

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204803Orig1s000

SUMMARY REVIEW



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

**Cross-Discipline Team Leader Review
 and Division Director Summary Review**

Date	February 1, 2021
From	Martha A. Van Clief, MD; Rigoberto Roca, MD
NDA Number	204803
Applicant	Durect Corporation
Date of Original Submission	April 12, 2013 Complete Response letter issued February 12, 2014
Date of Complete Response Submission	June 27, 2019
PDUFA Goal Date	December 27, 2019
Proprietary Name	Posimir
Established or Proper Name	Bupivacaine solution
Dosage Form Strength	Solution for infiltration, 660 mg bupivacaine/ 5mL (132 mg/mL)
Applicant Proposed Indication	Indicated for single-dose instillation into the surgical site to produce post-surgical analgesia in adults.
Applicant Proposed Dosing Regimen	The recommended dose of POSIMIR is 5 mL (660 mg) directly into the surgical incision(s) or other relevant anatomic spaces. (b) (4)
Regulatory Action	Approval
Indication	Indicated for administration into the subacromial space under direct arthroscopic visualization to produce post-surgical analgesia for up to 72 hours following arthroscopic subacromial decompression.
Dosing Regimen	Administer the entire 5 mL dose of Posimir into the subacromial space using an 18 gauge or larger-bore needle. Confirm correct placement of the needle tip within the subacromial space by direct arthroscopic visualization.

Material Reviewed/Consulted	
OND Action Package, including reviews by:	
Medical Officer Review	Renee Petit-Scott, MD
Statistical Review	Kate Meaker; Jinglin Zhong, Ph.D., Mark Rothmann, PhD; Ya-Hui Hsueh, PhD and Eugenio Andraca-Carrere, PhD
Pharmacology Toxicology Review	Misol Ahn, PhD; Jay H. Chang, PhD; Dan Mellon, PhD, Tim McGovern, PhD
OPQ Review	Drug Product: Valerie Amspacher, PhD and Julia Pinto, PhD, Manufacturing: Jonathan Swoboda, PhD and Ubrani Venkataram, PhD; Microbiology: Bernary Marasa, PhD and Neal Sweeney, PhD, ATL: Valerie Amspacher; Branch Chief: Julia Pinto, PhD
Microbiology Review	Bernard Marasa, PhD and Neal Sweeney, PhD;

OND=Office of New Drugs OPQ=Office of Pharmaceutical Quality

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Benefit-Risk Assessment Framework

This is the second review cycle for NDA 204803. The initial NDA was submitted on April 12, 2013, and a Complete Response Letter (CRL) was issued on February 12, 2014, based on unresolved safety concerns identified during the review and not adequately addressed in response to the Discipline Review Letter (DRL), issued on January 14, 2014. The primary clinical reviewer of the initial NDA submission, Dr. Arthur Simone, identified clinical deficiencies related to both efficacy and safety of SABER-bupivacaine, which were communicated in the DRL. The Applicant submitted information to address the identified deficiencies on February 3, 2014, and Dr. Simone determined that the efficacy deficiencies had been adequately addressed, such that the CRL included only the following safety concerns.

- 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

Subsequent to the CRL, an End-of-Review-Cycle Meeting was held on September 23, 2014, at which time the Applicant was advised to conduct an additional study in a soft tissue model to support the proposed postsurgical analgesic indication. The Applicant stated at that time that a post-arthroscopic shoulder indication would no longer be pursued. The Applicant submitted a Formal Dispute Resolution Request (FDRR) on November 21, 2014, which asked for an additional determination of safety and efficacy, despite the fact that the CRL contained only safety-related deficiencies. Dr. Mary Thanh Hai, the Office Deputy Director at the time, concluded that because only modest efficacy was demonstrated in two surgical models, arthroscopic subacromial decompression and inguinal hernia repair, a more careful consideration of the risks was required. Dr. Thanh Hai and the review team discussed the potential path(s) forward to address the identified safety deficiencies with the Applicant, including an additional clinical evaluation to better characterize the benefit-risk profile of SABER-bupivacaine or for the Applicant to submit all the information provided in the End-of-Review Meeting background materials with justification as to why it was supportive of a favorable benefit-risk profile for SABER-bupivacaine. On January 15, 2015, an FDRR denial letter was issued. For additional information regarding the regulatory history of this NDA and corresponding IND, refer to the clinical review completed during the second review cycle by Dr. Renee Petit-Scott.

Regarding the efficacy of SABER-bupivacaine, results from Study BU-002-IM, an evaluation in patients undergoing arthroscopic subacromial decompression, demonstrated a statistically significant difference in mean pain intensity with movement through 72 hours (calculated as area under the curve) between the SABER-bupivacaine and SABER-placebo treatments. Dr. Thanh Hai and the review team concluded during review of the FDRR that because the primary efficacy endpoint had been met, despite the minimally invasive surgical procedure and lack of a demonstrated benefit over immediate-release bupivacaine, efficacy in this surgical population had been established. Dr. Thanh Hai and the review team noted that while Study CLIN803-006-0006 in patients undergoing open inguinal hernia repair met the primary efficacy endpoint, a similarly conducted study, CLIN005-0010, did not.

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Subsequent to the FDRR denial, the Applicant conducted an additional randomized, parallel-group, double-blind Phase 3 study, C803-028 (PERSIST), evaluating the safety and efficacy of SABER-bupivacaine in patients undergoing laparoscopic cholecystectomy (lap chole). During review of this protocol, the Division advised the Applicant to include active comparator and non-SABER control groups to better characterize the true clinical benefit of SABER-bupivacaine and the safety profile of the SABER component of the drug product. The Applicant did not initially incorporate our recommendations into the protocol, therefore, the study was conducted in two parts; Part 1 used saline placebo and Part 2 used bupivacaine as an active comparator. Results from this study failed to demonstrate efficacy, pain intensity with movement from 0 through 72 hours, over saline placebo or bupivacaine; however, the Applicant terminated Part 1 early due to the introduction of the bupivacaine active comparator arm such that it was not adequately powered to demonstrate efficacy. Additionally, there were no statistically significant differences in any of the secondary efficacy endpoints, including total IV morphine-equivalent dose and proportion of patients taking no opioid rescue.

During review of the NDA resubmission, Dr. Petit-Scott concluded that the Applicant did not provide 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, did not recommend approval. She stated that the administration of SABER-bupivacaine into surgical wounds has not been demonstrated to reliably and consistently improve post-operative pain or reduce post-operative opioid analgesic use. She further stated that the 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 Division agrees with her conclusion regarding the lack substantial evidence of effectiveness for open inguinal hernia repair, given that two studies had conflicting results; i.e., one study demonstrated superiority over SABER-placebo and the second study did not. The Division does not, however, agree with her conclusions regarding the efficacy demonstrated during arthroscopic shoulder surgery.

Dr. Petit-Scott had three concerns regarding the evaluation of safety and efficacy of SABER-bupivacaine in patients undergoing shoulder procedures. First, she was concerned that shoulder procedures were the only orthopedic model in which SABER-bupivacaine was evaluated, and that superiority was demonstrated only in arthroscopic subacromial decompression, the least invasive procedure evaluated and likely less painful than other procedures such as rotator cuff repair. The two other studies in patients undergoing shoulder procedures included more invasive and complex procedures, and the results did not demonstrate a statistically or clinically significant difference between SABER-bupivacaine and SABER-placebo treatment groups on the primary efficacy endpoint. Second, Dr. Petit-Scott expressed concern that only Study BU-002-IM included bupivacaine as an active comparator and there was no statistically significant difference between the SABER-bupivacaine and bupivacaine treatment groups on the primary efficacy endpoint of mean pain intensity with movement through 72 hours. And third, Dr. Petit-Scott noted that patients treated with SABER-bupivacaine had minimal improvement in pain intensity with movement over 72 hours compared to those treated with SABER-placebo after arthroscopic subacromial decompression; i.e., a mean difference of 1.3 on an 11-point pain scale.

While her points are valid, the Division does not agree that efficacy has not been demonstrated and SABER-bupivacaine should not be approved.

