" may be more appropriate.

There was also an attendant significant decrease in opioid consumption over 0-72 hours for patients treated with TRADENAME 5 mL compared to patients treated with placebo (67% reduction in median morphine equivalents, p= 0.013). The clinical benefit of this reduced opioid consumption was not demonstrated in this clinical study.

I recommend deletion of p-values and % reduction.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID M PETULLO
02/19/2014

JANICE A DERR
02/19/2014

NDA 204803

COMPLETE RESPONSE

DURECT Corporation
10260 Bubb Road
Cupertino, CA 95014

Attention: Jill H. K. Burns
Senior Director, Regulatory Affairs

Dear Ms. Burns:

Please refer to your New Drug Application (NDA) dated April 12, 2013, received April 12, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for POSIMIR (bupivacaine extended-release solution for instillation) 660 mg/ 5mL (132mg/mL), 13.2%.

We acknowledge receipt of your amendments dated April 25 and 26, May 23, June 6, July 2, August, 20, September 3, 10, and 25, October 23, November 6 and 26, and December 6, 20, 30, and 31, 2013, and January 16 and February 3, 2014.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. The application does not contain sufficient information to demonstrate that POSIMIR is safe when used in the manner described in the proposed label. Specifically, we have identified the following deficiencies:

    a. There were adverse events related to the shoulder joint and surrounding tissues in subjects who underwent follow-up assessments at 18 months, after their arthroscopic subacromial decompression surgery. There were insufficient data due to the limited number of subjects and the lack of an appropriate comparator to permit a determination of whether SABER-bupivacaine causes adverse reactions affecting the joint or the surrounding structures to a clinically relevant greater extent than either bupivacaine HCl or a non-SABER containing placebo.

    b. The risk of bruising, hematoma, pruritus, and dehiscence occurred following administration of SABER-containing products (SABER-bupivacaine and SABER-placebo) substantially more often than following administration of bupivacaine HCL. There were insufficient data to determine whether the risk is greater with SABER-bupivacaine than for either bupivacaine HCl or a non-

SABER containing placebo following the surgical procedures studied and whether the risk was greater with only certain surgical procedures.

c. There was a marked increased risk of neurologically related adverse events, i.e., dizziness, dysgeusia, headache, hypoesthesia, paresthesia, and somnolence, which occurred with substantially greater frequency following administration of SABER-containing products compared to bupivacaine HCl. There were insufficient data to determine whether the risk is greater with SABER-bupivacaine than for either bupivacaine HCl or a non-SABER containing placebo following each of the surgical procedures studied and clinical impact of these reactions, e.g., whether they delayed discharge from the post-anesthesia care unit or affected time to ambulation.

Information needed to resolve the deficiency:

Conduct additional studies to adequately characterize the risk profile of SABER-bupivacaine to address the deficiencies listed above. Specifically, the following types of studies need to be conducted:

a. A safety study evaluating the occurrence of adverse reactions associated with the shoulder joint and the surrounding tissues, including the skin, following arthroscopic subacromial decompression. Safety assessments need to be performed at appropriate intervals following the administration of study drug to capture the onset and duration of the reactions and need to be carried out for an appropriate period of time to capture late-onset events. Input should be solicited from expert consultants to help design the study, particularly with respect to appropriate assessments, their frequency and the duration of follow-up.

   The treatments need to include SABER-bupivacaine and either bupivacaine HCL or a non-SABER containing placebo (or both). The study needs to be randomized and double-blinded in design and needs to include enough subjects to detect reactions with an incidence rate of ≥ 1%. Efficacy data must be collected during the study to allow the safety data to be placed in clinical context when the benefit:risk analysis is performed.

   We strongly recommend that you discuss the design of this study with the Division prior to implementation.

b. A safety study evaluating the occurrence of adverse reactions associated with the skin and underlying tissues. Safety assessments need to be performed at appropriate time intervals following administration of study drug to capture the onset and duration of the reactions and to be carried out until complete healing of the surgical wound has occurred. The protocol needs to incorporate standardized definitions for the reactions observed thus far in the clinical development program, e.g., hematoma, ecchymosis, dehiscence, to assure uniform classification of the reactions among investigators.

