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CLINICAL REVIEW(S)

CLINICAL REVIEW

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(Proposed) Trade Name	Posimir
Applicant	DURECT Corporation
Dosage Form(s)	Solution for infiltration
Applicant Proposed Dosing Regimen(s)	660 mg/5 mL for instillation into the surgical wound
Applicant Proposed Indication(s)/Population(s)	For single-dose instillation into the surgical site to produce post-surgical analgesia
Recommendation on Regulatory Action	Complete Response Action

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
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
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

NDA 204803, Posimir
Bupivacaine solution for infiltration use

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

1. Executive Summary

1.1. Recommendation on Regulatory Action

This is the second review cycle for SABER-bupivacaine, a new formulation of the local anesthetic bupivacaine developed with the intent to extend the duration of postsurgical analgesia beyond that provided after administration of immediate-release bupivacaine. The original NDA action was a Complete Response (CR). As articulated collectively in the CR Letter (CRL), End-of-Review Cycle Meeting minutes, and Formal Dispute Resolution Letter, the original NDA failed to adequately define the safety of the drug product, particularly its effects on the central nervous system (CNS) and surgical wound healing. To address the clinical deficiencies identified, the Agency required the Applicant to conduct an additional clinical study to better characterize the benefit-risk profile of SABER-bupivacaine or submit all the information provided in the End-of-Review meeting background materials with justification as to why it is supportive of a favorable benefit-risk profile for SABER-bupivacaine.

For this resubmission, I recommend a CR Action based on inadequate information to resolve the previously identified deficiencies surrounding observed imbalances in the incidence of certain adverse events in SABER-treated patients compared to patients treated with a non-SABER control. Specifically, the PERSIST study was designed to address the CNS- and wound-related adverse events that had been observed more frequently in SABER-treated patients in previously conducted clinical studies, and to provide supportive information for Posimir's safe use as a postsurgical analgesic. Results from this study, however, demonstrated similar imbalances in the incidence of specific adverse events, including visible bruising in both parts of the study, surgical site bleeding in Part 1, and drainage from surgical incisions, wound hematoma, and surgical site infection in Part 2. Therefore, there are unresolved safety issues that appear to be related to administration of a SABER-containing product.

Additionally, the totality of the data indicate that SABER-bupivacaine is unlikely to be consistently effective in reducing acute post-operative pain in clinical practice. Specifically, there were conflicting efficacy results observed in the two inguinal hernia repair studies (Studies CLIN803-006-0006 and CLIN005-0010), the only soft tissue model to demonstrate statistical significance on the primary efficacy endpoint. Based on these reasons, in combination with the risks associated with inadvertent intravascular injection discussed during, and subsequent to, the Advisory Committee meeting, discussed below, there are insufficient data to support approval of SABER-bupivacaine for the proposed broad indication of post-surgical analgesia.

The Division Director is recommending approval of SABER-bupivacaine for limited use in a single surgical population, arthroscopic subacromial decompression. If that were not the course of regulatory action taken, I would recommend the following deficiencies be conveyed to the Applicant along with the information required to address them.

Deficiency 1

You have not demonstrated that the potential risks associated with benzyl alcohol exposure and those associated with the surgical wound(s) outweigh the benefits of SABER-bupivacaine administration during soft tissue surgical procedures. While the reanalyses of safety data from studies completed in support to the original NDA submission appear to improve the safety profile of SABER-bupivacaine, results from the PERSIST study indicate there are on-going and unresolved safety concerns. Specifically, in Part 1 of the study there was an increased incidence of somnolence, dizziness, headache, dysgeusia, peri-incisional bruising, and surgical site bleeding in patients treated with SABER-bupivacaine compared to those treated with saline placebo. In Part 2 of the study, there was an increased incidence of somnolence, headache, pruritis, dysgeusia, peri-incisional bruising, drainage from the surgical site, wound hematoma, and surgical site infection in patients treated with SABER-bupivacaine compared to those treated with bupivacaine HCl.

Information needed to address this deficiency

Because the results from the PERSIST study have not adequately addressed the safety concerns potentially associated with benzyl alcohol exposure and the surgical wound(s), you need to conduct an additional study in a soft tissue model to further characterize these adverse events. This study must include a non-SABER comparator and we strongly recommend use of an active comparator treatment.

Deficiency 2

The totality of the data does not support the proposed indication. In the soft tissue surgical procedures evaluated, you have not adequately demonstrated the efficacy of SABER-bupivacaine.

Information needed to address this deficiency

Demonstrate the efficacy of SABER-bupivacaine by conducting one or more additional studies in a soft tissue surgical model. Although you may evaluate a surgical procedure previously evaluated during your clinical development program, we are concerned about conflicting efficacy data, similar to what has occurred in the inguinal hernia model evaluations. Use of a non-SABER placebo and an active comparator group is strongly recommended. Evaluated efficacy endpoints should reflect what is currently known about the duration and extent of postsurgical analgesia after administration of SABER-bupivacaine.

During the Advisory Committee meeting, several members emphasized the risk of inadvertent intravascular injection and the potential catastrophic outcome. Based on internal discussions and responses to Information Requests post-AC meeting, the pharmacology-toxicology review team concluded that, "Based on the data to date, we cannot state that there is minimal risk should the product be injected intravascularly. If the potential risks of the inadvertent injection of Posimir and clinical mitigation strategies and risk assessments provided by the Applicant are not considered to be sufficient to dismiss potential safety concerns, ... nonclinical studies to

investigate the potential toxicity of inadvertent intravascular injection can be conducted to further inform the benefit:risk profile for this product and inform labeling in case of overdose or Local Anesthetic Systemic Toxicity (LAST).” If the Division Director was in agreement with the CR action for this application, the following nonclinical deficiencies would be conveyed to the Applicant.

Nonclinical Deficiency 1

You have not adequately characterized the potential toxicity of your drug product if it is inadvertently administered into the intravascular space. To address this deficiency, conduct a nonclinical intravenous toxicity study that includes both an acute and delayed timepoint with full histopathology to determine the ultimate impact of the drug product and fate of the vehicle. The study should include collection of pharmacokinetic data to determine if intravascular injection results in more rapid release of the bupivacaine dose from the vehicle. We recommend a small pilot study prior to the pivotal study to confirm that IV administration does not result in catastrophic moribundity.

Nonclinical Deficiency 2

You have not provided adequate data to conclude that standard treatments with lipid infusions can be effective if LAST were to occur following use of this drug product. Conduct a nonclinical toxicology study to confirm that lipid infusions will counteract the adverse effects due to LAST or provide adequate justification that lipid infusions will be successful to treat LAST should this occur in the clinical setting. Ultimately, provide recommendations on how prescribers should treat LAST should it occur following use of this drug product.

Because Posimir will be approved for a limited post-surgical analgesic indication, these nonclinical deficiencies will be addressed via post-approval studies. Refer to the review completed by Dr. Misol Ahn for additional information.

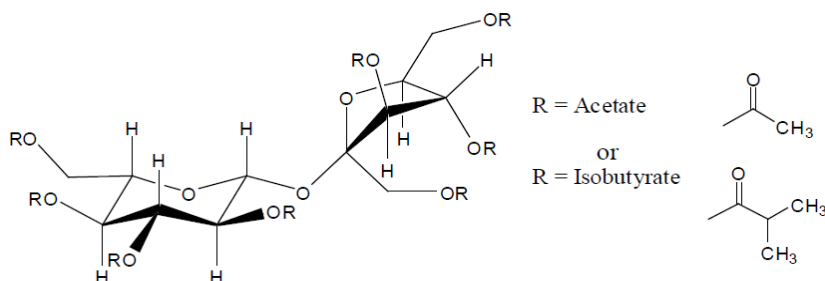
1.2. Product Introduction

SABER-bupivacaine solution is composed of 12% bupivacaine (132 mg/mL) in 22% benzyl alcohol (BA; (b) (4)) and 66% sucrose acetate isobutyrate (SAIB; (b) (4)). The proposed route of administration is direct instillation of the solution into surgical wound(s) prior to closure. BA, an aromatic alcohol used in a variety of cosmetic formulations and as a food additive, reduces the viscosity of the SABER-bupivacaine solution and after administration, rapidly diffuses into the surrounding tissue and is cleared from circulation within 24 hours. The amount of benzyl alcohol in the 5 mL dose of SABER-bupivacaine is 1210 mg, a dose close to the 1000 mg of benzyl alcohol contained in the approved parenteral drug product, Faslodex (NDA 21344). The pharmacology-toxicology review team considered the slightly increased exposure after administration of SABER-bupivacaine acceptable based, in part, on the fact that Faslodex is administered biweekly for three doses and then monthly, so the cumulative benzyl alcohol exposure is higher than that observed after single-dose administration of SABER-bupivacaine. It

is important to note that Faslodex is approved for a form of breast cancer, thereby justifying greater risk than that associated with administration of an extended-release local anesthetic.

SAIB, pictured below, is a strongly hydrophobic, biodegradable, fully esterified sucrose derivative with isobutyrate and acetate, and when added to bupivacaine, forms a viscous depot of bupivacaine, which is then released over 72 hours into the surgical site.

Figure 1. SAIB Structural Formulation



Source: Type C, End-of-Review Meeting Background Package, Aug. 14, 2014, p. 6 (PDF).

The Applicant has indicated, based on results from their pharmacokinetic (PK) evaluation, there is no evidence of bupivacaine dose-dumping and that it can be measured in the plasma for up to 72 hours after administration. The clinical pharmacology and biopharmaceutics review teams agreed with the Applicant and felt that the risk of dose-dumping in the context of surgical wound administration was low. Additionally, they did not think that bupivacaine release from the SABER formulation would occur in the presence of an isotonic salt solution, such as normal saline, based on the hydrophobic components in the formulation. The SAIB component remains in the tissues for an indeterminate period of time, but may be as long as one year based on nonclinical data. SABER-bupivacaine is also reportedly stable at room temperature and is administered via a needle-less syringe or through a large gauge needle or catheter.

For purposes of this clinical review, the nomenclature for the investigational product will include SABER-bupivacaine and Posimir™ (the proposed tradename). The general term of SABER products includes SABER-bupivacaine and SABER-placebo.

1.3. Conclusions on the Substantial Evidence of Effectiveness

As described in Section 7.2 of this review, the Applicant identified a total of six adequate and well-controlled studies, two of which the Applicant has characterized as “pivotal.” All studies used a placebo control; five used SABER-placebo and one used saline placebo. Two studies included a bupivacaine control. DURECT argued that the other completed studies should be de-emphasized in the assessment of effectiveness.

The clinical development program for SABER-bupivacaine demonstrated a statistically significant decrease in pain scores with movement when compared to SABER-placebo in two

Phase 2 clinical studies: open inguinal hernia repair and arthroscopic subacromial decompression. However, the totality of the data from the original NDA submission (received April 12, 2013) and the NDA resubmission (received June 27, 2019) does not support a clinically significant effect of SABER-bupivacaine administration for five reasons.

First, there was conflicting efficacy data from the surgical models upon which the Applicant is claiming effectiveness. Specifically, additional studies conducted in the same (i.e., inguinal hernia repair) or similar (i.e., arthroscopic subacromial decompression plus other rotator cuff procedures) surgical models did not demonstrate improved pain scores with movement over SABER-placebo. Furthermore, the clear separation of pain curves between SABER-bupivacaine and SABER-placebo was noted over 0 to 24 hours and the separation from 24 to 72 hours was of a lower magnitude, such that statistical significance was driven by an early, versus extended, analgesic benefit.

Second, only a single orthopedic (boney) surgical site was evaluated. Previous applications may have been approved based efficacy (and safety) data from a single boney model. The Division's current thinking, however, is that the demonstration of efficacy in a single study in a single orthopedic model is not supportive of a broad post-surgical analgesic indication, but that it may support a narrow site- or procedure-specific indication. Similarly, of all the soft tissue models evaluated in the Applicant's clinical development program, only a single study in a single model showed statistically significant improvement in pain scores.

Third, the demonstration of efficacy was compared to SABER-placebo treatment. While the regulatory threshold for evaluation may include statistically significant differences from placebo treatment, the Division's current thinking is that approval of the newer, extended-release, reportedly longer-acting, local anesthetic formulations is dependent upon evaluations compared to standard of care treatment, which is immediate-release bupivacaine. In the studies in which SABER-bupivacaine was compared to bupivacaine HCl, a statistically significant difference in pain with movement was not demonstrated, therefore, the benefit of this product over immediate-release bupivacaine HCl has not been demonstrated. The demonstration of marginal efficacy in combination with unresolved safety concerns does not support approval for broad postsurgical administration.

Fourth, the statistically significant difference in pain scores in patients treated with SABER-bupivacaine and SABER-placebo is not clinically meaningful. Specifically, the pivotal studies (as designated by the Applicant) in inguinal hernia repair and arthroscopic subacromial decompression demonstrated only a modest improvement in mean pain intensity; a 1.1 to 1.3 difference, on an 11-point pain scale, above SABER-placebo treatment for mean pain intensity on movement over 72 hours' post-surgery. It is hard to imagine how such a small change in post-operative pain above that observed from a placebo treatment would provide any meaningful benefit to the patient. And lastly, in patients in whom SABER-bupivacaine is not efficacious in managing post-operative pain, alternate treatment is limited to oral or IV analgesics, including opioids. Additional administration of local anesthetics through 96 hours

will be contraindicated based on the PK evaluation of SABER-bupivacaine.

For these reasons, I do not recommend approval of SABER-bupivacaine. An argument could be made that because a statistically significant difference in pain with movement was demonstrated in two studies in two different surgical models, SABER-bupivacaine could be approved for use in arthroscopic subacromial decompression alone and inguinal hernia repair, as was the apparent recommendation subsequent to the clinical review of the original NDA. However, I do not recommend that based on ongoing wound-related and CNS-related safety concerns, discussed in detail in Section 8. Furthermore, while mitigating off-label, broad postsurgical use may not be within the purview of the Agency, in the context of the ongoing opioid crisis and the intense pressure for clinicians to reduce opioid analgesic prescribing and use, it is clear that this would be a major problem with approval of this drug product for a narrow indication.

1.4. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Bupivacaine HCl was first approved in the United States in 1972 (NDA 016964) and has been widely used in the management of postsurgical pain, as well as other painful conditions, since that time. It is safe and effective for use via wound infiltration, peripheral nerve blockade, and neuraxial anesthesia in a variety of clinical settings and for a range of surgical procedures. Based on the well-known safety profile and demonstrated effectiveness, in combination with the ongoing opioid epidemic, there is considerable interest in developing bupivacaine products with extended-release profiles in an effort to prolong the analgesic effect. Currently, there are no such products marketed. DURECT has developed SABER-bupivacaine, a formulation of bupivacaine in a sucrose acetate isobutyrate formulation, in an attempt to extend the duration of action of bupivacaine such that post-operative opioid analgesic use is reduced.

The clinical development program for SABER-bupivacaine demonstrated a decrease in pain intensity with movement through 72 hours' post-operatively compared to SABER-placebo when administered during arthroscopic subacromial decompression (Study BU-002-IM) and open inguinal hernia repair (Study CLIN803-006-0006). For Study BU-002-IM, the second primary efficacy endpoint of opioid rescue analgesia through 72 hours was also statistically significant. The secondary efficacy endpoints of pain scores at each time point and time to first opioid rescue supported the primary findings. For Study CLIN803-006-0006, the second primary efficacy endpoint of proportion of patients receiving opioid rescue through 72 hours was not statistically significantly different between treatment groups when all opioid use was considered (versus only that coded as 'rescue'). There was, however, a statistically significant difference between treatment groups in time to first opioid rescue use.

The interpretation of the results from these studies, however, is challenging based on the inconsistent demonstration of efficacy in any of the many other surgical models evaluated, including laparotomy, laparoscopic cholecystectomy, laparoscopic-assisted colectomy, abdominal hysterectomy, and more invasive and open shoulder procedures. Additionally, there was a second study conducted in patients undergoing open inguinal hernia repair which failed to demonstrate efficacy. Subsequent to issuance of the CRL, the Applicant conducted a study in patients undergoing laparoscopic cholecystectomy, mainly to address the identified safety concerns, but to also provide additional efficacy information. The two parts of the study included administration of saline placebo in Part 1 and bupivacaine HCl in Part 2. A statistically significant difference in pain intensity with movement, through 72 hours for Part 1 and 48 hours for Part 2, between SABER-bupivacaine and the respective comparator was not demonstrated. There were no statistically significant differences in any secondary efficacy endpoints, including total IV morphine-equivalent dose and proportion of patients taking no opioid rescue. No patient in either part of the study in any treatment group was opioid-free post-operatively.

The totality of the efficacy data suggests that while a clinical benefit of administration of SABER-bupivacaine may have been demonstrated in

two surgical models, this benefit was not consistently replicated and never duplicated. Furthermore, in studies which included a bupivacaine treatment group, SABER-bupivacaine failed to demonstrate added clinical benefit. It appears that these studies were designed for patients in the bupivacaine treatment groups to have less analgesia (i.e., low-dose and lack of epinephrine). Lack of consistent efficacy compared to placebo or low-dose, epinephrine-free bupivacaine presents real challenges to conclusions about effectiveness for this product.

The Applicant has indicated that a potential benefit of SABER-bupivacaine over injectable bupivacaine products is the proposed route of administration, instillation via a needle-less syringe, during soft tissue surgical procedures. The Applicant has indicated that the risk of inadvertent intravascular administration is low based on the route of administration, surgeon (versus anesthesiologist) administration, and the improbability of drug swapping or medication errors (due to the viscosity and amber color of SABER-bupivacaine). Several members of the Advisory Committee, however, voiced concern during the meeting about the proposed use of a large bore needle to draw the SABER-bupivacaine into a syringe, and because little is known about the ability to safely rescue patients using either supportive measures, including cardiopulmonary bypass, or lipid emulsion therapy, a nonclinical study may be required. Additionally, some members suggested that inclusion of a device for drug withdrawal may mitigate intravascular injection if a needle is never attached to the syringe.

Regarding the risks and safety concerns associated with administration SABER-bupivacaine, the application received a Complete Response during the first review cycle based on the following:

- Insufficient data to fully characterize adverse events 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 (i.e., dizziness, dysgeusia, headache, hypoesthesia, paresthesia, and somnolence) in patients treated with SABER products.

In response to the CR letter, the Applicant conducted four additional evaluations in patients previously treated in the clinical studies submitted in support of the original NDA. These evaluations included orthopedic surgeons re-reading MRIs concerning for chondrolysis, a radiologist and orthopedic surgeon 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. The majority of treated patients in all shoulder studies had follow-up data available for review and it did not appear that there were definitive cases of chondrolysis. It is worth noting, however, that only a single study (BU-002-IM) used a non-SABER comparator, such that there is limited comparative information available.

The Applicant's evaluation of wound-related adverse events consisted of analysis of additional safety information provided from previously completed studies and data from the PERSIST study. The totality of the data suggests that there is an increased incidence in peri-incisional

bruising and hematoma in patients treated with SABER-bupivacaine, which is likely due to the reported vasodilation, inhibition of platelet aggregation, and hemolysis associated with SABER-bupivacaine administration. There also appeared to be an increased incidence of surgical site bleeding (generally involving the umbilical incision) categorized as 'soaked dressing' and surgical site infection in patients treated with SABER-bupivacaine in the PERSIST study. An additional concern regarding administration of SABER-bupivacaine is the persistence of the SAIB component in tissues for up to one year and the potential for foreign body reactions, as reported in nonclinical studies. Because there is the possibility of future surgical procedures in the same anatomic location, residual SAIB formulation or excessive scar tissue may result in more challenging surgical dissection, longer operating and anesthetic times, increased blood loss and risk of transfusion, increased risk of damage to surrounding tissues and organs, and post-operative pain. In the PERSIST study, there was an increase in mean creatine kinase levels on study day 4 in patients treated with SABER-bupivacaine, suggesting that there may also be muscle damage indicative of a more extensive local reaction.

Similar to the evaluation of wound-related adverse events, the Applicant's evaluation of nervous system adverse events possibly related to benzyl alcohol exposure consisted of analysis of additional safety information provided from previously completed studies and data from the PERSIST study. The Applicant stated that the previously observed imbalance in these adverse events was the result of spontaneous versus solicited adverse event reporting, such that cross study comparisons may not reflect the true incidence. The Applicant 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. In the PERSIST study, there was an observed increased incidence in somnolence (Part 1 and 2), headache (Part 1), and dysgeusia (Part 1 and 2) in patients treated with SABER-bupivacaine compared to those treated with a respective control. Nausea and vomiting were reported with an increased incidence in patients treated with bupivacaine HCl. Because benzyl alcohol has a relatively short half-life, as described in the Applicant's PK evaluation, nervous system adverse events which occurred within six hours of administration were evaluated. It appears that patients treated with SABER-bupivacaine had an increase incidence of somnolence, headache, pruritus, and dysgeusia when compared to patients treated with saline placebo or bupivacaine HCl within six hours of administration. An argument could be made that these adverse events occurred with a low incidence, are non-specific, and could be related to the administration of general anesthesia; however, until more comparative data are available with non-SABER treatment groups, exposure to benzyl alcohol is presumed to be the cause.

There did not appear to be any cases of LAST reported throughout the clinical development program. As discussed during the Advisory Committee meeting, there is limited information available regarding the risks associated with inadvertent intravascular injection of SABER-bupivacaine and the required resuscitation effort, including both the duration and scope. Additionally, the concerns surrounding intravascular injection extends to the SABER vehicle, including SAIB and benzyl alcohol, and include the formation emboli and intravascular hemolysis. The Applicant's proposed mitigation primarily includes clear labeling language, including a box warning for embolic risk. The pharmacology-

toxicology review team concluded that if the clinical mitigation strategies and risk assessments were not adequate to address the safety concerns associated with inadvertent intravascular injection, nonclinical studies would be need pre-approval.

In conclusion, the limited analgesic benefit of SABER-bupivacaine administration in patients undergoing any surgical procedure evaluated to date does not outweigh the identified safety risks. As was the case during review of the original NDA, an argument could be made that the demonstration of efficacy in a single soft tissue and a single orthopedic study is sufficient to recommend approval of SABER-bupivacaine for administration during those procedures only and that these results meet the statutory requirements for effectiveness. However, it appears that consideration for approval for limited indications results in additional challenges and liabilities. Specifically, approval for use in inguinal hernia repair alone is complicated by the fact that a similar study in the same surgical model did not win on the primary efficacy endpoint, so inclusion of results in the label from a study that won and a study that lost appears contradictory and not at all useful for the clinician. Additionally, approval for use in subacromial decompression alone is complicated by the relatively benign nature of the procedure and the route of administration using a large bore needle, an issue discussed extensively during and after the AC meeting. Furthermore, based on clinical experience with another bupivacaine formulation advertised as having an extended-release profile, a limited label indication is unlikely to prevent widespread post-operative administration, particularly in the context of the current opioid epidemic.

Because the majority of clinical studies included SABER-placebo only, there are limited comparative data available for non-SABER controls, such that the true incidence of wound and nervous system adverse events related to the SABER vehicle is difficult to determine. Describing the identified safety concerns in the drug product label is a potential mitigation strategy; however, in my clinical judgment, that would not limit use or prevent the occurrence of wound- and nervous system-related adverse events in a large percentage of post-operative patients. Therefore, the risk to surgical patients is too high to justify approval of SABER-bupivacaine for a limited post-operative analgesic benefit.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Inguinal hernia repair is a common soft tissue surgical procedure, performed either laparoscopically, Robot-assisted, or via the open technique. The open procedure is generally reserved for large, incarcerated, or strangulated hernias, or for patients with a history of previous major abdominal surgery. Postsurgical pain is generally increased	While exposure to bupivacaine may be low in the general population, patients undergoing a surgical procedure have a high likelihood of receiving bupivacaine. Post-market exposure to SABER-bupivacaine is anticipated to be higher in males undergoing inguinal hernia repair than females, based

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	after open inguinal hernia repair compared to laparoscopic or Robot-assisted repairs. • Arthroscopic subacromial decompression is not a procedure generally performed in isolation, but is performed in combination with other procedures including, but not limited to, acromioclavicular debridement, distal clavicle excision, and rotator cuff repair. The more invasive procedures and those involving the rotator cuff tend to cause substantial post-operative pain and are generally managed with a brachial plexus nerve block (i.e., interscalene nerve block). Pain after subacromial decompression alone can be managed with administration of local anesthetic either into the subacromial space and/or the port sites. • A large number of surgical procedures, including arthroscopic subacromial decompression and open inguinal hernia repair, are performed in outpatient ambulatory surgical centers, where adequate postsurgical pain management is key to maintaining efficiency, lowering health care costs, and improving patient satisfaction. • Rapid onset and extended duration of action are the goals of all postsurgical pain management strategies and while there are a number of opioid analgesics that meet these criteria, the large numbers of opioid-related adverse events and deaths are a clear indication that alternate treatment options are needed.	on the disease process and anatomic differences. The exposure will likely be similar in males and females undergoing arthroscopic subacromial decompression. Both inguinal hernias and shoulder pathology can be bilateral and can require re-exploration and/or intervention, potentially resulting in repeat exposure to bupivacaine products, either in the same or a new location. Inguinal hernia repair is an ideal surgical model to evaluate the safety and efficacy of local anesthetic products because it is a common and relatively benign surgical procedure, and rarely results in life-threatening complications. Arthroscopic shoulder surgery is a more challenging model to evaluate the safety and efficacy of local anesthetic products for two reasons. First, based on concerns regarding the development of glenohumeral joint chondrolysis, clinicians are hesitant to administer bupivacaine products into the shoulder. And second, peripheral nerve block is likely the most common anesthetic technique employed for patients undergoing arthroscopic or open shoulder procedures. Subacromial decompression in isolation does not typically require administration of a nerve block, such that would infiltration is more likely in this model.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Current treatment options for postsurgical pain include the following: - opioid analgesics - non-opioid analgesics - local anesthetics for wound infiltration, peripheral nerve blockade, or neuraxial anesthesia - non-traditional strategies, including acupuncture and massage therapy - physical therapy • Of the local anesthetics available for postsurgical pain management, lidocaine, ropivacaine, and bupivacaine, with and without epinephrine, are the most commonly used. Ropivacaine and bupivacaine are considered longer-acting than lidocaine and generally provide up to six hours of postsurgical pain relief when administered via wound infiltration. • There are currently no approved local anesthetics with an extended-release profile that have demonstrated reliable prolonged postsurgical analgesia. A continuous infusion of a dilute concentration of bupivacaine via a peripheral nerve or neuraxial catheter appears to be the only available mechanism to prolong the duration of action of bupivacaine. This route of administration, however, is contraindicated in patients undergoing shoulder surgery, based on case reports of post-operative chondrolysis.	While there are several marketed, approved bupivacaine products for use in the management of postsurgical pain, none have an extended-release profile that reliably and significantly prolongs postsurgical analgesia beyond that observed with administration of immediate release bupivacaine.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Benefit</u>	• Bupivacaine has been used for decades in the treatment of postsurgical pain when administered for wound infiltration, peripheral nerve blockade, or neuraxial anesthesia/analgesia. It is an effective local anesthetic with a well-established safety profile. • For soft tissue surgical procedures, bupivacaine is most commonly administered via wound infiltration, which reduces postsurgical pain for a short period of time, generally up to six hours. For orthopedic procedures of the upper or lower extremities, bupivacaine is administered either via wound infiltration, peripheral nerve block, or for neuraxial anesthesia. Depending on the technique, postsurgical analgesia can last for several hours or days, if necessary. • For soft tissue surgical procedures, the route of administration, via wound instillation without a needle, confers a degree of safety not currently observed with injectable bupivacaine products • Well-controlled post-operative pain results in the following: - Improved patient outcomes, including decrease length of hospital stay - Improved patient satisfaction, which may translate into reimbursement assurances - Less time lost from work and school - Ability to perform procedures on an out-patient basis - Improved mobility and ambulation, and less time for return to baseline function, depending on the procedure performed	Approval of SABER-bupivacaine would offer clinicians an additional bupivacaine product to administer for postsurgical pain management after open inguinal hernia repair and arthroscopic subacromial decompression. SABER-bupivacaine does have a delayed T_{max} compared to immediate-release bupivacaine and appears to improve post-operative analgesia through 72 hours compared to placebo treatment. The clinical development program for SABER-bupivacaine conducted by the Applicant demonstrated a statistically significant decrease in pain intensity with movement through 72 hours' post-operatively compared to SABER-placebo when administered during arthroscopic subacromial decompression and open inguinal hernia repair. Post-operative opioid rescue analgesia was also decreased in patients treated with SABER-bupivacaine compared to SABER-placebo after subacromial decompression, but not after open inguinal hernia repair. The route of administration, instillation via a needle-less syringe or blunt tip catheter, likely confers a degree of safety during soft tissue surgeries above injectable bupivacaine products. While intravascular exposure to SABER-bupivacaine can still occur and result in toxicity, inadvertent direct injection seems unlikely.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Potential decreased health care cost and burden due to short-term disability	
Risk and Risk Management	The safety issues of greatest concern with administration of SABER-bupivacaine include the development of LAST, shoulder joint adverse events, wound-related adverse events, neurological adverse events possibly related to benzyl alcohol exposure, and residual SAIB in the wound and the associated foreign body reaction(s). <u>LAST</u> - Factors influencing the development of LAST include the site of administration and total dose administered. The proposed dose of bupivacaine in SABER-bupivacaine, 660 mg, is substantially higher than the recommend dose in the Marcaine™ product label, 175 mg without epinephrine. Use of a higher than currently recommended dose may lead to increased incidence of LAST depending on the surgical location, specifically the vascularity of the surrounding tissue. - Because the PK profile of SABER-bupivacaine is variable in the surgical populations evaluated, use of the product in other surgical models or for other painful conditions is not recommended. Bupivacaine has a long history of clinical use and the safety profile is well-established, however, it is highly cardiotoxic and increased systemic exposure poses the greatest risk for the development of toxicity. SABER-bupivacaine instillation into highly vascular sites is likely to increase the risk	There were no reported cases of LAST throughout the Applicant's clinical development program, despite some patients (in all studies with available PK data) having serum bupivacaine concentrations > 1000 ng/mL. It is worth noting that because the preference is to perform surgical procedures in an out-patient setting, a large number of patients who receive SABER-bupivacaine will be in an unmonitored setting at C_{max}. The proposed route of administration of SABER-bupivacaine in soft tissue procedures appears to minimize the risk of intravascular injection; however, administration during arthroscopic shoulder procedures does require use of needle, thereby increasing the risk of an intravascular injection. Because there are inadequate nonclinical data to define this risk, it appears that the resulting toxicity of intravascular SABER-bupivacaine administration would be catastrophic and require extensive and prolonged resuscitation, based on exposure to the SAIB vehicle and the risk of emboli, and exposure to bupivacaine 660 mg and the risk of LAST. Adverse events related to the shoulder joint were thoroughly evaluated during the Applicant's drug

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	above what has been characterized in the Applicant's clinical studies. • An additional concern regarding the variable PK profile of SABER-bupivacaine is the likelihood of patients being in an unmonitored setting during maximum plasma concentration (C_{max}), a time when the risk of toxicity is the highest. This can potentially be mitigated by adequate and comprehensive patient education regarding the signs and symptoms associated with bupivacaine toxicity. <u>Shoulder Joint Adverse Events</u> • The Applicant submitted additional safety information from previously completed studies, suggesting that there was no clinically significant difference in glenohumeral joint function or pain in patients treated with SABER-bupivacaine. • The data from Study BU-002-IM, the single study which evaluated a non-SABER comparator, bupivacaine, was the least supportive of the safety of SABER-bupivacaine administration during arthroscopic shoulder surgery. Specifically, mean change from baseline Constant-Murley (C-M) scores was the lowest (less subjective and objective improvement) in patients treated with SABER-bupivacaine at the 6-month follow-up visit. Furthermore, of the seven patients with worsening C-M scores post-operatively, five were treated with SABER-bupivacaine and two were treated with SABER-placebo. None were treated with bupivacaine HCl. The 6-month follow-up MRIs did not	development program and, in general, it does not appear that there are any consistent, clinically significant changes in the glenohumeral joint after administration of SABER-bupivacaine to patients with an intact rotator cuff. The safety profile in patients with substantial rotator cuff tears has not been evaluated and is not recommended based on previous findings of chondrolysis in patients receiving continuous bupivacaine infusions into the joint capsule. Wound-related adverse events, including bruising, hematoma, pruritus, and dehiscence, were reported with increased frequency in patients treated with a SABER-product compared to patients treated with bupivacaine HCl. Additional safety information submitted from previously completed studies partially addresses this concern; however, data from the PERSIST study, completed subsequent to the CRL, suggests on-going wound issues, including bruising, hematoma, and surgical site infection. Additionally, a larger proportion of SABER-bupivacaine-treated patients experienced increases in leukocytes and neutrophils $\geq 30\%$ of baseline on study day 4 compared to patients treated with saline placebo or bupivacaine HCl, suggesting a more pronounced inflammatory reaction. While the increased incidence of surgical site infections was not observed during review of the data presented in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	identify cases of bone erosion or destruction of articular cartilage and were generally reported as unchanged from baseline. <u>Wound-Related Adverse Events</u> - Throughout the Applicant's clinical development program there was an increased incidence in several wound-related adverse events, including peri-incisional bruising, hematoma, pruritus, and dehiscence, in patients treated with a SABER-product. The Applicant conducted an additional Phase 3 study in patients undergoing lap chole to address these concerns and determined that peri-incisional bruising and hematoma continue to occur with an increased incidence in patients treated with SABER-bupivacaine compared to respective controls. While the bruising and hematoma formation did not appear to lead to more clinically significant wound concerns, they are not completely benign conditions in and of themselves. Specifically, bruising may mask a surgical site infection or cellulitis, and the presence of a hematoma may increase the risk of developing a surgical site infection or be catastrophic within specific locations in the body (i.e., epidural space). - Surgical site infection was reported with a higher incidence in SABER-bupivacaine-treated patients undergoing lap chole than control-treated patients. <u>Neurological Adverse Events</u>	the original NDA submission, it raises the concern that administration of SABER-bupivacaine in different locations in the body may present different wound-related adverse events, such that a broad postsurgical analgesic indication is not supported. Should this product gain marketing approval, the indicated population will reflect only those procedures thoroughly evaluated for safety (and effectiveness). There appears to be an increased incidence in neurologically-related adverse events in patients treated with a SABER-product, that is likely related to the benzyl alcohol component of the vehicle. Should SABER-bupivacaine gain marketing approval, drug product labeling will include specific adverse event information, including time to onset, and any necessary warnings or precautions. Foreign body reactions and the persistence of SAIB in tissues for up to one year after administration of SABER-bupivacaine, as described in nonclinical studies, has been an ongoing concern. Specifically, the long-term impact of residual components in tissue for this length of time, including the possibility of development of a chronic inflammatory process, is not known. Additionally, the impact of SAIB remnants on future surgical exploration is unknown. Patients not uncommonly undergo either repeat or associated

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In the previously completed studies, there was an increased incidence of neurologically-related adverse events, including dizziness, dysgeusia, headache, hypoesthesia, paresthesia, and somnolence, in patients treated with a SABER-product compared to patients treated with bupivacaine HCl. These adverse events are believed to be related to the benzyl alcohol in the SABER product. • In the PERSIST study, there continued to be an increase in solicited nervous system adverse events, including somnolence (Part 1 and 2), headache (Part 1), and dysgeusia (Part 1 and 2) in patients treated with SABER-bupivacaine compared to saline (in Part 1) or bupivacaine HCl (in Part 2). Nausea and vomiting were reported with increased frequency in patients treated with bupivacaine HCl. • Based on the relatively short half-life of benzyl alcohol, adverse events which occurred within six hours of administration of SABER-bupivacaine were evaluated in the PERSIST study. Those results indicate an increased incidence of somnolence, headache, pruritus, and dysgeusia when compared to patients treated with saline placebo or bupivacaine HCl. • Some of these adverse events could be a result of exposure to general anesthetics and unrelated to administration of SABER-bupivacaine; however, because there is limited data available for comparison of SABER-bupivacaine to non-SABER products, the assumption is that exposure to benzyl	surgical procedures in the same anatomic area and it is not known how the presence of residual SAIB components will impact the ability to dissect and visualize the anatomy. A more challenging surgical procedure can result in increased risks to patients including, but not limited to, prolonged exposure to general anesthetics (depending on the type of procedure performed), increased risk of bleeding and need for transfusion of blood products, increased risk of technically difficult surgical dissection with subsequent increased risk of damage to surrounding tissues and organs, and increased postsurgical pain. In conclusion, I do not believe the marginal benefits of administration of SABER-bupivacaine outweigh the associated risks of wound-related adverse events, nervous system-related adverse events, and inadvertent intravascular injection, and, therefore, do not recommend approval of SABER-bupivacaine for the management of postsurgical pain.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	alcohol increases these risks. <u>Residual SAIB in the wound</u> • Foreign body reactions and the persistence of SAIB in tissues for up to one year after administration of SABER-bupivacaine, as described in nonclinical studies, has been an ongoing concern. • The Applicant has indicated that other injectable extended-release products (i.e., Exparel® and Sustol®) also result in foreign body reactions and granulomatous inflammation. While the nonclinical data may suggest a local, granulomatous reaction after subcutaneous injection of Exparel®, the clinical studies in addition to post-market surveillance do not suggest there is a clinically significant difference in local toxicity between Exparel® and bupivacaine HCl or placebo, and given the duration of marketing, it seems unlikely that post-operative wound complications have yet to be identified. The comparison to Sustol® is not valid based on the route of administration in healthy tissue. • An additional concern aside from foreign body reactions, is how SAIB remnants may impact future surgical exploration.	

1.5. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
☐	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify)	
☒	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Given the current opioid crisis facing the United States, postsurgical pain management has become a rapidly advancing field. The goal is to decrease opioid prescriptions and use post-operatively via a multimodal peri-operative approach, including use of local anesthetics for

wound infiltration, peripheral nerve blockade, and neuraxial blockade. A variety of soft tissue surgical procedures are amenable to local anesthetic administration and, depending on the location, patient comorbid conditions, concomitant medications, and contraindications, is considered standard of care. The local anesthetics currently approved for use in the management of post-operative pain are considered immediate-release and there are no approved products labeled for extended-release.

The Applicant has stated that because SABER-bupivacaine has demonstrated the PK profile of an extended-release drug product, postsurgical analgesia will be prolonged beyond what is observed after administration of immediate release products. While the data from the Applicant's pharmacokinetic studies is supportive of delayed maximum concentration, T_{max} , compared to Marcaine™, clinically, the pharmacokinetics of local anesthetics do not translate into efficacy, or in this case prolonged analgesia. More simply stated, the PK profile does not correlate to the pharmacodynamic (PD) responses. Additionally, for extended-release labeling, drug products must demonstrate a decrease in dosing frequency when compared to immediate-release products, suggesting that comparative efficacy studies are needed. Furthermore, prolonged bupivacaine release may ultimately have an adverse impact on the safety profile of the drug product. As will be discussed throughout this review, the determination of safety and efficacy of local anesthetic products developed to extend the analgesic benefit of immediate release products is complicated. While the opioid epidemic in the U.S. is an overwhelming challenge facing practitioners, researchers, and pharmaceutical companies alike, product development that is unsafe or no more efficacious than currently available standard of care products may predictably result in equally serious adverse outcomes.

2.2. Analysis of Current Treatment Options

The management of postsurgical pain involves a multimodal approach utilizing local anesthetics, non-opioid analgesics, and opioid analgesics. Anti-depressants and anti-seizure medications are also commonly used depending on the comorbid medical conditions of the patient and the procedure performed. Opioid analgesics have been the mainstay for the management of not only acute pain conditions, including post-operative pain, but also for chronic pain conditions. Current strategies, however, are focused on alternate pain treatments, including local anesthetic wound infiltration, peripheral nerve blockade, and neuraxial anesthesia. This paradigm shift has resulted in increasing interest in developing products that prolong the efficacy of immediate release local anesthetics, such as SABER-bupivacaine. As previously mentioned, however, there is no approved extended-release local anesthetic product that has reliably and predictably extended the duration of analgesia observed after administration of immediate-release local anesthetics.

The following table summarizes the local anesthetics most commonly used in the peri-operative period for analgesia.

Table 1. Summary of FDA-Approved Local Anesthetics for Postsurgical Analgesia

Product Name NDA #	Relevant Indication	Route of Administration	Efficacy Information	Important Safety and Tolerability Issues
Exparel (022496)	For single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia	Local infiltration	Liposomal bupivacaine HCl used for postsurgical analgesia. No clear efficacy benefit demonstrated when compared to bupivacaine HCl.	The safety issue with all local anesthetics involves systemic and local toxicities. LAST presents as central nervous system excitation and/or depression and cardiotoxicity. As documented in the Adverse Reactions section of the bupivacaine labeling, but applicable to all local anesthetics, the following LAST reactions are described by system: <u>Central nervous system</u> Excitation and/or depression; restlessness, anxiety, dizziness, tinnitus, blurred vision, tremors, convulsions <u>Cardiovascular system</u> High doses or inadvertent intravascular injection may result in myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmias, cardiac arrest. Bupivacaine HCl is considered the most cardiotoxic local anesthetic due to its potency in blocking nerve conduction and depressing cardiac contractility. Local reactions can include persistent anesthesia, paresthesia, weakness, or paralysis
Bupivacaine HCl (016964)	Production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures	Local infiltration	First approved in 1972. Many approved bupivacaine products are widely used for postsurgical analgesia, either as wound infiltrate or nerve block. Considered a long-acting local anesthetic with a duration of action ranging from 4 to 18 hours, depending on the route and site of administration.	
Ropivacaine HCl (20533)	Production of local or regional anesthesia for surgery and for acute pain management	Local infiltration	Similar efficacy benefits as bupivacaine HCl but with more favorable cardiotoxicity profile. Considered a long-acting local anesthetic with a duration of action ranging from 4 to 18 hours.	
Mepivacaine HCl (12250)	Production of local or regional analgesia and anesthesia by local	Local infiltration	Considered an intermediate-acting local anesthetic with a	

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Bupivacaine solution for infiltration use

Product Name NDA #	Relevant Indication	Route of Administration	Efficacy Information	Important Safety and Tolerability Issues
	infiltration, peripheral nerve block techniques, and central neural techniques		duration of action ranging from 90 to 180 minutes.	
Lidocaine HCl (006488)	Production of local or regional anesthesia by infiltration techniques and intravenous regional anesthesia, by peripheral nerve block techniques, and by central neural techniques, when the accepted procedures for the techniques as described in standard textbooks are observed.	Local infiltration	First approved in 1948 as Xylocaine® 2% injectable solution. Considered an intermediate- acting local anesthetic with a duration of action ranging from 90 to 180 minutes.	

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This bupivacaine product has not been marketed anywhere in the world. Bupivacaine immediate-release has a long history of clinical use with the following indications, per the Marcaine™ product label, 2018:

Bupivacaine HCl is indicated for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures

3.2. Summary of Presubmission/Submission Regulatory Activity

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

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Bupivacaine solution for infiltration use

reformulated using BA and the (b) (4) was removed. The Applicant submitted a request to reactivate the IND on December 23, 2005, which was acknowledged by the Division on January 10, 2006.

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

Table 2. Regulatory History

Meeting / Communication / Date	Event / Key Clinical Issues
IND 066086 opened / Oct. 23, 2002	Formulation contained (b) (4) 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 reactivated on January 10, 2006, and the Sponsor submitted 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, 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

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Meeting / Communication / Date	Event / Key Clinical Issues
	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.
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

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	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: - Conduct an additional clinical study to better characterize the benefit-risk 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 benefit-risk profile for SABER-bupivacaine.
Phase 3 protocol synopsis received /	Sponsor proposed to evaluate the safety and efficacy of SABER-

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Feb. 22, 2015	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 • A favorable SPID72 is not evidence of a 72-hour duration of effect.
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 / March 10, 2017	There were no further safety concerns and the protocol was allowed to proceed.
NDA 204803 Resubmission received /	Initial review determined the submission was a Complete Response to

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June 27, 2019	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 in soft tissue surgical models. Specifically, regarding the lack of efficacy in Study CLIN005-0010, the Applicant suggested that an imbalance in patient age between the active treatment and placebo groups may have contributed to lack of efficacy and reanalysis of the data using analysis of covariance (with treatment as the main effect, age as the covariate, and the interaction of age and treatment) pooled with the results from Study CLIN803-006-0006, demonstrated a statistically significant treatment effect of SABER-bupivacaine compared to SABER-placebo in inguinal hernia repair.

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 hernia repair had been provided and that efficacy concerns would not be included in the pending Complete Response Letter (CRL). 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 CRL, 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 $\geq 1\%$. 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 any planned studies with the Division prior to implementation.

In response to the CRL, the Applicant requested a formal dispute resolution (FDRR), 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. As mentioned, the CRL included only the Division's identified safety concerns. However, because the Applicant requested a determination of both safety and efficacy in the FDRR, Dr. Thanh Hai conducted an additional review of the efficacy data. Her conclusion was as follows:

"...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.” (Source: Dr. Mary Thanh Hai’s response to the FDRR, dated January 15, 2015.)

Regarding the safety concerns, Dr. Thanh Hai proposed the following two paths forward for the Applicant: a) conduct an additional clinical study to better characterize the benefit-risk 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 benefit-risk 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:

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

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Routine audits were not conducted during this review cycle, and there were no facility inspection issues noted during the initial review cycle that would prevent approval.

4.2. Product Quality

The Office of Product Quality (OPQ) has no concerns with the drug product stability data, manufacturing facilities, or microbiology data and recommends approval. Of note, the Applicant did change drug product manufacturers subsequent to the CRL issued in April 2013. Drug product comparability data was acceptable to the OPQ review team.

As summarized from Dr. Christopher Breder’s CDTL review, dated January 22, 2014, the proposed drug product is a sterile, nonpyrogenic, clear to light yellow to amber solution of bupivacaine. The excipients used in the SABER-bupivacaine include BA and the SAIB, as

discussed in Section 1.1, Product Introduction. SAIB is used as a stabilizer of emulsions of flavoring oils in nonalcoholic beverages; however, it has not been used in approved drug products and is considered a novel excipient.

4.3. Nonclinical Pharmacology / Toxicology

The Applicant has conducted two additional non-GLP nonclinical studies, one in beagle dogs and one in minipigs, to address concerns regarding wound healing, specifically bruising, after administration of SABER products in full-thickness surgical incisions. The results of these studies will be discussed in detail in the Pharmacology-Toxicology Review completed by Dr. Misol Ahn. Briefly, peri-incisional bruising appeared in the dogs on post-operative day (POD) 1 and resolved by POD 7. There were no other reported findings, including pain or abnormal wound healing. In the minipig study, peri-incisional bruising was noted within eight hours of surgery and resolved by POD 4. As in the dog study, there were no reports of abnormal wound healing.

A major concern identified during review of the original NDA submission is persistence of the SAIB component of the drug product at the injection site for extended periods of time, beyond one year in some animals. Specifically, in a subcutaneous injection study conducted in rats (Study 7116-109), inflammation was observed through six weeks post-injection. There was concern that the observed ongoing inflammation may actually underestimate the degree of potential changes observed after a surgical procedure, where additional inflammation is anticipated. Additionally, a 12-month study ((b) (4)-434007) conducted in rabbits indicated that SAIB was found to be unchanged and present at 12 months post-injection. At 52 weeks post-injection, several pathological changes were identified, including severe fibrosis, epidermal ulceration (present 2- and 4-weeks post-treatment), full-thickness epidermal necrosis, granulomatous inflammation (present in animals throughout the study but decreased in severity over time), and dermal fibrosis (present 4 to 52 weeks post-treatment).

Based on these findings, the pharmacology-toxicology supervisor did not recommend approval during the first review cycle. He noted that while the nonclinical program was sufficient, and the systemic safety and drug product quality issues were adequately addressed, "...the product itself is not toxicologically neutral with instillation to wound sites and this effect appears to be maintained for weeks at minimum and perhaps months, a situation which is not observed with immediate release bupivacaine and which far exceeds the intended pharmacologic benefit of SABER-bupivacaine." (Dr. Christopher Breder's Clinical NDA Review, p. 14)

During this review cycle, the pharmacology-toxicology team also expressed concern over the residual SAIB components and local tissue reactions; however, the larger issues discussed subsequent to the AC meeting were the risks associated with inadvertent intravascular injection, including those related to emboli and the development of LAST. The team has concluded that, "If the potential risks of the inadvertent injection of Posimir and clinical mitigation strategies and risk assessments provided by the Applicant are not considered to be sufficient to dismiss potential safety concerns, ... nonclinical studies to investigate the potential

toxicity of inadvertent intravascular injection can be conducted to further inform the benefit/risk profile for this product and inform labeling in case of overdose or Local Anesthetic Systemic Toxicity (LAST).” I recommend the identified nonclinical deficiencies be conveyed to the Applicant in the CR Letter.

4.4. Clinical Pharmacology

There was no new clinical pharmacology data submitted in the NDA resubmission. Conclusions discussed in this section are based on information taken from the original NDA submission and the clinical pharmacology and biopharmaceutics reviews.

Study BU-001-IM, a study in patients undergoing abdominal hysterectomy, assessed the relative bioavailability of SABER-bupivacaine compared to Marcaine. Results from this study indicated that bupivacaine is detected in the plasma through 72 hours after SABER-bupivacaine administration. Mean C_{max} after administration of SABER-bupivacaine 660 mg was 625 ng/mL compared to 342 ng/mL after administration of Marcaine 100 mg. Mean area under the curve (AUC) values were substantially higher after administration of SABER-bupivacaine compared to Marcaine (36830 ng.h/mL versus 5740 ng.h/mL, respectively). SABER-bupivacaine did demonstrate linear pharmacokinetics after administration of a 2.5 mL and a 5 mL dose.

Conclusions based on the PK data from eight clinical studies, including one in healthy subjects, two in inguinal hernia repair, two in subacromial decompression, one in appendectomy, one in hysterectomy, and one in laparotomy procedures, and described in the original clinical pharmacology review are as follows:

- The systemic bupivacaine concentrations were observed for up to 72 hours after administration of SABER-bupivacaine 5 mL in all evaluated surgical procedures and no dose-dumping was observed
- Observed bupivacaine C_{max} and AUC values were not significantly different in abdominal, shoulder and hernia procedures for the same SABER-bupivacaine dose; however, the abdominal procedures had the highest reported bupivacaine levels
- Observed bupivacaine C_{max} and AUC values were not significantly different when 5 mL SABER-bupivacaine was administered via subcutaneous, infiltration, or instillation routes of administration
- No correlation was observed between bupivacaine C_{max} and AUC and surgical incision lengths, as all 5 mL SABER-bupivacaine was administered in all surgical procedures
- No dosage adjustment may be warranted due to weight, age, gender, and race since it is a locally acting product.

In response to an Information Request sent on Sept. 23, 2019, for additional pharmacokinetic data, the Applicant provided the following summary table for PK information captured across their clinical development program. Note that the studies provided in this table are not the same as those identified in the original NDA submission for supportive PK information.

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Table 3. Pharmacokinetics Data By Surgical Site or Procedure

Surgical Site or Procedure	POSIMIR dose	C _{max} (ng/mL)	AUC _{0-t} (h*ng/mL) ^[a]	AUC _{0-inf} (h*ng/mL)	T _{max} (h)	T _{1/2} (h)
Open (Linear) Incisions	660 mg (5.0 mL)					
BU-001-IM Abdominal hysterectomy	N	59	59	54	59	54
	Mean	625.0	35232.0	37321.0	37.3	21.9
	SD	310.35	18718.57	20401.29	16.47	9.03
	Median	595.0	33023.3	34222.4	36.0	19.8
	Minimum	119.0	4420.9	4474.5	4.0	11.3
	Maximum	1740.0	105324.5	119532.5	95.9	58.1
C803-025, Cohort 1 Laparotomy	N	30	30	Insufficient data to compute.	30	Insufficient data to compute.
	Mean	955.6	41942.1		40.4	
	SD	484.51	24343.83		19.08	
	Median	947.5	38451.7		48.1	
	Minimum	133.0	634.8		2.2	
	Maximum	1870.0	96625.2		72.8	
C803-025, Cohort 3 Laparoscopically-assisted colectomy	N	129	129		129	
	Mean	849.6	39601.7		40.4	
	SD	477.56	24049.46		17.75	
	Median	794.0	36444.5		46.6	
	Minimum	92.3	1626.3		1.1	
	Maximum	2850.0	136308.9		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	752.1	30996.6		23.3	
	SD	306.96	12679.82		15.74	
	Median	703.0	30565.2		24.3	
	Minimum	357.0	11100.2		1.03	
	Maximum	1850.0	68107.7		48.6	
Surgical Site or Procedure	POSIMIR dose	C _{max} (ng/mL)	AUC _{0-t} (h*ng/mL) ^[a]	AUC _{0-inf} (h*ng/mL)	T _{max} (h)	T _{1/2} (h)
Inguinal Hernia Repair Surgery	660 mg (5.0 mL)					
CLIN803-006-0006 Open inguinal hernia repair	N	14	14	14	14	14
	Mean	866.6	40823.0	41461.4	17.4	28.6
	SD	426.61	20311.58	20220.87	8.10	13.37
	Median	695.0	33682.7	34182.2	24.0	25.4
	Minimum	383.0	15337.9	18088.5	4.0	20.9
	Maximum	1650.0	78602.0	78909.2	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	593.2	19395.0	19962.9	7.0	16.4
	SD	299.07	12056.31	12587.42	6.58	5.077
	Median	590.5	18805.1	19213.9	5.9	15.0
	Minimum	70.4	1028.3	1051.2	1.0 ^[b]	8.4
	Maximum	1320.0	55369.2	58965.7	24.0	28.9
CLIN005-0006 Arthroscopic subacromial decompression	N	18	18	18	18	18
	Mean	1005.5	47015.4	47648.5	10.6	26.1
	SD	453.57	20040.49	20115.61	8.51	8.22
	Median	937.5	49057.7	49243.0	8.0	23.7
	Minimum	172.0	7246.9	7345.9	2.1	16.6
	Maximum	1940.0	85980.2	86447.7	26.9	50.8

[a] t = last

[b] The BU-002-IM minimum value for T_{max} 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).

Note: Values have been converted to identical units, as needed.

Source: Applicant's response to Information Request sent on Sept. 23, 2019, Applicant's submission, NDA 204803.

There was no PK data reported during the PERSIST study.

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As discussed in the primary clinical pharmacology review, the pharmacokinetics of SABER-bupivacaine varied depending on how and where on the body it was administered. For additional information, refer to the Clinical Pharmacology Review completed by Dr. David Lee.

The pharmacokinetic profile of benzyl alcohol was assessed in 24 patients treated in Study BU-001-IM. The reported mean maximal concentration, C_{max} , was 0.388 mg/L and was reached at the first measurement time, one hour, and decreased rapidly, within 4.7 hours ($t_{1/2}$), and by 24 hours BA was below or close to the lower limit of measurement (5 ng/mL). The pharmacokinetics of BA was not assessed in any other clinical study.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

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Table 4. Clinical Studies Evaluated for Efficacy

Study Identity	Study Design	Treatment Arms (n)	Primary Study Endpoints	Surgical Procedure	No. and Location of Sites
<i>Orthopedic Procedures</i>					
BU-002-IM	R, assessor-blinded, active and pbo-controlled	SABER-bupiv 5 mL (53) SABER-pbo 5 mL (25) Bupiv HCl 0.25%, 50 mg (29)	- Mean pain intensity with movement through 72h (AUC_{72M}) - Total opioid rescue analgesia through 72h (RES₇₂)	Arthroscopic subacromial decompression, with or without distal clavicle excision, bursectomy, synovectomy, removal of loose body, resection of coracoacromial ligament and subacromial spurs, and minor debridement.	11 sites in Europe
CLIN005-0006	R, DB, pbo-controlled, & open-label PK sub-study	<u>Cohort 1</u> SABER-pbo 5 mL subacromial + SABER-bupiv 5 mL subQ (14) SABER-bupiv 5 mL subacromial + SABER-pbo 5 mL subQ (10) SABER-pbo 5 mL subacromial + SABER-pbo 5 mL subQ (16) <u>Cohort 2</u> – entire volume injected subacromially at the end of surgery SABER-pbo 5 mL (24) SABER-pbo 7.5 mL (4) SABER-bupiv 5 mL (21) SABER-bupiv 7.5 mL (3)	- AUC_{72M} - Mean pain intensity at rest through 120h (AUC_{120R})	Variety of shoulder procedures, 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.	5 sites in U.S. 1 site in New Zealand
C803-017 (C803-017e)	R, DB, pbo-controlled	SABER-bupiv 5 mL (40) SABER-pbo 5 mL (20)	- AUC_{72M} - RES₇₂	Arthroscopic subacromial decompression and open Mumford procedure.	10 sites in Australia and New Zealand

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Study Identity	Study Design	Treatment Arms (n)	Primary Study Endpoints	Surgical Procedure	No. and Location of Sites
is safety extension study)					
<i>Soft Tissue Surgeries</i>					
CLIN803-006-0006	R, DB, pbo-controlled	<u>Cohort 1</u> SABER-bupiv 2.5 mL (43) SABER-pbo 2.5 mL (16) <u>Cohort 2</u> SABER-bupiv 5 mL (47) SABER-pbo 5 mL (16)	- AUC _{72M} - Proportion of patients taking opioid rescue during the study (Days 0-15), changed to 72 hours post-hoc	Open inguinal hernia repair	5 sites in Australia and New Zealand
CLIN005-0010	R, DB, pbo-controlled	<u>Cohort 1</u> SABER-pbo 5 mL subaponeurotic + SABER-bupiv 5 mL subQ (13) SABER-bupiv 5 mL subaponeurotic + SABER-pbo 5 mL subQ (18) SABER-pbo 5 mL subaponeurotic + SABER-pbo 5 mL subQ (14) <u>Cohort 2</u> – entire volume injected into the inguinal canal SABER-pbo 5 mL (21) SABER-pbo 7.5 mL (0) SABER-bupiv 5 mL (22) SABER-bupiv 7.5 mL (1)	- AUC _{120M} - AUC _{120R} - Pain control		7 sites in U.S. 1 site in New Zealand
BU-001-IM	R, DB, active and pbo-controlled	SABER-bupiv, 5 mL (61) SABER-pbo 5 mL (27) Bupiv 0.25%, 100 mg (27)	- AUC _{72M} - RES ₇₂	Total abdominal hysterectomy	14 sites in Europe
C803-025	R, DB, active	SABER-bupiv 5 mL	- AUC _{72M}	Laparotomy (cohort 1)	9 sites in U.S.

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Study Identity	Study Design	Treatment Arms (n)	Primary Study Endpoints	Surgical Procedure	No. and Location of Sites
	and pbo-controlled	Cohort 1 (26) Cohort 2 (30) Cohort 3 (125) SABER-pbo Cohort 3 (77) Bupiv (150 mg) Cohort 1 (17) Cohort 2 (20)	- RES ₇₂	Lap chole (cohort 2) Lap-assisted colectomy (cohort 3)	2 sites in Oceania
C803-028	R, DB, pbo-controlled	<u>Part 1</u> SABER-bupiv 5 mL (48) Saline pbo 5 mL (46) <u>Part 2</u> SABER-bupiv 5 mL (148) Bupiv HCl (75 mg) (148)	- Part 1: AUC _{72M} - Part 2: AUC _{48M}	Lap chole	23 sites in U.S.

5.2. Review Strategy

6. Review of Relevant Individual Trials Used to Support Efficacy

In the original NDA submission, the Applicant identified two clinical studies as “pivotal” and supportive of the reported efficacy of SABER-bupivacaine and the proposed indication of post-operative analgesia. Study BU-002-IM was conducted in patients undergoing arthroscopic subacromial decompression and Study CLIN803-006-0006 was conducted in patients undergoing open inguinal hernia repair. This section will briefly discuss the previously completed studies, by procedure, and include information from the original clinical NDA review completed by Dr. Arthur Simone, as needed, and a thorough discussion of the PERSIST study.

6.1. Studies Reviewed In the Original NDA Submission

6.1.1. Shoulder Surgery

The Applicant conducted three clinical studies, summarized in the following table, to assess the efficacy of SABER-bupivacaine administered into the subacromial space using a large bore needle following shoulder surgery.

Table 5. Shoulder Studies Evaluated in the Original NDA Submission

Trial Number Location Start-Stop Dates	Number of patients treated with sub-acromial drug			Duration of Follow-up	Follow-up Assessments	Surgery
	SABER® - Bupivacaine 5 mL	SABER® - Placebo 5 mL	Bupivacaine HCl 50 mg			
CLIN-005-0006 US & NZ 2006-2007	*62	**44	0	14 days	AE, PE, Labs	Rotator cuff repair, sub-acromial decompression, labral repair, or biceps tendon repair
C803-017 Australia & NZ 2008-2009	40	20	0	18 Mo	MRI, AE, PE, Pain	Sub-acromial decompression without major rotator cuff tears
BU-002-IM Europe 2009-2010	53	25	29	6 Mo	MRI Shoulder function	Sub-acromial decompression with intact rotator cuff
Total	155	89	29	Overall Total = 273 Patients		

Source: Clinical study reports

* 3 patients received 7.5 mL SABER-Bupivacaine

** 4 patients received 7.5 mL SABER-Placebo

Source: Type C End-of-Review Meeting Background Package, p. 36 (PDF).

Note: The actual study dates are as follows: Study CLIN005-0006 (.....), Study C803-017 (December 11, 2008 - October 29, 2009), and Study BU-002-IM (April 29, 2009 - February 4, 2011)

While the three studies were similar in that they were all performed in patients undergoing an arthroscopic shoulder procedure, studies CLIN005-0006 and C803-017 also enrolled patients undergoing more extensive and open shoulder procedures, as described below. In contrast, no patient treated in Study BU-002-IM underwent an open procedure and in the cases of anchor or suture placement, the patient was considered a randomization failure and was withdrawn from the study. The variability in the three surgeries is not surprising for Phase 2 studies; however, the inconsistency in evaluated procedures impacts the interpretation of the reported efficacy results.

The first study, CLIN005-0006, was conducted in patients undergoing a variety of shoulder procedures, 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 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 (AUC_{72M} 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.

The third study, BU-002-IM, was conducted in patients undergoing arthroscopic subacromial decompression with an intact rotator cuff, confirmed via MRI. Patients may have also had a distal clavicle excision, bursectomy, synovectomy, removal of loose body, resection of coracoacromial ligament and subacromial spurs, rotator cuff debridement, and minor debridement of articular cartilage. There were no open shoulder procedures performed during this study. This study did demonstrate a statistically significant difference in post-operative pain (AUC_{72M}) for SABER-bupivacaine-treated patients compared to those treated with SABER-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 (RES_{72}). While there was improvement in pain intensity with movement in the SABER-bupivacaine treatment group compared to the bupivacaine HCl treatment group in the first 24 hours post-operatively, there was no difference at later time points, including at 72 hours.

It is worth noting that while the majority of treated patients underwent several of the above-mentioned associated procedures, there was a discrepancy in the frequency of those considered more painful between treatment groups. Specifically, as indicated in the table below, it appears that patients in the SABER-placebo treatment group underwent procedures considered more painful than others compared to patients treated with either SABER-bupivacaine or bupivacaine.