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In response to her concern regarding the minimally invasive nature of the procedures performed in Study BU-002-IM, the results from the studies evaluating more invasive procedures favored SABER-bupivacaine treatment. Furthermore, minimally invasive surgical procedures are not painless, such that additional analgesia is not clinically meaningful. The Division agrees that while efficacy comparisons to an active treatment are more meaningful than comparisons to placebo treatments, the demonstration of superiority over SABER-placebo meets the regulatory standard for drug approval. Regarding her concern that the improvement in post-operative pain was minimal, there was a larger difference observed during the first 12 hours post-operatively. Specifically, review of the curves for mean pain intensity scores demonstrated an approximate difference of 2 to 3 points on the 11-point pain scale between the two treatment groups. Because arthroscopic subacromial decompression is a less invasive shoulder procedure, pain relief in the first 12 hours is clinically meaningful. Furthermore, during the initial review cycle, Mr. David Petullo, statistical reviewer, examined the second co-primary endpoint, amount of opioid rescue medication consumed through 72 hours (RES₇₂) and he concluded that there was a significant treatment effect noted for SABER-bupivacaine but not for bupivacaine, and that patients treated with SABER-bupivacaine on average used less rescue medication than placebo subjects. Mr. Petullo also noted that the median time to first use of post-operative rescue medication was longer in patients treated with SABER-bupivacaine compared to those treated with either SABER-placebo or bupivacaine; 15.8 hours, 1.3 hours, and 1.7 hours respectively. Therefore, the Division does not agree with Dr. Petit-Scott and concludes that the results from Study BU-002-IM demonstrate a statistically and clinically significant benefit in patients treated with SABER-bupivacaine over those treated with SABER-placebo.

Regarding the safety data for SABER-bupivacaine, the Division believes that the Applicant has adequately addressed the deficiencies identified in the CRL. The Applicant conducted four additional evaluations in patients undergoing shoulder surgery in their clinical studies, which included re-reading MRIs concerning for chondrolysis, re-reading all MRIs in Study C803-017 and Study C803-017e, review of data from follow-up physical examinations, and review of long-term follow-up for patients in Study BU-002-IM and Study CLIN005-0006. Results of these additional evaluations indicated that the majority of treated patients in all studies had some follow-up data available for review, and, consistent with Dr. Simone's conclusion during the initial review cycle, there did not appear to be any cases of chondrolysis identified during the additional evaluations. It is worth noting, however, that of the three shoulder studies conducted, Study BU-002-IM was the only one which included a non-SABER comparator and provided the least supportive safety information.

In addition to providing additional efficacy information, Study C803-028 was designed to better characterize the benefit-risk profile of SABER-bupivacaine with respect to several adverse events of interest. Because this study incorporated non-SABER placebo and active comparator treatment groups, the adverse events possibly related to the SABER vehicle (the SAIB formulation) were better characterized. Consistent with the reported results described in Dr. Simone's clinical review of the initial submission, results from Study C803-028 indicated an increased incidence of surgical site bruising, and the area of bruising was larger than that observed in either the saline placebo or bupivacaine treatment groups. In addition, there was a trend toward an increased incidence in wound hematoma and surgical site infections requiring antibiotics in the SABER-bupivacaine treatment group. Because these wound-related adverse events appeared to resolve without long-term sequelae, information included in the drug product labeling can inform clinicians and potentially mitigate these risks.

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Regarding the neurologic-related adverse events, results from Study C803-028 demonstrated that there was an increased incidence in somnolence, headache, pruritus, and dysgeusia in patients treated with SABER-bupivacaine compared to those treated with saline placebo or bupivacaine within six hours of administration. Because somnolence, headache, dysgeusia, and pruritus were also reported with an increased incidence in SABER-treated patients in the clinical studies evaluated during the initial NDA review, there is still concern that systemic exposure to the benzyl alcohol in the SABER formulation may in fact be the cause. However, it is worth noting that all patients in Study C803-028, and those treated in the studies reviewed during the initial NDA review cycle, received general anesthesia during the surgical procedure, which may have impacted these reported results. Additionally, no patients were discontinued, required additional treatment, or suffered long-term sequelae as a result of these neurologic-related adverse events. Similar to the proposed mitigation strategy for wound-related adverse events, the Division believes that information included in the drug product labeling can inform clinicians and potentially mitigate the neurologic-related risks.

There did not appear to be any definitive cases of local anesthetic systemic toxicity (LAST) reported throughout clinical development. As discussed during the Advisory Committee (AC) meeting held on January 16, 2020, there is limited nonclinical information available regarding the risks associated with inadvertent intravascular injection of SABER-bupivacaine, and the required clinical management should this occur. The concerns surrounding inadvertent intravascular injection include both the systemic exposure to the large dose of bupivacaine (660 mg) and to the SABER vehicle, the SAIB and benzyl alcohol components. While the Applicant conducted some in vitro assessments and modeling to determine the amount of bupivacaine that would be released over time, it is not clear if the rate of bupivacaine release from the SABER vehicle in an artificial lab setting is the same in the vasculature. Additionally, it does appear, based on nonclinical data, that the SABER vehicle may form clinically significant emboli when exposed to whole blood. As noted in nonclinical studies, intravascular hemolysis is also a concern should this product be inadvertently administered into the intravascular space. Subsequent to the AC meeting, these concerns were discussed with the Applicant, and potential mitigation strategies included a boxed warning for the embolic risk and additional language describing avoidance of intravascular injection using direct arthroscopic visualization during administration. While Dr. Petit-Scott believes that without adequate (nonclinical) data to characterize the risk and guide clinical management strategies, the risks of inadvertent intravascular administration and unknown resuscitation measures outweigh the potential benefits, particularly because approval for use during arthroscopic subacromial decompression is the single model which requires use of a needle for administration. The Division agrees with the Applicant, however, that administration under direct arthroscopic visualization during shoulder arthroscopy will mitigate the risk of intravascular injection, such that language in the drug product label, including the boxed warning, is an acceptable mitigation strategy until such time as more data, clinical and nonclinical, are available.

The pharmacology-toxicology review team concluded that because there is limited data available, it cannot be concluded that there is minimal risk associated with inadvertent intravascular injection, and that the following nonclinical studies are required to further characterize the safety profile of SABER-bupivacaine (adapted from Dr. Misol Ahn's pharmacology-toxicology review).

1. 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

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- determine if intravascular injection results in more rapid release of the bupivacaine dose from the vehicle. A small pilot study should be performed prior to the pivotal study to confirm that IV administration does not result in catastrophic moribundity.
2. A nonclinical toxicology study to confirm that lipid infusions will counteract the adverse effects due to LAST, or provide adequate justification that lipid emulsion therapy 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.

In summary, the totality of the data submitted in the initial NDA submission and resubmission supports the approval of SABER-bupivacaine for administration during arthroscopic subacromial decompression. While there are clearly gaps in knowledge regarding the risks of inadvertent intravascular administration and required resuscitation measures, the Division believes that the limited postsurgical indication and the proposed mitigation strategy of additional labeling language are acceptable until such time as more data become available, including data from the nonclinical studies proposed by the pharmacology-toxicology review team.

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Benefit-Risk Dimensions (adapted from Dr. Petit-Scott's clinical review)

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 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 arthroscopic 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.	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 joint. And second, peripheral nerve block is the most common anesthetic technique employed for patients undergoing more invasive arthroscopic shoulder procedures, such as repair of a rotator cuff, or open shoulder procedures. Shoulder arthroscopy with subacromial decompression in isolation is less painful and does not typically require administration of a nerve block.

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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.
Benefit	• 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	Approval of SABER-bupivacaine would offer clinicians an additional bupivacaine product to administer for postsurgical pain management for shoulder arthroscopy with subacromial decompression. SABER-bupivacaine demonstrates a delayed T_{max} compared to immediate-release bupivacaine and appears to improve post-operative

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	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 - More rapid return to activities of daily living	analgesia compared to placebo treatment and may reduce post-operative opioid rescue analgesia.
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	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 the time of maximum plasma concentration (T_{max}). Patients and family members should be informed of the potential for a delayed onset of adverse events related to SABER-bupivacaine. During the Advisory Committee Meeting, held on January 16, 2020, several committee members expressed concern regarding inadvertent intravascular administration of

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	sites is likely to increase the risk 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 6-month follow-up MRIs for Study BU-002-IM did not 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 in 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	SABER-bupivacaine, particularly during procedures in which administration required use of a needle. Because there is limited information available regarding this risk and the required resuscitation measures, the pharmacology-toxicology review team is recommending additional non-clinical studies to characterize the potential sequelae of an inadvertent intravascular injection and to further define the benefit-risk profile of SABER-bupivacaine. Because specific language in the label, describing administration only under direct arthroscopic visualization, is an acceptable mitigation strategy, these studies can be conducted post-approval. The Applicant has adequately addressed the deficiencies identified in the CRL. Specifically, the deficiency related to the shoulder joint and surrounding tissue was addressed with follow-up data from the completed shoulder studies. In patients undergoing arthroscopic subacromial decompression with an intact rotator cuff, the risk of chondrolysis of the glenohumeral joint is low. There are ongoing concerns regarding wound-related adverse events after examination of the data from Study C803-028. However, most of these adverse events

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	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> • 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 Study C803-028, 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 study C803-028. 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 alcohol increases these risks.	appeared to resolve over time. In arthroscopic subacromial decompression, where the drug product is administered into the subacromial space, the risk of wound-related adverse events appeared to be lower than observed in the soft tissue abdominal surgical procedures. However, the drug product label will include the most commonly reported wound-related adverse events across all studies, given the likelihood of off-label use. Most of the neurologic-related adverse events were considered mild in severity and resolved by the end of the study. However, similar to wound-related adverse events, the drug product label will include the most commonly reported neurologic-related adverse events across all studies.

