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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

AMENDED CLINICAL REVIEW

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Division / Office	DAAP/ODE 2
Reviewer Name	Arthur Simone, MD, PhD
Amended Review Completion Date	October 7, 2011
Established Name	Bupivacaine extended-release liposome injection
(Proposed) Trade Name	Exparel
Therapeutic Class	Amide local anesthetic
Applicant	Pacira Pharmaceuticals, Inc.

Formulation(s)	Extended-release liposome injection in single-use vials: (b) (4)
Dosing Regimen	Single dose by local infiltration into the surgical wound prior to the end of surgery
Indication(s)	To produce postsurgical analgesia
Intended Population(s)	Patients 18 years of age and older undergoing surgical procedures

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The purpose of this addendum is to update the original review with the final recommendations from the Chemistry, Manufacturing and Controls review team and the Microbiology review team and to expand the discussion in some subsections of the safety review. The amended sections include: 4.1, 4.2, 7.3.4, 7.4.1, and 7.4.5. The amended information is identified at the beginning of each section. Minor edits to correct typographical errors and clarify certain comments were also made in sections 1 and 7.

None of the new information or expanded discussion affects the original recommendations regarding the regulatory action for this NDA.

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that an approval action be taken for this New Drug Application.

In two placebo-controlled clinical trials, the Applicant demonstrated that Exparel provides postoperative analgesia lasting up to 24 hours. One surgical procedure was evaluated in each of these pivotal studies: hemorrhoidectomy and bunionectomy. The dose and method of administration differed for each of the studies; this precludes extrapolating dosing and efficacy to other surgical procedures.

In the hemorrhoidectomy study, a 30 mL dose of Exparel was infiltrated in 5 mL aliquots at six points surrounding the anal sphincter corresponding to the positions of the even numbers on a clock face. In the bunionectomy study, an 8 mL dose of Exparel was infiltrated into the surgical wound with 4 mL infiltrated into the tissues immediately surrounding the cut bone, 2-3 mL infiltrated into tissues lateral, dorsal and ventral to the osteotomy, and the remaining 1-2 mL infiltrated into the subcutaneous tissue overlying the wound.

The safety of Exparel was compared to bupivacaine HCl and placebo in multiple studies. Overall, the systemic and local effects of Exparel did not differ substantially from bupivacaine HCl.

(b) (4)

1.2 Risk Benefit Assessment

The risk benefit assessment relied heavily on the similarity in the safety profiles for Exparel and unencapsulated bupivacaine HCl. (b) (4)

In the placebo controlled studies, Exparel was significantly better than placebo for reducing pain intensity during the first 12 hours following administration. This effect diminished over the next 12 hours such that by 24 hours after administration, there was no clinically relevant difference in the pain experienced by subjects treated with Exparel compared to those treated with normal saline. Based on the demonstration of Exparel's efficacy versus placebo, its pharmacodynamics being similar to those of unencapsulated bupivacaine HCl, and its safety profile also being similar to that of unencapsulated bupivacaine HCl, the benefits were considered to outweigh the risks. This finding, however, is limited to the two surgical procedures studied in the placebo-controlled pivotal studies. The manner in which Exparel was administered and the doses used in those studies were so dissimilar that it is not possible to extrapolate a dose or method of administration that would be efficacious for other surgical procedures. To resolve this issue, additional adequate and well-controlled studies would be needed.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Based on the safety profile of Exparel and the vast experience the Agency has with unencapsulated bupivacaine HCl, Postmarket Risk Evaluation and Mitigation Strategies are not indicated at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

Following approval, it is recommended that pediatric studies be conducted to assess safety, efficacy and appropriate dosing of Exparel in pediatric patients. These studies should initially be conducted in older patients with studies in younger patients commencing in a sequential fashion, provided the product has been found to be safe and effective in the preceding age group. If necessary, the product should be modified to meet the dosing requirements of younger children.

2 Introduction and Regulatory Background

2.1 Product Information

Exparel consists of microscopic spherical liposomes that are multivesicular and composed of a honeycomb-like structure of numerous non-concentric internal aqueous chambers containing bupivacaine. Each chamber is separated from adjacent chambers by lipid membranes. (b) (4) The liposomes are part of an extended-release drug delivery system that is similar to DepoFoam that is used in two currently marketed products: DepoCyt (NDA 21-041) and DepoDur (NDA 21-671). The liposomes used in Exparel (b) (4) contain a novel lipid excipient, dierucoylphosphatidylcholine (DEPC).

The active ingredient of the formulation is bupivacaine, which is released from the liposomes by a mechanism that involves reorganization of the barrier lipid membranes and subsequent diffusion of the drug over an extended period of time. Bupivacaine is the active ingredient in a currently marketed product (Marcaine, NDA 16-964), which is referenced by the Applicant in this 505(b)(2) submission.

The Applicant has proposed the following wording for the indication of Exparel:

> EXPAREL™ is an (b) (4) liposome injection of bupivacaine, an amide-type local anesthetic (b) (4) indicated for single-dose local administration into the surgical (b) (4) to produce postsurgical analgesia.

(b) (4)

2.2 Currently Available Treatments for Proposed Indications

There are a number of local anesthetics that are currently marketed and that can be used for infiltration into surgical wounds to provide analgesia early in the postoperative period. Among these is unencapsulated bupivacaine HCl, which has the same active ingredient, bupivacaine, as Exparel.

2.3 Availability of Proposed Active Ingredient in the United States

There are two marketers of bupivacaine in the United States, Hospira and APP Pharmaceuticals. (b) (4)

2.4 Important Safety Issues with Consideration to Related Drugs

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

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

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The first interaction between the Applicant and the Agency was at a pre-IND meeting on October 2, 2002. At that time, the Sponsor, SkyePharma, intended the drug product, then referred to as SKY0402, to be indicated for (b) (4) The Division raised several concerns at that time including:

1. The use of bupivacaine HCl as an active-control as bupivacaine HCl was not indicated for (b) (4)
2. The safety of SKY0402 needed to be better assessed in animals in terms of its potential for (b) (4)
3. SKY0402, in the clinical setting, would likely be used for other routes of administration that should be considered as part of the clinical development program including local infiltration, regional anesthesia/field blocks, and neuraxial anesthesia

The initial Investigational New Drug (IND) application (IND 69,198) for SKY0402 was submitted on December 9, 2004. At that time, SKY0402 was to be evaluated in a study of patients undergoing inguinal hernia repair and a second study of patients undergoing bunionectomy. Following the review of those protocols, the Sponsor inactivated the IND for safety reasons on January 6, 2005. Specifically, there were additional preclinical issues that needed to be performed and minor changes to the protocols that needed to be made. These issues were discussed with the Sponsor in a follow-up teleconference on March 30, 2005, after the sponsor had provided proposals for animal studies to address the Division's safety concerns.

On May 24, 2005, the Division issued a letter to the Sponsor indicating that the toxicity studies they had proposed would be sufficient to support the use of SKY0402 in incisional infiltration (e.g., hernia repair), peripheral nerve block, and neuraxial block (e.g., lumbar epidural) in clinical studies in humans.

After inactivating their IND, the Sponsor conducted trials outside the United States, and prior to reactivating the IND, requested an End-of-Phase 2 meeting that took place on January 12, 2006. (b) (4)

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17 (b) (4)

18. It may not be necessary to study the effect of hepatic and renal impairment on PK of SKY0402. However, a proposal for how to administer and label the product for these patients is needed.
19. A thorough QT study may not be required if PK data demonstrates exposure with maximum doses of SKY0402 are within the range considered safe with unencapsulated bupivacaine HCl.
20. All subjects should monitored continuously by EKG because preliminary PK data indicated that peak blood levels of bupivacaine following administration of SKY0402 can achieve a level that is 70% of minimum reported level associated with QT prolongation (1 mcg/mL). A Holter analysis will not be sufficient; patients will need to be observed clinically with real-time assessment of their EKG until blood levels are expected to be well below the threshold associated with QT prolongation.
21. Laboratory testing should be performed for variables associated with previously identified abnormalities, e.g., those found on CBC in preclinical studies. The Sponsor stated they have observed no trends of concern so far in laboratory parameters.

On March 7, 2006, the Applicant requested that the IND be reactivated, and clinical trials were allowed to proceed. On July 21, 2006, the Applicant requested advice from the Division regarding modifications that were being made to the clinical development plan. Specifically, the proposed indication for SKY0402 would be limited to postoperative pain, with SKY0402 administered only by wound infiltration. The Division agreed that limiting the indicated route of administration to wound infiltration would eliminate the need for additional animal studies to evaluate the effects of inadvertent intravascular administration and that exposure in 500 patients receiving SKY0402 by wound infiltration would be an adequate safety database to support the proposed indication provided it included the elderly and patients having serious comorbidity classified as ASA 3 and 4. The Division also noted that labeling for the product will need to contain a strong caution against the use of SKY0402 by other routes of administration that would otherwise be used for local anesthetics in typical clinical practice, but appear to be unsafe for SKY0402.

On June 6, 2007, the Applicant requested that (b) (4) The Agency (b) (4) noting that the request should be amended and resubmitted after the following issues were addressed:

1. There is insufficient safety information from juvenile animals and adult patients exposed to the product (b) (4)
2. (b) (4) require adequate and well-controlled clinical trials of bupivacaine HCl because its administration is unapproved in the pediatric population and efficacy cannot be extrapolated from studies of adults. Studies will need to include the entire pediatric patient age range and exposure by all routes of administration commonly used in clinical practice.
3. In summary, study in infants and neonates (b) (4) may be deferred until additional information becomes available to support the safe use of SKY0402 in adults. The minimum safety population in adults is anticipated to be 300 to 500 patients for each route of administration. When sufficient adult safety information is available to enable studies in pediatric patients, older children at lower risk for systemic toxicity should be studied before neonates and infants to help define dosing and to determine whether reformulation is needed to address safety requirements imposed by small patient size and hepatic immaturity.

On May 20, 2009, the Applicant was informed that the proposed proprietary name, Exparel, was acceptable and that a request for a second review of the name should be made with the submission of the NDA.

(b) (4)

(b) (4)

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7. The ISS needs to include all human safety data generated during development. This includes data that you own or have a right of reference to, even if such data were not collected under the IND, e.g., the data from Maruho in Japan.

8. The Applicant is obligated to evaluate safety based on an integrated database.

2.6 Other Relevant Background Information

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

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of adequate quality and well enough organized with complete datasets to allow meaningful review. The intent of the Applicant was to have Exparel approved (b) (4) and a dosing paradigm based on (b) (4) the type of surgery. (b) (4) It became necessary to separate the data from the lower-dose, placebo-controlled studies to characterize the risk profile and to rely on the comparisons that could be made between Exparel and bupivacaine HCl from the higher dose studies to assess possible worst case scenarios for Exparel.

3.2 Compliance with Good Clinical Practices

The clinical trials were conducted in compliance with Good Clinical Practices. For each of the pivotal studies, the Applicant included the statements:

> Prior to enrolling subjects into this study, each study site will obtain the approval of a properly constituted Institutional Review Board (IRB). Attention is directed to the basic elements that are required to be incorporated into the Informed Consent Form (ICF) under the United States (US) Food and Drug Administration (FDA) Title 21 of the Code of Federal Regulations (CFR) for the Protection of Human Subjects (Part 50.25) and the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP; E6).
>
> This study will be conducted in accordance with the clinical research guidelines established by the FDA Title 21 CFR, Parts 50, 54, 56, and 312 and the ICH GCP.

3.3 Financial Disclosures

The Applicant certified the following for each of the Investigators involved with the pivotal studies:

> As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(1).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

At the time the initial Clinical review was filed on September 23, 2011, the Chemistry Manufacturing and Controls (CMC) review team, i.e., Drs. Arthur Shaw and Prasad Peri, could not recommend that the NDA be approved to a number of outstanding issues. These issues included:

- A number of cGMP issues listed in their review filed on August 14, 2011
- Clearance by the Office of Compliance of (b) (4), the facility responsible for testing the quality of the (b) (4) used in manufacturing Exparel
- Input from the Clinical Microbiology review team as to whether they had any concerns regarding CMC issues

Since that review was filed, each of these issues was addressed to the satisfaction of the chemistry review, which now finds no CMC impediment for approving Exparel. In addition, the team has no recommendations for Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps.

The CMC team has indicated that the Applicant's use of the phrase (b) (4) in describing the bupivacaine content of Exparel is inappropriate. They state that the formulation should be expressed as having 13.3 mg/mL bupivacaine, (b) (4) and all specifications, tests, etc. should conform to this expression of strength.

NOTE: Throughout this review, the Applicant's specification of 15 mg/mL for Exparel's bupivacaine content has been used. This reflects the performance of these two reviews in parallel and not a disagreement with the chemistry review team's conclusion. (b) (4)

4.2 Clinical Microbiology

At the time the initial Clinical review was filed on September 23, 2011, the Clinical Microbiology review team, Drs. Robert Mello and John Metcalfe, had not finalized their review of the NDA. In their review filed on September 28, 2011, they noted no

deficiencies in application that would preclude the product's approval and had no recommendations for Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps.

4.3 Preclinical Pharmacology/Toxicology

The review of Drs. Bond and Wasserman finds no impediment to approving Exparel based on preclinical pharmacological or toxicological issues. They recommend several modifications to the proposed labeling, but have no recommendations for additional nonclinical studies.

4.4 Clinical Pharmacology

The Clinical Pharmacology review team, Drs. Zhihong Li and Yun Xu, found no impediment to approval of Exparel in their review of the NDA. The following bullet points are excerpts from their Clinical Pharmacology Summary highlight the key points of their review that have clinical implications.

- Bupivacaine is primarily metabolized by liver. In a study evaluating the pharmacokinetics of SKY0402 in patients with hepatic impairment, bupivacaine exposure in subjects with moderate hepatic impairment showed approximate 1.5- and 1.6-fold increases in the mean values of C_{max} and AUC_{inf}, respectively. The bupivacaine metabolite PPX showed similar exposure increase in subjects with moderate hepatic impairment with an approximate 1.9-fold increase in C_{max} and 1.6-fold increase in AUC_{inf}. Since SKY0402 is a local acting product, no dose adjustment is recommended in patients with mild to moderate hepatic impairment. However, the product should be used cautiously in patients with hepatic disease as indicated in Marcaine label.
- The QT effect following the administration of SKY0402 was evaluated in two QT studies - Study SKY0402-C-105 and Study SKY0402-C-107. Review of these two studies was consulted with the Interdisciplinary Review Team for QT Studies (IRT-QT). No apparent QT prolongation effect of bupivacaine (SKY0402 at 300, 450, 600, and 750 mg) was detected in the two QT studies. Bupivacaine appears to be associated with a concentration-dependent QTc interval shortening. The detected QTc interval shortening was not considered as clinically meaningful according to the review by IRT-QT group.

4.4.1 Mechanism of Action

Exparel consists of microscopic spherical, multivesicular liposomes that are composed of a honeycomb-like structure with numerous internal aqueous chambers containing bupivacaine. The chambers are separated from one another by lipid membranes. (b) (4) The released bupivacaine then exerts its anesthetic action when it comes in contact with nerve cells where it blocks sodium channels and prevents the initiation and transmission of nerve impulses.

4.4.2 Pharmacodynamics

The onset of action of Exparel was evaluated in clinical trials that assessed pain intensity (b) (4) These studies demonstrated that the onset of action for Exparel was less than 2 minutes, and was similar to conventional bupivacaine HCl. In the clinical trials described in the sections below, the duration of Exparel's analgesic effect appears to be no more than 24 hours and not longer than that of unencapsulated bupivacaine HCl.

4.4.3 Pharmacokinetics

Exparel is administered locally by infiltration into the tissues, where it exerts its effects as an analgesic agent. Although systemic absorption of the bupivacaine released by Exparel was noted during the clinical development program, as was the likely intravascular injection or absorption of Exparel itself, this type of exposure is not related to the product's efficacy, but does have implications for its safety profile. The systemic pharmacokinetics of Exparel were evaluated by the Clinical Pharmacology review team. In the summary section of their review, they noted the following:

- The mean plasma concentration-time profiles of bupivacaine after administration of Exparel by infiltration exhibit two peaks. There is an early peak at a median time of 0.25 to 2 hours followed by a second peak that occurs at a median time of 12 to 24 hours. Based on only the systemic exposure profile, Exparel demonstrates the characteristics of delayed T_{max} for an extended-release product. However, since Exparel is a locally administered drug and also exerts its action locally, systemic exposure should only be used as supportive evidence to determine if Exparel can be categorized as an ER product. Whether Exparel can be categorized as an ER product should also rely on other aspects (e.g. *in vitro* release profile), especially whether Exparel could reduce the dosing frequency clinically compared to IR formulation of bupivacaine HCl.

- Dose proportionality was evaluated in three surgical procedures. Exparel showed reasonably dose-proportional increase in the mean values of C_{max} and AUC_{inf} in the management of postoperative pain following inguinal hernia repair (SKY0402-C-201) and bunionectomy (SKY0402-C-203), (b) (4)

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Applicant has conducted 22 clinical studies in support of the NDA submission. These include nine Phase 1 studies, seven Phase 2 studies and six Phase 3 studies. The table below provides summary descriptions of these studies.

Table 1. Summary of clinical studies (based on Table 5.2 in the Clinical Study Reports section of the NDA)

Phase	Name	Objective	Design	Study Drugs, Dose and Route	Number of Subjects	Population	Duration of Treatment
1	SKY0402-002	Safety PK/PD	Randomized, double-blind, active-controlled	SKY0402 75 mg SKY0402 125 mg SKY0402 150 mg SKY0402 175 mg Bupivacaine HCl 0.5% Perineural block (15 mL)	6 7 6 6 12	Healthy subjects	Single dose
1	SKY0402-021	Efficacy Safety PK	Randomized, double-blind, crossover placebo- and active-controlled. Three subjects received both the lower dose of SKY0402 and Bupivacaine HCl in Stage 1; six subjects received both doses of SKY0402 and Bupiv. HCl in Stage 2.	SKY0402 10 mg SKY0402 50 mg (SKY0402 contained glucuronic acid as the pH adjusting/neutralizing agent) Bupivacaine HCl 0.125% Saline (placebo) Subcutaneous (Stage 1, four injections 2 mL each, for a total of 8 mL; Stage 2, four injections 2 mL each, for a total of 8 mL)	9 6 9 6 9	Healthy subjects	Single dose
1	SKY0402-C-103	Safety PK/PD	Randomized, double-blind, active-controlled	SKY0402 100 mg SKY0402 175 mg SKY0402 300 mg Bupivacaine HCl 50 mg epidural (20 mL)	8 8 8 6	Healthy subjects	Single dose
1	SKY0402-C-105	QT/QTc interval PK	Randomized, double-blind, placebo- and active-controlled crossover; all subjects received all doses. TQT	Saline (placebo) SKY0402 300 mg (20 mL) SKY0402 450 mg (30 mL) Subcutaneous Moxifloxacin Moxifloxacin-placebo tablet	47 47 47 49 48	Healthy subjects	Single dose of placebo or active drug per study period during two study periods

Phase	Name	Objective	Design	Study Drugs, Dose and Route	Number of Subjects	Population	Duration of Treatment
1	SKY0402-C-108	PK/PD of three lots of SKY0402	Randomized, double-blind, crossover; all subjects received two lots of SKY0402 at 300 mg.	SKY0402 300 mg Subcutaneous (20 mL)	30	Healthy subjects	Single dose of two different lots during two visits
1	SKY0402-C-107	QT/QTc interval PK	Sequential, open-label, placebo-controlled; TQT Subjects had also participated in Study SKY0402-C-105.	SKY0402 600 mg (40 mL) SKY0402 750 mg (50 mL) Saline (placebo) Subcutaneous	16 16 16	Healthy subjects	Single dose of SKY0402 per study period during two study periods (600 mg in Period 1 and 750 mg in Period 2); saline in both periods to establish baseline ECG
1	SKY0402-C-110	Safety PK Com-parison of subjects with normal hepatic function to subjects with moderate hepatic impairment	Open-label, parallel-group	SKY0402 300 mg Subcutaneous (20 mL)	18	Nine subjects with normal hepatic function and nine subjects with moderate hepatic impairment	Single dose

Phase	Name	Objective	Design	Study Drugs, Dose and Route	Number of Subjects	Population	Duration of Treatment
1	SKY0402-C-106	Safety Onset of action PD	Randomized, single-blind, placebo- and active-controlled crossover; subjects received SKY0402 in one arm and Bupiv. HCl in the other arm on one day and received SKY0402 in one arm and normal saline in the other arm on another day. Time to onset.	SKY0402 15 mg Bupivacaine HCl 0.25% Saline (placebo) Subcutaneous (1 mL)	161	Healthy subjects	Single dose of SKY0402 for two visits; single dose of Bupi HCl or saline at each visit
1	SKY0402-C-109	Safety Onset of action PD	Randomized, single-blind, active-controlled, sequential, crossover; subjects received SKY0402 in one arm and saline in the other arm on one day and Bupiv. HCl and normal saline on another day. Time to onset.	SKY0402 45 mg Bupivacaine HCl 0.25% Local infiltration (3 mL)	129 128	Healthy subjects	Single dose of SKY0402 for two visits; single dose of Bupi HCl or saline at each visit
2	SKY0402-C-201	Efficacy Safety PK	Randomized, double-blind, dose escalating, active-controlled	SKY0402 175 mg SKY0402 225 mg SKY0402 300 mg SKY0402 350 mg Bupivacaine HCl 0.25% Local infiltration (40 mL)	12 12 12 14 26	Subjects with postsurgical pain following inguinal hernia repair	Single dose

Phase	Name	Objective	Design	Study Drugs, Dose and Route	Number of Subjects	Population	Duration of Treatment
2	SKY0402-C-207	Efficacy Safety	Randomized, double-blind, active-controlled	SKY0402 105 mg SKY0402 180 mg SKY0402 345 mg Bupivacaine HCl 0.25% Local infiltration (42 mL)	25 24 25 24	Subjects with postsurgical pain following inguinal hernia repair	Single dose
[redacted]							(b) (4)
2	SKY0402-C-209	Efficacy Safety	Randomized, double-blind, active-controlled	SKY0402 75 mg SKY0402 225 mg SKY0402 300 mg Bupivacaine HCl 0.25% Local infiltration (30 mL)	24 25 25 26	Subjects with postsurgical pain following hemorrhoidectomy	Single dose
[redacted]							(b) (4)
3	SIMPLE Hemorrhoidectomy 312	Efficacy Safety	Randomized, double-blind, active-controlled	SKY0402 300 mg Bupivacaine HCl 0.25% Local infiltration (40 mL)	101 103	Subjects with postsurgical pain following hemorrhoidectomy	Single dose
[redacted]							(b) (4)

Phase	Name	Objective	Design	Study Drugs, Dose and Route	Number of Subjects	Population	Duration of Treatment
3	SKY0402-C-316	Efficacy Safety PK	Randomized, double-blind, placebo-controlled	SKY0402 300 mg Saline (placebo) Local infiltration (30 mL)	95 94	Subjects with postsurgical pain following hemorrhoidectomy	Single dose
3	SKY0402-C-317	Efficacy Safety PK	Randomized, double-blind; placebo-controlled	SKY0402 120 mg Saline (placebo) Local infiltration (8 mL)	97 96	Subjects with postsurgical pain following bunionectomy	Single dose
2	SKY0402-C-203	Efficacy Safety PK	Randomized, double-blind, active-controlled	SKY0402 175 mg SKY0402 225 mg SKY0402 350 mg Bupivacaine HCl 0.5% Perineural ankle nerve block (25 mL)	12 12 14 20	Subjects with postsurgical pain following bunionectomy	Single dose
[redacted]							(b) (4)

5.2 Review Strategy

This review takes into consideration all the clinical studies conducted by the Applicant and the 120-Day Safety Update for evaluating the safety and efficacy of Exparel and performing the benefit risk analysis that served as the basis for the recommendation for regulatory action. Relevant information pertaining to safety from the chemistry, preclinical and clinical pharmacology sections of the NDA submission were also taken into consideration along with input from members of each of the respective review teams. The expertise of the statistical reviewers was also relied upon for the analysis of the efficacy data contained in the pivotal trials.

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

The focus of the safety evaluation was on three aspects of Exparel therapy:

1. The local effects of Exparel on
    a. The surgical incision, e.g., erythema, edema, infection
    b. (b) (4)
    c. Surgical wound healing
2. The risk of systemic exposure to either Exparel or the bupivacaine released by it with emphasis on:
    a. Neurotoxicity
    b. Cardiotoxicity

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

5.3 Discussion of Individual Studies/Clinical Trials

Details of the individual studies supporting efficacy are provided in Section 9.4 below. The Applicant conducted two sets of studies that were similar in overall design but differed in terms of the comparator, placebo versus active.

6 Review of Efficacy

Efficacy Summary

The Applicant conducted five pivotal trials designed to demonstrate the efficacy of Exparel. The individual trials are described in detail in Section 9.4 of this review. In these studies, the primary endpoints were the area under the curve (AUC) of the numeric rating scale (NRS) of pain intensity through various durations (b) (4) [redacted] The Applicant then went on to conduct two clinical studies comparing Exparel to placebo (normal saline). In both of these trials, Exparel was demonstrated to be superior. The findings of these two sets of studies, i.e., active controlled and placebo controlled, are described in greater detail sections below. The table below summarizes the trials.