The treatments need to include SABER-bupivacaine and either bupivacaine HCL or a non-SABER containing placebo (or both). The study needs to be randomized and double-blinded. The study must evaluate subjects undergoing each of the surgical procedures studied to date, with the numbers of subjects undergoing each of the procedures evenly distributed. Efficacy data must be collected during the study to allow the safety data to be placed in clinical context when the benefit:risk analysis is performed.

We strongly recommend that you discuss the design of this study with the Division prior to implementation.

c. A safety study evaluating the occurrence of adverse reactions associated with neurotoxicity. Safety assessments need to be performed at appropriate time intervals following administration of study drug to capture the onset and duration of the reactions and to be carried out for the duration of systemic exposure to benzyl alcohol. The clinical impact of the adverse reactions needs to be captured, e.g., delayed discharge due to somnolence; delayed time to ambulation due to dizziness.

The treatments need to include SABER-bupivacaine and either bupivacaine HCL or a non-SABER containing placebo (or both). The study needs to be randomized and double-blinded in design. The study must evaluate subjects undergoing each of the surgical procedures studied to date, with the numbers of subjects undergoing each of the procedures evenly distributed. Efficacy data must be collected during the study to allow the safety data to be placed in clinical context when the benefit:risk analysis is performed.

We strongly recommend that you discuss the design of this study with the Division prior to implementation.

LABELING

1. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have

such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Ayanna Augustus, PhD, RAC, Sr. Regulatory Project Manager, at ayanna.augustus@fda.hhs.gov or (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Deputy Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RIGOBERTO A ROCA
02/12/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204803

APPEAL DENIED

Durect Corporation
10260 Bubb Road
Cupertino, CA 95014

Attention: Todd D. McIntyre, PhD
Vice President, Regulatory Affairs

Dear Dr. McIntyre:

Please refer to your New Drug Application (NDA) submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Posimir (bupivacaine extended-release solution for instillation) 660 mg/ 5mL (132mg/mL),13.2%.

We also refer to your November 21, 2014, request for formal dispute resolution (FDRR) received on November 21, 2014. The appeal concerned the February 12, 2014 Complete Response letter from the Division of Anesthesia, Analgesia, and Addiction Products.

We also refer to the meeting held between FDA and Durect Corporation on December 16, 2014, hereafter referred to as the FDRR meeting, where the issues raised in your request for formal dispute resolution were discussed.

Dr. Curtis J. Rosebraugh, MD, MPH, has delegated your Office of Drug Evaluation II (ODE II) level appeal to me, the Deputy Director of ODE II.

I have carefully reviewed the materials you submitted in support of your appeal, FDA reviews, including but not limited to the clinical and statistical reviews for NDA 204803, End-of-Phase 2 and pre-NDA meeting minutes, issued on October 12, 2007 and July 27, 2012, respectively, and a Special Protocol Assessment No-Agreement letter issued on September 18, 2008. I have also consulted with Staff in the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), hereafter referred to as the Division, and Dr. Rosebraugh from ODE II.

Your FDDR requested resolution regarding the decision rendered by the Division in the Complete Response (CR) letter, the End-of-Review (EOR)-Cycle meeting held on September 23, 2014, and corresponding minutes to that meeting from the Division and Durect.[1] At the FDRR meeting I informed you that I had reviewed the EOR meeting package and the minutes to this meeting. I was aware that there were differences between Durect's and the Division's minutes captured for this meeting. I informed you that I would not adjudicate the EOR meeting minutes as I was not in attendance at the EOR meeting and would not be able to verify the discussions

[1] Formal Dispute Resolution Request: Type A Meeting Request dated November 21, 2014

that actually took place between the Division and Durect on September 23, 2014. I informed you that I advised the Division to review your meeting minutes and determine if any amendment to FDA's version was appropriate. I reminded you that this is in line with the Agency's policy on resolution of disputes about minutes.[2] The FDRR meeting therefore focused on the Division's Discipline Review (DR) letter issued on January 14, 2014, Durect's response to the DR letter dated February 3, 2014, and the Complete Response letter.

I have completed my review of your request for formal dispute resolution and also considered the discussions at the FDRR meeting and deny your appeal. I describe below the basis for my decision and provide recommendations for two possible paths forward: 1) work with the Division to design a prospective trial(s) to better characterize the benefit-risk profile of Posimir or 2) respond to the CR action through a resubmission addressing the deficiencies based on additional information presented in your EOR background materials and a justification to conclude that this additional information supports a favorable benefit-risk profile of Posimir.