1. Background

This document will serve as the Cross-Discipline Team Leader (CDTL) review and the Division Director Summary Review of the Applicant's complete response to the Division's Complete Response Letter (CRL), issued February 12, 2014, to New Drug Application (NDA) 204803, originally submitted on April 12, 2013.

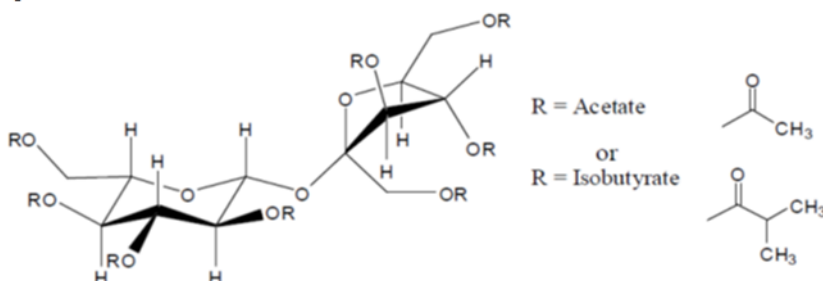
This document will also capture the final outcomes of any items that were still under discussion at the time of finalization of Dr. Petit-Scott's clinical review.

The following information is reproduced from Dr. Petit-Scott's clinical review.

SABER-bupivacaine solution is composed of 12% bupivacaine (132 mg/mL) in 22% benzyl alcohol (BA; (b) (4) mg/mL) and 66% sucrose acetate isobutyrate (SAIB; (b) (4) mg/mL). 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.

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, according to the Applicant, 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 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 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.

The following table, reproduced from Dr. Petit-Scott's clinical review, summarizes the interactions between DURECT Corporation and the Division beginning with issuance of the Discipline Review Letter (DRL), on January 14, 2014, through the AC meeting held on January 16, 2020.

Meeting / Communication / Date	Event / Key Clinical Issues
Discipline Review Letter (DRL) / Jan. 14, 2014	The risk of chondrolysis and select adverse events, and efficacy issues were included in the DRL.
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 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:

Meeting / Communication / Date	Event / Key Clinical Issues
	- 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.
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 / Feb. 22, 2015	Sponsor proposed to evaluate the safety and efficacy of SABER-bupivacaine in patients undergoing laparoscopic cholecystectomy.
Advice Letter / June 15, 2015	Division provided feedback for proposed Phase 3 study.
Phase 3 protocol received / Aug. 31, 2015; Protocol Amendment 1 received / Oct. 22, 2015	Comments sent 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

Meeting / Communication / Date	Event / Key Clinical Issues
	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 / June 27, 2019	Initial review determined the submission was a Complete Response to the identified deficiencies noted in the CRL dated Feb. 21, 2014.
Advisory Committee Meeting / January 16, 2020	There were three topics presented for discussion; whether the Applicant provided sufficient information to support approval for the proposed indication, whether there were issues with the Complete Response resubmission that warrant additional studies and, if so, should these studies be conducted before or after approval, and whether the efficacy, safety, and overall benefit-risk profile of Posimir support the approval of this application. AC members were presented with the following single voting question: <i>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.</i> The committee vote was an even split; six 'yes' votes and six 'no' votes.

2. Product Quality

There were no product quality deficiencies identified during the initial review cycle. In the NDA resubmission, the Applicant did submit new stability data, specifically aimed at ensuring there are no differences in the product stability between the previous drug manufacturer, (b) (4), and the new/current manufacturer, Renaissance. According to the review team, the stability data are similar and remain within specification. The team recommends a shelf life of 36 months for the drug product, Posimir, when stored at 20-25°C (see USP controlled room temperature) and protected from light. The container closure system has not changed, and the manufacturing inspection was deemed adequate.

Similar to the conclusion made during the initial NDA review, the product quality team, including facilities and microbiology reviewers, recommends approval.

The Division concurs that there are no approvability issues related to drug product quality.

3. Nonclinical Pharmacology/Toxicology

As previously noted, there were no nonclinical deficiencies identified during the initial review cycle; however, as described in the review completed during this cycle by Dr. Misol Ahn, the primary pharmacology/toxicology reviewer, there were no data provided regarding direct intravascular, either intravenous or intra-arterial, administration of SABER-bupivacaine in an animal model, and that the in vitro studies did demonstrate hemolysis. Dr. Gary Bond, the primary pharmacology/toxicology reviewer during the first cycle, noted that both SABER-bupivacaine and SABER-placebo caused in vitro hemolysis when added to human whole blood. He also noted that the blood had a viscous (and, for SABER-placebo, cloudy) macroscopic appearance, with globules resembling bubbles visible microscopically. He stated that while SABER-bupivacaine is not intended for intravascular injection and, therefore, the risk of hemolysis should be low, the concern should be addressed by the clinical review team. Dr. Roca's Deputy Division Director Summary review, dated February 12, 2014, notes that there was not an in vivo nonclinical evaluation of the adverse effects of intravascular injection, because it was believed that, based on 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."

In the NDA resubmission, there were no new in vivo data, either nonclinical or clinical, to inform the risks associated with inadvertent intravascular administration. During the AC meeting, several members of the committee expressed concern regarding the potential risks of inadvertent intravascular administration of SABER-bupivacaine. To ensure that this concern was adequately addressed, Information Requests (IRs) were sent to the Applicant subsequent to the AC meeting regarding a safety assessment and potential mitigation strategies associated with such an injection. The Applicant responded with additional in vitro data to inform both the risk of LAST, due to the large dose of bupivacaine (660 mg), and the formation of emboli, due to the SABER vehicle, should an intravascular injection occur. Specifically, as noted in Dr. Ahn's review, the Applicant argued that the likelihood of inadvertent intravascular

administration was low based on the following: estimated incidence of LAST (calculated to be 5.7 per 100,000); limited use of needles for SABER-bupivacaine administration; a larger bore needle for SABER-bupivacaine administration during shoulder surgery compared to the needle size used for immediate-release local anesthetic administration; and the physical properties of SABER-bupivacaine, including the color (light amber) and the viscosity, compared to immediate-release local anesthetics.

The Applicant also stated that based on the release rate of bupivacaine following subcutaneous administration (injection), there does not appear to be bupivacaine dose-dumping, and the bupivacaine release rate appeared to be stable over 72 hours. As Dr. Ahn noted, however, it is not clear if the release rate data after subcutaneous administration can be extrapolated to administration in the intravascular space, particularly if small droplets with larger surface area or emboli form. The Applicant has indicated that they would be willing to conduct an animal study post-approval to evaluate both the risks of intravascular injection and the ability to treat LAST with lipid emulsion. Additionally, based on the results from an in vitro study evaluating the risk of emboli formation and the potential for clinically significant pulmonary emboli, the Applicant proposed including a boxed warning in the label regarding the risk of emboli with intravascular injection. The data from the in vitro study suggest that addition of a 5 micrometer filter into the bovine serum tubing system, to simulate passage through capillary beds, required higher pressures for the SABER-bupivacaine droplets to pass through the system. The required pressure increased with increased exposure time to SABER-bupivacaine. Whether the pressure requirement would be the same at normal body temperature is not clear.

In response to the IRs, the Applicant also discussed the risk for intravascular hemolysis, and concluded that SABER-bupivacaine would not cause clinically relevant hemolysis based on the amount of benzyl alcohol required to cause this adverse effect. Specifically, the Applicant suggested the concentration of benzyl alcohol injected intravascularly is 1000 times less than that required to hemolyze red blood cells in vitro. Dr. Ahn noted that this risk reduction is based on a theoretical calculation of the concentration of benzyl alcohol under steady state concentrations in the systemic circulation, and, therefore, does not address the potential for higher local concentrations of benzyl alcohol at the injection site.