Table 2. Summary of pivotal trials for demonstrating the efficacy of Exparel

Trial Number	Surgical Procedure	Comparator	Dose of Exparel (mg)	Method of Administering Study Drug	Duration of Pain Assessments for Primary Endpoint (hours)	Exparel Demonstrated to be Superior ? [Y/N] (p value)
(b) (4) [redacted]						
SIMPLE Hemorrhoidectomy - 312	hemorrhoidectomy	bupivacaine HCl (150)	300	Infiltration if incision was >3 cm in length	96[R]	N (0.15)
(b) (4) [redacted]						
SKY0402-C-316	Hemorrhoidectomy	normal saline	300	Infiltration in 6 locations around the anal sphincter	72[R]	Y (<.0001)
SKY0402-C-317	Bunionectomy	normal saline	120	Infiltration into incision site and the soft tissue around the osteotomy	24[N]	Y (0.001)

[A] Pain level with activity
[P] Pain level at rest
[N] Pain level at set time point regardless of activity level

Although the two placebo-controlled studies demonstrated the superior efficacy of Exparel over placebo, the primary endpoint for the hemorrhoidectomy study, AUC_{0-72} for NRS of pain intensity, suggests that the duration of the superior efficacy is for the entire 72 hours. This is not the case. As described in Section 6.1.9, the analgesia derived from Exparel does not differ from placebo, at least not in a clinically meaningful way, beyond 24 hours.

Only two types of surgical procedures were evaluated in the pivotal studies that succeeded in demonstrating efficacy, and for each procedure a different dose of Exparel and a different technique of infiltration were used. This makes it impossible to extrapolate the dosing and infiltration methods to other surgical procedures with a reasonable expectation of efficacy.

(b) (4) They were successful in demonstrating Exparel is superior to placebo for providing up to 24 hours of postoperative analgesia following bunionectomy and hemorrhoidectomy when infiltrated into the surgical wound in a very specific manner.

6.1 Indication

The Applicant has proposed the following wording as the indication for Exparel:

> EXPAREL™ is an (b) (4) liposome injection of bupivacaine, an amide-type local anesthetic/(b) (4) indicated for single-dose local administration into the surgical (b) (4) to produce postsurgical analgesia.

The Applicant has also proposed the following dosing regimen for use with the product:

Table 3. Proposed dosing and administration (from Applicant's proposed product label)

(b) (4)/Surgery	Dose of EXPAREL*	Volume of EXPAREL*
(b) (4)		

*EXPAREL should be injected slowly into soft tissue via local administration.

6.1.1 Methods

The Phase 3 trials were appropriately designed for evaluating the analgesic properties of Exparel. The trials were all prospective, randomized, subject- and assessor-blinded, with controls - either bupivacaine HCl as an active control or normal saline as a placebo control. All the trials were designed to demonstrate that Exparel was superior to the comparator.

In the pivotal trials, the primary efficacy endpoint was the area under the curve (AUC) of the numerical rating scale (NRS) pain scores collected for different durations. Some of the pain scores were collected while the subject was at rest, others were collected while the subject was active, and others were collected regardless of the activity level (see Table 2).

Numerous secondary endpoints were evaluated in the pivotal studies. Although the Applicant made statistical comparisons between treatment groups for these endpoints, they made no prespecified adjustments to the analyses to account for multiple comparisons. Therefore, at best, the findings for the comparisons of the secondary endpoints can be considered supportive, at best. The secondary efficacy endpoints from the pivotal studies include the following:

- AUC of pain intensity scores using the NRS at rest (NRS-R) for the Full Analysis set.
- AUC of pain intensity scores using the NRS-R – with worst observation carried forward and last observation carried forward (wWOCF+LOCF) - Intent-to-Treat population.
- Pain intensity scores at rest – wWOCF+LOCF – Intent-to-Treat.
- Percentage of pain free subjects.
- Percentage of subjects receiving opioid rescue medication.
- Total postoperative consumption of supplemental opioid medication.
- Time to first postoperative use of supplemental opioid medication.
- Subject's satisfaction with postoperative analgesia or blinded care provider's satisfaction with postoperative analgesia.

Other secondary endpoints related to opioid sparing were also evaluated by the Applicant, but were not included in all of the pivotal trials. These included:

- such as bowel movements
- postoperative nausea and vomiting (PONV)
- occurrence of constipation through 72 hours

The inclusion and exclusion criteria were similar across the pivotal trials. The following criteria applied to these trials:

1. Males and females (b) (4) ≥18 years of age at the time of enrollment.

2. Non-pregnant females.
3. American Society of Anesthesiology (ASA) Physical Class 1-4 for each of the active controlled studies, 1-3 for the placebo-controlled hemorrhoidectomy study and not specified for the bunionectomy study.
4. Slated to electively undergo the specified procedure.
5. Clinical laboratory values that were within or not substantially outside the boundaries for normal limits.
6. Neurologically intact for peripheral sensation.
7. Without concurrent painful conditions or surgical procedures that require analgesic therapy.
8. Ability to provide informed consent, adhere to the study visit schedule and complete all study assessments and language specific questionnaires.

Current use of systemic glucocorticosteroids or use of glucocorticoids was not permitted for the placebo-controlled trials but was not an exclusion criterion for the active-controlled trials.

6.1.2 Demographics

The table below contains the summary subject demographic information for each of the pivotal trials. This table was constructed from the data available on subjects who received study drug and was based on actual drug administered not the assigned treatment. The data indicate that within each individual study there were no substantial differences between subjects in the two treatment groups for any of the demographic categories.

Due to the discrepancy in the findings of the pivotal trials (i.e., the placebo-controlled studies were wins for Exparel treatment, but the active-controlled studies were all losses for Exparel), subject demographics were reviewed from two additional perspectives. The first was whether there was a demographic difference between the subjects enrolled in the studies that failed to show efficacy for Exparel and those enrolled in the successful outcome studies. The second was whether the demographics of subjects in the successful studies adequately represent those of the patients likely to receive the product in the clinical setting if it is approved. Each perspective is considered below.

Comparing the characteristics for the subjects in the placebo-controlled studies to those in the active-controlled studies is relevant only for the two hemorrhoidectomy trials. In these two trials, the following observations regarding the subjects' demographics were noted:

1. The age distribution was similar in both studies.

2. The placebo-controlled study had approximately twice as many males as females compare to the more evenly distributed numbers in the active-controlled study.
3. All subjects in the placebo-control study were Caucasian whereas their counterparts in the active-controlled study were approximately 80% Caucasian.
4. There is a difference in the ASA-Physical Status distribution between the two studies with the active-control study being skewed toward subjects with more serious underlying medical conditions.

None of these differences were likely to have a substantial impact on the outcomes.

For the bunionectomy study, the demographics of the subjects reflect those of the general patient population with a predominance of females and age < 65 years old at the time of surgery. Similarly, the demographics of the subjects partaking in the hemorrhoidectomy study reflect those of the general population, in the United States, with males presenting more often than females for treatment, although no sex predilection has been reported, and age < 65 years old at the time of surgery.

Table 4. Subject demographics for the pivotal studies

Demographic		Study Type and Treatment Group						(b) (4)
		Placebo Control						
		Bunionectomy		Hemorrhoidectomy		Hemorrhoidectomy		
		Exparel (120 mg)	Saline	Exparel (300 mg)	Saline	Exparel (300 mg)	Bupivacaine HCl (100 mg)	
Age (years)	18-64	96	91	86	84	95	93	
	≥65	1	5	9	10	6	10	
	≥75	0	0	2	2	2	3	
Gender	Male	22	12	63	67	53	53	
	Female	75	84	32	27	48	50	
Race	White	66	72	95	94	80	77	
	Black	25	21	0	0	13	10	
	Other	6	3	0	0	8	16	
ASA-PS	1	78	82	57	49	29	38	
	2	19	14	36	42	57	56	
	3	0	0	2	3	15	9	
	4	0	0	0	0	0	0	

6.1.3 Subject Disposition

The following table contains the subject disposition information from each of the pivotal studies.

Table 5. Subject disposition for the pivotal studies

Study	Screening Failures	Randomized	Received Treatment	Discontinued	Lost to follow-up	Excluded from analysis	Analyzed for efficacy
C-316	45	190	189	3	0	5	184
C-317	72	195	193	8	0	6	187
(b) (4)	30	251	245	15	3	27	218
C-312	33	220	204	6	6	6	198
(b) (4)	5	146	136	54[2]	2	14	122

[1] These studies were identified by numbers that were contained in the protocol numbers:
(b) (4)
C-312: SIMPLE Hemorrhoidectomy 312
(b) (4)

[2] 45 subjects were discontinued for an "Administrative Reason."

The disposition of the subjects from screening through analysis for efficacy is unremarkable (b) (4)

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint for each of the pivotal studies was the area under the curve (AUC) for the numeric rating scale (NRS) of pain intensity through various durations as indicated in Table 2. **Summary of pivotal trials for demonstrating the efficacy of Exparel** the endpoint was chosen as it reflects both magnitude and duration of effect for the treatments in relieving pain. This endpoint has been used as the primary endpoint in clinical trials of efficacy for other types of analgesics, and the Division concurred that this was an acceptable primary endpoint at the End-of-Phase 2 meeting which took place in 2006.

The design of the pivotal trials was appropriate for the indications sought and satisfied the regulations on well-controlled trials (21 CFR §314.126). The Applicant's efforts at minimizing the potential for bias were reasonable and appeared to be adequate; these included treatment randomization, protocol-specified methods for assuring the blinding of Investigators to the study drug administered, and protocol-specified statistical analysis plans.

Based on the study results for the primary endpoints, Exparel was demonstrated to be superior at providing post operative analgesia for two surgical procedures. The duration of that effect and the adequacy of dosing are discussed in Sections 6.9 and 6.8 below, respectively.

The table below presents the primary endpoints and outcomes for each of the pivotal studies.

Table 6. Pivotal study treatments, primary endpoints and outcomes

Study	Primary Endpoint	Treatment	Treatment Result [mean (SD)]	Outcome [win/loss] (p value)
(b) (4)				
C-312	AUC NRS pain intensity from 0-96[R] hours post-op	Exparel 300 mg	396 (213)	Loss (0.15)
		Bupivacaine HCl 150 mg	359 (194)	
(b) (4)				
C-316	AUC NRS pain intensity from 0-72[R] hours post-op	Exparel 300 mg	142 (101)	Win (<.0001)
		Normal saline	202 (104)	
C-317	AUC NRS pain intensity from 0-24[N] hours post-op	Exparel 120 mg	125 (48)	Win (0.001)
		Normal saline	146 (43)	

[A] Pain level with activity
[P] Pain level at rest
[N] Pain level at set time point regardless of activity level

6.1.5 Analysis of Secondary Endpoints(s)

In each of the pivotal studies, the Applicant included dozens of secondary endpoints (see the lists of these endpoints in the reviews of the individual studies in Section 9.4). These endpoints primarily assessed efficacy by comparing the AUC for pain scores at multiple time points, pain intensity scores at multiple time points, and the use of rescue analgesics (e.g., time to first rescue, total opioid usage during study period), Endpoints were also selected to assess the occurrence of adverse events related to opioid use (e.g., nausea, vomiting, constipation). The statistical analysis plan did not utilize a

hierarchical structure for analyzing these endpoints. Despite this shortcoming, only a few of the endpoints were reported by the Applicant to "significantly" differ between the treatment groups. (b) (4)

- (b) (4)
- SIMPLE Hemorrhoidectomy 312 (with over 60 secondary endpoints)
  - adjusted mean NRS-R score at the 84 hour time point (p=0.04) [in favor of bupivacaine HCl]
  - mean integrated NRS-R pain intensity scores and supplemental opioid pain medication consumption at the 84 hour time point (p=0.03) [in favor of bupivacaine HCl]
- (b) (4)

(b) (4)

For the placebo-controlled studies, the following secondary efficacy endpoints "significantly" differed between treatment groups, all favoring Exparel, as reported by the Applicant:

- SKY0402-C-317 [bunionectomy] (over 20 secondary endpoints)
  - mean pain intensity score [in the full analysis (FA) set]
    - before first use of rescue medication
    - at 2 hours
    - at 4 hours
  - percentage of subjects who were pain free [defined as an NRS of 0 or 1 (FA set)], at 2, 4, 8, and 48 hours
  - percentage of subjects who received no rescue pain medication through 8, 12, 16, 20, and 24 hours
  - total amount of postoperative Percocet use (FA set) at 24 hours
  - median time to first use of Percocet
- SKY0402-C-316 [hemorrhoidectomy] (over 20 endpoints)
  - median time to first opioid use (14 hours in the Exparel group versus 1 hour in the placebo group)
  - opioid use for through 72 hours (22 mg in the Exparel group compared to 29 mg in the placebo group)
  - percentage of subjects who required no opioids (opioid-free) up to 72 hours (28% for Exparel treated subjects versus 10% for placebo treated subjects

While the study results for the secondary endpoints in the placebo-controlled studies were supportive of the primary endpoint results, (b) (4)

6.1.6 Other Endpoints

Exploratory endpoints were not included in the pivotal studies.

6.1.7 Subpopulations

Efficacy across subpopulations was performed by the Drs. Petullo and Price from the statistics review team. They conducted their assessment using data from the subjects who

were enrolled in the placebo-controlled pivotal trials and looked for differences in outcomes due to age, gender, race, and country where the study site was located.

For study C-316, all patients were classified as Caucasian so no analysis was performed for race. In this study, there was no significant treatment interaction for gender or age; however, there was a significant treatment interaction with country. The magnitude of the treatment effect in the Republic of Georgia was much larger than the treatment effect observed in Poland or Serbia. As there was a treatment effect observed in all countries and the study was not powered to detect treatment effects in individual countries, this finding was not considered to have a substantial impact on the efficacy findings.

For Study C-317, it was noted that there were more females enrolled than males, which is consistent with the patient populations presenting for bunionectomy. There were no significant interactions of treatment with any of the subgroups; however, it was noted that a treatment effect was not observed at the site in San Marcos, TX. As the Applicant did not provide an explanation, an exploratory analysis of baseline characteristics (age, gender, race, and baseline pain score) was performed by the statistics team, and no significant differences in this site from the other sites was found.

Lastly, in Study C-316, it was reported by the Applicant that nine patients had pain scores that were "completed with a hand of the investigator based on verbal interview with patients." As an exploratory analysis, these patients were removed from the primary analysis by the statistics team, and a significant treatment effect in favor of Exparel was still present.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Based on the pivotal studies, the Applicant has proposed three doses of Exparel for clinical use:

(b) (4)

(b) (4)

For the two remaining dosing recommendations, there is a single study involving a single surgical procedure, which the Applicant relies upon for the evidence of dosing

efficacy. While the study findings were supportive of the dosing regimen, it is not clear how the findings can be extrapolated to incision lengths for other surgical procedures.

In the bunionectomy study, there was no stipulation as to the length of the surgical incision. Incision lengths are frequently longer than 3 cm for this procedure, yet that is the upper limit of incision size that this study is purported to support. Furthermore, the study drug was injected deep into the soft tissue around the osteotomy as well as the cut edges of the surgical wound, which confounds making a determination of the utility of this dose for other surgical procedures.

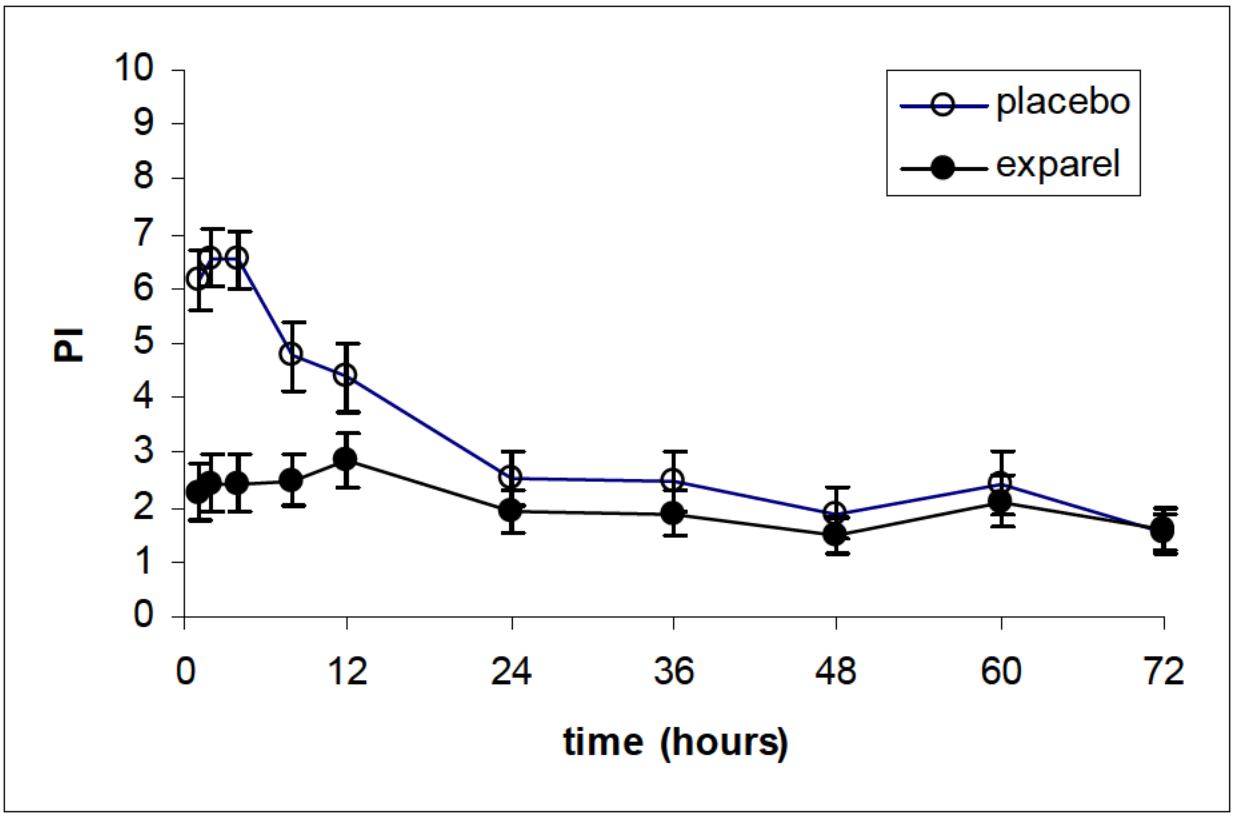
In the hemorrhoidectomy study, the entry criteria stipulated that the incision length had to be at least 3 cm and the protocol dictated that the Milligan-Morgan technique be used. However, this technique results in three triangular-shaped wounds that are left open to avoid abnormal narrowing of the anal canal as the wounds heal, and the protocol also dictated that 5 mL of the study drug should be infiltrated in six locations around the anal sphincter based on the even numbers of a clock face.

It is not clear how the results from either of these studies can be extrapolated to other surgical incisions either longer or shorter than 3 cm. However, the studies do support the use of Exparel for the surgical procedures evaluated using the techniques described in the protocols.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

It is important to note that the use of an AUC endpoint is helpful as it provides an assessment of both the magnitude and duration of the parameter assessed. However, the AUC value alone cannot represent the full clinical picture; examination of the plots of the raw data can provide a substantial insight into the meaning and relevance of the AUC finding. This is particularly true for the two placebo-controlled studies for Exparel. In the figures below, the mean pain intensity scores are plotted as a function of time. It was from these plots that the AUC values were determined.

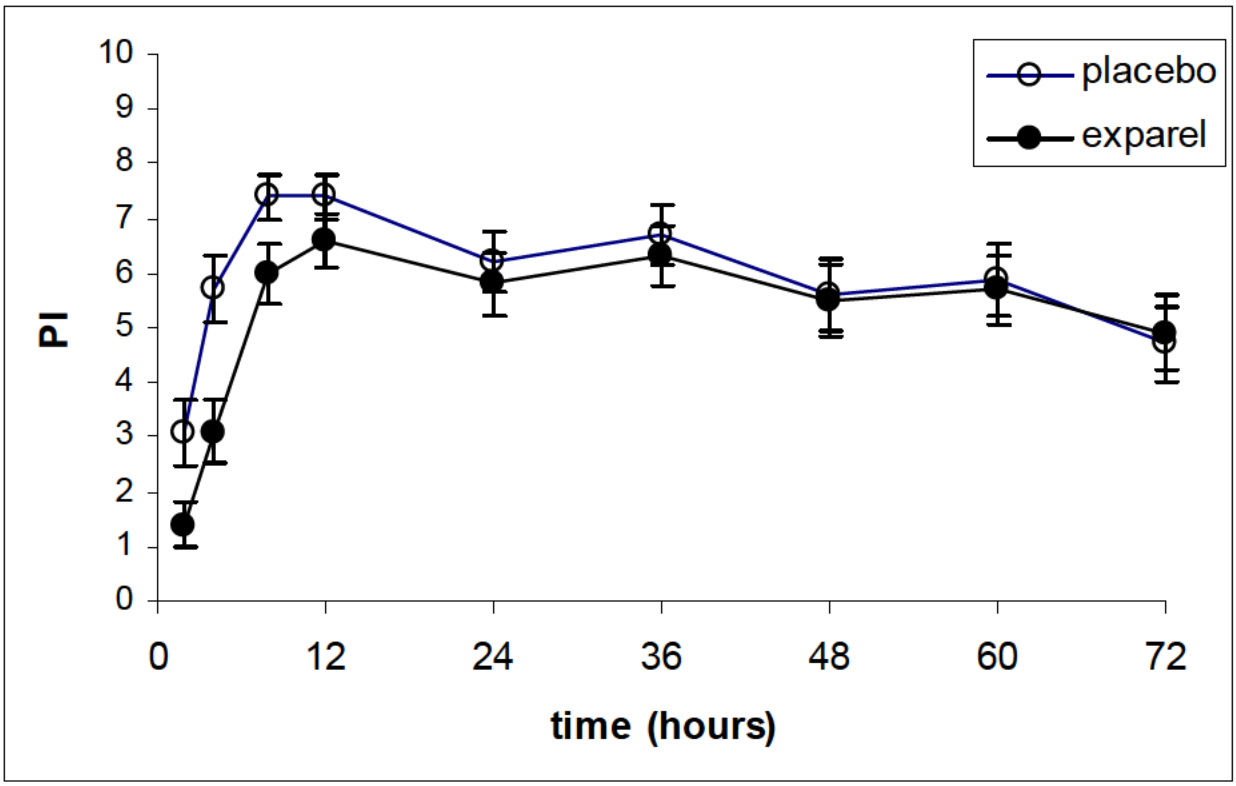
Figure 1. Mean Pain Intensity versus Time plot for hemorrhoidectomy study (C-316)



The plot for the hemorrhoidectomy study indicates that the difference between treatment groups occurs only during the first 24 hours following study drug administration. Between 24 and 72 hours, there is minimal to no difference between treatments; clearly there is no clinically relevant difference in the treatments for this time period. The plot makes it evident that the differences in AUCs for the two treatments over the 72-hour period is driven by the analgesic effects of Exparel during the first 24 hours following treatment, (b) (4)

The plot for the hemorrhoidectomy study, in the figure below, indicates that the efficacy of Exparel compared to placebo is superior only for the first 24 hours, which was the time period that the Applicant used for determining the AUCs. Had the AUCs been calculated out to 72 hours for this study, Exparel would likely still have significantly differed from placebo in a manner similar to that observed in the bunionectomy study.

Figure 2. Mean Pain Intensity versus Time plot for bunionectomy study (C-317)



In summary, the primary efficacy endpoints used in the pivotal studies were appropriate and support a finding of efficacy for Exparel but only compared to placebo. (b) (4) [redacted] Furthermore, the raw data used to calculate the primary endpoints for the placebo-controlled studies indicate that the analgesic effects of Exparel exceed those of placebo for up to 24 hours when administered following bunionectomy and hemorrhoidectomy procedures.

6.1.10 Additional Efficacy Issues/Analyses

There were no additional efficacy issues or analyses.

7 Review of Safety

Safety Summary

The safety of Exparel needs to be considered from two perspectives: toxicity related to systemic exposure and local toxicity. Each is considered separately below.

Systemic Toxicity

Systemic exposure includes not only bupivacaine absorbed from the tissues infiltrated with Exparel but also the absorption, and possible injection, of the bupivacaine-containing liposomes into the vasculature. Plasma bupivacaine levels were measured in several studies, and in a number of instances were found to be high enough that adverse events would be considered as likely to happen based on reports in the literature indicating severe toxicity occurring at levels of 1 mcg/mL and higher. In the eight studies where plasma bupivacaine levels were evaluated, there were 38 subjects who had bupivacaine levels > 750 mcg/L. There were 25 subjects with bupivacaine levels measured at > 1,000 mcg/L, and 3 subjects with levels > 10,000 mcg/L recorded. These findings are discussed in detail in Section 7.3.4 below.

Not unexpectedly, higher doses of Exparel were associated with higher systemic exposures. The three highest plasma levels reported were 12,936 mcg/L, 34,331 mcg/L, and 42,662 mcg/L. In the review of the adverse events reported for these subjects, only one subject had an event suggestive of neurological or cardiac toxicity: mild lethargy. Review of the adverse events reported for the all of these subjects indicated that neurological or cardiac adverse events occurred only in subjects dosed with 450 mg (n=2) or 600 mg (n=12) of Exparel. All but three of the 22 adverse events for this group of subjects were reported as mild; two (confusion and hallucinations) were reported as moderate; and one (over sedation) was reported as severe and was associated with narcotic use in addition to Exparel. These adverse events are discussed further in Section 7.3.4 below. It should be noted that none of the adverse events more commonly associated with the early stages of local anesthetic induced neurotoxicity (e.g., tinnitus, perioral numbness, metallic taste sensation) were reported by any of these subjects.