On page 3 of your FDRR, you requested the following:

> "The Agency's agreement that the efficacy and safety of POSIMIR™ (SABER®-Bupivacaine) have been established in the original NDA (204803), and the clarifications offered in the pre-meeting package submitted August 15, 2014 in support of the End-of-Review-Cycle meeting (September 23, 2014)."

You acknowledged that upon "re-reading the NDA in light of receiving the DR letter and subsequent CR letter" you had not unambiguously presented the safety data and that unclear descriptions may have contributed to the Division's CR action. Your proposed corrective action, as described in your EOR meeting package and your FDRR, included more detailed explanations for the safety concerns identified as deficiencies in your NDA, longer-term follow-up information of patients in your arthroscopic shoulder surgery trials, and re-analyses of adverse events related to potential neurotoxicity. While there was some debate at the FDRR meeting as to what constituted new information, I would point to page 7 in your FDRR where you stated the following (with emphasis in bold):

> "Importantly, at the September 23 meeting we did share some **new** information, i.e., that DURECT had conducted a survey of all shoulder investigators after receiving the DRL/CRL…..We recognize that this survey data **was not in the original NDA**, but we do believe that it has value in attenuating concerns."

Please note that throughout this letter I have emphasized what information provided in your FDRR was not in the original NDA, as this is relevant to my final decision on your appeal.

In reviewing the CR letter, I am aware that the deficiencies summarized by the Division dealt only with safety concerns. However, by virtue of your above-stated request, my consideration of your FDRR includes a review of *both* efficacy and safety for your product. This decisional letter

[2] See Section XI. Resolution of Dispute About Minutes in *Guidance for Industry Formal Meetings Between the FDA and Sponsors or Applicants*. http://www.fda.gov/downloads/Drugs/Guidances/ucm153222.pdf

will first discuss efficacy of Posimir followed by safety concerns related to shoulder surgeries, surgical incision site, and potential neurotoxicity.

Efficacy

To evaluate Posimir, "*an extended-release bupivacaine, an amide-type local anesthetic indicated for administration into the surgical incision to produce post-surgical analgesia,*" the primary efficacy endpoints in your pivotal and supportive trials were based on pain-intensity after surgery. In addition, supportive efficacy endpoints included opioid-sparing and reduction in opioid-related side effects.

In the DR letter you were informed that efficacy of Posimir was demonstrated for arthroscopic acromial decompression surgery but not for other surgical procedures. In your response to the DR letter, you presented your arguments for concluding efficacy of Posimir in "soft tissue" surgeries. As noted earlier, the CR letter did not mention efficacy as a deficiency so one might assume that the Division accepted your arguments and agreed that efficacy has been established with Posimir. However, submission of your FDRR requesting my determination of *both* efficacy and safety of your product required me to review all evidence in your NDA. Upon doing so, it was apparent that there was not concurrence on efficacy within the review team.

You submitted the results of 7 active- and placebo-controlled studies in support of efficacy. The following table summarizes these 7 studies. Studies CLIN 803-006-0006 and BU-002-IM were considered pivotal by you.

Table 1. Clinical Studies Reviewed for Efficacy*

Study	Surgery	Treatment Groups		
		Posimir N	SABER-placebo N	Bupivicaine HCL N
CLIN 803-006-0006 CLIN 005-0010	Inguinal hernia	47 21	32 21	
BU-002-IM C803-017 CLIN005-0006	Arthroscopic shoulder	53 40 21	25 20 28	
803-025	Laparotomy (Cohort 1) Lap Cholecystectomy (Cohort 2) Lap-assisted Colectomy (Cohort 3)	26 30 125	 77	17 20
BU-001-IM	Hysterectomy	60	27	27

*Some studies included Posimir 2.5 and 7.5 mL doses which were not included in this table

At the FDRR meeting, I asked the Division to explain the reason why it did not believe efficacy had been established for surgeries other than the arthroscopic shoulder surgeries. Dr. Simone summarized the primary efficacy results for each of the "soft tissue" surgical procedures in Table 1 and noted that while the designated pivotal trial CLIN803-006-0006 met the primary efficacy endpoint analysis for reduced pain in inguinal hernia repairs, another similarly designed trial, CLIN005-0010, failed to demonstrate efficacy. I would add that the FDA statistical review for both these trials also concluded efficacy was demonstrated for CLIN803-006-0006 but not for CLIN005-0010. Furthermore, the statistical reviewer evaluated a supportive measure of

efficacy, proportion of subjects using *all* opioids, not just those coded as rescue medication, and for CLIN803-006-0006, there were fewer patients requiring opioids with Posimir whereas for CLIN005-0010, placebo-treated patients had less post-surgical pain and used less rescue medication.