Table 6. Frequency of Most Painful Procedures Performed, Study BU-002-IM

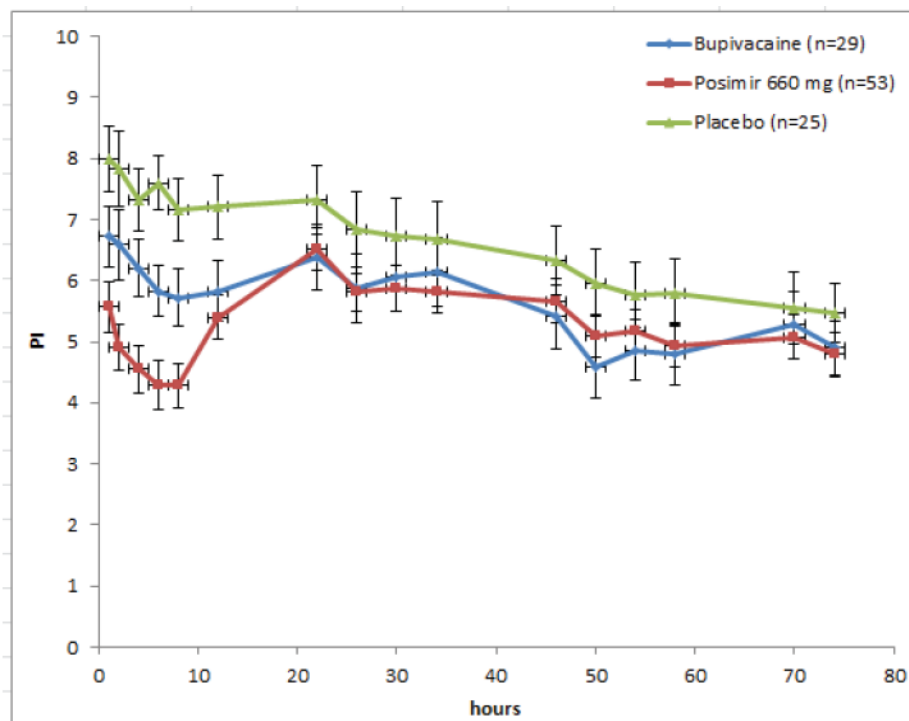
Most Painful Procedures	SABER-bupivacaine n/N (%)	SABER-placebo n/N (%)	Bupivacaine HCl n/N (%)
Distal clavicle excision (Mumford procedure)	2/53 (4%)	6/25 (24%)	1/29 (3%)
Rotator cuff debridement	24/53 (45%)	13/25 (52%)	11/29 (38%)
Removal of spurs	38/53 (72%)	19/25 (76%)	20/29 (69%)

Source: Reviewer’s analysis.

These findings suggest that patients in the SABER-placebo treatment group may have had more postsurgical pain compared to patients in the SABER-bupivacaine treatment group, resulting in an improved efficacy profile for SABER-bupivacaine. Furthermore, it appears that the percentage of patients who underwent more painful procedures in the SABER-bupivacaine and bupivacaine treatment groups was approximately the same, which may explain the lack of an improved efficacy benefit of SABER-bupivacaine over bupivacaine.

Evaluation of the pain curves for each treatment group, presented in the following figure, indicated that while there was a statistically significant difference in mean pain intensity through 72 hours between the SABER-bupivacaine and SABER-placebo treatment groups, the benefit appears to be greatest between 0 to 24 hours. This suggests that the statistical significance is driven by an early, versus extended, analgesic benefit.

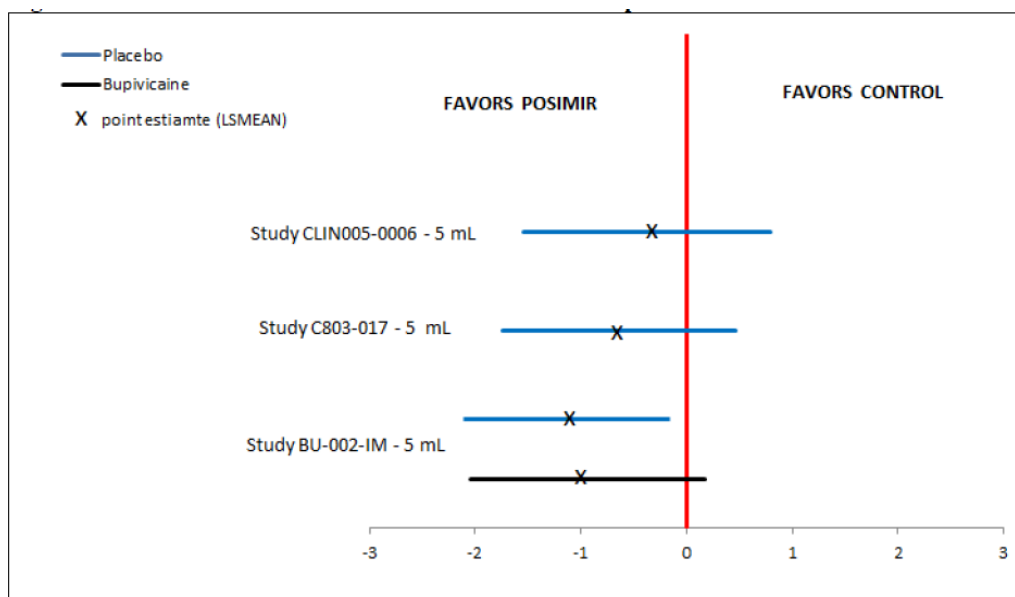
Figure 2. Mean Pain Intensity Scores at Each Measured Time Point (Study BU-002-IM)



Source: Statistical Review by Mr. David Petullo, dated Dec. 27, 2013.

The point estimates for the shoulder surgery studies are included in the following figure, taken from the statistical review completed by Mr. David Petullo.

Figure 3. Difference in Pain Intensity (normalized AUC₇₂) For Arthroscopic Shoulder Surgery



Source: Statistical Review by Mr. David Petullo, dated Dec. 27, 2013.

Mr. Petullo concluded that while statistical significance was not reached in Studies CLIN005-0006 or C803-017, SABER-bupivacaine did appear to reduce post-operative pain and the amount of post-surgical opioid medication required; however, the clinical benefit beyond 12 hours is unclear.

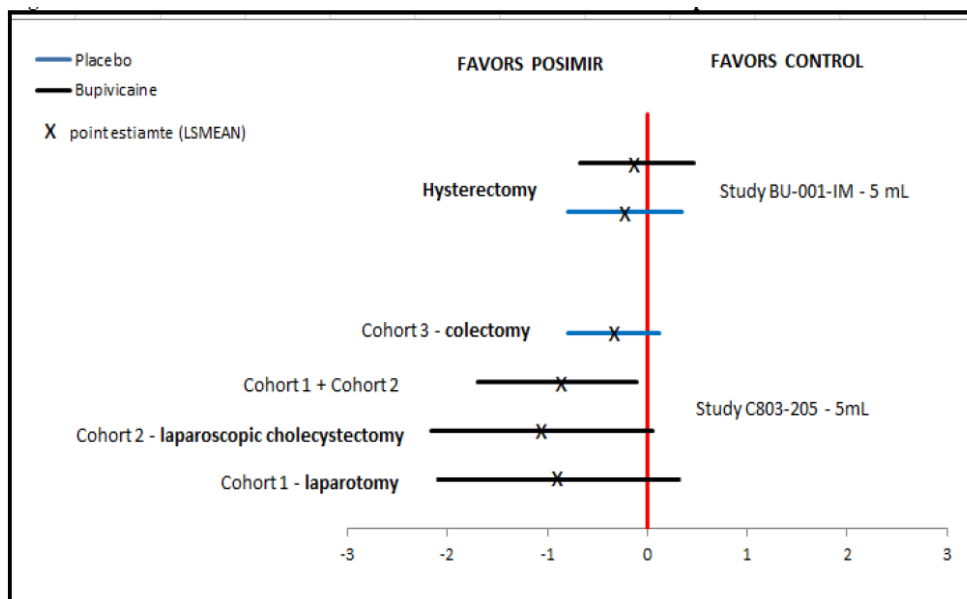
6.1.2. Abdominal and Pelvic Procedures

Study BU-001-IM was conducted in patients undergoing total abdominal hysterectomy (TAH). Treatment groups included SABER-bupivacaine, SABER-placebo, and bupivacaine HCl. There was no statistically significant difference in primary efficacy endpoint results (AUC_{72M} and RES_{72}) between SABER-bupivacaine and the other two treatment groups.

Study C803-025 was a Phase 3 study conducted in patients undergoing one of three surgical procedures; laparotomy (Cohort 1), lap chole (Cohort 2), and lap-assisted colectomy (Cohort 3). Cohorts 1 and 2 used the active comparator bupivacaine HCl and neither demonstrated a statistically significant difference between treatment groups. Pooling the efficacy data from the two cohorts did reach statistical significance, but was determined to be inappropriate based on the clear differences in surgical procedures evaluated. Cohort 3 evaluated efficacy between SABER-bupivacaine and SABER-placebo treatment groups. There was no statistically significant difference between the two groups on the primary efficacy endpoints, AUC_{72M} and RES_{72} .

The following figure demonstrates the inconsistent and statistically insignificant results across the studies evaluating the efficacy of SABER-bupivacaine in patients undergoing abdominal and pelvic procedures.

Figure 4. Difference in Pain Intensity (normalized AUC_{72}) For Abdominal Soft Tissue Procedures



Source: Statistical Review by Mr. David Petullo, dated Dec. 27, 2013.

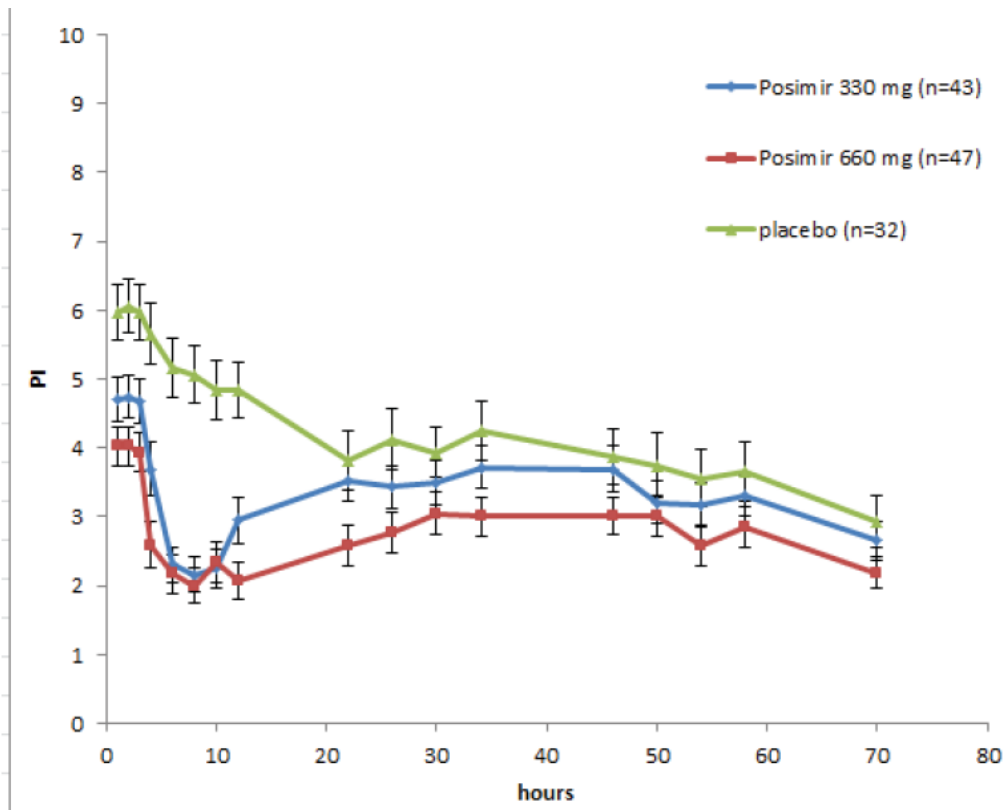
6.1.3. Inguinal Hernia Repair

The Applicant conducted two Phase 2 studies in patients undergoing inguinal hernia repair; Study CLIN005-0010, conducted primarily in the U.S., and Study CLIN803-006-0006, conducted in Australia and New Zealand. Both studies evaluated the same dose and route of administration (half the dose of study drug administered into the floor of the inguinal canal and half into the subcutaneous space) of SABER-bupivacaine compared to SABER-placebo.

Study CLIN005-0010 was conducted first and failed to demonstrate superiority of SABER-bupivacaine over SABER-placebo on pain intensity with movement through 120 hours. Because this was not the primary efficacy endpoint evaluated in Study CLIN803-006-0006, the statistical reviewer evaluated pain intensity with movement through 72 hours, which indicated that SABER-placebo resulted in lower mean pain intensity scores.

Study CLIN803-006-0006 was conducted using the same doses, same route of administration, and same site of administration as Study CLIN005-0010. Additionally, the evaluated patient populations were considered similar despite different countries of study conduct. In this study, SABER-bupivacaine was demonstrated to be superior to SABER-placebo on the primary efficacy endpoint of AUC_{72M} , but not on the second primary endpoint of proportion of patients using opioid rescue through day 15. Similar to the findings in Study BU-002-IM, an evaluation of pain curves for each treatment group demonstrated clear separation from 0 to 24 hours in the SABER-bupivacaine 5 mL, 660 mg, treatment group, but the benefit did not appear to extend from 24 to 72 hours, suggesting the statistically significant result is likely driven by the early analgesic benefit. Refer to the following figure for the pain intensity curves for each treatment group in this study.

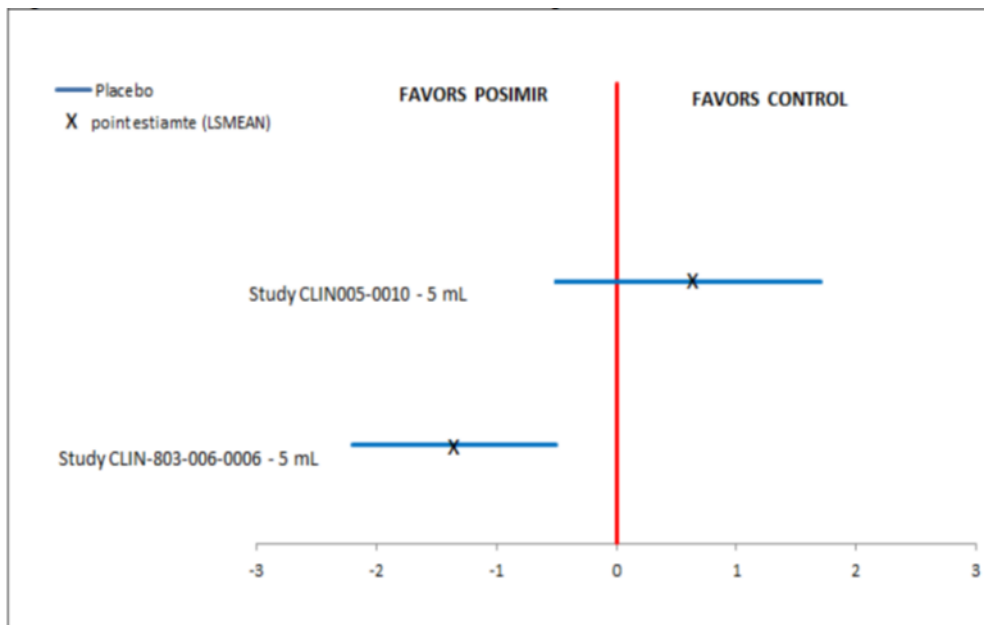
Figure 5. Mean Pain Intensity Scores at Each Time Point (Study CLIN803-006-0006)



Source: Statistical Review by Mr. David Petullo, dated Dec. 27, 2013.

The following figure demonstrates the inconsistent results from the two inguinal hernia repair studies. Note that mean pain intensity with movement through 72 hours was not the primary efficacy endpoint for Study CLIN005-0010, but this endpoint comparison was made in an attempt to determine why two similar studies did not report similar efficacy results.

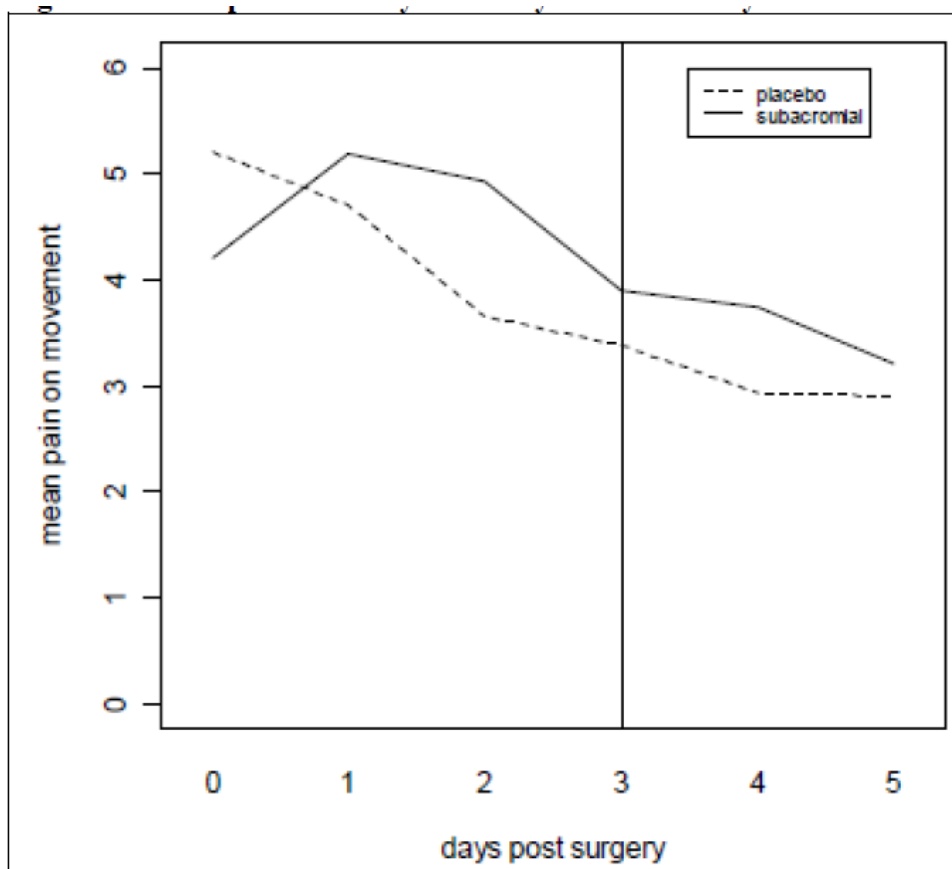
Figure 6. Difference in Pain Intensity (normalized AUC₇₂) For Inguinal Hernia Repair



Source: Statistical Review by Mr. David Petullo, dated Dec. 27, 2013.

Because the reported AUC_{72M} data between the treatment studies were so different, the statistical reviewer evaluated the pain intensity scores by time that were used to generate the AUC data for Study CLIN005-0010. The following figure, taken from the statistical review and included in the Applicant's original NDA submission, demonstrates an actual increase in reported pain in the first 24 hours after SABER-bupivacaine administration.

Figure 7. Mean Pain Intensity Scores by Time, Study CLIN005-0010



Note: the solid line identified as “subacromial” is an editorial error and actually represents the data for patients treated with SABER-bupivacaine. There is no subacromial space in the abdominal cavity.

Source: Statistical Review by Mr. David Petullo, dated Dec. 27, 2013.

It is unclear why the post-operative pain scores appeared to increase in the SABER-bupivacaine treatment group and why nearly identical clinical studies in the same surgical population did not demonstrate the same efficacy results. In addition to the country of study conduct contributing to the contradictory efficacy results, the Applicant argues that there was a large imbalance in patient age between the SABER-bupivacaine and placebo treatment groups, and that reanalysis of the pooled efficacy data from both studies using an analysis of covariance, age as the covariate, there was a statistically significant difference in the treatment groups. In the efficacy discussion included in the NDA resubmission, the Applicant states that Study CLIN005-0010 is no longer considered an adequate and well controlled study for the following reasons, summarized:

- Study design issues
 - efficacy endpoints not clearly defined
 - primary efficacy endpoint listed as both pain at rest and on movement
 - route of administration changed from subaponeurotic and subcutaneous injections to inguinal canal and abdominal wall instillation (protocol)

- Amendment 3), the route of study drug administration in Study CLIN803-006-0006
- dose of study drug increased from 5.0 mL to 7.5 mL (protocol Amendment 3) and back to 5.0 mL (protocol Amendment 4)
- Unreliable method of assessment; bias not minimized
 - patients recorded pain and opioid use data on paper diary cards (unverified time of recording; potential error and recall bias)
- Inadequate analysis of results
 - primary endpoint assessment based on PP rather than ITT population
 - sample size estimate based on Cohort 1 only
 - 120-hour duration of primary pain analysis too long
 - inappropriate pooling of placebo comparators (different volumes and routes of administration)

While some of the stated study design, assessment, and analysis issues may have adversely impacted the reported efficacy results for Study CLIN005-0010, the identification of these issues post hoc impacts their interpretation and relevance. Furthermore, reclassifying a study that did not demonstrate a statistically significant difference in observed treatment effect from adequate and well-controlled to a 'clinical experience' appears to be an attempt to minimize the impact on the overall efficacy conclusions for SABER-bupivacaine.

6.2. A Placebo-controlled (Part 1) or active-controlled (Part 2) trial of SABER® -Bupivacaine for the management of postoperative pain following laparoscopic cholecystectomy (PERSIST) (Study C803-028)

Overview

This study was conducted, in part, to address the safety concerns identified during review of the initial NDA, outlined in the CRL and reiterated in the FDRR denial letter. This study focused on an evaluation of relevant safety parameters, including specific post-operative wound-healing complications that could potentially be the result of treatment with the SABER-bupivacaine formulation. Additionally, specific neurological symptoms that could potentially be the result of exposure to the benzyl alcohol or bupivacaine components of the formulation were evaluated.

The study was also intended to provide additional supportive efficacy information for SABER-bupivacaine as an adequate post-operative analgesic. The Applicant argues, however, that while Part 1 was considered adequate and well-controlled, a series of requested protocol changes by the Division after study initiation resulted in the inability to provide the statistical power to measure clinical benefit. They further argue that the interpretation of the efficacy data in Part 2 is limited based on the change to active comparator after study initiation. Specifically, the Applicant argues that Part 2 is not adequate and well-controlled, per 21 CFR 314.126, for the following reasons:

- Protocol amendments increased variability and led to attenuation of the observed treatment effect between study drug and control
- Due to a lack of comparison between active control and placebo, assay sensitivity cannot be assessed
- Pooling of data from Part 1 and Part 2 is inappropriate for statistical analyses and efficacy conclusions

Based on this rationale, the Applicant concludes that, *“A succession of major midstream revisions to the design and conduct of the trial made in response to ongoing FDA advice, including an important change to the experimental hypothesis, had a deleterious effect on the trial that was sufficient to render Part 2 “inadequate” from an efficacy standpoint and Part 1 too underpowered to contribute to an assessment of analgesic efficacy”* and that the study should be considered a thorough evaluation of previously identified safety concerns. While I agree that Part 1 was adequate and well-controlled, but underpowered for an efficacy determination based on early termination and transition to Part 2, I do not agree with the Applicant’s rationale for excluding data from Part 2 in the overall efficacy evaluation for the following three reasons.

First, the number of protocol amendments would not impact the reported efficacy. Protocol amendment three is a stand-alone, adequate and well-controlled study designed to evaluate efficacy. Second, lack of assay sensitivity between placebo and bupivacaine HCl is a study design issue that could have been resolved had the Applicant included a third treatment arm, as discussed during the End-of-Review Meeting held on September 23, 2014. Specifically, the Applicant was advised during this meeting that, *“Ultimately, you will likely need three treatment arms (Posimir, bupivacaine HCl, and non-SABER placebo). However, the numbers of subjects required to be enrolled may vary substantially based on the design of the trial.”* And lastly, the argument against pooling data from Parts 1 and 2 is valid; however, the Division did not advise to pool data and the results from Part 2 should stand alone.

A brief overview of the regulatory communication with the Applicant involving the conduct of this study is included in the following table.

Table 7. Regulatory Communication Regarding PERSIST Study

Date	Communication / Correspondence / Event
Feb. 17, 2015	Teleconference with the Applicant to discuss additional surgical models to evaluate safety and efficacy of SABER-bupivacaine. Hemorrhoidectomy and bunionectomy were discussed.
Feb. 27, 2015	The Applicant submitted a synopsis of the proposed Phase 3 protocol evaluating the safety and efficacy of SABER-bupivacaine in patients undergoing lap chole. There was no active comparator treatment arm included in the proposed study.
June 15, 2015	The Division sent an Advice Letter indicating no major objections to the proposed protocol.
Aug. 31, 2015	PERSIST study protocol was received.

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Date	Communication / Correspondence / Event
Oct. 22, 2015	Protocol amendment 1 was received.
Jan. 11, 2016	Advice Letter issued requesting additional adverse event and PACU monitoring and the recommendation for an active comparator treatment arm.
Feb. 23, 2016	Protocol amendment 2 received, which addressed some the previously identified safety concerns, but had not included an active comparator.
April 5, 2016	Teleconference between the Division and the Applicant, which included a discussion regarding the need for an active comparator in the study.
April 26, 2016	DURECT notified the Division, via email, that an active bupivacaine HCl treatment group would be included in the PERSIST study.
May 16, 2016	Advice Letter issued regarding unresolved safety and statistical concerns.
June 6, 2016	Protocol amendment 3 received, which incorporated an active control, bupivacaine HCl, and revised primary efficacy endpoint of mean pain intensity to 0 to 48 hours, and recommended safety monitoring. The saline placebo treatment group was dropped and the Applicant incorporated Part 2 of the study.
Sept. 19, 2016	Advice Letter issued regarding the dose of bupivacaine HCl and unresolved safety concerns, 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.
Jan. 19, 2017	Protocol amendment 4 received, which addressed the proposed dose of bupivacaine HCl, measurement of wound-healing issues, and use of post-operative anticoagulant and antiplatelet medications.
Feb. 7, 2017	Teleconference to discuss ongoing safety concerns, including wound-related serious adverse events, cardiac and neurological serious adverse events, stopping criteria, benzyl alcohol safety monitoring, and exclusion criteria.
March 10, 2017	Protocol amendment 5 received, which included recommended safety monitoring. There were no outstanding issues and the protocol was allowed to proceed.

6.2.1. Study Design

Objectives (verbatim)

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 (lap chole).

Part 2 (initiated after the bupivacaine HCl active control group was added)

To evaluate the safety and efficacy of SABER-Bupivacaine for alleviating postoperative pain on movement compared with bupivacaine HCl in patients undergoing lap chole.

The objectives of the study were modified during the study in accordance with FDA guidance and included an active comparator, bupivacaine HCl, in Part 2. The Applicant suggests that because the comparator was changed from normal saline to bupivacaine HCl after the study

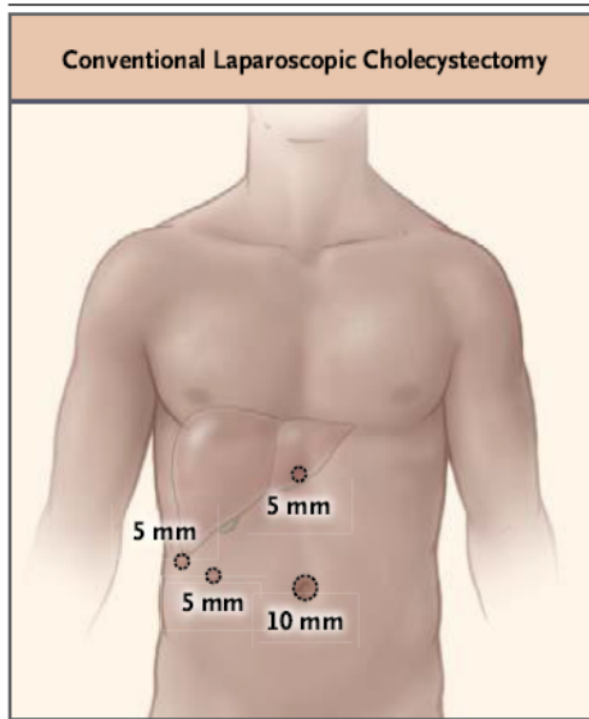
was initiated places the “experimental integrity (i.e., adequacy) of the trial in doubt”, such that the reported efficacy results must viewed with caution.

Trial Design

This 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 in patients undergoing elective outpatient laparoscopic cholecystectomy (lap chole). The initial protocol was designed and powered to test for superiority of SABER-bupivacaine over saline placebo for pain on movement from 0 to 72 hours post-surgery. The anticipated treatment difference in determining the sample size was 0.75, on an 11-point pain scale, with a planned sample size of 153 patients per treatment group. Protocol Amendment 3 was designed and powered to test for superiority of SABER-bupivacaine over bupivacaine HCl for pain on movement from 0 to 48 hours post-surgery. The anticipated treatment difference in determining the sample size was 0.8, on an 11-point pain scale, with a planned sample size of 132 patients per treatment group. The Applicant shortened the observation time to facilitate detection of a statistically significant difference between SABER-bupivacaine and bupivacaine HCl in post-operative pain this surgical model, based on the idea that post-operative pain decreases between 48 to 72 hours regardless of treatment in patients after a lap chole.

The surgical procedure was the four-port lap chole, which used standard trocar sizes of 5 millimeter (mm) and either 10 mm or 12 mm with four abdominal wall incisions, pictured in Figure 8 below. The Applicant has indicated that the number of larger diameter trocars could have been either one or two, with either three or two smaller diameter trocar sites, respectively. Other laparoscopic procedures used to remove the gallbladder, including the natural orifice transluminal endoscopic surgery (NOTES), single incision procedures, and robotic-assisted surgical procedures, were not permitted, nor was the use of smaller size trocars (i.e., 3 mm). A surgical procedure that required conversion to an open technique was an exclusion criterion, based on differences in reported post-surgical pain.

Figure 8. Standard Four-Port Laparoscopic Cholecystectomy Procedure



Source: Baron *et al*, NEJM, 2015.

The Applicant selected the four-port lap chole as an additional surgical model to evaluate the safety and efficacy of SABER-bupivacaine for the following reasons:

- Prevalence of lap chole in the U.S.
- Standardized surgical procedure
- Ability to extrapolate postsurgical analgesia to other laparoscopic procedures
- Relatively young, healthy patient population
- Higher local drug exposure in shorter versus longer surgical incisions, such that wound healing and integrity could potentially be impacted more
- Sufficiently painful surgical procedure, but not so severe that high dose opioids are routinely administered
- Incisional pain is more intense than the intra-abdominal pain
- A previous exploratory study (C803-025) of SABER-bupivacaine in patients undergoing a lap chole demonstrated safe administration using a needle-less technique and improved analgesia in post hoc analyses

The acceptability of the Applicant's rationale for evaluating the safety and efficacy of SABER-bupivacaine in patients undergoing a lap chole is discussed in Section 7.3, Integrated Assessment of Effectiveness. In general, the rationale is acceptable. It's worth mentioning, however, that while Study C803-025, Cohort 2, did demonstrate an improvement in post-operative pain in patients treated with SABER-bupivacaine compared to those treated with bupivacaine HCl, post-operative pain scores were lower than those reported for laparotomy

and lap-assisted colectomy, procedures evaluated in the other cohorts (1 and 3). Furthermore, it is not clear why the Applicant did not evaluate the safety and effectiveness of SABER-bupivacaine in patients undergoing hemorrhoidectomy, as previously proposed.

The surgery was performed under general anesthesia (propofol induction, sevoflurane or desflurane maintenance). Intra-operative analgesia was provided with fentanyl IV, maximum dose 2.5 µg/kg during the first hour of surgery. Additional fentanyl doses were permitted after the first hour, with a maximum dose of 1 µg/kg for each 30-minute surgical interval. Lidocaine IV, up to 40 mg, was permitted during induction to relieve burning associated with propofol administration. A single IV dose of a 5-HT₃ antagonist (i.e., ondansetron, granisetron, dolasetron) was administered to all patients for nausea prophylaxis.

Patients were administered a single dose of study medication during wound closure. For the SABER-bupivacaine treatment group, study drug was administered via a plastic syringe-tip applicator inserted into the wound and directed down to the level of the fascia prior to tying the final subcuticular or interrupted suture. While the surgeon pulled mildly upward on the free ends of the suture to create an intra-incisional space, the prescribed quantity of SABER-bupivacaine drug was instilled into the incision. The applicator was then withdrawn gradually while instilling study drug and ensuring even distribution throughout the wound and no study drug leakage. The final knot was tied skin adhesive was applied per investigator discretion.

For both parts of the study, patients received either 5 mL SABER-bupivacaine (132 mg/mL, 660 mg total dose) or a control treatment. For Part 1, the control group received 5 mL normal saline and for Part 2, the control group received 15 mL bupivacaine HCl 0.5% (75 mg total dose). The randomized treatments were administered as follows:

Table 8. Test Drug Distribution into Laparoscopic Port Sites

Port size ^[1]	SABER-Bupivacaine 5 mL or Sterile Normal Saline 5 mL		Bupivacaine HCl 0.5% 15 mL	
	Target Volume	Percentage of Total	Target Volume	Percentage of Total
4 ports				
5 mm	0.5 mL	10%	1.5 mL	10%
5 mm	0.5 mL	10%	1.5 mL	10%
10-12 mm	2.0 mL	40%	6.0 mL	40%
10-12 mm	2.0 mL	40%	6.0 mL	40%
5 mm	0.8 mL	16%	2.4 mL	16%
5 mm	0.8 mL	16%	2.4 mL	16%
5 mm	0.8 mL	16%	2.4 mL	16%
10-12 mm	2.6 mL	52%	7.8 mL	52%

[1] Refers to the trocar diameter. The actual incision length may have been longer and could have varied depending on the method of abdominal entry.

Source: C803-028 PERSIST Report Body, p. 51 (PDF), Applicant's submission, NDA 204803.

Following surgery, patients were monitored in the post-anesthesia care unit (PACU) for a minimum of two hours, and then discharged once center-approved criteria were met. Rescue medication included intravenous (IV) fentanyl 12.5 to 25 µg per dose, as frequent as every five minutes, while in the PACU, and acetaminophen 500 mg or 1000 mg for mild to moderate pain (not to exceed 4000 mg in 24 hours) and oxycodone (immediate-release, IR) 5 mg or 10 mg for moderate to severe pain self-administered as needed after discharge (not less than four-hour intervals). No combination analgesics (i.e., oxycodone-acetaminophen) or extended-release products were permitted.

Patients were issued an electronic diary (LogPad) at the screening visit and were instructed to complete post-operative pain intensity assessments, document analgesic medication use, including acetaminophen, and the occurrence of adverse events, as summarized in Table 8.

Table 9. Patient LogPad Documentation Schedule

Trial Procedures	Screening	Day of Surgery (Study Day 1)					Study Day 2-4 (Postoperative Day 1 to 3)				Study Day 5-8 (Postop Day 4 to 7)
	Target time	Hours post-dose					Target time (± 1 hour)				until Visit 4 (POD 7)
	20:00 (±1 hour)	1 +1 hour	4 (±30 minutes)	6	8	10	08:00	12:00	16:00	20:00	
Scheduled pain intensity at rest and on movement ¹	√ ² (5-7 days for training)	√ ³	√	√	√	√	√	√	√	√	
Solicited AE checklist ⁴				√		√				√	
Pain at rest and on movement score prior to oral rescue ^{1,5}		Oral med pain scores recorded on LogPad through POD 3 IV med pain scores recorded on chart									
Oral rescue analgesia ⁵		Subject recorded oral rescue medication on LogPad Site recorded IV rescue medication on chart									

AE = adverse event; POD = postoperative day

Note: Subjects were issued a LogPad during screening and returned it at Visit 4 (Study Day 8, POD 7).

- Subjects rested in the supine position for 2 minutes prior to recording their pain-at-rest score. Subjects then recorded their pain-on-movement score by sitting up, or attempting to do so, from a supine position and recording the worst pain experienced during the sit up. If the subject were unable to sit up all the way due to severe pain, weakness, or lack of recovery from anesthesia, the subject was instructed to make his or her best attempt, and that score was recorded.
- During Screening subjects were assigned a LogPad and completed pain intensity at rest and on movement practice diaries for a minimum of 5 days and up to 7 days following LogPad assignment. An additional pain intensity practice diary was done on the day before surgery if the planned Screening period were longer than 7 days. Subjects who were incapable of operating the electronic diary (LogPad) and/or missed more than 1 of the practice assessments (i.e., were less than 80% compliant) during Screening should not have been randomized.
- Investigative site personnel entered the time of test drug dosing into the LogPad prior to the subject awakening from anesthesia.
- At each point of contact with the subject, investigative site personnel followed-up with the subject regarding severity, frequency, duration, and action taken of any AEs (including dizziness, somnolence, constipation, nausea, vomiting, pruritus, headache, dysgeusia, hypoesthesia, and paresthesia) reported on the LogPad.
- Only oral rescue medication was recorded in the LogPad. IV rescue medication and corresponding pain at rest and on movement scores were recorded by the site in the subject's chart and eCRF.

Source: C803-028 PERSIST Report Body, p. 63 (PDF), Applicant's submission, NDA 204803.

Efficacy assessments included the following:

- Evaluations of pain intensity using an 11-point Numeric Pain Rating Scale (NPRS) at rest, with movement, at scheduled intervals, and prior to each analgesic rescue medication dose (with movement involved patients sitting, or attempting to sit, up)
- Use of rescue analgesic medications

Safety assessments included the following:

- Adverse event monitoring, including local anesthetic systemic toxicity (LAST) and benzyl alcohol toxicity assessments
 - Emphasis was on the presence of 10 symptoms of interest at 6 and 10 hours' post-operatively, and then daily by phone on POD 1 and 2 and during the follow-up visit on POD 3
 - the 10 symptoms of interest included dizziness, somnolence, constipation, nausea, vomiting, pruritus, headache, dysgeusia, hypoesthesia, and paresthesia, the latter three added in protocol amendment 2 at the request of the Division
 - If a patient entered a symptom of interest in the LogPad, an email alert notified the investigative center of a required follow-up assessment and the reported symptom was documented as an adverse event
 - Serious cardiac or neurological adverse events that occurred within 48 hours of dosing triggered a blood sample for measurement of serum bupivacaine and benzyl alcohol concentrations
- Physical examination, vital signs
- ECGs (screening and on study days 29 and 60)
- Lab evaluations including chemistry, hematology, urinalysis
- Wound healing assessments
 - serial wound examinations focused on the presence of bruising, hematoma, dehiscence, infection, bleeding, or drainage
 - bruising was measured in centimeters, intensity assessed, presence or degree of blanching assessed, and location documented
 - patient questioning during follow-up phone calls on study days 2 and 3 regarding healing and the presence of wound complications

The following table summarizes the definitions used by the Applicant for surgical site complications.

Table 10. Surgical Site Complication Definitions

Surgical Site Complication	Definition
Peri-incisional Bruising	An area of visible skin discoloration due to extravasation of blood from the incision into the surrounding subcutaneous tissue. May appear within hours of surgery and continue to increase in area over a few days. Initially may have a reddish or maroon color that gradually darkens to a brownish color over a period of days. The bruise should not blanch to finger pressure. If the reddish initial bruising does blanch, then the surgical site should be evaluated for superficial surgical site infection. Over time, the bruise will fade to yellow and then return to normal skin color.
Wound Hematoma	A wound hematoma is a collection of blood and clot in the wound that may produce elevation and discoloration of the wound edges, discomfort, and swelling. Blood may leak through skin sutures. Treatments may include percutaneous drainage or opening the wound for evacuation of the hematoma. A hematoma is almost always caused by imperfect hemostasis. A peri-incisional bruise is not to be termed a hematoma.
Surgical Site Complication	Definition
Wound Dehiscence	<i>Superficial dehiscence:</i> separation of only the cutaneous suture closure. May range from a small partial separation to complete separation of the entire cutaneous suture line. May be treated by re-suturing or allowed to heal by secondary intention. <i>Fascial dehiscence:</i> Separation of the fascial suture closure, with or without concomitant separation of cutaneous layer. May be complicated by extrusion of abdominal viscera. Generally requires operative repair.
Surgical Site Infection	The definitions and diagnostic criteria adopted by the Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network (NHSN) were used for this study (Appendix 5 of the protocol).
Surgical Site Bleeding	Defined as blood emanating from the surgical incision after wound closure. Mild bleeding is defined as spotting of blood on the dressing that does not progress and does not require treatment. Moderate bleeding may soak the entire dressing and requires dressing change. Severe bleeding extends beyond the dressing and may require surgical intervention for treatment.
Drainage from the Surgical Incision(s)	Drainage from the surgical incision is defined as the seeping or oozing of fluid from the wound. If the drainage fluid is straw colored, it should be recorded as serous drainage. If the fluid is tinted red, the drainage is termed serosanguinous. If the fluid contains pus, the drainage is termed purulent.

Source: C803-028 PERSIST Report Body, p. 69-70 (PDF), Applicant's submission, NDA 204803.

As summarized in the following table, patients were contacted via telephone on study days 2 and 3 (post-operative days (POD) 1 and 2) for prespecified safety assessments. Patients

returned to the investigative site for four additional follow-up assessments on study days 4, 8, 15, and 29 (PODs 3, 7, 14, 28). Patients enrolled after protocol amendment five was implemented underwent additional safety assessments on study day 60 (POD 59). All safety visits recorded spontaneously-reported and solicited adverse events, and included serial examinations of the surgical wound.

Table 11. Schedule of Events

	Visit 1	Visit 2	Follow-up Call 1	Follow-up Call 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Screening ≥5 days (starts ≤30d and ≥5d pre-op)	Day of Surgery (Study Day 1)	Study Day 2	Study Day 3	Study Day 4	Study Day 8 (±1 day)	Study Day 15 (±2 days)	Study Day 29 (±3 days)	Study Day 60 (±3 days)
Trial Procedures			POD 1	POD 2	POD 3	POD 7 (±1 day)	POD 14 (±2 days)	POD 28 (±3 days)	POD 59 (±3 days)
Informed Consent (prior to any trial procedures)	√								
Demographics and Medical & Surgical History	√								
Physical Examination (including height and weight)	√							√ ¹	√ ¹
Inclusion / Exclusion Criteria	√	√ ²							
Safety Labs (Chemistry, Hematology, Urinalysis)	√ ³				√			√	√
Pregnancy Test	√ ⁴	√ ⁵							
12-lead ECG	√							√	√
Vital Signs ⁶ (BP, HR, RR, T) and SpO ₂ ⁷	√	√ ⁷			√	√	√	√	√
Dispense LogPad and Train in Use	√								
Subject Watches Training Video ⁸	√ ⁹	√							
Adverse Events ^{10,11}									
Prior and Concomitant Medications									
IWRS Randomization		√ ¹²							
Review LogPad Instructions Pre-op		√							
Surgery		√							
Dosing of Test Drug		√							
Re-dispense LogPad to Subject after Enter Time of Dosing		√							
mPADSS and PACU time of discharge ¹³		√							
Subject LogPad Evaluations ¹⁴	√								
Rescue Medication and Pain Scores ¹⁵									
Surgical Site Exam and Assessment of Surgical Site AEs		√ ¹⁶			√	√	√	√	√
Discharge from hospital/surgicenter (≥ 2 hours post-dose)		√							
Rescue Medication Reconciliation/Pill Count		√ ¹⁷			√	√	√	√	*

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Surgical Complications Questionnaire			√	√					
Level of Activity (ambulation, sleeping, eating, and surgical wound pain ¹⁸)			√	√	√	√ ¹⁸	√ ¹⁸	√ ¹⁸	*
Medical Resource Utilization Assessment			√	√	√	√	√	√	*
Review LogPad data		√	√	√	√	√			

AE = adverse event; BP = blood pressure; d = day; ECG = electrocardiogram; eCRF = electronic case report form; HR = heart rate; IV = intravenous; IWRS = interactive web response system; mPADSS = modified Post-Anesthesia Discharge Scoring System; NSAID = non-steroidal anti-inflammatory drug; PACU = post-anesthesia care unit; POD = postoperative day; RR = respiratory rate; SpO₂ = oxygen saturation; T = temperature

Note: Subjects enrolled prior to IRB approval of Amendment 5 did not need to return for a Study Day 60 visit.

- 1 Weight only
- 2 Review Inclusion/Exclusion Criteria to confirm subject is still eligible
- 3 In addition to safety labs, a urine drug screen for opiates, oxycodone, cannabinoids, amphetamines, cocaine, and methadone was performed. Three to 7 days were allowed for central safety laboratory to process and provide results.
- 4 Serum pregnancy test for females of childbearing potential.
- 5 Urine pregnancy test for females of childbearing potential.
- 6 Vital signs were measured after 5 minute rest (supine or sitting).
- 7 Vital signs and pulse oxygen saturation (SpO₂) were measured on Visit 2 pre- and post-surgery. The vital signs (BP, HR, RR, temperature) and SpO₂ were recorded on the eCRF at 15-minute intervals for a period of at least 2 hours after surgery.
- 8 All subjects watched the training video which was designed to inform the subject of the research goals of the trial, how to properly estimate their pain scores, and how to appropriately use rescue medications.
- 9 Subjects completed the Post Video Training Assessment.
- 10 AE collection started from the time the subject signed the consent form and continued through final visit/early termination. All AEs were followed until resolution. Resolution meant no further changes in the event were expected, i.e., the point at which a subject experiencing such an AE was appropriately treated and stabilized even though he or she may have continued to experience lingering sequelae that may never have resolved.
- 11 Follow-up on both the pre-specified subject-reported AEs (including dizziness, somnolence, constipation, nausea, vomiting, pruritus, headache, dysgeusia, hypoesthesia, and paresthesia) solicited on the LogPad through POD 3, as well as spontaneous AEs.
- 12 If all Screening (i.e., pre-operative) Inclusion/Exclusion criteria were met randomization can be done up to 1 business day prior to surgery.
- 13 Eligibility for PACU discharge was assessed by mPADSS. The mPADSS was administered starting at 30 minutes after admission to the PACU and were repeated at 15 minute intervals until a score of 9 or greater was reached, indicating discharge eligibility.
- 14 Subjects rested in the supine position for 2 minutes prior to recording their pain-at-rest score. Subjects then recorded their pain-on-movement score by sitting up, or attempting to do so, from a supine position and recording the worst pain experienced during the sit up. If the subject were unable to sit up all the way due to severe pain, weakness, or lack of recovery from anesthesia, the subject was instructed to make his or her best attempt, and that score was recorded. Subjects completed assessments per the schedule detailed in Table 3.
- 15 See Rescue Medication Regimen. Pre-rescue pain on movement score for oral rescue was recorded in the LogPad through Study Day 4. The site recorded IV rescue medication taken and corresponding pain score in the subject's chart and eCRF. The subject recorded oral opioid and acetaminophen rescue medication taken on the LogPad until Study Day 8. After Study Day 8 all rescue medication were recorded in the investigative site source documents and Concomitant Medication eCRF. NSAIDs were not allowed until after Study Day 8.
- 16 On the day of surgery, Surgical Site Examination was done at time of discharge to home (or hospital admission).
- 17 Record details of opioid prescription and acetaminophen dispensed for home use (identity, dose, amount dispensed, and dosing instructions) and if permitted, retain a copy of the opioid prescription in the source documents.
- 18 The site asked the subject to rate their current surgical wound pain at Visit 4, 5, and 6.

* To be done only if completed as part of an Early Termination Visit

Source: C803-028 PERSIST Report Body, p. 61-62 (PDF), Applicant' submission, NDA 204803.

Key Eligibility Criteria

Inclusion Criteria

- Scheduled for elective outpatient lap chole using a conventional 4-port procedure
- Male or female adult patients, 18 years or older
- American Society of Anesthesiologists (ASA) Class I, II, or III
- If child-bearing, had to agree to use a medically acceptable method of contraception to prevent pregnancy for the duration of their participation in the trial. Medically acceptable methods of contraception that could be used by the subject and/or the partner included: oral contraception or patches (consistently or 3 months prior to trial dosing), NuvaRing®
- Able to comply with scheduled follow-up visits

Exclusion Criteria

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- Pregnant or lactating
- Absolute and relative contraindications to lap chole
- Prior midline incision presenting a risk for adhesions that could complicate the procedure or post-operative pain assessments
- Emergent or urgent surgery needed
- Planned hospital admission
- Amide local anesthetic sensitivity
- Chronic pain unrelated to gallbladder disease
- Depression, psychosis
- Long-term opioid or other analgesic therapy
- Alcohol dehydrogenase deficiency (self-reported)
- Intra-operative exclusion criteria
 - procedure converted to open
 - unplanned additional procedures
 - high intra-operative fentanyl doses required
 - placement of fifth port or surgical drain

Study Endpoints

Primary Efficacy Endpoints

- Part 1: Pain intensity on movement (defined as sitting, or attempting to sit, up) measured at scheduled time points from 0 to 72 hours following test drug administration. Because patient enrollment was stopped prematurely based on advice provided by the Division to include an active comparator arm, the number of treated patients was lower than planned, resulting in 50% power based on the original effect size assumption. Therefore, the efficacy outcomes for Part 1 are descriptive only.
- 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 mixed model of repeated measures (MMRM). The rationale for changing the primary outcome measurement interval to 0 to 48 hours was based on results from an earlier lap chole study (C803-025, Cohort 2), indicating the effect size for pain on movement from 0 to 48 hours could be increased by as much as 20% when compared to the 0 to 72-hour interval.

Key Secondary Efficacy Endpoints

- Part 1: Total IV morphine-equivalent dose of rescue opioids used during 0 to 72 hours
- Part 2: Pain intensity on movement measured at scheduled time points from 0 to 72 hours

Additional Secondary Efficacy Endpoints

- Total IV morphine-equivalent dose of rescue opioids used during 0 to 72 hours following test drug administration

- Composite endpoint of Silverman's Integrated Analgesic (SIA) assessment score over 0 to 72 hours
- Proportion of patients taking no opioid rescue medication from PACU discharge through 72 hours
- Time to first opioid rescue after PACU discharge
- Time to PACU discharge eligibility using the Modified Post-Anesthesia Discharge Scoring System (mPADSS).

Exploratory Efficacy Endpoints

- Percentage of patients with at least 75% of scheduled pain intensity on movement scores less than or equal to three and no more than one dose of opioid rescue analgesia during a 24-hour assessment. Only data after PACU discharge were used to determine whether a patient was a responder
- Pain intensity at rest measured at scheduled time points from 0 to 72 hours (Part 1) and 0 to 48 hours (Part 2)
- Time to actual discharge from PACU. For sites with a Phase 2 recovery unit, this endpoint was defined as the time to hospital discharge.

Safety Endpoints

- Incidence of adverse events, including both pre-specified, solicited and spontaneously reported
- Incidence of LogPad-solicited symptoms at any time
- Incidence of LogPad-solicited symptoms in the first six hours (later revised to within the first 10 hours)
- Time to occurrence of solicited symptoms
- Time to PACU discharge
- ECG changes from screening to study day 29 (revised to study day 60 in protocol amendment five)
- Laboratory test result changes from screening to study day 29 (revised to study day 60 in protocol amendment five)
- Change in vital signs from screening to each scheduled visit
- Prevalence at each scheduled visit, and the times to onset and to resolution of six surgical site complications of interest and an assessment of surgical wound healing as normal or abnormal

Statistical Analysis Plan

Part 1 efficacy endpoints were analyzed over a 0 to 72 hour post-treatment period, as specified in the protocol prior to the addition of Part 2. Because full enrollment was not completed, Part 1 efficacy comparisons to saline placebo are descriptive only and presented as either a mean or ratio. The Part 2 primary efficacy endpoint was analyzed over a 0 to 48-hour post-treatment period and the Applicant indicated this would increase treatment effect size and study power. Part 2 secondary and exploratory efficacy endpoints, however, were computed over a 72-hour

period, and to provide increased statistical power, data from the SABER-bupivacaine arms in both Part 1 and Part 2 were combined for the comparison with bupivacaine HCl. The Applicant stated, however, that the prespecified pooling of SABER-bupivacaine data from Parts 1 and 2 for comparison with bupivacaine HCl data was not justified, given the difference in objectives and methodology between the two study parts.

All efficacy endpoints were analyzed using a modified intent-to-treat (mITT) population, defined as all randomized patients who received any test drug.

Refer to the statistical review by Dr. Kate Meaker for additional information.

Protocol Amendments

There were five protocol amendments to the original protocol, dated Aug. 26, 2015, implemented over the course of this study. Protocol amendment three was the most clinically significant and involved a change in comparator drugs from normal saline to bupivacaine HCl and, as indicated above, was implemented at the request of the Division. The following table summarizes the key changes implement with each amendment and the corresponding date.

Table 12. Protocol Amendments, Key Clinical Changes

Amendment and Date	Key Clinical Changes
1 Oct. 6, 2015	- Clarified pain data capture - Added urine drug screening - Clarified study drug administration instructions
2 Feb. 22, 2016	- All AEs should be followed to resolution - Dysgeusia, paresthesia, and hypoesthesia added to listed of AEs of special interest* - Added/clarified additional vital sign capture* - Dehiscence, hematoma, and infection added as SAEs* - Additional stopping criteria added* - Statistical analysis revisions
3 June 2, 2016	- Bupivacaine HCl treatment group added* - Revised efficacy endpoints based on additional treatment group - Intra-operative fentanyl dosing clarified - Additional stopping criteria* - Increased PACU monitoring time*
4 Jan. 9, 2017	- Blinding procedures emphasized - Stopping criteria and safety committee charter modified * - Pre-operative insertion of cholecystostomy tube listed as exclusion criterion
5 March 8, 2017	- Study Day 60 visit added* - Clarified permitted medications through day 60 - Blood sample collection in the event of cardiac or neurological SAE*

Amendment and Date	Key Clinical Changes
	- Self-reported alcohol dehydrogenase deficiency listed as exclusion criterion* - Stopping criteria and safety committee charter modified *

*Based on FDA advice.

6.2.2. Study Results

Compliance with Good Clinical Practices

Per the study report for PERSIST, *“This study was conducted in accordance with the principles of Good Clinical Practice set forth in the International Conference on Harmonisation, the United States Code of Federal Regulations (Title 21), the Health Insurance Portability and Accountability Act of 1996, and any local requirements.”*

Financial Disclosure

There were no clinical investigators who appeared to have a financial interest in or arrangement with the Applicant. Two studies, BU-002-IM and BU-001-IM, were sponsored, conducted and statistically analyzed by (b) (4) partner of the Applicant. Responsibility for the studies has recently been transferred to the Applicant, therefore, clinical investigators from the two studies have been included on Form FDA 3454.

Patient Disposition

Overall, 399 patients were randomized and included in the intent-to-treat (ITT) population; 94 patients in Part 1 and 305 patients in Part 2. Eleven patients were randomized but not treated based on pre-operative anesthetic requirements, intraoperative complications, and procedure delay beyond the 30-day screening window. There were 388 patients in the safety population and 388 in the modified ITT population. A combined total of 193 patients were treated with SABER-bupivacaine in Parts 1 and 2.

There were 46 patients treated in each group in Part 1 and 148 patients treated in each group in Part 2 (mITT). One patient was randomized to the SABER-bupivacaine group, but received saline placebo, resulting in a change in the number of patients in each group between the safety and mITT populations. A total of four patients, all in the bupivacaine HCl treatment group, did not complete the study. One patient (b) (6) developed acute biliary pancreatitis and was discontinued. Three patients (b) (6) withdrew on study days 31, 59, and 24, respectively, due to difficulty attending post-operative follow-up visits.

Patient disposition is summarized in the following table.

Table 13. Patient Disposition, Part 1 and Part 2

	Part 1		Part 2		Parts 1 & 2	Study Total
	SABER-Bupivacaine	Saline Placebo	SABER-Bupivacaine	Bupivacaine HCl	SABER-Bupivacaine	
Screen failures	–	–	–	–	–	92
Subjects randomized (ITT Population)	48	46	153	152	201	399
Randomized and dosed prior to Amendment 5	46	46	103	103	149	298
Randomized, not dosed prior to Amendment 5 ^[1]	2	0	5	3	7	10
Randomized and dosed under Amendment 5	NA	NA	45	45	45	90
Randomized, not dosed under Amendment 5 ^[1]	NA	NA	0	1	0	1
Safety Population ^[2]	45	47	148	148	193	388
mITT Population	46	46	148	148	194	388
Study completion, n (%)						
Completed on Day 29 (prior to Amendment 5) ^[3]	46 (100)	46 (100)	103 (69.6)	102 (68.9)	149 (76.8)	297 (76.5)
Completed on Day 60 (under Amendment 5) ^[3]	N/A	N/A	45 (30.4)	42 (28.4)	45 (23.2)	87 (22.4)
Total completing study	46 (100)	46 (100)	148 (100)	144 (97.3)	194 (100)	384 (99.0)
Did not complete study	0	0	0	4 (2.7)	0	4 (1.0)
Primary reason for discontinuation, n (%)						
Lost to Follow-up	0	0	0	0	0	0
Adverse event	0	0	0	1 (0.7)	0	1 (0.3)
Lack of Efficacy	0	0	0	0	0	0
Subject decision	0	0	0	1 (0.7)	0	1 (0.3)
Investigator Decision	0	0	0	0	0	0
Death	0	0	0	0	0	0
Other	0	0	0	2 (1.4)	0	2 (0.5)

ITT = intention-to-treat; mITT = modified intention-to-treat; N/A = not applicable

Note: Percentages are based on the mITT population.

[1] "Randomized not dosed" included subjects who met intra-operative exclusion criteria, were given non-allowed peri-operative medication, had their surgery delayed, or withdrew consent prior to surgery.

[2] Difference in treatment group N between the Safety and mITT populations is due to a dispensing error deviation for Subject (b) (6), which led to a difference in planned versus actual treatment received

[3] Subjects enrolled before protocol Amendment 5 (8 March 2017) completed the study at Visit 6 on Study Day 29. Subjects enrolled under Amendment 5 completed the study at Visit 7 on Study Day 60.

Source: C803-028 PERSIST Report Body, p. 90 (PDF), Applicant's submission, NDA 204803.

Protocol Violations/Deviations

The majority of protocol deviations were in the visit/procedure required (28% of patients), concomitant medications (26% of patients), and non-compliance (11% of patients) categories. No deviation resulted in the patient being excluded from the efficacy or safety analyses. The following table summarizes the protocol deviations by study part and treatment group.

Table 14. Protocol Deviations, All Randomized Patients

Deviation Category	Part 1		Part 2		Combined Parts 1 & 2 SABER- Bupivacaine (N=201)	Study Total (N=399)
	SABER- Bupivacaine (N=48)	Saline Placebo (N=46)	SABER- Bupivacaine (N=153)	Bupivacaine HCl (N=152)		
Enrollment Criteria	2 (4.2%)	1 (2.2%)	0 (0.0%)	3 (2.0%)	2 (1.0%)	6 (1.5%)
Informed Consent	5 (10.4%)	0 (0.0%)	18 (11.8%)	15 (9.9%)	23 (11.4%)	38 (9.5%)
Non-Compliance	0 (0.0%)	0 (0.0%)	26 (17.0%)	18 (11.8%)	26 (12.9%)	44 (11.0%)
Dosing	1 (2.1%)	1 (2.2%)	2 (1.3%)	0 (0.0%)	3 (1.5%)	4 (1.0%)
Concomitant Medications	16 (33.3%)	15 (32.6%)	35 (22.9%)	37 (24.3%)	51 (25.4%)	103 (25.8%)
Regulatory	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)	1 (0.5%)	2 (0.5%)
Laboratory	0 (0.0%)	1 (2.2%)	8 (5.2%)	1 (0.7%)	8 (4.0%)	10 (2.5%)
Visit/Procedure Required	23 (47.9%)	16 (34.8%)	34 (22.2%)	39 (25.7%)	57 (28.4%)	112 (28.1%)
Visit Schedule	7 (14.6%)	6 (13.0%)	12 (7.8%)	11 (7.2%)	19 (9.5%)	36 (9.0%)
Other	2 (4.2%)	1 (2.2%)	0 (0.0%)	1 (0.7%)	2 (1.0%)	4 (1.0%)

Source: C803-028 PERSIST Report Body, Table 14.1.2 p. 166 (PDF), Applicant's submission, NDA 204803.

One patient ((b) (6)) in Part 1 was randomized to receive SABER-bupivacaine but was treated with saline placebo. For the mITT population (and all efficacy analyses), this patient was included in the SABER-bupivacaine treatment group and for the safety population (and all safety analyses), this patient was included in the saline placebo treatment group.

There were four patients in Part 1, investigative site 17, who may have had their drug assignment revealed to blinded staff due to notes taken by the circulating OR nurse. Further investigation suggested that unblinding did not occur and no deviation was reported. This site, however, did not participate in Part 2 of the study.

There were 38 patients in the “noncompliance” category in Part 2 who may have also been unblinded to study staff. Apparently, information regarding study drug, volume, or route of administration was included in the patient's medical record and was not redacted prior to including the record in the study file. The major deviations that included unblinding of the study drug name or volume were reviewed prior to database lock. Those that revealed the route of administration were not reviewed as terms were used interchangeably (i.e., injection and infiltration) to convey the same route of administration. The Applicant did not exclude any of the 38 patients from the efficacy analyses based on the following rationale:

- primary efficacy endpoint data was patient-reported pain scores and analgesic use
- the timing of when the hospital record would have been available to blinded study staff likely would not have impacted in-hospital data collection
- the protocol and SAP specified the mITT population would be used
- post-hoc sensitivity analysis conducted without the 38 patients did not change the primary efficacy endpoint results

Demographic and Baseline Characteristics

Demographic and other baseline characteristics are presented in the following table. Briefly, the majority of treated patients were White (89%), female (74%), not Hispanic or Latino (66%), and the mean age was 45 years. Based on the disease process, a younger and larger female distribution is expected. Differences in demographics across treatment groups included the following:

- A lower percentage of patients > 65 years of age treated with saline placebo in Part 1
- A higher percentage of female patients treated in Part 2 compared to Part 1
- A higher percentage of African Americans in the SABER-bupivacaine treatment group in Part 1 compared to the other treatment groups
- A higher percentage of Hispanic or Latino patients treated in Part 2 compared to those treated in Part 1
- A higher percentage of ASA 1 physical status patients treated in Part 2 compared to those treated in Part 1

Some of the above-noted differences between the parts of the study may have been due to a larger number of patients treated in Part 2 and are unlikely to significantly impact the reported safety or efficacy conclusions. Refer to the following table for additional demographic information.