While laboratory error may account for an occasional high value, the number seen in these studies suggest the possibility of another phenomenon, e.g. Exparel in the systemic circulation releasing its bupivacaine during sample preparation for the analysis. Regardless of the cause, the elevated plasma levels of bupivacaine were not associated with any adverse events that posed a substantial risk to patients.

In addition to the clinical experience described above, there were animal studies conducted which evaluated safety when the DepoFoam excipient or the final drug

product, Exparel, were injected intravenously. As indicated in the Pharmacology-Toxicology team's review, described below in Section 7.2.3, there is animal support for the safety of an inadvertent injection of up to 60 mg of Exparel in humans, which would represent a worse case scenario.

Overall, there were no findings that indicated infiltration of Exparel resulted in systemic exposure to levels of bupivacaine that were associated with either neurological or cardiac toxicity. Comparison of Exparel to bupivacaine HCl and to placebo in the pivotal studies indicated that doses of Exparel up to 600 mg were associated with adverse events, suggestive of systemic exposure, that were similar in nature and frequency to those of 100 mg and 200 mg doses of bupivacaine HCl and to placebo. Animal toxicology studies suggested that doses of Exparel up to 60 mg could be injected intravenously without toxicity related to either the bupivacaine exposure or potential embolic effects of the liposomes.

Local Toxicity

Local toxicity includes consideration of the effects of Exparel on the tissues into which it is injected, the wound healing process, (b) (4) .

Wound healing was evaluated postoperatively in seven studies including both placebo-controlled pivotal studies (b) (4) In these studies, assessments of wound status were made at Day 8 or Day 10 (Day 8|10), and at Day 30 or Day 36 (Day 30|36) following treatment, depending on the study. Wound status, i.e., erythema, edema, induration and drainage, were very similar between the > 300 mg doses of Exparel and combined doses of bupivacaine HCl at Day 8|10; lower doses of Exparel were consistently associated with slightly less favorable outcomes for each of the parameters, but the difference is not expected to be clinically significant.

At the Day 30|36 assessment, the two Exparel and combined bupivacaine HCl treatment groups were similar in all assessments. All of these treatment groups were associated with slightly more erythema and drainage than placebo, but the differences are not expected to be clinically relevant.

The Clinician's overall level of satisfaction with wound healing, wound status, and wound scarring was similar between the Exparel and bupivacaine HCl groups

As for other types of local toxicity, the bunionectomy study results suggested that Exparel does not have a toxic effect on bone healing following osteotomy (b) (4)

Overall, the local toxicity of Exparel appeared to be no different than that of either bupivacaine HCl or placebo.

In summary, the safety profile of Exparel does not appear to differ in a clinically significant way from bupivacaine HCl. For the doses studied as part of the clinical development program, there is no evidence that Exparel produces tissue toxicity in the short or long term, that it adversely affects wound healing (b) (4), or that it is anymore likely than bupivacaine HCl to cause neurological or cardiac toxicity with systemic absorption or inadvertent injection.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety database was derived from the 22 clinical studies conducted by the Applicant and listed in Table 1 located in section 5. These consisted of eight controlled Phase 1 trials, which included two QTc and one hepatic impairment studies; seven controlled Phase 2 trials; five controlled Phase 3 trials and a single Phase 3 observational study.

All studies conducted with Exparel involved acute use, i.e., a single administration, of the product, with the exception of 180 subjects who participated in some of the early Phase 1 studies and the thorough QTc studies. Those subjects who received multiple doses generally underwent a washout period between doses. A total of 1307 subjects received a dose of Exparel. Doses administered ranged from 10 mg to 750 mg. All subjects who received a dose of study drug were included in the disposition tables for each study pool.

7.1.2 Categorization of Adverse Events

For the ISS, all adverse events (AEs) were coded by the Applicant using the Medical Dictionary for Regulatory Activities (MedDRA) version 12.1. Only treatment-emergent AEs (TEAEs), defined as an AE with an onset date and time on or after the start of study drug administration were included in the summaries. Treatment-emergent AEs were analyzed by the Applicant according to overall incidence, severity, relationship to study drug, classification as a serious adverse event (SAE), and related SAEs for each of the five study sets. Adverse events were also analyzed on the bases of age, gender, ethnicity, race, and ASA class for each of the sets.

The tabulations of AEs by severity included the categories 'severe,' 'moderate,' and 'mild.' Adverse events with missing severity had severity set to 'severe' by the Applicant. In the tabulations of AEs by relationship to study drug, "related" AEs were defined as those that had a relationship of 'possibly,' 'probably/related,' 'definitely,' 'related,' and 'Yes.' AEs with missing causal relationship were categorized as related by the Applicant.

The Applicant's categorization of neurological and cardiac adverse events were assessed by this reviewer by random comparisons of the verbatim terms to the preferred terms used by investigators and subjects, focusing on the events leading to dropouts or other changes in treatment.

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

In assembling their integrated safety database, the Applicant included any subject who received any portion of study drug. They reported that the pooled database was constructed from the CDISC SDTM migrated data for each study and put into their analysis dataset model. Migration to SDTM data before pooling was done to ensure that the data variable names, labels, and formats were consistent across the studies being pooled.

The Applicant noted that there were two subjects in Study SKY0402-C-316 and two in Study SKY0402-C-317 whose treatment could not be confirmed. Therefore, they elected to analyze these subjects based on the treatment group to which they were randomized. The Applicant also noted that in some of the studies, there were subjects whose treatment was confirmed as different from that to which they were randomized. There were a total of 9 such subjects in all of the clinical studies; five of these subjects were enrolled in pivotal studies. All of these subjects were analyzed based on the treatment they actually received.

The Applicant divided the safety dataset into five sets based on the use of their product within the study. These sets included the following:

1. All Wound Infiltration Studies (Phase 2 and 3 wound infiltration studies)
2. (b) (4)
3. (b) (4)
4. Phase 1 Studies
5. All Studies (all Phase 1, 2, and 3 studies)

Throughout their Integrated Summary of Safety (ISS) and their Summary of Clinical Safety (SCS), the Applicant placed their emphasis on the All Wound Infiltration Studies

data, as these were most relevant to the target population for the proposed indication. In addition to the All Wound Infiltration Studies pool, data from the All Studies pool were presented in the SCS. Safety data for the (b) (4) Phase 1 Studies pool were provided in the ISS.

In the All Wound Infiltration Studies pool, the Applicant noted that a total of 823 subjects received Exparel, which exceeded the minimum of 500 subjects requested by the Agency in July of 2006, when the development program underwent its final modifications. They also noted that there were 171 subjects ≥65 years of age and 135 subjects classified as ASA PS 3 or 4, which met the specifications of the Agency for at least 125 subjects for each of these groups.

The doses of Exparel ranged from 10 mg to 750 mg in the clinical studies; however, in the Phase 2 and Phase 3 studies, the highest dose of Exparel administered was 600 mg, (b) (4)

7.2 Adequacy of Safety Assessments

The timing and types of safety assessments made by the Applicant during the clinical development program were adequate to capture the potential toxicities related to the use of local anesthetics and liposomes both in the short and long term following administration of the drug product. The use of bupivacaine HCl as an active comparator in several of the pivotal studies as well as some of the earlier studies allowed a safety comparison that focused on whether there was any increased risk associated with Exparel relative to the product that it would likely replace, for its approved indications, in clinical practice. (b) (4)

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exparel is intended as a single application product. Therefore, the relevant parameters for the safety assessments include dosing and demographics. The Applicant studied an adequate range of doses (b) (4) and has captured safety data for higher doses as well. The subject demographics sufficiently reflect the populations that will likely be treated with Exparel in the clinical setting. As this is a locally infiltrated product, there are no demographics that would likely require special consideration.

7.2.2 Explorations for Dose Response

The Applicant conducted multiple dose exploration studies prior to selecting the doses used in the pivotal studies. (b) (4)

7.2.3 Special Animal and/or In Vitro Testing

Animal studies were conducted to support the doses and routes of administration for Exparel that were to be utilized in the clinical development program. Among these, there were animal studies conducted which evaluated safety when the DepoFoam excipient or the final drug product, Exparel, were injected intravenously. These were particularly important in assessing the potential risk for inadvertent intravascular injection. Regarding these studies, the Pharmacology-Toxicology team's review states:

> Intravenous SKY0402 (7.5 mg/kg) was not toxic at lethal doses of bupivacaine HCl (2.5 mg/kg) when injected into rats. However, the dose of SKY0402 tested (0.5 mL/kg and 1.2 mg/kg HED) was not high enough to be able to conduct a nonclinical-based human safety assessment for all the proposed clinical doses assuming inadvertent human intravenous injection is 100% of the total dose. However, this occurrence is not likely. Assuming inadvertent intravenous injection of 10% of the highest proposed human dose (b) (4) all proposed human doses would be supported for inadvertent intravenous dosing.
>
> Intravenous administration of SKY0402 Placebo resulted in clinical signs in one study and lethality in another at the dose volume of 1 mL/kg using the same batch of SKY0402 placebo. That would be 1 death in 28 rats and clinical signs in 3 of 28 including the one that died at a dose volume comparable to that of the highest proposed human dose of SKY0402. At a 10% inadvertent intravenous injection in the clinic, the inadvertent intravenous clinical dose would be equal to the NOAEL in the two nonclinical studies just mentioned (b) (4) kg SKY0402 Placebo).

7.2.4 Routine Clinical Testing

Appropriate routine clinical testing was performed throughout the clinical development program. The findings of these evaluations indicated no areas of special safety concerns.

7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolism, clearance and interaction of Exparel are not expected to differ from that of DepoFoam or bupivacaine HCl. The clinical studies provided no evidence that such a difference exists.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The two types of toxicities of major concern related to the use of local anesthetics are neurological and cardiac; both of which result from elevated systemic exposures due to either inadvertent intravascular administration or absorption of the drug product. The 0.5% Marcaine label states the following:

> Local anesthetics should also be used with caution in patients with hypotension or heart block. Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be performed after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.
>
> Because amide-local anesthetics such as MARCAINE are metabolized by the liver, these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations. Local anesthetics should also be used with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by these drugs.
>
> Injection of repeated doses of local anesthetics may cause significant increases in plasma levels with each repeated dose due to slow accumulation of the drug or its metabolites, or to slow metabolic

degradation. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with their age and physical status.

7.3 Major Safety Results

The table below provides a summary of the doses of Exparel and comparators evaluated in the studies that constitute the safety database. The table also includes the reasons for the subects' early termination from the study.

Table 7. Summary of study drug doses and subject dispositions for the safety database

Study Drug	**SKY0402**																				**Bupiv. HCl**	**Pla-cebo**
Dose (mg)	10	15	45	50	75	100	105	120	125	150	175	180	225	300	345	350	450	600	750	All		
Safety Population [1]	9	161	129	6	31	8	25	97	7	55	38	24	49	381	25	28	73	229	16	1307	622	239
Subjects Who Terminated Early [n (%)]	0 (0)	5 (3)	4 (3)	0 (0)	2 (7)	0 (0)	1 (4)	4 (4)	1 (14)	1 (2)	0 (0)	2 (8)	0 (0)	5 (1)	1 (4)	0 (00)	0 (0)	34 (15)	0 (0)	60 (5)	54 (9)	7 (3)
Death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)
Adverse Event [2]	0 (0)	4 (3)	3 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	8 (1)	3 (1)	1 (0)
Lost to Follow-up	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	2 (1)	0 (0)	5 (4)	13 (2)	0 (0)
Withdrawal by Subject	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	5 (1)	0 (0)	0 (0)	0 (0)	3 (1)	0 (0)	12 (19)	8 (1)	6 (3)
Other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	3 (3)	1 (14)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	26 (11)	0 (0)	32 (2)	27 (4)	0 (0)
Not Reported	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	3 (0)	2 (0)	0 (0)

7.3.1 Deaths

Two deaths were reported during the clinical development program. (b) (4) These included subject 208-032-7002, who was treated with 600 mg of Exparel and subject 208-005-3030 who was treated with a 150 mg dose of bupivacaine HCl.

Subject 208-032-7002
Subject 208-032-7002 was a 69 year old Caucasian female who presented on (b) (6) (b) (6), for total knee arthroplasty (TKA). She had a past medical history significant for hypertension, bipolar depression, hypothyroidism, osteoporosis, osteoarthritis, status-post two cerebral vascular accidents, obesity and a rash. Her medications at the time of entry into the study were lisinopril, amlodipine, ziprasidone, divalproex sodium, benzotropine, levothyroxine, ibandronate sodium, Vitamin D, propoxyphene, acetaminophen, and clobetasol cream.

The subject received a 600-mg dose of Exparel via wound infiltration at the end of her surgical procedure. In the post-anesthesia care unit, the subject received 16 mg of morphine and was reported to have used her morphine PCA. She became "unresponsive," but when treated with naloxone and 3 L/m oxygen, she became responsive.

Two days after her surgery, the subject was reported to have "altered mental status" that was classified as an SAE as it was considered immediately life-threatening. At that time she was discontinued from the study by the Investigator. The CRF states that "due to the subject's altered mental status, the subject can not continue to give adequate consent, therefore all further study procedure will be discontinues. This is due to a pre-existing condition in which was stable at screening." The CRF also notes that, on Day 4 postdose, her mentation cleared, and she was alert and oriented to time, place, and person.

Three days following surgery and study drug administration, the subject was found to be anemic, hematocrit was reported at 20%, which was attributed to intraoperative blood loss. Two units of packed red blood cells were administered and the hematocrit was noted to have increased to 25%.

The subject's remaining hospital course was complicated by urinary retention that was treated with insertion of a Foley catheter. The narrative states that "urological studies (not specified) were evaluated" and that the subject was eventually "weaned from her Foley when her cognition improved." At an unspecified time thereafter, the subject developed bladder and bowel distention. A CT scan was done, which indicated "some genitourinary problems as well as a mild ileus." After having a bowel movement, the subject was prepared for discharge. On September 29, 2008, the study site was

notified by the subject's surgeon that she had died on (b) (6) An autopsy conducted at the time concluded that the cause of death was "complications of marked haemorrhagic cystitis." The Investigator assessed the cause of death as not related to study treatment; the Applicant concurred with the assessment.

After reviewing the CRF and narrative for this subject, I concur with the Applicant that the cause of death was not related to study treatment.

Subject 208-005-3030
Subject 208-005-3030 was a 71-year old Caucasian female subject who died on postdose Day 4. Her medical history included degenerative joint disease, hypertension, hyperlipidemia, edema, left total knee replacement four months earlier, hysterectomy, sleep apnea managed with CPAP, anxiety, obesity, and fractures of the leg and thumb. The subject received 150 mg bupivacaine HCl via wound infiltration during TKA surgery on (b) (6) Her initial course was uneventful, and she was weaned from morphine PCA on (b) (6) The next morning, while ambulating in the hall, the subject became dizzy, lost consciousness, and fell back striking her head. Initially she was semi-conscious, hypotensive, and had low oxygen saturation. She was transferred to the Intensive Care Unit where she rapidly deteriorated and required cardiopulmonary resuscitation for several minutes. A pulmonary angiogram was performed, which confirmed the diagnosis of bilateral pulmonary emboli. The subject received thrombolytic therapy with tissue plasminogen activator (TPA) at the time of resuscitation from the initial arrest in the ICU.

The subject's course continued to decline over the next several days with hypotension, bradycardia, pulseless electrical activity requiring resuscitation, status epilepticus requiring induction of a coma with propofol and subsequent anoxic encephalopathy. Interventions were limited at the request of the subject's family to comfort care. The subject died on post-dose Day 4.

The Investigator assessed the cause of death as unlikely related to study treatment. The Applicant's assessment was that the event was not related to study treatment.

After reviewing the CRF and narrative for this subject, I concur with the Applicant that the cause of death was not related to study treatment.

7.3.2 Nonfatal Serious Adverse Events

There were 51 serious adverse events (SAEs) across all studies. Of these, 25 occurred in subjects treated with Exparel, 24 occurred in subjects treated with bupivacaine HCl, and 2 occurred in subjects treated with placebo.

With one exception, the Investigators and Applicant concurred that all of the SAEs for Exparel-treated subjects were unrelated to study drug. After reviewing the CRF and narrative for these subjects, I concur with the Applicant and Investigators that the SAEs were not related to study treatment. The SAE where the Investigator and Applicant differed is summarized below:

The subject (Subject 105-001-0030) was a 29-year-old White (not Hispanic or Latino) female healthy subject, who experienced an SAE of acute hepatitis. She had no relevant medical history. There were no abnormalities found on the screening physical exam and the drug screen was negative. The subject was a non-smoker. Relevant concomitant medications included ibuprofen for headache and an antihistamine for hay fever.

The subject received 450 mg Exparel via subcutaneous injection on Day 1 as part of a thorough QT study. On Day 48 postdose, the subject was found to have acute hepatitis. The follow-up laboratory tests performed on Day 73 postdose showed a slight increase in aminotransferases: AST 40 IU/L (normal 0-31 IU/L) and ALT 38 IU/L (normal 10-35 IU/L). The other biochemistry parameters were within their normal ranges including bilirubin, alkaline phosphatase, GGT, and CK.

The subject was recalled on Day 76 postdose, for a repeat biochemistry test. At this time, she did not report any adverse events; however, the results of biochemistry tests showed that she had worsening liver function tests indicating possible acute hepatitis:

- Bilirubin 71 µmol/L (normal 0-20 µmol/L)
- Indirect Bilirubin 17 µmol/L (normal <15 µmol/L)
- Direct Bilirubin 54 µmol/L (normal 0-5 µmol/L)
- ALP 245 IU/L (normal 35-104 IU/L)
- AST 405 IU/L (normal 0-31 IU/L)
- ALT 981 IU/L (normal 10-35 IU/L)
- GGT 239 IU/L (normal 9-35 IU/L)
- Fasting glucose 6.9 mmol/L (normal 3.9-5.8 mmol/L)

Additional extensive testing was done while supportive therapy was provided. No cause for the hepatitis was identified. By Day 81 postdose, the subject's physical examination and laboratory assessments were all within normal limits, and the SAE was considered fully resolved.

The Investigator consulted a toxicologist, who believed it was unlikely that Exparel or DepoFoam was responsible for causing the hepatitis.

On review of the CRF and the narrative, I do not think it is possible to rule out Exparel as the cause of the hepatitis based on the information available; however, I would consider it possibly related rather than probably related.

In the bupivacaine HCl group, 24 subjects experienced one or more SAEs. Seven of the SAEs (scar, hypoglycemia, hemarthrosis, joint swelling, arthrofibrosis [n=2 subjects], and knee arthroplasty) were assessed by an Investigator as related to study drug. After reviewing the related documents, I concur with the Investigators.

In the placebo group, two subjects experienced an SAE. Both SAEs were assessed by the Investigator as not related to study drug. I concur with their conclusions.

7.3.3 Dropouts and/or Discontinuations

Among subjects who received any study drug, there were 13 subjects who withdrew from a study due to an adverse event. Eight of the subjects were enrolled in a Phase 1 study; two subjects were enrolled in a Phase 2 study; and three subjects were enrolled in a Phase 3 study. In addition to these, there was one subject who was withdrawn from a study due to a pretreatment adverse event.

Three of the 13 subjects had received both Exparel and bupivacaine HCl, four subjects had received Exparel alone (with or without saline control), four subjects had received bupivacaine HCl alone (with or without saline control), and one subject had received placebo.

Review of the documentation provided for each of the subjects who withdrew failed to indicate a clinically relevant safety issue related to the use of Exparel.

7.3.4 Significant Adverse Events

[This section has been amended to provide an expanded discussion of the elevated plasma bupivacaine levels reported in the clinical studies.]

A key element to characterizing the risk profile of local anesthetic agents is evaluation of the potential for systemic absorption and subsequent cardiac and neurological toxicity related to the sodium-channel blocking action of these products. For bupivacaine, plasma levels > 1 mcg/mL have been reported in the literature as being associated with seizure activity and cardiac arrhythmias. In the pharmacokinetic studies of Exparel, plasma levels of bupivacaine were measured at several orders of magnitude greater than the 1 mcg/mL threshold as indicated in the table below. The table and discussion that follows exclude a subject who was treated with placebo but had a plasma bupivacaine level measured at 867 mcg/mL with no adverse events recorded.

Based on Table 11 of the Clinical Pharmacology review and the study reports for the thorough QTc studies, 311 subjects undergoing surgical procedures had PK assessments; 65 subjects had PK measurements as part of the two QTc studies (16 of those participated in both studies); and 18 subjects had PK assessments following subcutaneous injections of Exparel as part of the study evaluating the PK profile in subjects with moderate hepatic impairment. As the surgical population is most relevant for this safety assessment, and no subjects in the QTc studies or the hepatic impairment study had a bupivacaine Cmax > 700 ng/mL following their subcutaneous injections, only the surgical population is considered in the analyses below.

Table 8. Elevated plasma bupivacaine levels reported in the clinical trials

Exparel Dose	Plasma Bupivacaine Concentration (mcg/L)			
	750-999 n (%)	**1,000-1,999 n (%)**	**2,000-9,999 n (%)**	**> 10,000 n (%)**
150 [N=26]		1 (4)	1 (4)	
300 [N=62]	6 (10)	8 (13)	1 (2)	
350 [N=28]	1 (4)			
450 [N=26]	1 (4)			2 (8)
600 [N=25]	4 (16)	11 (44)		1 (4)
Total	12	20	2	3

Based on the findings above, it would be expected that most, if not all, of these subjects would have experience severe adverse events or death related to their bupivacaine exposures. This was not the case. As indicated in the table below, only the two highest doses of Exparel, 450 mg and 600 mg, were associated with either neurological or cardiac adverse events, and all of these events were labeled as mild to moderate. The most life-threatening of the reactions, ventricular tachycardia, was labeled as mild in severity; it lasted less than 1 minute, and resolved spontaneously. In addition, the other adverse events reported are not uncommon in the post-operative setting and may be attributed, in part or in whole, to anesthetic agents, surgical stress and post-operative pain.

Table 9. Cardiac and neurological adverse events associated with systemic bupivacaine levels ≥ 750 mcg/mL

Treatment Emergent Adverse Events		**Exparel Dose for Subjects with Systemic Bupivacaine Levels ≥ 750 mcg/mL**		
System	**MedDRA Code**	**450 mg [N=3] n (%)**	(b) (4)	**Total [N=19]**
Neurological	Anxiety	1 (33)		1 (5)
	Confusion or Hallucination			3 (16)
	Dizziness			3 (16)
	Lethargy, Sedation or Fatigue			4 (21)
	Headache	1 (33)		1 (5)
Cardiac	Bradycardia			2 (11)
	Tachycardia			7 (37)
	Ventricular Tachycardia			1 (5)

These findings suggest that the plasma bupivacaine levels reported do not accurately reflect systemic exposure to Exparel. The possibility that Exparel was being absorbed or inadvertently injected into the systemic circulation might explain the findings, especially if the bupivacaine content of the liposomes was released in the process of preparing specimens for analysis. The Applicant, in response to this concern, indicated that the freezing of specimens and the use of organic solvents in preparing specimens for PK analyses would destroy the Exparel liposomes and allow release of their bupivacaine content. These processes made it impossible to reassess the specimens for the presence of Exparel, but might explain the findings above. The finding of a high plasma bupivacaine level in a placebo-treated subject also raises the possibility of laboratory error; however, the number of incidents of elevated levels and their occurrence over the course of the development program suggest that this is not the cause.

In summary, plasma bupivacaine levels that would likely be associated with toxic effects were not infrequently measured in the PK studies conducted with Exparel. The clinical safety assessments of the subjects with these elevated bupivacaine levels failed to demonstrate signs or symptoms of toxicity that would normally be expected with these types of exposures. As clinical management of patients treated with local anesthetics is predicated on monitoring for adverse events, and treating them when they arise, rather

then on monitoring of plasma concentrations of these anesthetic agents, these unexpected findings for Exparel exposure should not have an impact on patient safety in the clinical setting. These findings could impact the ability to determine the causes of neurological or cardiac adverse events after the fact, in that the etiology of an adverse event may be attributed to an elevated level of plasma bupivacaine when the true etiology lies elsewhere, but this would not impact the care of the patient at the time of the adverse event, when plasma bupivacaine levels would not be immediately available, and an underlying cause for the event would need to be presumed based on the patient's medical history, surgical procedure, and concomitant medications (including Exparel). These findings should be included in the product labeling to alert clinicians to the study results and to allow them to take them into consideration when they decide to treat a patient with the product.

7.3.5 Submission Specific Primary Safety Concerns

The special safety concerns related to neurological and cardiac toxicity are described above in the Summary of Safety.

7.4 Supportive Safety Results

[Note: Section 7.4.1 was modified to provide more detailed information on commonly occurring adverse events, and Section 7.4.5 was modified to expand on the findings from the wound studies originally described only in the Summary of Safety.]

7.4.1 Common Adverse Events

[This section has been amended to provide more detailed discussion of the common adverse events.]

Overall, the common adverse events (AEs) associated with Exparel were similar in nature and frequency to those associated with bupivacaine HCl. Many of the AEs reported commonly occur in the perioperative period and can be related to the anesthetic technique (e.g., throat irritation following intubation for a general anesthetic), anesthetic medications (e.g., changes in blood pressure and heart rate), the surgical procedure or technique (e.g., operative hemorrhage and post-operative anemia), or a combination of surgical stress and anesthetic medications (e.g., nausea, vomiting, constipation). The table below provides a listing of the more common adverse events that were reported in the five pivotal studies. Adverse events from the Phase 1 and 2 studies were deliberately excluded to provide a more homogeneous population (i.e.,

subjects who underwent surgical procedures rather than partook in the thorough QTc studies) that was exposed to the proposed doses of Exparel and for which similarly homogeneous comparator groups were available.