While the additional information provided by the Applicant in response to the IRs is useful, the Division does not agree that the data from the in vitro studies alone adequately characterizes the risks associated with intravascular injection and there are still gaps in knowledge regarding the clinical management required to resuscitate patients. The Division agrees with pharmacology-toxicology review team that additional nonclinical studies are required (described below). There was some discussion whether these studies were required pre-approval. The Division believes, however, that a limited postsurgical indication in combination with specific administration instructions and information regarding the risk of inadvertent intravascular injection included in drug product labeling are acceptable until such time as more data become available.

The following are the required nonclinical studies (adapted from Dr. Ahn's review):

- 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. A small pilot study prior to the pivotal study should be performed to confirm that IV administration does not result in catastrophic moribundity.
- 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.

4. Clinical Pharmacology

No new clinical pharmacology data were submitted with this resubmission.

5. Clinical Microbiology

SABER-bupivacaine (Posimir) is not a therapeutic antimicrobial, therefore no microbiology data were included in this resubmission.

6. Clinical/Statistical- Efficacy

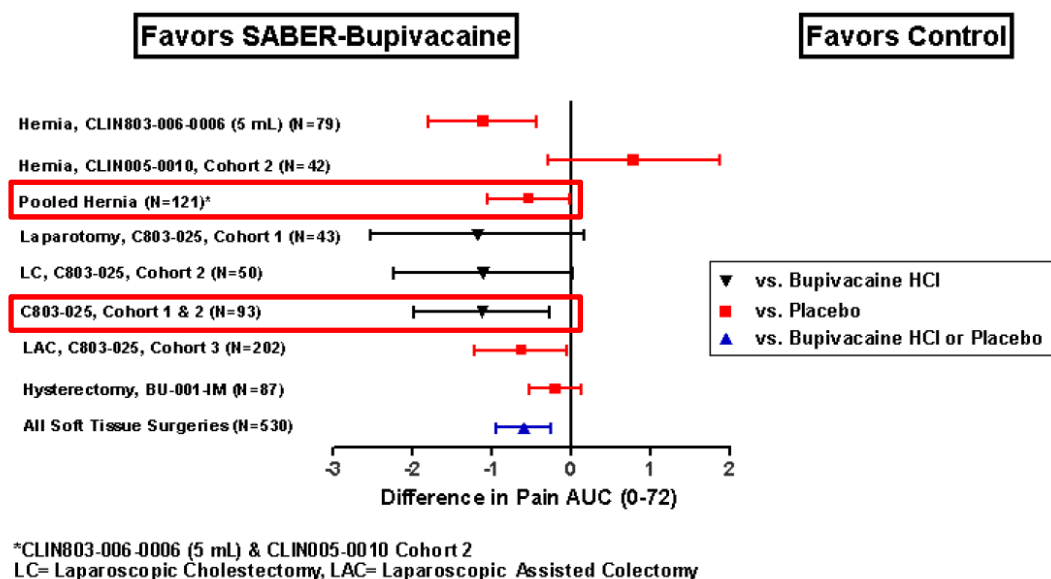
Background

In the initial NDA submission, the Applicant identified two Phase 2 clinical studies as “pivotal” and supportive of the reported efficacy of SABER-bupivacaine and the proposed indication of postsurgical 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. The results of these studies are well-described in Dr. Simone’s clinical review, dated January 8, 2014, and his two main clinical concerns were included the DR Letter issued on January 14, 2014 (verbatim):

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

The finding of inadequate evidence of efficacy in soft tissue surgical procedures was based on results from several soft tissue surgical models, including total abdominal hysterectomy, laparotomy, lap chole, and laparoscopic-assisted colectomy. Additionally, the efficacy results from two similarly conducted inguinal hernia studies were conflicting; i.e., one demonstrated efficacy the other did not.

A teleconference was held with the Applicant on January 17, 2014, to discuss the deficiencies and the Applicant submitted additional information on February 3, 2014, which included re-analyses of the efficacy data from the studies conducted in soft tissue surgical models. The following forest plot was generated based upon these post-hoc analyses.



Source: Applicant's February 3, 2014 submission, page 6.

Of note, the Applicant presented two sets of pooled data (red boxes in the forest plot above) to support a treatment difference; one from the two inguinal hernia repair studies, and the other from two cohorts of patients undergoing unrelated soft tissues surgical procedures (laparotomy and lap chole) in Study C803-025. The Division generally does not accept pooled data from different clinical trials as evidence of efficacy to support a regulatory decision.

It is clear from the forest plot that the results from a single study in soft tissue surgical models, Study CLIN803-006-0006 in inguinal hernia repair, demonstrated superiority of SABER-bupivacaine over placebo, which was generally SABER-placebo. While the results from the studies in the other soft tissue surgical models demonstrated an apparent treatment difference favoring SABER-bupivacaine, the difference did not reach statistical significance.

Furthermore, as indicated in the forest plot above, the results from the second study in patients undergoing inguinal hernia repair, Study CLIN005-0010, favored SABER-placebo. On February 12, 2014, Dr. Simone completed an amendment to his clinical review completed on January 8, 2014, which included an assessment of the acceptability of the Applicant's re-analyses of clinical data from the two studies conducted in patients undergoing inguinal hernia repair. He stated that Study CLIN005-0010 may have been more exploratory in nature than

Study CLIN803-006-0006, and concluded that SABER-bupivacaine was efficacious compared to SABER-placebo for arthroscopic subacromial decompression and inguinal hernia repair. Based on ongoing safety concerns, however, the application received a CRL.

In response to the CRL, the Applicant submitted an FDRR on November 21, 2014, requesting an additional determination of both safety *and* efficacy. Therefore, a re-evaluation of the efficacy data was conducted as part of the FDRR review. Dr. Mary (Parks) Thanh Hai, the Office Deputy Director at the time, concluded that the efficacy of SABER-bupivacaine was “modest and inconsistent across different surgical procedures”, and that “precludes complete dismissal of the safety concerns raised by the Division.” Regarding the differing results from the two inguinal hernia repair studies, she concluded that “the inconsistency between these two studies which evaluated efficacy in the same surgical procedure (inguinal hernia repair) could not be attributed to any notable difference in conduct, design or demographics. Even though the failed trial may not have enrolled a sufficient number of patients to demonstrate superiority of Posimir to placebo, one would have at least anticipated a point estimate favoring Posimir.” She acknowledged the Applicant’s explanation regarding the lack of efficacy for Study CLIN005-0010, which included differences in patient age between the active and placebo groups and the fact that re-analysis of the data (using covariance including treatment as main effect, age as the covariate and the interaction of age and treatment) and pooling results demonstrated a statistically significant difference between the SABER-bupivacaine over SABER-placebo treatment groups. However, she also acknowledged that these analyses and the demonstration of statistical significance with the pooled data were post-hoc, and concluded that the effect of age on treatment “should be considered exploratory and not explanatory.”

Regarding the re-evaluation of the efficacy of SABER-bupivacaine in patients undergoing arthroscopic subacromial decompression, Dr. Thanh Hai agreed with the review team that efficacy had been demonstrated in Study BU-002-IM, but that any benefit needed to be weighed against the identified safety concerns.

As described in the FDRR denial letter, Dr. Thanh Hai proposed two possible paths forward for the Applicant (verbatim).

- 1) Work with the Division to design a prospective trial(s) to better characterize the benefit-risk profile of Posimir or
- 2) Respond to the CR action through a resubmission addressing the deficiencies based on additional information presented in your EOR background materials and a justification to conclude that this additional information supports a favorable benefit-risk profile of Posimir.

Subsequent to the FDRR denial letter, the Applicant elected to conduct an additional study, C803-028 or PERSIST (A **P**lacebo-controlled trial of **SABER**®-Bupivacaine for the management of po**S**toperati**V**e pain following laparo**S**copic cholecys**T**ectomy) to better characterize the benefit-risk profile of SABER-bupivacaine. The following is a high-level summary of the design and results of this study. Refer to the clinical review completed by Dr. Petit-Scott and the statistical review completed by Ms. Katherine Meaker for additional information.

Study C803-028

Design, Objectives, and Endpoints

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 5 mL in patients undergoing elective outpatient laparoscopic cholecystectomy.

The objective of the study was modified between Part 1 and Part 2, as described below.