Table 15. Summary of Demographic and Baseline Characteristics (Safety Population)

	Part 1		Part 2		Parts 1 & 2	Study Total (N=388)
	SABER- Bupivacaine (N=45)	Saline Placebo (N=47)	SABER- Bupivacaine (N=148)	Bupivacaine HCl (N=148)	SABER- Bupivacaine (N=193)	
Age (years)						
Mean (SE)	46.6 (2.13)	41.4 (1.88)	44.9 (1.07)	45.3 (1.13)	45.3 (0.95)	44.8 (0.68)
SD	14.28	12.87	12.96	13.72	13.26	13.42
Median	45.0	42.0	44.0	45.0	44.0	44.0
Min, max	22, 76	18, 67	19, 74	18, 77	19, 76	18, 77
Age group, n (%)						
<45 years	21 (46.7)	24 (51.1)	79 (53.4)	72 (48.6)	100 (51.8)	196 (50.5)
45 to 65 years	19 (42.2)	22 (46.8)	55 (37.2)	62 (41.9)	74 (38.3)	158 (40.7)
>65 years	5 (11.1)	1 (2.1)	14 (9.5)	14 (9.5)	19 (9.8)	34 (8.8)
Sex, n (%)						
Male	16 (35.6)	17 (36.2)	36 (24.3)	34 (23.0)	52 (26.9)	103 (26.5)
Female	29 (64.4)	30 (63.8)	112 (75.7)	114 (77.0)	141 (73.1)	285 (73.5)
Race, n (%)						
Asian	2 (4.4)	2 (4.3)	5 (3.4)	6 (4.1)	7 (3.6)	15 (3.9)
Black or African American	6 (13.3)	4 (8.5)	6 (4.1)	9 (6.1)	12 (6.2)	25 (6.4)
White	37 (82.2)	41 (87.2)	136 (91.9)	131 (88.5)	173 (89.6)	345 (88.9)
Other	0	0	1 (0.7)	2 (1.4)	1 (0.5)	3 (0.8)
Ethnicity, n (%)						
Hispanic or Latino	7 (15.6)	8 (17.0)	64 (43.2)	55 (37.2)	71 (36.8)	134 (34.5)
Not Hispanic or Latino	38 (84.4)	39 (83.0)	84 (56.8)	93 (62.8)	122 (63.2)	254 (65.5)
Body Mass Index (kg/m ²)						
Mean (SE)	30.7 (0.95)	32.2 (1.10)	30.7 (0.58)	32.3 (0.56)	30.7 (0.50)	31.4 (0.35)
SD	6.36	7.53	7.12	6.79	6.93	6.98
Median	30.9	30.8	29.0	31.3	29.3	30.5
Min, max	18, 51	21, 61	16, 59	18, 55	16, 59	16, 61
	Part 1		Part 2		Parts 1 & 2	Study Total (N=388)
	SABER- Bupivacaine (N=45)	Saline Placebo (N=47)	SABER- Bupivacaine (N=148)	Bupivacaine HCl (N=148)	SABER- Bupivacaine (N=193)	
ASA physical status classification, n (%)						
I (normal healthy patient)	14 (31.1)	13 (27.7)	87 (58.8)	76 (51.4)	101 (52.3)	190 (49.0)
II (patient with mild systemic disease)	27 (60.0)	26 (55.3)	55 (37.2)	63 (42.6)	82 (42.5)	171 (44.1)
III (patient with severe systemic disease)	4 (8.9)	8 (17.0)	6 (4.1)	9 (6.1)	10 (5.2)	27 (7.0)

ASA = American Society of Anesthesiologists; Max = maximum; Min = minimum; mITT = modified intent-to-treat; SD = standard deviation; SE = standard error

Source: C803-028 PERSIST Report Body, p. 93-94 (PDF), Applicant's submission, NDA 204803.

Other Baseline Characteristics

The most common medical histories reported in patients in all treatment groups included gallbladder disorder, biliary colic, cholelithiasis, headache, hypertension, and GERD. The majority of patients had multiple episodes of biliary colic and no prior treatment for gallstones. The prevalence of protocol-specified medical history, which included smoking, alcohol use (occasional and daily), Type 1 or 2 diabetes, anxiety (mild, moderate, on medication), depression, or headaches (occasional, frequent, migraine), did not vary significantly between treatment groups or across parts of the study, with the following exceptions:

- There was a higher percentage of current smokers in the saline placebo treatment group compared to other treatment groups in both parts of the study

- There was a higher percentage of patients with a history of Type 2 diabetes in the bupivacaine HCl-treated patients in Part 2 compared to other treatment groups. This may be clinically relevant given the known correlation between poor glycemic control and post-operative wound infection, a key clinical concern identified with administration of SABER-bupivacaine.
- There was a higher percentage of patients in the saline placebo (Part 1) and bupivacaine HCl (Part 2) treatment groups with a history of mild anxiety compared to both SABER-bupivacaine treatment groups.
- A lower percentage of patients treated with SABER-bupivacaine in Part 1 had a history of migraine headache. This may be clinically relevant considering an adverse event of interest associated with BA toxicity is headache.

A history of previous abdominal surgery is relevant in this study because of the potential for the development of intraabdominal adhesions, which can lead to complications such as bowel obstruction and technical difficulties during surgical re-exploration. The Applicant identified a single patient ((b) (6)) treated with bupivacaine HCl in Part 2 of the study who had adhesions reported during the surgical procedure; however, it does not appear there were any intraoperative complications as a result. Caesarean delivery was the most common abdominal surgery reported, with a prevalence of 17% across the study. There was a similar incidence of previous abdominal surgery across treatment groups with the following exceptions:

- There was a higher percentage of patients treated in Part 1, compared to Part 2, with a history of:
 - colectomy
 - previous laparoscopy
- There was a higher percentage of patients treated with SABER-bupivacaine in Part 1 with a history of:
 - total abdominal hysterectomy
 - umbilical hernia repair
- There was a higher percentage of patients treated in Part 2, compared to Part 1, with a history of:
 - caesarean delivery
 - female sterilization

The differences in previous medical or surgical history likely did not impact the reported safety and efficacy conclusions for SABER-bupivacaine.

The majority of patients (77%) across the study had prior medication use. The most common prior medications used are summarized by Anatomic Therapeutic Class in the following table.

Table 16. Prior Medication Use Reported for $\geq 10\%$ of Treated Patients (Safety Population)

ATC Class 1	Part 1		Part 2		Parts 1 & 2	Study Total (N=388)
	SABER- Bupivacaine (N=45)	Saline Placebo (N=47)	SABER- Bupivacaine (N=148)	Bupivacaine HCl (N=148)	SABER- Bupivacaine (N=193)	
Subjects receiving any chronic prior medication, n (%)	34 (75.6)	34 (72.3)	105 (70.9)	105 (70.9)	139 (72.0)	278 (71.6%)
Medication class, n (%)						
Alimentary tract and metabolism	18 (40.0)	21 (44.7)	75 (50.7)	61 (41.2)	93 (48.2)	175 (45.1)
Blood and blood forming organs	7 (15.6)	4 (8.5)	19 (12.8)	16 (10.8)	26 (13.5)	46 (11.9)
Cardiovascular system	19 (42.2)	13 (27.7)	40 (27.0)	45 (30.4)	59 (30.6)	117 (30.2)
Genitourinary system and sex hormones	9 (20.0)	6 (12.8)	20 (13.5)	21 (14.2)	29 (15.0)	56 (14.4)
Musculoskeletal system	11 (24.4)	8 (17.0)	21 (14.2)	25 (16.9)	32 (16.6)	65 (16.8)
Nervous system	7 (15.6)	7 (14.9)	21 (14.2)	30 (20.3)	28 (14.5)	65 (16.8)
Respiratory system	9 (20.0)	7 (14.9)	19 (12.8)	33 (22.3)	28 (14.5)	68 (17.5)

mITT = modified intent-to-treat

Note: any medication taken prior to the earliest pre-anesthesia treatment for at least 30 days was summarized as a chronic prior medication.

Source: C803-028 PERSIST Report Body, p. 98 (PDF), Applicant's submission, NDA 204803.

Patients with a history of depression, psychosis, or chronic pain receiving chronic analgesic therapy were excluded from participation in the study. Post-randomization, or intra-operative, exclusion criteria included the following:

- procedure converted to open cholecystectomy
- unexpected intra-operative complications
- additional surgical procedure(s) performed, aside from cholangiogram or lysis of adhesions
- increased intra-operative narcotic requirement
- additional port or surgical drain required

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study drug compliance was 100% for patients who received treatment.

The majority of concomitant medications administered during the surgery were anesthetics, analgesics, sedatives, paralytics, antibiotics for surgical site infection prophylaxis, and antiemetics.

Permitted rescue medication included IV fentanyl while in the PACU, and oral immediate-release oxycodone and acetaminophen for home use. Combination or extended-release analgesics or NSAIDs were prohibited during the study. The overall use across different treatment groups is described throughout this review, as pertinent to efficacy data.

Characteristics of the Surgical Procedure

As previously discussed, the lap chole surgery was described as a four-port procedure, with two to three 5 mm ports and one to two 10 to 12 mm ports. If three 5 mm and one 10 to 12 mm ports were used, the cumulative incision length would be between 25 to 27 mm (2.5 to 2.7 cm). If two 5 mm and two 10 to 12 mm ports were used, the cumulative incision length would be between 30 to 34 mm (3 to 3.4 cm). The mean cumulative incision length is described in the table below, in addition to other characteristics of the surgical procedure.

Table 17. Characteristics of the Surgical Procedure

	Part 1		Part 2		Parts 1 & 2
	SABER-Bupivacaine (N=45)	Saline Placebo (N=47)	SABER-Bupivacaine (N=148)	Bupivacaine HCl (N=148)	SABER-Bupivacaine (N=193)
Cumulative incision length, cm					
Mean (SE)	4.6 (0.26)	5.0 (0.22)	4.2 (0.15)	4.1 (0.14)	4.3 (0.13)
Median	4.8	5.3	3.5	3.1	3.6
Min, Max	2.0, 9.5	2.6, 9.0	2.5, 9.0	1.7, 8.5	2.0, 9.5
Bupivacaine dose per cm, mg/cm					
Mean (SE)	165.7 (9.77)	0.0 (0.00)	183.9 (5.41)	21.4 (0.62)	179.6 (4.75)
Median	137.5	0	191.3	24.6	183.3
Min, Max	69.5, 330.0	0.0, 0.0	73.3, 264.0	8.8, 44.1	69.5, 330.0
Duration of surgery, min					
Mean (SE)	43.2 (2.34)	41.4 (2.31)	49.8 (1.91)	49.3 (1.88)	48.3 (1.57)
Median	39	36	44	46	43
Min, Max	20.0, 83.0	20.0, 87.0	20.0, 178.0	13.0, 156.0	20.0, 178.0
Difficulty of surgery, n (%)					
Easy	22 (48.9%)	20 (42.6%)	71 (48.0%)	63 (42.6%)	93 (48.2%)
Moderate	22 (48.9%)	22 (46.8%)	65 (43.9%)	70 (47.3%)	87 (45.1%)
Difficult	1 (2.2%)	5 (10.6%)	12 (8.1%)	15 (10.1%)	13 (6.7%)
Details of surgical procedure, n (%)					
Placement of percutaneous surgical drain	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Intraoperative cholangiogram	23 (51.1%)	30 (63.8%)	38 (25.7%)	39 (26.4%)	61 (31.6%)
Procedure to remove common duct stones	1 (2.2%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.5%)
Port incision extended for gall bladder extraction	8 (17.8%)	4 (8.5%)	29 (19.6%)	24 (16.2%)	37 (19.2%)

Intraoperative complications, n (%)					
Evidence of intraoperative infection	0 (0.0%)	0 (0.0%)	5 (3.4%)	3 (2.0%)	5 (2.6%)
Excessive bleeding or hemorrhage	0 (0.0%)	0 (0.0%)	5 (3.4%)	5 (3.4%)	5 (2.6%)
Injury to bile ducts	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.0%)	0 (0.0%)
Common bile duct stones retained	1 (2.2%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.5%)
Bile spilled	9 (20.0%)	11 (23.4%)	30 (20.3%)	31 (20.9%)	39 (20.2%)
Stones left in peritoneum	0 (0.0%)	0 (0.0%)	1 (0.7%)	3 (2.0%)	1 (0.5%)
Any unexpected pathology discovered	1 (2.2%)	0 (0.0%)	0 (0.0%)	2 (1.4%)	1 (0.5%)
Other operative complications	0 (0.0%)	0 (0.0%)	2 (1.4%)	1 (0.7%)	2 (1.0%)

Max = maximum; Min = minimum; SE = standard error

Source: C803-028 PERSIST Report Body, p. 100 (PDF), Applicant's submission, NDA 204803.

Approximately 37% (145/388) of treated patients had cumulative incision lengths of 50 mm (5 cm) or longer, with 95 mm (9.5 cm) the maximum cumulative length reported in the study. There did not appear to be clinically significant differences in the percentage of patients with longer cumulative incision lengths between treatment groups in each part of the study, suggesting there was likely no difference in reported pain across treatment groups as a result of longer incisions. An additional consideration relative to the incision length is the amount of medication administered. Specifically, shorter incisions will have a larger volume of medication per millimeter of wound compared to longer incisions, which may have an impact on wound healing, including complications of drainage, infection, and dehiscence. Refer to the safety discussion in section 8.2.5 for additional information regarding wound healing and surgical site complications.

Other notable findings in the above table include a reported higher level of difficulty in more comparator treatment groups, saline placebo (Part 1) and bupivacaine HCl (Part 2), than in the respective SABER-bupivacaine treatment groups. Increase surgical difficult could imply a longer or more extensive surgical dissection potentially resulting in more tissue damage and post-operative pain. Additionally, the SABER-bupivacaine-treated patients had a higher incidence of incision extension for gallbladder removal than patients treated with saline placebo in Part 1 of the study.

Efficacy Results – Primary and Secondary Endpoints

Unless otherwise indicated, the efficacy analyses were conducted on the mITT population, which was defined as those patients randomized and treated, regardless of collected efficacy data. The results for the primary efficacy endpoints for Part 1 and Part 2 are summarized in the following table.

Table 18. Primary Efficacy Endpoint Results For Part 1 and Part of the Study (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 \(Appendix 16.1.9\)](#).

Source: C803-028 PERSIST Report Body, p. 102 (PDF), Applicant's submission, NDA 204803.

For Part 1, the comparison was between SABER-bupivacaine (Part 1 patients only) and saline placebo and for Part 2, the comparison was between SABER-bupivacaine (Part 2 patients only) and bupivacaine HCl. The Part 2 analysis was considered the primary analysis for efficacy. Part 1 was considered descriptive because only 30% of the planned sample had been treated; however, the observed results were consistent with the anticipated treatment difference of 0.8 on the 11-point pain scale. Katherine Meaker agreed with the Applicant in that had Part 1 continued enrolling for the planned sample size, there likely would have been sufficient data to detect a statistically significant difference between the two groups.

The Applicant states that despite the lack of a statistically significant difference in post-operative pain between SABER-bupivacaine and bupivacaine HCl-treated patients in Part 2, there was a trend toward improved pain in patients treated with SABER-bupivacaine. Furthermore, the Applicant states that the post-operative analgesic benefit of administration of SABER-bupivacaine appears to be similar to that of immediate-release bupivacaine. Because a formal noninferiority analysis was not conducted, however, this statement is not supported by the reported data. However, it is worth noting that the difference in the bupivacaine dose is such that a more than 'trend' should have been observed.

A prespecified pooled sensitivity analysis, all SABER-bupivacaine-treated patients (Part 1 + Part 2) compared to bupivacaine HCl-treated patients, did reach statistical significance ($p = 0.0438$).

The results of the key secondary efficacy analyses are as follows:

- Part 1
 - No significant difference in total IV opioid rescue from 0 to 72 hours between patients treated with SABER-bupivacaine and saline placebo
- Part 2
 - No significant difference in pain intensity on movement from 0 to 72 hours between patients treated with SABER-bupivacaine (Part 1 + Part 2) and patients treated with bupivacaine HCl
 - No significant difference in total IV opioid rescue from 0 to 72 hours between patients treated with SABER-bupivacaine and bupivacaine HCl

The following table summarizes total IV morphine-equivalent dose through 72 hours'.

Table 19. Total IV Morphine-Equivalent Dose 0 to 72 hours' Post-Operatively (mITT Population)

	Part 1		Part 2		Combined Parts 1 & 2
	SABER- Bupivacaine (N=46)	Saline Placebo (N=46)	SABER- Bupivacaine (N=148)	Bupivacaine HCl (N=148)	SABER- Bupivacaine (N=194)
Total Morphine-Equivalent Dose 0 to 72 Hours (mg)					
n (%)	46 (100%)	46 (100%)	148 (100%)	148 (100%)	194 (100%)
Mean (SE)	21.1 (2.73)	29.8 (3.45)	21.5 (1.60)	22.6 (1.58)	21.4 (1.37)
Standard Deviation	18.49	23.38	19.41	19.20	19.15
Median	13.8	21.7	16.9	17.3	16.3
Q1, Q3	7.5, 34.0	12.0, 43.9	6.3, 31.2	8.5, 33.9	6.3, 32.1
Min, Max	0.0, 82.5	0.0, 91.3	0.0, 96.9	0.0, 98.1	0.0, 96.9

Source: C803-028 PERSIST Report Body, p. 278 (PDF), Applicant's submission, NDA 204803.

It is worth noting, as indicated in the table, that there was no patient in any treatment group that did not required any opioid analgesia post-operatively.

Additional secondary efficacy endpoints:

- Opioid rescue analgesic use in the first 72 hours post-operatively showed no statistically significant difference between treatment groups. In an exploratory analysis using drug

accountability records instead of LogPad entries for oxycodone use, median opioid use over 72 hours was lower in SABER-bupivacaine-treated patients compared to saline placebo in Part 1.

- The Silverman's Integrated Analgesic Assessment Score over 72 hours did not demonstrate a statistically significant difference across treatment groups.
- There was no meaningful difference in patients requiring no post-operative opioid, from PACU discharge through 72 hours, across treatment groups (refer to the following table).
- The time to first opioid rescue did not differ between treatment groups.
- Time to PACU discharge eligibility was similar across all treatment groups.

Table 20. Patients Not Taking Rescue Medication From PACU Discharge to 72 hours Post-Operatively (mITT Population)

	Part 1		Part 2		Combined Parts 1 & 2
	SABER- Bupivacaine (N=46)	Saline Placebo (N=46)	SABER- Bupivacaine (N=148)	Bupivacaine HCl (N=148)	SABER- Bupivacaine (N=194)
Did Not Take Opioid Rescue Medication					
n (%)	14 (30.4%)	7 (15.2%)	43 (29.1%)	42 (28.4%)	57 (29.4%)
95% CI	(17.7%, 45.8%)	(6.3%, 28.9%)	(21.9%, 37.1%)	(21.3%, 36.4%)	(23.1%, 36.3%)
Combined SABER-Bupivacaine versus Bupivacaine HCl p-value ^[1]					0.8781
Did Not Take Acetaminophen Rescue Medication					
n (%)	6 (13.0%)	12 (26.1%)	21 (14.2%)	36 (24.3%)	27 (13.9%)
95% CI	(4.9%, 26.3%)	(14.3%, 41.1%)	(9.0%, 20.9%)	(17.7%, 32.1%)	(9.4%, 19.6%)
Did Not Take Rescue Medication					
n (%)	2 (4.3%)	0 (0.0%)	10 (6.8%)	12 (8.1%)	12 (6.2%)
95% CI	(0.5%, 14.8%)	(0.0%, 7.7%)	(3.3%, 12.1%)	(4.3%, 13.7%)	(3.2%, 10.6%)
Combined SABER-Bupivacaine versus Bupivacaine HCl p-value ^[1]					0.4077

Source: C803-028 PERSIST Report Body, p. 278 (PDF), Applicant's submission, NDA 204803.

Exploratory efficacy endpoints:

- There was no difference in the number of patients responding to treatment, mean pain intensity at rest, and time to PACU discharge did not differ across treatment groups.

Data Quality and Integrity

There were no concerns identified regarding data quality or integrity with this study.

Dose/Dose Response

For this study, a single dose of SABER-bupivacaine was administered during both parts of the study. A dose response was, therefore, not observed.

Durability of Response

Administration of SABER-bupivacaine did not result in a statistically significant reduction in pain intensity with movement or opioid rescue analgesic use through 72 hours when compared to

either saline placebo or bupivacaine HCl.

7. Integrated Review of Effectiveness

7.1. Data Presented in the Original NDA Submission, Response to Discipline Review Letter, and End-of-Review-Cycle Meeting Package

As summarized in Dr. Arthur Simone's clinical review of the original NDA submission, and provided in the table below, there were seven clinical studies conducted to evaluate the efficacy of SABER-bupivacaine. Two studies, CLIN803-006-0006 in patients undergoing inguinal hernia repair and BU-002-IM in patients undergoing shoulder surgery, were described as "pivotal" by the Applicant.

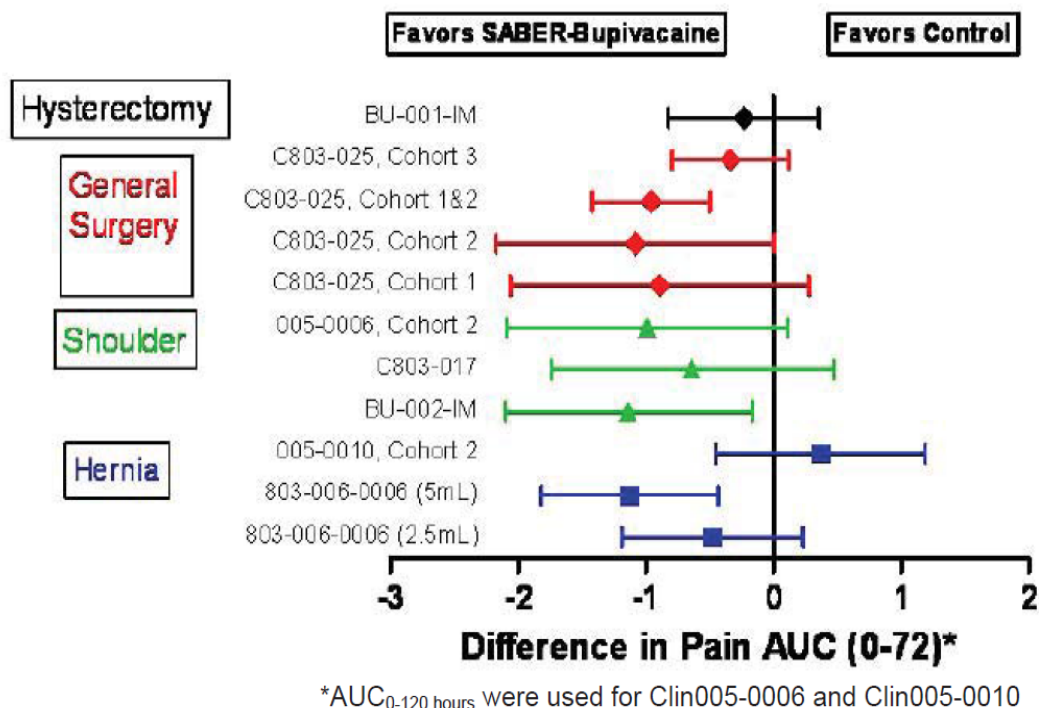
Table 21. Summary of Studies Evaluating Efficacy (Original NDA Submission)

Study Number	Phase	Comparator	Surgical Procedure	Pivotal
CLIN803-006-0006	2	SABER-placebo	inguinal hernia repair	Y
BU-002-IM	2	SABER-placebo and bupivacaine HCl	arthroscopic subacromial decompression	Y
CLIN005-0010	2	SABER-placebo	inguinal hernia repair	N
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: Adapted from Dr. Arthur Simone's Clinical Review, p. 43 (PDF), Jan. 8, 2014.

The following figure, taken from Dr. Simone's clinical review, provided by the Applicant, summarizes the efficacy results for normalized pain intensity AUCs for SABER-bupivacaine using a Forest Plot, in the seven clinical studies conducted by the Applicant in support of the original NDA.

Figure 9. Normalized Pain Intensity AUC



Source: Dr. Arthur Simone's NDA 204803 Clinical Review, p. 43 (PDF), Jan. 1, 2014.

Dr. Simone concluded that the Applicant was able to demonstrate superiority of SABER-bupivacaine over SABER-placebo in one of three studies conducted in patients undergoing (mostly) arthroscopic shoulder surgery. The other two studies demonstrated a treatment effect that favored SABER-bupivacaine, most impressive through only 12 hours, but the results did not meet statistical significance. All three studies utilized the same dose, the same method of administration, and the same comparator. Additionally, Study BU-002-IM was unable to demonstrate a statistically significant difference between SABER-bupivacaine and immediate-release bupivacaine HCl (50 mg). Based on the findings 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 during the first review cycle. Dr. Simone further concluded that "SABER-bupivacaine has an analgesic effect, but the appropriate dose (or possibly, the appropriate formulation) for surgical procedures other than shoulder arthroscopy [have] not been identified."

I agree that Study BU-002-IM did demonstrate a statistically significant difference in pain intensity with movement through 72 hours between SABER-bupivacaine and SABER-placebo in patients undergoing arthroscopic subacromial decompression only. However, I have two comments, regarding the overall efficacy reported for this surgical procedure. First, the surgical procedure performed varied in the three studies. In Study CLIN005-0006, patients may have also undergone a rotator cuff repair, subacromial decompression, glenoid labrum repair or debridement, and biceps tendon repair. The majority of cases in this study were completed

arthroscopically, but six cases were completed via a combination of arthroscopic and open techniques. In Study C803-017, after a large proportion of patients were enrolled, a protocol amendment allowed for enrollment of patients undergoing a Mumford procedure (open distal clavicle excision). Study BU-002-IM appears to be the only shoulder study conducted by the Applicant in which all included patients underwent only arthroscopic procedures, including subacromial decompression, distal clavicle excision, bursectomy, synovectomy, removal of loose body, resection of coracoacromial ligament and subacromial spurs, and minor debridement of articular cartilage. The lack of consistent efficacy findings across evaluated shoulder procedures suggests that SABER-bupivacaine may not be efficacious when administered to patients for post-operative analgesia for more invasive procedures aside from arthroscopic subacromial decompression.

And second, while Study BU-002-IM did demonstrate efficacy compared to SABER-placebo, it did not demonstrate a statistically significant difference between SABER-bupivacaine and immediate-release, low-dose bupivacaine HCl (50 mg), suggesting there may be no benefit of SABER-bupivacaine beyond immediate-release bupivacaine.

It did not appear that efficacy was demonstrated for SABER-bupivacaine over SABER-placebo in any non-orthopedic procedure evaluated, with the exception of a single study in patients undergoing inguinal hernia repair, Study CLIN803-006-0006. Specifically, there was a statistically significant improvement in post-operative pain intensity with movement in the SABER-bupivacaine treatment group over SABER-placebo treatment group; however, there was not a statistically significant difference between treatment groups on the secondary efficacy endpoint of opioid rescue analgesia through day 15. Furthermore, given the conflicting results from a similar study (CLIN005-0010) conducted in the same surgical population, interpretation of these results is challenging and the clinical benefit of SABER-bupivacaine in this single, soft-tissue surgical model appears modest at best.

Based on my review of the data submitted in the original NDA, and the information submitted in response to the Discipline Review Letter and in the End-of-Review-Cycle Meeting Materials, SABER-bupivacaine demonstrated a statistically significant improvement in post-operative pain intensity over SABER-placebo in patients undergoing arthroscopic subacromial decompression alone, without rotator cuff repair or other procedures on the shoulder, and inguinal hernia repair. However, narrowly winning against placebo in a single controlled clinical study, when others conducted in the same or similar models failed, does not instill a large degree of confidence that this drug product will provide any clinically meaningful improvement in post-operative analgesia such that patient outcomes, including opioid use, and satisfaction are improved over current standard of care regimens. This efficacy data, in combination with data from the PERSIST study and an overall evaluation of the safety data, may not support a favorable benefit-risk profile for marketing approval.

7.2. Data Presented in the NDA Resubmission

Adequate and Well-Controlled Efficacy Studies

Primary Clinical Review
Petit-Scott, M.D.

In the NDA Resubmission, the Applicant has reevaluated previously submitted efficacy data and has determined six studies should now be considered adequate and well-controlled for purposes of supporting the proposed indication for SABER-bupivacaine and are listed in the following table.

Table 22. Adequate and Well-Controlled Studies to Support the Safety and Efficacy of SABER-bupivacaine

Study Number	Phase	Comparator	Surgical Procedure	Pivotal
CLIN803-006-0006	2	SABER-placebo	inguinal hernia repair	Y
BU-002-IM	2	SABER-placebo and bupivacaine HCl	arthroscopic subacromial decompression	Y
C803-017	2b	SABER-placebo	arthroscopic subacromial decompression	N
C803-025 Cohort 3	3	SABER-placebo	lap-assisted colectomy	N
BU-001-IM	2	SABER-placebo and bupivacaine HCl	total abdominal hysterectomy	N
C803-028 – Part 1	3	Saline placebo	Lap chole	N

The Applicant has provided post hoc explanations as to why several previously identified supportive studies are no longer considered adequate and well-controlled and why the results are no longer representative of the true efficacy of SABER-bupivacaine. These other studies should now be considered “clinical experiences” aimed at determining the appropriate dose and volume administered, and evaluations of different delivery methods. In addition to studies CLIN005-0010 and CLIN005-0006, previously discussed, the other studies also determined to no longer be adequate and well-controlled for purposes of supporting the efficacy of SABER-bupivacaine include studies C803-025 (Cohorts 1 and 2) and C803-028 (Part 2). The Applicant’s rationale for the failure of Study C803-025 (Cohorts 1 and 2) to meet the criteria for an adequate and well-controlled study is based on inadequate analysis of the efficacy results. While there may be some validity to the explanations provided, the results from post hoc analyses are generally not considered as valid as original results. Furthermore, it is interesting that these study design issues were only identified as a result of demonstration of lack of efficacy. Reanalyzing a failed study to alter the efficacy conclusion is a questionable practice and interpretation of such re-analyses are challenging.

Reanalysis of the efficacy results and reclassification of studies CLIN005-0010 and CLIN005-0006 as no longer adequate and well-controlled appears to be the most problematic in assessing the overall efficacy of SABER-bupivacaine for two reasons. First, these studies were conducted in the same surgical populations for which the Applicant is claiming SABER-bupivacaine has been determined to be efficacious in the management of post-operative pain. Specifically, Study CLIN005-0010, conducted in patients undergoing inguinal hernia repair, and Study CLIN005-0006, conducted in patients undergoing arthroscopic subacromial decompression, were models in which the Applicant has determined, in other studies, SABER-bupivacaine is efficacious. And second, the rationale for why the studies are no longer considered adequate and well-

controlled and did not demonstrate efficacy are nearly identical, suggesting that study conduct issues serious enough to result in not meeting the criteria for adequate and well-controlled definitions would have been detected prior to the completion of two large clinical studies conducted to support marketing approval. Refer to the following table for the Applicant's rationale for why these two studies are no longer considered adequate and well-controlled and no longer supportive of the efficacy of SABER-bupivacaine.

Table 23. Efficacy Studies No Longer Considered Adequate and Well-Controlled

Study CLIN005-0010 (inguinal hernia repair)	Study CLIN005-0006 (arthroscopic subacromial decompression)
– Efficacy endpoints not clearly defined – Primary efficacy endpoint listed as both pain at rest and pain with movement – Change in route of administration not prospectively defined – Change in dose not prospectively planned – Paper diary used to document pain intensity and opioid use (prone to error of recall, unverified entry time, recall bias) – Statistical analyses conducted on PP versus ITT population – Sample size estimate based on Cohort 1 only – 120-hour pain analysis for primary efficacy endpoint too long – Inappropriate pooling of pbo comparators	– Efficacy endpoints not prospectively defined – Primary efficacy variable listed as both pain at rest and with movement – Change in route of administration not prospectively planned – Change in dose not prospectively planned – Inclusion of non-arthroscopic procedures not prospectively planned – Paper diary used to document pain intensity and opioid use (prone to error of recall, unverified entry time, recall bias) – Statistical analyses conducted on PP versus ITT population – Sample size estimate based on Cohort 1 only – 120-hour pain analysis for primary efficacy endpoint too long – Inappropriate pooling of pbo data from Cohorts 1 and 2 (different doses and routes of administration)

Source: Adapted from Applicant's Table 2, p. 35-36 (PDF), ISE, Applicant's submission, NDA 204803.

PERSIST Study

The rationale for Study C803-028 (Part 2) to no longer be considered an adequate and well-controlled study supportive of the efficacy of SABER-bupivacaine has been briefly discussed in Section 6.2, and generally involves the change in comparator treatment, requested by the Division. Specifically, the Applicant argues that the change from saline placebo to bupivacaine HCl control treatment was not prospectively planned and occurred after the study was initiated, therefore bias was not minimized and experimental variability was increased.

The Applicant also argues that the change in primary efficacy endpoint from 0 to 48 hours, from 0 to 72 hours, does not allow integration of the results from this study with other study results. This is true, however, the Division, did not advise the Applicant regarding the change in endpoint; therefore, that appears to be their miscalculation. Furthermore, the Applicant claims

that bupivacaine is released from the SAIB vehicle over 72 hours, suggesting that the analgesic benefit should extend over 72 hours. Not only was that not demonstrated, but an analgesic benefit over 48 hours was not demonstrated either, suggesting that SABER-bupivacaine is not an effective treatment option for acute post-operative pain.

Regarding the change in recommended comparator treatment, the Applicant was advised during the End-of-Review meeting, held on September 23, 2014, prior to initiation of the study, to include bupivacaine HCl as a comparator treatment in any future clinical study. The advice provided in the revised meeting minutes, dated February 13, 2015, is as follows:

“The choice of comparator(s) has several options. You will need to include a bupivacaine HCl arm to address the concerns that the safety profile for Posimir is inferior to that of bupivacaine HCl. If you opt to compare Posimir to bupivacaine HCl for the purpose of demonstrating its efficacy, you could conduct a noninferiority trial. However, this approach will require a clinically relevant justification for the selection of a delta value in powering the study and may also require a non-SABER placebo treatment arm for the purpose of demonstrating assay sensitivity. Additional discussions with the Division are strongly encouraged, if you choose to utilize this option. Alternatively, a non-SABER placebo treatment group would be sufficient for evaluating efficacy in a superiority designed trial. The trial would be powered to address the efficacy and safety issues; whichever requires the greater number of subjects. Ultimately, you will likely need three treatment arms (Posimir, bupivacaine HCl, and non-SABER placebo). However, the numbers of subjects required to be enrolled may vary substantially based on the design of the trial.”

Dr. Kathryn Meaker, statistical reviewer, will discuss the potential impact on the reported efficacy as a result of a change in comparator treatment and the Applicant's rationale. It is worth mentioning, however, that the efficacy of SABER-bupivacaine was evaluated in patients undergoing a lap chole in another study, C803-025 (Cohort 2), which also failed when compared to bupivacaine HCl. The Applicant provided a reasonable rationale as to why this surgical model was selected for evaluation of SABER-bupivacaine (refer to Section 6.2); however, there are two reasons why lap chole may not have been a good surgical model to evaluate the efficacy of SABER-bupivacaine. First, incisional pain after a lap chole may not be the main source of post-operative pain. The majority of patients undergoing lap chole complain initially of referred shoulder and back pain, as a result of insufflation of carbon dioxide into the abdominal cavity. And second, surgeons may have used either one or two 10 to 12 mm port sites. The longer incisions result in more post-operative discomfort such that efficacy may have been adversely impacted by the number of longer incisions.

During discussions with the Applicant regarding resolution of the deficiencies identified in the CRL, the Division suggested the Applicant evaluate an additional soft tissue model aside from inguinal hernia repair. Specifically, hemorrhoidectomy (or bunionectomy) was proposed as an alternate model to evaluate the safety (and efficacy) of SABER-bupivacaine and to address CRL

deficiencies. In a teleconference with the Applicant held on February 17, 2015, the following discussion was noted:

“The Division strongly encouraged the Sponsor to conduct an additional clinical trial in another soft-tissue model, such as hemorrhoidectomy or bunionectomy, rather than another study in patients undergoing hernia repair, as this would support a soft-tissue indication for their drug product.”

“A second efficacy study in a soft tissue surgery population other than hernia would strengthen the efficacy portion of the Sponsor’s complete response submission.”

“The Sponsor agreed to consider conducting an additional efficacy study in a hemorrhoid surgery model. However, the Sponsor expressed concern about conducting a third efficacy trial in a patient population for which they have limited experience designing and implementing clinical trials in this setting. The Sponsor will review available information on the design and implementation of an efficacy study in patients undergoing hemorrhoidectomy.” (Meeting minutes, dated March 12, 2015)

An Action Item from this teleconference was for the Applicant to investigate the possibility of conducting a study in patients undergoing hemorrhoidectomy. The initial protocol synopsis for the PERSIST study, in patients undergoing lap chole, was received on Feb. 27, 2015, 10 days after the teleconference. It is unclear why the choice of evaluated surgical population changed from what had been discussed during the teleconference and why the lap chole model was not discussed during that meeting or at any time prior to protocol submission. While the Division did not explicitly comment on the choice of evaluated surgical population *after* protocol submission, lap chole was not the surgical procedure previously discussed.

7.3. Integrated Assessment of Efficacy

While meeting the regulatory threshold for approval, an efficacy evaluation of a new product compared to placebo treatment is not clinically meaningful. Because post-operative pain management includes local anesthetic wound infiltration, conclusions about the efficacy of a new drug product, and its ability to reduce opioid analgesic use, must be based on standard of care comparisons. The Applicant has not provided substantial evidence of effectiveness for SABER-bupivacaine for the claimed indication of “...single-dose instillation into the surgical site to produce post-surgical analgesia” and, in combination with the ongoing safety concerns, I do not recommend approval. The administration of SABER-bupivacaine into surgical wounds has not been demonstrated to reliably and consistently improve post-operative pain or opioid analgesic use. Results from the two surgical models that demonstrated a statistically significant difference in mean pain intensity with movement through 72 hours between SABER-bupivacaine and SABER-placebo treatment were not duplicated, in the case of open inguinal hernia repair, nor replicated, in the case of shoulder surgery.

The overwhelming majority of the efficacy findings were derived from Phase 2 clinical studies,

which can be considered adequate to demonstrate efficacy (and safety) depending on the study design; however, as described in detail in Dr. Simone's clinical review of the original NDA, several of the Applicant's Phase 2 studies involved protocol amendments after patient enrollment that impacted the interpretation of the reported efficacy findings. Protocol changes during exploratory Phase 2 studies are acceptable and often anticipated depending on the nature of the study; however, the resulting efficacy findings may be difficult to interpret, particularly when used to support marketing approval. Furthermore, biased selection of favorable efficacy data is a concern. The Applicant conducted only two confirmatory Phase 3 studies, Study C803-025 and Study C803-028, and both failed to demonstrate a statistically significant difference between SABER-bupivacaine and the respective comparator treatments (SABER-placebo for Study C803-025, and saline placebo and bupivacaine HCl for Study C803-028).

Regarding evaluated orthopedic procedures, substantial evidence of effectiveness has not been demonstrated for three reasons. First, only a single surgical site, the shoulder, was evaluated. The Applicant chose to conduct three studies in patients undergoing shoulder surgery, despite the fact that the first two failed to demonstrate a statistically significant efficacy benefit of SABER-bupivacaine over SABER-placebo. Second, of the procedures evaluated in the three shoulder studies, it appears that SABER-bupivacaine won over SABER-placebo in only the study (BU-002-IM) in which the least invasive, and likely least painful, procedures were performed. And third, efficacy of SABER-bupivacaine was not demonstrated over low-dose, immediate release bupivacaine HCl (50 mg). While superiority over a placebo treatment has generally been the accepted regulatory standard for approval, as previously discussed, such comparisons are not clinically meaningful, particularly in the setting of acute post-operative pain where local anesthetics, administered via wound infiltration, peripheral nerve block, or as a neuraxial anesthetic, are considered standard of care in the absence of contraindications.

Unlike the orthopedic evaluation, the soft tissue evaluations included a variety of surgical procedures including TAH, lap chole, laparotomy, lap-assisted colectomy, and inguinal hernia repair. These surgical procedures represent a diverse efficacy evaluation, which included both laparoscopic and open procedures, as well as intrabdominal and pelvic procedures. I do not think substantial evidence of effectiveness has been demonstrated in the soft tissue models, however, for four reasons. First, of all the surgical procedures and sites evaluated, it is concerning that only a single study in a single model demonstrated a statistically significant improvement in post-operative pain over placebo treatment. Furthermore, there were conflicting efficacy results from the two studies conducted in patients undergoing inguinal hernia repair. The Applicant has provided possible explanations as to why the two studies did not have similar results, including differences in patient age between the SABER-bupivacaine and SABER-placebo treatment groups; however, a single study in a single soft tissue model does not seem to meet the regulatory threshold of substantial evidence of effectiveness. Furthermore, the clear separation of pain curves between SABER-bupivacaine and SABER-placebo was noted over 0 to 24 hours and the separation from 24 to 72 hours was of a lower magnitude, such that statistical significance was driven by an early, versus extended, analgesic

benefit.

Second, the demonstration of efficacy was compared to SABER-placebo treatment. As previously mentioned, the regulatory threshold for approval may include statistically significant differences between active and placebo treatments, however, the Division's current thinking is that approval of the newer, extended-release, reportedly longer-acting, local anesthetic formulations is dependent upon evaluations compared to standard of care treatment, which is immediate-release bupivacaine. In the studies in which SABER-bupivacaine was compared to bupivacaine HCl (BU-001-IM, C803-025, and C803-028), a statistically significant difference in pain with movement was not demonstrated, suggesting the benefit of this product over immediate-release bupivacaine HCl has not been demonstrated. Furthermore, the dose of bupivacaine administered was low in some of these studies, which appears to be an intentional study design consideration. In Study C803-028, bupivacaine 75 mg was administered in Part 2, despite SABER-bupivacaine not demonstrating efficacy over bupivacaine 150 mg in Study C803-025, Cohort 2. This suggests that the dose of bupivacaine selected for evaluation was meant to favor efficacy of SABER-bupivacaine. During the AC meeting, members also commented that the lack of epinephrine in the bupivacaine solution may have also contributed to less clinical benefit observed in this control group. Lack of consistent efficacy compared to placebo or low-dose, epinephrine-free bupivacaine presents real challenges to conclusions about effectiveness for this product.

Third, the pivotal studies (as designated by the Applicant) in inguinal hernia repair and arthroscopic subacromial decompression demonstrated only a modest improvement in mean pain intensity; a 1.1 to 1.3 difference, on an 11-point pain scale, above SABER-placebo treatment for mean pain intensity on movement over 72 hours post-surgery. It is hard to imagine how such a small change in post-operative pain above that observed from a placebo treatment would provide any meaningful benefit to the patient. The fact that SABER-bupivacaine did not demonstrate even this degree of improvement in post-operative pain in the majority of the soft tissue models studied is very concerning and clearly not supportive of its efficacy.

And lastly, in patients in whom SABER-bupivacaine is not efficacious in managing post-operative pain, alternate treatment is limited to oral or IV analgesics, including opioids. Administration of additional local anesthetics through 96 hours will be contraindicated based on the PK profile of SABER-bupivacaine. Given the overall lack of demonstrated benefit of SABER-bupivacaine administration, it seems there will be a high percentage of post-operative patients who would be impacted by this limitation.

Regarding the PERSIST study, I agree with the Applicant's rationale that Part 1 of the PERSIST study failed to demonstrate efficacy based on early termination. I do not agree, however, that Part 2 failed because it was not an adequate and well-controlled study based on protocol amendments and variability, lack of assay sensitivity between saline and bupivacaine control groups, and inappropriate pooling of Part 1 and Part 2 efficacy data. Part 2 of the study,

initiated with Protocol Amendment 3, should have been considered a stand-alone efficacy study because the statistical analysis plan, sample size, and primary hypotheses were all revised to demonstrate superiority of SABER-bupivacaine over bupivacaine HCl. The Applicant's independent decision to discontinue the saline placebo treatment group resulted in a lack of assay sensitivity between the saline placebo and bupivacaine controls, thereby creating one reason they argue the study is no longer adequate and well-controlled. Additionally, the Division did not advise the Applicant to pool efficacy data from Part 1 and Part 2. Again, Part 2 should be considered a stand-alone study.

In conclusion, SABER-bupivacaine may provide limited post-operative analgesia after inguinal hernia repair and arthroscopic subacromial decompression; however, it does not appear that the demonstrated benefit is an improvement over standard of care immediate-release bupivacaine, which does not have the same safety concerns as the SABER products. Furthermore, the dose of bupivacaine in SABER-bupivacaine is significantly higher than that of commonly administered bupivacaine products, such that it is difficult to understand why efficacy was not more prominently and more consistently demonstrated. As was the case during review of the original NDA, an argument could be made that the demonstration of efficacy in a single soft tissue and a single orthopedic study is sufficient to recommend approval and the label indication could be modified to include only those procedures. However, based on my experience with another bupivacaine formulation advertised as having an extended-release profile, product labeling will not prevent widespread post-operative use, particularly in the context of the current opioid epidemic.

8. Review of Safety

8.1. Safety Review Approach

This application is a Class 2 Resubmission under the 505(b)(2) pathway. The Applicant is relying on the Agency's previous findings of safety and efficacy for Marcaine™, approved under NDA 016964, and information in the published literature. Additionally, the Applicant has completed a clinical development program to define the adverse event profile of SABER-bupivacaine.

The evaluation of the safety profile for SABER-bupivacaine involved a comprehensive review of adverse events suspected to be related to bupivacaine and those suspected to be related to the novel SAIB formulation and added excipients. As previously discussed, the original NDA received a CRL based on the benefit-risk analysis, such that the safety profile for SABER-bupivacaine was unacceptable when administered into post-operative wounds. Specifically, there were concerns regarding the development of adverse events related to the shoulder joint 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 has addressed the identified safety concerns outlined in the CRL as follows:

- 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:
 - Regarding wound-related adverse events –
 - o 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
 - o Reanalyzed wound complication data to decrease potential influences from treatment groups, surgical procedures, and patient populations
 - Regarding neurological adverse events –
 - o Reanalyzed solicited and spontaneously-reported potential benzyl alcohol-induced neurological adverse events
 - o Vital sign analysis during T_{max} for benzyl alcohol
 - Regarding possible chondrolysis –
 - o Evaluated baseline and 18-month post-surgical MRIs for patients in Study C803-017/C803-017e
 - o Surveyed investigators in Study CLIN005-006, regarding reported outcomes over the 10 years since study completion
 - o Reanalyzed safety data from Study BU-002-IM, including baseline and 6-month post-operative MRIs, functional assessments, and wound healing assessments

This safety review will focus on whether the previously identified clinical deficiencies have been adequately addressed and whether there is an increased incidence in the following adverse events after administration of SABER-bupivacaine in patients undergoing lap chole:

- Local anesthetic systemic toxicity (related to the bupivacaine component)
- Neurological adverse events (possibly related to the benzyl alcohol component)
- Wound healing (potentially related to the SAIB formulation)

8.2. Safety Results for Study C803-028 (PERSIST)

8.2.1. Background

This study in patients undergoing lap chole included more intensive and longer duration evaluations and assessments for concerning neurological symptoms, both solicited and spontaneously reported, and complications related to wound healing. The safety monitoring included the following (refer to Section 6.4 for additional information regarding the study design):

- Solicited symptoms - preprogrammed LogPad provided to each patient to record the incidence of 10 symptoms of interest, requested by the Agency, which included somnolence, nausea, dizziness, headache, vomiting, constipation, pruritus, dysgeusia, paresthesia, and hypoesthesia. 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. LogPad symptom recording continued through study day 4.
- Spontaneously-reported symptoms and adverse events - patients were queried by investigators for the occurrence of adverse events at each clinic visit and by telephone on study days 2 and 3 (POD 1 and 2). The queries were open-ended and intended to track spontaneously-reported adverse events.
- Serial physical examinations of the four laparoscopic port sites by a blinded investigator were performed on study days, 1, 4, 8, 15, 30, and for those enrolled after protocol amendment five, 60. The presence of six specific wound-related adverse events were evaluated including, peri-incisional bruising, wound hematoma, wound dehiscence (superficial and fascial), surgical site infection, surgical site bleeding, and drainage from the surgical incision.
- Clinical lab testing was done at screening, study day 4 and at the final (study day 29 or 60) visit.
- Additional monitoring employed after protocol amendments two through five included the following:
 - Dysgeusia, paresthesia, and hypoesthesia were added to the list of symptoms of interest, as described above
 - Vital signs, including pulse oximetry, monitored at 15-minute intervals for a minimum of two hours before discharge from the PACU.
 - 60-day post-operative follow-up visit added for evaluation of abnormal wound healing or late-onset complications (87 of 209 patients enrolled in Part 2 completed this 60-day visit)
 - Serious neurological or cardiac adverse event required evaluation of bupivacaine and benzyl alcohol systemic concentrations

8.2.2. Exposure

There were 399 patients randomized, 11 patients did not receive study treatment based on post-randomization exclusion criteria. Of the remaining 388, 45 patients in Part 1 and 148 patients in Part 2 received SABER-bupivacaine. Forty-seven received saline placebo in Part 1 and 148 received bupivacaine HCl 0.5% in Part 2. One subject was randomized to receive SABER-bupivacaine but inadvertently received saline placebo.

8.2.3. Deaths, Serious Adverse Events (SAE), and TEAE-Related Study Discontinuations

There were no deaths during this study. Fourteen patients reported fifteen SAEs during this study. There were nine patients, six treated with SABER-bupivacaine and three treated with

bupivacaine HCl, who experienced SAEs during the study. Two patients had SAEs during screening, and three patients were randomized but not treated. The Applicant states that none of the SAEs were considered related to study drug administration. The following table summarizes the reported SAEs.

Table 24. Reported Serious Adverse Events

Subject ID	Sex	Age	Adverse Event Description	AE Preferred Term	Study Day/Date Onset to Resolution	Causality	Study Status	Treatment
(b) (6)	M	63	Intra-abdominal abscess	Abdominal abscess	10 to 31	Not related	Treated	Bupivacaine HCl
	F	76	Oropharyngeal trauma during intubation	Pharyngeal injury	(b) (6)	Not related	Randomized, not dosed	None
	M	84	Malignant tumor of gallbladder with metastasis to right lung	Gallbladder cancer metastatic		Not related	Randomized, not dosed	None
	F	87	Muscle spasm	Muscle spasms		Not related	Screen failure	None
	F	34	Elevated liver enzymes	Hepatic enzyme increased	22 to 61	Not related	Treated	SABER-Bupivacaine
	F	72	Dizziness, hospitalization for over 24 hours	Dizziness	1 to 2	Not related	Treated	SABER-Bupivacaine
	F	30	Gallstone pancreatitis, cholecystitis, cholelithiasis, abnormal liver function	Pancreatitis, cholecystitis, cholelithiasis, liver function test abnormal	(b) (6)	Not related	Screen failure	None
	F	41	Acute biliary pancreatitis	Pancreatitis acute	2 to 99	Not related	Treated	Bupivacaine HCl
	M	44	Cystic duct leak	Biliary tract disorder	(b) (6)	Not related	Randomized, not dosed	None
	F	44	Bile leak	Post procedural bile leak	6 to 7	Not related	Treated	SABER-Bupivacaine
	M	55	Common duct stone pancreatitis	Bile duct stone pancreatitis	18 to 21	Not related	Treated	SABER-Bupivacaine
	F	52	Intramucosal carcinoma of the rectum	Rectal cancer	17 to 57	Not related	Treated	SABER-Bupivacaine
	M	51	Dehydration, hypotension	Dehydration, hypotension	4 to 16	Not related	Treated	SABER-Bupivacaine
	M	51	Hypotension	Hypotension	54 to 56	Not related	Treated	SABER-Bupivacaine
	F	32	Gastritis unspecified without bleeding	Gastritis	21 to 22	Not related	Treated	Bupivacaine HCl

Source: Listing 16.2.7.1, Listing 16.2.7.3, and Section 14.3.3, SAE Narratives.

Source: C803-028 PERSIST Report Body, p. 128 (PDF), Applicant's submission, NDA 204803.

The majority of the reported SAEs were related to the underlying gallbladder disease or post-operative complications unrelated to the study drug treatment. One patient ((b) (6)) required hospital admission for dizziness, which the investigator indicated was likely due to the administration of IV opioid analgesics. Briefly, this was a 72-year-old, 83 kg, female with past medical history of coronary artery disease status post stent placement, hyperlipidemia, and hypertension. Home medications include clopidogrel, aspirin, atorvastatin, metoprolol, and lisinopril. She underwent an uneventful lap chole and received SABER-bupivacaine, 5 mL, in the port sites as directed in Part 1 of the study. Over the initial 95-minute post-operative time, the patient received fentanyl 150 µg IV and hydromorphone 0.6 mg IV. One hour after the last dose of rescue opioid analgesia, the patient complained of dizziness and requested hospital admission. Review of the adverse event database indicates she also complained of drowsiness, dysgeusia, nausea, and vomiting approximately five to nine hours after admission to the PACU. Vital signs through 240 minutes post-PACU arrival were stable, with the lowest blood pressure, 105/52 mmHg, recorded at 180 minutes (heart rate 62 beats per minute), which was not significantly different from her screening baseline, 112/56 mmHg (heart rate 82 beats per minute) or prior to surgery, 119/48 mmHg (heart rate 71 beats per minute). She was reportedly stable overnight with no other adverse events and was discharged home the next evening at 6:40 pm.

Based on the entirety of her symptoms, LAST should have been considered as a possible diagnosis and plasma bupivacaine levels should have been assessed. The post-operative dose of opioid analgesic rescue medication does not appear to be high or unexpected for this procedure, particularly if the local anesthetic medication (SABER-bupivacaine) was not efficacious. Additionally, the intra-operative dose of fentanyl was 75 µg, which is considered low in the absence of additional analgesic medication administration, such as an NSAID.

Another patient ((b) (6)) experienced dehydration and hypotension. This was a 51-year-old male patient with past medical history of hypertension, hyperlipidemia, Type 2 diabetes mellitus, chronic renal insufficiency, and obesity, status post-gastric bypass, who was treated with SABER-bupivacaine 5 mL in Part 2 of the study. Home medications included liraglutide, lisinopril, and simvastatin. On POD 3, the patient was noted to be hypotensive (blood pressure measurement 73/46 mmHg), requiring ER evaluation. He was diagnosed with dehydration, and was treated with IV fluids, antiemetics, and antibiotics for possible small bowel obstruction. He complained of feeling weak, dizzy, and nauseous. The patient left the hospital the next day against medical advice (AMA). He was readmitted three days later with similar complaints and hypotension. He had been instructed to discontinue his home lisinopril medication, but had not done so. During the second admission, he was again treated with IV fluids, antiemetics, and antibiotics, in addition to morphine for pain and prednisone for an unspecified reason. He was discharged home two days later. Follow-up on POD 14 indicated the dehydration and hypotension had resolved. The patient again presented to the ER approximately two months after the lap chole with similar complaints and also noted to be hypotensive. The events were felt to be unrelated to study drug administration.

There was a single patient ((b) (6)) in the bupivacaine HCl treatment group who withdrew from the study due to the SAE of acute pancreatitis. The patient was hospitalized on POD 2 and recovered from this SAE within one month. This SAE is unlikely related to study drug treatment, and more likely related to the disease process and surgical procedure.

The remaining SAEs appeared to be related to the surgical procedure or the disease process, not the study drug treatment, and therefore will not be discussed further.

8.2.4. Adverse Events

It is worth mentioning that in response to an Information Request regarding inconsistencies between the ISS and clinical study report data, the Applicant clarified that different algorithms were used to define spontaneously-reported and solicited adverse events, such that the PERSIST dataset incorrectly assigned 186 adverse events to the solicited category when they should have been included in the spontaneously-reported category, based on event timing. Statisticians reviewing the safety data for this application were, in general, eventually able to reproduce the results from the Applicant's analyses, but there were still instances where the number of specific adverse events did not exactly match. These discrepancies did not result in different safety conclusions, but they do suggest lack of attention to detail.

During the study, 99% of treated patients reported at least one treatment-emergent adverse event (TEAE). The overall incidence between treatment groups was similar. The incidence of spontaneously-reported TEAEs was similar across treatment groups and Part and 1 and Part 2 of the study. The incidence of solicited TEAEs was higher in both treatment groups in Part 2 compared to Part 1. A summary of TEAEs are presented in the following table.

Table 25. Summary of Treatment-Emergent Adverse Events (Safety Population)

	Part 1		Part 2		Parts 1 & 2	Study Total (N=388)
	SABER- Bupivacaine (N=45)	Saline Placebo (N=47)	SABER- Bupivacaine (N=148)	Bupivacaine HCl (N=148)	SABER- Bupivacaine (N=193)	
At Least One TEAE	43 (95.6%)	47 (100%)	148 (100%)	146 (98.6%)	191 (99.0%)	384 (99.0%)
At Least One Spontaneously-reported TEAE	43 (95.6%)	45 (95.7%)	148 (100%)	138 (93.2%)	191 (99.0%)	374 (96.4%)
At Least One LogPad-Solicited TEAE	36 (80.0%)	39 (83.0%)	134 (90.5%)	132 (89.2%)	170 (88.1%)	341 (87.9%)
At Least One Serious TEAE	1 (2.2%)	0 (0.0%)	5 (3.4%)	3 (2.0%)	6 (3.1%)	9 (2.3%)
At Least One TEAE Leading to Study Discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.3%)
Maximum Relationship to Study Drug						
Related ^[1]	32 (71.1%)	26 (55.3%)	125 (84.5%)	104 (70.3%)	157 (81.3%)	287 (74.0%)
Not Related ^[2]	11 (24.4%)	21 (44.7%)	23 (15.5%)	42 (28.4%)	34 (17.6%)	97 (25.0%)
Maximum Severity						
Mild	13 (28.9%)	22 (46.8%)	83 (56.1%)	92 (62.2%)	96 (49.7%)	210 (54.1%)
Moderate	23 (51.1%)	25 (53.2%)	55 (37.2%)	49 (33.1%)	78 (40.4%)	152 (39.2%)
Severe	7 (15.6%)	0 (0.0%)	10 (6.8%)	5 (3.4%)	17 (8.8%)	22 (5.7%)
At Least One Severe and Related TEAE	5 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (2.6%)	5 (1.3%)
At Least One Serious and Related TEAE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fatal TEAE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

SAE = serious adverse event; TEAE = treatment-emergent adverse event

Note: Unless explicitly stated in the row label, spontaneously-reported and LogPad-solicited TEAEs are summarized together in this table.

Note: Two subjects ((b) (6)) who were Screen Failures and three subjects ((b) (6)) who were Randomized Not Dosed are not included in the above. These SAEs are discussed in the safety section of the clinical study report.

Note: The following symptoms were solicited from subjects on the LogPad electronic diary: Dizziness, Somnolence, Constipation, Nausea, Vomiting, Pruritus, Headache, Dysgeusia, Hypoesthesia, and Paresthesia.

Note: Subjects reporting more than one adverse event are counted only once.

[1] Includes all events reported as "Possible", "Probable", or missing relationship to study drug.

[2] Includes all events reported as "Unlikely" or "Not Related" relationship to study drug.

Source: C803-028 PERSIST Report Body, p. 116 (PDF), Applicant's submission, NDA 204803.

Spontaneously-Reported Treatment-Emergent Adverse Events and Symptoms of Interest

The majority of spontaneously-reported TEAEs occurred in the first four post-operative days and were noted during the follow-up phone calls on study days 2 and 3 and the clinic visits on study days 1, 4, 8, 15, 30, and 60 (for those enrolled after Protocol Amendment 5). The following table summarizes the spontaneously-reported adverse events by System-Organ-Class (SOC).

Table 26. Spontaneously-Reported TEAEs With Incidence $\geq$ 2% by SOC (Safety Population)

System Organ Class/Preferred Term	Part 1		Part 2		Parts 1 & 2	Study Total (N=388)
	SABER- Bupivacaine (N=45)	Saline Placebo (N=47)	SABER- Bupivacaine (N=148)	Bupivacaine HCl (N=148)	SABER- Bupivacaine (N=193)	
Subjects reporting at least one treatment-emergent adverse event	43 (95.6%)	45 (95.7%)	148 (100%)	138 (93.2%)	191 (99.0%)	374 (96.4%)
Injury, poisoning and procedural complications	43 (95.6%)	41 (87.2%)	145 (98.0%)	128 (86.5%)	188 (97.4%)	357 (92.0%)
Post procedural contusion	41 (91.1%)	33 (70.2%)	141 (95.3%)	110 (74.3%)	182 (94.3%)	325 (83.8%)
Procedural pain	19 (42.2%)	21 (44.7%)	32 (21.6%)	35 (23.6%)	51 (26.4%)	107 (27.6%)
Incision site haemorrhage	3 (6.7%)	0 (0.0%)	10 (6.8%)	6 (4.1%)	13 (6.7%)	19 (4.9%)
Post procedural discharge	1 (2.2%)	1 (2.1%)	8 (5.4%)	6 (4.1%)	9 (4.7%)	16 (4.1%)
Incision site pain	0 (0.0%)	2 (4.3%)	5 (3.4%)	8 (5.4%)	5 (2.6%)	15 (3.9%)
Incision site pruritus	1 (2.2%)	0 (0.0%)	4 (2.7%)	7 (4.7%)	5 (2.6%)	12 (3.1%)
Incision site erythema	0 (0.0%)	0 (0.0%)	5 (3.4%)	4 (2.7%)	5 (2.6%)	9 (2.3%)
Incision site haematoma	0 (0.0%)	0 (0.0%)	6 (4.1%)	2 (1.4%)	6 (3.1%)	8 (2.1%)
Gastrointestinal disorders	11 (24.4%)	13 (27.7%)	50 (33.8%)	46 (31.1%)	61 (31.6%)	120 (30.9%)
Nausea	3 (6.7%)	6 (12.8%)	19 (12.8%)	19 (12.8%)	22 (11.4%)	47 (12.1%)
Diarrhoea	2 (4.4%)	3 (6.4%)	11 (7.4%)	7 (4.7%)	13 (6.7%)	23 (5.9%)
Vomiting	2 (4.4%)	2 (4.3%)	11 (7.4%)	6 (4.1%)	13 (6.7%)	21 (5.4%)
Constipation	2 (4.4%)	1 (2.1%)	11 (7.4%)	6 (4.1%)	13 (6.7%)	20 (5.2%)
Flatulence	0 (0.0%)	3 (6.4%)	4 (2.7%)	4 (2.7%)	4 (2.1%)	11 (2.8%)
Abdominal distension	0 (0.0%)	0 (0.0%)	6 (4.1%)	3 (2.0%)	6 (3.1%)	9 (2.3%)
Abdominal pain	2 (4.4%)	0 (0.0%)	5 (3.4%)	1 (0.7%)	7 (3.6%)	8 (2.1%)
Abdominal pain upper	1 (2.2%)	0 (0.0%)	5 (3.4%)	2 (1.4%)	6 (3.1%)	8 (2.1%)

System Organ Class/Preferred Term	Part 1		Part 2		Parts 1 & 2	Study Total (N=388)
	SABER- Bupivacaine (N=45)	Saline Placebo (N=47)	SABER- Bupivacaine (N=148)	Bupivacaine HCl (N=148)	SABER- Bupivacaine (N=193)	
Nervous system disorders	4 (8.9%)	5 (10.6%)	23 (15.5%)	13 (8.8%)	27 (14.0%)	45 (11.6%)
Headache	1 (2.2%)	4 (8.5%)	11 (7.4%)	6 (4.1%)	12 (6.2%)	22 (5.7%)
Dizziness	1 (2.2%)	1 (2.1%)	5 (3.4%)	4 (2.7%)	6 (3.1%)	11 (2.8%)
Dysgeusia	1 (2.2%)	0 (0.0%)	5 (3.4%)	3 (2.0%)	6 (3.1%)	9 (2.3%)
Musculoskeletal and connective tissue disorders	4 (8.9%)	6 (12.8%)	13 (8.8%)	17 (11.5%)	17 (8.8%)	40 (10.3%)
Back pain	3 (6.7%)	3 (6.4%)	5 (3.4%)	11 (7.4%)	8 (4.1%)	22 (5.7%)
Infections and infestations	2 (4.4%)	4 (8.5%)	20 (13.5%)	10 (6.8%)	22 (11.4%)	36 (9.3%)
Urinary tract infection	1 (2.2%)	0 (0.0%)	3 (2.0%)	5 (3.4%)	4 (2.1%)	9 (2.3%)
General disorders and administration site conditions	1 (2.2%)	2 (4.3%)	16 (10.8%)	13 (8.8%)	17 (8.8%)	32 (8.2%)
Pyrexia	1 (2.2%)	1 (2.1%)	6 (4.1%)	6 (4.1%)	7 (3.6%)	14 (3.6%)
Respiratory, thoracic and mediastinal disorders	8 (17.8%)	4 (8.5%)	12 (8.1%)	7 (4.7%)	20 (10.4%)	31 (8.0%)
Oropharyngeal pain	5 (11.1%)	2 (4.3%)	5 (3.4%)	2 (1.4%)	10 (5.2%)	14 (3.6%)
Cough	0 (0.0%)	2 (4.3%)	6 (4.1%)	1 (0.7%)	6 (3.1%)	9 (2.3%)
Skin and subcutaneous tissue disorders	2 (4.4%)	1 (2.1%)	15 (10.1%)	10 (6.8%)	17 (8.8%)	28 (7.2%)
Rash	1 (2.2%)	1 (2.1%)	3 (2.0%)	5 (3.4%)	4 (2.1%)	10 (2.6%)
Pruritus	1 (2.2%)	0 (0.0%)	3 (2.0%)	4 (2.7%)	4 (2.1%)	8 (2.1%)
Vascular disorders	1 (2.2%)	2 (4.3%)	6 (4.1%)	9 (6.1%)	7 (3.6%)	18 (4.6%)
Hypertension	0 (0.0%)	2 (4.3%)	5 (3.4%)	7 (4.7%)	5 (2.6%)	14 (3.6%)

Source: C803-028 PERSIST Report Body, p. 118-119 (PDF), Applicant's submission, NDA 204803.