The inconsistency between these two studies which evaluated efficacy in the same surgical procedure (inguinal hernia repair) could not be attributed to any notable difference in conduct, design or demographics. Even though the failed trial may not have enrolled a sufficient number of patients to demonstrate superiority of Posimir to placebo, one would have at least anticipated a point estimate favoring Posimir.

In your response to the DR letter you stated that the lack of efficacy in CLIN005-0010 was traced to a large imbalance in patient age between the active and placebo groups and reanalyzed the data using an analysis of covariance including treatment as main effect, age as the covariate and the interaction of age and treatment. By pooling the results of the two hernia trials, you were then able to show a statistically significant treatment effect of Posimir over SABER-placebo for hernia repairs. While I am aware of your objection to the Division's previous characterization of your analyses as post-hoc, I would, without reservation, consider this re-analysis as post-hoc as you were clearly aware of the results under the pre-specified analysis plan but determined what differences existed between the two trials and then selected a different analysis based on that information. I also refer you to FDA advice given in your End-of-Phase 2 meeting minutes under Question 11.

> **The mean pain intensity will be analyzed using an analysis of covariance model with site and treatment as factors. You state, "Additional covariates such as baseline characteristics may be included to evaluate their impact on the main ANCOVA findings." Any covariates that are to be included in the primary efficacy analysis should be pre-specified. Additional covariates may be evaluated as exploratory analyses.**

At best, the effect of age on treatment from your analysis should be considered exploratory and not explanatory.

There were four other studies in Table 1 that evaluated the efficacy of Posimir in "soft tissue" surgeries. Trial C803-025 evaluated Posimir in different types of major abdominal surgeries and BU-001-IM was conducted in patients undergoing hysterectomies. The three different surgical procedures in C803-025 were laparotomy (Cohort 1), laparoscopic cholecystectomy (Cohort 2), and laparoscopic assisted colectomy (Cohort 3). Cohorts 1 and 2 employed an active control, bupivacaine HCl, whereas Cohort 3 compared Posimir to SABER-placebo. BU-001-IM compared Posimir to SABER-placebo or bupivacaine HCl.

The following table, adapted from your NDA clinical study report, summarized the primary efficacy results for the three different cohorts in C803-025.

Table 2. Efficacy Results in Study C803-025

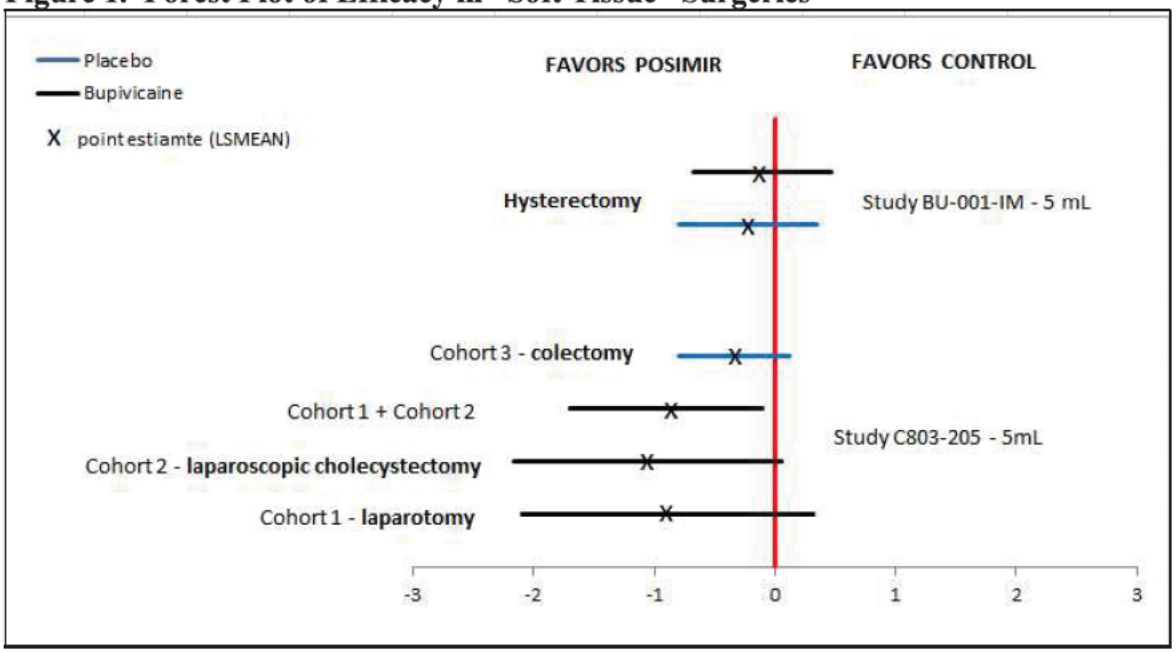
Cohort	Normalized AUC_{72}			p-value
	Control	Posimir 5 mL	Difference (95% CI)	
1	5.8	4.9	-0.9 (-2.1, 0.3)	0.15
2	3.9	2.8	-1.1 (-2.2, 0.05)	0.06
3	5.1	4.8	-0.34 (-0.8, 0.12)*	0.15