The table includes those adverse events that occurred in ≥ 5% of the treatment population for each dose of Exparel and bupivacaine HCl. All placebo patients were grouped together. The following points are noted:

1. The only dose-dependent AE for the Exparel-treated subjects was constipation; however, these rates were consistent with those for the bupivacaine HCl-treated subjects, and higher rates would be expected for patients undergoing major surgery (b) (4)
2. Dizziness, an AE that has been associated with high systemic levels of bupivacaine, did not increase in incidence with increasing doses of Exparel and was consistent at all doses with incidences observed in both the bupivacaine HCl and placebo groups. The 16% incidence of dizziness for placebo-treated subjects suggests that the etiology of this AE is due to factors other than the study drugs.
3. The AEs for the highest dose of Exparel were similar to those of the bupivacaine HCl and placebo treatment groups.

In summary, the more common adverse events reported for the three doses of Exparel evaluated in the pivotal studies did not differ from those of either bupivacaine HCl or placebo. In addition, there was no evidence of an Exparel dose-dependent relationship for any of these adverse events

Table 10. Adverse events occurring with a frequency ≥ 5% in pivotal studies.

Adverse Event	Treatment					
	Exparel		(b) (4)	Bupivacaine HCl		Placebo [N=190] n (%)
	120 mg [N=97] n (%)	300 mg [N=196] n (%)		100 mg [N=103] n (%)	200 mg [N=194] n (%)	
Anemia					28 (14)	
Anemia Postoperative					10 (5)	
Arthralgia	1 (1)	2 (1)		3 (3)	9 (5)	2 (1)
Constipation	2 (2)	18 (9)		22 (21)	93 (48)	6 (3)
Diarrhea		2 (1)		5 (5)	2 (1)	1 (1)
Dizziness	11 (11)	3 (2)		4 (4)	5 (3)	31 (16)
Headache	6 (6)	3 (2)		7 (7)	7 (4)	8 (4)
Hypotension	1 (1)	1 (1)			4 (2)	1 (1)
Insomnia		1 (1)		1 (1)	13 (7)	
Muscle Spasms	1 (1)				12 (6)	2 (1)
Nausea	52 (54)	63 (32)		94 (91)	166 (86)	85 (45)
Edema Peripheral				1 (1)	5 (3)	
Procedural Pain		2 (1)		1 (1)	12 (6)	
Pruritus	3 (3)	4 (2)		5 (5)	30 (15)	1 (1)
Pruritus Generalized	6 (6)	1 (1)		2 (2)	3 (2)	11 (6)
Pyrexia	2 (2)	9 (5)		1 (1)	16 (8)	1 (1)
Somnolence	8 (8)				2 (1)	2 (1)
Tachycardia				1 (1)	11 (6)	
Vomiting	39 (40)	22 (11)		13 (13)	37 (19)	34 (18)

7.4.2 Laboratory Findings

No laboratory finding indicated a special concern for the safety of Exparel.

7.4.3 Vital Signs

None of the vital sign assessments of subjects receiving Exparel indicated a special concern for safety.

7.4.4 Electrocardiograms (ECGs)

None of the ECG assessments of subjects receiving Exparel indicated a special concern for safety.

7.4.5 Special Safety Studies/Clinical Trials

[This section has been amended to include a detailed discussion of wound healing.]

In this section, the findings from two sets of studies are considered. These deal with the effects of Exparel on surgical wound healing and the effects of Exparel on the QT interval of the electrocardiogram.

7.4.5.1 Assessments of Wound Healing and Wound Status

Wound healing was evaluated postoperatively in seven studies including both placebo-controlled pivotal studies (b) (4) In these studies, blinded care provider's satisfaction was assessed using a 0 to 10 numeric rating scale where 0 = completely unsatisfied with wound healing and 10 = completely satisfied with wound healing. The assessments were made at Day 8 or Day 10 (Day 8|10), and at Day 30 or Day 36 (Day 30|36) following treatment, depending on the study. At the Day 8|10 assessments, the blinded care provider's mean overall satisfaction with wound healing was 9 for all doses of Exparel, and 9 for the bupivacaine HCl group. There were no wound healing assessments made for placebo treated subjects at this time point. The blinded care provider's mean overall satisfaction with wound healing at the time of the Day 30|36 assessments was 8 for all the Exparel treated subjects. However, it was 7 for the subjects treated with ≤ 300 mg of Exparel

and 9 for those treated with > 300 mg of Exparel. For bupivacaine HCl treated subjects the mean score was 9, and for the placebo groups, the mean score was 5.

Wound status, i.e., erythema, edema, induration and drainage, were assessed on the same postoperative days as wound healing, but these assessments were made in a different set of studies. (b) (4) Wound status was not assessed in the placebo group at the Day 8|10 time point. At the Day 8|10 assessment, most subjects in the ≤ 300 mg Exparel doses, > 300 mg Exparel doses and the bupivacaine HCl-treatment groups exhibited no to very slight erythema; no drainage; no or very slight edema; and no or minimal induration as indicated in the table below.

Table 11. Wound status at Day 8|10

Assessment Finding	Treatment Group		
	Exparel ≤ 300 mg doses [N=275] n (%)	Exparel > 300 mg doses [N=278] n (%)	Bupivacaine HCl all doses [N=317] n (%)
No Erythema	106 (39)	144 (52)	167 (53)
Very Slight Erythema	55 (20)	86 (31)	102 (32)
No Drainage	162 (59)	232 (84)	277 (87)
No Edema	72 (26)	90 (32)	123 (39)
Very Slight Edema	76 (28)	102 (37)	106 (33)
No Induration	88 (32)	150 (54)	188 (59)
Minimal Induration	64 (23)	70 (25)	85 (27)

At the Day 30|36 assessment, most subjects in each treatment group (≤ 300 mg Exparel dose, > 300 mg Exparel doses, bupivacaine HCl, and placebo) exhibited no erythema or very slight erythema; no drainage; no or very slight edema; no or minimal induration as indicated in the table below. There were no instances of “severe” assessments in any of these parameters for Exparel-treated subjects.

Table 12. Wound status at Day 30|36

Assessment Finding	Treatment Group			
	Exparel ≤ 300 mg doses [N=275] n (%)	Exparel > 300 mg doses [N=278] n (%)	Bupivacaine HCl all doses [N=317] n (%)	Placebo All Doses [N=96]
No Erythema	156 (57)	175 (63)	197 (62)	60 (63)
Very Slight Erythema	60 (22)	41 (15)	44 (14)	31 (32)
No Drainage	223 (81)	223 (80)	245 (77)	90 (94)
No Edema	134 (49)	149 (54)	283 (51)	187 (59)
Very Slight Edema	77 (28)	56 (20)	133 (24)	54 (17)
No Induration	134 (49)	149 (54)	187 (59)	34 (35)
Minimal Induration	77 (28)	56 (20)	54 (17)	42 (44)

The Clinician's overall level of satisfaction with wound healing, wound status, and wound scarring was similar between the Exparel and bupivacaine HCl groups

Exparel potential effects on orthopedic wound healing were examined by follow-up assessments of the subjects in study SKY0402-C-317 (bunionectomy). At the 4-6 week postoperative visit, follow-up radiographs and office notes were collected for 82% of the subjects. It was expected that by that time evidence of improperly healing osteotomy leading to malunion or non-union would be manifest. No abnormal findings were noted in the subjects who received Exparel. This study suggests that Exparel does not have a toxic effect on tissues deeper than the cutaneous and subcutaneous layers of skin.

7.4.5.2 Thorough QTc Studies

Two studies were conducted to assess the effect of Exparel on QT prolongation. These studies were reviewed by the Interdisciplinary Review Team for QT Studies. They concluded that no apparent QT prolongation effect of Exparel for 300 mg, 450 mg, 600 mg and 750 mg was detected in the two thorough QT studies (Study SKY0402-C-105 and Study SKY0402-C-107). Bupivacaine appeared to be associated with concentration-dependent QTc interval shortening, and a similar negative concentration-QT relationship was observed for all tested dose groups across two QT studies. The review team also noted the following:

Conclusions on the QT prolongation effect of SKY0402 up to 750 mg based on Study SKY0402-C-105 and Study SKY0402-C-107 are drawn without assay sensitivity being demonstrated in either of the two QT studies. 1.) Study SKY0402-C-107 did not include a positive control arm (e.g., 400 mg moxifloxacin) to demonstrate assay sensitivity. 2.) Assay sensitivity was not established in the second stage of Study SKY0402-C-105, where the QT effect of SKY0402 was assessed. Even though assay sensitivity in the first stage of Study SKY0402-C-105 was established, as evident by the 24-hour moxifloxacin ECG profile (Figure 4) and the largest lower bound of the two-sided 90% CI of ΔΔQTcI greater that 5 ms, using the first stage assay sensitivity to claim assay sensitivity in the second stage is not valid. The conclusions on "no apparent QT prolongation effect" are drawn mainly because SKY0402 shortens QT interval in a concentration-dependent manner. To establish assay sensitivity using 400 mg moxifloxacin is only important to quantify small increases in QT interval. Because QT prolongation is not anticipated for drugs shorten QT interval, to demonstrate assay sensitivity is not critical in the QT studies.

7.4.6 Immunogenicity

No immunogenicity issues related to the use of Exparel were identified during the non-clinical and the clinical development programs.

7.5 Other Safety Explorations

[Note: Section 7.5.1 was modified to further discuss the differences in neurotoxicity observed between Exparel and bupivacaine HCl.]

7.5.1 Dose Dependency for Adverse Events

(b) (4)

. For the pooled analyses, there were fewer TEAEs reported for Exparel doses ≤

300 mg compared with the >300-750 mg group. It should be noted that the incidence of TEAEs in the bupivacaine HCl group falls between these combined dose groups.

When the Exparel All Doses group is compared to the bupivacaine HCl group, the TEAE rates are similar. (b) (4) These occurred with greater frequency for Exparel then bupivacaine HCl and included anxiety (5% versus 1%), confusional state (2% versus 1%), lethargy (3% versus 0%), and dizziness (8% versus 5%). There was no such difference for cardiac TEAEs. It is not possible to attribute these neurotoxicity differences to the treatments alone or to draw a conclusion about the safety of one treatment over the other in this regard for three reasons:

1. These TEAEs are not uncommon following surgical procedures and can be attributed, in part, to anesthetic agents used during the surgical procedure and the stress of surgery itself.
2. As systemic exposure data are not available for all of these TEAEs, it is not possible to compare either the exposures resulting from different doses of Exparel when used for different surgical procedures or form the two different treatment groups.
3. From a clinical perspective, the incidence of these events was relatively low, and the differences between the treatment groups were small.

7.5.2 Time Dependency for Adverse Events

The time dependency of TEAEs for Exparel should be considered from three perspectives based on when they occur:

1. Immediately following injection
2. When systemic exposure reaches C_{max}
3. Long enough after the surgical procedure that the healing process would be expected to be complete

The TEAEs related to the first perspective would include neurological and cardiac toxicity related to intravascular injection of the drug product and anaphylactic reactions. Neither was observed in the clinical trials. The TEAEs of concern occurring at T_{max} would be the same as those related to intravascular injection, i.e., neurological and cardiac toxicity. Such adverse events were not reported for the clinical studies. In addition, TEAEs related to Exparel did not appear substantially different than those for bupivacaine HCl for both of these time periods.

TEAEs of concern that occur during the healing process include reactions at the incision site (e.g., infection, dehiscence, irritation, inflammation and edema), delayed healing due to interactions between the drug product and deeper tissues (e.g., delayed or incomplete healing at the osteotomy site for the bunionectomy [redacted (b) (4)]. In these regards, there was no clinically significant difference between Exparel and bupivacaine HCl.

7.5.3 Drug-Demographic Interactions

The safety of Exparel did not appear to grossly differ from bupivacaine HCl among subjects based their age, gender, and race. It should be noted that >90% of subjects were less than 60 years of age, > 85% were Caucasian; and > 80% were classified as ASA-PS 1 and 2.

7.5.4 Drug-Disease Interactions

Exparel is administered to provide local analgesia. It is not intended to treat any disease condition. Exparel is not indicated for infiltration related to the excision of superficial skin lesions, e.g., skin cancers. It is not know what effect, if any, it would have on these diseases.

7.5.5 Drug-Drug Interactions

No clinical drug-drug interaction studies were conducted for this NDA. The Applicant intends to incorporate the bupivacaine-drug interactions noted in the Marcaine label into the Exparel label. In addition to those interactions, there is a known lidocaine-DepoFoam interaction that will also be included in the product labeling. This interaction was noted in a mini-pig model that demonstrated increased systemic exposure to bupivacaine when local administration of lidocaine with epinephrine was followed within 5 or 10 minutes by a dose of Exparel. The exposure was affected by the doses of the two drugs as well as the time interval separating their administration. Bupivacaine exposure was substantially reduced when doses were separated by 20 or 40 minutes. The Applicant concluded from the study that the potential risk of a clinically relevant interaction can be minimized by allowing 20 minutes to elapse between infiltration of lidocaine and administration of Exparel. This interaction is described in the DepoDur label.

7.6 Additional Safety Evaluations

[Note: Section 7.6.3 was modified to reflect the outcome of the Pediatric Review Committee's recommendations regarding the Applicant's requests of a deferral (b) (4) for various pediatric studies.]

7.6.1 Human Carcinogenicity

Exparel is intended as an acute use product; therefore, evaluation of its carcinogenicity potential was not required and is not necessary to fully assess the product's safety.

7.6.2 Human Reproduction and Pregnancy Data

Exparel was not evaluated for use in pregnant subjects. Its use in this population should not be recommended, and the Pregnancy Category section of the Exparel label should be the same as that for bupivacaine HCl in this regard.

7.6.3 Pediatrics and Assessment of Effects on Growth

Exparel has not been administered to pediatric subjects. Based on the proposed acute indication for Exparel, it is not anticipated that it would have an adverse effect on growth.

The Applicant has requested that a pediatric program be deferred until the product has been approved for use in adults. At that time, the Applicant will initiate its pediatric development program conducting clinical studies in older children, 12 (b) (4) years of age, first and then evaluating Exparel in children 6-11 years of age followed by studies in children 2-5 years of age. (b) (4)

It is appropriate that the pediatric program be deferred at this time. Evaluating Exparel in pediatric patients in an age-wise progression from older to younger is also appropriate. (b) (4) Bupivacaine HCl is currently used in this age group, and Exparel may be suitable for these patients as well. If studies in older children indicate that Exparel poses no greater risk than bupivacaine HCl, and Exparel is found

to be efficacious in older patients, studies in the youngest group of patients should be conducted.

On October 5, 2011, the Division discussed the proposed pediatric development program with the Pediatric Review Committee (PeRC). The committee concurred with the deferral of pediatric studies as proposed by the Applicant (b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The potential for overdose with Exparel exists if the drug is injected intravascularly. As indicated in sections above, small doses injected intravenously are not likely to result in harm. Labeling the product to require frequent aspiration with the syringe as the product is being administered will help to reduce that risk. Bupivacaine, the active ingredient of Exparel, is not associated with any abuse; therefore, the risk with Exparel is expected to be equally as low. Exparel is intended for single dose application; therefore, withdrawal and rebound are not issues of concern.

7.7 Additional Submissions / Safety Issues

There were no additional safety issues.

8 Postmarket Experience

Exparel is not currently marketed in the United States or elsewhere in the world.

9 Appendices

9.1 Literature Review/References

The Applicant did not submit a comprehensive literature review as part of this NDA. Such a review was not requested or required by the Division.

9.2 Labeling Recommendations

The following changes to the proposed labeling are recommended based on the findings in this review:

1. Indications should be modified to postoperative analgesia following hemorrhoidectomy or bunionectomy.
2. Dosing and Administration should be modified to reflect the methods and doses of Exparel that were used in the two placebo-controlled pivotal studies.
3. Warnings and Precautions should be limited to those apropos the use of a local anesthetic for infiltration into surgical wounds. Inclusion of information regarding neuraxial and regional anesthesia is not necessary for this product and could suggest to some that these uses are appropriate.
4. Warnings and Precautions should be modified to clearly reflect that Exparel is not recommended for administration by any method other than local infiltration and for any other surgical procedures other than hemorrhoidectomy and bunionectomy.

9.3 Advisory Committee Meeting

An Advisory Committee was not convened to review data or provide input regarding any issue related to this application because there were no issues identified that warranted such input.

9.4 Reviews of Individual Clinical Studies

9.4.1 SKY0402-C-316

A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Local Administration of SKY0402 for Prolonged Postoperative Analgesia in Subjects Undergoing Hemorrhoidectomy

Objectives

Primary Objective

To evaluate the magnitude and duration of the effect of a single intraoperative administration of 300 mg SKY0402 compared with placebo (0.9% sodium chloride for injection) in the reduction of postoperative pain.

Secondary Objectives

1. To evaluate additional efficacy parameters
2. To characterize the safety profile of SKY0402 in comparison with placebo
3. To assess the pharmacokinetics of clearance of bupivacaine from the blood plasma.

Study Design

This was a Phase 3, multicenter, placebo-controlled, randomized, double-blinded, study designed to evaluate the efficacy and safety of 300 mg SKY0402 compared to placebo (normal saline) administered by local infiltration for postoperative analgesia in subjects undergoing hemorrhoidectomy under general anesthesia.

Study Population

Subjects were enrolled from the population of patients presenting for hemorrhoidectomy that was to be performed under general anesthesia who met the criteria listed below, copied from the final study report.

Inclusion Criteria

1. ≥18 years of age at the Screening Visit.
2. American Society of Anesthesiology (ASA) Physical Class 1-3.
3. Scheduled to undergo 2- or 3-column excisional hemorrhoidectomy for internal or internal/external hemorrhoids, under general anesthesia using the Milligan-Morgan technique, including modified approaches with specialized instruments, such as LigaSure™ or harmonic scalpel, with a cumulative incision length of a minimum 3 cm.
4. Applies to female subjects only: Postmenopausal, surgically sterile, or willing to use acceptable means of contraception for at least 30 days after surgery including any of the following: hormonal contraceptives (e.g., oral, injectable, implantable starting at least 30 days before study drug administration), effective double-barrier methods (e.g., condoms with spermicide), intrauterine device, lifestyle with a personal choice of abstinence, nonheterosexual lifestyle, or a strictly monogamous relationship with a partner who has had a vasectomy.
5. Clinical laboratory values less than twice the upper limit of normal or, if abnormal, deemed not clinically significant per the Investigator.
6. Ability to provide informed consent, adhere to the study visit schedule and complete all study assessments and language specific questionnaires.

Exclusion Criteria

1. Currently pregnant, nursing, or planning to become pregnant during the study or within one month after study drug administration.
2. Use of any of the following medications within the times specified before surgery:
    a. NSAID including selective COX-2 inhibitor, opioid, SSRI, tricyclic antidepressant, gabapentin, pregabalin within three days of surgery.
    b. Use of acetaminophen/paracetamol within 24 hours of surgery.
3. Concurrent painful physical condition or concurrent surgery that may require analgesic treatment (such as NSAID, opioid, SSRI, tricyclic antidepressant, gabapentin, pregabalin) in the postoperative period for pain that is not strictly related to the hemorrhoidectomy procedure and may confound the postoperative assessments (e.g., rheumatoid arthritis, chronic neuropathic pain, concomitant vasectomy, fissurectomy).

4. Chronic user of analgesic medications, including taking opioid medications for more than 14 days in the last 3 months, or non-opioid pain medications more than 5 times per week.
5. Current use of systemic glucocorticosteroids (e.g. Decadron) or use of glucocorticoids within one month of enrollment into this study.
6. History of hepatitis (other than hepatitis A).
7. History of, suspected, or known addiction to or abuse of illicit drug(s), prescription medicine(s), or alcohol within the past 2 years.
8. Failure of presurgical drug and alcohol screen.
9. Body weight less than 50 kilograms (110 pounds).
10. History of hypersensitivity or idiosyncratic reactions to amide-type local anesthetics, opioids, or propofol.
11. Administration of an investigational drug within 30 days prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study.
12. Previous participation in an SKY0402 study.
13. Uncontrolled anxiety, schizophrenia, or other psychiatric disorder that, in the opinion of the Investigator, may interfere with study assessments or compliance.
14. Significant medical conditions or laboratory results that, in the opinion of the Investigator indicate an increased vulnerability to study drug and procedures, and expose subjects to an unreasonable risk as a result of participating in this clinical trial.
15. Single-column hemorrhoidectomy or hemorrhoidectomy without an internal component.
16. Concurrent fissurectomy.
17. Any clinically significant event or condition uncovered during the surgery (e.g., excessive bleeding, acute sepsis) that might render the subject medically unstable or complicate the subject's postoperative course.
18. A cumulative incision length of less than 3 cm.

Stopping Criteria

This study involved a single dose of study medication; therefore, individual stopping criteria were not related to continued administration of study drug, but rather the ability of subjects to continue to participate in the follow-up evaluations. The following clinical situations and the methods of follow-up to deal with them were included in the protocol:

1. If a subject experienced an adverse event (AE) that rendered him or her incapable of continuing with the remaining study visits and assessments, a

final evaluation visit was to have been performed, so that the subject's study participation could be terminated in a safe and orderly manner.
2. Subjects were to be free to discontinue from the study at any time, without prejudice to future treatment. These subjects were to have been encouraged to complete at least the study safety assessments.
3. A subject may have been discontinued from the study if he or she refused either study drug administration or to comply with study procedures. Reasons for discontinuation from the study were to be documented on the case report form (CRF).
4. A subject could be discontinued from the study by the Investigator, if it was considered to be in the best interest of the subject. If the discontinuation occurred after administration of the study drug, a final evaluation visit was to be performed, so that the subject could be terminated in a safe and orderly manner.

The protocol did not specify any study stopping criteria.

Efficacy Endpoints

Primary Efficacy Endpoint

The area under the curve of numeric rating scale at rest (NRS-R) pain intensity scores through 72 hours (NRS-R AUC_{0-72}) for subjects receiving SKY0402 versus placebo.

Secondary Efficacy Endpoints

1. Area under the curve of NRS-R through 12, 24, 36, 48, and 60 hours. (NRS-R AUC0-xx, where xx = 12, 24, 36, 48, and 60).
2. The proportion of subjects who were pain free (defined as an NRS-R of 0 or 1) at 72 hours and other time points.
3. Average daily pain with NRS-BM.
4. Proportion of subjects who received no supplemental opioid pain medication.
5. Total postoperative consumption, in mg, of supplemental opioid pain medication through 12, 24, 36, 48, 60, and 72 hours.
6. Time to first postoperative use of opioid medication.
7. Brief Pain Inventory.
8. PONV-free time through 72 hours.
9. Percentage of subjects with postoperative constipation through 72 hours.
10. Use of antiemetic medication (i.e., any medication given postoperatively to treat nausea and/or vomiting) administered through 12, 24, 36, 48, 60, and 72 hours.
11. Time to first bowel movement through 72 hours.

12. Subject's satisfaction with postoperative analgesia.
13. Date subject returns to work or normal daily activities.

Safety Assessments

1. Clinical laboratories at Baseline and Day 8.
2. AEs and SAEs through Day 30.
3. Vital signs (temperature, resting heart rate, and blood pressure) at Screening, Baseline, 0.5, 1, 1.5, and 2 hours following study drug administration and on Days 8 and 30.
4. Caregiver's satisfaction with wound healing at Day 30.

Pharmacokinetic Measurements

Blood samples for the determination of plasma bupivacaine concentrations were to be collected from approximately 50 subjects at specified sites at Baseline and at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after the start of study drug infiltration.

Methods

Subjects were to have been screened within 30 days of study drug administration. The assessments that were to have been made during the screening process are listed in the schedule of study procedures in the section below.

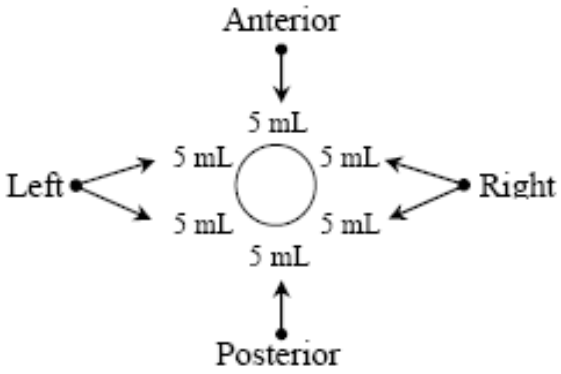
Prior to the surgical procedure, baseline assessments, also listed in the schedule of study procedures in the section below, were to have been conducted. The surgical procedure was to have been performed while the subjects were under general anesthesia with standard monitoring as determined by the individual study sites. At the end of the surgical procedure, continuing eligibility was to have been assessed based on exclusion criteria 17 and 18 (i.e., verify that no serious intraoperative complications have occurred and that the incision is at least 3 cm in length).