There were consistent differences in the incidence of spontaneously-reported adverse events between treatment groups in the injury, poisoning, and procedural complications SOC. Specifically, the adverse events reported more frequently in the SABER-bupivacaine groups compared the control groups in both parts of the study included post-procedural contusion, incision site hemorrhage, and post-procedural discharge. In Part 1, there was higher incidence of incision site pruritis in patients treated with SABER-bupivacaine compared to patients treated with saline. In Part 2, incision site erythema and hematoma were both reported with a higher frequency than in the bupivacaine HCl group. In the gastrointestinal disorders SOC, there was a consistently higher incidence of constipation, abdominal pain, and abdominal pain upper in the SABER-bupivacaine treatment groups in both parts of the study compared to the respective controls. Additionally, in Part 2 there was an increased incidence of diarrhea, vomiting, and abdominal distention. In the nervous system SOC, there was an increased incidence of dysgeusia in the SABER-bupivacaine treatment groups in both parts 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 spontaneously-solicited TEAEs were mild in severity. Nineteen patients reported at least one severe spontaneously-reported 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.

As previously discussed, patients were frequently monitored for symptoms possibly related to benzyl alcohol toxicity, including during the minimum two-hour PACU stay and at 6 and 10 hours' post-operatively and at 8 pm on post-operative days 1 through 3. Because the T_{max} for benzyl alcohol is one hour and the $t_{1/2}$ is 4.7 hours, adverse events related to benzyl alcohol toxicity would likely be captured during these monitoring periods. In addition to the solicited reporting of 10 symptoms of interest requested by the Division, the Applicant also summarized the spontaneously-reported incidence (refer to the following table).

Table 27. Incidence of Spontaneously-Reported Symptoms of Interest (Safety Population)

	Part 1		Part 2	
	SABER-bupivacaine (N=45)	Saline placebo (n=47)	SABER-bupivacaine (N=148)	Bupivacaine HCl (N=148)
Somnolence	0	0	0	1 (1%)
Nausea	3 (7%)	6 (13%)	19 (13%)	19 (13%)
Dizziness	1 (2%)	1 (2%)	5 (3%)	4 (3%)
Headache	1 (2%)	4 (9%)	11 (7%)	6 (4%)
Vomiting	2 (4%)	2 (4%)	11 (7%)	6 (4%)
Constipation	2 (4%)	1 (2%)	11 (7%)	6 (4%)
Pruritis				

	Part 1		Part 2	
	SABER-bupivacaine (N=45)	Saline placebo (n=47)	SABER-bupivacaine (N=148)	Bupivacaine HCl (N=148)
Wound	1 (2%)	0	4 (3%)	7 (5%)
Generalized	1 (2%)	0	3 (2%)	4 (3%)
Dysgeusia	1 (2%)	0	5 (3%)	3 (2%)
Paresthesia	0	0	2 (1%)	0
Hypoesthesia	0	0	3 (2%)	0

Source: Adapted from Applicant's data.

In general, the overall incidence of spontaneously-reported symptoms of interest was low across both parts of the study and in all treatment groups; however, there were observed differences between the SABER-bupivacaine and control treatment groups. Specifically, symptoms that were reported with an increased incidence in patients treated with SABER-bupivacaine compared to the control treatments included constipation, pruritus, and dysgeusia in Part 1 and headache, vomiting, constipation, dysgeusia, paresthesia, and hypoesthesia in Part 2. These subtle findings support an increased incidence in some of the symptoms potentially associated with benzyl alcohol systemic exposure. The following discussion regarding the incidence of solicited symptoms further supports the Division's previous concerns about benzyl alcohol systemic exposure and possible toxicity.

Solicited Symptoms and Adverse Events

The 10 solicited symptoms of interest related to possible benzyl alcohol toxicity were reported as adverse events, but were not coded using MedDRA. The following table summarizes the observed differences in the frequency of the 10 solicited symptoms of interest at *any* of the solicited times; i.e., 6 and 10 hours post-operatively and at 8 pm on post-operative days 1 through 3.

Table 28. Incidence of Solicited-Reported Symptoms of Interest (Safety Population)

Dictionary-Derived Term (Verbatim LogPad Term)	Part 1		Part 2		Parts 1 & 2	Study Total (N=388)
	SABER- Bupivacaine (N=45)	Saline Placebo (N=47)	SABER- Bupivacaine (N=148)	Bupivacaine HCl (N=148)	SABER- Bupivacaine (N=193)	
Subjects reporting at least one solicited adverse event ^[1] , n (%)	36 (80.0%)	39 (83.0%)	134 (90.5%)	132 (89.2%)	170 (88.1%)	341 (87.9%)
Somnolence (Drowsiness)	25 (55.6%)	22 (46.8%)	89 (60.1%)	76 (51.4%)	114 (59.1%)	212 (54.6%)
Constipation (Constipation)	20 (44.4%)	20 (42.6%)	71 (48.0%)	65 (43.9%)	91 (47.2%)	176 (45.4%)
Nausea (Nausea)	15 (33.3%)	19 (40.4%)	64 (43.2%)	73 (49.3%)	79 (40.9%)	171 (44.1%)
Headache (Headache)	17 (37.8%)	15 (31.9%)	59 (39.9%)	57 (38.5%)	76 (39.4%)	148 (38.1%)
Dizziness (Dizziness)	11 (24.4%)	10 (21.3%)	46 (31.1%)	49 (33.1%)	57 (29.5%)	116 (29.9%)
Pruritus (Itching)	5 (11.1%)	11 (23.4%)	31 (20.9%)	29 (19.6%)	36 (18.7%)	76 (19.6%)
Vomiting (Vomiting)	7 (15.6%)	7 (14.9%)	15 (10.1%)	26 (17.6%)	22 (11.4%)	55 (14.2%)
Events Added with Amendment 2, n (%)	(N=23)	(N=22)	(N=148)	(N=148)	(N=171)	(N=341)
Dysgeusia (Metallic Taste in Mouth)	4 (17.4%)	2 (9.1%)	38 (25.7%)	29 (19.6%)	42 (24.6%)	73 (21.4%)
Paraesthesia (Tingling)	2 (8.7%)	2 (9.1%)	20 (13.5%)	22 (14.9%)	22 (12.9%)	46 (13.5%)
Hypoaesthesia (Numbness)	0 (0.0%)	0 (0.0%)	8 (5.4%)	9 (6.1%)	8 (4.7%)	17 (5.0%)

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 adverse event, subjects reporting more than one adverse event are counted only once.

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

Source: C803-028 PERSIST Report Body, p. 123 (PDF), Applicant's submission, NDA 204803.

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.

Three patients reported at least one severe solicited TEAE. One patient treated with SABER-bupivacaine in Part 1 had severe vomiting and two patients in Part 2, one each treatment group, had severe nausea and vomiting. The Applicant concluded that these severe TEAEs were not related to study drug treatment.

Because benzyl alcohol has a relatively short half-life 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 than the overall incidence described in the previous table, Table 26. The Applicant summarized the 10 symptoms of interest observed within 10 hours' post-operatively in the following table.

Table 29. Incidence of Solicited Symptoms of Interest Within 10 Hours Post-Operatively (Safety Population)

Dictionary-Derived Term (Verbatim LogPad Term)	Part 1		Part 2		Parts 1 & 2	Study Total (N=388)
	SABER- Bupivacaine (N=45)	Saline Placebo (N=47)	SABER- Bupivacaine (N=148)	Bupivacaine HCl (N=148)	SABER- Bupivacaine (N=193)	
Subjects reporting at least one solicited adverse event ^[1] , n (%)	29 (64.4%)	31 (66.0%)	121 (81.8%)	119 (80.4%)	150 (77.7%)	300 (77.3%)
Somnolence (Drowsiness)	20 (44.4%)	21 (44.7%)	82 (55.4%)	68 (45.9%)	102 (52.8%)	191 (49.2%)
Nausea (Nausea)	15 (33.3%)	16 (34.0%)	56 (37.8%)	62 (41.9%)	71 (36.8%)	149 (38.4%)
Dizziness (Dizziness)	7 (15.6%)	6 (12.8%)	37 (25.0%)	40 (27.0%)	44 (22.8%)	90 (23.2%)
Headache (Headache)	8 (17.8%)	7 (14.9%)	36 (24.3%)	33 (22.3%)	44 (22.8%)	84 (21.6%)
Vomiting (Vomiting)	5 (11.1%)	4 (8.5%)	13 (8.8%)	20 (13.5%)	18 (9.3%)	42 (10.8%)
Constipation (Constipation)	2 (4.4%)	5 (10.6%)	15 (10.1%)	15 (10.1%)	17 (8.8%)	37 (9.5%)
Pruritus (Itching)	1 (2.2%)	1 (2.1%)	12 (8.1%)	7 (4.7%)	13 (6.7%)	21 (5.4%)
Events Added with Amendment 2, n (%)	(N=23)	(N=22)	(N=148)	(N=148)	(N=171)	(N=341)
Dysgeusia (Metallic Taste in Mouth)	4 (17.4%)	2 (9.1%)	35 (23.6%)	27 (18.2%)	39 (22.8%)	68 (19.9%)
Paraesthesia (Tingling)	1 (4.3%)	0 (0.0%)	7 (4.7%)	11 (7.4%)	8 (4.7%)	19 (5.6%)
Hypoaesthesia (Numbness)	0 (0.0%)	0 (0.0%)	5 (3.4%)	5 (3.4%)	5 (2.9%)	10 (2.9%)

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: C803-028 PERSIST Report Body, p. 124 (PDF), Applicant's submission, NDA 204803.

In Part 1, patients treated with SABER-bupivacaine reported an increased incidence of dizziness, headache, vomiting, dysgeusia, and paresthesia compared to patients treated with saline placebo. In Part 2, SABER-bupivacaine-treated patients reported an increased incidence of somnolence, headache, pruritus, and dysgeusia compared to those treated with bupivacaine HCl. Headache and dysgeusia were reported with higher frequency in SABER-treated patients compared to the control-treated patients in both parts of the study.

Based on T_{max} and the $t_{1/2}$ of BA, the Applicant provided a similar summary table (Table 28) of solicited symptoms occurring within 6 hours of administration in response to an Information Request.

Table 30. Incidence of Solicited Symptoms of Interest Within 6 Hours Post-Operatively (Safety Population)

Dictionary-Derived Term (Verbatim LogPad Term)	Part 1		Part 2		Parts 1 & 2	Study Total (N=388)
	SABER- Bupivacaine (N=45)	Saline Placebo (N=47)	SABER- Bupivacaine (N=148)	Bupivacaine HCl (N=148)	SABER- Bupivacaine (N=193)	
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.

This table indicates that patients treated with SABER-bupivacaine 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, there is concern that exposure to systemic BA may in fact be the cause.

Subgroup analysis of these symptoms of interest by sex, age, and race did not demonstrate a consistent trend in the incidence of TEAEs and did not suggest one subgroup was more prone to TEAEs than another.

8.2.5. Surgical Site Complications

The surgical sites were evaluated at each follow-visit by blinded, trained medical personnel, 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. The incisions were evaluated on study days 4, 8, 15, and 30. An additional visit on study day 60 was completed after Protocol Amendment 5 was implemented. The following table summarizes the incidence of these six adverse events.

Table 31. Surgical Site Complications – Six Prespecified Adverse Events (Safety Population)

Pre-Specified Surgical Site Complication, n (%)	Part 1		Part 2		Combined Parts 1 & 2	Risk Ratio ^[1] (95% CI)
	SABER-Bupivacaine (N=45)	Saline Placebo (N=47)	SABER-Bupivacaine (N=148)	Bupivacaine HCl (N=148)	SABER-Bupivacaine (N=193)	
Visible bruising	41 (91.1%)	33 (70.2%)	142 (95.9%)	105 (70.9%)	183 (94.8%)	1.336 (1.199, 1.489)
Surgical site bleeding	22 (48.9%)	20 (42.6%)	19 (12.8%)	24 (16.2%)	41 (21.2%)	1.310 (0.830, 2.067)
Drainage from surgical incision(s)	2 (4.4%)	3 (6.4%)	11 (7.4%)	6 (4.1%)	13 (6.7%)	1.661 (0.647, 4.268)
Wound hematoma	0 (0.0%)	0 (0.0%)	6 (4.1%)	2 (1.4%)	6 (3.1%)	2.301 (0.471, 11.235)
Wound dehiscence	0 (0.0%)	0 (0.0%)	2 (1.4%)	3 (2.0%)	2 (1.0%)	0.511 (0.087, 3.020)
Surgical site infection	0 (0.0%)	0 (0.0%)	2 (1.4%)	1 (0.7%)	2 (1.0%)	1.534 (0.140, 16.753)

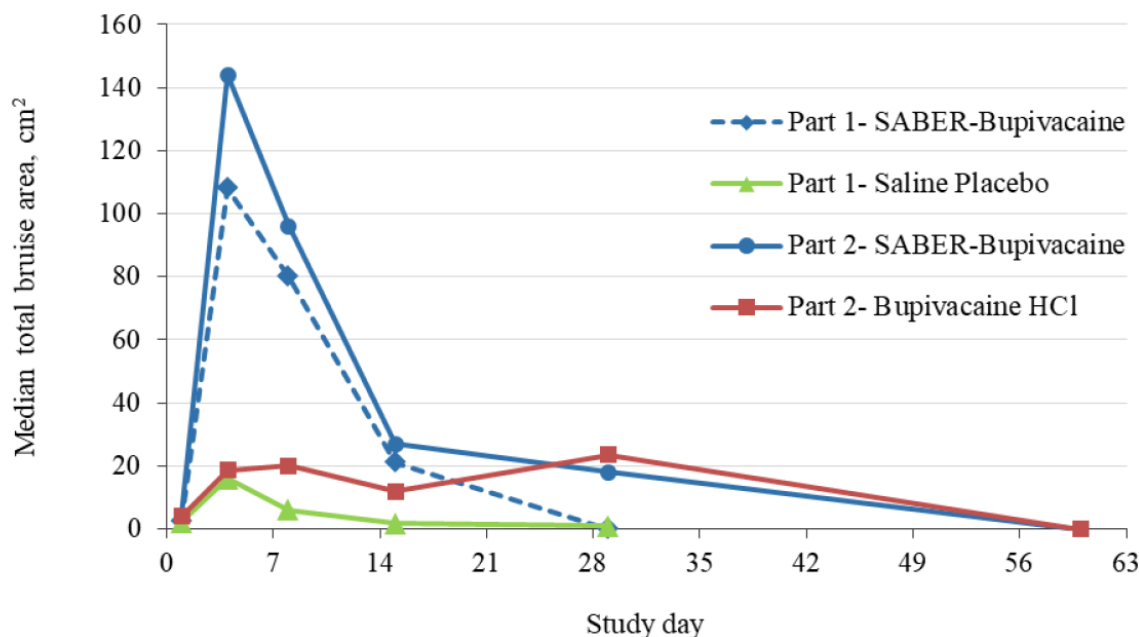
[1] (Combined Parts 1 & 2 SABER-Bupivacaine) / (bupivacaine HCl)

Source: C803-028 PERSIST Report Body, p. 129 (PDF), Applicant's submission, NDA 204803.

Surgical Site Bruising

Visible bruising consistently occurred with increased frequency in patients treated with SABER-bupivacaine in both parts of the study, maximal on study day four. As discussed in Section 8.11, bruising appears to be a consistently reported adverse event in patients treated with SABER-bupivacaine. Additionally, the area of bruising appeared to be larger, as indicated in the following figure, and require more time for complete resolution in patients treated with SABER-bupivacaine, in both Parts 1 and 2.

Figure 10. Total Area of Bruising (all wounds) By Study Day (Safety Population)



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](#)

Source: C803-028 PERSIST Report Body, p. 131 (PDF), Applicant's submission, NDA 204803.

Analysis of the per-incisional bruising data indicates that all patients with a bruise surface area of 100 cm² (15.5 in²) or greater, 39 patients total, were treated with SABER-bupivacaine. For reference, 100 cm² equals 15.5 in², which represents a circular area approximately 4.4 inches in diameter. The largest bruise was reportedly 440 cm² (68 in²) in a patient treated with SABER-bupivacaine, in contrast to the largest bruise reported in the saline placebo group was 40 cm² (6.2 in²) and for the bupivacaine HCl group was 66 cm² (10.2 in²).

While it does not appear that a large area of bruising resulted in the development of more serious surgical site complications, such as infection or dehiscence, in SABER-bupivacaine-treated patients in the surgical populations evaluated by the Applicant, there is concern that the development of a large bruise in specific locations within the body may be less well-tolerated. Specifically, the anticipated post-market patient population may include patients undergoing lumbar spine or foot and ankle procedures where bruising could result in more serious adverse events leading to long-term complications.

Additionally, the potential impact of bruising on long-term skin changes in non-white patients is not known. Dr. Simone, in his clinical review of the original NDA, expressed concern regarding hypertrophic scarring or keloid formation in patients with darker skin color treated with SABER-bupivacaine. Similar to the evaluated demographic groups in the earlier clinical studies, there were too few non-white patients treated in the PERSIST study to make a definitive

determination regarding the long-term implications of local adverse reactions in patients with darker skin color.

Surgical Site Bleeding

In Part 1, it appears 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.

Surgical site bleeding was rated as spotting of the dressing, soaking of the dressing, or continuous bleeding throughout the study. The majority (> 92%) of bleeding from the umbilical incision on the day of surgery involved only spotting of the dressing; however, in Part 1 of the study, there was a higher incidence of a soaked dressing in the SABER-bupivacaine group compared to the saline group; 6% versus 0%, respectively. In Part 2 of the study, the incidence of soaked dressing bleeding was similar between treatment groups on the day of surgery. The incidence of bleeding by treatment group and study day is summarized in the following table.

Table 32. Incidence of Surgical Site Bleeding by Study Day (Safety Population)

External bleeding at one or more incisions, n (%)	Part 1		Part 2	
	SABER-Bupivacaine (N=45)	Saline Placebo (N=47)	SABER-Bupivacaine (N=148)	Bupivacaine HCl (N=148)
Day of Surgery	21 (46.7%)	18 (38.3%)	18 (12.2%)	23 (15.5%)
Day 4	6 (13.3%)	5 (10.6%)	1 (0.7%)	2 (1.4%)
Day 8	2 (4.4%)	1 (2.1%)	2 (1.4%)	0 (0.0%)
Day 15	0 (0.0%)	1 (2.1%)	1 (0.7%)	0 (0.0%)
Day 29	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day 60	—	—	0 (0.0%)	0 (0.0%)

Source: C803-028 PERSIST Report Body, p. 134 (PDF), Applicant's submission, NDA 204803.

A concerning finding in the above table is the duration of surgical site bleeding after treatment with SABER-bupivacaine compared to treatment with either control in each part of the study. Specifically, it appears that there is a higher incidence of bleeding through day 8 (POD 7) in patients treated with SABER-bupivacaine. Additionally, there was a patient treated with SABER-bupivacaine in Part 1 of the study who had a soaked dressing at the epigastric incision on study day 4. The reported incisional bleeding on day 8 was spotting of the dressing only for all treatment groups.

Drainage From the Surgical Incision

There was a higher incidence of drainage in the saline placebo treatment group in Part 1 and in the SABER-bupivacaine treatment group in Part 2 of the study. The drainage was most commonly described as serosanguinous. There was a single case of purulent wound discharge observed in a patient treated with bupivacaine HCl in Part 2 of the study on day 29, which reportedly resolved within one week without treatment.

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.

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.

The Applicant argues that because the lap chole incisions are shorter in length than the other abdominal procedures evaluated, each incision would have a higher local study drug exposure such that if wound dehiscence were a real concern with SABER-bupivacaine, it would have been apparent in this study. This is not necessarily true considering there were four incision sites for the lap chole procedure, each receiving on average 1.25 mL of SABER-bupivacaine. Based on the number of larger diameter trochars (10 to 12 mm) used, however, the amount of study drug per incision site would likely depend on the length, such that the longer incisions would receive more and the shorter incisions would receive less. Therefore, the overall exposure per incision is probably similar regardless of the length of the incision.

Surgical Site Infection (SSI)

There were seven patients with surgical site infections; five treated with SABER-bupivacaine and two 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 following table summarizes the surgical site infections.

Table 33. Surgical Site Infections

Subject ID	Study Part	Treatment Group	Infection Description	Study Day Start, End	Treatment (Verbatim)	Data Source
(b) (6)	2	SABER-Bupivacaine	Incision site infection	11, 16	Augmentin	AE Listing only
	2	Bupivacaine HCl	Superficial incisional infection - umbilical and midaxillary	54, 78	Bactrim DS	Surgical site infection and AE Listings
	2	Bupivacaine HCl	Postprocedural cellulitis	3, 26	Bactrim DS	AE Listing only
	1	SABER-Bupivacaine	Stitch abscess	21, 26	Keflex	AE Listing only
	2	SABER-Bupivacaine	Superficial incisional infection - umbilical	11, 24	Bactrim DS	Surgical site infection and AE Listings
	2	SABER-Bupivacaine	Incision site infection	32, 60	Cephalexin, Amoxicillin-Clavulanic Acid	AE Listing only
	2	SABER-Bupivacaine	Superficial incisional infection - umbilical	15, 29	Topical Neosporin, Bactrim DS, Keflex	Surgical site infection and AE Listings

AE = adverse event

Sources: [Listing 16.2.7.5.5](#) (surgical site infections), [Listing 16.2.5.6](#) (concomitant medications), and [Listing 16.2.7.1](#) (AEs)

Note: The adverse event was reported according to protocol instructions, and/or included as an adverse event.

Source: C803-028 PERSIST Report Body, p. 136 (PDF), Applicant's submission, NDA 204803.

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. While I agree that the incidence may not be unexpectedly high and there were no subsequent complications, I do not agree that surgical site infections are not a concern 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. Furthermore, the likely broad post-market exposure and the potential impact on many surgical patients undergoing a variety of surgical procedures is concerning.

While not directly implicated in the development of surgical site infections, 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 may make surgical re-exploration challenging with increased risk of surgical complications.

Abnormal Wound Healing

Abnormal wound healing at each of the laparoscopic port sites was assessed as normal or abnormal on the day of surgery, and on days 4, 8, 15, 29, and 60 for those patients treated under Protocol Amendment 5. Abnormal healing at one or more port sites is included in the following table.

Table 34. Patients with Abnormal Healing at Any Incision Site (Safety Population)

Subjects with abnormal healing, n (%)	Part 1		Part 2	
	SABER-Bupivacaine (N=45)	Saline Placebo (N=47)	SABER-Bupivacaine (N=148)	Bupivacaine HCl (N=148)
Day of surgery	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day 4	0 (0.0%)	0 (0.0%)	5 (3.4%)	2 (1.4%)
Day 8	0 (0.0%)	0 (0.0%)	4 (2.7%)	5 (3.4%)
Day 15	0 (0.0%)	0 (0.0%)	2 (1.4%)	2 (1.4%)
Day 29	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Day 60 ^[1]	—	—	0 (0.0%)	0 (0.0%)

[1] Only Part 2 subjects enrolled under Protocol Amendment 5 (n=45 for each treatment group) were required to complete the study Day 60 visit.

Source: C803-028 PERSIST Report Body, p. 137 (PDF), Applicant's submission, NDA 204803.

In Part 2 of the study, there were nine patients treated with SABER-bupivacaine and seven patients treated with bupivacaine HCl noted to have abnormal healing during the study. Most cases of abnormal healing included the same predefined complications discussed above, with the exception of bruising, which investigators were instructed to not describe as abnormal healing. Most abnormalities were reported on days 4 or 8 and involved the umbilical or epigastric incisions. All cases of abnormal healing were resolved by study day 29, with the exception of a single patient in the bupivacaine HCl treatment group who developed an umbilical hernia requiring surgical correction. The Applicant concludes that the SABER-formulation did not affect normal wound healing compared to treatment with bupivacaine HCl.

The Applicant has indicated that all cases of abnormal wound healing reported for patients treated with SABER-bupivacaine were resolved by study day 60.

8.2.6. Laboratory Findings

Hematology

There were no clinically relevant changes in reported hematology lab results across all treatment groups through study day 4, with the exception of measured leukocyte (WBC) and

neutrophil counts. Specifically, there was an increase in both overall leukocyte count and neutrophil count in the SABER-bupivacaine-treated patients compared to the saline and bupivacaine HCl treatment groups. The following table summarizes the number and percentage of patients per treatment group who had an increase of 30% or greater in either absolute WBC or neutrophil count at any time during the study and at evaluated time points. Note that not all increases resulted in abnormal lab values.

Table 35. Increases of $\geq 30\%$ From Baseline in Leukocyte and Neutrophil Count, All Treatment Groups (Safety Population)

Treatment Group	Leukocyte Increase $\geq 30\%$ n (%)	Neutrophil Increase $\geq 30\%$ n (%)
SABER-bupivacaine		
• Part 1*	11 (24%)	16 (36%)
Day 4	11 (24%)	14 (31%)
Day 29	1 (2%)	5 (11%)
• Part 2*	37 (25%)	63 (44%)
Day 4	28 (19%)	53 (37%)
Day 29	11 (7%)	19 (13%)
Day 60	2 (1%)	11 (8%)
Unscheduled	-	2 (4%)
Saline placebo (Part 1) *	7 (15%)	17 (36%)
Day 4	5 (11%)	15 (32%)
Day 29	2 (4%)	5 (11%)
Bupivacaine HCl (Part 2) *	27 (18%)	44 (30%)
Day 4	22 (7%)	41 (27%)
Day 29	9 (6%)	13 (9%)
Day 60	2 (1%)	3 (2%)
Unscheduled	1 (1%)	3 (2%)

*Some patients had elevated WBC count on more than one evaluated time point.

#Unscheduled evaluations occurred in all but one patient with infection-related AEs.

Source: Reviewer's analysis.

In general, the difference in the number of treated patients across the treatment groups with a 30% or greater increase in cell counts is not clinically significant; however, the increases are consistent with the increased incidence in wound-healing adverse events, such as bruising and surgical site infections.

Review of the hematology data presented in the original NDA submission identified a transient, clinically insignificant decrease in mean red blood cell count across all treatment groups in Study BU-001-IM and Study BU-002-IM over study days 1, 2, and 3, as discussed in the primary clinical review by Dr. Arthur Simone. The mean change observed in the PERSIST study did not consistently demonstrate similar decreases; however, labs were collected only at screening (baseline) and study day 4, so acute changes were not captured.

Chemistry

There did not appear to be any treatment-related changes in measured chemistry parameters, including bicarbonate, sodium, potassium, calcium, chloride, and phosphate. There were elevations in liver function tests (LFTs) observed across all treatment groups during the study, some of which persisted through the end of the study, day 29 or 60 depending on the status of Protocol Amendment 5. Specifically, there were 206 patients who had a shift from normal to abnormal in at least one of the following measured LFTs: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, and direct bilirubin. It does not appear that a single treatment group had a larger number of affected patients or larger increases in measured lab values and most abnormal shifts were observed in AST and ALT values. There were no reports of jaundice or severe hepatocellular injury; therefore, the clinical significance of the elevations in measured LFTs is not known. It is worth noting that insufflation of the abdomen with carbon dioxide (CO₂) can impede hepatic blood flow, resulting in a transient “enzyme leak”, which would likely resolve by the end of the study.

It is reassuring that during the clinical review of the original NDA, Dr. Arthur Simone did not identify a hepatic safety signal. Furthermore, there were no cases during this study that met Hy’s Law criteria.

Mean lactate dehydrogenase (LDH) levels were increased in SABER-bupivacaine-treated patients while decreased in the comparator treatment groups in both parts of the study; however, the number of patients who experienced increases of 30% or greater than baseline was similar across all treatment groups in both parts of the study. Because LDH can be elevated in a variety of disease processes, the clinical significance of these findings is not known, and may be due to tissue damage during the surgical procedure.

Mean creatine kinase (CK) levels increased in SABER-bupivacaine-treated patients and decreased in the control treatment groups in both parts of the study. The following table summarizes the change in measured CK for all treatment groups in both parts of the study.

Table 36. Mean Creatine Kinase Levels Across All Treatment Groups, Part 1 and Part 2 (Safety Population)

Laboratory Parameter (units) Visit / Time Point	Part 1		Part 2	
	SABER- Bupivacaine (N=45)	Saline Placebo (N=47)	SABER- Bupivacaine (N=148)	Bupivacaine HCl (N=148)
Creatine Kinase (U/L)				
Baseline ^[1]				
n (%)	45 (100%)	47 (100%)	148 (100%)	148 (100%)
Mean (SE)	108.5 (10.65)	100.3 (8.76)	110.4 (8.32)	109.0 (6.98)
Standard Deviation	71.45	60.03	101.22	84.96
Median	86.0	80.0	90.5	86.5
Min, Max	20, 336	34, 352	33, 1103	29, 754
Study Day 4				
n (%)	42 (93.3%)	46 (97.9%)	143 (96.6%)	147 (99.3%)
Mean (SE)	168.5 (37.71)	82.5 (7.60)	128.7 (8.78)	82.0 (3.64)
Standard Deviation	244.37	51.56	104.97	44.16
Median	107.0	67.0	98.0	69.0
Min, Max	19, 1598	26, 299	22, 721	24, 296
Change from Baseline to Study Day 4				
n (%)	42 (93.3%)	46 (97.9%)	143 (96.6%)	147 (99.3%)
Mean (SE)	58.7 (37.62)	-18.4 (8.09)	17.7 (10.86)	-27.4 (6.22)
Standard Deviation	243.79	54.89	129.81	75.47
Median	15.5	-14.5	6.0	-13.0
Min, Max	-181, 1538	-254, 97	-922, 565	-694, 130
Change from Baseline to Study Day 29				
n (%)	45 (100%)	47 (100%)	148 (100%)	145 (98.0%)
Mean (SE)	-8.9 (7.22)	-1.0 (9.74)	-4.8 (9.04)	-2.0 (6.53)
Standard Deviation	48.41	66.77	109.97	78.67
Median	-4.0	-3.0	-6.0	-2.0
Min, Max	-241, 50	-173, 338	-922, 566	-614, 389

Source: C803-028 PERSIST Report Body, p. 734 (PDF), Applicant's submission, NDA 204803.

There were a larger number of patients in the SABER-bupivacaine treatment groups compared to the control groups in both parts of the study who had CK levels increase from normal to abnormal on study days 4 or 29, or 60 depending on the status of Protocol Amendment 5. Additionally, of the seven patients with the highest shift from normal to abnormal CK levels, six were treated with SABER-bupivacaine in Part 2 of the study. Furthermore, review of the lab data from the ISS suggests that while there were a low number of treated patients with elevations in CK post-operatively, the majority of reported cases occurred in patients who received either SABER-bupivacaine or SABER-placebo. The clinical significance is not entirely understood, but could potentially be related to increased muscle and tissue damage, particularly considering the consistent reported increased post-operative bruising, associated with SABER-bupivacaine administration.

Urinalysis

There were no clinically relevant changes in measured urinary parameters across treatment groups during the study.

8.2.7. Vital Signs

Based on recommendations by the Agency, vital signs were measured every 15 minutes for two hours after study drug administration. The intensive monitoring was intended to capture any hemodynamic or oxygenation changes as a result of systemic exposure to benzyl alcohol.

Heart Rate

There did not appear to a clinically significant change in heart rate in any treatment group across the study. The changes that were observed in the immediate post-operative period, increases and decreases, did not appear to be concentrated in any particular treatment group. There were three reported cases of post-operative bradycardia; one saline-treated patient and one bupivacaine HCl-treated patient on study day 1, and one bupivacaine HCl-treated patient on study day 7. Tachycardia was reported for a single patient treated with bupivacaine HCl on study day 1.

Respiratory Rate

There were reportedly no clinically significant changes in respiratory rate between treatment groups throughout the two-hour intensive monitoring period or throughout the study. There were reports of patients with rates less than 10 breaths per minute; however, it appears those occurred most commonly within the first two hours of PACU admission. There were no cases of apnea reported. A single patient, (b) (6), in the SABER-bupivacaine group had an adverse event of respiratory depression 45 minutes after PACU admission. Respiratory rate was 7 breaths per minute, which increased to 10 bpm 60 minutes after PACU admission.

Blood Pressure

There were no clinically significant changes in measured blood pressure throughout the two-hour intensive monitoring period or throughout the study. Diastolic blood pressure (DBP) did decrease over the PACU admission by approximately 2 to 4 mm Hg, however, this was not felt to be clinically significant and did not vary between treatment groups. There were no differences in the number of outlier DBP measurements across the treatment groups.

Systolic blood pressure (SBP) also decreased slightly over the PACU admission, but there were no differences observed between treatment groups, either in duration or severity of changes. There were no differences in the number of outlier SBP measurements across treatment groups.

Pulse Oximetry

There were no clinically significant changes in pulse oximetry measurements throughout the two-hour intensive PACU monitoring period or throughout the study. In Part 1, there were no desaturations less than or equal to 90%. In Part 2, 10 patients in the SABER-bupivacaine treatment group and 13 patients in the bupivacaine HCl treatment group who had one or more

desaturations less than or equal to 90% and they appeared to be evenly distributed across the two hours. Most were a single event. Only one patient ((b) (6)) had prolonged desaturation episodes, lasting approximately 75 minutes, which was felt to be secondary to opioid administration. Oxygen saturation was reportedly within normal limits at the time of discharge.

8.2.8. Electrocardiograms (ECG)

Twelve-lead ECGs were captured during the screening visit and the end of study, day 29 or 60 depending on the implementation of Protocol Amendment 5. Continuous ECG monitoring was employed intra-operatively per standard ASA guidelines. In general, there did not appear to be any clinically significant morphological changes or arrhythmias related to the administration of SABER-bupivacaine at the highest recommended dose, 660 mg. There were two patients, one in the saline treatment group and one in the bupivacaine HCl treatment group, who had abnormal ECGs which were included as TEAEs. The patient treated with bupivacaine HCl had an abnormal T wave and there was no additional information provided for the patient in the saline group.

These findings support the cardiac safety of SABER-bupivacaine administration and are consistent with those reported in the clinical review of the original NDA by Dr. Arthur Simone.

8.2.9. QT Evaluation

The study did not specifically evaluate the potential for SABER-bupivacaine to prolong the QT interval; however, there were no clinically significant changes in mean QT intervals across treatment groups, particularly increases above 450 msec. There was a single patient ((b) (6)) in the bupivacaine HCl-treatment group who had a measured QTc interval of 562 msec on study day 29. The screening and study day 60 ECGs had normal QTc intervals reported. The prolongation observed at study day 29 was not felt to be related to study drug treatment.

8.3. Evaluation of Additional Safety Information From Previously Completed Studies

In the End-of-Review Meeting Package, submitted Aug. 15, 2014, the Applicant presented post hoc 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. Because the data were not contained in the NDA submission, the new analyses could not be used to resolve the CRL deficiencies. This information was included in the NDA resubmission and will be discussed here.

8.3.1. Adverse Events Related to Shoulder Joint

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 (Dias *et al*, 2005). 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 following table summarizes the shoulder surgery studies conducted by the Applicant, with relevant follow-up duration and assessments.

Table 37. Summary of Studies Evaluating SABER-Bupivacaine in Patients Undergoing Shoulder Surgery

Trial Number / Location / Start-Stop Dates	Number of patients treated with subacromial drug			Duration of Follow-up	Follow-up Assessments	Surgery
	SABER-Bupivacaine 5 mL	SABER-Placebo 5 mL	Bupivacaine HCl 50 mg			
CLIN-005-0006 US & NZ 2006-2007	62 ^[1]	44 ^[2]	0	14 days	AE, PE, labs	Rotator cuff repair, subacromial decompression, labral repair, or biceps tendon repair
C803-017 Australia & NZ 2008-2009	40	20	0	18 months	MRI, AE, PE, pain	Subacromial decompression without major rotator cuff tears
BU-002-IM Europe 2009-2010	53	25	29	6 months	MRI, shoulder function, wound healing	Subacromial decompression with intact rotator cuff
Total	155	89	29	Overall Total = 273 Patients		

[1] 3 patients received 7.5 mL SABER-Bupivacaine

[2] 4 patients received 7.5 mL SABER-placebo

Source: ISS, p. 30 (PDF), Applicant's submission, NDA 204803.

The Applicant has conducted four additional evaluations in patients undergoing shoulder surgery in their clinical studies, including re-reading MRIs concerning for chondrolysis, re-reading all MRIs in Study C803-017 and Study C803-017e, follow-up physical examinations, and long-term follow-up for patients in Study BU-002-IM and Study CLIN005-0006, described in detail below.

1. The first additional evaluation involved two independent orthopedic surgeons blindly re-reading baseline and 18-month follow-up MRIs 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.

Briefly, the three patients identified during the clinical review of the original NDA included two patients with "evidence of chondrolysis" on post-operative checklist.

- 66-year-old male (b) (6) with history of repeated right shoulder trauma who underwent uncomplicated arthroscopic shoulder surgery and continued to have

- pain, limited range of motion, and impingement sign at 18 months. He was treated with SABER-bupivacaine.
- 30-year-old male ((b) (6)) with history of right frozen shoulder (or adhesive capsulitis) who underwent arthroscopic subacromial decompression and continued to have pain. He underwent non-study surgery six months later and continued to have pain, limited range of motion, and impingement sign at 18 months. He was treated with SABER-placebo.

The Applicant has clarified that both patients had baseline MRI findings that were unchanged on the 18-month post-operative MRI and that the “evidence of chondrolysis” checkbox was marked in error. There was no clinical correlation consistent with chondrolysis and the investigators did not report either case as an adverse event.

The third patient, a 27-year-old female ((b) (6)), underwent two procedures, one during Study C803-017, in which she received SABER-bupivacaine, and one non-study procedure 15 months later. During the non-study procedure, the glenohumeral head was noted to be entirely intact with a small, 1 to 2 mm, area of minor fraying on the humeral head. Because the patient had participated in a clinical study, the investigator biopsied the glenoid for “scientific purposes” and the pathology report indicated “mild myxoid degeneration” and the diagnosis was “mild degenerative change”. The investigator reported this finding as an SAE, later coded as chondropathy. At the 18-month examination, three months following the non-study procedure, the patient was pain-free, had a normal shoulder examination, no impingement sign, and the MRI did not identify any abnormality of the glenohumeral joint.

There were two additional patients with adverse events reported in Study C803-017e that were discussed in the End-of-Review Meeting. The details of those cases are described below:

- 36-year-old female ((b) (6)) underwent right shoulder surgery in the SABER-placebo treatment group and was reported to have bursitis on study day 553. Her baseline pain score was 9 on NRS and her post-operative pain score was 5. She had reduced range of motion at the 18-month follow-up. It appears her baseline diagnosis was bursitis, which did not appear to worsen post-operatively.
- 68-year-old male ((b) (6)) underwent right shoulder surgery in the SABER-placebo treatment group and was reported as having a partial rupture of the right shoulder biceps tendon on study day 313 while lifting a shovel. This patient had a history of right breast cancer, with frequent CT scanning, and requested a waiver for MRI scanning during this study due to claustrophobia. The Applicant states that while ideal imaging is not available for this patient, full passive and active range of motion were observed at the 18-month follow-up visit. Additionally, the Applicant notes that this patient had a lymph node dissection as part of the breast cancer evaluation, which may have contributed to shoulder pathology.

2. The second additional evaluation involved a blinded radiologist (b) (4) re-reading 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. Two patients had ultrasound examinations in lieu of MRIs due to claustrophobia and anxiety in one patient and an implantable MRI-sensitive device in the other patient. The following table summarizes the patients and imaging by study and treatment group.

Table 38. Summary of Patients and Radiographic Images Available for Re-Read

Parameter	C803-017		C803-017e	
	SABER-Bupivacaine	SABER-Placebo	SABER-Bupivacaine	SABER-Placebo
Total subjects enrolled	40	20	31	16
Subjects with MRI imaging	39	18	29	14
Subjects with ultrasound imaging ^[1]	1	1	1	1
Subjects with no imaging ^[2]	0	1	0	1
MRI images available for central reading	24	13	27	14
Shoulder physical examination	40	20	31	16

[1] Subject (b) (6) was claustrophobic and could not tolerate MRI; Subject (b) (6) had an implanted nerve stimulator that precluded MRI examination. The central MRI scoring system could not evaluate ultrasound images and each parameter for these two subjects was scored as “Not evaluable”. These two patients are not included in the summary table, but the ultrasound data will be presented separately.

[2] Subject (b) (6) was claustrophobic and could not tolerate an MRI. However, a CT scan of the right shoulder was done before enrollment. No scans were done at the 18-month visit.

Source: ISS, p. 33 (PDF), Applicant’s submission, NDA 204803.

Note: In response to IR sent on Dec. 6, 2019, the Applicant clarified that in Study C803-17e, the number of subjects with no imaging should be one, such that the number without imaging (1), plus the number with ultrasound imaging (1), plus the number with MRI imaging (29) equals the total number enrolled (31).

There were 13 patients in Study C803-017 who did not participate in the 18-month follow-up study, C803-017e, for reasons summarized in the following table.

Table 39. Patient Disposition, Study C803-017e

Reasons for Not Enrolling in C803-017e	SABER-Bupivacaine	SABER-Placebo
Site 03 declined to participate	5	2
Lost to follow-up	2	1
Did not meet enrollment criterion	2	1

Source: ISS, p. 33 (PDF), Applicant’s submission, NDA 204803.

Of the two patients treated with SABER-bupivacaine and lost to follow-up, one moved out of the country but was reported as having no ongoing issues with the operative shoulder.

The second patient had significant post-operative pain, rated a 10 on NRS, required large doses of rescue medication, and withdrew from the study on POD 1. During a five-month follow-up visit, the surgeon reported that shoulder pain was resolving, range of motion had “stabilized”, and physical therapy was underway. The Applicant states that the disposition numbers summarized in the above table are not unexpected given that patients were unaware of the required follow-up for Study C803-017e at the time of informed consent for Study C803-017.

Site 03 declined to participate in Study C803-107e because the investigator opted to unblind patients prior to enrollment in Study C803-017e. The investigator did provide follow-up information for all patients not enrolled in the extension study, which indicated that three patients in the SABER-bupivacaine group developed painful, stiff shoulders within two to five months of surgery. All three recovered with hydrodilation therapy (ultrasound-guided injections of normal saline, local anesthetic, and steroid into the shoulder joint).

Aside from the three cases discussed, there was an additional case of frozen shoulder reported during Study C803-017 and Study C803-017e. The patient was treated with SABER-bupivacaine and developed frozen shoulder on study day 10, POD 9, which reportedly ended on study day 11, POD 10. The adverse event was reported as severe and treated with diclofenac. Given the time of onset and quick resolution with minimal intervention, this does not appear to be a true case of frozen shoulder.

For those patients with available follow-up imaging, the pre-operative and postoperative images were read side by side on two screens and a detailed scoring system was used to grade 38 individual anatomic features in the shoulder images. Areas of interest in the shoulder included the following seven locations:

- gleno-humeral joint and humeral head
- rotator cuff and labrum
- muscle bodies of the rotator cuff
- subacromial space–acromion
- acromio-clavicular joint
- bursa and soft tissue
- coracoid

Once the MRIs were read by the radiologist, an orthopedic surgeon with experience in shoulder surgery ((b) (4)) reviewed the images with the radiologist to assess the clinical relevance of any radiological findings. Their staged reading process led to the following (verbatim):

- 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

Appendix 13.1 includes a summary table of the results of the staged MRI reading.

There were positive MRI findings, summarized below in both treatment groups at 18 months. Specifically,

- There were two patients treated with SABER-bupivacaine who had teres minor fatty infiltration compared to none in the SABER-placebo group
- There were two patients treated with SABER-bupivacaine who had normal subacromial spaces at baseline but abnormal at 18 months, compared to no patient treated with SABER-bupivacaine
- Four patients had changes in the acromioclavicular joint at 18 months; one treated with SABER-bupivacaine and three treated with SABER-placebo. Additionally, one patient treated with SABER-placebo went from mild to severe joint effusion/synovitis at 18 months
- A higher percentage of patients had moderate subacromial bursitis at 18 months in the SABER-bupivacaine group compared baseline and compared those treated with SABER-placebo

Because the observed radiological changes over 18 months were infrequent, inconsistent, and did not demonstrate a clear pattern, the Applicant concludes that treatment with either SABER-bupivacaine or SABER-placebo did not result in healing abnormalities of the shoulder joint or surrounding tissue.

For the two patients who underwent ultrasound imaging due to MRI contraindications, there were no identified changes in shoulder anatomy.

3. The third additional evaluation involved follow-up physical examinations of patients treated in Study C803-017 by still blinded investigators 18 months post-operatively. The focus of the exams was on the following:
 - Surgical site healing and tissue condition (refer to Table 39 for a summary of healing data)
 - Pain intensity (0 to 10 on the 11-point NRS) when elevating the operative shoulder (forward flexion to 90°)
 - Presence or absence of impingement sign (pain on forward flexion or abduction)
 - Presence or absence of full passive range of motion
 - Clinical assessment of a normal or abnormal shoulder exam (refer to Table 40 for a summary of physical examination results)

Table 40. Surgical Site Healing and Local Tissue Conditions, 18 Months' Post-Operatively (C803-017)

	SABER-Bupivacaine (N=31)	SABER-Placebo (N=16)
Surgical Site Healing		
Unexpected/Abnormal	0	0
As Expected	31 (100.0%)	16 (100.0%)
Local Tissue Conditions		
Unexpected/Abnormal	0	0
As Expected	31 (100.0%)	16 (100.0%)
Surgical Site Infection		
Yes	0	0
No	31 (100.0%)	16 (100.0%)
Surgical Site Bleeding		
Yes	0	0
No	31 (100.0%)	16 (100.0%)
Surgical Site Discoloration		
Yes	0	0
No	31 (100.0%)	16 (100.0%)
Surgical Site Dehiscence		
Yes	0	0
No	31 (100.0%)	16 (100.0%)

Note: Treatment groups represent actual treatment in study C803-017

Source: ISS, p. 41 (PDF), Applicant's submission, NDA 204803.

These results indicate that there were no concerning surgical site healing or local tissue conditions observed at the 18-month follow-up visit.

Table 41. Summary of Shoulder Examination Results at 18 Months' Post-Operatively (C803-017)

	SABER-Bupivacaine (N=31)	SABER-Placebo (N=16)
Pain Intensity		
Mean (SE)	0.9 (0.36)	1.2 (0.55)
Standard Deviation	2	2.2
Median	0	0
Min, Max	0, 7	0, 7
Positive Impingement Sign, n (%) ^[1]		
Yes	3 (9.7%)	3 (18.8%)
No	28 (90.3%)	13 (81.3%)
Full Passive Range of Motion, n (%) ^[1]		
Yes	27 (87.1%)	13 (81.3%)
No	4 (12.9%)	3 (18.8%)
Clinical Assessment, n (%) ^[1]		
Normal	27 (87.1%)	13 (81.3%)
Abnormal	4 (12.9%)	3 (18.8%)

Note: Treatment groups represent original treatment group assignment from study C803-017.

[1] Percentages based on non-missing responses

Source: ISS, p. 42 (PDF), Applicant's submission, NDA 204803.

The results summarized in the above table are consistent with reports in the published literature regarding post-operative functional changes and physical examination findings. It is interesting, however, that patients treated with SABER-placebo appear to have worse functional capacity and physical examination findings than those treated with SABER-bupivacaine.

- The fourth and final additional evaluation involved the Applicant reviewing long-term follow-up data from patients who completed Study BU-002-IM and Study CLIN005-0006.

Study BU-002-IM

Patients in this study underwent six-month follow-up which included MRI and a physical examination. A total of 103 treated patients (96%) returned for the six-month evaluation, which included the MRI for 101 treated patients. The patients in this study had intact rotator cuffs such that there was separation between the subacromial space and the glenohumeral joint, likely preventing the spread of subacromially-administered drug into the joint capsule. This is a much different clinical scenario than bupivacaine infusions into the joint capsule, which have the highest reported risk of chondrolysis. Additionally, the Applicant states that the development of bupivacaine-related chondrolysis can generally occur within six months of surgery, such that the duration of follow-up in this study was likely adequate to capture cases of post-operative chondrolysis.

The six-month follow-up MRIs assessed five regions of interest, including bone erosion and edema, musculotendinous abnormalities, the shoulder joint, tissue abnormality or scarring, or vehicle or joint effusion. Residual SAIB would be reported as a “vehicle effusion”. The MRIs were assessed as improved, no change, or worsened (further rated as mild, moderate, or severe). In general, the Applicant reports no consistent findings suggestive of worsening shoulder pathology or development of new pathology between baseline and follow-up assessments and across the different treatment groups. The results from follow-up MRIs are summarized in the following table.

Table 42. MRI Changes from Baseline at 6-Month Follow-up Examination (BU-002-IM)

Category	Rating of MRI Change from Baseline	SABER- Bupivacaine	SABER- Placebo	Bupivacaine HCl
Safety population		53	25	29
Subjects with baseline MRI ^[1]		52	25	28
Subjects with evaluable 6-month MRI ^[2]		51	25	25
Bone erosion and edema, n (%)	Improved	2 (3.9)	1 (4.0)	1 (4.0)
	No change	43 (84.3)	22 (88.0)	20 (80.0)
	Worsened			
	Mild	3 (5.9)	0 (0.0)	3 (12.0)
	Moderate	3 (5.9)	2 (8.0)	1 (4.0)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)
Musculo-tendinous abnormalities, n (%)	Improved	0 (0.0)	1 (4.0)	1 (4.0)
	No change	50 (98.0)	23 (92.0)	24 (96.0)
	Worsened			
	Mild	1 (2.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	1 (4.0)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)
Shoulder joint, n (%)	Improved	4 (7.8)	0 (0.0)	1 (4.0)
	No change	46 (90.2)	22 (88.0)	23 (92.0)
	Worsened			
	Mild	1 (2.0)	3 (12.0)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)	1 (4.0) ^[3]
Tissue abnormality or scarring, n (%)	Improved	0 (0.0)	0 (0.0)	0 (0.0)
	No change	50 (98.0)	25 (100.0)	25 (100.0)
	Worsened			
	Mild	1 (2.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)
Vehicle or joint effusion, n (%)	Improved	5 (9.8)	2 (8.0)	4 (16.0)
	No change	37 (72.5)	14 (56.0)	12 (48.0)
	Worsened			
	Mild	8 (15.7)	5 (20.0)	7 (28.0)
	Moderate	1 (2.0)	3 (12.0)	1 (4.0)
	Severe	0 (0.0)	1 (4.0) ^[4]	1 (4.0) ^[3]

Overall assessment of change from baseline, n (%)	Improved	6 (11.8)	2 (8.0)	6 (24.0)
	No change	31 (60.8)	14 (56.0)	9 (36.0)
	Worsened			
	Mild	12 (23.5)	5 (20.0)	9 (36.0)
	Moderate	2 (3.9)	4 (16.0)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)	1 (4.0) ^[3]

Note: percentages are based on the number of subjects with an evaluable 6-month MRI.

[1] Baseline MRIs were obtained at the screening visit.

[2] An MRI obtained at 6-month follow-up was considered evaluable if it had an accompanying baseline MRI for comparison.

[3] Subject (b) (6) was noted to have "severe fluid collection within subacromial/subdeltoid bursa; massive bone edema adjacent to acromion-clavicular joint; severe marked joint effusion causing bulging of the joint capsule."

[4] Subject (b) (6) was noted to have "severe effusion in subcoracoid bursa."

Source: ISS, p. 52-53 (PDF), Applicant's submission, NDA 204803.

The majority of 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. There were two patients who had severe worsening in a region of interest noted during the follow-up exam.

- 51-year-old male treated with bupivacaine HCl had severe worsening of the joint, which included severe fluid collection in the subacromial/subdeltoid bursa, severe joint effusion causing bulging of the joint capsule, and massive bone edema adjacent to the acromioclavicular joint. His functional assessment, using the Constant-Murley score, was reportedly normal (65 out of 75 available points for this study).
- 63-year-old male treated with SABER-placebo had a severe effusion in the subcoracoid bursa. Physical examination had reportedly improved slightly, but was still experiencing limited range of motion.

Surgical site examinations did not identify any healing or soft tissue concerns at six months.

The following table summarizes the Constant-Murley (C-M) scores for patients in this study, which is a 100-point clinical assessment of the shoulder involving both subjective (pain and activities of daily living) and objective (strength and range of motion) variables. In this study, strength was not assessed, such that patients were scored out of 75 possible points.

Table 43. Constant-Murley Scores 6-Months' Post-Operatively (BU-002-IM)

	Treatment	Number in Safety Population	Number with Data	Mean	SD	Median	Min	Max
Screening	SABER-Bupivacaine 5 mL	53	53	44.7	12.5	47	14	65
	SABER-placebo	25	25	41.7	11.7	42	21	66
	Bupivacaine HCl	29	29	42	11.3	43	17	60
6-Month Follow-up	SABER-Bupivacaine 5 mL	53	52	61.6	15.2	65	6	75
	SABER-placebo	25	25	63.2	12.4	66	36	75
	Bupivacaine HCl	29	26	65.6	6.8	66	53	75
Change from Screening ^[1]	SABER-Bupivacaine 5 mL	53	52	16.6	12.1	17	-13	39
	SABER-placebo	25	25	21.6	13.8	20	-11	41
	Bupivacaine HCl	29	26	22.2	11.7	22	2	46

[1] P-value for differences among the treatment groups = 0.1

Source: ISS, p. 54 (PDF), Applicant's submission, NDA 204803.

The mean scores for all treatment groups appear to have increased at the six-month follow-up visit. However, it also appears that the mean change from baseline was highest in the bupivacaine HCl group and lowest in the SABER-bupivacaine group. There were seven patients with worsening scores post-operatively, as summarized in the following table.

Table 44. Patients With a Decrease in Constant-Murley Scores at 6-Months (BU-002-IM)

Treatment Group	Subject Number	Constant-Murley Score			Comment from MRI Expert Report Regarding Decrease in Constant-Murley Score	MRI Change from Baseline in Glenohumeral Joint
		Screening	6-Month Follow-up	Change (%) from Baseline		
SABER-Bupivacaine 5 mL	(b) (6)	56	46	-10 (-17.8%)	No MRI finding to explain this	No change
SABER-Bupivacaine 5 mL		19	6	-13 (-68.4%)	No MRI finding to explain this	No change
SABER-Bupivacaine 5 mL		45	40	-5 (-11.1%)	No change to explain this	No change
SABER-Bupivacaine 5 mL		23	21	-2 (-8.7%)	Osteoarthritis in the acromio-clavicular joint can explain this	No change
SABER-Bupivacaine 5 mL		37	32	-5 (-13.5%)	No explanation on MRI for this change	Improvement of intra-articular fluid (decrease as compared to baseline)
SABER-placebo		52	41	-11 (-21.2%)	Mild sub-deltoid inflammation at follow-up	No change
SABER-placebo		44	36	-8 (-18.2)	No explanation on MRI for this change	No change

Source: ISS, p. 56 (PDF), Applicant's submission, NDA 204-803.

These patients' MRIs were examined to identify any radiological changes that may have contributed to the decrease in the observed post-operative scores, as noted in the table. The results indicate that while the C-M score decreased, and in some cases substantially (i.e., greater than a 10-point decrease), the six-month post-operative MRI was unchanged from baseline for the majority of patients. It is hard to reconcile, what would appear to be, significant decline in clinical function without observed changes in the glenohumeral joint or

surrounding tissue detectable via MRI. Furthermore, it is noteworthy that all patients with a decline in the C-M score in this study were treated with a SABER drug product. Entry of an extended-release bupivacaine product into the joint capsule and the potential resulting damage is a main concern; however, the SAIB component of the SABER drug products and potential damage to the joint is also a concern, particularly considering the safety issues identified during review of the results from the soft tissue surgical models.

The supplemental safety data provided from this study is less supportive of the safety profile of SABER-bupivacaine administration during shoulder surgery than that provided for Study C803-17 and Study C803-017e. However, given that the study was completed 10 years ago, it seems unlikely that persistent clinically relevant changes have yet to be reported.

Study CLIN005-0006

This was the first study evaluating SABER-bupivacaine in patients undergoing arthroscopic shoulder surgery. The final post-operative follow-up visit, on study day 14, did not include an MRI examination. There were 62 patients treated with SABER-bupivacaine and 44 treated with SABER-placebo. In response to the CRL, study investigators were contacted via phone and asked whether any study patient had developed chondrolysis in the treated shoulder. All contacted investigators indicated that they were “certain” no study patient developed chondrolysis. This additional information was provided during the FDRR Meeting, and the Division stated that “verifiable evidence of long-term recovery post-exposure to POSIMIR” may be adequate to address this safety concern. In response, the Applicant sent each investigator 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. Therefore, the Applicant states that there is additional, long-term follow-up information for all 106 treated patients in this study, and further notes that this study was completed more than 10 years ago.

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 the low incidence of wound-related adverse events compared to those observed in the soft tissue surgical procedures.

8.3.2. Adverse Events Related to Wound-Healing

The wound-related adverse events of interest, as described in the CRL, included bruising, hematoma, pruritus, and dehiscence. To address these issues, the Applicant has evaluated follow-up data from Studies C803-025, BU-001-IM, CLIN803-006-0006, and the previously

discussed studies in patients undergoing shoulder surgery, BU-002-IM and C803-017e, in addition to the safety data from the PERSIST study, completed after issuance of the CRL.

Wound healing in Study C803-025

During the original NDA review, it was noted that patients treated with SABER-bupivacaine or SABER-placebo had an increased incidence of wound dehiscence when compared to patients treated with bupivacaine HCl. Specifically, a total of 16 patients, all treated with a SABER product, reportedly experienced wound dehiscence documented as an adverse event. An additional two patients, one treated with SABER-bupivacaine and one treated with bupivacaine HCl, had dehiscence noted on the eCRF but not included as adverse events. An additional 25 patients reported wound separation (dehiscence) in response to the structured wound questionnaire conducted via telephone during the 30-day follow-up evaluation, four of which were treated with bupivacaine HCl, suggesting less of an imbalance between the SABER treatment groups and the bupivacaine treatment group.

This information, including the following table, was presented during the EOR Meeting, and the Division stated that self-reported adverse events may not have been accurate and that any additional physical examination information would be informative in assessing the risk of wound dehiscence after administration of a SABER product.

Table 45. Overall Incidence of Wound Dehiscence in Study C803-025

Assessment Method	Cohort 1		Cohort 2		Cohort 3		Total N=305
	SABER®- Bupivacaine N=30	Bupivacaine HCl N=18	SABER®- Bupivacaine N=30	Bupivacaine HCl N=20	SABER®- Bupivacaine N=129	SABER- Placebo N=78	
AE reports	3	0	1	0	7	5	16
Surgical wound examination	0	1	0	0	1	0	2
Structured wound questionnaire	3	2	1	2	14	3	25
Total Unique Patients, n (%)	6 (20%)	3 (17%)	2 (7%)	2 (10%)	22 (17%)	8 (10%)	43 (14%)

Source: C803-025 BESST Report Addendum, p. 3 (PDF), Applicant's submission, NDA 204803.

In response to advice provided during the EOR Meeting, the Applicant reviewed clinical records for 24 of the 25 patients (one clinical record for patient (b) (6) could not be located) with self-reported dehiscence and determined that 19 patients had undergone additional post-study physical examinations. Of these 19, and only three patients, all treated with SABER-bupivacaine, had documented evidence of wound dehiscence. Those results are summarized in the following table.

Table 46. Review of Information for Patients Self-Reporting Wound Separation, Study C803-025

BESST Cohort	Surgery for Cohort	Patients with self-reported Wound Separation (n)	Patients that had clinical follow-up visit (n)	Patients with confirmed dehiscence at clinic follow-up (n)	Sites audited by DURECT (n)
Cohort 1	Laparotomy	5	5	1	3 of 4
Cohort 2	Laparoscopic Cholecystectomy	3	1	0	1 of 1
Cohort 3	Laparoscopic Assisted Cholectomy	17	13	2	6 of 6
	TOTAL	25	19	3	10 of 11

Source: C803-025 BESST Report Addendum, p. 5 (PDF), Applicant's submission, NDA 204803.

Based on this information, the Applicant concludes that when assessed as adverse events alone, the risk of superficial wound dehiscence is higher in SABER-treated patients. When wound dehiscence is assessed via a variety of both subjective and objective assessments, the difference in incidence between treatment groups is less impressive. It is worth mentioning, however, that based on the number of patients with self-reported wound separation and the number with confirmed cases, it appears self-examination of the surgical wound may not be a reliable assessment tool for capturing clinically relevant wound dehiscence.