*Table 15 in your CSR should have had a negative sign before 0.34. This error has been verified with FDA statistician.

While the treatment difference favored Posimir in all three cohorts, none reached statistical significance. You concluded efficacy based on the pooled analysis of Cohorts 1 and 2; however, the FDA statistical and clinical reviewer deemed such an analysis inappropriate as the two study populations and surgical procedures were different.

In BU-001-IM, the comparison of Posimir to SABER-placebo or bupivacaine favored Posimir but failed to show superiority. Similar to the forest plot submitted in your response to the DR letter (Figure 1 on page 8 of 14), the following plot was created by FDA to summarize only the results from the 4 "soft tissue" surgeries.

Figure 1. Forest Plot of Efficacy in "Soft Tissue" Surgeries



Dr. Simone summarized the above findings at the FDRR meeting, and you commented that other efficacy assessments should be taken into consideration including use of opioid medications. You also presented figures from your EOR meeting package for repeated measures analyses performed to evaluate pain control over the 72-hr post-surgical period. These graphs (page 14 and 15 of your EOR meeting package) were for Studies BU-002-IM (shoulder) and Clin 803-006-0006 (hernia), not the above "soft tissue" surgeries. Furthermore, your briefing material specifically referred to these as "exploratory analyses."

You raised the importance of opioid sparing with Posimir and that this endpoint should be factored in FDA's final benefit-risk assessment. The effect of rescue opioid medications and use of non-opioid analgesics was evaluated by FDA reviewers. In general, if the trial was able to show a statistically significant reduction in pain intensity score (primary endpoint), reduced use of opioids also supported the primary endpoint. Similarly, trials which failed to show superiority of Posimir over comparator also failed to show a statistically significant difference in opioid usage. In other words, the secondary assessment of opioid sparing tracked with the primary efficacy findings, so that in trials in which you were not able to established efficacy on the pre-defined primary endpoint, looking to opioid sparing did not yield a different conclusion.

As an example, your NDA evaluated total morphine equivalent opioid medication use from 0-72 hours in the subgroup of "soft tissue" surgery trials. As has already been described in Figure 1, these trials did not produce a statistically significant treatment effect of Posimir over comparators. In line with that finding, the treatment difference between Posimir and SABER-placebo on total morphine equivalent opioid medication use was not significant.[3] Hence, while we agree that adequate pain management that also leads to reduced opioid use is an important public health finding, this was not consistently evident for the "soft tissue" surgical procedures.

As explained to you at the FDRR meeting, FDA's conclusion regarding efficacy is not based solely on achieving statistical significance on an agreed-upon primary endpoint. The robustness of the finding and consistency of results across multiple subgroups or trials are also factored into our final determination. Secondary endpoints are often considered supportive of an observed benefit based on the primary endpoint. Reliance on secondary endpoints to counter a negative or non-significant finding on the primary endpoint is nearly always deemed inappropriate. Finally, the overall benefits of a therapy cannot be judged with efficacy results alone. The efficacy must be weighed against the risks. Robust and unequivocal efficacy supporting a clinically meaningful treatment effect may justify tolerating certain risks. Marginal or modest efficacy requires more judicious consideration of those same risks.