For those subjects who were still eligible to partake in the study, the study drug was then to have been administered by a member of the surgical team. The

study drug was to have been prepared in the syringe covered with a finger cot, to assure blinding, and administered using the following infiltration method:

1. All injections were to be performed with an infiltrative *moving needle* technique, with frequent aspirations to reduce the chance for accidental intravascular injection. If blood was aspirated into the syringe, the needle was to have been moved to a different location and aspiration was to be performed again. This process was to be repeated until no blood was aspirated.
2. Study drug was to have been injected in small increments at any given location and only after negative aspiration.
3. A gauze pad was to have been placed on the skin over the needle insertion site to absorb any fluid that might be expelled onto the skin as the needle was withdrawn to avoid inadvertent unblinding.
4. The total volume of study drug to have been used for infiltration was to be 30 mL.
5. A standard anal block procedure was to have been performed by infiltrating the perianal tissues (just outside the external sphincter) with 5 mL of study drug injected at the 2, 4, 6, 8, 10 and 12 o'clock positions as indicated in the figure below.

Figure 3 Anal block procedure for infiltration of study drug. The circle in the center represents the anal sphincter. (From p. 27 of final study report)



The start of administration of study drug was to have served as the reference time point for all further assessments through 72 hours; the day of study drug administration was to have been used to mark Day 1 of the study. Subjects were to have been hospitalized for at least 72 hours after surgery thereby allowing postoperative analgesia and the collection of study data to take place under the supervision of study staff.

For the first 3 hours after study drug administration, the following procedures and assessments were to have been executed:

1. Measure vital signs (temperature, resting heart rate, and blood pressure) at 0.5, 1, 1.5, and 2 hours.
2. Conduct NRS-R at the end of general anesthesia, before the first dose of rescue morphine, if applicable, and at 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours.
3. Draw blood samples for plasma bupivacaine from approximately 50 subjects at specified centers at 0.25, 0.5, 1, and 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after beginning of administration of study drug.
4. Record all rescue morphine and other concomitant medications (including antiemetics).
5. Record occurrence and duration (start and stop times) of any nausea and vomiting.
6. Record date and time of first and every bowel movement or occurrence and duration of constipation and conduct NRS-BM, if applicable.
7. Record all AEs and SAEs.
8. Administer BPI questionnaire at 24 and 72 hours.
9. Record subject's satisfaction with postoperative analgesia at 24 and 72 hours.

During the postoperative period, subjects were to have been instructed to avoid constipation by eating a high fiber diet and drinking plenty of non-caffeinated liquids. Stool softeners and laxatives were to have been prescribed as necessary. At the discretion of the surgeon, the surgical area could be cleaned using shallow warm baths (sitz baths) three times a day and after each bowel movement for the first week after surgery. The use of topical or intrarectal medication was not to have been permitted unless necessary to treat an adverse event.

On Day 8, subjects were to have returned to the study site for assessments of vital signs, performing clinical laboratory assessments, and recording of adverse events, particularly those suggestive of local toxicity, including sensory or motor impairment and signs of nerve or tissue irritation.

At the 30 day visit the final assessments were to have been made including:

1. The caregiver's satisfaction with wound healing was to have been assessed. The caregiver was to respond to the following question, "On a scale of 0 to 10, where 0 = completely satisfied and 10 = completely unsatisfied, how satisfied are you with the subject's wound healing?"
2. Subject productivity was to have been recorded as the date on which the subject was able to return to work or, if the subject did not work outside the home or had a strenuous job, was able to return to normal daily activities (e.g., care for one's self, get dressed, prepare meals,

short trips outside the home). Normal daily activities were not to necessarily include all activities that the subject was able to accomplish before surgery (e.g., participation in sports; heavy lifting or cleaning).

Schedule

(Schedule begins on next page.)

Table 13. Schedule of study procedures (based on Table 1; p. 39 of Clinical Study Report)

Procedure					After Study Drug Administration										
						4-72 Hours								Site Visit	Site Con-tact
						4	8	12	24	36	48	60	72		
	Study Day	Day -30 to -1	Day -1 to 1	1	1	1	1	1	2	2	3	3	5	8	30
	Time Window (±h)					0.25	.5	.5	1	2	2	4	4	24	96
Informed consent		X													
Drug Screen		X													
Clinical Labs[B]		X												X	
Assess/confirm eligibility		X	X												
Medical history, demographics and baseline characteristics		X	X												
Train self-assessments		X	X												
Pregnancy test (women of childbearing potential)			X												
Physical examination			X												
Randomize subject & prepare study drug			X												
Vital signs[C]		X	X		0.5, 1, 1.5, & 2									X	X
Study drug administration				X											
NRS-R[D]			X		1 & 2	X	X	X	X	X	X	X	X		
Subject's satisfaction with postoperative analgesia									X				X		

Procedure					After Study Drug Administration										
						4-72 Hours								Site Visit	Site Con-tact
						4	8	12	24	36	48	60	72		
	Study Day	**Day -30 to -1**	**Day -1 to 1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**3**	**5**	**8**	**30**
	Time Window (±h)					**0.25**	**.5**	**.5**	**1**	**2**	**2**	**4**	**4**	**24**	**96**
Brief Pain Inventory		X							X				X		X
Record occurrence and duration of nausea/vomiting					X	X	X	X	X	X	X	X			
Record occurrence and duration of constipation					X	X	X	X	X	X	X	X			
Record date/time of each BM and conduct NRS-BM					X	X	X	X	X	X	X	X			
Caregiver's satisfaction with wound healing															X
Subject productivity (date subject returned to work or normal daily activities)															X
Concomitant medications[E]		X[F]	X[F]	X	X	X	X	X	X	X	X	X	X		
Record AEs and SAEs (starting at signing of ICF)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood draw for pharmacokinetics at specified center only			X		0.25, 0.5, 1 and 2h	X	X	X	X	X	X	X	X		

[A] Screening was to be conducted within 30 days before the administration of study drug.
[B] Clinical labs were to include Chem-12 and CBC
[C] Temperature, heart rate, and blood pressure were to be measured after the subject had rested for at least 5 minutes in the supine position.
[D] In addition to scheduled assessments, NRS-R was to be assessed at the end of the anesthetic and before the first dose of rescue IM morphine.

[E] At each scheduled NRS-R assessment, all postoperative medication the subject had used was to be recorded.
[F] All medication the subject used within 3 days before the scheduled surgery was to be recorded; was to include medication name, date, and time.

Amendments to the Protocol

No amendments to the protocol were made and no changes to the planned analyses were made prior to breaking the blind.

Post Hoc Changes

What was described as an “exploratory post hoc analysis” was conducted in which the NRS pain intensity scores were summarized at each time point using a wWOCF+LOCF imputation.

Conduct of the Study

The first subject was screened on May 11, 2009, and the last subject underwent the final evaluation on August 18, 2009.

The Applicant reported 114 protocol deviations involving 53 subjects. Of these deviations, five qualified as protocol violations by the Applicant and resulted in the exclusion of the four subjects from the per-protocol population.

Most of the deviations were relatively minor, e.g., completing assessments outside of the allowed time range. The table below describes the violations as reported by the Applicant.

Table 14. Protocol violations resulting in exclusion from the per-protocol population.

Subject ID	Protocol Violation
020-0004	Patient received Paracetamol (Perfalgan) within 72 hours after study drug administration (20 Aug 2009, 14:00) due to fever 37.5 C.
020-0004	PK concentrations don't fit the profiles (i.e. assignment either to active drug or placebo) for subjects 020-0004 randomized on 17 AUG 2009 at 15:54:20 and 020-0008, randomized on 17 AUG 2009 at 16:08:23
020-0005	Patient received 5 mg of MF during the surgery, approximately 10 min. before the start of study drug administration.
020-0008	PK concentrations don't fit the profiles (i.e. assignment either to active drug or placebo) for subjects 020-0004 randomized on 17 AUG 2009 at 15:54:20 and 020-0008, randomized on 17 AUG 2009 at 16:08:23
031-0002	NRS-R patient diary card for this patient is lost

It should be noted that four of the five deviations and three of the four exclusions from the per-protocol population occurred at site 020. At the same site, there were eight deviations reported as pain scores "completed with a hand of Investigator based on verbal interview with patients." This deviation occurred only once at a different site. The subjects from site 020 included:

0001, 0004, 0005, 0008, 0009, 0013, 0015, and 0020

The other subject with whom this deviation occurred was 024-0001.

Results as Reported by the Applicant

Primary Efficacy Analysis

The primary endpoint was the area under the curve of NRS-R pain intensity scores through 72 hours (NRS-R AUC_{0-72}). SKY0402 demonstrated a statistically significant reduction in pain through 72 hours compared with placebo ($p<0.0001$). The mean (standard deviation) values of NRS-R AUC_{0-72} for SKU0402 and placebo were 142 (101) and 202 (104), respectively.

Secondary Efficacy Analyses

Multiple secondary endpoint results also demonstrated a significant advantage for SKY0402:

1. The median time to first opioid use was 14 hours in the SKY0402 group ($p<0.0001$) and was 1 hours in the placebo group.
2. At all time points up to 72 hours, there was a statistically significant reduction in opioid use for the SKY0402 treated subjects compared with placebo; through 72 hours, this difference was 22 mg in the SKY0402 group compared to 29 mg in the placebo group ($p=0.0006$).
3. The percentage of subjects who required no opioids (opioid-free) up to 72 hours was 28% for SKY0402 treated subjects versus 10% for placebo treated subjects ($p=0.0007$).

Pharmacokinetic Findings

Plasma bupivacaine concentrations following administration of 300 mg SKY0402 were assessed with individual and summary parameter estimates.

1. The mean C_{max} value was 867 ng/mL.
2. The median T_{max} value was 0.5 hours for 25 subjects.
3. The T_{max} occurred at 36 hours in 1 subject, 24 hours in 1 subject, and 12 hours in 2 subjects.

4. Half-life values had a mean of 24 hours.
5. Plasma clearance was 19 L/hr for 24 subjects.
6. A PK/PD relationship could not be established in this study.

Brief Summary of Safety
The Applicant reported the following safety outcomes for this study.

The adverse event incidence for SKY0402 was similar to placebo. The incidence of gastrointestinal treatment emergent adverse events (TEAEs) was higher in the placebo group than in the SKY0402 group.

The gastrointestinal AEs more frequently reported in the placebo group were anal hemorrhage, vomiting, and painful defecation. The Applicant stated his may be related to the increased opioid use in the patients receiving placebo.

There were no deaths or withdrawals due to adverse events. There was one SAE of mild thrombophlebitis in the placebo group, which resolved the next day after treatment.

There were no clinically meaningful shifts in any of the chemistry or hematology values from Screening to the Day 8 visit. Vital signs (temperature, heart rate, blood pressure) did not change in a clinically significant manner from baseline to the last visit in either treatment group.

Mean scores for overall satisfaction with the subject's wound healing were not statistically significantly different between treatment groups.

Discussion of Results

There was concern for how the study was designed and whether or not bias may have been introduced. Specifically, the use of a finger cot to mask the content of the syringes containing study drug was a novel approach to blind the Investigator from the study treatment; however, the Investigator was charged with aspirating this same syringe and assessing whether blood was present in its barrel mixed with the study drug. This raised the concern that the Investigator was able to discern whether the original content of the syringe was clear, i.e., placebo, or milky white, i.e., SKY0402, and therefore, was not blinded. This would have possibly introduced bias into the study. To assess this possibility, the Division requested, and the Applicant submitted, a sample of the drug product for evaluation. Using a latex finger cot, it was noted, by this reviewer and the Cross Disciplinary Team Leader, that blinding was not likely jeopardized provided the study was conducted as per the protocol.

In addition to the above, the number of incidents in which data that were to have been recorded by the subjects but were actually recorded by the Investigator was disconcerting. Whether the Investigator accurately entered the subjects' responses raises the concern that the results may not be accurate. This concern was partially mitigated when the possibility for unblinding the Investigators at the time of study drug administration was determined to be low.

The Division of Scientific Investigations agreed to investigate the sites used for this study. Their investigation revealed no irregularities in the data collection process.

To further assure that the results were not biased by these deviations, Dr. David Petullo, the statistical reviewer, analyzed the data from this study with and without the results reported from site 20 where all but one of the Investigator entries of data to be recorded by the subjects occurred. He found that SKY0402 continued to demonstrate a statistically significant reduction in pain through 72 hours compared with placebo when data from site 20 was excluded from the analysis. This information is useful only if it can be demonstrated that the methods used in the study did not result in unblinding the Investigators.

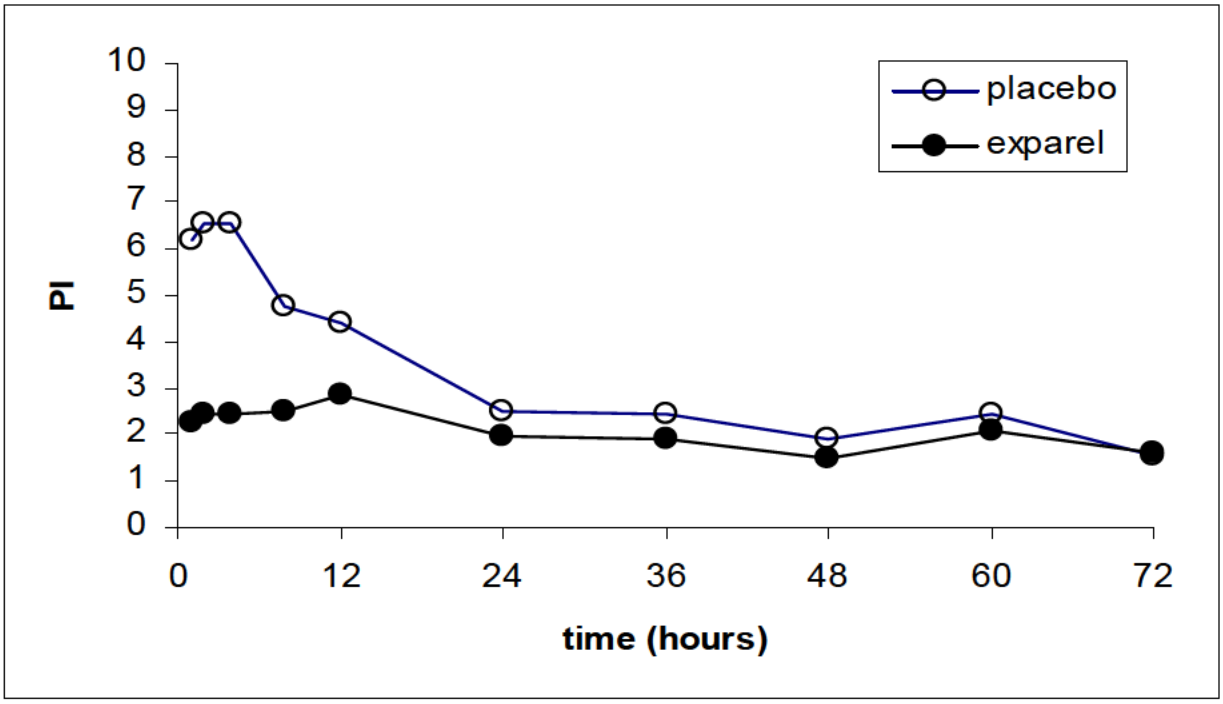
With the above concerns can be laid to rest, it appears that SKY0402 was superior to placebo based on the primary endpoint, NRS-R AUC_{0-72}. This finding was supported by some of the more than 30 secondary efficacy endpoints, most notably narcotic usage, although it was not tied to a clinically relevant benefit.

While the study results for the primary endpoint demonstrated a superior effect for SKY0402 versus placebo, that superiority was due only to the differences observed within the first 12-24 hours following study drug administration. The statistical review team generated a graph (shown below) of pain intensity as a function of time. The graph is important for two reasons:

1. It demonstrates that by 24 hours after study drug administration there is no difference between treatment groups.
2. The protocol specified combination of analgesics and SKY0402 kept average pain scores in the mild range (0-3) throughout the 72 hour observation period; whereas, the combination of analgesics and placebo resulted in moderate levels of pain during the first 24 hours of observation. This suggests a clinically relevant difference between treatments during this time period, provided analgesic use was equivalent between the treatment groups or less for the SKY0402-treatment group.

The apparent lack of efficacy after 24 hours should be an important consideration for labeling, if the product is approved, especially, as the primary endpoint for this pivotal study was the AUC for pain intensity over the first 72 hours following study drug administration.

Figure 4. Mean Pain Intensity Scores versus Time (Figure 1 from the Statistics review)



The maximum plasma levels of bupivacaine following the 300 mg dose of SKY0402 ranged from 144 ng/mL to 1535 ng/mL with a mean value (standard deviation) of 867 (353) ng/mL. C_{max} occurred 4 hours (range: 0.5 h to 36 h) following injection. It should be noted that neurotoxicity related to bupivacaine has been reported to occur at plasma levels on the order of 1 mcg/mL.[1] Convulsions have been reported at levels of ≥ 4 mcg/mL.[2]

Conclusions

This study has demonstrated that a 300 mg dose of SKY0402 is effective, compared to placebo, at reducing post-operative hemorrhoidectomy pain. Although the primary endpoint was the AUC for pain intensity during the first 72 hours postoperatively, the two treatments differed significantly and clinically only during the first 24 hours.
The Applicant has also demonstrated that a 300 mg dose of SKY0402, when used by the prescribed method of administration for hemorrhoidectomy; can result in plasma concentrations of bupivacaine that have been associated with literature-reported neurotoxic outcomes.

9.4.2 SKY0402-C-317

A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Safety and Efficacy of a Single Administration of SKY0402 for Prolonged Postoperative Analgesia in Subjects Undergoing First Metatarsal Osteotomy (Bunionectomy)

Objectives

Primary Objective

Evaluate the magnitude and duration of the effect of a single intraoperative administration of SKY0402 120 mg, compared with placebo (0.9% sodium chloride for injection) in the reduction of postoperative pain following bunionectomy

Secondary Objectives

1. Evaluate additional efficacy parameters
2. Characterize the safety profile of SKY0402 in comparison with placebo
3. Assess the pharmacokinetics of clearance of bupivacaine from the blood plasma

Study Design

This was a Phase 3, randomized, placebo-controlled, double-blinded, multicenter study to evaluate the efficacy and safety of intraoperative administration of SKY0402, compared to normal saline, administered by local infiltration when used for post-operative analgesia following a first metatarsal osteotomy.

Study Population

Subjects were enrolled from the population of patients presenting for first metatarsal osteotomy (bunionectomy) that was to be performed under Mayo block and intraoperative sedation who met the criteria listed below, copied from the final study report.

Inclusion Criteria

1. Age ≥18 years of age at the Screening Visit.
2. Scheduled to undergo primary unilateral first metatarsal osteotomy without hammertoe.
3. Ability to receive Mayo block for intraoperative local analgesia.
4. Ability to receive propofol and/or midazolam for intraoperative sedation.
5. Female subjects must have been surgically sterile or at least two years menopausal, or using an acceptable method of birth control. If of childbearing potential, there must have been a documented negative blood or urine pregnancy test within 24 hours before surgery.
6. Clinical laboratory values less than or equal to twice the upper limit of normal or, if abnormal, deemed not clinically significant per the Investigator.
7. Ability to provide informed consent, adhere to the study visit schedule, and complete all study assessments.

Exclusion Criteria

1. Currently pregnant, nursing, or planning to become pregnant during the study or within one month after study drug administration.
2. Chronic users of analgesic medications, including taking opioid medications for more than 14 days in the last 3 months, or non-opioid pain medications more than 5 times per week.
3. Use of any NSAID including selective COX-2 inhibitor within three days of surgery.
4. Use of selective serotonin reuptake inhibitors (SSRIs), gabapentin, pregabalin (Lyrica), or duloxetine (Cymbalta) within three days of surgery
5. Use of acetaminophen within 24 hours of surgery.
6. Use of systemic glucocorticosteroids or use of systemic glucocorticoids within one month of enrollment into this study.
8. Peripheral neuropathy including diabetic neuropathy, chemotherapy-induced neuropathy, or HIV neuropathy.
9. History of hepatitis.
10. History of suspected or known addiction to or abuse of drugs or alcohol within the past two years.
11. Failure to pass drug screen.
12. Current evidence of alcohol abuse (greater than 4 units of alcohol per day: 1 unit = ½ pint of beer, 1 glass of wine, or 1 oz. of spirits).
13. Evidence of peripheral ischemic disease.
14. Type I or Type II diabetes.
15. Current acute or chronic medical or major psychiatric disease that, in the opinion of the Investigator, would interfere with the evaluation of study drug efficacy or safety.
16. Malignancy in the last 2 years, with the exception of non-metastatic basal cell or squamous cell carcinoma of the skin or localized carcinoma in situ of the cervix.
17. History of hypersensitivity or idiosyncratic reactions to amide-type local anesthetics or to opioid medication.

18. Administration of an investigational drug within 30 days prior to study drug administration or planned administration of another investigational product or procedure during the subject's participation in this study.
19. Previous participation in an EXPAREL study.
20. Significant medical conditions or laboratory results that, in the opinion of the Investigator, indicated an increased vulnerability to study drugs and procedures.
21. Current painful physical conditions or concurrent surgery other than bunionectomy that may require analgesic treatment (such as NSAID or opioid) in the postoperative period for pain that is not strictly related to the bunionectomy procedure and may confound the postoperative assessments.

In addition, the subject was to be ineligible to receive study drug if he or she met the following criteria during surgery:

22. Any clinically significant event or condition uncovered during the surgery (e.g., excessive bleeding, acute sepsis) that might render the subject medically unstable or complicate the subject's postoperative course.

Stopping Criteria

This study involved a single dose of study medication; therefore, individual stopping criteria were not related to continued administration of study drug, but rather the ability of subjects to continue to participate in the follow-up evaluations. The following clinical situations and the methods of follow-up to deal with them were included in the protocol:

1. If a subject experienced an adverse event (AE) that rendered him or her incapable of continuing with the remaining study visits and assessments, a final evaluation visit was to have been performed, so that the subject's study participation could be terminated in a safe and orderly manner.
2. Subjects were to be free to discontinue from the study at any time, without prejudice to future treatment. These subjects were to have been encouraged to complete at least the study safety assessments.
3. A subject may have been discontinued from the study if he or she refused either study drug administration or to comply with study procedures. Reasons for discontinuation from the study were to be documented on the CRF.
4. A subject could be discontinued from the study by the Investigator, if it was considered to be in the best interest of the subject. If the discontinuation occurred after administration of the study drug, a final evaluation visit was to be performed, so that the subject could be terminated in a safe and orderly manner.

The protocol did not specify any study stopping criteria.

Efficacy Endpoints

Primary Efficacy Endpoint

Area under the curve (AUC) of NRS through 24 hours (NRS AUC_{0-24}).

Secondary Efficacy Endpoints

1. AUC of NRS through 36, 48, 60, and 72 hours. (NRS AUC0-xx , where xx = 36, 48, 60, 72).
2. Proportion of subjects who were pain free (defined as an NRS of 0 or 1) at 24 hours and other time points.
3. Proportion of subjects who received no rescue pain medication (Percocet or ketorolac).
4. Total postoperative consumption, in mg, of Percocet through 24, 36, 48, 60, and 72 hours.
5. Total amount of postoperative Percocet use through 24, 36, 48, 60, and 72 hours.
6. Time to first use of Percocet.
7. Time to first use of IV ketorolac.
8. Subject's satisfaction with postoperative analgesia at 24 and 72 ±8 hours.

Safety Assessments

1. Vital signs (temperature, resting heart rate, and blood pressure) at Baseline and at 24 hours and 72 ± 8 hours and Day 30 ±4 after study drug administration.
2. Wound healing and status at 30 ± 4days.
3. Clinical laboratory values at Baseline and the 72 ± 8 hour visit.
4. Treatment Emergent AEs (TEAE) and SAEs were to be collected during the timeframe noted in Methodology.

Methods

Screening was to have occurred up to 30 days prior to the scheduled surgical procedure and was to have required that the following assessments be performed:

- Obtain written informed consent
- Assess subject eligibility (inclusion/exclusion criteria)
- Obtain relevant medical/surgical history; record demographic and baseline characteristics
- Train subject on use of self-assessment measures (e.g., NRS scores)
- Conduct alcohol screen
- Instruct subject to discontinue excluded medications
- Obtain clinical laboratory samples

All subjects who were screened but did not meet eligibility criteria or who declined to participate were to have the reasons for the failure to be enrolled documented.

On the day of the surgical procedure, Day 1, the following procedures were to have been conducted before administration of the study drug and initiation of the surgical procedure:

- Reconfirm eligibility
- Review medical history
- Record adverse events that have occurred since the subject signed the informed consent document and the actions taken to treat the events
- Record the date and time of all medications taken within 3 days before the scheduled surgery
- Conduct a pregnancy test for female subjects of childbearing potential
- Conduct a urine drug screen
- Measure vital signs (temperature, resting heart rate, and blood pressure)
- Verify laboratory values are within appropriate range
- Perform a physical examination
- Review subject training for use of self-assessment measures
- Randomize subject and prepare study drug
- Conduct NRS for pain
- Obtain blood sample for plasma bupivacaine quantitation from approximately 50 subjects from selected sites; the combined number of subjects to comprise the PK population was capped at approximately 50

At the time of the surgical procedure, the following assessments and procedures were to have been performed:

- Sedate the subject using midazolam and/or propofol.
- Perform a Mayo block using lidocaine recording the start time.
- Monitor the subject intraoperatively according to the site's standard procedures.
- Record the date and time of the start of surgery.
- Confirm eligibility based on exclusion criteria (i.e., verify that no serious intraoperative complications have occurred).
- Administer study drug; record the start time of study drug administration. (At least 30 minutes must elapse between the start time of the lidocaine Mayo block and the start time of the administration of study drug.)
- Record the time of the end of surgery.
- Record all concomitant medications administered intraoperatively.
- Record all AEs.