Wound healing in Study BU-001-IM (abdominal hysterectomy)

Treated patients underwent a 6-month clinical evaluation to assess healing of the Pfannenstiel incision. Additionally, a subset of patients underwent an MRI evaluation of the pelvis to assess scar formation. The evaluations of the surgical incision did not identify clinically meaningful differences between patients treated with SABER-bupivacaine, SABER-placebo, or bupivacaine HCl. MRIs from 21 patients were evaluated by an independent radiologist. There were no abnormal findings and the scar thickness was similar across treatment groups. A single patient treated with SABER-bupivacaine was noted to have "small focal edema", not believed to be related to a foreign body reaction. The Applicant concludes that all wounds healed normally by six months.

Wound healing in Study BU-002-IM (arthroscopic shoulder surgery)

Treated patients underwent a 6-month clinical evaluation of the operative shoulder, which included assessments of the wound healing and related local tissue conditions. In summary, there were no clinically significant differences across treatment groups and no tissue abnormalities were reported. Follow-up MRI results were presented above. Additional evaluations of the incisional scars and underlying soft tissue did not identify clinically meaningful differences between treatment groups. The Applicant concludes that all wounds healed normally and there were no observed adverse effects related to administration of the SABER formulation.

Wound healing in Study C803-017e (arthroscopic shoulder surgery)

Treated patients underwent a long-term follow-up examination at 18 months post-operatively, which included a physical examination and MRI. Of the 40 patients treated with SABER-bupivacaine and the 20 patients treated with SABER-placebo, 31 and 16 patients, respectively, were evaluated in this extension study. All 47 patients evaluated at 18 months reportedly had normal healing of the surgical incision, and normal scar and soft tissue as identified in the MRIs. The Applicant concludes that all wounds healed normally and there were no observed adverse effects related to administration of the SABER formulation.

Wound healing in Study CLIN803-006-0006 (inguinal hernia repair)

Treated patients underwent follow-up examinations at three and six months' post-operatively. All examinations were reportedly normal at three months with the exception of a single patient treated with SABER-bupivacaine, 2.5 mL, who had a scrotal hematoma that resolved by the six-month visit. The Applicant concludes that all surgical wounds healed normally for all patients, suggesting the SABER formulation does not interfere with normal wound healing or result in long-term adverse effects.

Because the nonclinical studies indicated a foreign body reaction after administration of SABER products, the Applicant enlisted Dr. James M. Anderson, M.D., Ph.D., an expert on biocompatible injectable and implantable 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. His review 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)

Dr. Ahn concluded in her pharmacology-toxicology review that local effects observed after administration of SABER-bupivacaine “were consistent 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”, and that while the bupivacaine is released over 72 hours, the SAIB vehicle is “expected to remain at injection sites for a year or longer.” Dr. Ahn's conclusion appears to contradict Dr. Anderson's; however, it does appear that while some portion of the vehicle remains in tissues for up to one year, the clinical significance is unknown.

The Applicant further suggests that administration of other extended-release injectable products, such as Exparel® and Sustol®, also results in a foreign body, granulomatous reaction. This may be true, however, Exparel® was approved for postsurgical local analgesia in 2011, such that any concerns regarding wound healing would have been identified and Sustol® is a single injection in healthy tissue, a much different situation than a surgical wound injection.

8.3.3. Neurological Adverse Events Related to Benzyl Alcohol Exposure

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 has 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. In the SABER-placebo-controlled studies, potential benzyl alcohol-related adverse events were solicited and recorded using daily diaries. In the bupivacaine HCl-controlled studies, the same adverse events were reported spontaneously and not queried, such that there may have been a falsely observed increase in the SABER-placebo-controlled studies. 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.

The following table summarizes the nervous system adverse events, potentially benzyl alcohol-related, from only bupivacaine HCl-controlled studies.

Table 47. Nervous System Adverse Events in Studies with a Bupivacaine HCl Control Group

	SABER- Bupivacaine 5 mL (N=178)	SABER- Bupivacaine/ Bupivacaine HCl (N=82)	SABER- Placebo (N=52)	Bupivacaine HCL (N=124)
Nervous system disorders	46 (25.8%)	32 (39.0%)	5 (9.6%)	32 (25.8%)
Dizziness	20 (11.2%)	10 (12.2%)	4 (7.7%)	10 (8.1%)
Somnolence	5 (2.8%)			6 (4.8%)
Dysgeusia	4 (2.2%)	1 (1.2%)		1 (0.8%)
Paraesthesia	2 (1.1%)	3 (3.7%)		3 (2.4%)

Source: ISS, p. 41 (PDF), Applicant's original NDA submission, received April 12, 2013.

Review of this data does suggest that the incidence of the previously concerning, potentially benzyl alcohol-related adverse events is less disparate than observed in the SABER-placebo-controlled studies; however, the incidence of dizziness and dysgeusia are still increased in the SABER-bupivacaine treatment group compared to the bupivacaine HCl treatment group.

While I agree that there is likely an adverse event reporting bias in the studies which employed a diary-elicited checklist compared to those which relied on spontaneous reporting or observation, the adverse event information from the PERSIST study does suggest that there continues to be an increased incidence in nervous system adverse events in patients treated with SABER-bupivacaine likely related to benzyl alcohol exposure.

8.4. Review of the Safety Database

8.4.1. Overall Exposure

A total of 735 patients were administered a single 5 mL dose of the to-be-marketed formulation of SABER-bupivacaine in the clinical development program. An additional 50 patients were treated with SABER-bupivacaine 2.5 mL. With the exception of 14 healthy volunteers in studies SABER01-01 and CLIN005-0008, all patients received SABER-bupivacaine during a surgical procedure. The clinical studies evaluated postsurgical analgesia after representative soft tissue surgical procedures and a single boney surgical procedure utilizing different doses and routes of administration. Evaluated surgical procedures did capture diverse anatomic spaces with varying degrees of vascularity and resultant post-operative pain and included, arthroscopic shoulder surgery with and without rotator cuff repair, open and laparoscopic abdominal procedures, abdominal hysterectomy, and inguinal hernia repair. Evaluated routes of administration included subcutaneous injection, wound infiltration, and wound instillation. The following table summarizes the clinical studies used to assess the safety of SABER-bupivacaine.

Table 48. Clinical Studies Used to Assess Safety

Protocol Number	Phase	Surgery	Type of Administration	Number of Safety Subjects
SABER01-01 ^A	1	Healthy subjects	Subcutaneous (SC) trailing injections	12
CLIN005-0008	1	Healthy subjects	IV infusion, patch, or SC trailing injection	5
CLIN004-0001	2	Inguinal hernia repair	SC trailing injections and infiltration	81
CLIN004-0009	2	Inguinal hernia repair	SC trailing injections or SC trailing injections + infiltration	42
CLIN005-0002	2	Appendectomy	SC trailing injections or infiltration + SC trailing injections	21
CLIN005-0006	2	Subacromial decompression	Subacromial instillation or subacromial instillation + SC trailing injections	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	Subacromial instillation	107

NDA 204803, Posimir
Bupivacaine solution for infiltration use

Protocol Number	Phase	Surgery	Type of Administration	Number of Safety Subjects
		decompression		
C803-017	2	Subacromial decompression	Subacromial instillation	60
C803-017e ^B	2	Follow-up to C803-017	N/A	47
C803-025	3	Laparotomy, lap chole, colectomy	Instillation or infiltration	305
C803-027	2	Laparotomy, colectomy	Instillation	10
C803-028	3	Lap chole	Instillation	388

^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 C803-017 and were not counted twice in determining the total number of safety subjects.

Source: Adapted from ISS, p. 14-15 (PDF), Applicant's original submission, NDA 204803.

The Applicant has pooled data from treated patients according to SABER-bupivacaine exposure and comparator treatment group. The pooling strategies are described as follows:

- Pooled Group A includes patients treated in studies BU-001-IM, BU-002-IM, C803-025 (Cohorts 1 and 2), and C803-028 (Part 2 only), which used bupivacaine HCl as a comparator treatment
- Pooled Group B includes patients treated in studies 005-0002, 005-0006, 005-0010, 006-0006, 803-017, and 803-025 (Cohort 3 only), which used SABER-placebo as a comparator treatment
- Pooled Group C includes all patients treated with the to-be-marketed formulation of SABER-bupivacaine, as summarized in the following table.

Table 49. Patient Disposition (Pooled Group C)

	Saline- Placebo 5 mL	SABER- Placebo 2.5-10 mL	SABER- Bupivacaine 2.5 mL	SABER- Bupivacaine 5.0 mL	Bupivacaine HCl 6.25-150 mg	SABER- Bupivacaine + Bupivacaine HCl ^[1]
Subjects Randomized (Modified)	46	277	51	761	282	91
Subjects Dosed without Randomization ^{[2] [3] [4]}	0	0	6	10	0	5
Subjects Randomized but not Dosed	0	9	1	25	10	0
Safety Population ^{[5] [6]}	47 (100%)	268 (100%)	50 (100%)	735 (100%)	272 (100%)	91 (100%)
Completed Study						
Yes	47 (100%)	261 (97.4%)	48 (96.0%)	725 (98.6%)	266 (97.8%)	89 (97.8%)
No	0	7 (2.6%)	2 (4.0%)	10 (1.4%)	6 (2.2%)	2 (2.2%)
Primary Reason for Discontinuation						
Adverse Event	0	1 (0.4%)	0	1 (0.1%)	2 (0.7%)	0
Lost to Follow-up	0	1 (0.4%)	0	4 (0.5%)	0	0
Physician Decision	0	1 (0.4%)	0	0	0	0
Protocol Violation	0	0	2 (4.0%)	0	0	1 (1.1%)
Withdrawal by Subject	0	3 (1.1%)	0	4 (0.5%)	2 (0.7%)	1 (1.1%)
Other	0	1 (0.4%)	0	1 (0.1%)	2 (0.7%)	0

Note: Pooled Group C consists of subjects from all trials using the final formulation.

Note: The Modified Randomized Subjects Population consists of all subjects randomized plus all subjects who received study treatment but were not randomized.

Note: The Safety Population consists of All subjects who received any amount of study drug. Denominators for percentages are the number of subjects in the Safety Population. In the summaries of study completion and discontinuation, subjects are summarized by the actual treatment received.

- [1] Subjects who were treated with SABER-Bupivacaine 7.5 mL are summarized in the SABER-Bupivacaine + bupivacaine HCl treatment group.
- [2] Six subjects in Cohort 1 of study 004-001 received SABER-Bupivacaine 2.5 mL without randomization. These subjects are summarized in the SABER-Bupivacaine 2.5 mL treatment group.
- [3] Five subjects in the 005-0008 crossover study received SABER-Bupivacaine 5 mL in addition to other analgesics. These five subjects received active treatment without randomization and are summarized in the SABER-Bupivacaine + bupivacaine HCl treatment group.
- [4] Ten subjects in the single-arm study C803-027 received SABER-Bupivacaine 5 mL without randomization. These subjects are summarized in the SABER-Bupivacaine 5 mL treatment group.
- [5] In study CLIN005-0010, subject (b) (6) was randomized to SABER-placebo, but actually received SABER-Bupivacaine 5 mL; subject (b) (6) was randomized to SABER-Bupivacaine 5 mL, but actually received SABER-placebo.
- [6] In study C803-028, subject (b) (6) was randomized to SABER-Bupivacaine 5 mL, but actually received saline placebo.

Source: ISS, p. 116 (PDF), Applicant's submission, NDA 204803.

8.4.2. Adequacy of the safety database:

The totality of the safety database is adequate to determine the risks associated with administration of SABER-bupivacaine into surgical wounds; however, the evaluation of SABER-bupivacaine in a single orthopedic model may not be adequate to extend the indication beyond arthroscopic subacromial decompression, should this product be approved. Furthermore, the majority of the clinical studies were Phase 2 evaluations with relatively low numbers of treated patients; however, the overall safety database appears adequate to identify the safety issues likely observed post-market.

8.5. Adequacy of Applicant's Clinical Safety Assessments

The additional information provided in the NDA resubmission to further assess the safety profile of SABER-bupivacaine in the previously conducted studies, in combination with the safety assessments conducted during the PERSIST study, appears adequate to characterize the risks associated with administration of SABER-bupivacaine in postsurgical wounds. Specifically, the Applicant provided the results from detailed evaluations (both radiological and physical) of patients after shoulder surgery, comprehensive examinations of postsurgical wounds, and repeated assessments for the presence of symptoms concerning for benzyl alcohol toxicity.

Throughout the clinical development program, the Applicant appears to have done an adequate evaluation of the risks of local anesthetic systemic toxicity after administration of SABER-bupivacaine. The clinical studies evaluated during the original NDA submission included proactive assessments for signs and symptoms of neurotoxicity and cardiac monitoring in addition to PK assessments at scheduled time points and when clinically indicated. Dr. Simone concluded that there were no safety signals suggesting SABER-bupivacaine posed an increased risk of LAST compared to either SABER-placebo or bupivacaine HCl. Of note, there were adverse events suggestive of LAST noted in the previously completed clinical studies, including somnolence, dizziness, and dysgeusia; however, they were observed in both SABER-bupivacaine and SABER-placebo treatment groups, suggesting exposure to benzyl alcohol is the causal factor and not bupivacaine.

8.5.1. Issues Regarding Data Integrity and Submission Quality

There did not appear to be major issues regarding the data integrity or the overall quality of the submission, such that the Applicant's conclusions are considered invalid; however, the statisticians who worked closely with the clinical team during review of the safety information indicated that there were numerous inconsistencies between the ISS datasets and clinical study reports that required several Information Requests, clarifications, and re-submission of an originally corrupted dataset. While these issues do not necessarily imply data integrity issues or misrepresentations, they do reduce our confidence in the data and the associated conclusions.

8.6. Safety Results From Previously Completed Studies

8.6.1. Deaths

As discussed in detail in Dr. Simone's clinical review of the original NDA submission, there was a single patient death during drug development. The patient was an 82-year-old male who was treated with SABER-bupivacaine in Study C803-025 and underwent lap-assisted hemicolectomy. The patient had a complicated post-operative course, including episodes of atrial fibrillation, renal failure, neurological deterioration, anemia, and hypotension. His death on POD 40 was felt to be unrelated to study drug administration. Refer to Dr. Simone's clinical review for additional information regarding this patient.

8.6.2. Serious Adverse Events

Dr. Simone reported there were 74 treatment-emergent serious adverse events in the previously completed studies. The Applicant reported the SAEs appeared equally distributed across all treatment groups and they were generally related to the surgical procedure, anesthesia, analgesics, or co-morbid conditions. In the SABER-bupivacaine treatment group, SAEs were most frequently reported in the gastrointestinal disorders SOC, with ileus the most frequently reported preferred term, and in the injury, poisoning, and procedural complications SOC, with wound dehiscence the most frequently reported preferred term. In contrast, in the bupivacaine HCl treatment group, SAEs were most commonly reported in the infections and infestations SOC and in the respiratory, thoracic, and mediastinal disorders SOC.

Approximately 11% of the SAEs occurred during the first post-operative hour, approximately 20% occurred within 72 hours, the remaining 69% occurred later than 72 hours' post-operatively. Approximately 50 of the patients treated with SABER-bupivacaine or bupivacaine who reported an SAE had plasma bupivacaine measurements, which indicated C_{max} ranged from 52 to 1870 ng/mL. Of the 11 patients with $C_{max} > 1000$ ng/mL, the reported SAEs occurred after T_{max} , suggesting bupivacaine exposure likely did not contribute to the SAE.

Of the cardiac SAEs reported in the previously completed studies, Dr. Simone felt that the Applicant's explanation for their unrelatedness to study drug administration appeared adequate. No cases were felt to be related to SABER-bupivacaine administration or LAST. Regarding the SAEs associated with the surgical site, Dr. Simone noted that there was an increased incidence of wound-related SAEs in patients treated with SABER-bupivacaine compared to control treatment. Specifically, there was one scrotal hematoma, one vaginal hematoma, two cases of fascial wound dehiscence, and one wound infection after administration of SABER-bupivacaine. This is in contrast to one case of wound dehiscence following SABER-placebo and no wound-related SAEs related to bupivacaine HCl administration.

As previously discussed, there were 14 patients with 15 SAEs in the PERSIST study. The majority of SAEs were due to complications of the underlying disease process or complications of the surgery. There was one SAE of dizziness reported in a 72-year-old female patient who received SABER-bupivacaine during the lap chole. The Applicant concluded the dizziness was likely the result of high-dose opioid analgesic administration during her 95-minute PACU admission. She received a total of fentanyl 150 µg and hydromorphone 0.6 mg while in the PACU. After the last dose, she complained of dizziness and requested hospital admission. The post-operative dose of opioid analgesic rescue medication does not appear to be high or unexpected for this procedure, particularly if the local anesthetic medication (SABER-bupivacaine) was not efficacious. Additionally, the intra-operative dose of fentanyl was 75 µg, which is considered low in the absence of additional analgesic medication administration, such as an NSAID. Review of the adverse event database indicated that she also complained of drowsiness, dysgeusia, nausea, and vomiting approximately five to nine hours after admission to the PACU. This constellation of symptoms could have been related to LAST, however, because plasma

bupivacaine levels were not measured, a definitive cause cannot be determined.

Another patient experienced SAEs of dehydration and hypotension. Based on the time course and repeat complaints approximately two months post-operatively, these SAEs were felt to be unrelated to SABER-bupivacaine administration.

8.6.3. Dropouts and/or Discontinuations Due to Adverse Effects

As previously discussed in Section 8.2, there was a single patient ((b) (6)) treated with bupivacaine HCl who developed acute biliary pancreatitis and was discontinued from the study.

8.6.4. Treatment Emergent Adverse Events

The treatment emergent adverse events most concerning to the Division are discussed in detail in Section 8.3.

8.6.5. Laboratory Findings

As described in Dr. Simone's clinical review, there did appear to be a transient decrease in red blood cell counts in all treatment arms post-operatively, suggesting that the in vitro hemolysis observed with mixing of SABER-bupivacaine and human plasma, does not appear to result in systemic hemolysis of clinical consequence.

8.6.6. Electrocardiograms (ECG)

Studies BU-001-IM, BU-002-IM, and C803-025 were included in the integrated ECG data analysis. Each study used the same treatment groups, collected ECG data at defined time points, and had the ECG parameters analyzed at central laboratories. Study C803-025 employed continuous Holter monitoring. Dr. Simone concluded in his clinical review that the ECG data did not indicate clinically relevant ECG changes associated with administration of SABER-bupivacaine 5 mL.

8.6.7. QT

A thorough QT evaluation, which involved integrated ECG analysis of 526 patients in one of three treatment groups (SABER-bupivacaine, SABER-placebo, and bupivacaine HCl), was conducted and results submitted in the original NDA. Dr. Breder concluded, in his CDTL memo, that there were no consistent differences in QT duration across the three treatment groups. For those patients with a QTc duration > 500 msec, the plasma bupivacaine concentrations were well below those known to cause cardiac toxicity. He further stated that the ECG data indicated that clinically relevant changes in morphology were unlikely to occur after administration of SABER-bupivacaine 5 mL.

8.7. Additional Safety Explorations

8.7.1. Pediatrics and Assessment of Effects on Growth

SABER-bupivacaine has not been evaluated in pediatric patients during the clinical development program. Prior to the original NDA submission, the Applicant did not submit a pediatric study plan (PSP), but in the NDA submission, also in the resubmission, requested a waiver for evaluation of SABER-bupivacaine for neonates and children less than three years of age. The justification for the waiver is based primarily on the concerns for benzyl alcohol toxicity. The clearance of benzyl alcohol and benzoic acid, a metabolite, is reduced in neonates, which may lead to metabolic acidosis, encephalopathy, respiratory depression with gasping (neonatal gasping syndrome), and death. Because the amount of BA in SABER-bupivacaine would result in administration of doses similar to or in excess of those known to cause toxicity, the Applicant requests a waiver for this pediatric population.

The Applicant has also indicated that the risk of bupivacaine accumulation due to reduced clearance in pediatric patients supports the waiver request for children less than three years of age. There is evidence in the published literature for decreased plasma protein binding and reduced hepatic metabolism of bupivacaine in pediatric patients; however, the specific age at which this risk is greatest is unclear.

In the original NDA review, Dr. Simone indicated that he agreed with the Applicant's justification for a pediatric study waiver in children less than three years of age and recommended granting the waiver. I agree with granting the requested waiver based on the risk of benzyl alcohol toxicity in children less than three years of age. The risk of bupivacaine accumulation is less concerning to me, and I think it could be adequately addressed by accurate dose adjustment.

8.7.2. Local Anesthetic Systemic Toxicity

Local anesthetics such as bupivacaine HCl have a well-characterized toxicity profile, commonly referred to as LAST, which generally relates to high systemic concentrations. The relative risk of experiencing LAST is dependent on many factors, including systemic absorption from different sites of administration. Specifically, inadvertent intravascular administration is associated with the highest plasma concentration and results in the fastest onset and typically most severe signs and symptoms, followed by intercostal nerve block, caudal/epidural block, brachial plexus block, and lastly subcutaneous administration (Open Anesthesia, 2018).

The toxicities associated with local anesthetic administration initially manifest as central nervous system (CNS) symptoms followed by cardiovascular system symptoms (CVS). Historically, it has been reported in the published literature that plasma concentrations of bupivacaine ≥ 2000 ng/mL may result in CNS toxicity and concentrations ≥ 4000 ng/mL may result in CVS toxicity; however, there have been reports of LAST symptoms occurring at concentrations much lower than those commonly referenced. Because the prolonged release bupivacaine products, such as SABER-bupivacaine, have a different, and potentially more variable, pharmacokinetic profile than that observed with the immediate release products, the

Agency agrees with the findings by Scott et al (1989), suggesting that bupivacaine toxicity may be observed at systemic concentrations > 1000 ng/mL. The following table summarizes the CNS and CVS symptoms commonly associated with bupivacaine toxicity.

Table 50. CNS and CVS Symptoms of Bupivacaine and Other Local Anesthetic Toxicity

Symptom
<u>CNS</u>
– Tinnitus, blurred vision, tongue paresthesias, circumoral numbness, lightheadedness
– Nervousness, agitation, restlessness, disorientation, tremor
– Tonic-clonic seizures
– CNS depression, respiratory failure
– Coma
<u>CVS</u>
– Decreased electrical excitability, conduction disturbances including heart block, myocardial contraction, PR interval, QRS, and QT prolongation
– Bradycardia
– Arteriolar dilation, hypotension
– Ventricular fibrillation, CV collapse
– Death

Source: Adapted from Gadsden, 2017.

There are weight-based dosing guidelines aimed at reducing the risk of LAST. Specifically, the maximum recommended dose of immediate-release bupivacaine with or without epinephrine should not exceed 2 to 3 mg/kg, with an approximate duration of action of 1.5 to 8 hours.

Treatment of LAST

As described in the review article by Christie et al (2015), the management of LAST begins with immediate recognition of the associated signs and symptoms and resuscitation measures focused on maintaining airway, breathing, and circulation, as per Advanced Cardiac Life Support (ACLS) guidelines. Cardiopulmonary resuscitation (CPR) may be necessary in cases of cardiac arrest. Seizures should be treated with benzodiazepines or possibly propofol depending the hemodynamic status of the patient. Cardiac arrhythmias, conduction blocks, and hypotension can be managed according to ACLS protocols; however, low doses of epinephrine ($\leq 1 \mu\text{g/kg}$) are recommended and vasopressin is not recommended. Lidocaine should not be administered for treatment of ventricular arrhythmias in this situation.

The development of Intralipid®, a lipid emulsion comprised of soya oil, glycerol, and egg phospholipids, has positively impacted the resuscitation outcomes after documented cases of LAST and the American Society of Regional Anesthesia (ASRA) includes lipid emulsion therapy, such as Intralipid®, in the practice advisory on local anesthetic systemic toxicity (Neal et al, 2018). Cardiopulmonary bypass, while not used often, is still a viable treatment option in the setting of refractory toxicity in the critically ill patient.

The nonclinical studies suggest that when administered via wound infiltration there is no bupivacaine dose-dumping; however, there were no nonclinical studies conducted that

evaluated IV administration of SABER-bupivacaine. There were discussions during the AC meeting surrounding the risks of inadvertent intravascular administration and the likelihood of resuscitating a patient exposed to bupivacaine 660 mg intravascularly. The Applicant provided a three-pronged risk assessment, including the likelihood of inadvertent intravascular administration, the risks of intravascular administration, and potential mitigation strategies. The Applicant stated that the likelihood of intravascular administration is low during soft tissue surgical procedures due to administration via a needle-free technique and during arthroscopic subacromial decompression due to arthroscopic visualization of administration with a large bore needle. They further stated that the viscosity of SABER-bupivacaine limits the ability to administer it through a standard size needle (i.e., 22 gauge) and the amber color prevents drug swapping with other local anesthetic solutions. The Applicant also indicated that arthroscopic subacromial decompression is considered a highly vascular surgery, based on resection of the acromion, and because systemic exposure (i.e., mean C_{max}) was similar to that observed in other surgical models, SABER-bupivacaine is unlikely to result in the development of LAST when administered during highly vascular surgeries.

If SABER-bupivacaine were administered intravascularly, the Applicant has indicated that because there is no evidence of dose-dumping and the release profile from SABER-bupivacaine is stable over 72 hours and similar to the delivery rates of infusion pumps, the risk of systemic exposure to 660 mg of bupivacaine in a short amount of time is low. The Applicant also stated that if 80% of 660 mg of bupivacaine was released into the intravascular space over 30 minutes, the expected C_{max} would be approximately 13,000 ng/mL, a plasma concentration that is amenable to lipid emulsion rescue as demonstrated in nonclinical studies, described in the published literature. The Applicant further stated that the duration of treatment would not exceed that currently recommended and the total dose of lipid emulsion required to rescue a patient would not exceed the recommended 12 mg/kg.

While I agree that administration of SABER-bupivacaine via a needle-free technique or under arthroscopic visualization, and the drug product's viscosity and color likely minimize the risk of inadvertent intravascular injection, I am not certain that bupivacaine release from the SABER vehicle will be the same intravascularly as it is in tissue or in vitro. Furthermore, if intravascular bupivacaine release is the same as that described in vitro, the duration of resuscitation, including lipid emulsion administration, may be up to 72 hours. It is worth noting that administration of lipid emulsion is not without inherent risks, which increase with increasing dose and duration of treatment. The Applicant's argument that even if 80% of 660 mg (or 528 mg) of bupivacaine was released from the SABER vehicle in 30 minutes, patients could be successfully resuscitated with lipid emulsion seems theoretical at best, and it is not clear how 80% was determined a meaningful amount, versus 100%, nor is it clear why 30 minutes was selected as the release time. The Applicant further suggested that bupivacaine release over a period of six hours or less, with resulting plasma concentrations > 3000 ng/mL and > 5000 ng/mL, would be amenable to lipid emulsion therapy at doses currently recommended, based on nonclinical information in the published literature.

Potential mitigation strategies for the risk of inadvertent intravascular injection proposed by the Applicant consist of primarily drug product labeling language regarding dose and administration, and warnings and precautions.

8.7.3. Risk of Emboli

The risks of an intravascular injection include not only exposure to high concentrations of bupivacaine, but also to the SABER vehicle, which includes SAIB and benzyl alcohol. Because nonclinical studies did not evaluate intravascular administration, it is not clear whether patients may be at risk to develop ischemia secondary to emboli of a viscous solution or hemolysis, which was demonstrated when SABER-bupivacaine and SABER-placebo were mixed with human blood. In response to Information Requests subsequent to the AC meeting, the Applicant provided additional in vitro data suggesting that emboli resulting in ischemia, and hemolysis are unlikely. Specifically, the Applicant used plastic tubing, bovine plasma, a peristaltic pump, and a filter to mimic venous circulation and the pulmonary capillary bed, and observe the effects of SABER-bupivacaine on the viscosity of blood and on red blood cells. These experiments demonstrated the formation of viscous droplets present for approximately one hour, with longer durations of exposure resulting in the need for increased peristaltic pressures to traverse the filter. This suggests that formed emboli/droplets would likely be retained in the pulmonary capillary bed, and could result in impaired gas exchange, or tissue ischemia if they were to reach the arterial side of the circulation. Furthermore, patients with cardiac anomalies, such as a patent foramen ovale or atrial septal defect, may be at higher risk for arterial emboli. The risk of emboli resulting in ischemia is likely higher with inadvertent intraarterial injection.

In addition to the previously described mitigation strategies for the risk of inadvertent intravascular injection, the Applicant has proposed to include the following box warning regarding potential emboli.

**WARNING: RISK OF POTENTIAL ADVERSE EMBOLIC EFFECTS
RESULTING FROM INADVERTENT INTRAVASCULAR INJECTION**

(b) (4)

(b) (4) must be used to confirm proper placement of the
needle tip before injecting Posimir.

Source: Response to Information Request, March 13, 2020, Applicant's submission, NDA 204803.

At the time of completion of this clinical review, future approval of SABER-bupivacaine would be for use in patients undergoing arthroscopic subacromial decompression only. Because administration of SABER-bupivacaine in this surgical model requires a needle, the risk of inadvertent intravascular injection remains a major concern of the Division, and discussed extensively during the AC meeting. As such, the Division is likely to require a nonclinical study pre-approval to evaluate the embolic risk associated with administration of this drug product.

8.8. Safety in the Postmarket Setting

8.8.1. Expectations on Safety in the Postmarket Setting

There may be an increased incidence in wound-related adverse events depending on the surgical site. Because there appears to be a risk of the development of a post-operative wound hematoma, the choice of administration site should consider whether development of a hematoma may present a safety risk (e.g., neurosurgical procedures) or disrupt the surgical repair.

8.8.2. Additional Safety Issues From Other Disciplines

The Division's current thinking regarding the approval of extended-release local anesthetic products is that because the PK profile generally differs depending on the site of administration and may depend on the total dose, method of administration, and the vascularity of the anatomical site, it should be characterized for all sites and methods of administration proposed to be included in the product labeling.

The clinical pharmacology review team did conclude that the observed bupivacaine C_{max} and AUC values "were not too drastically different" for the surgical procedures evaluated (i.e., abdominal, shoulder, and hernia procedures) and method of administration (i.e., subcutaneous, infiltration, and instillation) for the same SABER-bupivacaine dose. However, because the range of mean C_{max} values did vary for each procedure evaluated and there was a large difference in mean C_{max} values for two studies conducted in the same surgical population, arthroscopic shoulder surgery, each proposed labeling indication may need supportive PK data.

As previously discussed, while the pharmacology-toxicology team has not identified any specific nonclinical concerns preventing approval of this application, the team did conclude that absent adequate clinical mitigation strategies and risk assessments regarding inadvertent intravascular administration, the Applicant would need to conduct additional nonclinical evaluations to characterize intravascular toxicity and the effectiveness of rescue treatments, included lipid emulsion.

8.9. Integrated Assessment of Safety

The concerning safety issues identified during the clinical development of SABER-bupivacaine include changes in the glenohumeral joint after arthroscopic shoulder surgery, wound-related adverse events, and systemic exposure to benzyl alcohol and possible associated toxicity.

The development of chondrolysis, or other changes to the glenohumeral joint, and adhesive capsulitis can be catastrophic post-operative outcomes. While the surgical procedure and patient cooperation with post-operative rehabilitation play a role in the development of these conditions, so too does the administration of local anesthetic medication during the surgery. Specifically, it is well known that intra-articular infusions of local anesthetics following shoulder

surgery have resulted in glenohumeral chondrolysis, which generally presents with profound pain, decreased range of motion, and radiographic evidence of loss of cartilage. With newer, extended-release local anesthetic products, such as SABER-bupivacaine, there is concern that the continued exposure may also result in irreversible changes to the articular surfaces. An additional concern with administration of SABER-bupivacaine is the apparent local inflammatory, granulomatous reaction and what impact that may have on the shoulder joint post-operatively.

During review of the data submitted in the original NDA, there were three cases concerning for chondrolysis; two cases were noted based on MRI findings and one case was reported as an SAE of chondropathy. Based on my review of the additional information provided in the resubmission, it does not appear these cases were in fact chondrolysis or that there were radiographic findings consistent with destruction of the articular cartilage. Specifically, the two cases were reported based on post-operative MRI findings and a checked “evidence-of-chondrolysis” box on the post-operative questionnaire. Further review, however, suggests that the 18-month follow MRIs were unchanged from baseline and that neither case was reported as an adverse event. The third patient with the SAE of chondropathy underwent a non-study procedure 15 months after the study procedure and a biopsy at that time revealed mild degenerative changes. The patient was doing well, without pain, and had a normal shoulder physical and MRI exam at the 18-month follow-up visit (three months after the non-study surgery), suggesting the tissue diagnosis did not reflect the clinical picture of the patient.

Dr. Breder commented that the post-operative follow-up for the three shoulder studies may not have been adequate to capture all possible cases of chondrolysis, given that the median time for development after local anesthetic infusion has been reported to be 8.5 months (Healthcare Professionals Sheet). Symptoms can occur within two months (Anderson, 2010), however, and most patients will have pain and decreased range of motion by three to five months, with corresponding radiographic changes observed by five to six months’ post-operatively (Hansen, 2007). Furthermore, there was additional follow-up information for patients treated in Study CLIN005-0006 provided in the NDA resubmission. In response to the CRL, the Applicant contacted investigators and asked whether any treated patient developed chondrolysis subsequent to conclusion of the study and all investigators indicated that they were “certain” no study patient had. Additionally, this study included patients with rotator cuff tears, patients most at risk to develop chondrolysis due to local anesthetic seepage into the shoulder joint. Because this study was completed more than 12 years ago, it seems unlikely that there would be cases of chondrolysis that have yet to be reported.

The supplemental safety data provided from Study BU-002-IM is the least supportive of the safety profile of SABER-bupivacaine administration during shoulder surgery and the only study which used a non-SABER comparator treatment. There were observed changes in the 6-month MRIs in all treatment groups; however, there did appear to be an increase in some changes in the SABER-treated patients. Specifically, there was a higher percentage of patients treated with SABER-bupivacaine or SABER-placebo with moderate bone erosion and edema, mild to

moderate musculo-tendinous abnormalities, mild shoulder joint changes, and mild abnormal tissue or scarring compared to patients treated with bupivacaine HCl. The physical examination data for patients in this study did not identify significant changes between groups and mean Constant-Murley (C-M) scores increased in all groups post-operatively; however, the SABER-bupivacaine-treated patients demonstrated the smallest increase in C-M scores. Seven patients in this study experienced worsening C-M scores, all treated with either SABER-bupivacaine or SABER-placebo; however, the 6-month follow-up MRI imaging did not identify any contributory radiographic changes and most were reported as unchanged from baseline. Given that the study was completed 10 years ago, it seems unlikely that persistent clinically relevant changes have yet to be reported.

In my view, the Applicant has adequately addressed the risk of developing chondrolysis or other irreversible conditions related to the glenohumeral joint and articular surfaces resulting in clinically significant loss of function after administration of SABER-bupivacaine during arthroscopic subacromial decompression. While I do not believe there were any true cases during their clinical development program, it is worth noting that it appears the majority of treated patients had a relatively intact rotator cuff, thereby restricting bupivacaine to the subacromial space and limiting entry into the joint space. The Applicant states that because SABER-bupivacaine forms a viscous depot after administration, the likelihood that it would seep into the joint space is low and because the volume administered is only 5 mL, expansion of the subacromial space and resulting spread into the joint space is unlikely. Should this product be approved for use in patients undergoing shoulder surgery, information will be included in the product labeling that SABER-bupivacaine should not be administered in the joint space or to patients with major rotator cuff tears, where the integrity of the joint is in question.

One potential outstanding issue, however, regarding the safety evaluation of SABER-bupivacaine in patients undergoing shoulder surgery is the limited data available for comparison between patients treated with a SABER-containing product, SABER-bupivacaine or SABER-placebo, and those treated with a non-SABER-containing product. As previously mentioned, there were only 29 patients in Study BU-002-IM who were treated with a non-SABER-containing comparator, bupivacaine HCl, such that the available data to fully inform safety comparisons is limited. For example, in Study C803-017, the incidence of partial supraspinatus tears increased over 18 months in both the SABER-bupivacaine and SABER-placebo treatment groups; 21% to 26% and 46% to 50%, respectively. While the increased incidences appear to be consistent with reports in the published literature, it is unclear if the SABER component contributed to a higher incidence than may have been observed after treatment with either bupivacaine HCl or saline placebo.

Regarding wound-related adverse events observed during the clinical studies, the most frequently observed adverse event in patients treated with SABER-bupivacaine was peri-incisional bruising. The Applicant has indicated that vasodilation, inhibition of platelet aggregation, and hemolysis can occur after exposure to the benzyl alcohol component of the SABER formulation, resulting in peri-incisional bruising. Punch biopsy results from patients

treated in Study C803-027 confirm that bruising and skin discoloration are due to extravasation of blood from the surgical wound into subcutaneous tissue. The bruising generally appears on POD 1, with gradual resolution over two to four weeks. The bruising appears to be dose-related such that SABER-bupivacaine 7.5 mL has the highest incidence of bruising of any study treatment group. Additionally, patients treated with SABER-bupivacaine tended to have a larger sized bruise compared to patients treated with bupivacaine HCl. The most recently completed PERSIST study in patients undergoing lap chole evaluated bruising as a pre-specified finding and not simply as an adverse event, and is, therefore, considered a more thorough evaluation. The results indicated an increased incidence and larger area of peri-incisional bruising.

Regarding wound dehiscence, there were 25 cases reported in the original ISS. Three were considered SAEs and required surgical repair; two were true fascial dehiscence cases and one was a cutaneous dehiscence. All three patients were treated in Study C803-025, two received SABER-bupivacaine and one received SABER-placebo. The remaining cases of dehiscence were superficial and required no treatment other than local wound care. In the PERSIST study, wound dehiscence was extensively evaluated and reportedly occurred with an increased frequency in patients in the bupivacaine HCl treatment group in Part 2 of the study. As discussed in Section 8.2, the Applicant argues that shorter lap chole incisions have a higher local drug exposure such that any real concerns for wound dehiscence would have been observed in this study. I disagree with this rationale based on the fact that each of the four incisions received a smaller volume of medication (5 mL divided among four incisions), which likely results in the same local exposure as a larger incision receiving the full 5 mL. Regardless, I do agree that the PERSIST study improved the safety profile of SABER-bupivacaine with respect to wound dehiscence.

Similar to the previously completed studies, however, the incidence of post-operative wound hematoma was higher in the SABER-bupivacaine treatment group compared to the bupivacaine HCl treatment group in Part 2 of the PERSIST study. Specifically, the incidence of wound hematoma was 4% versus 1%, respectively, and two patients in the SABER-bupivacaine group and one patient in the bupivacaine HCl group had more than one wound hematoma. Almost all hematomas occurred at the umbilical incision, which is not surprising given the length of the incision and the one through which gall bladder extraction occurs. All hematomas in the SABER-bupivacaine treatment group resolved without medical or surgical intervention. A single patient in the bupivacaine HCl treatment group required percutaneous drainage.

Regarding the incidence of surgical site infections, in the previously completed studies reviewed in the first NDA submission cycle, there did not appear to be a clinically significant difference in the incidence of surgical site infections in patients treated with SABER-bupivacaine compared to respective study controls. Both Drs. Breder and Simone, however, commented that the increased incidence in wound hematoma and dehiscence could predispose patients to more serious wound complications, including surgical site infection. In the PERSIST study, there did appear to be an increased incidence in SSIs in patients treated with SABER-bupivacaine

compared to patients treated with either saline placebo or bupivacaine HCl. Specifically, there were seven cases of surgical site infection; five in patients treated with SABER-bupivacaine (3%) and two in patients treated with bupivacaine HCl (1%). The umbilical incision was most commonly involved and all resolved within 28 days with oral antibiotic administration. While the incidence does not appear to be out-of-range from what is reported in the published literature and is not generally alarming, the finding is consistent with previously identified wound-related adverse events reported in the SABER-bupivacaine-treated patients. Additionally, a larger percentage of patients treated with SABER-bupivacaine had an increase in white blood cell count greater than or equal to 30% from baseline on study day 4, suggesting a more clinically relevant inflammatory response in patients treated with SABER-bupivacaine than those treated with saline placebo in Part 1 or with bupivacaine HCl in Part 2.

An additional concern regarding administration of SABER-bupivacaine is observed foreign body reactions and the apparent duration of SAIB component detection in the wound. Specifically, in nonclinical studies, it appears that SAIB components are detectable in surgical wounds for up to one year. The Applicant acknowledges this, however, claims that other 'extended-release' injectable products, specifically Exparel® and Sustol®, also cause foreign body reactions with granulomatous inflammation. While the nonclinical data may suggest a local, granulomatous reaction after subcutaneous injection of Exparel®, the clinical studies in addition to post-market surveillance do not suggest there is a clinically significant difference in local toxicity between Exparel® and bupivacaine HCl or placebo. Furthermore, given that Exparel® was initially approved in 2011, it seems unlikely that post-operative wound complications would have not yet been identified.

The Applicant has correctly described the injection site reactions associated with Sustol® administration; however, the relevance of injection site reactions to the wound-related adverse events observed after administration of SABER-bupivacaine is not clear. Specifically, Sustol® is administered via subcutaneous injection in either the back of the upper arm or abdomen. It is not to be administered, "...anywhere the skin is burned, hardened, inflamed, swollen, or otherwise compromised" (Sustol® [package insert]. Redwood City, CA: Heron Therapeutics, Inc.; 2016). This is a much different clinical scenario than a product administered into a surgical wound, such that wound healing is a critical issue. Therefore, the Applicant's claim that the '*benefit-to-risk ratio of SABER-bupivacaine would be no less favorable than those approved products*' (ISS, p. 65, Applicant's submission) is not entirely accurate. Furthermore, observed increases from baseline in creatine kinase on study day 4 in patients treated with SABER-bupivacaine, compared to observed decreases in patients treated with either saline placebo or bupivacaine, in the PERSIST study suggest that there may be local muscle damage. CK levels in all treatment groups were close to baseline by study day 29. There were no reports of rhabdomyolysis or associated symptoms.

Because the SAIB components appear to remain detectable in tissues for up to one year, the concern aside from foreign body reaction alone, is how these remnants may impact future surgical exploration. Specifically, patients not uncommonly undergo either repeat or associated

surgical procedures in the same anatomic area and it is not known how the presence of the SAIB components will impact the ability to dissect and visualize the anatomy. A more challenging surgical procedure can result in increased risks to patients including, but not limited to, prolonged exposure to general anesthetics (depending on the type of procedure performed), increased risk of bleeding and need for transfusion of blood products, increased risk of technically difficult surgical dissection with subsequent increased risk of damage to surrounding tissues and organs, and increased postsurgical pain.

The final safety concern regarding SABER-bupivacaine is the systemic exposure to, and possible toxicity of, the benzyl alcohol component. During the first review cycle, it was noted that while the Applicant did not measure plasma or urine levels of benzyl alcohol throughout the clinical studies, it did appear that there was an increased incidence of somnolence, dizziness, and dysgeusia in patients treated with SABER-bupivacaine or SABER-placebo compared to those treated with bupivacaine HCl. These results are consistent with solicited adverse events reported in the PERSIST study. Specifically, in Part 1, SABER-bupivacaine-treated patients reported an increased incidence in somnolence, headache, and dysgeusia compared to patients treated with saline placebo. In Part 2 of the study, SABER-bupivacaine-treated patients had an increased incidence of somnolence and dysgeusia compared to patients treated bupivacaine HCl. It is worth mentioning that patients treated with bupivacaine HCl in Part 2 had an increased incidence of nausea and vomiting, symptoms that could also be associated with benzyl alcohol systemic exposure.

In my judgement, a clear advantage of SABER-bupivacaine over injectable bupivacaine products is the route of administration, instillation. Because SABER-bupivacaine is administered to the tissues with a needleless syringe or blunt-tip catheter, the risk of intravascular administration is low. Having said that, however, there is concern that the longer-acting, extended-release bupivacaine products can result in catastrophic LAST should they reach the intravascular space either by inadvertent injection, diffusion, or seepage from the administration site. The current treatment paradigm for LAST is based on exposure to immediate-release bupivacaine, generally administered via single-shot injection or continuous peripheral nerve block infusion. In these cases, the doses are limited and the infusion can be terminated. In the case of administration of 660 mg bupivacaine into a wound, it is unclear how a patient would be resuscitated (i.e., dose of intralipid, vasopressors, etc.) and for how long the resuscitation effort may last.

In conclusion, I do not think that the marginal efficacy benefit observed after administration of SABER-bupivacaine in two surgical models outweighs the consistently observed wound and nervous system adverse events, and, therefore, do not recommend approval. I do not think that SABER-bupivacaine has demonstrated a consistent and clinically relevant improvement in postsurgical pain over SABER-placebo or bupivacaine HCl in the various surgical models evaluated and the risks associated with the surgical wound and benzyl alcohol systemic exposure outweigh the benefits.

9. Advisory Committee Meeting

The Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) met on January 16, 2020, to discuss the data for the use of Posimir for postsurgical analgesia. Summarized below are the three discussion topics and the single voting question. Transcripts of the discussions are available at the Agency's website.

Discuss whether the Applicant has provided sufficient information to support the proposed indication.

Dr. Ronald Litman, the Chairperson, opened this discussion by stating that the committee felt “blind-sided” by the differing background packages submitted by the Applicant and the Division. He stated the Applicant and the Division focused on different aspects of the SABER-bupivacaine development program, thereby making it difficult to digest all the material presented. A few members commented that the additional safety information presented in the complete response submission was based on post hoc analyses.

There were members of the committee who felt that the difference in time to first opioid use for Study C803-006-0006 (a secondary endpoint) was supportive of the efficacy of SABER-bupivacaine, despite the fact that the second primary endpoint, proportion of patients taking opioid rescue, was not statistically significantly different between treatment groups. There was discussion regarding an extended-release indication for local anesthetic products and that potentially SABER-bupivacaine should have an indication that would more accurately reflect the efficacy data, which would be less than the proposed 72 hours. There was a robust discussion about the manner in which the efficacy data was presented by the Applicant and by the Division. Specifically, members commented that the pain curves and AUC visualizations, and Forest plots did not accurately represent the results. There was criticism that the Applicant did not specify whether the representations included standard error or standard deviation and that the Division had neither.

Several members commented that treatment with SABER-bupivacaine did not result in statistically significant differences in mean pain intensity compared to treatment with bupivacaine. There was also discussion regarding the separation of SABER-bupivacaine and bupivacaine pain curves within the first 24 hours post-operatively in Study BU-002-IM. Several members commented that the results presented from meta-analyses of the Applicant's data are difficult to interpret and may not be informative given the heterogeneity of the clinical studies and surgical procedures evaluated.

The route of administration for SABER-bupivacaine was discussed and some members were concerned whether 5 mL of SABER-bupivacaine could cover the entire incision length and what additional devices or catheters are needed for proper administration. One member suggested co-packaging the recommended administration device(s) with detailed administration

instructions.

Discuss 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.

A few committee members expressed concern regarding the systemic exposure to SABER-bupivacaine after other routes of administration, including inadvertent catastrophic intravenous administration. Some members suggested that preclinical studies evaluating intravenous administration and intralipid rescue should be conducted, but not necessarily pre-approval. Many members agreed that intravenous administration is likely to occur at some point post-market and information on how to rescue patients after an inadvertent IV injection is necessary.

One member suggested that an efficacy study that tightly controlled intra-operative opioid administration would be informative, and potentially more supportive of the efficacy of SABER-bupivacaine. A few members suggested a study in patients receiving either neuraxial or regional anesthesia, versus general, would be helpful in determining which neurological adverse events are related to benzyl alcohol exposure. There was agreement that exposure to general anesthetics confounds adverse event conclusions, particularly when intra-operative opioid and antiemetic use is not controlled. One member stated that the PERSIST study was conducted to address the previously identified safety concerns as well as provide additional efficacy data, but the results were not supportive of either the safety or efficacy of SABER-bupivacaine.

Discuss whether the efficacy, safety, and overall benefit-risk profile of Posimir support the approval of this application.

A few members felt that the limited demonstrated efficacy precluded a discussion of the safety issues. One member suggested that patient-reported pain scores and pain curves should not be primary endpoints, but that reduction in and time to first opioid use are the more clinically meaningful endpoints. He further stated that he recommends approval of SABER-bupivacaine despite marginal decreases in mean pain intensity through 72 hours. Another member stated that most patients have minimal post-operative pain after 16 hours, such that a long-acting local anesthetic may not be needed. Several committee members did express concern about the limited efficacy and the fact that the PERSIST study, while designed to address outstanding safety and efficacy concerns, did not win on primary endpoints for either Part 1 or Part 2.

Additional safety concerns discussed included the extent of post-operative peri-incisional bruising, adverse events associated with administration of general anesthesia, and the need to more thoroughly evaluate the incidence of concerning adverse events in the elderly population.

The meeting concluded with the following voting question:

Do you recommend approval of Posimir, bupivacaine extended-release solution, 660 mg/5 mL (132 mg/mL), for the proposed indication of single-dose instillation into the surgical site to produce post-surgical analgesia? Please discuss the rationale for your vote. If you voted “Yes,” please specify whether any post-approval studies should be required. If you voted “No,” please discuss what additional data are needed for approval.

The committee vote was an even split; six ‘yes’ votes and six ‘no’ votes.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

(b) (4)

The following is a high-level summary of edits made to the final prescribing information.

- **INDICATIONS AND USAGE:**
The Division limited the indication to use in patients undergoing arthroscopic subacromial decompression. Based on the concerns discussed throughout this review regarding the efficacy and safety of the drug product, a Limitations of Use statement is included in the label.
The indication is as follows:
POSIMIR contains an amide local anesthetic and is indicated in adults for administration into the subacromial space under direct arthroscopic visualization to produce post-surgical analgesia for up to 72 hours following arthroscopic subacromial decompression.

The Limitations of Use statement is as follows:
Safety and effectiveness have not been established in other surgical procedures, including soft tissue surgical procedures, other orthopedic procedures, including for intra-articular administration, and boney procedures, or when used for neuraxial or peripheral nerve blockade.
- **DOSAGE AND ADMINISTRATION:**
Edits to this section were intended to clarify the risks associated with bupivacaine administration, required personnel and equipment during Posimir administration, and avoidance of additional local anesthetic administration for 168 hours. Additionally, the

Division clarified that Posimir must be administered under direct arthroscopic visualization, with confirmation of correct needle placement.

- Safety information in the BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, or ADVERSE REACTIONS:

Based on concern for the development of emboli associated with inadvertent intravascular injection, the following boxed warning was included in the label:

**WARNING: RISK OF POTENTIAL ADVERSE EMBOLIC EFFECTS
RESULTING FROM INADVERTENT INTRAVASCAULAR INJECTION**

Inadvertent intravascular injection could cause POSIMIR droplets to be deposited in the pulmonary and other capillary beds. Administer POSIMIR into the subacromial space at the end of arthroscopic shoulder surgery. Direct arthroscopic visualization must be used to confirm proper placement of the needle tip before injecting POSIMIR. [see Warnings and Precautions (5.1)].

The risk of joint cartilage necrosis was included in Section 5, and the Division requested the Applicant include all relevant safety information from both soft tissue and shoulder studies in Section 6. The Division also requested the Applicant update the label with all relevant Marcaine information based on the most recent approved labeling, dated August 21, 2020.

- CLINICAL STUDIES:
The Division included a statement in this section indicating that of the eight (the Applicant counted each cohort in Study C803-025 as a separate study, therefore indicated there were 10) adequate and well-controlled clinical studies conducted by the Applicant, adequate evidence of effectiveness was demonstrated in one arthroscopic shoulder study. Data, including pain curves, from all three shoulder studies was included to inform the prescriber of the clinical utility of Posimir administration and guide expectations. Data from the soft tissue studies were not included in this section.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not indicated at this time. If the Agency becomes aware of future safety concerns, one may become necessary.

12. Postmarketing Requirements and Commitments

The original application was submitted prior to the requirement under FDASIA to submit a pediatric study plan (PSP), and because the application received a CRL, there was no

requirement to submit one with the resubmission.

The Applicant requested a waiver of pediatric patients from birth to less than three years of age and a deferral of studies in pediatric patients age 3 to less than 18 years of age. The Pediatric Review Committee (PeRC) recommended waiving the pediatric study requirement for all age groups based on the potential for benzyl alcohol toxicity in younger aged pediatric patients and the likelihood that the drug product does not represent a meaningful therapeutic benefit over existing products for all pediatric age groups. The Division agrees with the PeRC's recommendation and pediatric studies of SABER-bupivacaine are not required.

The pharmacology-toxicology review team has concluded that additional nonclinical studies are likely needed to assess the risk of inadvertent intravascular administration. I recommend any intravenous toxicity study perform an assessment of the ability to rescue using lipid emulsion therapy. Refer to the review completed by Dr. Misol Ahn for additional information.

13. Appendices

13.1. Results of Staged MRI Reading Process, Study C803-017e

Region of Interest Test Result	SABER Bupivacaine 5.0 mL		SABER Placebo 5.0 mL	
	Screening or Baseline	Month 18	Screening or Baseline	Month 18
Safety Subjects	40	31	20	16
Subjects with MRI	39	29	18	14
Subjects with MRI obtainable for the central review	24	27	13	14
Gleno-humeral Joint and Humeral Head				
Presence of focal defect- Humeral head, n (%)				
Yes	0	0	0	0
No	24 (100.0)	27 (100.0)	13 (100.0)	14 (100.0)
Presence of focal defect- Glenoid, n (%)				
Yes	1 (4.2)	1 (3.7)	0	0
No	23 (95.8)	26 (96.3)	13 (100.0)	14 (100.0)
<u>Comment:</u> Both focal defects are for the same patient (b) (6) and there was no change from baseline				
Presence of cartilage thinning- Humeral head, n (%)				
Grade 0: normal/none	23 (95.8)	26 (96.3)	13 (100.0)	14 (100.0)
Grade 1: mild	0	0	0	0
Grade 2: moderate	1 (4.2)	1 (3.7)	0	0
Grade 3: severe	0	0	0	0
<u>Comment</u> Both cases of cartilage thinning are for the same patient (b) (6) and there was no change from baseline.				
Presence of cartilage thinning- Glenoid, n (%)				
Grade 0: normal/none	24 (100.0)	27 (100.0)	13 (100.0)	14 (100.0)
Grade 1: mild	0	0	0	0
Grade 2: moderate	0	0	0	0
Grade 3: severe	0	0	0	0
Rotator Cuff and Labrum				
Supraspinatus tendon tear, n (%)				
No tear	15 (62.5)	16 (59.3)	5 (38.5)	5 (35.7)
Partial	5 (20.8)	7 (25.9)	6 (46.2)	7 (50.0)
Full thickness	1 (4.2)	1 (3.7)	1 (7.7)	0
Other findings	3 (12.5)	3 (11.1)	1 (7.7)	2 (14.3)
Supraspinatus- Other findings, n (%)				
Interstitial tear	0	0	0	0
Tendinosis	2 (8.3)	2 (7.4)	1 (7.7)	1 (7.1)
Surgically repaired tendon	0	0	0	1 (7.1)
Interstitial tear::Tendinosis	1 (4.2)	1 (3.7)	0	0
(blank)	21 (87.5)	24 (88.9)	12 (92.3)	12 (85.7)

NDA 204803, Posimir
Bupivacaine solution for infiltration use

Region of Interest Test Result	SABER Bupivacaine 5.0 mL		SABER Placebo 5.0 mL	
	Screening or Baseline	Month 18	Screening or Baseline	Month 18
Body of Muscles of the rotator cuff				
Supraspinatus, n (%)				
Normal	23 (95.8)	26 (96.3)	13 (100.0)	14 (100.0)
Atrophy	1 (4.2)	1 (3.7)	0	0
Fatty infiltration	0	0	0	0
Edema	0	0	0	0
Other	0	0	0	0
<u>Comment:</u> The atrophy is from the same patient (b) (6) and there was no change from baseline				
Infraspinatus, n (%)				
Normal	24 (100.0)	27 (100.0)	13 (100.0)	14 (100.0)
Atrophy	0	0	0	0
Fatty infiltration	0	0	0	0
Edema	0	0	0	0
Other	0	0	0	0
Subscapularis, n (%)				
Normal	24 (100.0)	27 (100.0)	13 (100.0)	14 (100.0)
Atrophy	0	0	0	0
Fatty infiltration	0	0	0	0
Edema	0	0	0	0
Other	0	0	0	0
Teres minor, n (%)				
Normal	24 (100.0)	25 (92.6)	13 (100.0)	14 (100.0)
Atrophy	0	0	0	0
Fatty infiltration	0	2 (7.4)	0	0
Edema	0	0	0	0
Other	0	0	0	0

Subacromial space- Acromion					
Acromion bony spur, n (%)					
Yes		3 (12.5)	1 (3.7)	0	0
No		21 (87.5)	26 (96.3)	13 (100.0)	14 (100.0)
Acromion bone resection, n (%)					
Yes		0	18 (66.7)	0	9 (64.3)
No		24 (100.0)	9 (33.3)	13 (100.0)	5 (35.7)
Acromion Signal abnormality (edema, fibrosis), n (%)					
Yes		2 (8.3)	2 (7.4)	3 (23.1)	2 (14.3)
No		22 (91.7)	25 (92.6)	10 (76.9)	12 (85.7)
Comments:					
1. SABER-Bupivacaine patients (b) (6) had signal abnormality at baseline and none at 18 months, whereas patients (b) (6) were normal at baseline and abnormal at 18 months.					
2. SABER-placebo patient (b) (6) was abnormal at baseline and normal at 18 mo. Patients (b) (6) were abnormal at both baseline and at 18 mo.					

Region of Interest Test Result	SABER Bupivacaine 5.0 mL		SABER Placebo 5.0 mL		
	Screening or Baseline	Month 18	Screening or Baseline	Month 18	
Acromio-Clavicular Joint					
Bone resection at Acromioclavicular joint/ postoperative changes?, n (%)					
Yes	0	10 (37.0)	0	4 (28.6)	
No	24 (100.0)	16 (59.3)	13 (100.0)	10 (71.4)	
Not evaluable	0	1 (3.7)	0	0	
Joint effusion/Synovitis, n (%)					
Grade 0: normal/none	8 (33.3)	9 (33.3)	1 (7.7)	2 (14.3)	
Grade 1: mild	12 (50.0)	9 (33.3)	11 (84.6)	7 (50.0)	
Grade 2: moderate	3 (12.5)	3 (11.1)	0	3 (21.4)	
Grade 3: severe	0	0	1 (7.7)	1 (7.1)	
Not evaluable	1 (4.2)	6 (22.2)	0	1 (7.1)	
Comments:					
1. Two SABER-Bupivacaine patients improved from moderate at baseline to mild at 18 mo.					
2. Four patients (3 Placebo, 1 SABER-Bupivacaine) went from mild at baseline to moderate at 18 mo.					
3. Placebo patient (b) (6) worsened from mild at baseline to severe at 18 mo. SABER-Bupivacaine patient (b) (6) improved from severe at baseline to mild at 18 mo.					
Bursa and Soft Tissue					
Subacromial bursa- Bursitis/Excess fluid, n (%)					
Grade 0: normal/none	11 (45.8)	18 (66.7)	4 (30.8)	5 (35.7)	
Grade 1: mild	12 (50.0)	6 (22.2)	6 (46.2)	9 (64.3)	
Grade 2: moderate	1 (4.2)	3 (11.1)	2 (15.4)	0	
Grade 3: severe	0	0	1 (7.7)	0	

<u>Comment:</u> Placebo patient (b) (6) was severe at baseline and mild at 18 mo.				
Subacromial bursa- Resection, n (%)				
Yes	0	0	0	0
No	0	0	1 (7.7)	0
Not evaluable	24 (100.0)	27 (100.0)	12 (92.3)	14 (100.0)
Subacromial bursa- Scar tissue, n (%)				
Yes	0	0	0	0
No	24 (100.0)	25 (92.6)	13 (100.0)	13 (92.9)
Not evaluable	0	2 (7.4)	0	1 (7.1)
Soft tissue scarring, n (%)				
Grade 0: normal/none	24 (100.0)	27 (100.0)	13 (100.0)	14 (100.0)
Grade 1: mild	0	0	0	0
Grade 2: moderate	0	0	0	0
Grade 3: severe	0	0	0	0
Not evaluable	0	0	0	0

Note: MRI images were retrospectively collected from the study sites and centrally reviewed by a musculoskeletal radiologist and orthopedic surgeon who were blinded to the purpose of the review and the treatments received. One subject in each treatment group who had ultrasound imaging in lieu of MRI was excluded from the review.

Note: Percentages are computed with respect to subjects with MRIs obtainable for the central review.

Source: ISS, pp. 37-38 (PDF), Applicant's submission, NDA 204803.

13.2. References

Anderson, S. Lance, et al. Chondrolysis of the Glenohumeral Joint After Infusion of Bupivacaine Through an Intra-Articular Pain Pump Catheter: A Report of 18 Cases. *Arthroscopy: The Journal of Arthroscopic & Related Surgery*. 2010;26(4):451–461.

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Scott DB, Lee A, Fagan D, Bowler GM, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesth & Analg.* 1989;69(5):563-9.

13.3. Financial Disclosure

Covered Clinical Studies (by study number):

- CLIN803-006-0006
- BU-002-IM
- CLIN005-0010
- BU-001-IM
- C803-017
- CLIN005-0006
- C803-025
- C803-028

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>338</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to	Yes ☐	No ☐ (Request information

NDA 204803, Posimir
Bupivacaine solution for infiltration use

minimize potential bias provided:		from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

APPEARS THIS WAY ON ORIGINAL

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/s/

RENEE L PETIT-SCOTT
01/19/2021 11:16:19 AM

RIGOBERTO A ROCA on behalf of MARTHA A VAN CLIEF
01/20/2021 11:07:19 AM

Medical Officer's Consultative Review Memorandum

Submission: NDA 204803

Sponsor: Durect Pharmaceuticals

Product: Posimir (SABER-bupivacaine) [Analgesia]

Requested by: Ayanna Augustus, PhD, Division of Anesthesia, Analgesia, and Addiction Products (DAAA)

Consulting reviewer: Brenda Ye, M.D., Division of Medical Imaging Products
Through: Louis Marzella, M.D., Ph.D., Director, DMIP

Consulting Division's Question:

The Division has received an NDA for a product called SABER bupivacaine, which 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 tissues and is cleared from the circulation over a 12 to 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 SAIB persists at the surgical site far longer than the bupivacaine; in an animal study, the substance was present in the injection site a year later and was associated with a foreign body reaction.

The Applicant has conducted three clinical trials in which SABER Bupivacaine or SABER placebo (SAIB, BA and saline) were injected into the periarticular space following arthroscopic shoulder surgery. Part of the safety assessments following the surgical procedure was an MRI evaluation of the affected shoulder. The Division would appreciate your input regarding the following issues:

1. The surgical intervention will cause changes in the joint and surrounding tissues. Is it likely that an MRI scan will be able to detect subtle, drug-associated pathology to the joint or the surrounding tissues at 3 or 6 months following surgery?
2. Is it known how long it generally takes, following this type of surgical procedure, for imaging to demonstrate the resolution of the acute changes to the joint and surrounding tissues?
3. If we are able to get copies of the MRIs, would there be someone in your division who could review these for us in a blinded manner?

DMIP consultant's response:

1. Chondrolysis induced by drugs can be a serious irreversible destruction of the cartilage. It is likely that an MRI could detect chondrolysis 3-6 months following surgery and later.