In conclusion, I acknowledge that you were able to demonstrate efficacy with Posimir in one of your "soft tissue" surgical studies for hernia repair. However, the observation that a similarly designed trial for the same surgical procedure favored placebo and four other "soft tissue" surgical trials failed to show superiority of Posimir over SABER-placebo leads me to conclude that your product's efficacy is modest and inconsistent thereby requiring a more careful consideration of risks.

I would highlight that the DR letter stated that you have adequately demonstrated efficacy of Posimir for arthroscopic acromial decompression surgery. While the benefits of Posimir for this type of surgical procedure still need to be judged against the risks, I would note that, unlike the "soft tissue" surgeries, I did not uncover differing conclusions on efficacy by FDA review staff for this type of shoulder surgery.

[3] Table 18, page 15 of Section 5.3.5.3 of NDA 204803

Safety

The DR letter identified the following safety concerns:

1. For arthroscopic acromial decompression surgery (Trials CLIN005-0006, C-803-017, and BU-002-IM) you have adequately demonstrated the efficacy of SABER-bupivacaine. However, the risk of chondrolysis, based on the incident observed with SABER-bupivacaine treatment, outweighs the benefit of SABER-bupivacaine for this surgical procedure.

2. For the other surgical procedures studied, you have not adequately demonstrated the efficacy of SABER-bupivacaine. In addition, the incidence of somnolence, dizziness, dysgeusia, hematoma, bruising, dehiscence, and pruritus were greater with SABER-bupivacaine, and SABER-placebo treatments than with bupivacaine HCl. Therefore, the risks of SABER-bupivacaine have outweighed the benefits for the non-arthroscopic procedures studied to date.

The CR letter reiterated some of the safety concerns from the DR letter. As I read the chronology of communications between the Division and Durect leading up to this FDRR, including the disputed minutes to the EOR meeting, I have identified instances where FDA communication was not clear. I have brought this to the attention of the Division. As a result, I sought clarification from the Division at the FDRR meeting. Specifically, I asked Dr. Simone if the second deficiency identified in the DR letter pertained only to the other surgical procedures or did some of these concerns involve the arthroscopic shoulder surgeries. He stated that AEs representing potential neurotoxicity concerns (somnolence, dizziness, and dysgeusia) were applicable to all surgeries but the surgical incision site AEs were specific to the "soft tissue" surgeries.

After meeting internally with the Division and considering the discussions at the FDRR meeting I will focus my assessment of safety for Posimir on the following:

1. Chondrolysis and other adverse events related to the shoulder joint and surrounding soft tissues
2. Surgical incision site complications, specifically hematoma and dehiscence
3. Potential neurotoxicity due to the high concentration of benzyl alcohol released acutely

Chondrolysis and Other AEs Related to the Shoulder Joint and Surrounding Soft Tissues

It is my understanding that for arthroscopic shoulder procedures, the concerns regarding chondrolysis were based on the cases identified in the NDA review and you have adequately addressed the specifics of those cases. However, the Division remains concerned about other adverse events related to the shoulder joint and surrounding soft tissue because of the nonclinical findings of chronic granulomatous inflammation in rats and rabbits and because the number of follow-up assessments at 18 months was too limited to address the long-term safety of Posimir.

At the FDRR meeting you referenced consultative reviews by outside pathologists who deemed the nonclinical findings to be a typical reaction to foreign body and subsequent wound healing observed with other approved products. You also referenced long-term follow-up data on patients in your arthroscopic surgical studies, including inquiries of patients out to 3 years post-surgery. You also referenced two published articles, not submitted to the original NDA. One publication, which was submitted in your EOR background package, described no risk of chondrolysis when local anesthetics were instilled only into the subacromial space.[4] The second publication, submitted in response to the DR letter, described that infusion of local anesthetics via a pain pump directly into the joint increased the risk of chondrolysis.[5]

I appreciate the concern raised by the Division on possible permanent damage to the joint based on the prolonged residence time of sucrose acetate isobutyrate (SAIB) in the tissues. This should not be viewed as a minor risk especially if one cannot conclude superiority of Posimir over the referenced approved product, bupivacaine HCl. However, I consider the follow-up data from two extension studies (6 months in BU-002-IM and 18 months in C803-017e) and new information on patients from a survey of investigators that suggest little evidence of chondrolysis or deterioration of shoulder function with follow up out to 3 years relevant for assessment of this potential risk. Although data from the extension studies and the survey are not controlled data, I believe that verifiable evidence of long-term recovery post-exposure to Posimir for a substantial number of patients may address this safety concern. However, as this is new information these data need to be reviewed by the Division first to determine if they adequately address this deficiency.