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

The recommendation to conduct an additional study using an active comparator, bupivacaine, was discussed with the Applicant during the End-of-Review-Cycle meeting, held on September 23, 2014. The Division recommended the use of both non-SABER-placebo (saline) and active comparator treatment groups to better characterize the safety concerns identified in the CRL. After the full protocol was submitted on October 22, 2015, the addition of the active comparator was discussed again in an advice letter dated January 11, 2016, and in a teleconference held on April 5, 2016. Amendment 3, received on June 6, 2016, indicated that the Applicant discontinued the saline placebo arm and added a bupivacaine arm. The rationale to discontinue the saline placebo arm is not clear, as the Division only recommended the addition of an active comparator arm, not discontinuation of the saline placebo arm.

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

Part 1: Patients were randomized to receive either SABER-bupivacaine 5 mL or saline placebo 5 mL by direct instillation into the four surgical incision sites (4-ports).

Part 2: Patients were randomized to receive either SABER-bupivacaine 5 mL by direct instillation into the four surgical incisions (4-ports) or bupivacaine HCl (75 mg) was infiltrated into the 4 incision sites.

The protocol-specified efficacy endpoints were as follows:

Primary efficacy endpoints

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

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

Key secondary efficacy endpoints

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

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

Part 1 was discontinued, after 92 subjects (46 per group) had been randomized and treated, to incorporate the active control into the study design. A total of 296 subjects were randomized and treated (148 per group) in Part 2 of the study.

Efficacy Results

The following table, reproduced from the complete study report for Study C803-028, summarizes the results of the primary efficacy endpoints for Part 1 and 2.

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

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

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

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

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

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

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

Neither the results from Part 1 or Part 2 of the study showed a statistically significant difference between SABER-bupivacaine treatment and the respective comparator arm. Ms. Meaker noted that Part 1 was stopped after only 30% of the planned sample had been treated, but the observed results at that time were consistent with the anticipated pre-specified

treatment difference, 0.8 points on an 11-point pain scale; therefore, the lack of sufficient evidence of efficacy can be attributed to the lack of study power.

The Applicant stated that Part 2 of the study did not meet the criteria for an adequate and well-controlled study, as described in 21 CFR § 314.126, for three main reasons. First, the number of protocol amendments (five) increased variability and led to attenuation of the observed treatment effect between study drug and control. Second, due to a lack of comparison between active control and placebo, assay sensitivity cannot be assessed. And lastly, that pooling of data from Parts 1 and 2 is inappropriate for statistical analyses and efficacy conclusions. Based on these three reasons, the Applicant argues that the results of Part 2 of the study should not be considered in the overall assessment of efficacy of SABER-bupivacaine. The Division disagrees with this assessment and considers each part of the study as a stand-alone adequate and well-controlled study. Part 2 was planned as an adequate and well-controlled study intended to show superiority over bupivacaine HCl for treatment of postsurgical pain on movement.

Discussion and Conclusions

Regarding the overall efficacy of SABER-bupivacaine, including the results from Study C803-028 and those from studies submitted in the initial NDA, Dr. Petit-Scott concluded that substantial evidence of effectiveness had not been established and, that in combination with the safety concerns, SABER-bupivacaine should not be approved. Regarding evaluated orthopedic procedures, she concluded that substantial evidence of efficacy had not been demonstrated for three reasons. First, she argued that only a single orthopedic surgical site, the shoulder, was evaluated, and questioned why a third similar study was conducted when the results from two previous studies failed to demonstrate a statistically significant efficacy benefit of SABER-bupivacaine over SABER-placebo. Second, she argued that 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, she concluded that efficacy of SABER-bupivacaine was not demonstrated over low-dose, immediate release bupivacaine HCl (50 mg). She acknowledged that while superiority over a placebo treatment has generally been the accepted regulatory standard for approval, 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.

The Division respectfully disagrees that adequate evidence of efficacy for arthroscopic subacromial decompression was not demonstrated such that a CR action is indicated. The efficacy of SABER-bupivacaine demonstrated in Study BU-002-IM was statistically significantly different from SABER-placebo treatment, and the Division agrees with the conclusions of the first cycle review team and Dr. Thanh Hai. While the Division agrees that Study BU-002-IM evaluated the least invasive surgical procedures of the three studies conducted in patients undergoing shoulder procedures, the Division does not agree that post-surgical analgesia even for minimally invasive surgeries is not clinically meaningful. Furthermore, the results from the studies which evaluated more invasive, painful procedures favored SABER-bupivacaine treatment over SABER-placebo.

Regarding Dr. Petit-Scott's concern that SABER-bupivacaine was no more efficacious than low-dose immediate-release bupivacaine, the Division concludes that the regulatory threshold of approval has been met. The Division does not disagree that the demonstration of superiority over an active comparator is more clinically meaningful; however, the demonstration of superiority over a placebo treatment meets the threshold for approval.

The Division acknowledges that the reduction in pain intensity associated with administration of SABER-bupivacaine is modest (i.e., a mean difference of 1.3 on an 11-point NRS), however, does not believe it is clinically insignificant. Specifically, while the mean difference in pain intensity between the SABER-bupivacaine and SABER-placebo treatment groups appears low, it does not take into account those patients who experienced a greater analgesic benefit. Additionally, during the first 12 hours' post-operatively, the separation of the mean pain intensity curves indicated that the difference between the two groups is greater, approximately 2 to 3 points on the 11-point pain scale. Shoulder arthroscopy with subacromial decompression is a less invasive surgical procedure, such that pain after 12 to 24 hours may be minimal regardless of administered analgesic, suggesting that relief in the first 12 hours may be clinically meaningful.

Furthermore, during the first review cycle, Mr. Petullo, the statistical reviewer, examined the second co-primary endpoint, amount of opioid rescue medication consumed through 72 hours. He concluded that there "was a significant treatment effect noted for Posimir 660 mg but not for bupivacaine. Subjects treated with Posimir 660 mg, on average used less rescue medication than placebo subjects, 13.7 mg versus 22.8 mg, respectively." While it is challenging to interpret the clinical significance of opioid reduction over 72 hours, the difference may confer some benefit to individual patients. Mr. Petullo also examined the time to first use of rescue medication and noted that the "median time to first use of post-operative rescue medication was 1.3 hours in placebo subjects, 15.8 hour in Posimir 660 mg treated subjects, and 1.7 hours in subjects treated with bupivacaine." This is likely a clinically meaningful difference between the SABER-bupivacaine and SABER-placebo treatment groups.

In her review, Dr. Petit-Scott expressed concern regarding the proposed route of administration of SABER-bupivacaine, use of a large bore needle, during arthroscopic subacromial decompression. The risk of intravascular injection, discussed elsewhere in this review, was discussed extensively during and after the AC meeting. The Division also has concerns regarding the use of a needle to administer 600 mg of bupivacaine into the shoulder; however, because the drug product is administered under direct arthroscopic visualization, the risk of inadvertent intravascular injection of SABER-bupivacaine is reduced, and information in the drug product labeling reinforces this requirement during administration of SABER-bupivacaine. Additionally, the Applicant has proposed to include a boxed warning describing the risk of clinically significant emboli should SABER-bupivacaine be injected intravascularly. The Division agrees with the boxed warning, as described in Section 11 of this review.

Regarding the efficacy evaluation in patients undergoing soft tissue surgical procedures, including those performed both open and laparoscopically, and those involving the abdomen and pelvis, Dr. Petit-Scott concluded that substantial evidence of effectiveness has not been demonstrated and SABER-bupivacaine should not be approved for use in soft tissue surgical

procedures for four reasons. First, she stated that of all the surgical procedures and sites evaluated, it is concerning that only a single study in a single model (i.e., open inguinal hernia repair in Study CLIN803-006-0006) demonstrated a statistically significant improvement in post-operative pain over placebo treatment. She further noted that clear separation of pain curves between SABER-bupivacaine and SABER-placebo in the successful study 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. Furthermore, she noted that the conflicting efficacy results from the two studies conducted in patients undergoing inguinal hernia repair was not adequately explained by the Applicant, and she concluded that a single study in a single soft tissue model does not seem to meet the regulatory threshold of substantial evidence of effectiveness.

Second, similar to her arguments regarding efficacy in the shoulder studies, Dr. Petit-Scott stated that the demonstration of efficacy compared to SABER-placebo treatment is not clinically relevant. She argued that while the regulatory threshold for approval may include statistically significant differences between active and placebo treatments, the Division's current thinking is that approval of the newer, extended-release, reportedly longer-acting, local anesthetic formulations should be based on evaluations compared to standard of care treatment, which is immediate-release bupivacaine. She stated the following in her review (verbatim):

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, Dr. Petit-Scott stated that the efficacy (mean pain intensity on movement over 72 hours) demonstrated in the inguinal hernia repair study was modest at best; i.e., a mean difference of 1.1 on an 11-point pain scale. She did not feel that 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, she concluded that 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.