2. Acute surgical changes seen on medical imaging often resolve weeks to months after the surgery. However depending on the specific type of changes, the duration of imaging findings vary. For example while soft edema often resolves in weeks, bone remodeling changes can be seen on imaging years after surgery. So it is difficult to precisely define how long it takes for the acute changes to resolve on an imaging test.

3. If you decide to proceed with a blinded re-read of the MRIs, our division recommends that this be done through external adjudication from a Special Government Employee (SGE). Of the currently available SGE pool, our division recommends Dr. Mark Kransdorf, a renowned musculoskeletal radiologist at Mayo Clinic:

Mark J. Kransdorf, MD, Email: Kransdorf.Mark@mayo.edu Tel: 480-301-7470

Apart from a blinded re-read, an SGE consultation with Dr. Mark Kransdorf could provide additional valuable insight to the application. Our Medical Imaging Division could assist in arranging the SGE consultation.

Review of Submission:

New drug application 204803 Posimir (SABER-bupivacaine) was submitted on April 12, 2013 for the treatment of post surgical analgesia. The Agency issued a Complete Response letter on February 12th 2014, primarily based on concerns of drug safety. Adverse reactions, such as chondropathy and neuropathy, were noted during the review cycle. The Applicant met with the review division at an End-of-Review-Cycle meeting on September 23, 2014 and then filed a Formal Dispute Resolution Request (FDRR) on November 21, 2014. The Applicant disagrees with the review division on the drug's safety concerns, including chondrolysis/chondropathy, skin discoloration (bruising) masking skin infections, wound dehiscence, and neurological adverse events. In particular with regard to this consult request, the applicant stated that the shoulder MRI images of patients with questionable chondrolysis/chondropathy have been blindly re-read by two orthopedic surgeons who found no evidence of chondrolysis. This appeal was denied on January 15, 2015.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRENDA Q YE
05/22/2015

LIBERO L MARZELLA
05/22/2015



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
Pharmacometrics Review	Okpo Eradiri, PhD / Elsbeth Chihale, PhD
Project Management Staff	Ayanna Augusts, PhD, Parinda Jani
Pediatric and Maternal Health Staff	Erica Radden MD / Hari Sachs, MD / Jeanine Best, MSN, RN, PNP / Lynn Yao, MD
OMP/OPDP	Eunice Chung-Davies, PharmD
OMPQ/DGMPA/NDMAB	Juandria Williams, PhD
OSI/DGCPC	Lauren Iacono-Connors, PhD / Janice Pohlman, MD, MPH / Kassa Ayalew, MD, MPH
OSE/DMEPA	Vicky Borders-Hemphill, PharmD / Morgan Walker, PharmD / Irene Chan, PharmD / Jamie Wilkins Parker, PharmD / Todd Bridges RPh / Carol Holquist RPh
OSE/DRISK	Kimberly Lehrfeld, PharmD / Claudia Manzo PharmD

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 25°C. 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 opioid-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)

General Product Considerations

Drug Substance

As noted in Dr. Jao's review, the drug substance is free base bupivacaine, which has previously approved for injectable products. The manufacturing sites are (b) (4). Dr. Jao notes that the quality and stability of the clinical batches of the drug substance are adequately demonstrated by release and stability data.

Drug Product

The drug product is a sterile, nonpyrogenic, clear, light yellow to amber solution. The target fill weight of each glass vial is (b) (4) mL, and the proposed dose is 5 mL. Each milliliter of Posimir contains bupivacaine 132 mg, benzyl alcohol 242 mg, and sucrose acetate isobutyrate (SAIB) 726 mg, the latter two components being considered novel excipients based on total dose and route of administration and will be discussed further below.

Dr. Jao notes that the proposed commercial manufacturing process adequate in-process and material controls in place and has been optimized and adequately validated. The process includes (b) (4)

The drug product will be packaged in 10 mL USP (b) (4) clear glass vials with 20 mm (b) (4) rubber stoppers coated with (b) (4) and sealed with 20 mm aluminum flip-off crimp seals. Stability data supports an expiration period of 36 months.

Facilities Review/Inspections

The manufacturing sites have been inspected and deemed “Acceptable,” as reported in the Establishment Evaluation System (EES).

Product Quality Microbiology

The proposed sterilization process and sterility controls have been evaluated by Dr. Sweeney, and he has concluded that they are adequate. No microbiology deficiencies were identified.

Specific Issues Identified in the Course of the Review

The following issues were identified by the review team, and resolved satisfactorily:

1. The target fill weight per vial.
2. The experimental conditions of the extractable studies.
3. The evaluation for the possibility of particulate contaminants due to the method of glass vial manufacturing.
4. The potential impact of the significant color change of the solution observed over the proposed 36-month shelf life (from light yellow to amber-brown).
5. The proposed specifications for impurity controls.

Outstanding or Unresolved Issues

I concur with the conclusions reached by Drs. Jao and Peri that the Applicant has provided sufficient information to assure the identity, strength, purity, quality, and batch-to-batch consistency for the commercial product. There are no outstanding or unresolved CMC issues that would preclude approval of this supplement.

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 bupivacaine free base and the degradants (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). 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 bupivacaine 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.

Special Populations

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) $<18.5 \text{ kg/m}^2$ had a lower C_{max} and AUC values than patients with a BMI $>18.5 \text{ kg/m}^2$. 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
<i>Arthroscopic Shoulder Procedure</i>				
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
<i>Inguinal Herniorrhaphy</i>				
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
<i>Major Abdominal/Hysterectomy</i>				
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 AUC₇₂ 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 (RES₇₂), 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

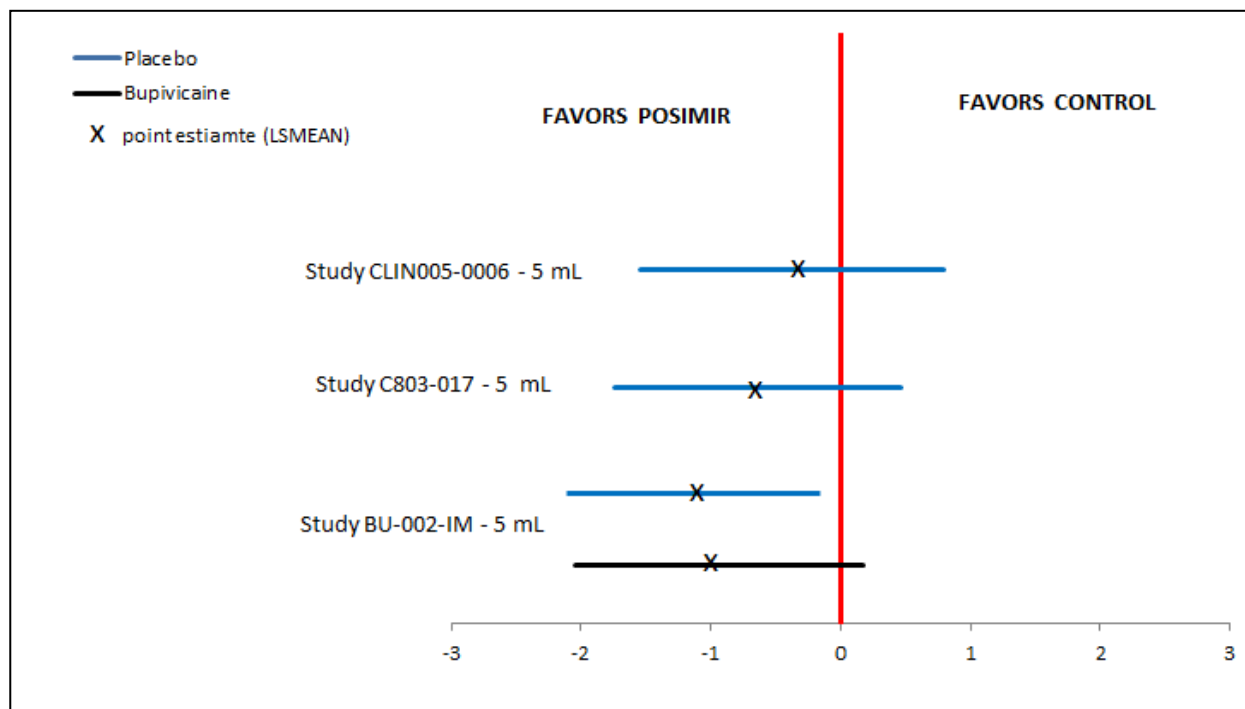
Treatment Group	Morphine Equivalent (mg) mean (stdev)	p-value
SABER-Placebo	22.8 (25.8)	-
SABER-Bupivacaine	13.7 (29.1)	0.01
Bupivacaine HCl	12.3 (17.6)	0.07

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, AUC₇₂ and RES₇₂. 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 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 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 be 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 AUC₇₂ 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, RES₇₂, 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

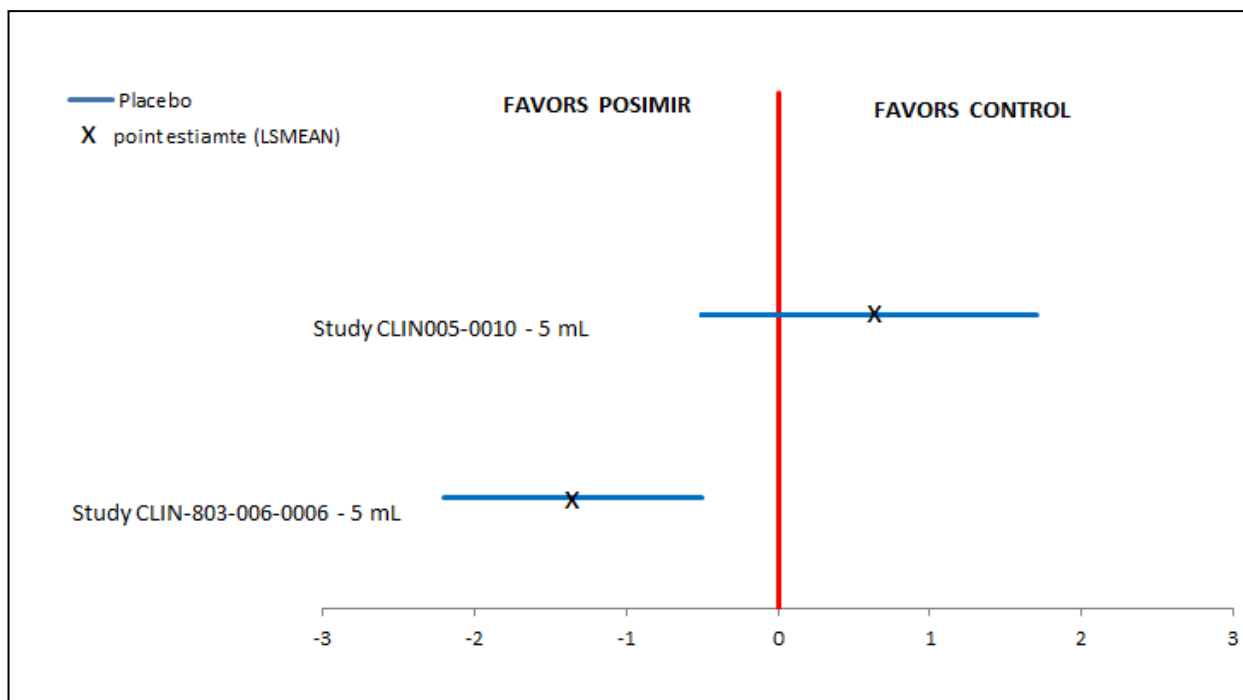
Mr. Petullo also conducted analyses of several secondary endpoints, as well as exploratory analyses to evaluate the extent of the treatment effect. The final conclusion by Mr. Petullo regarding Study CLIN803-006-0006 was as follows, reproduced from his review:

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, or 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, 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 AUC₇₂, 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 RES₇₂ 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 AUC₇₂ and RES₇₂. 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 RES₇₂ 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.

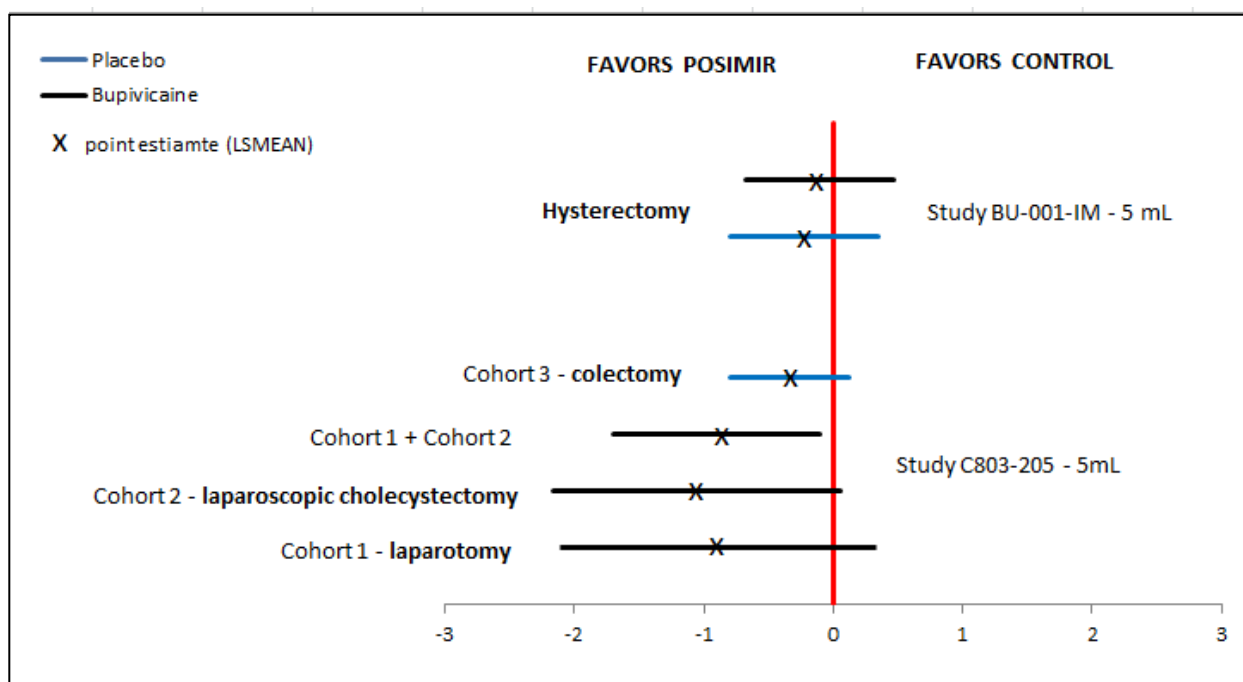
Table 20. Results of applicants' primary analysis from Study C803-025

Cohort	normalized 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

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 AUC₇₂. 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 laparoscopic 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 (DGCP) 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



FDA, Center for Drug Evaluation and Research,
Division of Anesthesia, Analgesia and Addiction Products
HFD-170, 10903 New Hampshire Ave., Silver Spring, MD 20993

**Clinical Review and Evaluation
Amendment to NDA Review**

NDA# (supporting document number):	204803 (019)
Drug Name (generic):	Posimir (SABER-Bupivacaine)
Sponsor:	Durect Corporation
Indication:	Postoperative analgesia
Type of Submission:	Response to Discipline Review Letter
Date of Submission:	February 3, 2014
Project Manager:	Ayanna Augustus, PhD
Reviewer:	Arthur Simone, MD, PhD

Executive Summary

The Applicant has provided responses to each of the two deficiencies identified in the primary clinical review that were shared in a Discipline Review (DR) Letter dated January 14, 2014, and discussed during a teleconference held on January 17, 2014. Based on the information provided, the recommendation for a Complete Response still applies; however, the deficiencies have been modified based on the information provided and a reconsideration of data contained in the original NDA submission. Specifically, the Applicant has provided adequate evidence of efficacy for the use of SABER-bupivacaine following both arthroscopic subacromial decompression and inguinal herniorrhaphy, not arthroscopic subacromial decompression alone. In addition, it is not possible to assert that chondrolysis occurred definitively in any subject in study C803-017e. However, there continues to be inadequate data to characterize risk associated with SABER-containing products both systemically and on tissues and joints near the instillation site. The lack of safety data are the basis for recommending a Complete Response action be taken for this NDA.

Discipline (Clinical) Review Letter

The following issues were shared with the Applicant in the DR letter issued on January 14, 2014:

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.

Applicant's Response to the DR Letter

Deficiency 1

The Applicant's response to the Reviewer's concern for chondrolysis following the administration of SABER-containing products included three points to consider:

1. Neither the Applicant nor any Investigator reported an adverse event specifically labeled as chondrolysis.
2. None of the three subjects for whom the review expressed concern about the possibility of chondrolysis met all three criteria that were used for determining its occurrence.
3. The literature indicates that avoidance of the infusion of bupivacaine into the joint capsule is sufficient to avoid the risk of chondrolysis, and SABER-bupivacaine was not injected into the capsule.

Reviewer's Comments

In this review, the focus was placed on the first two responses as they are most relevant to the use of SABER-bupivacaine following this type of surgical procedure. In this regard, both of the Applicant's statements are accurate. However, there remains a concern that SABER-bupivacaine (or possibly, SABER-containing products) may be associated with adverse reactions to the joint or surrounding tissues, and these reactions may include chondrolysis:

1. Each of the subjects experienced some of the Applicant's criteria for chondrolysis, specifically, limited range of motion and pain with movement. For two subjects, these reactions were severe enough to warrant further surgical intervention. It is possible that these events were unrelated to the study drugs; however, it is not possible to make that determination with any certainty with the data available.

2. One subject ((b) (6)), treated with SABER-bupivacaine) had a biopsy that indicated “mild degenerative changes” to the glenoid cartilage. That subject was determined to have “chondropathy” as a serious adverse event.
3. One subject ((b) (6)), treated with SABER-placebo) had a follow-up MRI scan that suggested progressive chondral deterioration in the 18 months following the original surgical procedure and several months following the second surgical intervention.
4. Only 31 of the 59 subjects who participated in the original study, C803-017, participated in the follow-up study. These 31 subjects were the only ones evaluated for a sufficiently long period to likely capture cases of chondrolysis and possibly other drug reactions that have a long duration to prodrome.
5. There were no subjects treated with a non-SABER placebo to permit assessment of the risk associated with either the benzyl alcohol or SAIB components. Animal data indicated that the SAIB component is present in the surgical wound for up to a year following its instillation and induces a foreign body reaction. Systemic toxicity related to benzyl alcohol has been reported to cause gasping syndrome in infants; it is unknown what effects it may have in adults. The quantity of benzyl alcohol in SABER is substantially greater than that used as a preservative for some injected drugs. For dermal and inhalational exposures in adults, benzyl alcohol has been associated with local tissue irritation.
6. Animal data demonstrate the occurrence of fibrosis and necrosis of joint cartilage for SABER-bupivacaine and SABER-placebo when they are injected into the joint capsule.

Based on the limited available human data, it is not possible to definitively associate SABER-bupivacaine with chondrolysis. However, the limited animal and human data suggest the product may produce adverse reactions within the joint or surrounding tissues. Given the small number of subjects evaluated for an appropriate duration following the administration of SABER-bupivacaine and SABER-placebo, the safety findings in three of those subjects, and the lack of a true placebo for comparison, there is insufficient information available to adequately characterize the risk associated with SABER-bupivacaine when used in this clinical setting.

Deficiency 2

In response to the second deficiency, the Applicant performed the following:

1. They generated new Forest Plot data that differed from the similar data that were presented in the Integrated Summary of Efficacy (ISE) by using a common analysis of scheduled pain AUC0-72 rather than the original analysis from each of the individual trial reports to obtain gives a more consistent assessment of the therapeutic effect.
2. They pooled the two hernia trials and analyzed them with the ANCOVA model.
3. They reanalyzed data from the hernia trial, CLIN005-0010, that did not show evidence of efficacy for the SABER-Bupivacaine treatment group that used the same drug instillation method and a similar placebo-controlled parallel design (Cohort 2) as in study CLIN-803-006-0006, which showed SABER-bupivacaine to

be superior to SABER-placebo. They found that the negative result could be traced to a large imbalance in patient age between the active and placebo groups. In order to correct for this imbalance in age, they reanalyzed the efficacy data using an analysis of covariance (ANCOVA) including treatment as main effect, age as the covariate and the interaction of age and treatment. When the two hernia trials are pooled and analyzed by ANCOVA adjusting for study, treatment as main effect, age as the covariate and the interaction of age and treatment, they found the pooled result for SABER-Bupivacaine to be statistically significant compared to SABER-Placebo.

Based on the post hoc reanalyses of the data, the Applicant concluded that the CLIN005-0010 trial, which was the only trial that did not have a positive treatment effect, should not detract from the evidence of “significant efficacy” in the CLIN803-006-0006 trial. They reiterated that all of the studies in abdominal surgery (BU-001-IM and C803-025) likewise showed evidence of a therapeutic effect. In the post hoc analyses, Study C803-025 Cohort 3 (normalized scheduled pain AUC0-72) and the combined Cohorts 1 and 2 results were statistically significant compared to placebo and active controls, respectively. They also stated that the final evidence for adequacy of efficacy of SABER-Bupivacaine compared to the pooled control (either SABER-Placebo or bupivacaine HCl) was shown by the significant result for all studies combined (All Soft Tissue Surgeries; $p=0.0006$). The original ISE compared SABER-Bupivacaine to SABER-Placebo and was also statistically significant ($p=0.0099$).

Reviewer's Comments

The use of post hoc exploratory analyses is appropriate for Phase 2 studies; however, the use of such analyses to provide proof of efficacy after the protocol-specified statistical analysis plan failed to do so, may not be an appropriate basis for rendering a regulatory decision. However, reliance on such analyses may not be necessary. The Applicant did conduct two controlled studies that demonstrated the efficacy of SABER-bupivacaine following arthroscopic subacromial decompression and inguinal herniorrhaphy. As for the failed inguinal herniorrhaphy study, it could be argued that it was more exploratory in nature than the successful study, and therefore, its results should not be weighed as heavily as those of the successful study for the purposes of making a regulatory decision regarding efficacy. This approach is further supported by the findings from the other trials which trended in the direction favoring the efficacy of SABER-bupivacaine over both SABER-placebo and bupivacaine HCl.

Deficiency 2 (continued)

Regarding the potential risk of SABER-Bupivacaine in non-arthroscopic procedures, the Applicant stated that the adverse event incidence rate between SABER-Bupivacaine and SABER-Placebo compared to bupivacaine HCl, should be based only on trials with a bupivacaine HCl control where the patient population, surgical model, and method of AE ascertainment (for example, use of an opioid AE checklist) are comparable. The Applicant also specifically addressed the incidence of application site discoloration and dehiscence stating the following:

1. As pointed out in the Discipline Review Letter, there is a higher incidence of bruising and hematoma in the SABER-Bupivacaine and SABER-Placebo treatment groups compared to the bupivacaine HCl treatment group. This is clearly due to the SABER formulation and the histology of this finding has been examined in detail in study C803-027. The histology findings are consistent with extravasation and spreading of small amounts of subcutaneous blood. No other pathological findings were observed.
2. The verbatim AE reports of bruising and hematoma were coded to the preferred term of Application Site Discoloration as described in the Integrated Summary of Safety (ISS). The bruising is by definition due to small amounts of subcutaneous blood from the surgical wound. This is a common finding in surgical wounds, but seems to be accentuated by the SABER formulation.
3. The verbatim AEs describing hematoma have been examined in detail. The majority of the cases refer to the initial erythema seen as the earliest manifestation of discoloration, and do not represent true hematomas. Several cases (about 6) did represent true hematomas, usually occurring in the second or third postoperative week, and were treated with aspiration or drainage of the collection of subcutaneous blood associated with the incision.
4. The postoperative bruising is a benign process that completely resolves, without intervention, over a period of weeks with no sequelae or deleterious effects on wound healing or subject outcome. Surgeons were able to differentiate the discoloration from cellulitis or true hematoma.
5. Most of the reported cases of dehiscence AEs were described as partial superficial dehiscence involving just a few subcuticular stitches, usually at the end of the suture line. For midline laparotomy incisions, the open stitches usually occurred at the inferior end of the incision where the abdominal skin is thinner. Most of the reported dehiscence AEs occurred during the 2nd or 3rd postoperative weeks and involved incisions with a median length of about 11 cm. There were two cases of fascial dehiscence and one case of full length superficial dehiscence that required surgical repair (Patient (b) (6) respectively). Among the 18 adverse events of dehiscence in the controlled trial experience, 16 were reported in the C803-025 trial. Study BU-001-IM reported one case and BU-002-IM reported one case. Both cases were small superficial opening of the subcuticular stitches and both were in SABER-Bupivacaine patients.
6. The majority of cases were from the C803-025 trial, which investigated wound healing in three different ways: spontaneously reported adverse events, physical examination of the surgical incisions at days 7 and 14, and a structured wound healing questionnaire administered on day 30. The structured wound questionnaire asked the following question about dehiscence: "Are there any areas of your wound that are opening or not healing together properly?" Cases of dehiscence were ascertained by each of the three methods of wound assessment. Many more cases were ascertained by the day 30 questionnaire than by spontaneous AE reporting. Discounting the cases reported via the structured wound questionnaire makes the apparent imbalance in dehiscence is no longer present. The overall incidence of superficial wound openings was

greatest in long midline incisions of the open laparotomy cases in Cohort 1, and there was no apparent difference between SABER-Bupivacaine and bupivacaine HCl treated patients. The overall rate of superficial subcuticular suture opening in the C803-025 trial is comparable to published rates. The two cases of fascial dehiscence in the C803-025 trial Cohorts 1 and 3 ($2/255 = 0.76\%$) are within the expected rate of 2.8 to 3.4% reported in the literature.

Reviewer's Comments

The pooling of the safety data as done in the original clinical review of the NDA was appropriate. While the Applicant is correct in stating that the surgical procedures differed and the protocols varied in the methods used to collect adverse event data, the trials were all double-blinded and randomized. Therefore, the overall differences observed for the treatment groups should depend on the treatment rather than differences in trial design and patient populations, provided the same treatments were utilized in all of the trials. While not all of the trials utilized all of the treatments, all treatments were utilized in at least one of the trials involving each type of surgical procedure, i.e. shoulder, hernia, abdominal/pelvic surgeries. The intermittent use of bupivacaine HCl and SABER-placebo may pose some limitation on the extent to which the pooled data can be relied upon to characterize the safety profile for SABER-bupivacaine; however, given the standardization of the SABER-bupivacaine dose, the argument can be made that systemic exposures to the product's components are likely to be similar regardless of surgical procedure (as the Applicant demonstrated for the bupivacaine component) and that the effects of the treatments on the local tissues are not likely to vary from one surgical site to another, i.e., there is no physiological or surgical basis for hematoma formation or wound dehiscence to occur more frequently with hernia repair compared to hysterectomy or colectomy or arthroscopic shoulder surgery. Thus, the concerns raised in the review of the original NDA submission still apply, both for the local tissue reactions and the system reactions.

The limited use of bupivacaine HCl as a comparator and the lack of a non-SABER placebo throughout the clinical development program greatly limit the ability to discern adverse events that arise due to the SABER components of the product. The need for a non-SABER placebo comparator was raised with the Applicant on several occasions, most notably in the response to their request for a special protocol assessment prior to the initiation of their pivotal shoulder surgery trial and their Phase 3 study. Yet even with the limited data available, there are clear differences between treatment groups that were observed where the risk appears to be associated with the SABER component of the product. This was most notable in the evaluation for evidence of neurotoxicity. There appeared to be no difference between SABER-bupivacaine and SABER-placebo, indicating there was no toxicity related to bupivacaine exposures; however, there were substantial differences between SABER treatments and bupivacaine HCl treatments, indicating an adverse reaction to the SABER component, as shown in the table below.

Table 1. Adverse events related to neurotoxicity

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%

Conclusions

Based on the reconsideration of the efficacy data in the original NDA submission and a review of the Applicant's responses to the DR letter, the following conclusions were drawn regarding the efficacy and safety of SABER-bupivacaine:

1. The product has been demonstrated to be efficacious compared to SABER-placebo for arthroscopic subacromial decompression and inguinal herniorrhaphy surgeries. Additional evidence of efficacy for these two procedures is not necessary.
2. The safety profile of SABER-bupivacaine has not been adequately characterized to permit a benefit:risk assessment. Specifically, the following deficiencies exist:
 - a. There were adverse events related to the shoulder joint and surrounding tissues in subjects who underwent follow-up assessments 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 if 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 if 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 what clinical impact these reactions have, e.g., whether they delayed discharge from the post-anesthesia care unit or affected time to ambulation.

Recommended Text for the Complete Response Letter

Deficiencies:

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 $\geq 1\%$. 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 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 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 recommend that you discuss the design of this study with the Division prior to implementation.

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/s/

ARTHUR F SIMONE

02/12/2014

CHRISTOPHER D BREDER

02/12/2014

Cross-Discipline Team Leader Review
Division of Anesthesia, Analgesia, and Addiction Products

Date	January 22, 2014
From	Christopher D. Breder, MD PhD Clinical Team Leader, Anesthetic Drugs Division of Anesthesia, Analgesia, and Anesthetic Drugs (DAAAP)
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supp #	204803 / 1
Proprietary / Established (USAN) names	Posimir® (Bupivacaine)
Dosage forms / strength	660 mg bupivacaine/5 mL (132 mg bupivacaine/mL), 13.2% solution, for instillation
Proposed Indication(s)	Post-surgical analgesia
Recommended:	Complete Response

1. Introduction to Review

The Applicant, Durect Corporation, submitted an NDA under 505 (b)(2) on April 12, 2013 for Posimir® (“SABER-bupivacaine”) with the claim of it being an extended-release solution of bupivacaine for postoperative analgesia. 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% (b) (4) to provide for reducing viscosity on initial instillation and sucrose acetate isobutyrate ((SAIB) 66% (b) (4) for the formation of a depot matrix for the extended release of bupivacaine.

This review will summarize the major findings of the discipline team reviews, focusing on issues relating to efficacy and safety. The efficacy portion, which is primarily derived from the primary Clinical and Statistical reviews, focuses on issues of the magnitude of the drug effect and the robustness of the single trials in each of the orthopedic and inguinal herniorrhaphy post-operative pain models. The safety portion of this review is derived from all of the primary reviews and the Pharmacology / Toxicology (“Pharm / Tox”) Supervisory review. The safety issues described in my review include the following general topics:

1. Systemic Effects potentially related to
 - a. Bupivacaine toxicity
 - b. Benzyl alcohol toxicity
2. Local effects of the drug product and its components on
 - a. Surgical wound healing, including
 - Long term presence and effects of the drug
 - Adverse effects at the surgical incision, e.g., erythema, edema, infection

- Risks associated with perineural administration
- b. The risk for chondrolysis

In the final section of my review, I will provide an integrated risk: benefit analysis that serves as the basis for my recommendation of a Complete Response.

2. Background

2.1. Regulatory History

The information in the Regulatory Background was extracted from the Clinical Review of Dr. Simone and supplemented with further detail as described in my review.

The Sponsor (now Applicant) opened IND 066086 on October 23, 2002 with a formulation that contained (b) (4) with carcinogenic potential. A prototype formulation of SABER-bupivacaine was used in a single clinical trial (SABER01-01) conducted in 2003. The formulation contained (b) (4) bupivacaine base, (b) (4), and (b) (4) sucrose acetate isobutyrate (SAIB) on a % w/w basis. The product was administered by subcutaneous (SC) injection using doses of 2.5 and 5 mL. The Applicant remarked that the study findings indicated the product did not produce any consistent analgesia, so a new formulation was developed. This new formulation contained a higher amount of bupivacaine base (12% w/w) and the solvent was changed to benzyl alcohol (BA¹) (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.

Several meetings were held with the Applicant discussing issues germane to topics in my review of the current application and primary reviews; these are noted below and discussed in further detail in my review, including the risk:benefit in Section 13.1:

- December 27, 2006 –The Sponsor proposed to conduct two Phase 3 studies in support of an NDA submission and to provide the required safety data.
- September 14, 2007 – End-of-Phase 2 meeting
 - 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.
 - 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.
 - The Applicant’s 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.

¹ The abbreviation BA is used throughout this review to represent “benzyl alcohol” and not ever to mean “bioavailability”

- The NDA application should address the safety of the novel use of both benzyl alcohol and SAIB in this product.
- March 10, 2008 – 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.
- August 1, 2008 – Request for a Special Protocol Assessment (SPA)
 - 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.
 - 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.²
 - 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.
- July 31, 2012 – pre-NDA Meeting
 - Only one adequate and well-controlled trial would be acceptable if the results of the trial were robust and able to withstand sensitivity analyses. 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. CMC/Microbiology

The information in the CMC/Microbiology section was extracted from the reviews of Drs. Jao and Sweeney unless noted.

3.1. General product quality considerations

The drug product Posimir is a sterile nonpyrogenic, clear, light yellow to amber solution of bupivacaine for instillation into surgical incision. The target fill weight of each glass vial is (b) (4)

² In the clinical program, the SABER vehicle or a bupivacaine arm were included in studies instead of a true placebo comparator. A saline comparator was included in some of the nonclinical studies. In this review, the term “placebo” represents the SABER-placebo or vehicle of SABER-bupivacaine unless specifically noted.

mL, and the dose is 5 mL. Each mL of Posimir contains bupivacaine 132 mg, BA 242 mg, and SAIB 726 mg. Upon administration, the BA is supposed to quickly diffuse away from the other components, resulting in the in-situ formation of an extended-release biodegradable gel like matrix which slowly releases the bupivacaine through diffusion over 72 hours.

The excipients used in the formulation are benzyl alcohol (BA) and sucrose acetate isobutyrate (SAIB). BA is USP grade. SAIB is a fully esterified sugar derivative, listed in 21 CFR 172.833 for direct food additive. It is used as a stabilizer of emulsions of flavoring oils in nonalcoholic beverages. However, it has not been used in approved drug products, and therefore is a novel excipient. DMF (b) (4) are incorporated by reference for the CMC information of SAIB. Both DMF are considered adequate to support this NDA. The drug product is manufactured by (b) (4). This establishment has received an acceptable recommendation from the Office of Compliance.

From a Microbiology perspective, the following comments on the application were made:

- The microbiological quality acceptance criteria comply with those specified by USP <1111> for non-sterile substances for pharmaceutical use.
- The manufacturing and sterilization processes and process controls were sufficiently described for the reviewer to assess the manufacturing and sterilization processes, and to determine which processes needed validation or requalification data for Section P.3.5 Process Validation and/or Evaluation.
- Validation/requalification studies and results were consistent with those delineated in the FDA Guidances for Industry (1) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, and (2) (b) (4) — Current Good Manufacturing Practice, as well as common industry practice.
- The drug product specification (sterility and bacterial endotoxins testing) and validations comply with USP <1> Injections, <71> Sterility Test, and <85> Bacterial Endotoxins Test, as well as FDA Guidance for Industry: Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.
- The submitted stability protocol, commitment and data comply with Guidances for Industry: (1) Q1A(R2) Stability Testing of New Drug Substances and Products, and (2) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.

3.1.1. Facilities review/inspection

At the time of this review, the facilities inspections were not completed.

3.2. Other notable issues (resolved or outstanding)

The following critical issues were identified in the application, and resolved satisfactorily according to the CMC review:

- The original target fill weight per vial was (b) (4) process variability. This represents (b) (4) of overfill at the upper limit, and much higher than the USP recommended 10% surplus for viscous liquid for injection. This amount of overfill raised safety concerns from clinical team. In response to the Agency's comments, the applicant has reduced the fill weight to an acceptable (b) (4). The clinical evaluation of this issue is included in Section 7.2.5 of my review.
- The original controlled extractable studies were conducted at room temperature. Given the high BA content in the drug product formulation (22%), the extraction conditions were not considered vigorous enough to assure all extractables reach their asymptotic levels. In addition, (b) (4) were not tested. Upon request by the Agency, another controlled extractable study was conducted using reflux conditions. More extractables were identified, and leachable data were reexamined against the new extractable profile. (b) (4) were not detected in this vigorous extraction stopper study. The Pharm/Tox team conducted a safety evaluation of the leachables and found no safety concerns. Dr. Jao commented that it would be acceptable to conduct routine testing for leachables for commercial batches.
- During the review cycle, another form of bupivacaine injection drug product was recalled due to observation of particulate contamination presumably as a result of contamination of the glass vials manufactured by (b) (4). In response to the Agency's inquiry, the applicant stated that only (b) (4) vials from the supplier were affected and the applicant confirmed that only (b) (4) vials will be used for the commercial Posimir product. A risk assessment was conducted and it was concluded that this potential risk can be adequately managed under the applicant's internal quality system.
- Posimir changes color from light yellow to brown (amber) over its proposed 36 month shelf life. The color change has been noted in all manufactured product lots. An investigation was undertaken and the proposed mechanism of bupivacaine catalyzed caramelization of the excipient SAIB was proposed as the root cause for the coloration of the drug product. The Pharm/Tox team concurred with the applicant's safety evaluation for the dark colored drug product. Therefore, the proposed acceptance criterion of (b) (4) for the degree of coloration of the drug product during shelf life is acceptable.
- The Pharm / Tox team concurred with the applicant's justification for impurity controls from the safety perspective, except that the criterion of no more than (NMT) (b) (4) for (b) (4) not being supported by local toxicity data (see Section 4.4 of my review). This acceptance criterion needed to be reduced to NMT (b) (4) per the Pharm/Tox team's recommendation. This was conveyed to the applicant in a teleconference on 1/7/2014, wherein the applicant agreed to tighten it to NMT (b) (4). Release data from eight batches of primary and supportive ICH batches, which were manufactured by the commercial process, met the proposed specification. The applicant has provided 36 months of long term stability data to support the proposed shelf life of 36 months. All stability data, including data from the

primary, supportive, and additional supportive batches met the specification, and the requested shelf life is granted.

Recommendation and Conclusion on Approvability

ONDQA

From the ONDQA perspective, this NDA is recommended for approval, pending on the final recommendation from the Office of compliance and agreement on the recommendations for the labeling.

Microbiology

Recommended for approval

Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

ONDQA

No

Microbiology

N/A

4. Nonclinical Pharmacology/Toxicology

The information in the Nonclinical Pharmacology / Toxicology section was extracted from the reviews of Drs. Bond (primary Pharm / Tox reviewer) and Wasserman (supervisory Pharm / Tox reviewer) unless noted.

4.1. General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

The issues raised by the nonclinical Pharm / Tox reviews of the primary reviewer, The primary Pharm / Tox reviewer and supervisory reviews were generally organized into descriptions of the systemic and local effects of Posimir.

Systemic toxicity

Bupivacaine toxicity

Several nonclinical studies described by the primary Pharm / Tox reviewer characterized the toxicity of SABER-bupivacaine and corresponding plasma levels of bupivacaine (see especially the toxicokinetic data in Section 5.2 of the primary Pharm / Tox review). The objective of this part of the nonclinical program was to characterize the toxicokinetics and associated clinical signs associated with exposure to bupivacaine from the drug product since the bupivacaine exposure from Posimir is greater than the expected exposure from the dose of

Marcaïn used for the same clinical scenario. According to the review of the supervisory Pharm / Tox reviewer, "...The submitted studies of single dose subcutaneous administration of SABER-bupivacaine in both rat and rabbit models provided exposures that, in the absence of clear nonclinical systemic toxicity (i.e. systemic NOAEL), exceed those achieved in the clinical trials. Therefore, the nonclinical data support the systemic safety of SABER-bupivacaine for use as proposed, though we note that clinical levels achieved are variable and may range to levels associated with clinical signs of toxicity."

Hemolysis

Since effects of the drug on blood cells are most likely to manifest as the drug spreads from the local to systemic body compartment, this issue is described in my discussion of 'systemic effects.' The primary Pharm / Tox reviewer described an in vitro study 01-11-803-X-VO-ATX where hemolysis and plasma compatibility were evaluated for several test articles were incubated in human blood. The test articles were the following:

- Test group 1 – SABER-bupivacaine
- Test group 2 – SABER placebo
- Test group 3 – SAIB
- Test group 4 – Sensorcaine (bupivacaine HCl)
- Test group 5 – 0.9% sodium chloride

SABER-bupivacaine and SABER-bupivacaine vehicle both caused hemolysis when added to human whole blood and resulted in a viscous (and, for the vehicle, cloudy) macroscopic appearance, with globules resembling bubbles visible microscopically, when added to human plasma. The primary Pharm / Tox reviewer hypothesized that the benzyl alcohol component of SABER-bupivacaine and SABER placebo may be involved in the hemolysis as bupivacaine and SAIB alone did not cause hemolysis.

The primary Clinical review noted a transient decrease in red blood cell counts in all treatment arms postoperatively which corrected after only a few days, so this signal does not appear to have significant clinical consequences.

Benzyl alcohol content

BA is an aromatic alcohol used in a variety of cosmetic formulations as a fragrance component, preservative, solvent, and viscosity-reducing agent. BA is also approved as a food additive. The primary Pharm / Tox reviewer commented that the safety database for BA is extensive and includes acute, subchronic, and chronic toxicity studies, carcinogenicity bioassays, genotoxicity assays, and reproductive/developmental toxicity studies. The primary Pharm / Tox reviewer also provided reference to the finding that no adverse effects of BA were seen in chronic (up to 2 years) exposure animal studies using rats and mice.

The proposed single subcutaneous dose for SABER-bupivacaine is ~20-25 mg/kg for a 50-60 kg human body weight range at 22% BA. At the Maximum Recommended Human Dose

(MRHD) for SABER-bupivacaine of 5 mL/person, the dose of BA would be 1.21 grams (5.5 grams times 22% or 242 mg/mL x 5 mL). The primary Pharm / Tox reviewer's review of currently approved drugs revealed that an approved parenteral product marketed as FASLODEX (NDA 21344 – 50 mg/mL) contains 10% BA (w/v) and is approved for intramuscular (IM) injection at a dose volume of 10 mL/person. Therefore, the approved dose of BA for FASLODEX is 1.0 gram/person, which is only slightly lower than the dose of BA from SABER-bupivacaine. Considering that the approved FASLODEX dosing is every 2 weeks for three doses then monthly, the level of BA in SABER-bupivacaine was considered by the primary Pharm / Tox reviewer as acceptable and supported for human safety as a single dose. The supervisory Pharm / Tox reviewer concurred the usage of Falsodex generally covers the usage of Posimir and provides some assurance of local, as well as systemic, safety

Local toxicity

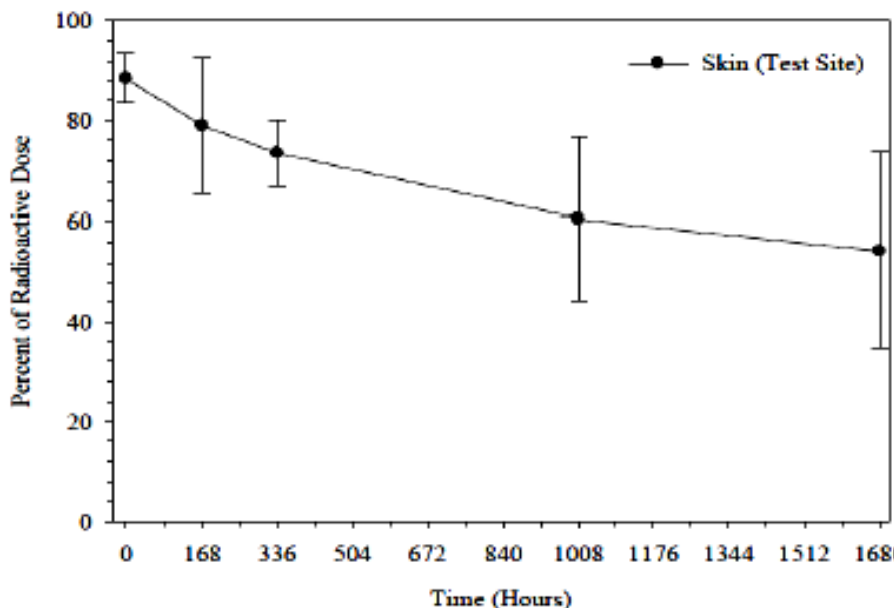
Persistence of SAIB for long-term in the injection site

The primary Pharm / Tox reviewer noted reports of the persistence of depot material in several nonclinical studies in this application.

In a study in of SC injection of SAIB in rats (Study 7116-109) 61% of SAIB radiolabel largely remains at the dose site past 6 weeks after dosing. Histological evaluation of the SC dosing site at 1 week after dosing identified subacute inflammation, characterized by slight to moderate lymphohistiocytic infiltrates and reactive fibrosis with or without aggregates of fibrin. At 2 weeks, subacute to chronic inflammation with slight lymphohistiocytic infiltrates, reactive fibroplasia, and fibrosis were observed. At 4 and 6 weeks, the SC dosing sites were surrounded by chronic inflammation, characterized by fibrosis and minimal lymphohistiocytic inflammation. Reversibility was not evident while inflammation persisted with severity similar at 4 and 6 weeks after dosing. It was noteworthy, to this reviewer that this magnitude of inflammatory effects was being described in the setting of a subcutaneous injection versus being used in the setting of an actual surgical wound, which would add additional inflammatory pathology.

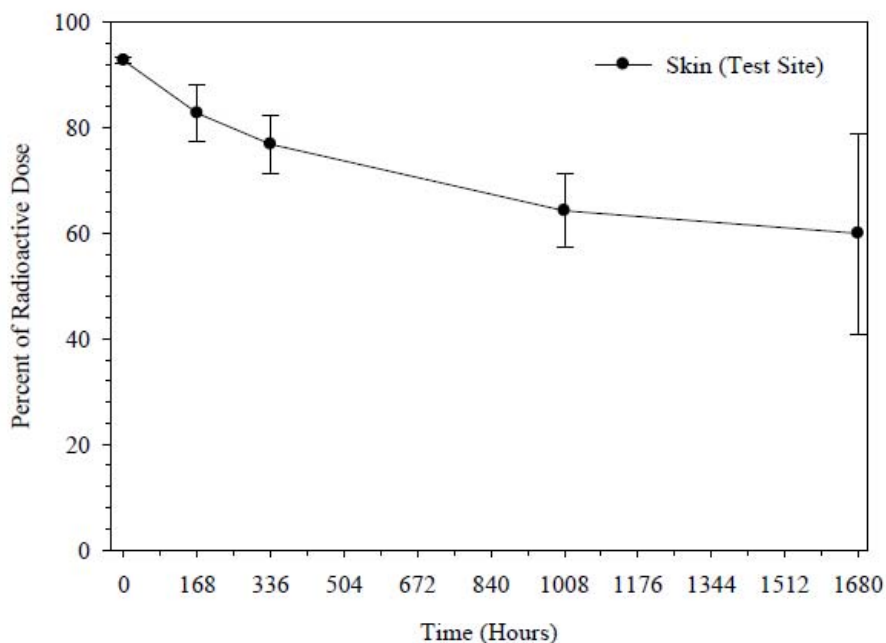
In Study 8255730, SAIB, as 440 mg/kg dose ¹⁴C-SAIB/BA, was applied to a surgical wound or injected SC. The mean percentage of dose remaining in the skin and subcutaneous tissues were 54 and 60% in the surgical wound and by the subcutaneous route, respectively, at 70 days post-administration. The following figures show the time course of SAIB disposition in this study.

Figure 1 Mean percent of radioactive dose in skin and subcutaneous tissues after a single surgical wound injection of ^{14}C -SAIB in rats



Source: p 45 of the primary Pharm / Tox reviewer's review

Figure 2 Mean percent of radioactive dose in skin and subcutaneous tissues after a single subcutaneous injection of ^{14}C -SAIB in rats



Source: p 46 of the primary Pharm / Tox reviewer's review

Since the drug product (presumably only the SAIB depot component) remained for a long time at the site of administration, the long term toxicity study (b) (4)-434007 titled

A repeated histopathological injection site evaluation up to 12 months following a single subcutaneous administration of SABER-bupivacaine in the rabbit

is particularly important in evaluating the safety of this drug product. This was a study performed in rabbits, 21 males/treatment group³ (placebo or SABER-bupivacaine). The test article in this study used the formulation with (b) (4), rather than BA as a vehicle. The primary Pharm / Tox review remarked that single doses of SABER-bupivacaine did not result in test article-related injection site reactions up to 52 weeks post-injection. 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 (i.e., local effects SABER-bupivacaine comparable to those of SABER placebo). Because of the inherent toxicity of the SABER-placebo, a more relevant comparator would have been saline.

SAIB was found to be essentially unchanged and still present 12 months after injection; essentially no (b) (4) was present ((b) (4)%) at that time. At 52 weeks, several observations are presented here as examples of the pathology at the injection site. The primary Pharm / Tox review includes a more detailed description.

- Fibrosis, severe in 1 of 3 placebo animals
- Epidermal ulceration was present at 2 weeks (1 of 3 placebo and 3 of 3 article-treated animals) and 4 weeks (2 of 3 article-treated animals) post-injection evaluations),
- Full-thickness epidermal necrosis was present in three of these animals (1/3 males in the placebo group and 2/3 males in the 37.5 mg/kg group),
- All animals with ulcerative and necrotic lesions had spaces in the epidermis, dermis and/or subcutis, suggesting that the presence of ulcers may have been related to local irritation and self-trauma
- Variably sized, discrete ovoid spaces, interpreted as the site of placebo or test article deposition, were noted in skin sections of all animals at all post-injection evaluations. Spaces were surrounded by thin bands of fibrous connective tissue and variable numbers of inflammatory cells. As the months progressed, the fibrous connective tissue surrounding the spaces tended to thicken.
- Granulomatous inflammation was present in animals throughout the study but decreased in severity and incidence as the months progressed.
- Dermal fibrosis was present in several animals at all post-injection evaluations from 4 to 52 weeks following dose administration and was characterized by abundant mature collagen, often with a marked reduction in adnexal structures.

³ Test article – (b) (4) bupivacaine, (b) (4) and (b) (4) Sucrose Acetate Isobutyrate (SAIB); Placebo – (b) (4) and 70% SAIB

- Minimal to moderate degeneration and regeneration of the panniculus muscle adjacent to spaces was present in some animals through the 6-week post-injection and in one animal at the 52-week post-injection evaluation.

These findings are concerning, not only because of the persistence or duration of effects but also because, as I noted with Study 7116-109, these toxicities emanated from subcutaneous injections and were not the pathological results of surgery or wound healing, in the classic sense of the phrase.

The primary Pharm / Tox reviewer comments that other injectable depots (e.g., Risperdal Consta, Eligard, Lupron depot, and Zoladex) have associated foreign body reactions and remarks that the relevance of this nonclinical data to human safety is to be determined by the medical review team in conjunction with consideration of the overall human benefit of the proposed drug. His reporting of such cases of precedence is valuable but each foreign body reaction must be considered in terms of the magnitude of the adverse effect and the benefit gained by implanting drug product. For example, Risperdal Consta is a depot injected because patients with schizophrenia are not well compliant with their oral medication regimen and the outcome of being noncompliant is relapse. The benefit of a similar foreign body reaction would be less justified for Posimir, considering the incremental improvement in analgesia.

He further notes that (b) (4), the test article solvent in this study that is not present in the proposed drug product, has been reported to cause reactions similar to those described in this study, so the design (from the perspective of the test products) of this study is not optimal for assessing this critical issue.

Orthopedic considerations

Several studies described by the primary Pharm / Tox reviewer compared intraarticular (IA) injection of drug product and SABER-placebo. Synovial hyperplasia, fatty degeneration, inflammation, fibrosis, and osseous metaplasia were the microscopic lesions observed in the stifle joints of rabbits treated with SABER placebo or SABER-bupivacaine. An increased incidence and severity were observed in the SABER-bupivacaine group suggesting a bupivacaine component of the observed histopathology. 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. In summary, The primary Pharm / Tox reviewer noted that there is potential for progressive joint necrosis after IA administration of SABER-bupivacaine which may be due to the vehicle (SABER placebo) with some enhancement of the severity by the presence of the bupivacaine.

While the intraarticular route is not being proposed by the Applicant, there is a risk of effects within the joint that is discussed in my review (Section 7.25)

Perineural toxicity

A single-dose toxicity study (022-010) with peri-sciatic nerve administration of bupivacaine solutions, pastes, or solids (including SABER-bupivacaine) in the Sprague Dawley rat followed by a 7-day recovery period. Local administration of SABER-bupivacaine as a single injection at a dose of 48 mg followed by a seven day recovery period resulted in an increased frequency of neuronal inflammation and axonal degeneration compared to untreated (right leg), saline treated, or Sensorcaine® treated groups. This effect appeared to result from both the presence of the vehicle, as well as the bupivacaine, since the frequency and/or severity of axonal changes showed incremental increases from control (right leg), to saline, to Sensorcaine®, to bupivacaine-treated groups. In addition, the dosage form appeared to play a role with the greatest neuronal inflammation and axonal degeneration occurring in the solution administration group. Inflammation within the intermuscular fasciae and perineural connective tissues and myofiber degeneration and regeneration also showed incremental increases in frequency and severity between the untreated control (right leg), vehicle, and test article groups. In contrast, these extra-neural changes were less frequent and severe compared to the paste/solid forms. While this has been described in other studies in this nonclinical program as an anticipated foreign body reaction due to the SAIB, the bupivacaine combined with SAIB and BA (SABER-bupivacaine) appears to contribute to a greater local reaction.

Wound healing

Studies in rat and mini-pig models of wound healing suggested SAIB-based formulations had no adverse effect on wound strength but were associated with histological inflammatory effects.

4.2. Carcinogenicity

For the pharmacological active ingredient, bupivacaine, a 505(b)(2) reference is made to the approved Marcaine (bupivacaine hydrochloride - NDA 16-964) label for carcinogenicity data for bupivacaine. No other carcinogenicity studies were conducted.

Genotoxicity studies (Reverse Mutation Assay and Chromosomal Aberrations Study of Bupivacaine Free Base, (b) (4) and In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay) of 12% SABER-bupivacaine and SABER-placebo) were negative (no signal of mutagenicity or clastogenicity)

4.3. Reproductive toxicology

Reproductive and Developmental Toxicology

For the pharmacological active ingredient, bupivacaine, a 505(b)(2) reference is made to the approved Marcaine (bupivacaine hydrochloride - NDA 16-964) label for reproductive and developmental toxicology data for bupivacaine. The listed embryonic fetal development study 11-11-803-R-SC-TT reviewed by the primary Pharm / Tox reviewer is an assessment of SABER placebo (no active ingredient). There was no increase in embryo lethality, no effect on

fetal body weight, and no fetal alterations (malformations or variations) attributed to SABER placebo at any dose tested.

No Prenatal and Postnatal Development studies were conducted.

The distribution and quantification of BA in selected tissues of the rat over time and the excretion of radioactivity into the milk of lactating rats after subcutaneous (SC) administration of SABER-bupivacaine containing [14C]-labeled BA was evaluated in Study RPOS/FKM/204. Excretion of radioactivity into the milk showed a maximum 4h after suckling with concentrations of radioactivity in plasma of dams and pups increased with increasing dose, with peaks being generally attained 1 h after subcutaneous dosing in milk. With respect to the human relevance of this observation, assuming 100% oral absorption of BA in human neonates after suckling, at the lower 5% level for birth weights (~1 kg), the neonate dose would be 5 mg/kg (0.4% of the administered dose). On this basis, the neonate risk to BA toxicity at least 20-fold below the observed effects level with the assumption for 100% oral absorption of BA which is not likely. The actual human toxicological relevance of this is unknown but available data suggest that a single dose of SABER-bupivacaine presents minimal risk of neonatal toxicity through suckling. I agree with this opinion from the Pharm / Tox team, particularly considering the decreased likelihood of patient's nursing in the immediate post-operative period.

4.4. Other notable issues (*resolved or outstanding*)

Degradation of the drug product

The review team was concerned about the increasing darkness of the drug product solution over time (see Dr. Jao's discussion of this issue from a CMC perspective. A 4-week, repeat dose study with "aged, yellow" SABER-bupivacaine was considered adequate to support the proposed drug product specifications and satisfy repeat dosed testing for reformulated drug products.

Degradants and leachables

Specifications for [REDACTED] (b) (4) were considered adequate.

[REDACTED] (b) (4) is a potentially genotoxic/carcinogenic degradant. The specification was (b) (4) ppm. At this level and at the anticipated MRHD of 5 mL/person of SABER-bupivacaine, the dose of (b) (4) would slightly exceed the maximum dose of (b) (4) /person/day specified in the FDA Draft Guidance document for Genotoxic Impurities (December, 2008). The maximum anticipated human dose would be (b) (4) mcg/person/day vs. the recommended maximum dose of (b) (4) mcg/person/day for one day only. This was determined to be acceptable since the drug product was to be administered in single doses.

The specification for (b) (4) was NMT (b) (4)% but following a teleconference with the Applicant is now NMT (b) (4)% (see my discussion of this issue from Dr. Jao's review). In the 4 week dosing study in rats using aged drug product containing (b) (4), no toxicity was observed at the highest dose tested. Considering negative in vitro genotoxicity results with (b) (4) and that dosing with SABER-bupivacaine will be a single dose, NMT (b) (4)% is considered an adequate specification for potential systemic and local toxicity.

Recommendation and Conclusion on Approvability

The primary Pharm Tox reviewer recommended NDA approval from the nonclinical perspective. He noted that local toxicity persists after a single instillation of SABER-bupivacaine which requires clinical review team acceptance of the observed, anticipated local toxicity (foreign body reaction). He further noted that while systemic exposure to bupivacaine after dosing with SABER-bupivacaine exceeded levels reported for the approved, referenced drug Marcaine, the submitted nonclinical data supports human safety at the proposed dosing for SABER-bupivacaine.

The Pharm / Tox supervisor does not recommend approval based solely on the nonclinical information provided. He remarked that, overall, the systemic safety and drug product quality issues appear to be addressed and the nonclinical program appears broadly sufficient. However, "...the product itself is not toxicologically neutral with instillation to wound sites and this effect appears to be maintained for weeks at minimum and perhaps months, a situation which is not observed with immediate release bupivacaine and which far exceeds the intended pharmacologic benefit of SABER-bupivacaine."

Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The primary reviewer did not have any recommendations for Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps. The Supervisory review had the following comment:

Despite my concerns with some aspects of the design of the nonclinical studies submitted to support the NDA, should this application receive a Complete Response I do not believe additional nonclinical studies are warranted as the data obtained would be unlikely to alter my recommendation or greatly inform the clinical program beyond our current understanding.

5. Clinical Pharmacology/Biopharmaceutics

The information in the Clinical Pharmacology/Biopharmaceutics section was extracted from the reviews of Drs. David Lee and Okpo Eradir unless noted.

Ten studies were submitted in the NDA that were considered for clinical pharmacology review (see Table 1 of the primary Clinical Pharmacology review).

5.1. General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

Study BU-001-IM assessed the relative bioavailability of Posimir compared to Marcain. The individual curves from Posimir administration indicated that systemic bupivacaine concentrations may last until 72 hours post administration. Bupivacaine mean C_{max} value from Posimir (660 mg bupivacaine) was 625 ng/mL compared to 342 ng/mL with a typical dose of Marcain (100 mg) used in the same clinical scenario. Bupivacaine mean AUC value Posimir (660 mg bupivacaine) was 36830 ng.h/mL compared to 5740 ng.h/mL with Marcain (100 mg). Bupivacaine C_{max} and AUC values from the 2.5 and 5.0 mL Posimir exhibited linear pharmacokinetics.

5.2. Drug-drug interactions

No drug interaction studies were submitted. This is a 505(b)(2) application and the Applicant will rely upon Marcain Label.

5.3. Pathway of Elimination

Amide-type local anesthetics such as bupivacaine are metabolized primarily in the liver via conjugation with glucuronic acid. Pipecolylxylylidine (PPX) is the major metabolite of bupivacaine; approximately 5% of bupivacaine is converted to PPX. Elimination of drug depends largely upon the availability of plasma protein binding sites in the circulation to carry it to the liver where it is metabolized.

Benzyl alcohol

While the pharmacokinetic disposition of benzyl alcohol was not studied in detail in this program, Study BU-001-IM⁴, a study of post-operative pain in the abdominal hysterectomy surgical model provided bioavailability data on BA. BA reached maximum plasma concentrations at the first measuring point (1 hour), and decreased very rapidly ($t^{1/2}$ 4.73 hrs according to the table on p. 115 of the primary Clinical Pharmacology review) and by 24 hours post-dose individual benzyl alcohol plasma concentrations were either below or close to the lower limit of quantitation (5 ng/mL).

5.4. Demographic interactions/special populations

⁴ (2:1:1 ratio): a) 5.0 mL SABER-bupivacaine (132 mg/mL; 660 mg bupivacaine) instillation; b) 5.0 mL SABER-placebo instillation; and c) 40 mL standard bupivacaine hydrochloride (HCl) (100 mg bupivacaine) infiltration (commercially available bupivacaine solution 2.5 mg/ml (Marcain®; AstraZeneca)).

The following information on and recommendations for labeling regarding demographic interactions and special populations were provided in the primary Clinical Pharmacology review.

Age

Mean bupivacaine C_{max} and AUC values from Trial C803-025 indicated that both C_{max} and AUC values lower in younger patients (< 45 yr) than older patients (45 – 65 years and > 65 years), which appears reasonable since elderly may have lower renal function and bupivacaine is known to be excreted by the kidney. T_{max} was earlier in younger patients than older patients in the study. Considering this is a local acting drug and the variability (values overlap between younger and older patients), the observed differences between younger and older patients do not warrant dose adjustments.

Gender

Mean bupivacaine C_{max} and AUC values from Trial C803-025 indicated that male patients had lower C_{max} and AUC values than compared to the female patients. However, considering this is a local acting drug and the variability (values overlap between male and female patients), the observed differences between male and female patients do not warrant dose adjustments.

BMI

Mean bupivacaine C_{max} and AUC values from Trial C803-025 indicated that patients with BMI <18.5 kg/m had lower C_{max} and AUC values than patients with BMI >18.5 kg/m. However, considering this is a local acting drug and the variability (values overlap between male and female patients), the observed differences between male and female patients do not warrant dose adjustments.

Renal and hepatic impairment

No specific studies were conducted to evaluate the bupivacaine pharmacokinetics in special populations such as hepatic and renal impairments. In general, since bupivacaine is metabolized by the liver, Posimir should be used cautiously in patients with hepatic impairment. With respect to renal impairment, bupivacaine is known to be excreted by the kidney. Accordingly, Posimir should be used cautiously in patients with renal impairment.

Surgical populations

The following table (**Table 1**) was provided by the primary Clinical Pharmacology review to demonstrate the variability in C_{max} and AUC for bupivacaine in the different surgical models in this application. The following remark from the supervisory Pharm / Tox review is useful to consider when considering the risks present in the different surgical models

The acute systemic toxicity of bupivacaine is well known and has been generally thought to arise with serum concentrations in excess of 1000 ng/mL, with reports considering 2000-4000 ng/mL to be the range of clinical toxicity (Tucker 1986).

From my perspective, the upper limits of the Cmax ranges (Cmax range UL)⁵ were, with the exception those from two of the abdominal surgery studies, below 2000 ng/ml with abdominal procedures having the highest average Cmax, then shoulder surgeries, and finally hernia surgeries being the lowest average. In the latter procedure the positive, pivotal study had an upper range twice that of another hernia study, Clin004-0001.