Surgical Incision Site Complications

For any surgical procedure, the Division identified adverse events related to bruising, hematoma, pruritus, and dehiscence as possible signs of surgical incision site complications. Of these, hematoma and dehiscence were of the most concern because they might result in poor wound healing, increase the risk of post-operative infection, and require additional invasive corrective measures (e.g., incision and drainage or surgical repair).

For hematoma, you explained that the identification of this adverse event through review of verbatim terms identified only a few cases as true hematomas. You further directed me to Table 14 in your EOR background package, which showed similar rates of hematoma across the treatment groups, bupivacaine HCl, SABER-placebo, and Posimir. These hematoma cases required aspiration and drainage, but these patients did not develop poor wound healing nor did they require antibiotics due to a super-infection.

For dehiscence, you acknowledged a greater incidence in the SABER treatment groups but stated that the majority of these cases were superficial breaks of a few subcuticular stitches. However, you did identify two patients who experienced fascial dehiscence (Patients (b) (6) and (b) (6)) and one patient who had a full length superficial dehiscence (Patient (b) (6)). At the FDRR

[4] Busfield BT et al. Sub-acromial pain pump use is safe after arthroscopic rotator cuff repair. *J Orthopaedics.* 2014;11:64-67.
[5] Matsen FA and Papadonikolakis A. Published evidence demonstrating the causation of glenohumoral chondrolysis by postoperative infusion of local anesthetic via a pain pump. *J Bone Joint Surg Am.* 2013; 95-A (12):1126-1134.

meeting you confirmed that all three patients were in the SABER treatment groups and that the patients required surgical repair of the dehiscence, including repeat laparotomy in at least one patient. While three patients represent a small number, all three were in the SABER treatment group and repeat surgery for failed surgical site closure introduces additional risks to the patient.

I did not find your explanation in Table 4 of your response to the DR letter sufficient grounds to ignore the potential seriousness of dehiscence, if due to Posimir. Table 4 summarized three methods for collecting incidence rates of dehiscence in the C803-025 trial, which reported 16 of the 18 adverse events of dehiscence. You directed me to the number of cases reported on Day 30 via a structured wound healing questionnaire conducted by telephone. The question posed to the patient was, "Are there any areas of your wound that are opening or not healing together properly?" This questionnaire captured more events in the control arm (bupivacaine HCl) minimizing the imbalance between bupivacaine and SABER-treatment groups. As per your response to the DR letter, "the apparent imbalance in dehiscence is no longer present" based on the cases captured on Day 30 via telephone. However, at the FDRR, I commented that the question posed via telephone is non-specific and it is conceivable that a patient dissatisfied with the cosmetic appearance of his/her incision site could respond 'yes' and such a response would be counted as a report of dehiscence. You confirmed that affirmative responses were not followed up by a physical exam to determine the seriousness of the AE. Finally, the three cases noted above, which we can all agree to as serious because they resulted in additional surgical corrective time, were captured via spontaneous adverse event reporting – the same methodology in which an imbalance in rates of dehiscence between SABER treatment groups and bupivacaine HCl was observed. Reliance on the less specific questionnaire at Day 30 can obfuscate a true risk associated with Posimir.

At the FDRR meeting you attributed the dehiscence of the three concerning cases to other causes (e.g., large surgical incision site in obese patient and return to manual labor post-surgery). While these other circumstances could be causative, similar circumstances could have also been at play in the control group and yet no serious cases of dehiscence were reported in the bupivacaine HCl group. Regardless, I recognize this was a small database with few events and the imbalance in dehiscence could still be a chance finding. Of course, the limited size of the study also contributed to the difficult risk assessment by the Division.

In conclusion, I cannot dismiss the possibility of increased risk for surgical incision site complications. Of these adverse events, dehiscence is the most concerning. However, you have also presented explanations for some of these cases that may be causative or contributory to the dehiscence and the Division should review the validity of your arguments.