Based on review of all the available information, including information discussed during the first review cycle, the Division concludes that the Applicant has met the regulatory threshold for substantial evidence of effectiveness in the arthroscopic subacromial decompression surgical model, and is approving it for that indication alone. The Division agrees with Dr. Petit-Scott's conclusion that the regulatory threshold for approval has not been established for any other surgical procedure, including open inguinal hernia repair.

7. Safety

This section will focus first on the safety deficiencies identified in the CRL and the adequacy of the Applicant's response, followed by the safety results for Study C803-028, conducted post-CRL.

As previously discussed, NDA 204803 received a CRL on February 14, 2014, based on the following safety deficiencies:

1. There were adverse events related to the shoulder joint and surrounding tissues in subjects who underwent follow-up assessments at 18 months, after their arthroscopic subacromial decompression surgery.
2. The risk of bruising, hematoma, pruritus, and dehiscence occurred following administration of SABER-containing products (SABER-bupivacaine and SABER-placebo) substantially more often than following administration of bupivacaine HCL.
3. There was a marked increased risk of neurologically related adverse events, i.e., dizziness, dysgeusia, headache, hypoesthesia, paresthesia, and somnolence, which occurred with substantially greater frequency following administration of SABER-containing products compared to bupivacaine HCl.

The Applicant was advised to conduct additional studies to adequately characterize the risk profile of SABER-bupivacaine to address the deficiencies listed above. Specifically, the following types of studies needed to be conducted (verbatim from the CRL):

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

The treatments need to include SABER-bupivacaine and either bupivacaine HCL or a non-SABER containing placebo (or both). The study needs to be randomized and double-blinded in design and needs to include enough subjects to detect reactions with an incidence rate of $\geq 1\%$. 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.

2. 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.

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

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

It was strongly recommended that the Applicant discuss the design of any planned studies with the Division prior to implementation.

The Applicant's Post-Action Analyses of Safety Data

As previously discussed, in the End-of-Review meeting package, the Applicant presented additional information from post-action analyses of data submitted in the original NDA, and included supportive published literature articles, where needed, to address the three safety concerns identified in the CRL. The following information was included in the NDA resubmission.

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

The Applicant conducted four supplementary evaluations in patients who underwent shoulder surgery in their clinical studies, including a re-read of MRIs concerning for chondrolysis, a re-read of 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.

The first supplementary evaluation involved two independent orthopedic surgeons re-reading baseline and 18-month follow-up MRIs, in a blinded fashion, for the three patients from Study C803-017e with a reported serious adverse event (SAE) or concerning MRI findings for post-arthroscopic glenohumeral chondrolysis (PAGCL) or other 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. While concerns regarding damage to the articular cartilage or other joint structures was adequately addressed during the first review cycle and not included in the CRL, the additional information provided by the Applicant in the resubmission is further affirmation that no cases were identified in later study follow-up.

The second supplementary evaluation involved a radiologist re-reading, in a blinded fashion, the baseline and 18-month follow-up MRIs from “as many MRI images as possible” from Study C803-017 and Study C803-017e. Of the 45 follow-up MRIs completed at 18 months, 43 (96%) were available for re-read. Once the MRIs were read by the radiologist, an orthopedic surgeon, with experience in shoulder surgery, reviewed the images with the radiologist to assess the clinical relevance of any radiological findings. Their findings in the staged reading process were summarized as follows (verbatim from the ISS, page 35):

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

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

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

Study BU-002-IM

Most treated patients in all treatment groups had either improvement or no change at the six-month follow-up exam. There were no reports of cartilage thinning in the glenohumeral joint and no evidence that administration of SABER-bupivacaine resulted in abnormal healing or the shoulder joint or surrounding tissue. As noted in Dr. Petit-Scott’s review, the mean Constant-Murley (C-M) scores, which is an assessment of the shoulder involving both subjective and objective variables, for all treatment groups appeared to have increased at the six-month follow-up visit; however,

it 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 C-M scores post-operatively, all treated with either SABER-bupivacaine (five patients) or SABER-placebo (two patients). Review of these patients' MRIs indicated 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. Dr. Petit-Scott concluded that, "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." She further stated, "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 Division, however, believes that because there were no radiographic (MRI) findings to explain the changes in scores, it is unlikely that administration of SABER-bupivacaine resulted in structural changes leading to loss of shoulder joint function. Additionally, the Division believes that because this study was completed more than 10 years ago, clinically relevant long-term consequences would have become apparent during this time.

Study CLIN005-0006

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

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

B. Analysis of Follow-up Safety Data for Wound-Related Adverse Events

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

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

As described in Dr. Petit-Scott's review, for Study C803-025, the Applicant concluded that when wound dehiscence, the most concerning wound-related adverse event reported in this study, was assessed via a variety of both subjective and objective assessments, the difference in incidence between SABER and non-SABER treatment groups was less impressive, and that self-examination of the surgical wound may not be a reliable assessment tool for capturing clinically relevant wound dehiscence. The Division agrees with this conclusion; however, also believes that the risk of wound dehiscence may be related to size of the surgical incision, with increased risk associated with increased length.

Regarding the additional safety analyses for Study BU-001-IM, as described in Dr. Petit-Scott's review, treated patients underwent a 6-month clinical evaluation to assess healing of the Pfannenstiel incision, and a subset of patients underwent an MRI evaluation of the pelvis to assess scar formation. Review of 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, who concluded 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 concluded that all wounds healed normally by six months. The Division agrees with the Applicant's conclusion.

Regarding the additional safety analyses for Study CLIN803-006-0006, as described in Dr. Petit-Scott's review, 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. The Division agrees that there do not appear to be long-term wound-related adverse events due to SABER-bupivacaine; however, the Division does not agree that the previously described "short term" adverse events are not concerning.

Regarding the re-analyses of the imbalance in the incidence of bruising, hematoma, pruritis, and dehiscence in the shoulder studies, there does not appear to be any clinically meaningful differences between treatment groups and all wounds healed normally. The Division agrees with the Applicant's conclusions.

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

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

Dr. Ahn concluded in her pharmacology-toxicology review that local effects observed after administration of SABER-bupivacaine in rats and minipigs “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 differs slightly from Dr. Anderson’s; however, it does appear that while some portion of the vehicle remains in tissues for at least one year, there did not appear to be associated long-term pathology and the clinical significance of residual vehicle is unknown.

The Division concludes that while the additional information included in the resubmission for the wound-related safety issues identified in previously completed studies is a post-action analysis conducted by the Applicant instead of a prospective unbiased collection of data, the information is supportive of the safety of the wound after administration of SABER-bupivacaine.

C. Analysis of Follow-up Safety Data for Neurologic-Related Adverse Events

As described in the CRL, the Division noted an imbalance in the incidence of specific nervous system adverse events including somnolence, dizziness, and dysgeusia, potentially related to benzyl alcohol exposure in patients treated with a SABER product compared to those treated with bupivacaine HCl. The Applicant provided a rationale for this imbalance, indicating it was due to the varied methods for adverse event collection; that is whether these adverse events were spontaneously reported or queried. 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 that no event of headache resulted in more serious adverse events or delayed time to discharge from the PACU. These data are reassuring, however, based on results from the PERSIST study, discussed below, there does appear to be an increased incidence in some other neurologic-related adverse events.

Safety results in Study C803-028 in laparoscopic cholecystectomy

This study in patients undergoing lap chole included more intensive, which included a set of prespecified symptoms, and longer duration follow-up evaluations and assessments for concerning neurological symptoms, both solicited and spontaneously reported, and complications related to wound healing. In addition, results from this study allowed better characterization of the safety findings, both neurologic and wound-related, because the study included two Parts with different non-SABER comparators; i.e., Part 1 used a saline placebo and Part 2 used a bupivacaine comparator.

There were no deaths reported. Nine patients experienced SAEs during the study; six treated with SABER-bupivacaine and three treated with bupivacaine HCl. An additional five patients who had SAEs were not treated; 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, but related to underlying gallbladder disease or post-operative complications unrelated to the study drug treatment. The Division agrees with this conclusion.

During the course of the study, 99% of all patients (384/388 patients) reported at least one treatment-emergent adverse event (TEAE). The overall incidences of TEAEs and spontaneously-reported TEAEs were similar among the treatment groups and study parts. The majority of spontaneously-reported TEAEs were mild in severity. Nineteen patients reported at least one severe TEAE. In Part 1, there were six patients with severe TEAEs in the SABER-bupivacaine treatment group, including five with peri-incisional bruising and one with pruritis. There were no severe spontaneously-reported TEAEs in the saline group. All five cases of bruising were reported as related to study drug and all resolved without treatment. In Part 2, there were nine patients in the SABER-bupivacaine group and four in the bupivacaine HCl group with one or more severe spontaneously-reported TEAEs. All TEAEs reportedly resolved by the end of the study.