Table 1 Mean bupivacaine Cmax and AUC (SD) [range] values from all clinical pharmacology studies

Study	P	Surgery	Study Drug (Dose)	Type of Administration	Cmax ng/mL	AUC ng h/mL
CLIN005-0008	I	Healthy Subjects	Posimir 5.0 mL ^c	2 x 2.5 mL Trailing abdominal SC	638 ± 368 [238 – 1090]	42058.36 ± 17315.35 ^a [26161 – 69230]
CLIN004-0001	IIa	Hernia Repair Under general anesthetic	Posimir 2.5 mL ^d , and 5.0 mL	2 x 1.25 mL trailing SC 2 x 2.5 mL trailing SC	2.5 mL: 278 ± 109 [101 – 441] 5 mL: 470 ± 156 [317 – 695]	2.5 mL: 18173 ± 9610 [5792 – 28605] 5 mL: 37263 ± 17078 ^b [19474 – 60964]
CLIN004-0009	IIa	Hernia Repair With local anesthetic (Marcain)	Posimir 5.0 mL	Infiltration + trailing injection	- values not reliable due to use of local anesthetic in the study	
CLIN803-006-0006	II	Hernia Repair	Posimir 2.5, 5.0 mL)	Instillation	2.5 mL: 467 ± 226 [190 – 854] 5 mL: 867 ± 427 [383 – 1650]	2.5 mL: 18543 ± 9865 [7555 – 37399] 5 mL: 41461 ± 20221 ^a [18088 – 78909]
CLIN005-0006 (06-07)	II	Subacromial Decompression	Posimir 5.0 mL	2 x 2.5 mL SC trailing inj. 5 mL Subacromial Inj. N=4	SC: 965 ± 487 [172 – 1940] Subacr: 1146 ± 326 [813 – 1570]	SC: 45081 ± 21981 [7346 – 86448] Subac: 56635 ± 7797 ^a [49420 – 66929]
BU-002-IM (09-2010) ^e	II	Subacromial Decompression	Posimir 5.0 mL “leaked”	Subacromial Inj.	593 ± 299 [70 – 1320]	19960 ± 12600 ^a [1050 – 59200]
CLIN005-0002	II	Appendectomy	Posimir 5.0 mL	2 x 2.5 mL Trailing SC 2.5 mL Infiltration + 2.5 mL SC trailing inj.	SC 758.0 ± 320 [309 – 1260] Infiltration 1161.4 ± 595 [403 – 2170]	SC 51246.2 ± 22153 [26114 – 86241] Infiltration 69172.8 ± 25716 ^a [33365 – 107651]
BU-001-IM	II	Hysterectomy	Posimir 5.0 mL	Instillation /Infiltration	625 ± 310 [119 – 1740]	36830 ± 21060 ^a [4470 – 122170]

⁵ I emphasize this metric (upper limit of the Cmax range; Cmax range UL) because the subjects achieving these levels are most likely to experience bupivacaine toxicity, all other factors being equal).

Study	P	Surgery	Study Drug (Dose)	Type of Administration	Cmax ng/mL	AUC ng h/mL
C803-025	III	Laparotomy procedures ^b	Posimir 5.0 mL	Instillation /Infiltration	laparotomy 956 ± 485 [133 – 1870] laparoscopic cholecystectomy 752 ± 307 [357 – 1850] Laparoscopically-assisted colectomy 850 ± 478 [92 – 2850]	laparotomy 41942 ± 24344 [635 – 96625] laparoscopic cholecystectomy 30997 ± 12680 [11100 – 68108] Laparoscopically-assisted colectomy 39602 ± 24049 ^b [1626 – 136309]

The primary Clinical Pharmacology review made the following observations⁶ regarding the clinical pharmacology data in this NDA program:

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.

I did note that the variability of the Cmax range UL even within surgical models as is noted in **Table 2**, where the bupivacaine levels vary between 1320-1940 ng/mL in 3 studies. Considering the difference in surgical practice, it is reasonable to assume that the levels for certain patients may be greater than 2000ng/mL and put them at risk for bupivacaine toxicity.

Table 2 Pharmacokinetics of bupivacaine in shoulder surgeries

	Cmax (SD) ng/mL	AUC (SD) ng.h/mL
BU-002-IM Subacromial administration	593 (299) [Range 70 – 1320]	19960 (12600) [Range 1050 – 59200]
CLIN005-0006 Subacromial injection	1146 (326) [Range 813 – 1570]	56635 (7797) [Range 49420 – 66929]

⁶ The observations are reported verbatim from pp. 8-9 of his review.

	Cmax (SD) ng/mL	AUC (SD) ng.h/mL
CLIN005-0006 Subcutaneous injection	965 (487) [Range 172 – 1940]	45081 (21981) [Range 7346 – 86448]

Source: Table 21 Comparison of bupivacaine Cmax and AUC between trials CLIN005-0006 and BU-002-IM on p. 42 of the primary Clinical Pharmacology review.

The primary Clinical Pharmacology review notes⁷:

There were no clear explanations (by the Applicant) why Cmax and AUC values from Study BU-002-IM were approximately 50% less than CLIN005-0006 and all other studies. The plausible explanation provided by the Applicant was that Posimir leaked during the time of drug administration and wound closure.

5.5. Thorough QT study or other QT assessment

A thorough QT study was not performed as part of this development program. The QT assessment is described in Section 7.2.5 of my review.

5.6. Biopharmaceutics

The following summary statements were made in the Biopharmaceutics review:

- The Applicant's intent was to develop an in-vitro bupivacaine release characterization method to mimic in-vivo release of the drug from the depot or hydrophobic film formed in the wound over 72 h. However, an IVIVC or IVIVR could not be established. The dissolution method is acceptable for routine quality control release testing of the product.
- The dissolution method could not be shown to exhibit adequate discriminating power regarding potential alterations in the rate-controlling excipient content. However, the unintended or erroneous use of the HCl salt instead of bupivacaine base will be picked up by the method. The proposed dissolution method is found to be acceptable as a drug product quality control test.
- The Applicant's originally proposed dissolution acceptance criteria were not acceptable. The Agency's recommended dissolution acceptance criteria were communicated to the Applicant in an IR letter dated Oct 21, 2013. The Applicant accepted the Agency's recommended dissolution acceptance criteria and updated the Drug Product Specifications Table on Nov 6, 2013.

The issue of the extended release claim is discussed in more detail in the Clinical/Statistical section (7.1.4) of my review. I will note here, since it is mentioned in the primary Clinical Pharmacology review that the extended-release claim for locally acting, topically administered drugs, such as Posimir, does not depend on systemic bupivacaine levels, but rather is a

⁷ p. 4 of the primary Clinical Pharmacology review

consideration of the release profile and duration of the clinical effect. As the Biopharmaceutics review notes, an *in vitro* / *in vivo* correlation could not be established; the *in-vitro* bupivacaine release does not therefore mimic *in-vivo* release of the drug from the hydrophobic film formed in the wound.⁸

5.7. Other notable issues (*resolved or outstanding*)
None

Clinical Pharmacology Recommendation and Conclusion on Approvability

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted in the current application for Posimir™*. From a clinical pharmacology perspective, the information submitted in the NDA is acceptable, pending agreement on the labeling language.

Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

Biopharmaceutics Recommendation and Conclusion on Approvability

ONDQA-Biopharmaceutics recommends APPROVAL from a Biopharmaceutics perspective. The following dissolution method and acceptance criteria (**Table 3**) for Bupivacaine Extended-Release Solution for Instillation are agreed upon and acceptable:

⁸ Per the guidance for industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070239.pdf>

Table 3 Recommended dissolution method and acceptance criteria from the Biopharmaceutics review

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium
2	50 rpm	900 mL	37 ± 0.5 °C	0.03 % SDS in 0.025 M Phosphate Buffer (NaH ₂ PO ₄ ·H ₂ O) pH 7.4 ± 0.05

Time Point, hours	Acceptance Criteria
1	NMT ^{(b) (4)} %
8	^{(b) (4)} %
18	%
48	NLT ^{(b) (4)} %

Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None listed

6. Clinical Microbiology

There is no need for data pertaining to clinical microbiology for this application.

7. Clinical/Statistical

The information in the Clinical/Statistical section was substantially extracted from the Clinical Review of Dr. Arthur Simone and Mr. David Petullo and supplemented with further detail as described in my own review.

7.1. Efficacy

7.1.1. Dose identification/selection and limitations

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, the Clinical review notes that “...there is little to support [these] 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 [have] not been identified.”

I concur with Dr. Simone’s assessment of this issue.

7.1.2. Phase 3 / clinical studies essential to regulatory decision, including design, analytic features, and results

Seven studies were conducted that were considered either pivotal or supportive for the desired indication (**Table 4**). These utilized the to-be-marketed formulation and the methods of administration consistent with that proposed in the labeling. The Applicant grouped the trials into three groups according to the surgical type: orthopedic shoulder, inguinal herniorrhaphy, and abdominal soft tissue. Since the shoulder and hernia surgeries were considered to provide the supportive evidence for efficacy, I will focus on these models in this Section of my review. While these two models have several similarities, namely both have an element of incision pain and both were treated with superficial and deeper instillation of the drug product, they also have some major differences, the most important of which is the origin and mechanism of the pain upon movement, which is a critical variable in the outcome for was the primary endpoint. This issue will come into play when I discuss the issue of replication in my summation of the risk:benefit analysis (Section 13.1).

Table 4 Studies considered for the support of efficacy

Study #	Pivotal	# US / ExUS sites (location of ExUS sites)	Treatment Arms (N)	Primary Endpoint(s)	Efficacy Outcome ⁹ (p value)
Orthopedic Procedures					
BU-002-IM	Y	0 / 11 (Eastern and Western Europe)	a. S-b 5 mL ¹⁰ b. S-p c. 20 mL of 2.5% b	1. mean pain intensity (PI) on movement AUC over the time period 1 to 72 hours postsurgery (AUC72) 2. Total use of opioid rescue analgesia 0 to 72 hours post-surgery (RES72)	1. AUC72 Difference from S-p a. S-b 5 mL = -1.1 (0.02) b. b = -0.2 (0.1) 2. RES72 Rescue consumed (p-value based on difference from placebo) a. S-b 5 mL = 13.7 (0.01) ¹¹ b. b = 12.3 (0.07) c. S-p = 22.8 (n/a)

⁹ Efficacy results reported here are derived from applicant reported results or from the Primary Statistical reviewer's verification of these analyses if available. The reader should refer to the primary Statistical and Clinical reviews for details on efficacy outcomes.

¹⁰ A S-b 7.5 mL arm had been planned but was eliminated through a protocol amendment after the Data Monitoring Committee evaluated the results of the S-b 5 mL arm.

¹¹ Although the mean amount was less in the bupivacaine arm, the results of the nonparametric analysis resulted in a lower p value for the SABER-bupivacaine arm.

Study #	Pivotal	# US / ExUS sites (location of ExUS sites)	Treatment Arms (N)	Primary Endpoint(s)	Efficacy Outcome ⁹ (p value)
CLIN005-0006	N	5 / 1 (New Zealand)	a. S-p subacromial 5 ml +S-b sc 5 mL b. S-p sc 5 ml + S-b subacromial 5 ml c. S-p SC 5 mL + S-p subacromial 5 mL d. S-p subacromial 5 mL e. S-b subacromial 5 mL f. S-p subacromial 7.5 mL g. S-b subacromial 7.5 mL	1. Pain intensity on movement, AUC120m ¹² 2. Pain intensity on rest, AUC120r	1. AUC120m Tx.5 vs. Tx3 = -0.1 (.866) 2. AUC120r Tx 5 vs. Tx3 = -0.52 (0.315)
C803-017	N	0 / 10 (Australia / New Zealand)	a. S-p (20) b. S-b 5 mL (40)	1. AUC72m 2. RSE72	1. AUC72 difference from S-p = - 0.64 (0.3) 2. RES72 difference from S-p = -10.7 (0.3)
Inguinal Hernia Surgery					
CLIN-803-006-0006	Y	0 / 5 (Australia / New Zealand)	a. S-b 5 mL b. S-b 2.5 mL c. S-p (matching volumes)	1. AUC72m 2. RSE72	(only results for the S-b 5 mL arm are reported here, the 2.5 mL results were not positive) 1. AUC72 difference from S-p = () 2. RES72 difference from S-p = ()

¹² 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

Study #	Pivotal	# US / ExUS sites (location of ExUS sites)	Treatment Arms (N)	Primary Endpoint(s)	Efficacy Outcome ⁹ (p value)
CLIN005-0010	N	7 / 1 (New Zealand)	Volumes 5 mL each unless noted ¹³ a. S-p subaponeurotic + S-b SC b. S-p SC + S-b subaponeurotic c. S-p SC + S-p subaponeurotic d. S-p subaponeurotic + SC e. S-b subaponeurotic + SC f. S-b subacromial 7.5 mL ¹⁴	1. AUC120m 2. AUC120r 3. Pain Control	1. Tx. E AUC120m difference from Tx3 (pooled S-p) = +1.03 ¹⁵ (0.35) 2. Tx. E AUC120r difference from Tx3 (pooled S-p) = +0.89 ¹⁵ (0.14) 3. Pain Control (days 1-5) = There were no statistically significant differences in pain control between the two groups during the study, i.e., Days 1 through 5.
Abdominal Soft Tissue Surgery					

¹³ See the Primary Clinical review for a more detailed description of the instillation procedure

¹⁴ Only one subject received this treatment before the arm was removed by amendment

¹⁵ Represents a difference in favor of placebo

Study #	Pivotal	# US / ExUS sites (location of ExUS sites)	Treatment Arms (N)	Primary Endpoint(s)	Efficacy Outcome ⁹ (p value)
BU-001- IM¹⁶	N	0 / 14 (Eastern and Western Europe)	a. S-b 5 mL b. S-p c. B ¹⁷ 40 mL	1. AUC72m 2. RSE72	¹⁸ ...[for AUC72m] 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 RES72 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.

¹⁶ Post-hysterectomy pain model

¹⁷ Bupivacaine was injected into the muscle, distal layer and subcutaneously around the surgery site.

¹⁸ Results were reported in narrative form in both Primary Clinical and Statistical reviews, so I have maintained that structure.

Study #	Pivotal	# US / ExUS sites (location of ExUS sites)	Treatment Arms (N)	Primary Endpoint(s)	Efficacy Outcome ⁹ (p value)
C803-025 ^{19,20}	N	9 / 2 (Oceania)	a. S-b 5 mL b. S-p	1. AUC72 2. RSE72	1. AUC72 difference from S-p (p-value) i. Cohort 1 = -0.9 (0.15) ii. Cohort 2 = -1.1 (0.06) iii. Cohort 3 = 0.34 (0.15) 2. RES72 difference from S-p (p-value) ¹⁵ there were no significant differences noted for the comparison of Posimir to control for RES72, results not shown.

Abbreviations: **b** = bupivacaine; **S-b** – SABER bupivacaine; **S-p** – SABER placebo

¹⁹ Post-Colecotomy, laparotomy, or laparoscopic cholecystectomy pain trial

²⁰ This trial had 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.

The Applicant identified two of the post-operative pain studies as the primary supportive or “pivotal” studies containing the substantial evidence supporting the efficacy of this drug product for the purported claim of post-operative analgesia. These were BU-002-IM, a trial following arthroscopic shoulder surgery, and CLIN-803-006-0006, a trial following inguinal hernia surgery. I will provide a summary of these trials, as well as the second inguinal hernia trial, CLIN-005-0010, since the results of these 3 trials, along with the safety profile presented in the application, form the basis of the Primary Clinical and Statistical reviewer’s argument for a Complete Response. The other arthroscopic surgery trials are briefly described since, while not having been positive, they were considered supportive by both the Applicant and the primary reviewer’s. Finally, the abdominal soft tissue surgeries are not described in this review except to note that they failed to show a significant difference in favor of SABER-bupivacaine. Further, they represent a different type of procedure than those studies used to support the application with potentially different etiologies and mechanisms for the pain. A detailed discussion of each trial is found in Section 9.4 of the Primary Clinical review.

Orthopedic Shoulder Surgeries

BU-002-IM – A Phase 2 study of postoperative pain following arthroscopic shoulder surgery

Design

This was a randomized, 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 following SABER-bupivacaine instillation into the subacromial space

Key Inclusion²¹Criteria

1. Subacromial impingement syndrome, diagnosed by a positive subacromial impingement test, full passive range of motion and exclusion of shoulder instability
2. MRI with intact rotator cuff as judged by radiologist
3. Age 18 years of age and above
4. 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

Key Exclusion²¹ Criteria

1. 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
2. Connective tissue disorders (systemic lupus erythematosus, scleroderma, mixed connective tissue disease)
3. No shoulder instability procedures and biceps tenodesis, or biceptal tentomy
4. No open shoulder surgery.

²¹ Including surgical and anesthetic criteria

There are several general exclusion criteria that have the effect of narrowing the study population to a fairly healthy group.

Treatment Arms

- SABER-bupivacaine, 5 mL. This arm was to be studied sequentially before the SABER-bupivacaine 7.5 mL arm.
- SABER-bupivacaine, 7.5 mL (discontinued by protocol amendment based on a recommendation from the study's Data Review Committee after reviewing the results from the 5 mL arm, based on a belief that 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.)
- 2.5% bupivacaine HCl, 20 mL
- SABER-placebo (equal volume to SABER-bupivacaine)

Primary endpoints

- 1) Pain intensity (PI) on movement AUC over the period 1 to 72 hours post-surgery (AUC72) using an 11-point NRS for recording PI. A standardized assessment of pain "on movement" was performed for shoulder flexion to 90 degrees.
- 2) Total use of opioid rescue analgesia 0 to 72 hours post-surgery (RES72).

Primary Efficacy Results

AUC72 was to be tested for non-inferiority (NI) to placebo first, it 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 AUC72 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 RES72 would be compared between SABER-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). The primary statistical reviewer took a slightly different approach. Instead of using WOCF when subject used rescue medication, he 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 was larger than the recorded pain score. He also used a 4 hour window regardless of the rescue medication used.

Table 5 presents the results from analyses of the AUC72 that accounted for the use of rescue medication. Both the applicant and reviewer had similar results that likely differed because of different conventions used to account for rescue medications.

Table 5 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: Primary Statistical review

Table 6 contains the statistical evaluation for the primary endpoint for both Posimir 660 mg and Bupivacaine. The latter comparison was not required in the primary analysis but performed by the reviewer for exploratory comparison purposes. The primary statistical reviewer also did an exploratory comparison between the results of AUC72 between Posimir 660 mg and bupivacaine and the p-value was determined to be 0.7.

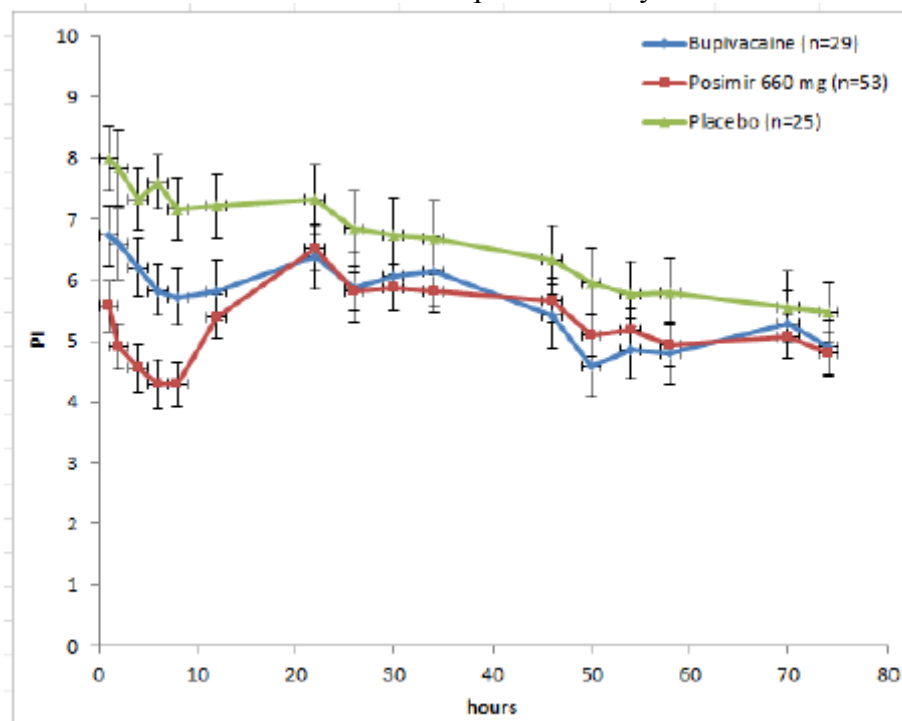
Table 6 Comparison of Posimir to placebo in Study BU-002

	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: Primary Statistical review

The primary statistical reviewer provided Figure 3 and Table 7 which illustrate the time course of the Posimir effect on pain intensity. The clinical benefit as measured by the pain intensity of SABER-bupivacaine 5 mL over SABER-placebo has duration between 12 and 20 hours and a benefit over placebo of about 12 hours.

Figure 3 Mean PI scores at each measured time point in Study BU-002-IM



Source: Primary Statistical review

Table 7 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: Primary Statistical review

The primary statistical reviewer also noted that the difference between Posimir and placebo is nominally significant out to 12 hours post-surgery. He remarked that this indicates that the significant difference noted in the comparison of AUC72 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 Table 7 and Figure 3, the clinical benefit of Posimir 660 mg in reducing post-surgical pain associated with shoulder repair surgery after 12 hours post-surgery is unclear.

For the second primary endpoint RES72, The primary statistical reviewer 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 his 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.

Table 8 Amount of rescue medication consumed through 72 hours post-surgery in Study BU-002

Treatment	Morphine Equivalent (mg)	p-value
	mean (stdev)	
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: Primary Statistical review

Secondary endpoints

- Mean pain intensity normalized AUC over the time period of 1 to 48 hours;
- Overall treatment satisfaction;
- Mean total opioid dose for analgesia rescue during the study; and
- Mean function activities (Days 1 through 5).
- The modified Brief Pain Inventory.
- 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).
- 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).
- 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/postoperative exercises,

cough) were collected on a 0 to 10 NRS with scores ranging from 0 (does not interfere) to 10 (completely interferes).

- 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

Secondary Efficacy Results:

- 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: $\pm$ 1.34), 3.43 (SD: $\pm$ 2.05) and 2.33 (SD: $\pm$ 1.76), respectively. SABER-bupivacaine was superior to SABER-placebo, but not to bupivacaine HCl, which was also superior to SABER-placebo.
- While not prespecified as a secondary endpoint in the protocol, 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 based on the log-rank test. There was not a significant difference between placebo and bupivacaine.
- Analyses of other secondary endpoints did not reveal any statistically significant differences between treatment groups.

Supportive Studies

CLIN005-0006: This was a randomized, double-blind, placebo-controlled phase 2 study conducted primarily in the US. Study drug was administered subcutaneously or into the subacromial space in subjects undergoing elective arthroscopic shoulder surgery under local or general anesthesia. The treatment arms are listed in

Table 9.

Table 9 Treatment arms for 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	35
4a	Placebo subacromial 7.5 mL	4
5a	Posimir subacromial 7.5 mL	3

Source: Primary Statistical review

The primary endpoint was changed by protocol amendment to a normalized AUC of PI scores for at rest and on movement at 120 hours post-surgery (AUC120) was evaluated comparing treatment arms using an ANOVA model where the comparison of interest was treatment arm 5 (see **Table 9**) versus pooled placebo, treatment arms 3 and 4. 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 AUC72 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 least square means for AUC72 were 5.6 and 5.2 for placebo and Posimir, respectively. The corresponding 95% CI for the difference between Posimir and placebo, [-1.7, 0.5], 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 SABER-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 AUC72 and RES72 as measured by morphine equivalent units. Results for the primary analyses are found in **Table 10**. Neither primary outcome variable favored Posimir significantly, though the means for both endpoints trended in favor of the study drug.

Table 10 Applicant's results for the primary analysis in Study C803-017

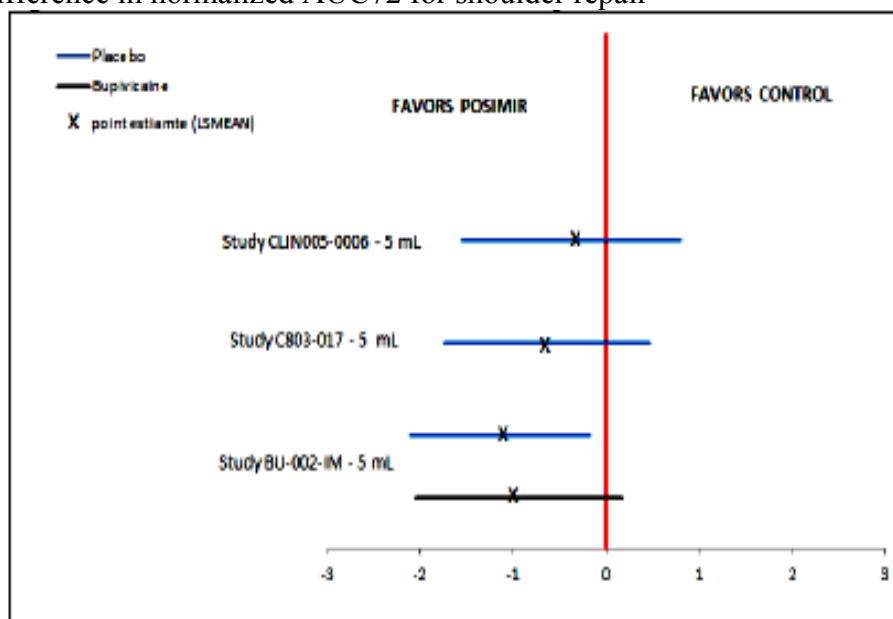
Endpoint	Placebo (n=20)	Posimir 5 mL (n=40)	Difference (95% CI)	p-value
AUC ₇₂ (pi)	5.8	5.4	-0.64 [-1.7, 0.47]	0.3
RES ₇₂ (mg)	49.9	44.5	-10.7 [-30.0, 9.6]	0.3

Source: Tables 14.1.8.1 and 14.1.9.1 from applicant's CSR

Overall Assessment of Shoulder Surgery Trials

The point estimate for AUC72 was in the right direction for each of these studies (**Figure 4**). The comparison of Posimir to bupivacaine in Study BU-002-IM, while not significant, did favor Posimir.

Figure 4 Difference in normalized AUC72 for shoulder repair



Source: Primary Statistical review

Inguinal Herniorrhaphy Surgeries

CLIN-803-006-0006 A Phase 2 study of postoperative pain following inguinal herniorrhaphy

Design

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

Key Inclusion¹ criteria

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

Exclusion inclusion¹ criteria

1. Presence of previous abdominal surgery with scar tissue that would limit patients' ability to participate

Treatment Arms

- SABER-bupivacaine 5.0 mL (660 mg of bupivacaine)
- SABER-bupivacaine 2.5 mL (330 mg of bupivacaine)
- SABER-placebo 5.0 mL
- 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.

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 through Day 15. (Post-hoc, the applicant changed the proportion of subjects using rescue through Day 15 to Day 3 or 72 hours.)

To account for the second primary endpoint, a step-down approach was used. If the comparison of AUC72 was statistically significant then the proportion of subjects using rescue was tested.

Primary Efficacy Results

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. Minor differences in the numbers seen in these tables are most likely a result of different conventions used to account for the use of rescue medications. No significant differences were observed between the SABER-bupivacaine 2.5-mL group and the SABER-placebo group. Minor differences in the numbers seen in these tables are most likely a result of different conventions used to account for the use of rescue medications (**Table 11**).

Table 11 Normalized AUC for Pain Intensity on movement from 1-72 hours

	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: Primary Statistical review

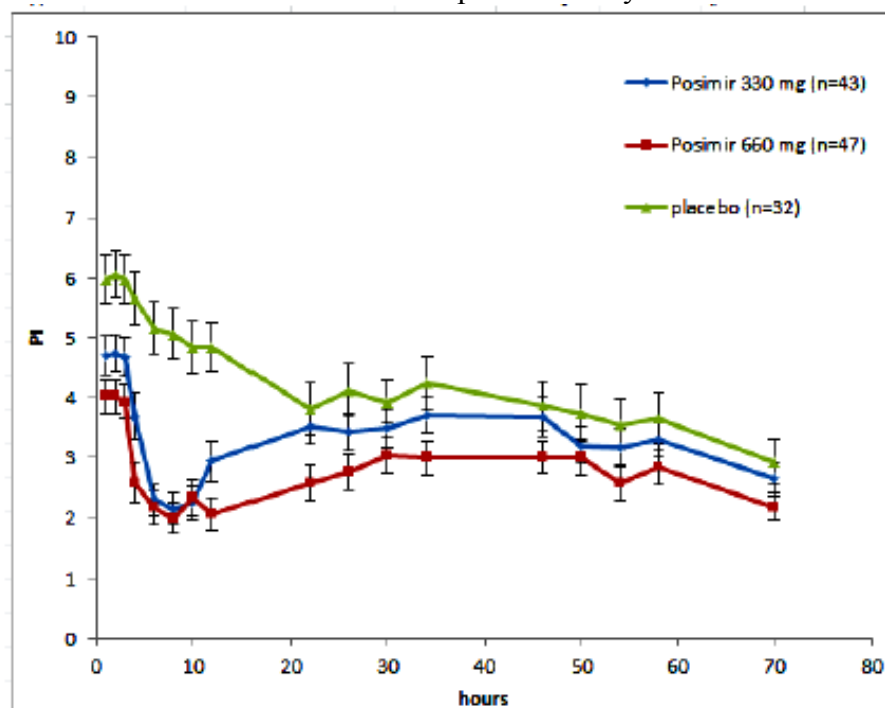
Table 12 Comparison of Posimir to SABER-placebo

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: Primary Statistical review

The following figure was generated by the primary statistical reviewer demonstrating the difference between treatment group for the pain intensity primary endpoint using an analysis that accounted for rescue medications and missing data (**Figure 5**).

Figure 5 Mean PI scores at each measured time point in Study CLIN-803



Source: Primary Statistical review

The primary statistical reviewer also examined the pain intensity primary endpoint at each time point using the same ANOVA method used for the primary analysis.

Table 13 Comparisons of PI scores at assessed time point in Study CLIN-803

Time point (hrs)	Difference from placebo (PI)					
	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: Primary Statistical review

The results for the SABER-bupivacaine 5 mL treatment (“Posimir 660 mg”) were statistically different from SABER-placebo to about 24 hours, whereas the SABER-bupivacaine 2.5 mL treatment (“Posimir 330 mg”) had timepoints significantly different from SABER-placebo only out to 12 hours. As Dr Petullo noted “... 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 AUC72 for the Posimir 660 mg arm may be influenced by the early separation in the pains curves.”

When the primary statistical reviewer examined the second primary endpoint, supplemental opioid rescue medication after surgery to Day 15 considering 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 he considered all opioids, not just those coded as rescue, there was no longer a significant treatment effect (**Table 14** and **Table 15**). Regardless of how opioids were coded, he noticed there was very little difference in the results from Day 3 versus Day 15.

Table 14 Post-operative analgesic requirements to Day 15

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: Primary Statistical review

Table 15 Post-operative analgesic requirements to Day 3

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: Primary Statistical review

Secondary Endpoints and Results

The mean pain intensity on movement normalized AUC from 1 to 48 hours was improved with SABER-bupivacaine versus SABER-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 SABER-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.

The primary statistical reviewer considered RES72 to be a clinically relevant endpoint, particularly since this was a co-primary endpoint in Study BU-002. Medications were converted to morphine equivalents using the conversion table provided by the applicant. The non-parametric Wilcoxon Rank Sum (WRS) test was utilized for reasons specified in the protocol. Results are shown in **Table 16**. The SABER-bupivacaine 5 mL arm demonstrated a significant difference from SABER-placebo, while the 2.5 mL SABER-placebo was considered to be borderline significant by the primary statistical reviewer.

Table 16 Amount of rescue medication consumed through 72 hours post-surgery in Study CLIN-803

Treatment	Morphine Equivalent (mg)	p-value
	mean (stdev)	
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: Primary Statistical review

Other planned secondary endpoints were not significant or not reported.

CLIN-005-0010 A Phase 2, Controlled Trial of Postoperative Pain following Inguinal Herniorrhaphy)

Design

This was 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

Key Inclusion Criteria

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.

Key Exclusion Criteria (verbatim from pp. 36-37 of the final study report)

1. 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).

Treatment Arms

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.

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.

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.

Primary Efficacy Results

The comparisons of interest in this study were Treatments 1 (subcutaneous), 2 (subaponeurotic), and 5 (both subcutaneous and subaponeurotic) administration. Treatments 1 and 2 did not demonstrate a significant difference from the pooled SABER-placebo group (**Table 17** and **Table 18**). In the contrast between the Treatment group 5 and the pooled

placebo group, the placebo group had a more favorable response that was statistically significant.

Table 17 Summary of AUC0-120 hours pain intensity on movement for Study CLIN005-0010

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 18 Summary of AUC0-120 hours pain intensity at rest for Study CLIN005-0010

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)

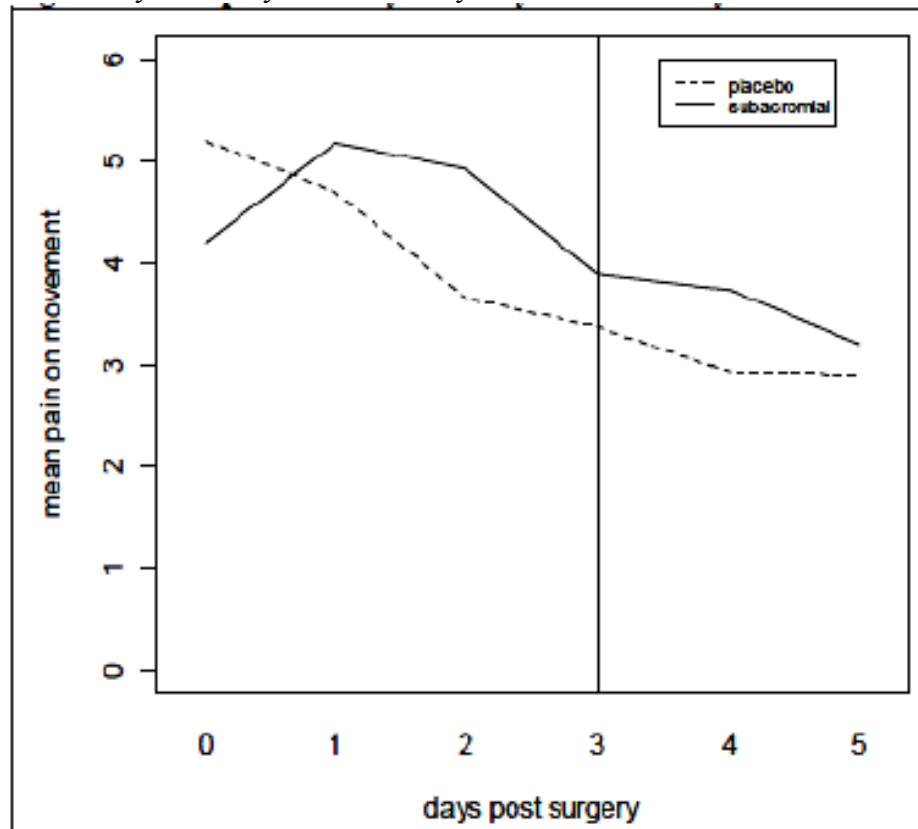
5 = SABER-Bupivacaine subaponeurotic and subcutaneous spaces (5.0 mL)

SABER-BUP =Treatments 2 and 5

Pooled Placebo = Treatments 3 and 4 (both SABER-placebo)

Figure 6 demonstrates the difference in the effect between SABER-bupivacaine and SABER-placebo with respect to pain intensity over time.

Figure 6 Mean pain intensity scores by time for Study CLIN005-0010



Source: Figure 3 from applicant's CSR

Similarly, the point estimate for Pain Control favored placebo versus Treatment 5 on several time points (**Table 19**). The primary statistical reviewer 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 used less rescue medication on average than subjects in the Posimir 660 mg arm.

Table 19 Pain control for Day 1 through Day 5 for Study CLIN005-0010

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

Secondary Efficacy Endpoints

1. The Modified Brief Pain Inventory evaluation of worst and least pain, assess 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

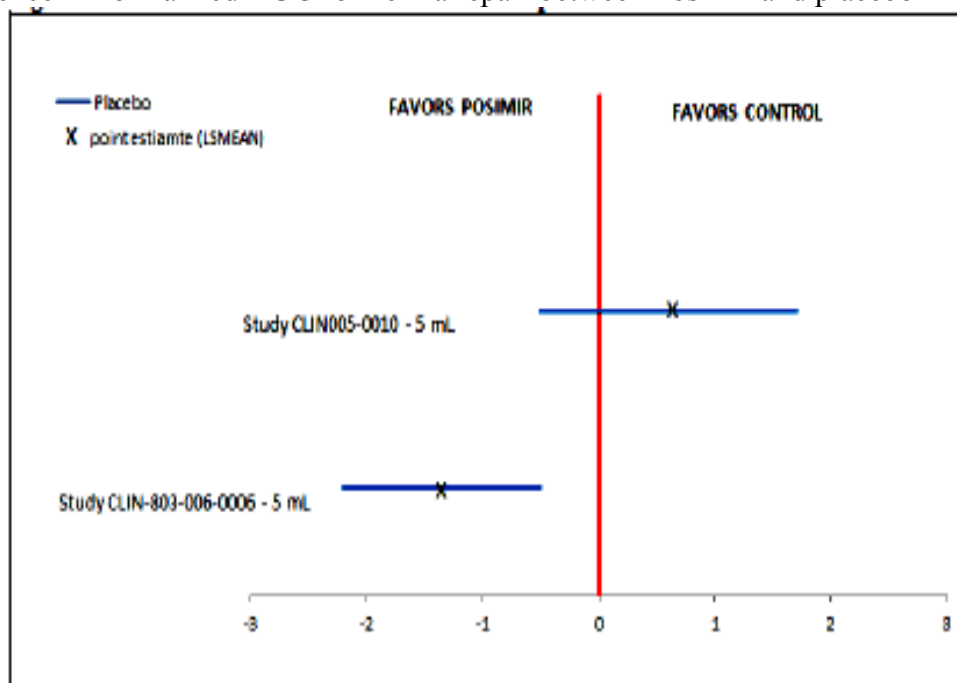
Secondary Results

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.

Further examination of these results by site location, United States versus Australia and New Zealand, did not reveal any significant findings.

Overall Assessment of Hernia Surgeries

Figure 7 Difference in normalized AUC for hernia repair between Posimir and placebo



7.1.3. Other efficacy studies

See **Table 4**

7.1.4. Discussion of notable efficacy issues (*resolved or outstanding*).

Extended-release claim

I briefly mentioned the Applicant's claim of being an extended-release drug with bupivacaine being the comparator drug. The Biopharmaceutics data does not support this claim, since the reviewer has noted that an *in vitro* / *in vivo* correlation could not be established; the *in-vitro* bupivacaine release does not therefore mimic *in-vivo* release of the drug from the hydrophobic film formed in the wound. From a clinical perspective, Posimir does not consistently provide an increased period of analgesia relative to bupivacaine. Therefore, if the drug were approved based on the current data, the claim of extended-release should not be granted.

7.2. Safety

7.2.1. General safety considerations

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 Applicant's and Primary Clinical Reviewer's evaluations of the product's safety (**Table 20**). For these trials, a total of 1109 subjects were randomized; the 1075 subjects who received any study drug were included in the safety

database. In these trials, 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.

Table 20 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

Cross-Discipline Team Leader Review Memo
Christopher D. Breder, MD PhD
NDA 204803
Posimir (SABER-bupivacaine)

Protocol Number	Phase	Surgery	Type of Administration	Number of Safety Subjects
BU-002-IM	2	Subacromial Decompression	Subacromial Instillation	107
C803-017	2	Subacromial Decompression	Subacromial Instillation	60
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.

Exposure to different treatment arm including SABER-bupivacaine, SABER-bupivacaine + bupivacaine, SABER-placebo, and bupivacaine are indicated in the table below.

Table 21 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			

Table 22 indicates the safety assessments used per study in the clinical development program. Four studies are noted to have long-term followup. This is important in the consideration of issues such as the impact of prolonged deposition of SAIB, the potential for chondrolysis, which may take months to manifest, and the effect of long-term inflammation at the surgical wound / incision.

The following are the periods of follow-up and long-term assessments for each of these studies:

- C803-017e - 18 month follow-up with exam and MRI of shoulder (31 subjects of a possible 60 participated).
- CLIN-803-006-0006 – 3 and 6 month follow-ups with physical exam (102 of the 124 were seen at 3 months and 94 were seen at 6 months).
- BU-001 – 6 month follow-up with physical exam and limit number of sites were to do MRI (113 of 115 completed the study; 21 had an MRI).
- BU-002 – 6 month follow-up with functionality score, physical exam, and MRI of shoulder (n=107)

Table 22 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	X ³	X	MRI
BU-002-IM	X	X	X	X	X	X	X ¹	X	X ³	X	MRI
C803-017	X	X	X	X	X	X			X ⁴		MRI
C803-017e	X	X				X				X	MRI
C803-025	X	X	X	X	X	X	X ¹	X			
C803-027	X	X	X	X	X	X	X				Punch biopsy and histopathology

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)

7.2.2. Safety findings from submitted clinical trials – general discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.

7.2.2.1.1. 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 Primary Clinical reviewer felt that the Applicant's conclusion that the death was unrelated to the study drug is supported and appropriate. I concur with the Primary Clinical reviewer's opinion.

7.2.2.1.2. Non-fatal SAEs

There were 74 treatment-emergent serious adverse events (SAEs), which are summarized in below. 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. The Primary Clinical reviewer presented a table of SAEs organized by treatment and MedDRA System Organ Class (SOC) and Preferred Term (PT) in Section 7.3.2 of his review.

Generally, the incidence of SAEs was low and balanced between treatment groups. However, the Primary Clinical reviewer noted that 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). The incidence in the context of the particular procedure was considered by the Primary Clinical reviewer to be significant, e.g., the vaginal hematoma incidence rises from < 1% in the whole database to > 2%. More importantly from a safety perspective is that none of the subjects treated with bupivacaine HCl experienced one of these SAEs.

The Applicant's 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 C_{max} data for the treatment emergent SAE cases showed that the median C_{max} was 730 [range: 52-1870] ng/mL. Eleven of the SAE cases had C_{max} >1000 ng/mL, however all but one of the cases occurred well after the T_{max}. Several SAEs were potentially indicative of neurotoxicity, or possibly cardiac toxicity, however the Primary Clinical reviewer's review of the narratives for these events suggested to him that the Applicant's rationale for these events not being related to the study drug were generally well supported. Based on the facts he reported in his review on these cases, I concur with his opinion.

The SAE of chondropathy was reported in the follow-up shoulder surgery trial C803-017e (the Primary Clinical review Section 7.3.2). 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. This issue is discussed further in Section 7.2.5 of my review.

7.2.2.2. Discontinuations due to AEs

Table 23 presents the disposition of subjects in the safety population of this application.

Table 23 Subject disposition for the safety population (Table 6, p. 24 of the ISS)

	SABER-Bupivacaine 2.5 mL	SABER-Bupivacaine 5 mL	SABER-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

The single-dose, intraoperative administration of the study drug largely precluded the discontinuation of study treatment due to adverse events. 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. The Primary Clinical reviewer noted that 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.

7.2.2.3.General AEs

The Primary Clinical reviewer created a table of common AEs 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 (see Table 35 of his review).

His 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 also occurred more frequently with SABER-placebo treatment compared to plain 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 BA contained in SABER-bupivacaine as discussed in Section 7.2.5. Little is reported in the literature about the toxicity of BA in adults. That which is reported relates to contact reactions with cosmetics and pulmonary reactions related to the inhalation of BA-containing saline solutions during nebulizer treatments. Based on the reaction of neonates to BA, the most common presenting symptoms and signs include metabolic acidosis, central nervous system depression, thrombocytopenia, hypotension, and respiratory distress.

I concur with the Primary Clinical reviewer's observations. I am also concerned by the difference in the incidence of AEs such as incision site hemorrhage, and dehiscence where the incidence in SABER treatments is strikingly more than in the bupivacaine treatment arm. This may represent a local toxicity that is increased by the SAIB or BA components of the drug product. I am similarly concerned about the difference between the SABER treatment groups and bupivacaine with respect to the incidence of AEs from the central nervous system SOC, such as tinnitus, dizziness, dysgeusia, headache, somnolence, hypoesthesia, and paraesthesia. This may be a systemic toxicity, possibly from BA exposure since this diffuses away from the injection site, though the increased incidence of the latter two events may be a local toxicity phenomenon.

7.2.2.4.Investigations - Laboratory tests, Vital Signs, and Electrocardiograms

Based on a review of the data, the Primary Clinical reviewer felt 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 based 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.

There did not appear to be any clinically relevant differences between SABER-placebo and SABER-bupivacaine treatments with respect to chemistry laboratories 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.

There did not appear to be any safety signals based on the protocol mandated vital sign assessments as suggested by the Applicant's reporting of the vital sign findings.

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.

A discussion of the QTc assessment is found in Section 7.2.5

7.2.3. Safety update

No additional safety issues were identified in the 120-day safety update.

7.2.4. Immunogenicity, where pertinent

No immunogenicity issues related to the use of SABER-bupivacaine were identified during the nonclinical and the clinical development programs.

7.2.5. Special safety concerns

Clinical implications of the fill volume

The Clinical team was concerned about the overage in fill volume since the extra Posimir could be administered, increasing the risk for bupivacaine toxicity. At one point the fill volume had been as high as (b) (4) (for up to as much as (b) (4) extra mL of Posimir). The Applicant was asked to provide information related to clinical signs of bupivacaine toxicity, particularly in subject who had received the 7.5 mL Posimir dose. The Applicant provided a response (email dated 31 October 2013) that included a summary of clinical safety (**Table 24**)

and pharmacokinetic experience of patients receiving 7.5 mL of Posimir (with or without additional bupivacaine HCl, representing from 990 to 1065 mg bupivacaine). A total of 75 patients had been treated with 7.5 mL of Posimir. The 75 patients receiving 7.5 mL are included in the data column entitled: SABER-bupivacaine/Bupivacaine HCl. In addition to the 75 patients treated with 7.5 mL of Posimir, this group also contains 16 patients treated with 5 mL of Posimir in combination with bupivacaine HCl).

Table 24 Adverse events in the Central Nervous System and Cardiac Disorder SOCs in the Posimir ISS dataset

System Organ Class	SABER-Bupivacaine 2.5 mL (N=50)	SABER-Bupivacaine 5 mL (N=542)	SABER-Bupivacaine/Bupivacaine HCl (N=91)	SABER-Placebo (N=268)
Cardiac disorders	10 (20%)	51 (9%)	4 (4%)	19 (7%)
Bradycardia	9 (18%)	18 (3%)	2 (2%)	9 (3%)
Tachycardia	1 (2%)	18 (3%)	1 (1%)	3 (1%)
Atrial fibrillation	0	2 (<1%)	0	3 (1%)
Palpitations	0	2 (<1%)	0	0
Ventricular tachycardia	0	0	1 (1%)	0
Nervous system disorders	33 (66%)	232 (43%)	40 (44%)	154 (57%)
Somnolence	20 (40%)	119 (22%)	3 (3%)	91 (34%)
Dizziness	14 (28%)	114 (21%)	12 (13%)	72 (27%)
Headache	15 (30%)	75 (14%)	23 (25%)	41 (15%)
Dysgeusia	6 (12%)	36 (7%)	3 (3%)	29 (11%)
Paraesthesia	9 (18%)	32 (6%)	4 (4%)	23 (9%)
Hypoaesthesia	2 (4%)	27 (5%)	2 (2%)	18 (7%)
Syncope	1 (2%)	4 (<1%)	1 (1%)	1 (<1%)
Presyncope	1 (2%)	2 (<1%)	1 (1%)	1 (<1%)
Dysarthria	0	1 (<1%)	0	1 (<1%)
Tremor	0	0	0	3 (1%)
Seizure	0	0	0	0

There was no indication in the data provided by the Applicant that the higher dose of Posimir is associated with a higher incidence of adverse events commonly assumed to be caused by bupivacaine, such as seizures or ventricular arrhythmias. The one case of ventricular tachycardia occurred in a healthy volunteer (#(b) (6)) in trial CLIN005-0008 prior to dosing of SABER-bupivacaine.

The Clinical team decided that the potential risks of administering extra bupivacaine could be managed through labeling.

QT Evaluation

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 C_{max} for the 5 ml dose was required. 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. In addition, Trial

C803-025 used continuous Holter monitoring to detect any pro-arrhythmic events. The mean ECG parameters were comparable between the three treatment groups, the QT interval decreased, the QTcF was unchanged, and the QTcB intervals increased from baseline which was consistent with the increased heart rate. All treatment groups were reported to have an increase in Δ QTcF 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 Δ QTcF close to zero. The initial increase in Δ QTcF 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 ($\Delta\Delta$ QTcF) 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.

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. 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.

Chondrolysis

Chondrolysis was identified by the Division and communicated to the Applicant as a potential safety issue of concern for this program. The Division's conveyed their concern regarding bupivacaine seeping into the joint capsule in their comment responding to the request for a Special Protocol Assessment (SPA) on August 1, 2008, for the trial involving arthroscopic shoulder surgery. (see Section 2.5 of the Primary Clinical review).

One such case was identified as an SAE and is discussed in that section of the Primary Clinical review. Two additional cases were identified where chondrolysis was suspected based on MRI findings but were not deemed to be AEs by the investigator (see Section 7.3.4 of the Primary Clinical review). The Primary Clinical reviewer noted that these cases raised his concern about the effects of SABER-bupivacaine on connective tissue. I concur with his concern over this issue.

The Applicant's recommended method of instilling Posimir in the shoulder surgery is instillation into the subacromial space. 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. This possibility was

described in a recent review of chondrolysis cases where local anesthetics had been infused through catheters placed in the subacromial space in vicinity of the glenohumeral joint (Busfield and Romero 2009).

Even with an adequate repair of the rotator cuff and underlying superior joint capsule, the repairs may not be watertight and may allow leakage of the pain pump contents into the glenohumeral joint.

Of the 3 shoulder trials the Applicant included, 2 had ‘long-term follow-up’, but only one, C803-017e had follow-up for more than one year. This was the study where the one confirmed and two suspected cases of chondrolysis occurred. The Primary Clinical reviewer referenced an Information for Healthcare Professionals sheet²² that noted chondrolysis was diagnosed within a median of 8.5 months after the infusion. Furthermore of the 60 subjects who participated in this trial, only 31 had a follow-up MRI and a functionality score was not part of the assessment. I therefore believe the long term follow-up in the Posimir shoulder surgery studies was not adequate in duration, number of subjects, or assessments to adequately characterize the risk of chondrolysis.

Systemic bupivacaine toxicity

The Primary Clinical reviewer felt that the Applicant rigorously evaluated 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.

Toxicity associated with Benzyl Alcohol

The BA 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 BA as a preservative. The toxic reactions that might occur following intravenous BA 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.

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

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<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm190302.htm>

products but only in 9% of bupivacaine HCl treated subjects. Since the central nervous system effects were presumably due to systemic effects of the drug, The Primary Reviewer believes that BA may be involved.

Toxicity associated with wound healing / at the site of instillation

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. The local tissue effects of SABER-containing products (i.e., SABER-placebo or SAIB) and SABER-bupivacaine in particular were explored by the Primary Clinical reviewer. The Applicant had combined a number of adverse events under the preferred term “application site discoloration,” e.g., hematomas, suffusions (often used to describe hematomas), bruising, and erythema. The Primary Reviewer separated these events out for analysis based on the verbatim terms. He reviewed the ISS database 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 his opinion) were identified and used to create a database for the analysis that follows. 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 25** summarizes the AEs by treatment group from his analysis.

Table 25. 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. They occurred with greater frequency following hysterectomy than the arthroscopic shoulder surgeries, and as indicated in **Table 26** below, the occurrence with the two SABER products is more striking than it is in the **Table 25** where the AEs are lumped across trials.

Table 26. Hematoma adverse events following hysterectomy

Primary SOC	SABER-bupivacaine N=60		SABER-placebo N=27		Bupivacaine HCL N=27		Total N=114	
Preferred term								
	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 that 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.

7.2.6. Discussion of primary reviewer's comments and conclusions

I was in agreement with most of the Primary Clinical and Statistical reviewer's assessments. Minor differences included, at least my interpretation of their opinions about the 'supportive trials' for the shoulder and hernia models. There were two trials beside BU-002-IM that the Applicant, and from my understanding of their reviews, the Primary Clinical and Statistical Reviewer, believed were supportive of the data from the pivotal trial. Considering the negative results, I do not believe they contribute supportive evidence.

Another difference in our descriptions of the Posimir clinical program is the level that I have expressed my concern regarding the absence of positive trials conducted with sites in the US. While the Primary Clinical reviewer notes this, I believe even the 'positive' results demonstrated in BU-002-IM and CLIN-803-006-0006 require a bridging study to demonstrate that they can be extrapolated to the US patient population.

These differences notwithstanding, I did agree with the Primary Clinical reviewer that the clinical benefit did not outweigh the risks we both discussed.

7.2.7. Pre-Approval Safety Conference

Not applicable

7.2.8. Discussion of notable safety issues (*resolved or outstanding*).

Safety issues are discussed in Section 7 of my review; Section 7.2.5 has Safety Issues that are specific to this application.

8. Advisory Committee Meeting

No advisory committee meeting was convened to discuss this application. An advisory committee meeting was not deemed necessary to judge whether the data were adequate to establish the efficacy or safety of Posimir™ (Bupivacaine) for the indication of post-surgical analgesia.

9. Pediatrics

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.

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 (once approved) 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.

A deferral for children greater than 3 years old should be granted if the adult studies are completed and ready for approval. This was the case, from the Applicant's perspective, prior to submission of the NDA and is likely to be the case if the final regulatory action is a Complete Response, since more Adult trials will likely be required to respond to the deficiencies.

(b) (4)

The Division requested clarification and justification of the one year timeframe from marketing approval to estimated protocol submission of the first pediatric study.

The Sponsor provided a response that the Division felt was generally reasonable and so we concur with the Sponsor's proposed timeline. This time for planning is critical to produce quality protocols using this bupivacaine product in pediatric patients.

10. Other Relevant Regulatory Issues

No other regulatory matters were discussed.

11. Financial Disclosure

No financial disclosure issues were found.

12. Labeling

At this time, the review of the Applicant's proposed product labeling is ongoing.

11.1. Proprietary name

The Office of Prescription Drug Promotion OPDP determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) concurred with the findings of OPDP's promotional assessment of the proposed name.

12. DSI Audits

Two clinical sites were chosen for inspection, Site 001 (Dr. Douglas Nicholson, Australia) and Site 005 (Dr. Richard Turner, Australia) on the basis of enrollment of large numbers of study subjects.

Based on the review of preliminary inspectional findings for clinical investigators Dr. Douglas Nicholson (Site 001) and Dr. John McBride (Site 005) the Study CLIN-803-006-0006, data appear reliable based on available information. The preliminary classifications for the inspections of Dr. Douglas Nicholson (Site 001) and Dr. John McBride (Site 005) are No Action Indicated (NAI).

13. Conclusions and Recommendations

13.1. Recommended regulatory action

I recommend a Complete Response for this application. Posimir has demonstrated a small, statistically significant effect in support of the indication of postoperative analgesia in two of its trials, BU-002-IM and CLIN803-006-0006. However, I am concerned that the Applicant has not demonstrated a significant effect in the target population geographically, namely pain patients from a trial conducted with clinical sites in the United States. The small clinical benefit demonstrated in these trials for Posimir offers over placebo, and even smaller benefit demonstrated over bupivacaine, does not outweigh the added risk from the safety issues discussed in this review that I will summarize below in the bulleted topics below.

- Efficacy – Demonstration and magnitude of the claimed effect

In BU-002-IM, Posimir demonstrated approximately a mean 1-point improvement on the normalized analysis on an 11-point pain scale. Bupivacaine demonstrated a slightly smaller

effect but did not achieve a significant response. Scores in all three treatments²³ remained in what is considered the part of the scale encompassing moderate pain (4 to 7 on the 11-point scale), despite use of study drug and rescue analgesic medication. This suggests a small clinical effect since the initial mean pain score for Posimir was already in this part of the pain scale. The Posimir mean pain intensity score was only statistically different from the placebo arm for the first 12 hours. This was also true for the bupivacaine arm. Both Posimir and bupivacaine arms used less rescue medications (13.7 and 12.3 mg morphine equivalents, respectfully versus 22.8 for placebo), which suggests that Posimir has an analgesic effect though not clinically different from bupivacaine. Most of the secondary endpoints, except AUC48 for pain intensity, were not statistically significant in favor of Posimir. While trending in the direction favoring Posimir, the two other shoulder surgery trials were not statistically positive on the primary endpoints and so I believe these do not lend much in the way of supportive evidence.

In CLIN-803-006-0006, the 5 mL treatment arm (“Posimir 660 mg”) demonstrated a slightly greater than 1 point mean difference that achieved statistical significance. About 20 percent fewer subjects required opioid rescue in the Posimir 660 mg arm than for placebo, however this was not significant according to the primary statistical reviewer’s analysis. The Applicant had specified a step-down method for testing the primary endpoints. Since the first primary was statistically significant, the trial was from a statistical sense, positive. In contrast to the shoulder surgery results, the Posimir 660 mg arm separated for about 34 hours from the placebo arm; at several time points the difference was greater than 2 on the 11-point scale. Secondary endpoints AUC48 and RES72 were positive for Posimir 660 mg, while others were not. In the second trial CLIN-005-0010 the point estimate of the Posimir treatment was less favorable than placebo.

In summary, I think the Sponsor has replicated a post-operative analgesic effect, albeit in different models. However, considering the small magnitude of the effect, particularly for the shoulder surgery model, and considering of the issues discussed in the bullets that follow, I recommend a Complete Response.

- Efficacy – Ability to extrapolate from foreign data

The two ‘positive’ clinical trials were conducted outside of the United States (US) and all of the trials with US sites were negative. While it is likely that the surgical and anesthetic techniques are similar between countries having study sites, there are numerous papers suggesting a cultural difference in pain perception and response in pain trials (Shields, Seikaly et al. 2003; Iorio, Kobayashi et al. 2007; Bjork, Trupin et al. 2011). These differences may even extend to patients perceptions in the US and New Zealand, where many of the clinical trial sites for this program were located (Tait, DeGood et al. 1982).

²³ Although the initial mean pain score for the placebo arm was approximately 8 in the analysis performed by the primary statistical reviewer.

The only significant identifiable difference between the positive trials and negative trials seems to be the location of the study sites. ICHE5(R1) discusses situations where a regulatory agency may have concerns that because of certain factors that may differ between the conduct of the trial between countries, data from a trial conducted in that ‘foreign’ country may not be able to be extrapolated to their own country. In this situation, the two ‘positive’ studies may not be able to contribute to the body of supportive evidence without this bridge for each post-operative pain model. In this instance a bridging study may be needed.

- Local Effects – Persistence of drug product components at the injection site

Nonclinical studies demonstrated long term deposition of drug product (the SAIB component) and long term pathology at the injection site including, fibrosis and chronic granulomatous inflammation. Notably, this long term study was not done with the to-be-marketed formulation.

A primary concern in the shoulder surgery model is the occurrence of chondrolysis. I have expressed my opinion about this issue in Section 7.2.5. In summary, the long term follow-up in the Posimir shoulder surgery studies was not adequate in duration, number of subjects, or assessments to adequately characterize the risk of chondrolysis.

Dr. Simone has also raised a concern about inflammatory skin reactions, particularly in non-white study subjects. His concern about promotion of hypertrophic scarring, particular in non-white subjects who are more at risk has merit from a clinical and scientific perspective considering the inflammatory sequelae associated with Posimir. The number of nonwhite subjects was sparse and the duration of safety assessments too short to fully assess this risk. Though no cases were reported in the safety database, I believe the composition of this dataset does not allow for adequate assessment of this risk.

- Local Effects - Wound healing

There was a 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 also occurred more frequently with SABER-placebo treatment compared to plain bupivacaine treatment suggesting the SABER component plays a role in these reactions, i.e., application site discoloration, contusion, wound secretion, and pruritus.

Clinically, some of these adverse events (e.g., hematoma, dehiscence) present a clear risk of more serious complications, such as wound infections or the need to return to the operating room for a surgical remedy.

- Local effects – Risk of perineural toxicity

Perineural administration of SABER-bupivacaine or its vehicle resulted in an increased frequency of neuronal inflammation and axonal degeneration compared to untreated (right leg), saline treated, or Sensorcaine® treated groups. This effect appeared to result from both the presence of the vehicle, as well as the bupivacaine, since the frequency and/or severity of axonal changes showed incremental increases from control (right leg), to saline, to Sensorcaine®, to bupivacaine-treated groups. While there were not any adverse events directly attributable to this type of toxicity, the followup in most of the trials was relatively short. Furthermore, once approved, surgeries involving perineural sites of instillation would be expected to be common even though they would not be described in labeling.

13.2. Safety concerns to be followed postmarketing

Not applicable

13.3. Risk Minimization Action Plan, if any

Not applicable

13.4. Postmarketing studies, voluntary or required (e.g., under PREA, Subpart H)

See my discussion of PREA studies in the Pediatrics, Section 9

13.5. Comments to be conveyed to the applicant in the regulatory action letter (e.g., deficiencies and information needed to resolve each deficiency)

1. You have presented data from trials for supportive evidence that were conducted outside of the United States while those conducted with sites in the United States were not supportive of your intended indication.

Information needed to resolve the deficiency

Provide an evidence based rationale as to why trials conducted with sites within the United States were negative, while some of those conducted outside of the United States were positive. If you are able to provide this rationale, provide a justification as to why the data from you positive trials may be extrapolated to the target populations in the United States.

Alternatively, conduct bridging studies to demonstrate that the evidence in your studies, BU-002-IM and CLIN-803-006-0006 may be extrapolated to the population in the United States. The results of these studies must be sufficiently robust, in terms of the treatment effect and supportive secondary endpoints, such that the clinical benefit offsets the risks of treatment.

Prior to conducting a trial for the postoperative shoulder surgery model, you will need to address the safety concern noted in Deficiency #2.

2. For the arthroscopic subacromial decompression surgery procedure, the risk of chondrolysis, based on the incidence observed with SABER-bupivacaine treatment, outweighs the benefit of SABER-bupivacaine for this surgical procedure and prevents its approval for this indication.

Information needed to resolve 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. Sufficient subjects should be exposed to SABER-bupivacaine at the intended dose to characterize the risks that occur in 1% of the treatment arm. The safety assessments must be of adequate in terms of duration and rigor to characterize the risk and should include radiologic and functional evaluations.

The post-operative shoulder surgery trial used to address Deficiency #1 may be used to address this deficiency.

3. For the non-orthopedic surgical procedures, the incremental benefit over bupivacaine does not justify the incidence of adverse effects.

Information needed to resolve the deficiency

Adequately demonstrate the efficacy of SABER-bupivacaine by either repeating the trials for non-arthroscopic procedures already assessed but using a 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. The adverse reactions in the post-operative pain models where you are able to demonstrate efficacy must occur at an incidence similar to that of bupivacaine HCl. Sufficient subjects should be exposed to SABER-bupivacaine at the intended dose to characterize the risks that occur in 1% of the treatment arm.