Potential Neurotoxicity Related to Benzyl Alcohol

Concern for potential neurotoxicity stems from the high amount of benzyl alcohol (BA) formulated in Posimir to enable the drug product to remain in solution for instillation. The 5 mL dose of Posimir contains 1210 mg of BA which apparently diffuses and is cleared systemically within 12-24 hrs, with the maximum level at approximately 1 hour post-dose. The Division noted imbalances in somnolence, dizziness, and dysgeusia occurring more frequently in the SABER treatment groups than in the bupivacaine group, and deemed these as possibly related to

benzyl alcohol. In your EOR background document you related the imbalance due to different methods for collecting these AEs (spontaneously reported versus queried) and that when trials utilizing similar methods for assessing potential neurologic AEs were evaluated, the only imbalance noted not favoring Posimir was headaches. At the FDRR meeting I asked if any of the neurologic AEs were deemed serious and both Durect and FDA concurred that these events resolved without serious sequelae. I also noted your analysis of time to discharge from the post-anesthesia care unit (PACU) and saw no difference between treatment groups, even among those patients who reported neurologic AEs.

Overall, I found your responses relevant for reconsideration by the Division; however, as re-analyses of previously submitted data are considered new information, I can not make a determination on your appeal based on this new information prior to the Division's assessment.

Conclusion

Your FDRR requested that I conclude Posimir to be safe and effective based on the data submitted in the original NDA and information provided in your EOR background materials. I have reviewed your FDRR and also held discussions with the Division and met with you at the FDRR meeting. After considering all the facts of your submission, I am denying your request for a determination that efficacy and safety of Posimir have been established in the original NDA.

In reviewing your FDRR and additional materials cited earlier, I believe efficacy is present with Posimir but it is modest and inconsistent across different surgical procedures. My conclusion on efficacy precludes complete dismissal of the safety concerns raised by the Division.

By your own admission, you did not present data in an 'unambiguous' manner and 'unclear descriptions' may have contributed to the CR action. While I would concur with you that your NDA submission and some of your data presentations in the FDRR lacked clarity, I do believe you have made a reasonable attempt to address the deficiencies in the CR letter through re-analysis of current trial data and by providing more extensive explanations of specific cases and new long-term safety data. However, I am unable to consider your re-analyses and new long-term safety data in the determination of efficacy and safety of Posimir, as requested in your FDRR. The *FDA Guidance for Industry and Review Staff on Formal Dispute Resolution: Appeals Above the Division Level*, clearly states that no new information should be submitted as part of a request for reconsideration of appeal. The Guidance also specifically states "new analyses of data previously reviewed should be considered new information".[6] Consequently, the new long-term safety data and re-analyses must first be reviewed by the Division to determine if they adequately address the deficiencies in your program. I would caution that such re-analyses and follow-up data may not fully address the deficiencies because they were not prospectively planned and can, therefore, generate a degree of skepticism on their validity. For this reason I recommend two potential pathways for you to address the deficiencies identified in the CR letter:

[6]http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm343101.pdf

1. Plan and discuss with the Division a prospective trial that will specifically assess the safety concerns related to surrounding tissues of the joint, surgical incision sites, and potential complications of acute exposure to high doses of benzyl alcohol, *or*

2. Prepare for resubmission the materials, re-analyses, and data presentation proposed in your End-of-Review briefing materials. This resubmission will be classified as a Class 2 resubmission as it will, at a minimum, include additional long-term data on patients not previously reviewed in the NDA. You are encouraged to discuss with the Division your proposed resubmission, which will be subject to a 6-month review cycle and may also be presented before a public advisory committee meeting should the Division deem it necessary to seek outside expert opinion on your application.

Questions regarding next steps as described in this letter should be directed to Ayanna Augustus, Regulatory Health Project Manager, Division of Anesthesia, Analgesia, and Addiction Products, at (301) 796-3980.

This constitutes the final decision at the ODE II level. If you wish to appeal this decision to the next level, your appeal should be directed to John Jenkins, MD, Director, Office of New Drugs, Center for Drug Evaluation and Research. The appeal should be sent to the IND administrative file as an amendment, and a copy should be sent to the Center's Formal Dispute Resolution Project Manager, Ms. Khushboo Sharma. Any questions concerning your appeal should be addressed to Ms. Khushboo Sharma at (301) 796-1270.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Deputy Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
01/15/2015