Preparation of the study drug took into account that SKY0402 and 0.9% sodium chloride are visually distinguishable, therefore, an unblinded pharmacist (or other unblinded member of the study team) was to have prepared 2 syringes as a sterile preparation (fitted with an 18-gauge to a 21-gauge needle) of study drug. Each syringe was to have

contained 4 mL of the study drug, for a total of 8 mL. Then, the needle of each syringe was to have been replaced with a 22 gauge to a 25 gauge injection needle. An opaque, non-powdered sterile glove was to have been obtained to cover the barrel of each syringe. A small circular opening (3-5 mm diameter) was to have been cut in the tip of the finger of the opaque sterile glove to allow the connector of the syringe (e.g. Luer lock) to pass through the opening without exposing the bottom of the barrel. The study staff preparing the syringes was to have ensured that the content of each syringe was completely concealed and that the finger of the glove fitted tightly around the barrel, so that it would not slide during the injection procedure. The glove was to have been trimmed appropriately allowing enough length to maintain the blind. The individuals preparing and administering study drug were to have performed all injections, with frequent aspirations to reduce the chance of accidental intravascular injection. If an aspiration drew blood, it should have been seen through the sterile glove covering the syringe, and the needle was to then have been moved and placed into a different location until the aspiration was negative. A sterile gauze pad was to have been placed over the needle insertion site to absorb any fluid that could be expelled as the needle was withdrawn to avoid inadvertent unblinding.

The time of administration of study drug was to have served as the reference time for all subsequent assessments and procedures. The study drug injection was to have occurred using the following technique.

Immediately prior to closure of the surgical wound, the soft tissue around the osteotomy as well as the cut edges of the soft tissue for the surgical wound were to have been infiltrated with study drug. All injections were to have been performed with an infiltrative moving needle technique, with frequent aspirations to reduce the chance of accidental intravascular injection. A total volume of 8 ml was to have been infiltrated using two syringes containing 4 mL of study drug in each. In order to ensure the study drug was adequately mixed, the syringes were to have been gently inverted and reverted prior to drug administration. The first syringe, filled with 4 ml of study drug, was to have been used to infiltrate into the soft tissue immediately medial to the cut bone in a fan pattern, ensuring that the infiltrated tissue extends 2 cm both distal and proximal to the wound, into the tissue, about 1 cm deep, immediately dorsal to the cut bone and into the soft tissue on the sole aspect of the cut bone, extending distal and proximal to the wound. Care was to have been taken to infiltrate around the cut bone surface as this was the most highly concentrated area for pain receptors on c-fibers. After this infiltration was completed, the next syringe was to have been used to infiltrate into the tissue lateral to the osteotomy and into the surface of the cut tissue, again extending 2 cm proximal and distal to the wound, and making sure that both the dorsal and ventral (or sole) aspect of the soft tissues were well infiltrated, especially around the periosteum. The final ml or so of study drug from this syringe was to have been administered to the subcutaneous tissue overlying the wound.

At least 30 minutes was to have passed between the end of the Mayo block and the start of study drug administration. The Mayo block was not to have included infiltration of medicine just under the incision itself, and the study drug was not to have been held in the syringe for more than four hours after preparation for administration.

During the first 24 hours following study drug administration, the following were to have been done:

- Measure vital signs (temperature, resting heart rate, and blood pressure) at 24 hours.
- Conduct NRS for pain at 2, 4, 8, 12, and 24 hours.
- Conduct NRS for pain at the first use of rescue pain medication, if applicable.
- Draw blood samples for plasma bupivacaine from approximately 50 subjects from selected sites at 0.25, 0.5, 1, 2, 4, 8, 12, 24, and 72+8 hours after beginning of administration of study drug; the combined number of subjects to comprise the PK population were capped at approximately 50.
- Record all rescue pain medication (Percocet and/or ketorolac).
- Administer subject's satisfaction with postoperative analgesia at 24 hours.
- Record all AEs.
- Record all concomitant medications.
- Record the date and time that subject is discharged from the surgical center.

From 24 through 72 hours post study drug administration, the subject was to conduct the following assessments and procedures:

- Record NRS at 36, 48, 60, and 72 hours; a staff member from the study center was to call subject at each time point to remind the subject of the need to assess and record in the subject diary the pain intensity using the 0-10 NRS scale and record the use of and rescue and other concomitant medications. The 72 hour pain assessment was to have occurred prior to traveling to study center for the 72 + 8 hour study center follow up visit. The 72 hour pain assessment and the 72+8 hour study center visit were not to be combined.
- Conduct NRS for pain at the first use of rescue pain medication, if applicable.
- Record rescue pain medication (Percocet).
- Record all concomitant medications.
- Record all AEs and SAEs in the subject diary.

At 80 hours after study drug administration, the subject was to have returned to the study site at which time, the following assessments were to have been made:

- Measure vital signs (temperature, resting heart rate, and blood pressure).
- Draw blood samples for plasma bupivacaine from approximately 50 subjects from selected sites; the combined number of subjects to comprise the PK population was capped at approximately 50.
- Record subject's satisfaction with postoperative analgesia.

- Obtain clinical laboratory samples.
- Retrieve subject diaries.
- Record all Investigator-reported and/or subject-reported AEs and SAEs. To elicit AEs pertinent to potential local toxicity, the subjects were particularly questioned about any residual sensory/motor impairment, or signs of nerve and/or tissue irritation.
- Record rescue pain medication (Percocet).
- Record all concomitant medications.

On Day 30 (±4 days), subjects were to have returned to the study site for assessment of the following:

- Vital signs (temperature, resting heart rate, and blood pressure).
- Wound healing and status score.
- Any adverse events that occurred since the Day 3 visit.

On Day 30, wound healing was also to have been assessed using the grading system in the table below.

Table 15. Wound Status Scoring Grades (Table 2 from Final Study Report, p. 45)

Parameter	Score	Scoring Criteria
Erythema	0	No erythema
	1	Very slight erythema (barely perceptible)
	2	Well defined erythema
	3	Moderate to severe erythema
	4	Severe erythema (beet redness) to slight eschar formation (injuries in depth)
Drainage	0	None
	1	Serous
	2	Serosanguinous
	3	Bloody
	4	Purulent
Edema	0	No edema
	1	Very slight edema (barely perceptible)
	2	Slight edema (edges well defined)
	3	Moderate edema (raised approx. 1 mm)
	4	Severe edema (raised >1 mm and beyond area of exposure)
Induration	0	None
	1	Minimal
	2	Mild (spongy tissue)
	3	Moderate (firm, warm)
	4	Severe (hard, red, hot or crepitus)

Schedule

(Schedule begins on next page.)

Table 16. Schedule of study procedures (based on Table 1; p. 41 of Clinical Study Report)

Procedure					After Study Drug Administration													
					In-Patient								At Home				On Site	On Site
	Time post-drug				.25 h	.5h	1h	2h	4h	8h	12 h	24 h	36h	48h	60h	72h	80h	720h
	Study Day	Day -30 to -1	Day -1 to 1	Day 1	1	1	1	1	1	1	1	2	2	3	3	4	4+ 8 h	30
	Time Window (±)								.25	.5	.5	1	1 h	1 h	1 h	1 h		4 d
Informed consent		X																
Assess/confirm eligibility		X	X															
Medical history, demographics and baseline characteristics[A]		X	X															
Pregnancy test (women of childbearing potential)			X															
Urine Drug Screen			X															
Clinical Labs[B]		X														X		
Physical examination			X															
Vital signs			X									X					X	X
Randomize subject & prepare study drug			X															
Study drug administration				X													X	X

Procedure					After Study Drug Administration													
					In-Patient								At Home				On Site	On Site
	Time post-drug				.25 h	.5h	1h	2h	4h	8h	12 h	24 h	36h	48h	60h	72h	80h	720h
	Study Day	Day -30 to -1	Day -1 to 1	Day 1	1	1	1	1	1	1	1	2	2	3	3	4	4+ 8 h	30
	Time Window (±)								.25	.5	.5	1	1 h	1 h	1 h	1 h		4 d
Pain Intensity NRS				X				X	X	X	X	X	X	X	X	X		
Reminder call to subject												X	X	X	X	X		
Blood draw for pharmacokinetics[C]				X								X					X	
Subject satisfaction with postoperative analgesia												X					X	
Retrieve subject diaries																	X	
Wound healing and status																		X
Concomitant medications			X	X	X			X	X	X	X	X	X	X	X	X	X	
Record AEs and SAEs (starting at signing of ICF)		X	X	X	X			X	X	X	X	X	X	X	X	X	X	X

[A] Demographics and alcohol screening were performed a screening only.
[B] Laboratory assessments consisted of Chem-12 and CBC.
[C] PK samples were taken for all subjects at selected sites only.

Amendments to the Protocol

No amendments were made to the protocol; although protocol clarifications were issued to the Investigators on May 4 and July 13, 2009. These were not of a nature that would be expected to substantially impact on the conduct or findings of the study.

Post Hoc Changes

A post-hoc analysis was conducted in which the primary efficacy endpoint was reassessed when data from a particular study site, San Marcos (site 200), was noted to substantially differ from that of the other sites. In the reanalysis, data from this study site were excluded. The findings from this analysis are described, as reported by the Applicant, below.

In addition to the above, an analysis of the percentage of subjects who received no rescue medication through 8, 12, 16, and 20 hours was added, and "pain free" was additionally defined as an NRS score of 0 and as an NRS score of 0, 1, or 2.

Conduct of the Study

The first subject was enrolled in the study on April 27, 2009, and the last subject completed the study on September 17, 2009. According to the Applicant, the study was conducted in accordance with the clinical research guidelines.

There were a total of 193 subjects enrolled (randomized and treated) in this study: 97 subjects received 120 mg SKY0402 and 96 subjects received placebo. Two subjects were randomized, but not treated: one subject was found to have elevated blood pressure after randomization, and one did not have surgery due to unstable vital signs.

Eight subjects did not complete the study: 4 subjects in the SKY0402 group and 4 subjects in the placebo group. Only one of these was due to an adverse event: hypotension that occurred on Day 2, in a subject treated with placebo.

The applicant reported a total of 74 protocol deviations: 25 in the SKY0402-treatment group and 48 in the placebo-treatment group. Most of these were related to missed assessments, assessments made outside the allotted timeframe, missed PK samples and PK samples taken outside of the allotted timeframe. Seven of the deviations were also considered as violations, which resulted in exclusion of the subjects from the Per Protocol analysis. Five of the violations were in the SKY0402-treatment group and 2

were in the placebo-treatment group. Of these, the only ones of note were one subject from each treatment group that was classified as "mis-randomized; actual treatment administered cannot be confirmed."

Results as Reported by the Applicant

Primary Efficacy Analysis
The primary efficacy endpoint, AUC of pain intensity scores through 24 hours using the wWOCF+LOCF imputation for NRS scores, was statistically different between SKY0402 and placebo (p=0.0005). The mean value for the SKY0402-treated subjects was 125; it was 146 for subjects treated with placebo.

Secondary Efficacy Analyses
The secondary endpoint results supported the primary endpoint finding. The AUC of pain intensity continued to be statistically significant through 36 hours (p=0.02).

The following secondary endpoints favored SKY0402:

1. The difference between treatment groups in the mean pain intensity score [in the full analysis (FA) set]
    - before first use of rescue medication
    - at 2 hours
    - at 4 hours
2. The difference between treatment groups in the percentage of subjects who were pain free [defined as an NRS of 0 or 1 (FA set)], at 2, 4, 8, and 48 hours.
3. The difference between treatment groups in the percentage of subjects who received no rescue pain medication through 8, 12, 16, 20, and 24 hours.
4. The difference between treatment groups in the total amount of postoperative Percocet use (FA set) at 24 hours.
5. The difference between the median time to first use of Percocet.

PK Analysis
The bupivacaine concentrations following administration of 120 mg of SKY0402 were assessed with individual and summary pharmacokinetic figures and parameter estimates. The mean Cmax value was 166 ng/mL and the median Tmax value was 2.0 hours for 26 subjects. The Tmax occurred at 24 hours in 4 subjects. Half-life values had a mean of 34 hours and plasma clearance was 19 L/hr for 22 subjects.

Exploratory analyses of possible PK/PD relationships were examined with regression analyses and graphical presentations. Regression analyses did not elucidate meaningful correlations between PK and PD variables.

Post Hoc Analysis

Examination of the data by site revealed that the mean value for the SKY0402 group in primary endpoint analysis (AUC of pain intensity scores through 24 hours using the wWOCF+LOCF imputation for NRS scores) from site 200 (San Marcos) was higher than the other sites, whereas the mean values in the placebo groups were similar among the sites such that there was no difference between the SKY0402 group and the placebo group at the San Marcos site. Thus, a post hoc exploratory analysis was performed excluding data from this site and including data from sites 100, 300, and 400 only. When results from this site were excluded and the results from the other three sites were reanalyzed, the primary endpoint remained statistically significant, and the AUC of the pain intensity was statistically significant through 48 hours (p=0.04).

Brief Summary of Safety

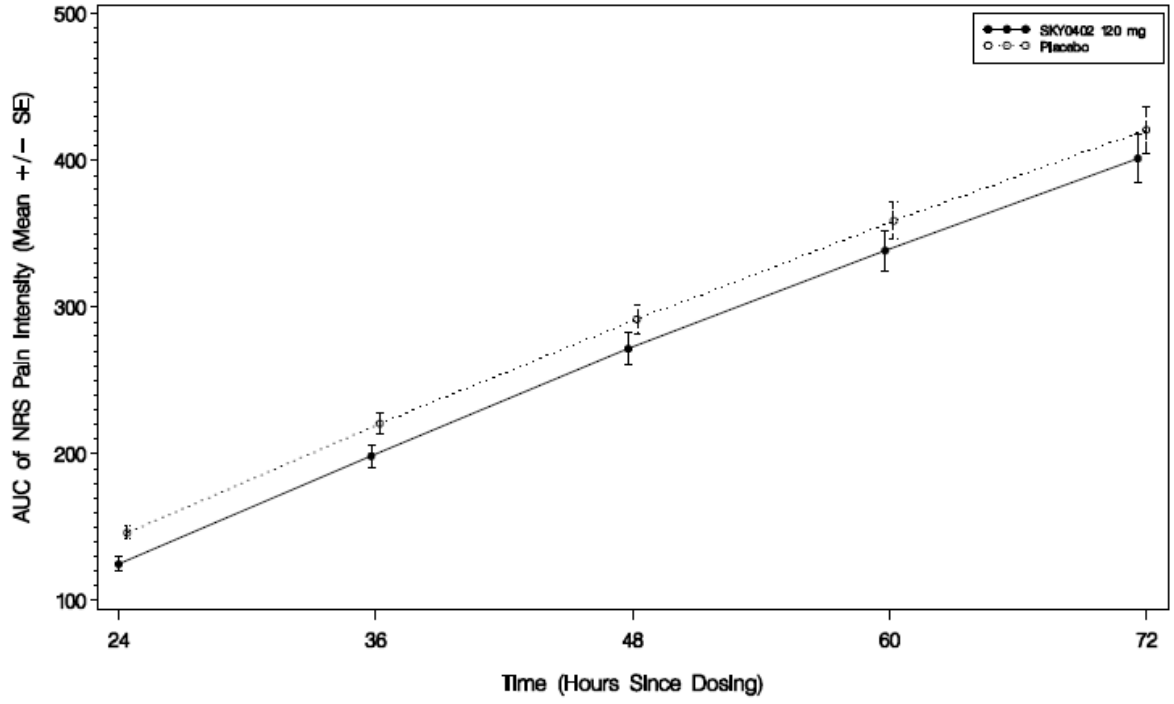
1. The incidence of systemic TEAEs was lower in the SKY0402 group (58%) compared with the placebo group (66%). This difference was largely accounted for by the higher incidence of dizziness in the placebo group (26%) compared with the SKY0402 group (11%).
2. The incidence of vomiting was higher in the SKY0402 group (27.8%) compared with the placebo group (18%).
3. Most TEAEs were reported as not related to study medication and were mild or moderate in severity.
4. The incidence of related systemic TEAEs was higher in the SKY0402 group (9%) compared with the placebo group (5%).
5. The incidence of severe TEAEs was higher in the SKY0402 group (11%) compared with the placebo group (5%); the incidence of moderate TEAEs was higher in the placebo group (21%) compared with the SKY0402 group (12%).
6. Severe vomiting was observed in 9% of subjects in the SKY0402 group compared with 2% of subjects in the placebo group.
7. There were no clinically meaningful shifts in any of the chemistry or hematology values from Screening to the 80 hour visit.
8. Vital signs (temperature, heart rate, blood pressure) did not change in a clinically significant manner from baseline to the last visit in either treatment group.
9. There was no statistically significant difference between treatment groups in the distribution of subjects across the assessment categories for any of the wound assessments (erythema, drainage, edema, and induration). Mean scores for overall satisfaction with the subject's wound healing were not statistically significantly different between treatment groups.
10. No subjects demonstrated any evidence of malunion or non-union on their routine podiatric follow-up visits.

Discussion of Results

The concerns regarding study drug blinding techniques that were raised in Study SKY0402-C-316, described above, applied to this study as well. The steps taken by the Division to evaluate the adequacy of the blinding technique also apply, and therefore, the issue is not one of concern. In addition, there were no issues related to protocol deviations in obtaining subject pain scores for this study, as there were with the previous one, which also reduced the concern for potential bias.

In terms of efficacy, SKY0402 was demonstrated to be superior to placebo for providing analgesia following a bunionectomy when used directed in the protocol and in conjunction with oxycodone, acetaminophen and ketorolac. This analgesic effect persisted up to 24 hours post-operatively, and depending on how the data are interpreted, the effect may persist up to 36 hours post-operatively. In the figure below, is a plot, by the Applicant, of AUC of NRS pain intensity as a function of time as determined using the full analysis set. In this plot, the AUC for SKY0402 nearly parallels that of placebo for the entire study period. Furthermore, the two are only minimally disparate at the first two time points, i.e., at 24 and 36 hours following study drug administration.

Figure 5. AUC of NRS Pain Intensity Scores Time Plot (Figure 14.2-1.1, p. 136 of the Final Study Report)

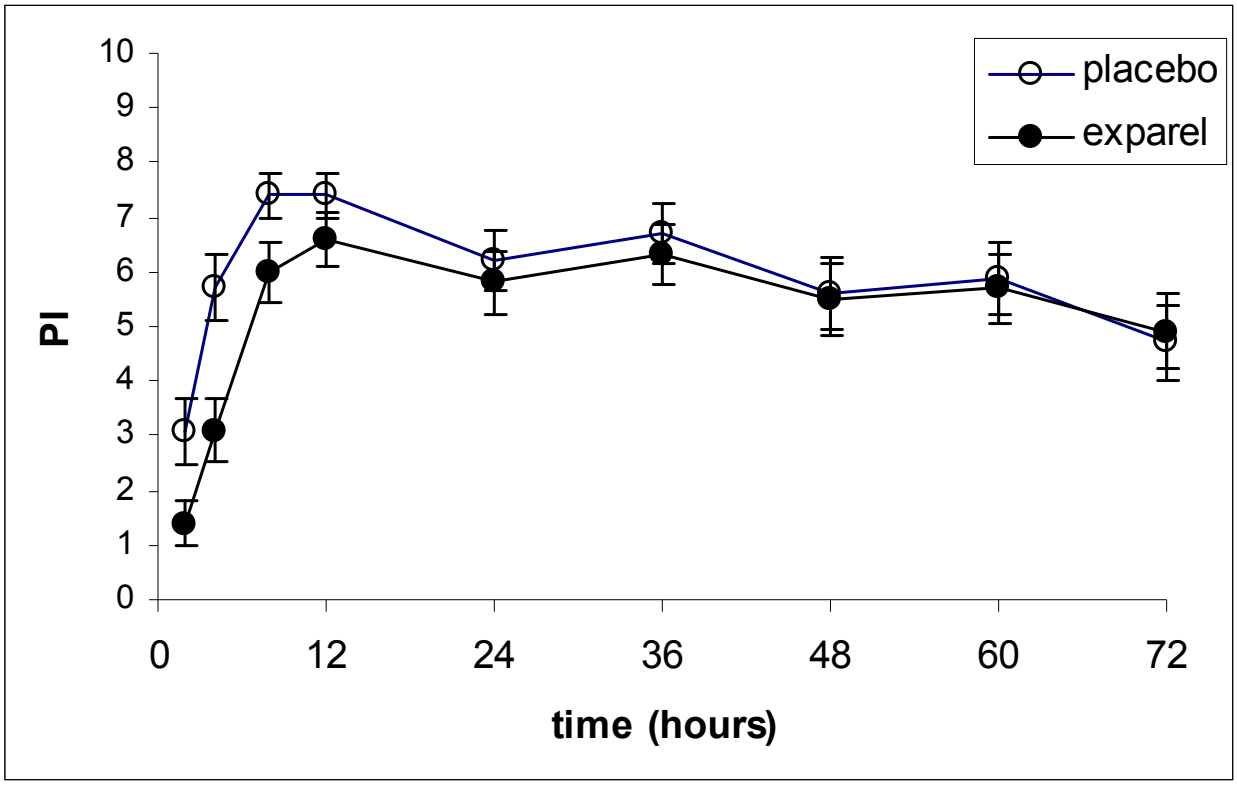


A better appreciation of the differences in analgesic effects of the two treatments may be obtained by examining the mean NRS pain intensity scores collected over the entire

study period. The Applicant has produced such a plot, which is reproduced in the figure below. In this figure, the differences between treatments are distinct from each other only up to the 12-hour post-administration assessment. After that the pain intensity for the two treatments are indistinguishable. The data from this plot indicate the following:

1. The analgesic effects of SKY0402 exceed that of placebo for somewhere between 12 and 24 hours.
2. At 2 hours following injection of the study drug, patients in both treatment groups are experiencing mild pain (defined as a pain score of 0-3), or are pain free based on the Applicant's revised definition of a pain score of 0-2. This is likely due to residual analgesia from the Mayo block. Nonetheless, there is a clear distinction between treatments favoring SKY0402.
3. By 4 hours after study drug injection, placebo-treated patients are experiencing moderate levels of pain (defined as a pain score of 4-7) as are SKY0402-treated patients, although to a substantially less extent.
4. At 8 hours after study drug administration, both treatment groups have mean scores that are indicative of moderate levels of pain, and by the Applicant's computation, are indistinguishable.
5. The moderate levels of pain that are experienced by both treatment groups persist until at least 48 hours, and for some subjects, until the end of the study period.

Figure 6. Mean Pain Intensity Scores versus Time (Figure 3 from the Statistics review)



To further assess the analgesic effects of the two treatment groups, the Applicant compared the percentages of subjects who received no rescue medication at nine time points. In the table below, this data, from the full analysis group, has been modified to show the number and percentages of subjects who did require rescue medication.

Table 17. Times to requirement of rescue pain medications for each treatment group.

	Subjects Who Required Rescue Medication N (%)								
Time After Study Drug Administration (hours)	8	12	16	20	24	36	48	60	72
Treatment									
SKY0402 (n = 97)	57 (59)	77 (79)	87 (90)	90 (93)	90 (93)	94 (97)	95 (98)	95 (98)	95 (98)
Placebo (n = 96)	87 (91)	93 (97)	94 (98)	95 (99)	95 (99)	95 (99)	95 (99)	95 (99)	95 (99)

The data in the table indicate that by 16 hours after administration of SKY0402, the need for rescue pain medications has reached the level that would be expected had the treatment been ineffective, i.e., at 16 hours after administration of SKY0402, the level of pain is such that patients will require rescue medication to the same extent as if they had not been treated at all.

Thus, while the study showed a significant difference between AUC of NRS pain intensity scores at 24 hours for the two treatment groups, it appears that the clinical utility of SKY0402 is greatest during the first 12 hours, for bunionectomy, and requires that rescue medication be available throughout that period.

In terms of its safety for use following a bunionectomy, SKY0402 appeared to be well tolerated. The maximum plasma level observed in the study was 530 ng/mL, which was substantially less than that observed in the hemorrhoidectomy study.

Conclusions

SKY0402 was demonstrated to be superior to placebo for providing analgesia following a bunionectomy when used in conjunction with oxycodone, acetaminophen and ketorolac. This analgesic effect persisted up to 12 hours and no more than 24 hours post-operatively. SKY0402 appears to pose little risk when used as described in this study and for this indication.

9.4.4 SIMPLE Hemorrhoidectomy 312

A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Active-Control Study to Evaluate the Safety and Efficacy of a Single Administration of SKY0402 for Prolonged Postoperative Analgesia in Subjects Undergoing Hemorrhoidectomy

Objectives

Primary Objective

To demonstrate the superiority of SKY0402 compared with bupivacaine HCl, with respect to the extent and duration of the analgesic effect achieved by a single administration of the study drug via local infiltration in subjects undergoing hemorrhoidectomy under general or spinal anesthesia.

Secondary Objectives

1. To evaluate additional efficacy parameters.
2. To characterize the safety profile of SKY0402 in comparison with bupivacaine HCl.

Study Design

This was a Phase 3, multicenter, parallel-group, active-control, randomized, double-blind study designed to evaluate the efficacy and safety of 300 mg of SKY0402 compared to 100 mg of bupivacaine HCl administered as a local infiltration for postoperative analgesia in subjects undergoing hemorrhoidectomy under general or spinal anesthesia.