The post-operative non-orthopedic surgery trial used to address Deficiency #1 may be used to address this deficiency.

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/s/

CHRISTOPHER D BREDER
01/22/2014

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 AUC_{0-72} , 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 AUC_{0-72} , 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 than 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.

Other Safety Concerns Related to the Use of SABER-Bupivacaine

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 through 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 be 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 than 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 opioid-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 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.

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 laparoscopically 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 $AUC_{0-72 \text{ hours}}$ 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_{0-120} ; 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 AUC₁₋₇₂ 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_{0-72} . 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_{0-72} 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/m²)		
≤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/m²)		
≤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/m²)		
≤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 $AUC_{0-72 \text{ hours}}$ 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.

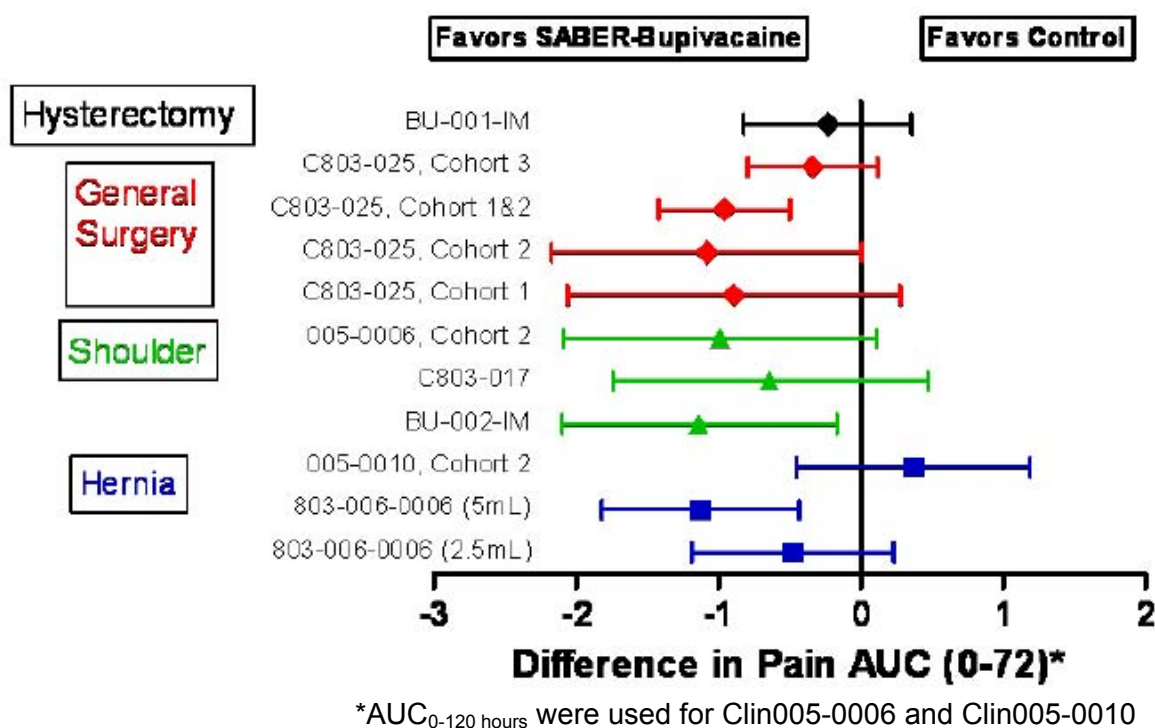


Figure 1. Forest plot of the differences in normalized pain AUC_{0-72} between SABER-bupivacaine and the control treatment for the randomized, double-blind, controlled trials

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 AUC₀₋₇₂ analyses.

Soft Tissue Surgical Procedures

For the primary endpoint, AUC₀₋₇₂ 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 AUC₀₋₇₂ 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 AUC₀₋₇₂ 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-statistic ¹	0.86	0.86
p-value ¹	<0.0001	<0.0001
Wilcoxon Rank Sum Test		
Median Difference ²	-12.4	
95% CI ²	(-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 AUC₀₋₇₂ 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 AUC₀₋₇₂ 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 AUC₀₋₇₂ 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 $AUC_{0-72 \text{ hours}}$ 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.

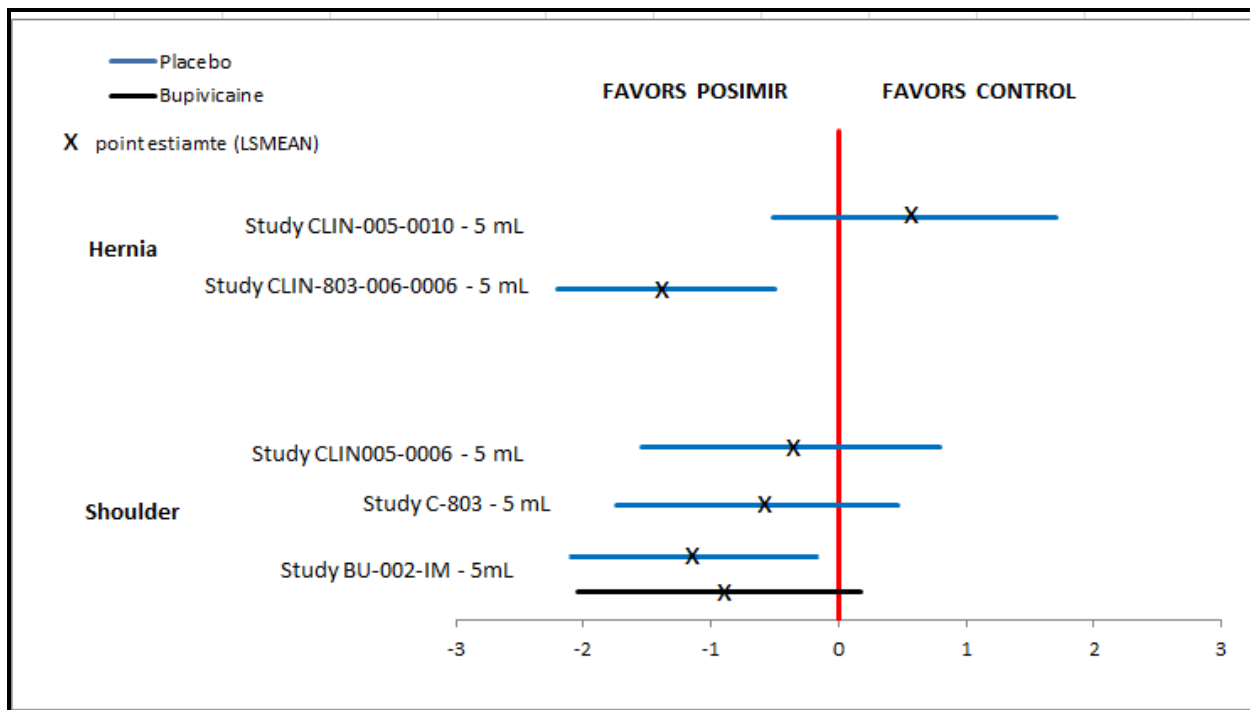


Figure 2. Forest plot of AUC₀₋₇₂ for pain intensity scores for trials involving subjects undergoing either herniorrhaphy or arthroscopic subacromial decompression (combined Figure 5, p 19, and Figure 8, p. 29, from the statistical review)

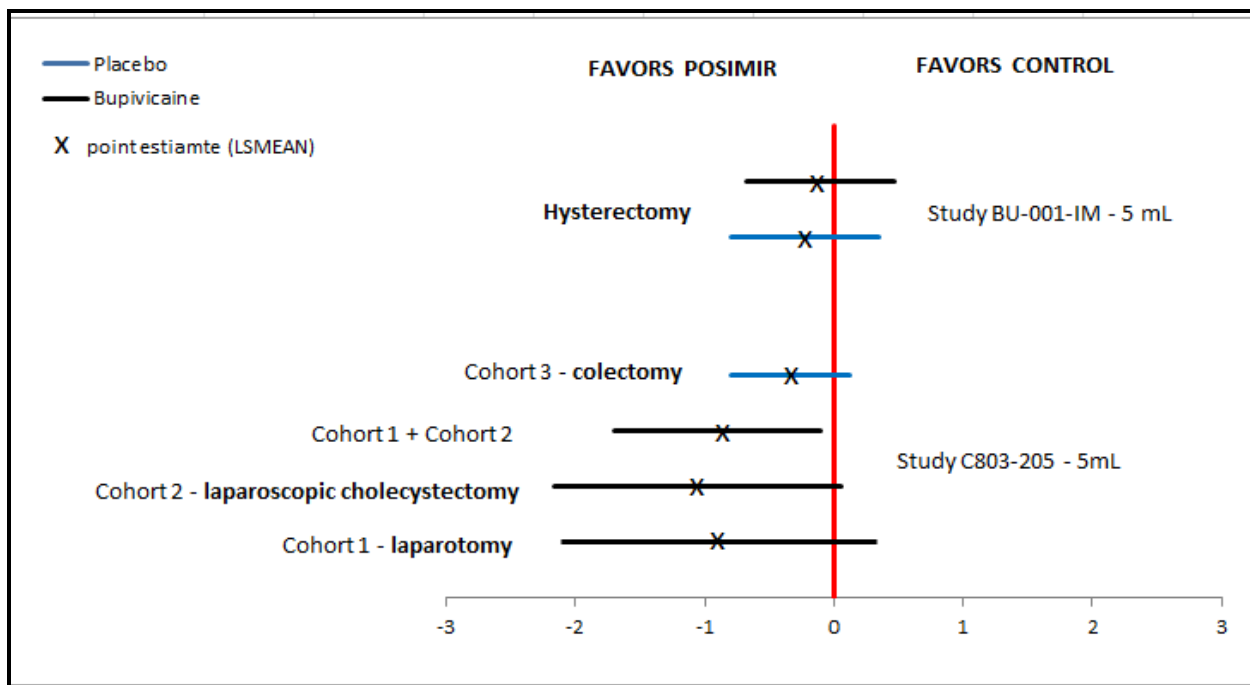


Figure 3. Forest plot of AUC₀₋₇₂ for pain intensity scores for trials involving subjects undergoing surgery other than herniorrhaphy or subacromial decompression (Figure 9, p. 32 of the statistical review)

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)

[†] 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) bupivacaine base, (b) (4) and (b) (4) sucrose acetate isobutyrate (SAIB) on a % w/w basis. The product was administered by subcutaneous injection using doses of 2.5 and 5 mL. 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 C803-017 and 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 “hypoesthesia” 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 (b) (4)-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	X ³	X	MRI
BU-002-IM	X	X	X	X	X	X	X ¹	X	X ³	X	MRI
C803-017	X	X	X	X	X	X			X ⁴		MRI
C803-017e	X	X				X				X	MRI
C803-025	X	X	X	X	X	X	X ¹	X			
C803-027	X	X	X	X	X	X	X				Punch biopsy and histopathology

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 T_{max} 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 C_{max} data for

the treatment emergent SAE cases showed that the median C_{max} was 730 [range: 52-1870] ng/mL. Eleven of the SAE cases had C_{max} >1000 ng/mL, however all but one of the cases occurred well after the T_{max}.

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 presyncope, syncope 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

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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, glenohumeral 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	SABER-bupivacaine N=60		SABER-placebo N=27		Bupivacaine HCL N=27		Total N=114	
Preferred term								
	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 C_{max} 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 based 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)) 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 T_{max}. 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 T_{max} and C_{max} 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 Δ QTcF 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 Δ QTcF close to zero. The initial increase in Δ QTcF 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 ($\Delta\Delta$ QTcF) 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 Δ QTcF. 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 C_{max} for SABER-bupivacaine were -9 msec and -4 msec for trails C803-025/BU-001 and BU-002, respectively. The estimated QTcF changes at C_{max} 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, they 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 compared 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 its 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 C_{max} 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 tenotomy
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 (b) (6) 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

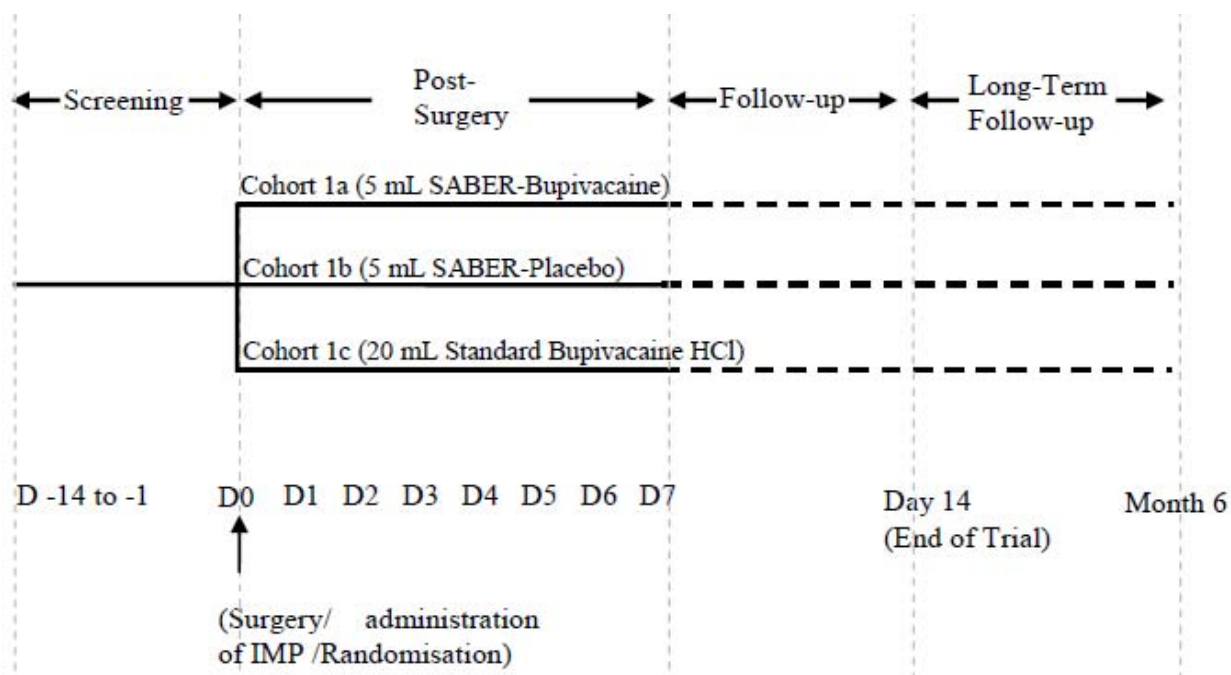


Figure 5. Study schematic (Figure 9-1, p.32 of the final study report)

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.

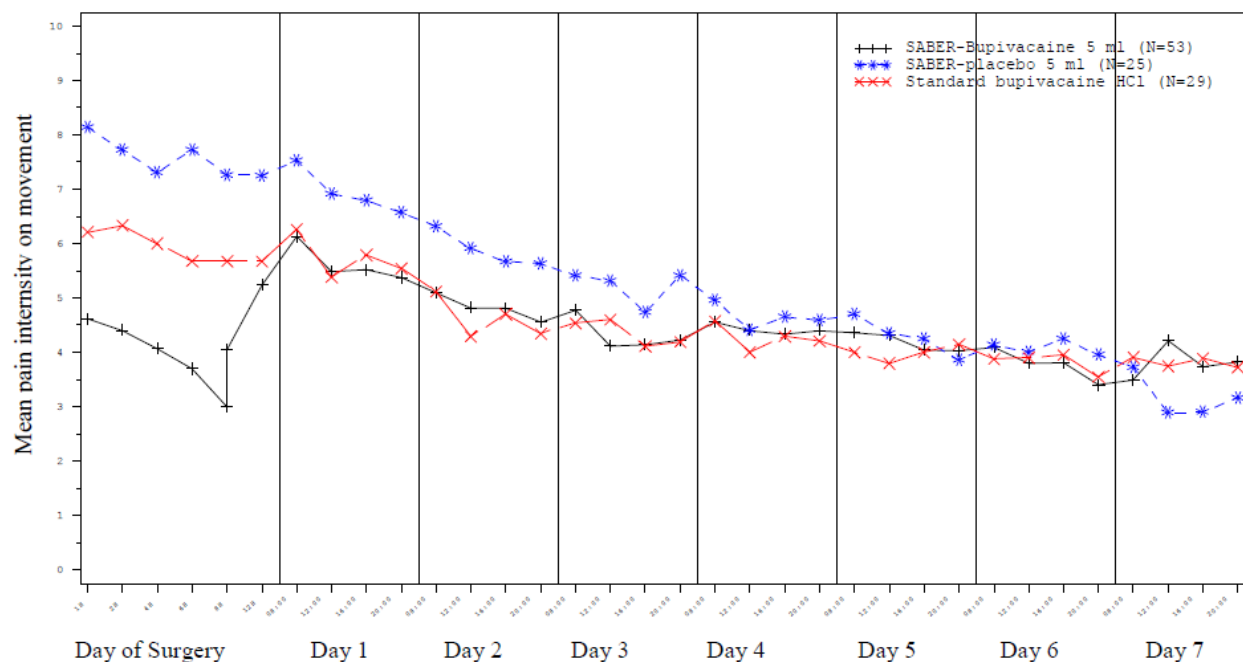


Figure 6. Pain intensity on movement over time in the ITT population (Figure 11-1, p. 80 of the final study report)

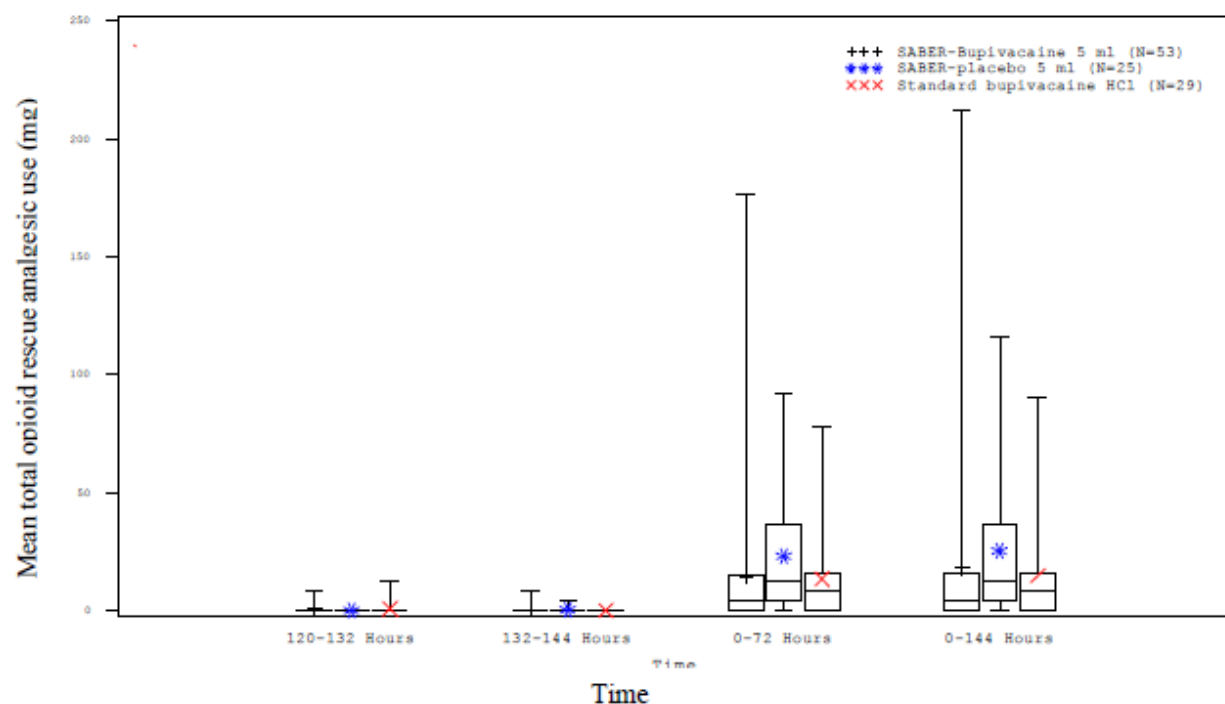


Figure 7. Mean total opioid rescue over time in the ITT population (Figure 11-2, p. 85 of the final study report)

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 SOC 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 SOC 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 $\geq 1\%$ 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.

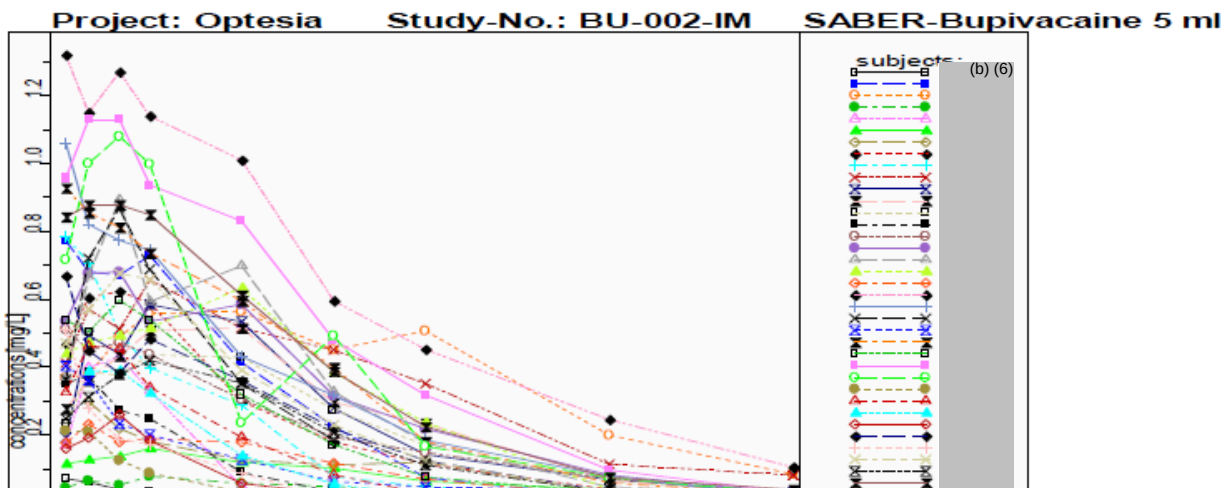


Figure 8. Individual total bupivacaine plasma concentrations following SABER-bupivacaine (Figure 11-3, p 105 of final study report)

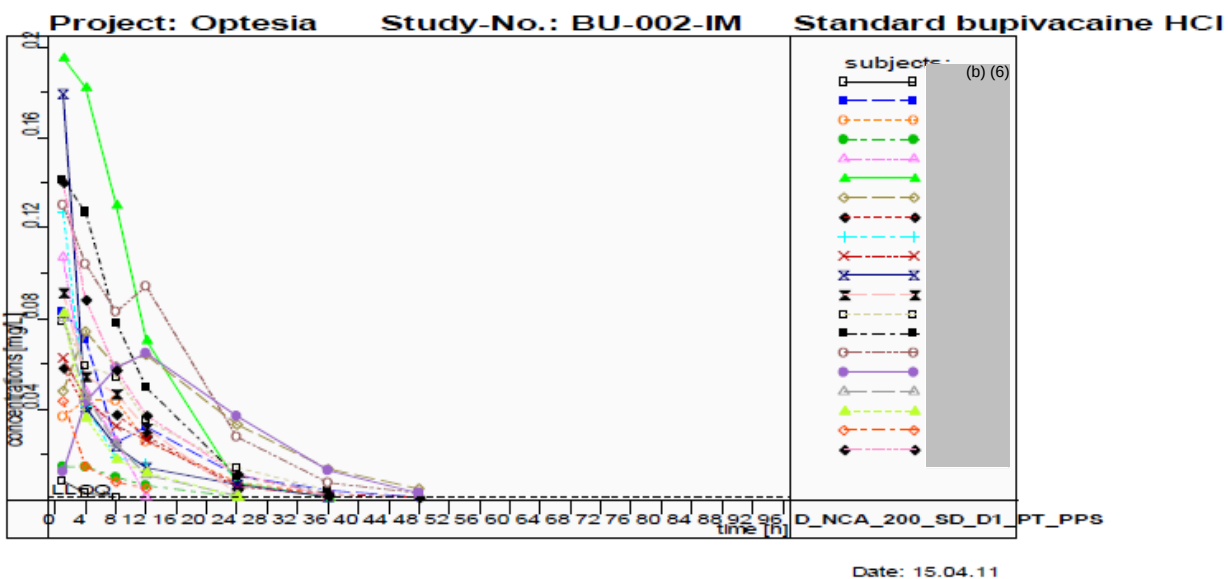


Figure 9. Individual total bupivacaine plasma concentrations following bupivacaine HCl (Figure 11-4, p 105 of final study report)

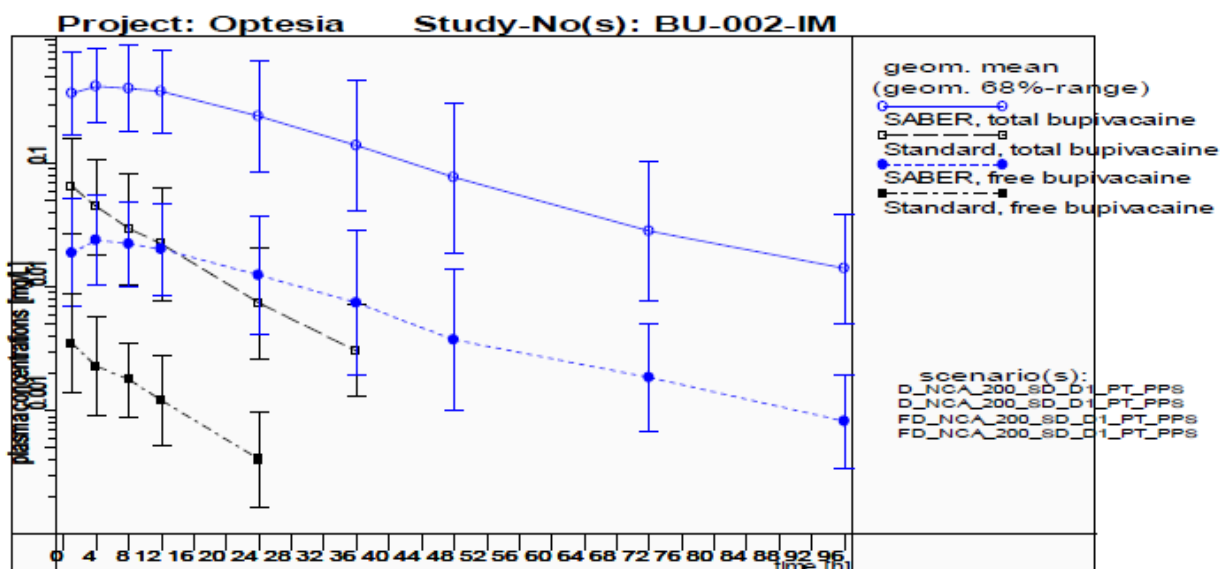


Figure 10. Geometric mean total and free bupivacaine plasma concentrations following SABER-bupivacaine and bupivacaine HCl administration (Figure 11-5, p. 106 of final study report)

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 tryptiline 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

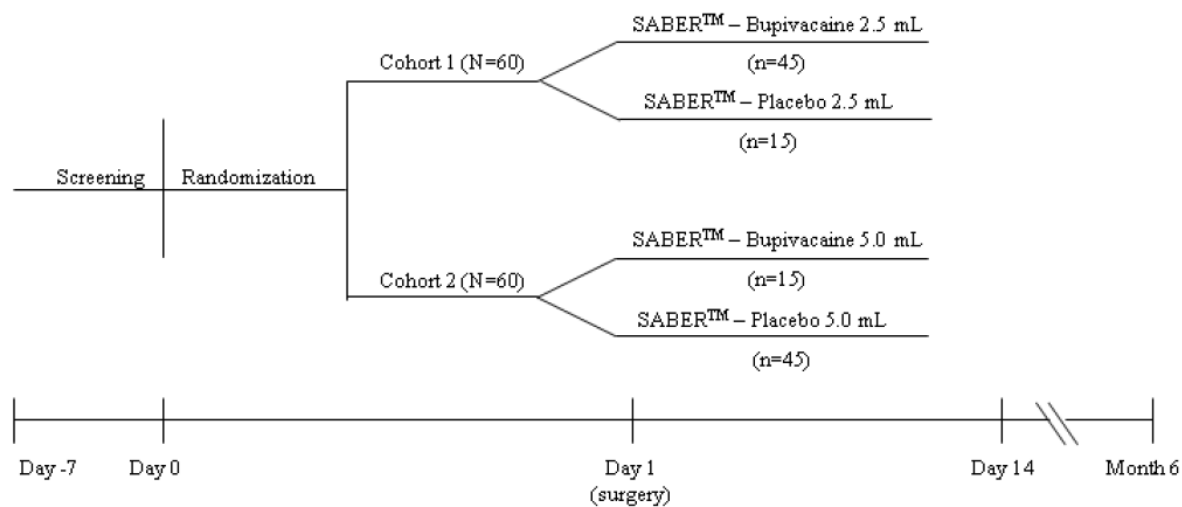
- ensure safety, pharmacokinetic, and pharmacodynamic trends remained acceptable
 - e. reducing the number of pharmacokinetic profiles required to a minimum of 32 complete profiles to be consistent with the removal of the 7.5 mL Cohort while ensuring adequate data collection within Cohorts 1 and 2
 - 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 discoloration	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/m²

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

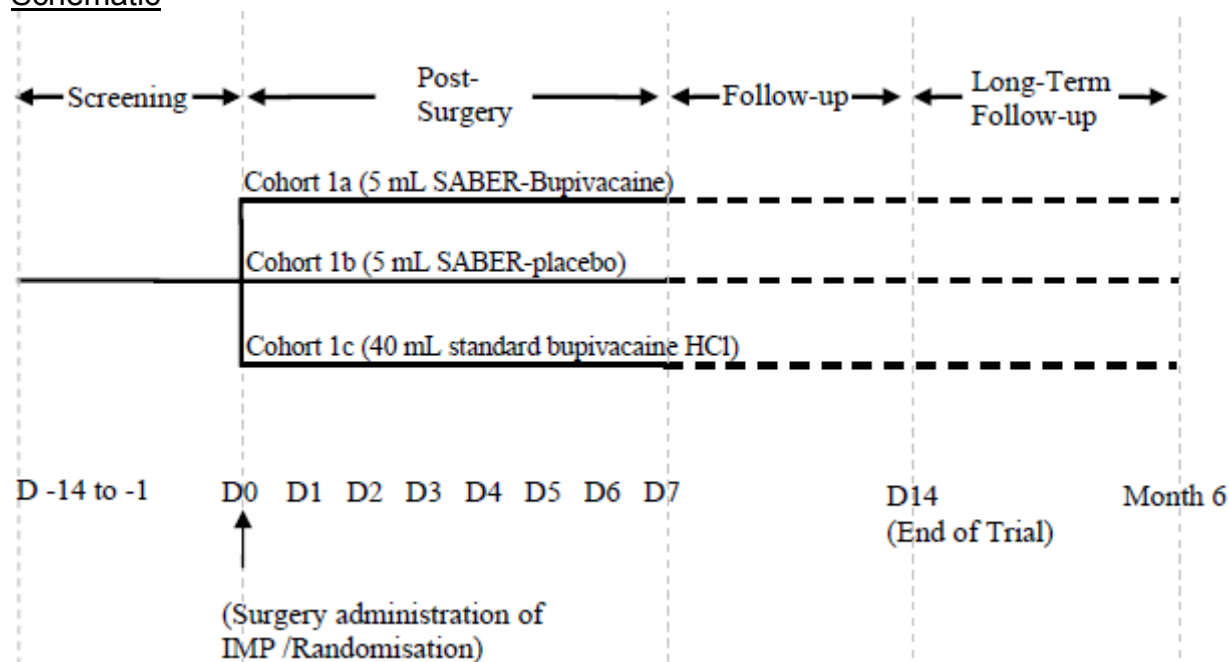


Figure 11. Study schematic (Figure 9-1 on p. 28 of the final study report)

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	

- 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.

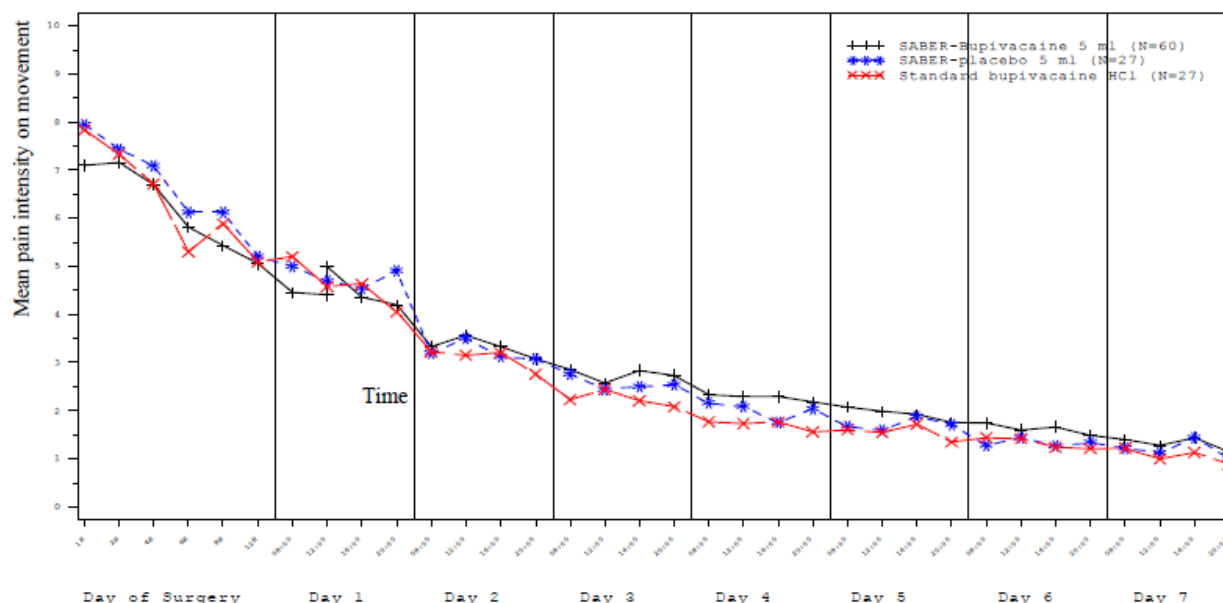


Figure 12. Mean pain intensity on movement over time for the ITT population (Figure 11-1, p. 73 of the final study report)

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.

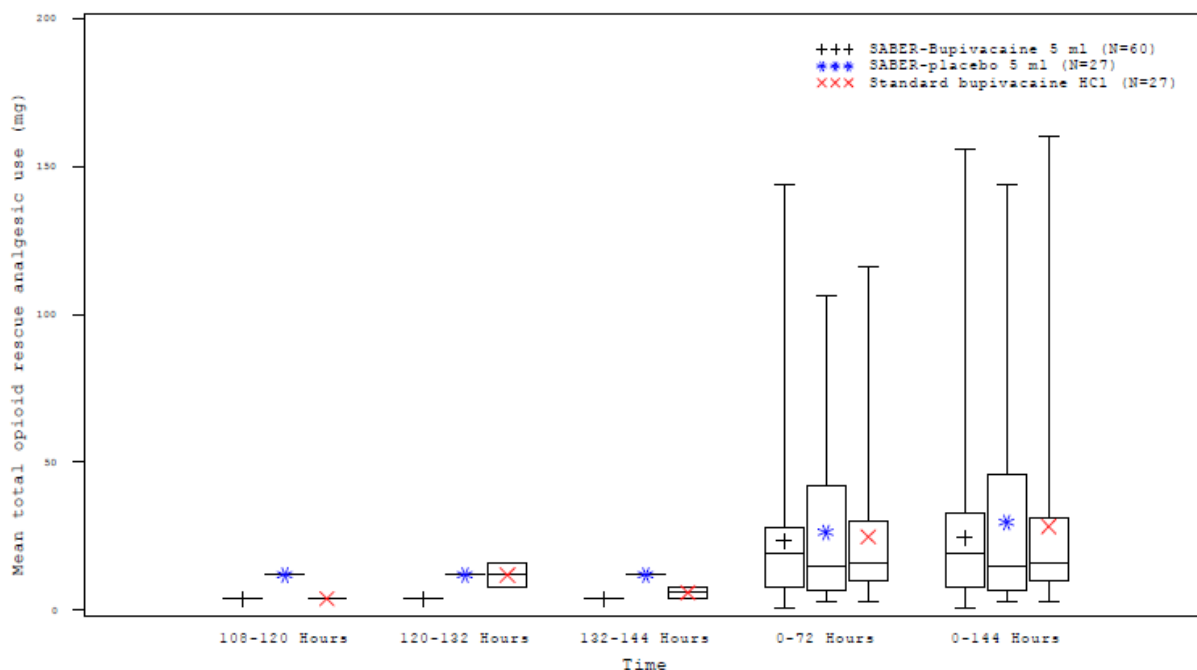


Figure 13. Mean total opioid rescue over time in the ITT population (Figure 3.3, p. 448 of the final study report)

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	SABER-bupivacaine N=60		SABER-placebo N=27		Bupivacaine HCL N=27		Total N=114	
Preferred term	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 SOC 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 C_{max} -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/m².
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)

<i>Study Phase</i>	Screening	Treatment	Follow-up			Study Completion
<i>Visit Name</i>		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_{0-120 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_{0-120 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 SABER-Placebo 5 mL+SABER-Bupivacaine 5 mL (n=11)	Treatment 2 SABER-Bupivacaine 5 mL+SABER-Placebo 5 mL (n=18)	Treatment 3 and Treatment 4 SABER-Placebo 5 mL+SABER-Placebo 5 mL and SABER-Placebo 5 mL (n=35)	Treatment 5 SABER-Bupivacaine 5 mL (n=21)	Treatment 5a 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 5 mL 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/m²
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 $\pm$ 1 day, a final clinic visit on Day 14 $\pm$ 3 days, and a 1-Month Follow-up Call on Day 30 $\pm$ 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.

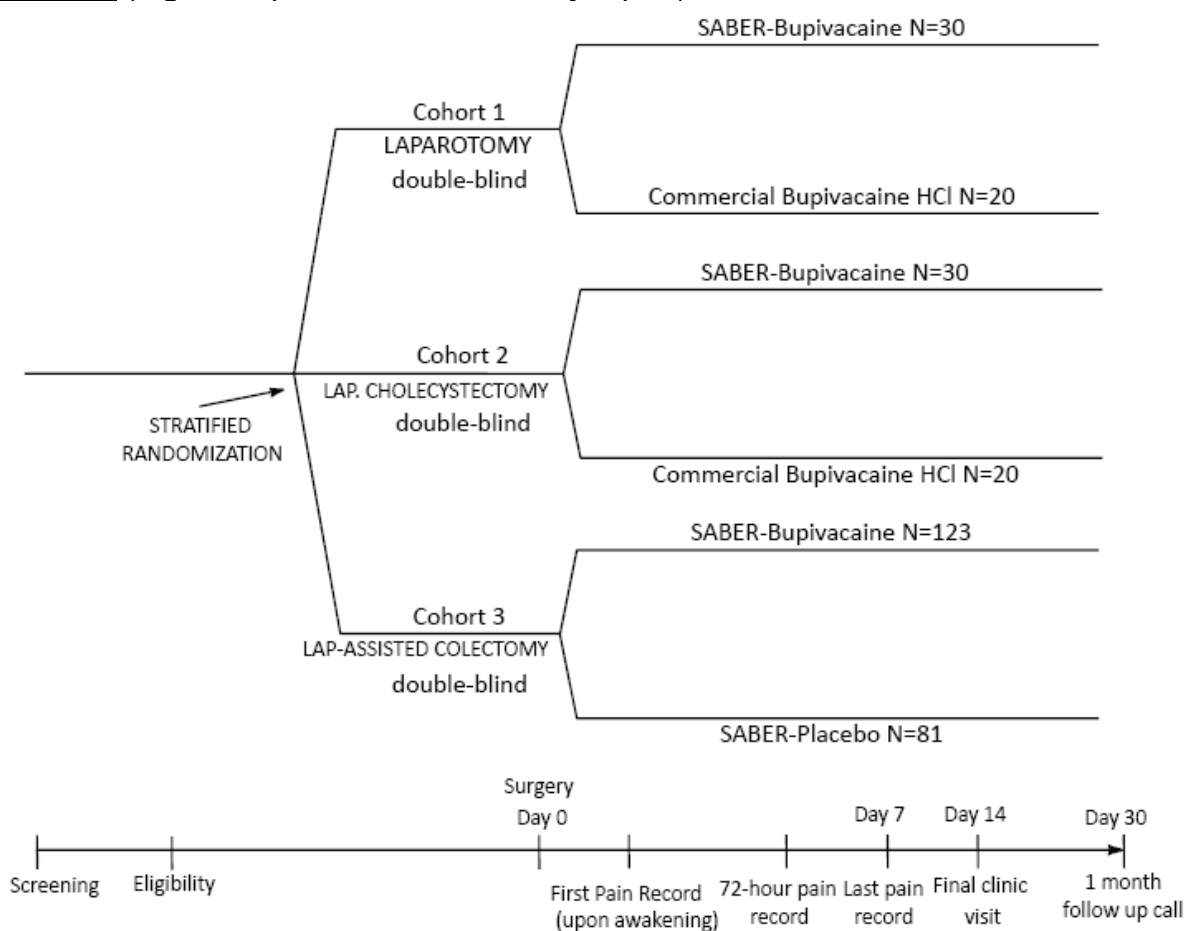
Amendments

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)

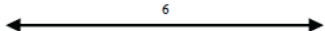
- e. Added that digital pictures of surgical wounds might be acquired at selected clinical sites to facilitate tracking of wound healing progress and support the description of observations around surgical incisions, with no planned systematic or standardized analysis of images
- f. Added descriptions 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)



Clinical Review
 Arthur Simone, MD, PhD
 NDA 204803
 Posimir (SABER-Bupivacaine)

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)	√					√	√	
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 a 10-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		Total
	SABER-Bupivacaine	Bupivacaine HCl	SABER-Bupivacaine	Bupivacaine HCl	SABER-Bupivacaine	SABER-Placebo	SABER-Bupivacaine	Bupivacaine HCl	
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).

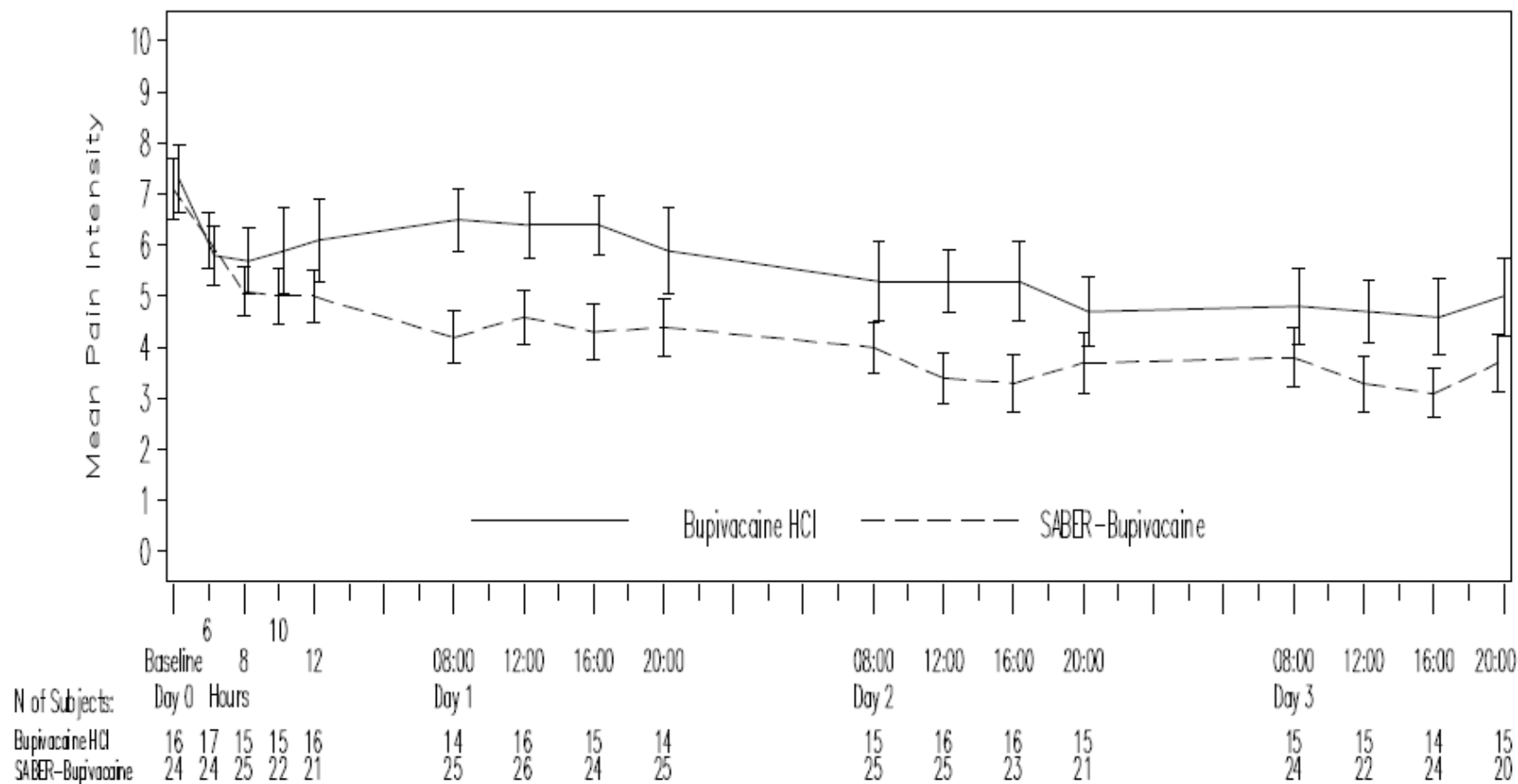
Both Cohorts 1 and 3 had higher pain intensity on movement AUC than Cohort 2, which involved a less extensive surgical procedure. In all 3 cohorts and all treatment groups, there was a 1 or 2-unit reduction in mean pain score (NRS 1-10) AUC over the 3-day observation period, with Cohort 2 reaching mild 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.

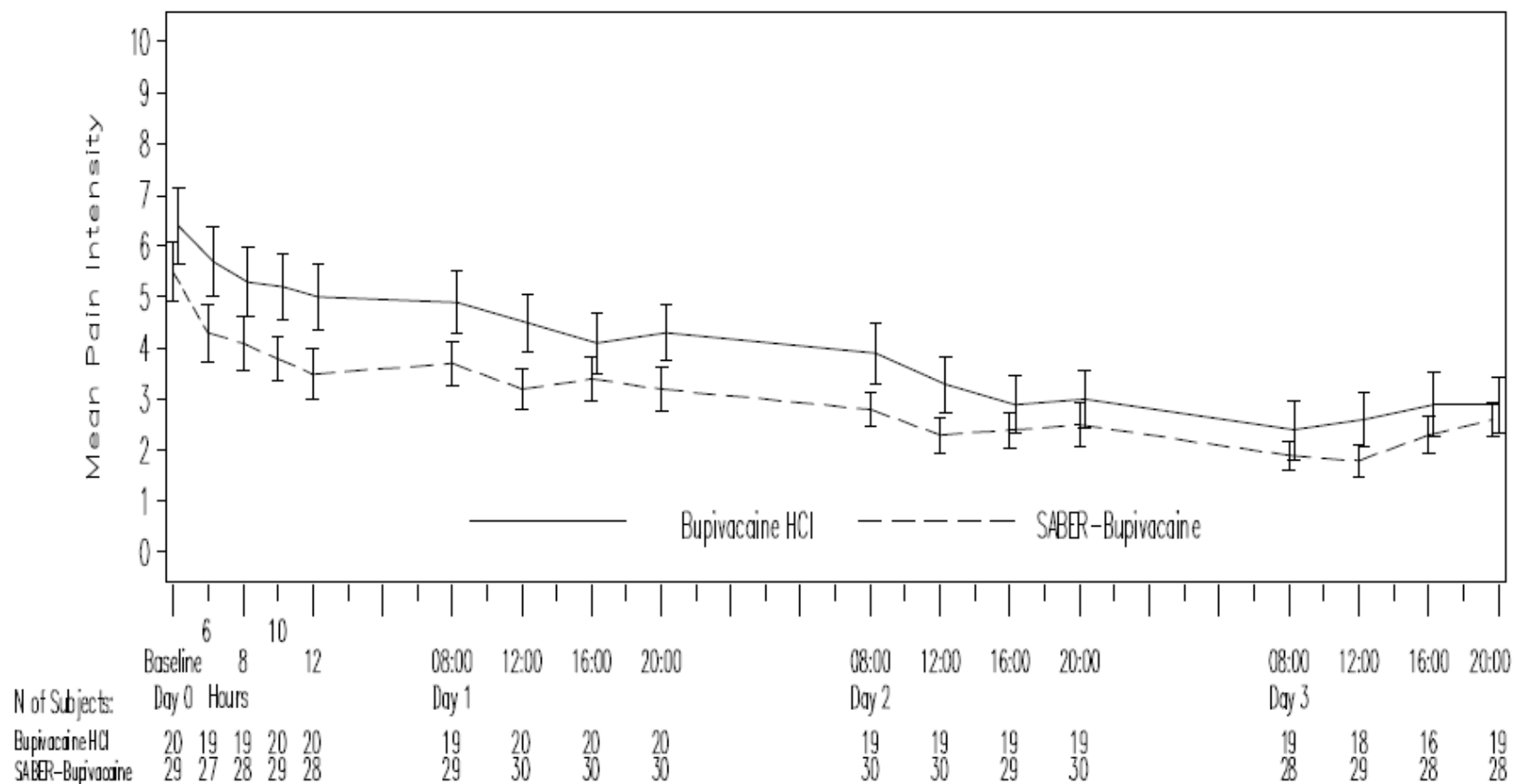
In Cohort 3 there was minimal, but consistent, pain relief compared to placebo over the 3-day period, although statistical significance was not achieved at any time interval. It was noted that there was extensive use of opioids in this treatment group and that the majority of the 5 mL of study drug volume 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 ($\pm$ SE) pain intensity on movement over time for Cohort 1 - Laparotomy (Figure 6. p. 85 of final study report)



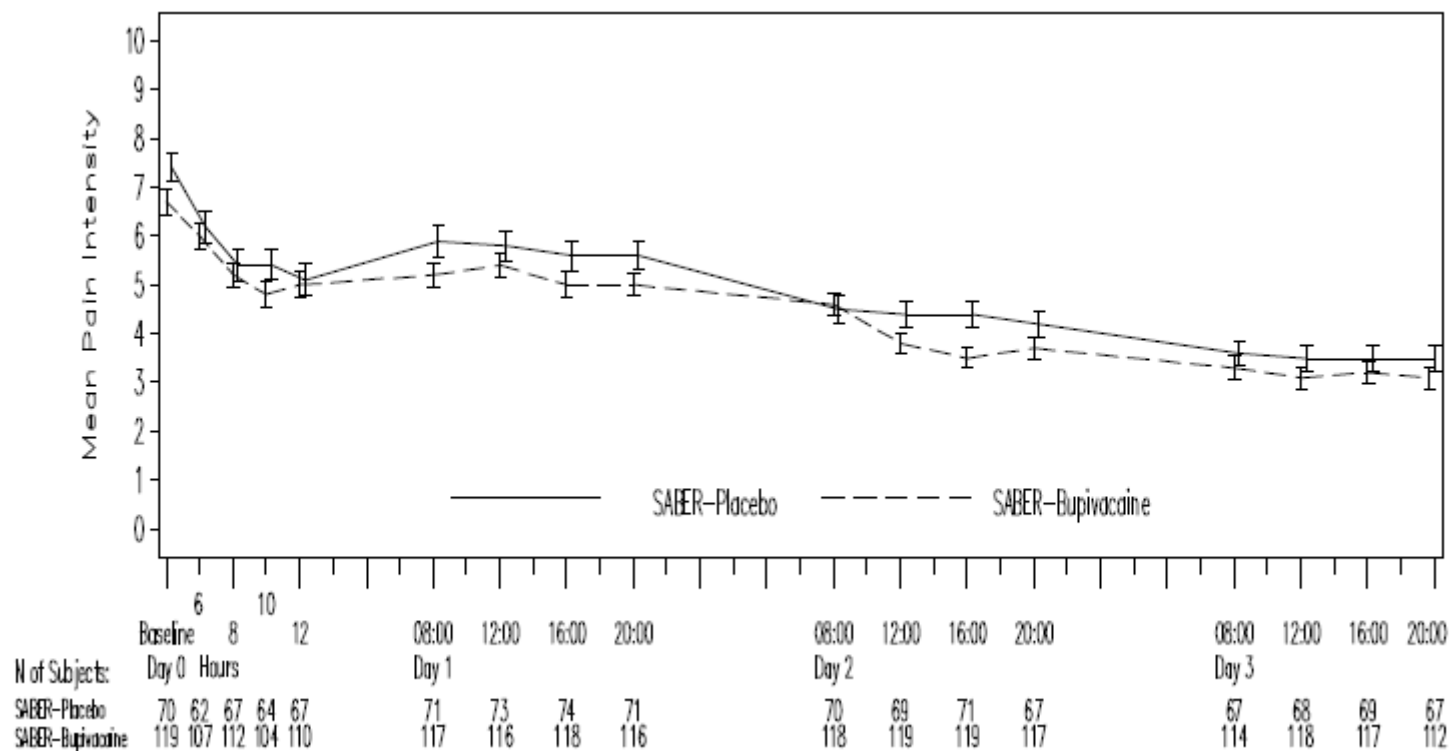
Note: Baseline was the first pain score recorded between end of treatment and 4 hours post-dose. Missing baseline pain scores were imputed with the worst value during first 24 hours.

Figure 15. Mean ($\pm$ 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 ($\pm$ 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 approximately 190 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 ($\Delta\Delta QT_{cF}$ and $\Delta\Delta QT_{btb}$). In the time-matched analysis, occasional mean peak $\Delta\Delta QT$ 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

$\Delta\Delta QTcF$ (24 hours) and $\Delta\Delta QTbtb$ (1 and 16 hours) and not at the time for the observed peak bupivacaine plasma peak levels (48 hours).

- Exposure response analysis of $\Delta\Delta QTc$ and $\Delta\Delta QTbtb$ does not provide evidence of bupivacaine-induced QT prolongation in this setting. Using the concentration effect model, predicted QT effect levels ($\Delta\Delta QTcF$ and $\Delta\Delta QTbtb$) 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 C_{max}. Importantly, there were no differences in the incidence of cardiovascular or neurological AEs with increasing C_{max}. There were no AEs suggestive of bupivacaine toxicity in any of the patients in the C_{max} >1500 ng/mL subgroup.

Summary of Reported Pharmacokinetic Findings

The PK findings for C_{max} and T_{max} 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)	Bupivacaine HCl (n=18)
	C _{max} (ng/mL) Mean (SEM) [Range]	955.6 (88.5) [133 – 1870]	250.6 (44.8) [19 – 551]
	T _{max} (hr) Median [range]	48.1 [2-73]	16.3 [1-48]
2		SABAER-bupivacaine (n=30)	Bupivacaine HCl (n=20)
	C _{max} (ng/mL) Mean (SEM) [Range]	752.1 (56.0) [357 – 1850]	370.5 (55.0) [101- 1170]
	T _{max} (hr) Median [range]	24.3 [1 – 49]	0.9 [1 – 24]
3		SABAER-bupivacaine (n=129)	SABER-placebo
	C _{max} (ng/mL) Mean (SEM) [Range]	849.6 (42.1) [92 – 2850]	N/A
	T _{max} (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 (PI_{move}) and pain intensity at rest (PI_{rest}), 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/m².
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 Visit Name	Screening	Treatment Day 0 ^a	Follow-up			Study Completion Day 14
			Days 1 to 3	Days 4 to 7	Days 8 to 13	
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 06-03 (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.

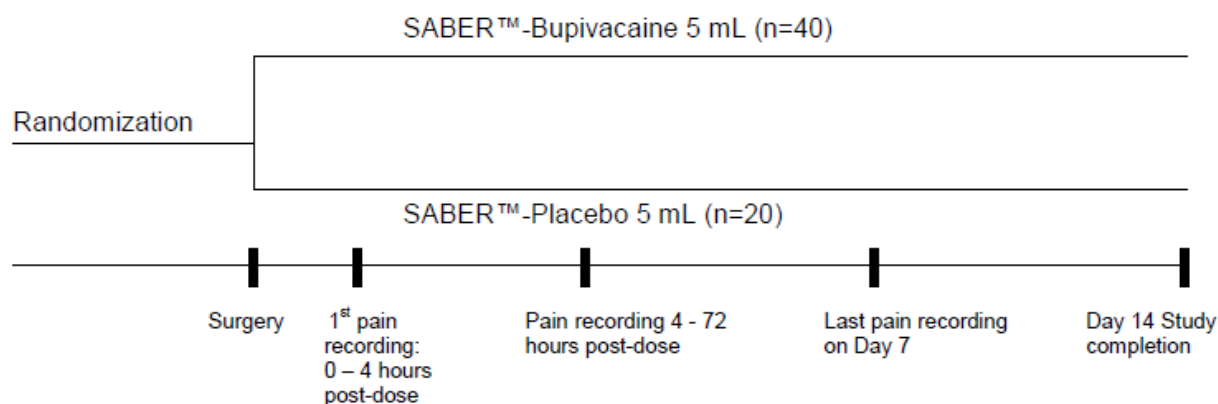
The trial was conducted at eight sites in Australia and two sites in New Zealand.

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 ($\pm$ 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

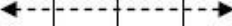
3. Serum pregnancy test for females of childbearing potential

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											
	Pre-Dose	Hours Post-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				

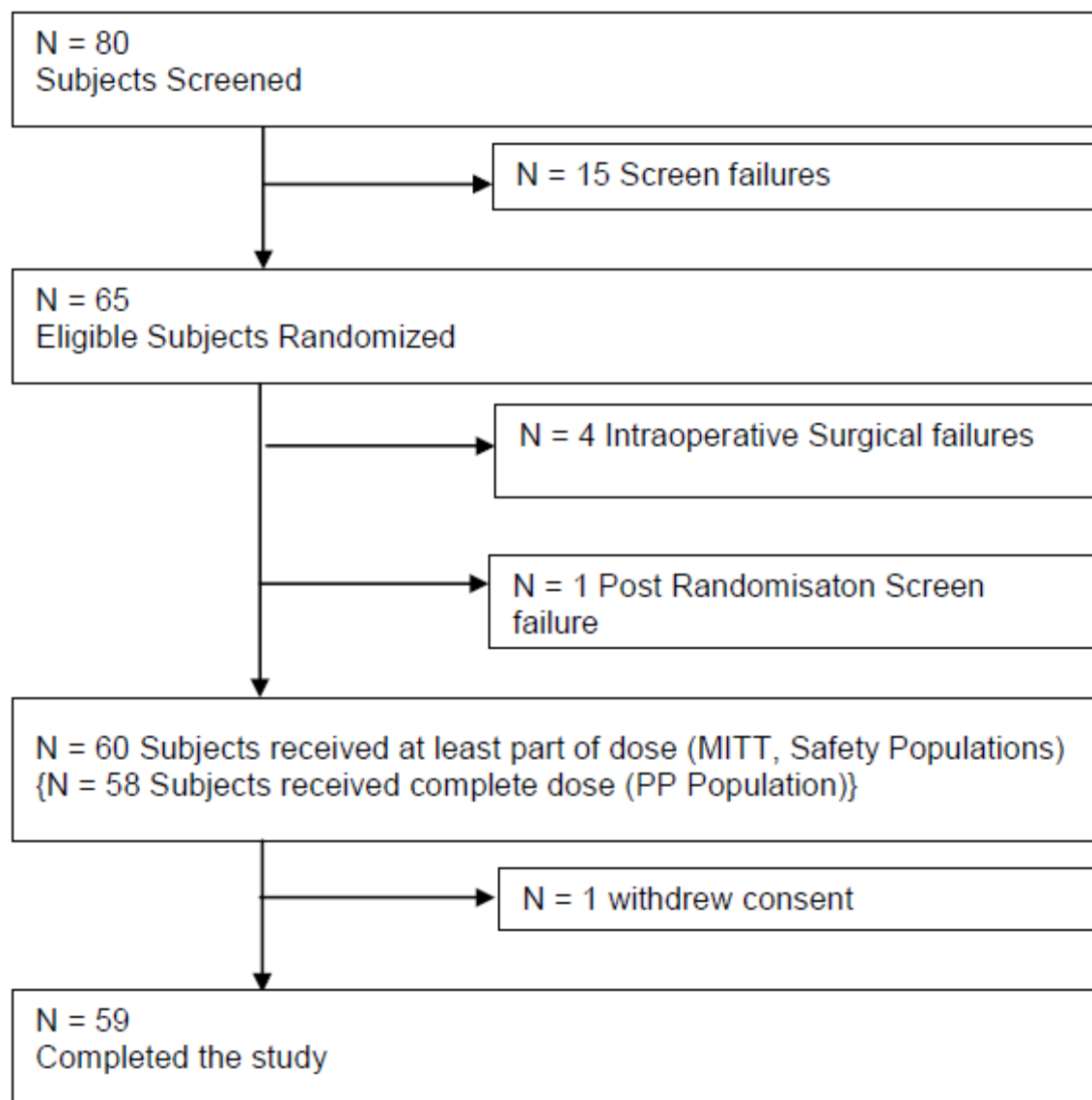
1. Pain intensity on movement evaluation was to be done prior to taking supplemental opioid analgesia and recorded in the paper diary; Supplemental analgesic taken was to be recorded in the paper diary
3. Specific details were to be recorded in the paper diary
4. Constipation, drowsiness, dizziness, 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 ($\pm$ 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 ($\pm$ 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:

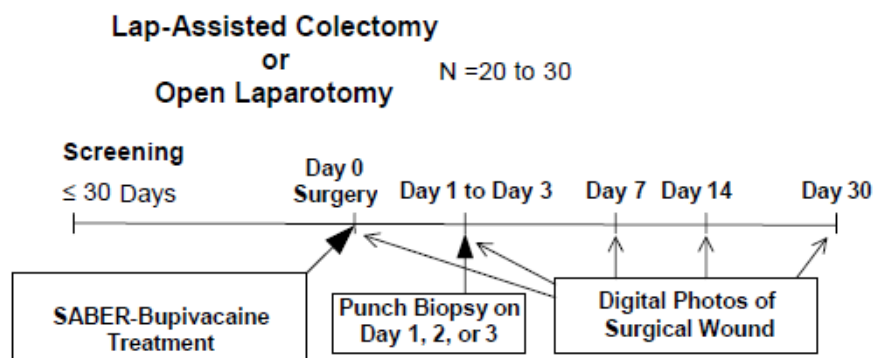
- Updated the medical monitor contact and increased the number of sites from three to four.

(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 90° angle to the main surgical wound, two at a +45° angle, and two at a -45° 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 to C803-025, the AUC₀₋₇₂ 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-Pietramaggiore 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 devices are 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 bupivacaine-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:

¹The 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