Neurologic-Related Adverse Events

There was an increase in certain spontaneously-reported neurologic-related AEs in both parts of the study. There was an increased incidence of dysgeusia in the SABER-bupivacaine treatment groups in both Part 1 and Part 2 of the study compared to the respective controls. In Part 2 of the study, there was an increased incidence of headache, vomiting, constipation, paresthesia, hypoesthesia, and tremor in the SABER-bupivacaine treatment group compared to the bupivacaine HCl treatment group. The majority of the spontaneously-reported TEAEs were mild in severity and resolved by the end of the study period.

The Division requested an evaluation of 10 symptoms of interest at 6 and 10 hours' post-operatively, and then daily by phone on post-operative days 1 and 2, and during the follow-up visit on post-operative day 3. The symptoms included somnolence, nausea, dizziness, headache, vomiting, constipation, pruritus, dysgeusia, paresthesia, and hypoesthesia, and were collected via a LogPad, which automatically queried patients at the prespecified time intervals. The 6- and 10-hour entries were specifically intended to capture potential benzyl alcohol exposure and toxicity, based on the pharmacokinetic data captured in Study BU-001-IM in patients undergoing total abdominal hysterectomy. Specifically, benzyl alcohol has a T_{max} of one hour, a half-life of 4.7 hours, and can be measured in the plasma up to 12 hours' after administration.

In Part 1, the solicited TEAEs that occurred with an increased frequency in the SABER-bupivacaine treatment group compared to the saline treatment group included somnolence, dizziness, headache, pruritus, and dysgeusia. In Part 2, the solicited TEAEs that occurred with increased frequency in the SABER-bupivacaine treatment group compared to the bupivacaine treatment group included somnolence, headache, pruritus, and dysgeusia. Those that occurred with increased frequency in the bupivacaine HCl treatment group included nausea, dizziness, vomiting, constipation, and paresthesia.

Based on the pharmacokinetic profile of benzyl alcohol, Dr. Petit-Scott was interested in the incidence of the 10 symptoms of interest early in the post-operative period, as those may be more likely related to benzyl alcohol exposure. The following table, submitted in response to an Information Request, summarizes the incidence of solicited symptoms occurring within 6 hours of SABER-bupivacaine administration in both Parts of the study.

Incidence of LogPad Solicited Adverse Events Within 6 hours Post-Treatment (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.

The table indicates that patients treated with SABER-bupivacaine had an increased incidence of somnolence, headache, and dysgeusia when compared to patients treated with saline placebo or bupivacaine HCl within 6 hours of administration. Somnolence, headache, and dysgeusia were also observed with greater frequency in SABER-treated patients in the clinical studies evaluated during the original NDA review, suggesting that systemic benzyl alcohol may be the cause. The clinical significance of this is unclear, however, based on the different incidences of spontaneously-reported adverse events and the fact that only a single patient reported a neurologically-related serious adverse event across the study. Briefly, a 72-year old female complained of dizziness approximately 2.5 hours post-operatively. Prior to the complaint of dizziness, she received fentanyl 150 mcg and hydromorphone 0.6 mg, which may have contributed to her complaint; however, review of the CRF indicated that she also complained of drowsiness, dysgeusia, nausea, and vomiting approximately five to nine hours after admission to the PACU. She was admitted for overnight observation and was discharged home on post-operative day one with no additional complaints.

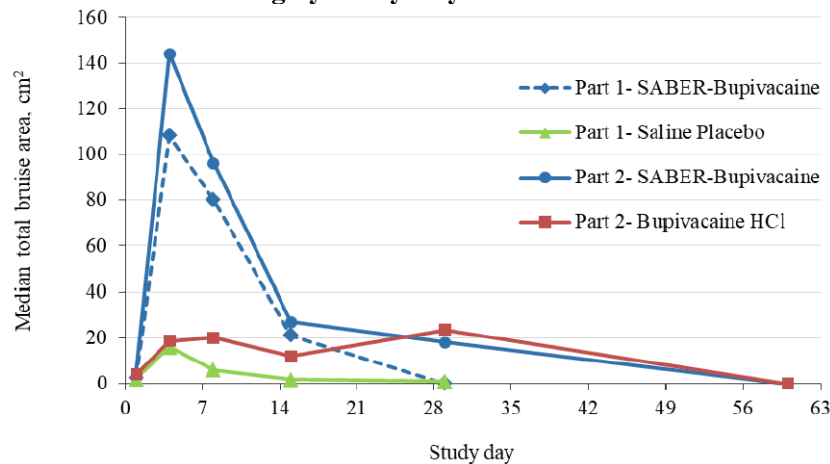
Wound-Related Adverse Events

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

Bruising

There was a clinically significantly higher incidence of peri-incisional bruising among SABER-bupivacaine-treated patients compared to control treatments in both parts of the study, which contributed to the overall increased incidence of treatment-related AEs in this group. Specifically, in Part 1 of the study 91%, and in Part 2 of the study 96% of SABER-bupivacaine-treated patients had peri-incisional bruising, compared to 70% of saline placebo-treated patients and 71% of bupivacaine HCl-treated patients. The prevalence of bruising was greatest on Day 4 and the size of the bruise in SABER-bupivacaine-treated patients was larger than those observed in the respective control groups. Most bruising resolved by Day 28. The following graph summarizes the time-course and size of bruising in patients in both parts of the study.

Total Area of Bruising by Study Day



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

Source: [Table 14.3.1.10.2](#)

Source: C803-028 PERSIST Report Body, p. 131, Applicant's submission.

Dr. Petit-Scott was concerned about the size of the bruise for two reasons. First, she was concerned that the large size may make detection of a surgical site infection or hematoma more challenging. And second, the bruising in specific locations in the body may result in more serious adverse events. Specifically, she stated that off-label use of SABER-bupivacaine in patients undergoing lumbar spine or foot and ankle procedures may result in more serious adverse events leading to long-term complications. The Division agrees that the size of the bruises is concerning, particularly for small incisions such as those made for lap chole procedures; however, the Division believes that descriptive information included in the drug product label is adequate to mitigate these risks. Furthermore, the narrow post-surgical indication for SABER-bupivacaine will likely limit off-label use.

Surgical Site Bleeding

Surgical site bleeding was rated as spotting of the dressing, soaking of the dressing, or continuous bleeding throughout the study. In Part 1, there was a slightly higher incidence of surgical site bleeding reported in patients treated with SABER-bupivacaine than those treated with saline; 49% versus 43%, respectively. In Part 2 of the study, the incidence was higher in patients treated with bupivacaine HCl compared to those treated with SABER-bupivacaine; 16% versus 13%, respectively. Dr. Petit-Scott expressed concern over the duration of surgical

site bleeding after treatment with SABER-bupivacaine compared to treatment with either control in each part of the study. Specifically, she noted that there was a higher incidence of bleeding through day 8 (POD 7) in patients treated with SABER-bupivacaine, compared to the respective control groups. 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 Division is less concerned with the reported surgical site bleeding because the incidences in general were low and all reported incisional bleeding on day 8 was spotting of the dressing only for all treatment groups.

Drainage from the Surgical Incision

As described in Dr. Petit-Scott's review, 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. Because the overall incidence of wound hematoma was low and there did not appear to be long-term adverse events, the Division does not feel the risk of this adverse event is clinically significant.

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.

Dr. Petit-Scott noted in her review that 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. She argues that 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.

The Division believes that there is a possibility longer abdominal incisions carry a greater risk of wound dehiscence than shorter length incisions. One possible explanation for this

possibility is that longer incisions may experience more tension and be susceptible to patient movement when compared to shorter length incisions. Regardless, because there was no concern of increased wound dehiscence in the shoulder studies, the Division believes that SABER-bupivacaine can be safely administered to patients undergoing limited shoulder procedures, and that information in the label alerts the prescriber to this risk when used in soft tissue abdominal procedures.

Surgical Site Infection (SSI)

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

As noted in Dr. Petit-Scott's review, the Applicant 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. Dr. Petit-Scott argues that despite the incidence of surgical site infections not being unexpectedly high and there were no subsequent complications, surgical site infections are still concerning with administration of SABER-bupivacaine in soft tissue surgical wounds. Any post-operative antibiotic treatment is concerning and is 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.