Study Population

The study population was drawn from patients presenting for either an internal or combination internal and external hemorrhoidectomy under either a general or a spinal anesthetic. The eligibility for enrollment was based on the criteria listed below.

Inclusion Criteria

1. Male or female, ≥ 18 years of age at the Screening Visit.
2. Female subjects only: Postmenopausal, surgically sterile, or willing to use acceptable means of contraception for at least 30 days after surgery including any of the following:
    a. hormonal contraceptives (e.g., oral, injectable, implantable starting at least 30 days before study drug administration)
    b. effective double-barrier methods (e.g., condoms with spermicide)
    c. intrauterine device
    d. lifestyle with a personal choice of abstinence
    e. non-heterosexual lifestyle
    f. a strictly monogamous relationship with a partner who has had a vasectomy
3. Scheduled to undergo 2- or 3-column excisional hemorrhoidectomy for internal or internal/external hemorrhoids, under general or spinal anesthesia, using Milligan-Morgan or Ferguson-type techniques, including modified approaches with specialized instruments, such as LigaSure™ or harmonic scalpel, with a cumulative incision length of a minimum 3 cm.
4. American Society of Anesthesiology (ASA) Physical Classification System class 1-4.
5. Able and willing to comply with all study visits and procedures.
6. Able to speak, read, and understand the language of the Informed Consent, study questionnaires, and other instruments used for collecting subject-reported outcomes, in order to enable accurate and appropriate responses to pain scales and other required study assessments.
7. Willing and capable of providing written informed consent.

Exclusion Criteria

1. Pregnancy, nursing, or planning to become pregnant during the study or within one month after dosing.
2. Use of any of the following medications within the times specified before surgery:
    a. Long-acting opioid medication within 3 days.
    b. Any opioid medication within 24 hours.
3. Concurrent painful physical condition or concurrent surgery that may require analgesic treatment in the postoperative period for pain that is not strictly related to the hemorrhoidectomy procedure and may confound the postoperative assessments (e.g., rheumatoid arthritis, chronic neuropathic pain, concomitant vasectomy) confound the postoperative study assessments.
4. Single-column hemorrhoidectomy or hemorrhoidectomy without an internal component.
5. Body weight less than 50 kilograms (110 pounds).

6. History of hypersensitivity or idiosyncratic reactions to amide-type local anesthetics, opioid medication, or any ingredients of the medications administered in this study (e.g., sulfites in Marcaine with epinephrine).
7. Contraindication to epinephrine, such as concurrent administration of ergot-type drugs, monoamine oxidase (MAO) inhibitors or antidepressants of triptyline or imipramine types, conditions where the production or exacerbation of tachycardia could prove fatal (e.g., poorly controlled thyrotoxicosis or severe heart disease), or any other pathological conditions that might be aggravated by the effects of epinephrine.
8. Contraindication to any of the pain-control agents planned for postoperative use (e.g., acetaminophen, morphine, oxycodone, morphine, ketorolac, ketoprofen, diclofenac, etc.).
9. Administration of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study.
10. Suspected, or known addiction to or abuse of illicit drug(s), prescription medicine(s), or alcohol within the past 2 years.
11. Uncontrolled anxiety, schizophrenia, or other psychiatric disorder that, in the opinion of the Investigator, may interfere with study assessments or compliance.
12. Significant medical conditions or laboratory results that, in the opinion of the Investigator, indicate an increased vulnerability to study drugs and procedures, and expose the subject to an unreasonable risk as a result of participating in this clinical trial, such as: debilitating diseases, acute illnesses, hypotension, partial or complete conduction block, impaired cardiac function, untreated hypertension, advanced arteriosclerotic heart disease, cerebral vascular insufficiency, pre-existing abnormal neurological or neuromuscular disease (e.g., epilepsy, myasthenia gravis), advanced liver disease, severe renal impairment, advanced diabetes, comorbid conditions associated with an immunocompromised status, such as blood dyscrasias, HIV/AIDS, or recent chemotherapy.
13. Any clinically significant event or condition uncovered during surgery (e.g., excessive bleeding, acute sepsis) that might render the subject medically unstable or complicate the subject's postoperative course.
14. A cumulative incision length less than 3 cm.

Stopping Criteria

This study involved a single dose of study medication; therefore, individual stopping criteria were not related to continued administration of study drug, but rather the ability

of subject's to continue to participate in the follow-up evaluations. The following clinical situations and the methods of follow-up to deal with them were included in the protocol:

1. If a subject experienced an adverse event (AE) that rendered him or her incapable of continuing with the remaining study visits and assessments, the subject was to be discontinued from further participation in the study. A final evaluation visit was to have been performed, so that the subject's study participation could be terminated in a safe and orderly manner.
2. Subjects were to be free to discontinue from the study at any time, without prejudice to future treatment. These subjects were to have been encouraged to complete at least the study safety assessments.
3. A subject may have been discontinued from the study if he or she refused either study drug administration or to comply with study procedures.
4. A subject could be discontinued from the study by the Investigator, if it was considered to be in the best interest of the subject. If the discontinuation occurred after administration of the study drug, a final evaluation visit was to be performed, so that the subject could be terminated in a safe and orderly manner.

Every effort was to be made to follow any ongoing AEs or serious adverse events (SAEs) until satisfactory resolution was obtained or further follow-up was otherwise no longer warranted.

The protocol specified only the following study stopping criteria:

> If Pacira, an Investigator, or officials from regulatory authorities discover conditions during the study that indicate that the study or study site should be terminated, this action may be taken after Pacira has notified the Investigator(s).

Efficacy Endpoints

Primary Efficacy Endpoint

Area under the curve of pain scores with activity, using the NRS-R through 96 hours.

Secondary Efficacy Endpoints

1. Total postoperative consumption of supplemental opioid pain medication through 12, 24, 36, 48, 60, 72, 84, and 96 hours.
2. Proportion of subjects receiving no supplemental opioid pain medication postoperatively through 12, 24, 36, 48, 60, 72, 84, and 96 hours.
3. AUC of NRS-R through 12, 24, 36, 48, 60, 72, and 84 hours.
4. Pain intensity evaluations on NRS-R at each assessed time point.
5. Pain with first bowel movement (NRS-BM).

6. Average daily pain with bowel movement (NRS-BM).
7. Time to first postoperative use of opioid medications.
8. Integrated rank assessment using the NRS-R scores and total postoperative opioid usage through 12, 24, 36, 48, 60, 72, 84, and 96 hours.
9. QOL questionnaire (EQ-5D).
10. Pharmacoeconomic questionnaire.
11. Time to first occurrence of PONV.
12. PONV-free time through 96 hours.
13. Postoperative use of antiemetic medication administered through 12, 24, 36, 48, 60, 72, 84, and 96 hours.
14. Discharge readiness.
15. Time to first bowel movement through 96 hours.
16. Subject's overall satisfaction with postoperative analgesia.
17. Blinded care provider's satisfaction with postoperative analgesia.
18. Time to return to work or normal daily activities.

Safety Assessments

1. AEs through Day 8 and SAEs and deaths through Day 30.
2. Vital signs (temperature, heart rate, and blood pressure) at Baseline, 0.5, 1, 1.5 and 2 hours and on Day 8.
3. Incidence of urinary retention, if reported by >5% of subjects.
4. Incidence of local hemorrhagic complications, if reported by >5% of subjects

Methods

Subjects were to be randomized in a 1:1 ratio to receive either 300 mg SKY0402 or 100 mg bupivacaine HCl with epinephrine 1:200,000. The randomization was to be stratified by site and modality of anesthesia (spinal or general anesthesia). Subjects who were randomized, but withdrew from the study before receiving study drug or did not undergo the planned surgical procedure were to be replaced.

The study drug (i.e., SKY0402 or bupivacaine HCl) was to be administered during surgery by an unblinded member of the surgical team. The unblinded study personnel were not to perform postoperative study assessments. If the adequate assignment of blinded and unblinded study personnel was not practical due to personnel shortages or other objective circumstances, alternative blinding arrangements could be implemented if mutually agreed upon by the Investigator and Pacira. For example, opaque syringes could be used to keep the person administering study drug blinded and enable him/her

to participate in postoperative study assessments. These alternative procedures were to be documented in writing and approved by Pacira.

The protocol for the study was broken down into three time periods: preoperative, intra-operative and postoperative. The procedures for each are described below.

Preoperative Procedures
Screening assessments were to be performed within 30 days before the scheduled surgical procedure. All subjects who were screened for enrollment, but did not meet eligibility criteria or who declined to participate, were to be documented on a screening log with a precise reason for non-participation.

On the day of the surgical procedure, Day 1, after the subject had arrived at the clinic, the subject's eligibility was to have been reconfirmed; a repeat pregnancy test was to have been performed on female subjects of child-bearing potential, a physical exam was to have been performed, baseline values for vital signs and responses to the Quality of Life (QOL) assessment were to have been obtained; and the subject was to have been randomized.

Intraoperative Procedures
The following assessments and procedures were to have been performed during surgical anesthesia, study drug administration, and surgery:

1. Administer general or spinal anesthesia to the subject.
2. Confirm eligibility based on exclusion criteria 13 and 14 (i.e., verify that no serious intraoperative complications had occurred and the incision was greater than 3 cm in length).
3. Administer study drug; record the start time of study drug infiltration.
4. Administer ketorolac IV(or appropriate alternative) at end of surgery.

Postoperative Procedures
All procedures were to have been timed from the start of the study drug administration. During the first three hours after the drug was administered, the following assessments and procedures were to have been performed:

1. Vital signs (temperature, resting heart rate, and blood pressure) were to have been measured at 0.5, 1, 1.5, and 2 hours.
2. NRS-R was to have been assessed at the time that the first dose of opioids were given, regardless of route of administration as well as at Hours 1 and 2.
3. As soon as a subject was able to tolerate oral medication, treatment with acetaminophen 1000 mg orally was to have been initiated and continued three times daily for four days.
4. Assessments of readiness for discharge at were to have been performed at Hours 1 and 2 and again at Hour 3, if the subject was still at the surgical facility at that point and his or her overall score was less than 9 at 2 hours.

5. All supplemental pain medications and other concomitant medications (including antiemetics) were to have been recorded.
6. The occurrence and duration (start and stop times) of any episodes of nausea and vomiting were to have been recorded.
7. The date and time of the first and every bowel movement and conduct NRS-BM, if applicable were to have been recorded.
8. The date and time that subject is discharged from the surgical center was to have been recorded.

From Hours 3 through 96 following study drug administration, each subject was to have undergone the following additional assessments and procedures:

1. NRS-Rs were to have been obtained at 4, 8, 12, 24, 36, 48, 60, 72, 84, and 96 hours.
2. Assessments of pain intensity during bowel movements using a numeric rating scale (NRS-BM) were to have been conducted.
3. The QOL questionnaire was to have been administered at 48, 72, and 96 hours.
4. The subject's overall satisfaction with postoperative analgesia was to have been assessed at 96 hours.

On Day 8 (± 24 hours), subjects were to have returned to the study site so that the following assessments and procedures could be conducted:

1. Measurement of vital signs (temperature, resting heart rate, and blood pressure).
2. Assessment of the blinded care provider's satisfaction with postoperative analgesia.
3. Recording subject's responses to the pharmacoeconomic questionnaire (region specific).
4. Recording all Investigator-reported and/or subject-reported AEs and SAEs, for which the subjects were to be particularly questioned about any residual sensory/motor impairment, or signs of nerve and/or tissue irritation.

On Day 30 (± 48 hours), the following actions were to have been taken:

1. Record the date the subject returned to work or normal daily activities.
2. Record any SAEs that occurred since the Day 8 visit and report to Pacira, as appropriate.
3. If subjects were unable to report to the study site or if this visit could not be otherwise conducted in person, the information listed above was to have been obtained through a phone interview with the subject.

The various assessments of the subjects for their levels of pain, use of analgesic products, vital signs, level of satisfaction and occurrence of treatment-emergent adverse reactions were to have been made in accordance with the study procedure schedule that follows.

Schedule

Table 21. Schedule of Study Procedures (taken from Table 1 on page v of the final study report)

Procedure		Screen	Base-line	Surgery	After Study Drug Administration												
						4-96 Hours											
						4	8	12	24	36	48	60	72	84	96		
	Study Day	**-30 - 1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**4**	**5**	**8**	**30**
	Time Window (±h)				**0.16**	**0.25**	**.5**	**.5**	**1**	**2**	**2**	**3**	**3**	**4**	**4**	**24**	**48**
Informed consent		X															
Assess/confirm eligibility		X	X	X													
Medical history, demographics and baseline characteristics		X															
Pregnancy test (women of childbearing potential)		X	X														
Physical examination			X														
Train self-assessments		X	X														
Vital signs[B]		X	X		0.5, 1, 1.5, & 2											X	
Randomize subject & prepare study drug			X														
Study drug administration				X													
Ketorolac 30 mg (or equivalent) at end of surgery				X													
NRS-R assessment					1 & 2[C]	X	X	X	X	X	X	X	X	X	X		
Acetaminophen 1000mg TID					X	X	X	X	X	X	X	X	X	X	X		
Assessment for discharge readiness					1, 2 & 3[D]												
Subject's overall satisfaction															X		

Procedure		Screen	Base-line	Surgery	After Study Drug Administration												
						4-96 Hours											
						4	8	12	24	36	48	60	72	84	96		
	Study Day	**-30 - 1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**4**	**5**	**8**	**30**
	Time Window (±h)				**0.16**	**0.25**	**.5**	**.5**	**1**	**2**	**2**	**3**	**3**	**4**	**4**	**24**	**48**
with postoperative analgesia																	
Blinded care provider's satisfaction with postop analgesia																X	
Quality of life questionnaire			X								X		X		X		
Record occurrence and duration of nausea/vomiting					X	X	X	X	X	X	X	X	X	X	X		
Record date/time of each BM and related pain (NRS-BM)					X	X	X	X	X	X	X	X	X	X	X		
Retrieve diaries and or worksheets																X	
Pharmacoeconomic questionnaire (region specific)																X	
Document return to work or basic daily activities																	X
Concomitant medications		X[E]	X[F]	X	X	X	X	X	X	X	X	X	X	X	X		
Record AEs (starting at signing of ICF)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record SAEs (starting at signing of ICF)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[A] Screening must be conducted within 30 days before the administration of study drug.
[B] Measure temperature, heart rate, and blood pressure after the subject has rested for at least 5 minutes in the supine position.
[C] In addition to the 1 and 2 hour assessments, assess NRS-R at the first dose of opioids (regardless of route of administration).
[D] Assess discharge readiness at 3 hours if the subject is still at the surgical facility at that point and his or her overall score was less than 9 at 2 hours.
[E] Instruct the subject to discontinue prohibited medications.
[F] Record all medication the subject used within 3 days before the scheduled surgery.

Amendments to the Protocol

The original protocol was not amended, but there were three "protocol clarification notes" distributed to the study centers and a change in the Medical Monitor. The Medical Monitor was changed from (b) (4) on July 28, 2008.

The protocol clarifications sent to the Investigators during the study included two pertaining to maintaining the double-blind during study drug administration, dated June 25, 2008, and August 1, 2008, and one pertaining to the use of antibiotics and intraoperative local administration of medication (e.g., epinephrine), dated June 27, 2008.

Post Hoc Changes

Prior to unblinding the study, the Applicant decided to pool all sites that enrolled fewer than 10 subjects.

It was also determined that only one site used spinal anesthesia; therefore, the mode of anesthesia was not used in the model.

The BMI data were calculated using an incorrect formula in the database, therefore the BMI data were removed from all tables and listings.

Conduct of the Study

The first subject was screened for enrollment into the study on July 28, 2008, and the last follow-up evaluation of a subject was conducted on February 24, 2009.

The Applicant stated that the clinical aspects of this study were conducted in accordance with the study protocol. Protocol waiver requests (not specified) were granted for the following three subjects: 28-1074, 28-1117, and 61-1170.

The following protocol deviations that were reported:

1. At Site 067, five subjects received 4000 mg of acetaminophen and three subjects received 5000 mg of acetaminophen during the 0-24 hour postoperative period. A corrective action plan was initiated at the site.
2. At Site 067, study drug for two subjects was inadvertently switched.

3. Site 020 failed to record vital signs in the recovery room per the protocol. However, the subjects were safely observed in the post-anesthesia recovery unit. Therefore, the lack of recorded vital signs did not create a safety concern.
4. Subject 057-1119 was randomized but did not give his consent to participate in the study. This subject did not receive any study drug.

These deviations were considered by the Applicant as minor and deemed inconsequential with respect to study results.

Results as Reported by the Applicant

Primary Efficacy Analysis
For the primary efficacy endpoint, AUC of the NRS-R pain intensity scores through 96 hours, SKY 0402 was compared to bupivacaine HCl using ANOVA with treatment and site as the main effects. As shown in the table below, the adjusted mean difference in the AUC of the NRS-R pain intensity scores through 96 hours was not statistically significantly different between the two treatment groups (p=0.15).

It was noted that the treatment groups were similar in their demographics for age, gender, race, ASA classification, weight and height.

Table 22. Primary Efficacy Analysis: NRS-R AUC0-96 hours (based on Table 7, p.55 of the Clinical Study Report)

Statistic	SKY0402	Bupivacaine HCl
N	99	99
Mean	396	359
Standard Deviation	213	194
Median	393	329
Minimum, Maximum Values	18, 866	3, 903
Adjusted Mean (Standard Error)	393 (20)	352 (21)
Difference of Adjusted Mean (Standard Error)	41 (28)	
95% CI for Difference of Adjusted Means	(-15, 6)	
p-value	0.15	

Secondary Efficacy Analyses
There were over 60 secondary endpoints evaluated by the Applicant when the analyses for individual endpoints at multiple timepoints during the study are taken into account, e.g., proportion of subjects receiving no supplemental opioid pain medication postoperatively through 12, 24, 36, 48, 60, 72, 84, and 96 hours. Of these, only 2 differed significantly between treatment groups, and in both cases, the difference

favored bupivacaine HCl over SKY0402. These differences included the adjusted mean NRS-R score at the 84 hour time point (p=0.04) and the mean integrated NRS-R pain intensity scores and supplemental opioid pain medication consumption at the 84 hour time point (p=0.03). There were no other statistically significant differences between the two treatment groups in any other efficacy variable at any time point. The table below summarizes the differences observed for this assessment.

Table 23. Secondary Efficacy Analysis: NRS-R Score at 84 Hours (based on Table 14.2.2.2, p.127 of the Clinical Study Report)

Statistic	**SKY0402** (N=99 enrolled)	**Bupivacaine HCl** (N=99 enrolled)
N (evaluable at this timepoint)	98	96
Mean	4	4
Standard Deviation	3	2
Median	4	3
Minimum, Maximum Values	0, 10	0, 10
Adjusted Mean (Standard Error)	4 (0.3)	4 (0.3)
Difference of Adjusted Mean (Standard Error)	0.7 (0.3)	
95% CI for Difference of Adjusted Means	(0, 1.4)	
p-value	0.04	

Table 24. Secondary Efficacy Analysis: NRS-R AUC0-84 (based on Table 14.2.2.7, p.142 of the Clinical Study Report)

Statistic	**SKY0402** (N=99 enrolled)	**Bupivacaine HCl** (N=99 enrolled)
N (evaluable at this timepoint)	98	96
Mean	-14	14
Standard Deviation	95	87
Median	-23	36
Minimum, Maximum Values	-190, 176	-182, 176
Adjusted Mean (Standard Error)	-16 (9)	13 (9)
Difference of Adjusted Mean (Standard Error)	-28 (13)	
95% CI for Difference of Adjusted Means	(-53, -3)	
p-value	0.03	

Table 25. Secondary Efficacy Analysis: Resumption of Work or Normal Daily Activities by Day 30 (based on Table 14.2.2.18, p. 162 of the Clinical Study Report)

Number of Days from Surgery	SKY0402 (N=99 enrolled)	Bupivacaine HCl (N=99 enrolled)
≤ 7 days (Day 8) [n (%)]	17 (17)	9 (9)
> 7 days - ≤ 14 days (Day 15) [n (%)]	39 (39)	38 (38)
> 14 days - ≤ 21 days (Day 22) [n (%)]	19 (19)	31 (31)
> 21 days [n (%)]	12 (12)	13 (13)
Not reported or did not return [n (%)]	12 (12)	8 (8)
p-value	0.06 (rounded from 0.0576)	

Brief Summary of Safety

The Applicant summarized the safety findings as follows:

1. There were no deaths in the study.
2. Three SAEs were reported during this study. In the SKY0402 group, one subject experienced an SAE of fecal impaction and one subject experienced an SAE of chronic postoperative pain. In the bupivacaine HCl group, one subject experienced an SAE of bleeding peptic ulcer. None of the SAEs was assessed by an Investigator as related to study drug.
3. Perioperative administration of SKY0402 via local infiltration was well tolerated in subjects undergoing hemorrhoidectomy under general or spinal anesthesia. The incidence of treatment emergent adverse events (TEAEs) was similar between the SKY0402 group (66%) and the bupivacaine HCl group (63%).
4. TEAEs common to both treatment groups with an incidence ≥5% were nausea, constipation, vomiting, In the SKY0402 treatment group alone, flatulence, abdominal pain, pyrexia, pruritus, and urinary retention also occurred with an incidence ≥5%. In the bupivacaine HCl treatment group, headache was the only other TEAE with an incidence ≥5%.
5. Headache and dizziness were the only two TEAEs (preferred terms) reported in the Nervous System Disorders system organ class (SOC). Three subjects in each treatment group experienced dizziness. The incidence of headache was lower in the SKY0402 group than in the bupivacaine HCl group. There was only one TEAE reported in the Cardiac Disorders SOC: one subject in the bupivacaine HCl group experienced tachycardia. There were no TEAEs in the Cardiac Disorders SOC reported in the SKY0402 group.

Discussion of Results

The study failed to show a difference between SKY0402 and the currently approved and marketed formulation of bupivacaine HCl. This failure was not only for the primary

endpoint of AUC of the NRS of pain intensity scores, at rest, through 96 hours after surgery, but for 36, 48, 60, 72, and 84 hours as well where the AUCs for SKY0402-treated subjects were greater than those for bupivacaine HCl-treated subjects. At 12 and 24 hours after surgery, the mean AUCs for SKY0402-treated subjects did exceed those of the bupivacaine HCl- treated subjects but the differences were 1 and 4 units, respectively, that would have no clinical significance. (b) (4) y a lack of difference in the following assessments:

- Total postoperative consumption of supplemental opioid pain medication through 12, 24, 36, 48, 60, 72, 84, and 96 hours.
- Proportion of subjects receiving no supplemental opioid pain medication postoperatively through 12, 24, 36, 48, 60, 72, 84, and 96 hours.
- Time to first postoperative use of opioid medications.
- Integrated rank assessment using the NRS-R scores and total postoperative opioid usage through 12, 24, 36, 48, 60, 72, 84, and 96 hours.
- Time to first bowel movement.
- Pain with first bowel movement (NRS-BM).
- Average daily pain with bowel movement (NRS-BM).
- QOL questionnaire (EQ-5D).
- Time to first occurrence of PONV
- Postoperative use of antiemetic medication administered through 12, 24, 36, 48, 60, 72, 84, and 96 hours.
- Discharge readiness.
- Subject's overall satisfaction with postoperative analgesia.
- Blinded care provider's satisfaction with postoperative analgesia.
- Time to return to work or normal daily activities.

Based on the safety assessments made, the two treatments appeared to be equally well tolerated. Of particular interest for these study drugs were the incidents of neurological and cardiac toxicity. The protocol did not include continuous ECG monitoring or specify assessments of neurotoxicity, which limits it utility for characterizing the risk profile of SKY0402; however, no serious adverse events related to these toxicities were reported, which provides some reassurance. It should be noted that the adverse events reported included 3% incidence of dizziness in both treatment groups, and a 1% incidence of moderate anxiety, mild tinnitus and mild blurred vision for SKY0402-treated (subjects 051-1102, 028-1154 and 063-2014, respectively), but not bupivacaine HCl-treated subjects. Each of the neurological adverse events was considered "not related" to study drug by the Investigator. This issue is addressed in the safety section of this review.

Conclusions

This study failed to show any statistically or clinically meaningful advantage of SKY0402 over bupivacaine HCl when used following hemorrhoidectomy despite a systematic assessment of over 60 different efficacy endpoints. Overall, SKY0402 appeared to be tolerated as well as bupivacaine HCl.

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References

[1] Tuominen M, Pitkänen M, Rosenberg PH. Postoperative pain relief and bupivacaine plasma levels during continuous interscalene brachial plexus block. Acta Anaesthesiol Scand. 1987 May; 31(4): 276-8.

[2] Jorfeldt L, Löfström B, Pernow B, Persson B, Wahren J, Widman B. The effect of local anaesthetics on the central circulation and respiration in man and dog. Acta Anaesthesiol Scand. 1968; 12(4): 153-69.

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/s/

ARTHUR F SIMONE
10/07/2011

RIGOBERTO A ROCA
10/07/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-496 **Applicant:** Pacira Pharmaceutical, Inc. **Stamp Date:** 9/28/10

Drug Name: Exparel **NDA/BLA Type:** NDA

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X* See below.			Indication sought: for single-dose local administration into the surgical wound to produce postsurgical analgesia
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?		X		
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2) Marcaine (bupivacaine) NDA 16-964
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Various Location in submission: Various	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: SKY0402-C-316 (hemorrhoidectomy) Indication: post-operative analgesia	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 SKY0402-C-317 (bunionectomy) Indication: post-operative analgesia				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		Studies were conducted in Western and Eastern European countries.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			Rationale for not conducting studies was provided.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X	X		
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	by the Division during pre-submission discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			This is included in the individual final study reports.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Not Applicable

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Labeling does not include Highlights section.