The Division believes, however, that the overall incidence in combination with the infection location (umbilical incision) is not concerning and does not adversely impact the ability to approve the drug product for use in patients undergoing shoulder surgery. It does not appear there was an increased number of surgical site infections in the shoulder studies, such that the narrow indication will likely limit the risk of surgical site infections.

Abnormal Wound Healing

As noted in Dr. Petit-Scott's review, there were nine patients in Part 2 of the study 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, and all cases resolved by day 60 of the study.

It does not appear that in the general category of abnormal wound healing there were increased reports in patients treated with SABER-bupivacaine. This is reassuring and supportive of the safety profile of this drug product.

Retained SAIB Formulation in the Wound

The long-term impact of residual SAIB formulation in the wound is unknown. Specifically, nonclinical data suggest components of the SAIB formulation persist in the wound for at least one year after administration, which may increase scarring or fibrotic tissue in the wound. As

noted by Dr. Petit-Scott, an increase in fibrotic tissue could result in adverse events such as development of adhesions and bowel obstruction after intra-abdominal procedures. Additionally, increased fibrotic tissue may impact surgical re-exploration with a potential increased risk of surgical complications. As discussed previously, Dr. Ahn's conclusion was that the local effects observed after administration of SABER-bupivacaine in rats and minipigs "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." She further stated that it does appear that while some portion of the vehicle remains in tissues for at least one year, there did not appear to be associated long-term pathology and the clinical significance of residual vehicle is unknown.

Conclusion

The Applicant has adequately addressed the safety-related deficiencies identified in the CRL.

The Applicant conducted an analysis of follow-up safety data for adverse events from previously completed studies related to the shoulder joint and surrounding tissues. In general, the four additional safety evaluations in patients undergoing shoulder surgery was adequate to address the shoulder related-safety deficiencies in the CR letter. Dr. Petit-Scott noted in her review that the incidence of decreased function in Study BU-002-IM, indicated by lower post-operative Constant-Murley Scores, in patients treated with a SABER product is concerning; however, because there were no radiographic (MRI) findings to explain the changes in scores, it is unlikely that administration of SABER-bupivacaine resulted in structural changes leading to loss of shoulder joint function. Additionally, the Division believes that because these studies were completed more than 10 years ago, clinically relevant long-term consequences would have become apparent during this time.

The Applicant also evaluated follow-up data from soft tissue and shoulder studies to assess the wound-related adverse events of interest described in the CRL. The post-action assessment of the studies did not identify any abnormalities in wound healing or long-term adverse events.

Lastly, the Applicant enlisted Dr. James M. Anderson, M.D., Ph.D., an expert on biocompatible injectable and implant materials and foreign body reactions to biomaterials, to review the two nonclinical studies, one in rats and one in rabbits, that demonstrated foreign body reactions to SABER-bupivacaine. He concluded that the findings "demonstrate the normal resolution of the inflammatory and healing responses with the expected foreign body reaction at the implant/tissue interface." Dr. Ahn's conclusion differs slightly from Dr. Anderson's; however, it does appear that while some portion of the vehicle remains in tissues for at least one year, there did not appear to be associated long-term pathology and the clinical significance of residual vehicle is unknown.

Study C803-028 was designed to better characterize the benefit-risk profile of SABER-bupivacaine. This study incorporated a non-SABER-placebo (saline) and an active comparator (bupivacaine) to better characterize adverse events that may be related to the SAIB vehicle formulation. The safety data has demonstrated that there is an increased incidence of surgical site bruising, which can extend over a larger surface area than bruising observed in the saline placebo or bupivacaine treatment groups. In addition, there appeared to be a trend toward an

increased incidence of wound hematoma and surgical site infections requiring antibiotics in the SABER-bupivacaine groups. The Division believes that because SABER-bupivacaine will be approved for limited use in select shoulder procedures, a surgical model that did not demonstrate an increased incidence in these adverse events, and information in the drug product label alerts prescribers, these risks have been adequately mitigated.

Regarding the concerns about neurologic-related adverse events, Study C803-028 demonstrated that 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 still a suggestion that systemic exposure to benzyl alcohol may be the cause, and Dr. Petit-Scott felt this adversely impacted the benefit-risk profile of SABER-bupivacaine further supporting her recommendation for a second CR action. The Division, however, does not agree for four reasons. First, with the exception of somnolence, the overall incidence of these adverse events was low. Second, the patients who experienced potential benzyl alcohol-related adverse events did not suffer long-term consequences, and all but one recovered by the time of discharge from the PACU. Third, the immediate post-operative period is a time when patients are recovering from the effects of anesthesia, and in this case general anesthesia, and receiving a variety of medications, including opioid analgesics, anti-emetics, and vasopressor or antihypertensive medications, such that it is challenging to make a definitive conclusion about the true cause of these adverse events. And lastly, the limited surgical indication and information included in the drug product label adequately mitigates these risks.

In conclusion, the Division believes that the identified risks associated with administration of SABER-bupivacaine can be adequately mitigated by the narrow arthroscopic subacromial decompression indication and with information in the drug product label.

8. 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 SABER-bupivacaine for postsurgical analgesia. The committee was presented with three discussion topics and a single voting question. The following is a high-level summary of the meeting. Additional information is included in Dr. Petit-Scott's clinical review and the full transcript is available at the Agency's website.

Regarding the first discussion topic, whether the Applicant provided sufficient information to support the proposed indication, the committee 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. 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.

Regarding the second discussion topic, whether there were issues with the 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.

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 Study C803-028 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.

Regarding the third discussion topic, whether the efficacy, safety, and overall benefit-risk profile of SABER-bupivacaine support the approval of this application, several committee members did express concern about the limited efficacy and the fact that Study C803-028, while designed to address outstanding safety and efficacy concerns, did not win on primary endpoints for either Part 1 or Part 2. 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. 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.

Regarding the concern raised by the AC of inadvertent intravascular injection of SABER-bupivacaine, the Division had several internal discussions and evaluated responses to

Information Requests following the AC meeting, and concluded that there is a need for additional non-clinical data to determine the risks associated with exposure to a large dose of bupivacaine (660 mg), intravascular hemolysis, and the formation of emboli. Based on the narrow shoulder indication and information in the drug product label, including a boxed warning for the formation of emboli and detailed administration instructions, these nonclinical studies can be conducted post-approval.

9. Pediatrics

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.

10. Other Relevant Regulatory Issues

Data Integrity and Submission Quality

As noted in Dr. Petit-Scott's review, 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 confidence in the data and the associated conclusions.

Exclusivity or Patent Issues of Concern

There are no outstanding patents or exclusivity periods, as indicated in the Approved Drug Products with Therapeutic Equivalence Evaluations publication, commonly referred to as the Orange Book. Refer to Dr. Petit-Scott's review for more information regarding financial disclosures.

Office of Scientific Investigations (OSI) audits

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.

Good Clinical Practice (GCP) issues

As noted in Dr. Simone's review from the initial review cycle, all clinical trials were 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.

11. Labeling

The Applicant proposed

(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 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 Division included the risk of joint cartilage necrosis in Section 5, and requested the Applicant include all relevant safety information from both soft tissue and shoulder studies in Section 6. The Division also requested the Applicant to update the label with all relevant Marcaine information based on the labeling supplement approved on 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 was not included in this section.

12. Postmarketing Recommendations

As previously noted, the concerns surrounding inadvertent intravascular injection discussed during and subsequent to the AC meeting must be addressed with data from additional nonclinical studies. Dr. Ahn has described the required studies in her completed pharmacology-toxicology review. The Division feels that because the indication is limited to one surgical procedure and the label includes detailed administration information, these studies can be conducted post-approval. The Applicant agreed to the two nonclinical studies PMRs and timetables described below:

4014-1	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 if it is inadvertently administered into the intravascular space. 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.
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Draft Protocol Submission: 02/2022

NDA 204803
Durect Corporation
Posimir (bupivacaine solution)

Final Protocol Submission:	08/2022
Study Completion:	06/2023
Final Report Submission:	09/2023

4014-2 Conduct a study to assess the potential serious risk of POSIMIR-induced Local Anesthetic Systemic Toxicity (LAST) following inadvertent intravenous route of administration and the ability of lipid infusions to treat the clinical manifestations of LAST.

Draft Protocol Submission:	05/2022
Final Protocol Submission:	11/2022
Study Completion:	06/2023
Final Report Submission:	09/2023

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RIGOBERTO A ROCA
02/01/2021 05:58:14 PM
I concur with Dr. Van Clief's recommendation.