Priority Review Request

The Applicant believes SKY0402 to be an important treatment option for the management of postsurgical pain and per FDA guidance, meets the criteria for priority review classification on the basis that SKY0402 may "eliminate or substantially reduce a treatment-limiting drug reaction." They state that, based on secondary endpoints in their pivotal trials, patients exposed to SKY0402 were less likely to use opioids, used fewer opioids when they were needed, and started taking them later in their hospital course while still maintaining an advantage regarding effective pain control. They contend that these advantages demonstrated that SKY0402 has the potential to allow patients to be discharged from the hospital or ambulatory center with fewer or no oral opioids and that SKY0402 may clearly eliminate or substantially reduce a public health issue from the misuse of opioid-based treatments and thus satisfies the criteria for Priority Review classification. (b) (4)

Reviewer Comments and Recommendation

While the Applicant may have demonstrated a reduced need for opioid analgesia when SKY0402 is administered post-operatively, they have not demonstrated that this reduction provides a benefit to either the patient or society. Specifically, they have not shown the reduced use of opioids to be associated with mitigation in their side effects or some other benefit such as a clinically relevant reduction in discharge time from the healthcare facility or return to normal activities. Neither the discharge of patients with fewer or no opioid medications nor the benefits of such discharges has been demonstrated in the studies submitted to the NDA.

Therefore, it is recommended that the request for a priority review be denied.

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/s/

ARTHUR F SIMONE
12/08/2010

RIGOBERTO A ROCA
12/08/2010

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	022-496
Priority or Standard	Standard
Submit Date(s)	September 28, 2010, 4/5/11
Received Date(s)	September 28, 2010
PDUFA Goal Date	June 28, 2011
Division / Office	DAAP/ODE 2
Reviewer Name(s)	Arthur Simone, MD, PhD
Review Completion Date	April 28, 2010
Established Name	Bupivacaine extended-release liposome injection
(Proposed) Trade Name	Exparel
Therapeutic Class	Amide local anesthetic
Applicant	Pacira Pharmaceuticals, Inc.
Formulation(s)	Extended-release liposome injection in single-use vials: (b) (4)
Dosing Regimen	Single dose by local infiltration into the surgical wound prior to the end of surgery
Indication(s)	To produce postsurgical analgesia
Intended Population(s)	Patients 18 years of age and older undergoing surgical procedures

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that an approval action be taken for this NDA provided the outstanding CMC issues regarding a site inspection have been resolved to the satisfaction of the Office of Compliance.

In two placebo-controlled clinical trials, the Applicant demonstrated that Exparel provides postoperative analgesia lasting up to 24 hours. One surgical procedure was evaluated in each of these pivotal studies: hemorrhoidectomy and bunionectomy. The dose and method of administration differed for each of the studies; this precludes extrapolating dosing and efficacy to other surgical procedures.

In the hemorrhoidectomy study, a 30 mL dose of Exparel was infiltrated in 5 mL aliquots at six points surrounding the anal sphincter corresponding to the positions of the even numbers on a clock face. In the bunionectomy study, an 8 mL dose of Exparel was infiltrated into the surgical wound with 4 mL infiltrated into the tissues immediately surrounding the cut bone, 2-3 mL infiltrated into tissues lateral, dorsal and ventral to the osteotomy, and the remaining 1-2 mL infiltrated into the subcutaneous tissue overlying the wound.

(b) (4)

The safety of Exparel was compared to bupivacaine HCl and placebo in multiple studies. Overall, the systemic and local effects of Exparel did not differ substantially from bupivacaine HCl.

(b) (4)

(b) (4)

1.2 Risk Benefit Assessment

The risk benefit assessment relied heavily on the similarity in the safety profiles for Exparel and unencapsulated bupivacaine HCl. (b) (4)

In the placebo controlled studies, Exparel was significantly better than placebo for reducing pain intensity during the first 12 hours following administration. This effect diminished over the next 12 hours such that by 24 hours after administration, there was not clinically relevant difference in the pain experienced by subjects treated with Exparel compared to those treated with normal saline. Based on the demonstration of Exparel's efficacy versus placebo, its pharmacodynamics being similar to those of unencapsulated bupivacaine, and its safety profile also being similar to that of unencapsulated bupivacaine, the benefits were considered to outweigh the risks. This finding, however, is limited to the two surgical procedures studied in the placebo-controlled pivotal studies. The manner in which Exparel was administered and the doses used in those studies were so dissimilar that it is not possible to extrapolate a dose that would be efficacious for other surgical procedures. In this regard, additional adequate and well-controlled studies are needed.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Based on the safety profile of Exparel and the vast experience the Agency has with unencapsulated bupivacaine HCl, Postmarket Risk Evaluation and Mitigation Strategies are not indicated at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

Following approval, it is recommended that pediatric studies be conducted to assess safety, efficacy and appropriate dosing of Exparel in pediatric patients. These studies should initially be conducted in older patients with studies in younger patients commencing in a sequential fashion, if the product has been found to be safe and effective in the preceding age group. If necessary, the product should be modified to meet the dosing requirements of younger children.

2 Introduction and Regulatory Background

2.1 Product Information

Exparel consists of microscopic spherical liposomes that are multivesicular and composed of a honeycomb-like structure of numerous non-concentric internal aqueous chambers containing bupivacaine. Each chamber is separated from adjacent chambers by lipid membranes. (b) (4) he liposomes are part of an extended-release drug delivery system that is similar to DepoFoam that is used in two currently marketed products: DepoCyt (NDA 21-041) and DepoDur (NDA 21-671). The liposomes used in Exparel (b) (4) contain a novel lipid excipient, dierucoylphosphatidylcholine (DEPC).

The active ingredient of the formulation is bupivacaine, a currently marketed product (Marcaine, NDA 16-964), which is released from the liposomes by a mechanism that involves reorganization of the barrier lipid membranes and subsequent diffusion of the drug over an extended period of time.

The Applicant has proposed the following wording for the indication of Exparel:

> EXPAREL™ is an (b) (4) liposome injection of bupivacaine, an amide-type local anesthetic (b) (4), indicated for single-dose local administration into the surgical (b) (4) to produce postsurgical analgesia.

(b) (4)

(b) (4)

2.2 Currently Available Treatments for Proposed Indications

There are a number of local anesthetics that are currently marketed and that can be used for infiltration into surgical wounds to provide analgesia early in the postoperative period. Among these is bupivacaine, the active ingredient in Exparel.

2.3 Availability of Proposed Active Ingredient in the United States

There are two marketers of bupivacaine in the United States, Hospira and APP Pharmaceuticals. (b) (4)

2.4 Important Safety Issues with Consideration to Related Drugs

The more important issues regarding the use of local anesthetics are generally related to systemic exposure and include the following:

1. Central nervous system reactions that range from CNS excitation with light-headedness, dizziness, paresthesias and acute anxiety at lower plasma levels to generalized tonic-clonic seizure activity, depression of conscious activity and respiratory arrest with profound depression of the medullary respiratory center at higher plasma concentrations.
2. Cardiac reactions including dose-dependent depression of myocyte activity with decreases in myocardial contractility beginning at doses that achieve sodium channel blockade. Life-threatening arrhythmias and cardiovascular collapse can occur at higher systemic exposures. Cardiac toxicity is related, in large part, to agent-specific kinetics of sodium channel block.
3. Allergic-type responses to local anesthetics range from contact hypersensitivity to anaphylactoid and anaphylactic reactions. The preservatives, methylparaben and metabisulfite, commonly used in multidose preparations may, independently of the local anesthetic, significantly increase the likelihood of an allergic-type response. Para-aminobenzoic acid (PABA), a metabolite of the ester local anesthetics, is commonly found in the environment and therefore, may serve as a significant source of allergic reactions as many patients present already sensitized to this compound.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The first interaction between the Applicant and the Agency was at a pre-IND meeting on October 2, 2002. At that time, the Sponsor, SkyePharma, intended the drug product, then referred to as SKY0402, to be indicated for (b) (4)

(b) (4)

(b) (4)

The initial Investigational New Drug (IND) application (IND 69,198) for SKY0402 was submitted on December 9, 2004. At that time, SKY0402 was to be evaluated in a study of patients undergoing inguinal hernia repair and a second study of patients undergoing bunionectomy. Following the review of those protocols, the Sponsor inactivated the IND for safety reasons on January 6, 2005. Specifically, there were additional preclinical issues that needed to be performed and minor changes to the protocols that needed to be made. These issues were discussed with the Sponsor in a follow-up teleconference on March 30, 2005, after the sponsor had provided proposals for animal studies to address the Division's safety concerns.

On May 24, 2005, the Division issued a letter to the Sponsor indicating that the toxicity studies they had proposed would be sufficient to support the use of SKY0402 in incisional infiltration (e.g., hernia repair), peripheral nerve block, and neuraxial block (e.g., lumbar epidural) in clinical studies in humans.

After inactivating their IND, the Sponsor conducted trials outside the United States, and prior to reactivating the IND, requested an End-of-Phase 2 meeting that took place on January 12, 2006. The Sponsor's intent was to reactivate their IND in early February (b) (4)

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(b) (4)

On March 7, 2006, the Applicant requested that the IND be reactivated, and clinical trials were allowed to proceed. On July 21, 2006, the Applicant requested advice from the Division regarding modifications that were being made to the clinical development plan. Specifically, the proposed indication for SKY0402 would be limited to postoperative pain, with SKY0402 administered only by wound infiltration. The Division agreed that limiting the indicated route of administration to wound infiltration would eliminate the need for additional animal studies to evaluate the effects of inadvertent intravascular administration and that exposure in 500 patients receiving SKY0402 by wound infiltration would be an adequate safety database to support the proposed indication provided it included the elderly and patients having serious comorbidity classified as ASA 3 and 4. The Division also noted that labeling for the product will need to contain a strong caution against the use of SKY0402 by other routes of administration that would otherwise be used for local anesthetics in typical clinical practice, but appear to be unsafe for SKY0402.

(b) (4)

On May 20, 2009, the Applicant was informed that the proposed proprietary name, Exparel, was acceptable and that a request for a second review of the name should be made with the submission of the NDA.

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7. The ISS needs to include all human safety data generated during development. This includes data that you own or have a right of reference to, even if such data were not collected under the IND, e.g., the data from Maruho in Japan.

8. The Applicant is obligated to evaluate safety based on an integrated database.

2.6 Other Relevant Background Information

Exparel has not been approved for use and has not been marketed outside the United States. Therefore, the data from the clinical development program are the only human data available for determining efficacy and characterizing the risk profile for Exparel.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of adequate quality and well enough organized with complete datasets to allow meaningful review. (b) (4)

[redacted]

3.2 Compliance with Good Clinical Practices

The clinical trials were conducted in compliance with Good Clinical Practices. For each of the pivotal studies, the Applicant included the statements:

> Prior to enrolling subjects into this study, each study site will obtain the approval of a properly constituted Institutional Review Board (IRB). Attention is directed to the basic elements that are required to be incorporated into the Informed Consent Form (ICF) under the United States (US) Food and Drug Administration (FDA) Title 21 of the Code of Federal Regulations (CFR) for the Protection of Human Subjects (Part 50.25) and the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP; E6).
>
> This study will be conducted in accordance with the clinical research guidelines established by the FDA Title 21 CFR, Parts 50, 54, 56, and 312 and the ICH GCP.

3.3 Financial Disclosures

The Applicant certified the following for each of the Investigators involved with the pivotal studies:

As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(1).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The chemistry review team, i.e., Arthur Shaw, Ph.D. and Prasad Peri, Ph.D., recommend that the NDA not be approved at this time due to a number of outstanding cGMP issues. In addition, they note that microbiology issues are still awaiting resolution and that a Drug Master File (DMF) for a critical excipient, (b) (4) is deficient.

The team also indicated that the use of the phrase (b) (4) is inappropriate. Therefore, the formulation should be expressed as 13.3 mg/mL bupivacaine, (b) (4) and all specifications, tests, etc. should conform to this expression of strength.

The team has no recommendations for Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps.

NOTE: Throughout this review, the Applicant's specification of 15 mg/mL for Exparel's bupivacaine content has been used. This reflects the performance of these two reviews in parallel and not a disagreement with the chemistry review team's conclusion. (b) (4)

4.2 Clinical Microbiology

The final Clinical Microbiology review was not available at the time this review was completed.

4.3 Preclinical Pharmacology/Toxicology

The review of Drs. Bond and Wasserman finds no impediment to approving Exparel based on preclinical pharmacological or toxicological issues. They recommend several modifications to the proposed labeling, but have no recommendations for additional nonclinical studies.

4.4 Clinical Pharmacology

The Clinical Pharmacology review team, Drs. Zhihong Li and Yun Xu, found no impediment to approval of Exparel in their review of the NDA. The following bullet points are excerpts from their Clinical Pharmacology Summary highlight the key points of their review that have clinical implications.

- Bupivacaine is primarily metabolized by liver. In a study evaluating the pharmacokinetics of SKY0402 in patients with hepatic impairment, bupivacaine exposure in subjects with moderate hepatic impairment showed approximate 1.5- and 1.6-fold increases in the mean values of C_{max} and AUC_{inf}, respectively. The bupivacaine metabolite PPX showed similar exposure increase in subjects with moderate hepatic impairment with an approximate 1.9-fold increase in C_{max} and 1.6-fold increase in AUC_{inf}. Since SKY0402 is a local acting product, no dose adjustment is recommended in patients with mild to moderate hepatic impairment. However, the product should be used cautiously in patients with hepatic disease as indicated in Marcaine label.
- The QT effect following the administration of SKY0402 was evaluated in two QT studies - Study SKY0402-C-105 and Study SKY0402-C-107. Review of these two studies was consulted with the Interdisciplinary Review Team for QT Studies (IRT-QT). No apparent QT prolongation effect of bupivacaine (SKY0402 at 300, 450, 600, and 750 mg) was detected in the two QT studies. Bupivacaine appears to be associated with a concentration-dependent QTc interval shortening. The detected QTc interval shortening was not considered as clinically meaningful according to the review by IRT-QT group.

4.4.1 Mechanism of Action

Exparel consists of microscopic spherical, multivesicular liposomes that are composed of a honeycomb-like structure with numerous internal aqueous chambers containing bupivacaine. The chambers are separated from one another by lipid membranes. (b) (4) The released bupivacaine then exerts its anesthetic action when it comes in contact with nerve cells where it blocks sodium channels and prevents the initiation and transmission of nerve impulses.

4.4.2 Pharmacodynamics

The onset of action of Exparel was evaluated in clinical trials that assessed pain intensity (b) (4). These studies demonstrated that the onset of action for SKY0402 was less than 2 minutes, and was similar to conventional bupivacaine HCl. In the clinical trials described in the sections below, the duration of Exparel's analgesic effect appears to be no more than 24 hours and not longer than that of bupivacaine HCl.

4.4.3 Pharmacokinetics

Exparel is administered locally, where it exerts its effects as an analgesic agent. Although systemic absorption of the product and the bupivacaine it releases were noted during the clinical development program, this exposure is not related to the product's efficacy, but does have implications for its safety profile. The systemic pharmacokinetics of Exparel were evaluated by the Clinical Pharmacology review team. In the summary section of their review, they noted the following:

- The mean plasma concentration-time profiles of bupivacaine after administration of SKY0402 by infiltration exhibit two peaks. There is an early peak at a median time of 0.25 to 2 hours followed by a second peak that occurs at a median time of 12 to 24 hours. Based on only the systemic exposure profile, SKY0402 demonstrates the characteristics of delayed T_{max} for an extended-release product. However, since SKY0402 is a locally administered drug and also exerts its action locally, systemic exposure should only be used as supportive evidence to determine if SKY0402 can be categorized as an ER product. Whether SKY0402 can be categorized as an ER product should also rely on other aspects (e.g. *in vitro* release profile), especially whether SKY0402 could reduce the dosing frequency clinically compared to IR formulation of bupivacaine.
- Dose proportionality was evaluated in three surgical procedures. SKY0402 showed reasonably dose-proportional increase in the mean values of C_{max} and AUC_{inf} in the management of postoperative pain following inguinal hernia repair (SKY0402-C-201) and bunionectomy (SKY0402-C-203), (b) (4)

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Applicant has conducted 22 clinical studies in support of the NDA submission. These include nine Phase 1 studies, seven Phase 2 studies and six Phase 3 studies. The table below provides summary descriptions of these studies.

Table 1. Summary of clinical studies (based on Table 5.2 in the Clinical Study Reports section of the NDA)

Phase	Name	Objective	Design	Study Drugs, Dose and Route	Number of Subjects	Population	Duration of Treatment
1	SKY0402-002	Safety PK/PD	Randomized, double-blind, active-controlled	SKY0402 75 mg SKY0402 125 mg SKY0402 150 mg SKY0402 175 mg Bupiv. HCl 0.5% Perineural block (15 mL)	6 7 6 6 12	Healthy subjects	Single dose
1	SKY0402-021	Efficacy Safety PK	Randomized, double-blind, crossover placebo- and active-controlled. Three subjects received both the lower dose of SKY0402 and Bupi HCl in Stage 1; six subjects received both doses of SKY0402 and Bupi HCl in Stage 2.	SKY0402 10 mg SKY0402 50 mg (SKY0402 contained glucuronic acid as the pH adjusting/neutralizing agent) Bupi HCl 0.125% Saline (placebo) Subcutaneous (Stage 1, four injections 2 mL each, for a total of 8 mL; Stage 2, four injections 2 mL each, for a total of 8 mL)	9 6 9 6 9	Healthy subjects	Single dose
1	SKY0402-C-103	Safety PK/PD	Randomized, double-blind, active-controlled	SKY0402 100 mg SKY0402 175 mg SKY0402 300 mg Bupi HCl 50 mg epidural (20 mL)	8 8 8 6	Healthy subjects	Single dose
1	SKY0402-C-105	QT/QTc interval PK	Randomized, double-blind, placebo- and active-controlled crossover; all subjects received all doses. TQT	Saline (placebo) SKY0402 300 mg (20 mL) SKY0402 450 mg (30 mL) Subcutaneous Moxifloxacin Moxifloxacin-placebo tablet	47 47 47 49 48	Healthy subjects	Single dose of placebo or active drug per study period during two study periods

Phase	Name	Objective	Design	Study Drugs, Dose and Route	Number of Subjects	Population	Duration of Treatment
1	SKY0402-C-108	PK/PD of three lots of SKY0402	Randomized, double-blind, crossover; all subjects received two lots of SKY0402 at 300 mg.	SKY0402 300 mg Subcutaneous (20 mL)	30	Healthy subjects	Single dose of two different lots during two visits
1	SKY0402-C-107	QT/QTc interval PK	Sequential, open-label, placebo-controlled; TQT Subjects had also participated in Study SKY0402-C-105.	SKY0402 600 mg (40 mL) SKY0402 750 mg (50 mL) Saline (placebo) Subcutaneous	16 16 16	Healthy subjects	Single dose of SKY0402 per study period during two study periods (600 mg in Period 1 and 750 mg in Period 2); saline in both periods to establish baseline ECG
1	SKY0402-C-110	Safety PK Com-parison of subjects with normal hepatic function to subjects with moderate hepatic impairment	Open-label, parallel-group	SKY0402 300 mg Subcutaneous (20 mL)	18	Nine subjects with normal hepatic function and nine subjects with moderate hepatic impairment	Single dose

Phase	Name	Objective	Design	Study Drugs, Dose and Route	Number of Subjects	Population	Duration of Treatment
1	SKY0402-C-106	Safety Onset of action PD	Randomized, single-blind, placebo- and active-controlled crossover; subjects received SKY0402 in one arm and Bupi HCl in the other arm on one day and received SKY0402 in one arm and normal saline in the other arm on another day. Time to onset.	SKY0402 15 mg Bupivacaine HCl 0.25% Saline (placebo) Subcutaneous (1 mL)	161	Healthy subjects	Single dose of SKY0402 for two visits; single dose of Bupi HCl or saline at each visit
1	SKY0402-C-109	Safety Onset of action PD	Randomized, single-blind, active-controlled, sequential, crossover; subjects received SKY0402 in one arm and saline in the other arm on one day and Bupi HCl and normal saline on another day. Time to onset.	SKY0402 45 mg Bupivacaine HCl 0.25% Local infiltration (3 mL)	129 128	Healthy subjects	Single dose of SKY0402 for two visits; single dose of Bupi HCl or saline at each visit
2	SKY0402-C-201	Efficacy Safety PK	Randomized, double-blind, dose escalating, active-controlled	SKY0402 175 mg SKY0402 225 mg SKY0402 300 mg SKY0402 350 mg Bupivacaine HCl 0.25% Local infiltration (40 mL)	12 12 12 14 26	Subjects with postsurgical pain following inguinal hernia repair	Single dose

Phase	Name	Objective	Design	Study Drugs, Dose and Route	Number of Subjects	Population	Duration of Treatment
2	SKY0402-C-207	Efficacy Safety	Randomized, doubleblind, active-controlled	SKY0402 105 mg SKY0402 180 mg SKY0402 345 mg Bupivacaine HCl 0.25% Local infiltration (42 mL)	25 24 25 24	Subjects with postsurgical pain following inguinal hernia repair	Single dose
(b) (4)							
2	SKY0402-C-209	Efficacy Safety	Randomized, double-blind, active-controlled	SKY0402 75 mg SKY0402 225 mg SKY0402 300 mg Bupivacaine HCl 0.25% Local infiltration (30 mL)	24 25 25 26	Subjects with postsurgical pain following hemorrhoidectomy	Single dose
(b) (4)							
3	SIMPLE Hemorrhoidectomy 312	Efficacy Safety	Randomized, double-blind, active-controlled	SKY0402 300 mg Bupivacaine HCl 0.25% Local infiltration (40 mL)	101 103	Subjects with postsurgical pain following hemorrhoidectomy	Single dose
(b) (4)							

Phase	Name	Objective	Design	Study Drugs, Dose and Route	Number of Subjects	Population	Duration of Treatment
3	SKY0402-C-316	Efficacy Safety PK	Randomized, double-blind, placebo-controlled	SKY0402 300 mg Saline (placebo) Local infiltration (30 mL)	95 94	Subjects with postsurgical pain following hemorrhoidectomy	Single dose
3	SKY0402-C-317	Efficacy Safety PK	Randomized, double-blind; placebo-controlled	SKY0402 120 mg Saline (placebo) Local infiltration (8 mL)	97 96	Subjects with postsurgical pain following bunionectomy	Single dose
2	SKY0402-C-203	Efficacy Safety PK	Randomized, double-blind, active-controlled	SKY0402 175 mg SKY0402 225 mg SKY0402 350 mg Bupivacaine HCl 0.5% Perineural ankle nerve block (25 mL)	12 12 14 20	Subjects with postsurgical pain following bunionectomy	Single dose
[redacted]							(b) (4)

5.2 Review Strategy

This review takes into consideration all the clinical studies conducted by the Applicant and the 120-Day Safety Update for evaluating the safety and efficacy of Exparel and performing the benefit risk analysis that served as the basis for the recommendation for regulatory action. Relevant information pertaining to safety from the chemistry, preclinical and clinical pharmacology sections of the NDA submission were also taken into consideration along with input from members of each of these review teams. The expertise of the statistical reviewers was also relied upon for the analysis of the efficacy data contained in the pivotal trials.

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

The focus of the safety evaluation was on three aspects of Exparel therapy:

1. The local effects of Exparel on
    a. The surgical incision
    (b) (4)
    c. Surgical wound healing
2. The risk of systemic exposure to either Exparel or the bupivacaine released by it with emphasis on:
    a. Neurotoxicity
    b. Cardiotoxicity

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

5.3 Discussion of Individual Studies/Clinical Trials

Details of the individual studies supporting efficacy are provided in Section 9.4 below. The Applicant conducted two sets of studies that were similar in overall design but differed in terms of the comparator, placebo versus active.

6 Review of Efficacy

Efficacy Summary

The Applicant conducted five pivotal trials designed to demonstrate the efficacy of Exparel. The individual trials are described in detail in Section 9.4 of this review. In these studies, the primary endpoints were the area under the curve (AUC) of the numeric rating scale (NRS) of pain intensity through various durations. (b) (4) The Applicant then went on to conduct two clinical studies comparing Exparel to placebo (normal saline). In both of these trials, Exparel was demonstrated to be superior. The findings of these two sets of studies, i.e., active controlled and placebo controlled, are described in greater detail sections below. The table below summarizes the trials.

Table 2. Summary of pivotal trials for demonstrating the efficacy of Exparel

Trial Number	Surgical Procedure	Comparator	Dose of Exparel (mg)	Method of Administering Study Drug	Duration of Pain Assessments for Primary Endpoint (hours)	Exparel Demonstrated to be Superior? [Y/N] (p value)
(b) (4)						
SIMPLE Hemorrhoidectomy - 312	hemorrhoidectomy	bupivacaine HCl (150)	300	Infiltration if incision was >3 cm in length	96[R]	N (0.15)
(b) (4)						
SKY0402-C-316	Hemorrhoidectomy	normal saline	300	locations around the anal sphincter	72[R]	Y (<.0001)
SKY0402-C-317	Bunionectomy	normal saline	120	Infiltration into incision site and the soft tissue around the osteotomy	24[N]	Y (0.001)

[A] Pain level with activity
[P] Pain level at rest
[N] Pain level at set time point regardless of activity level

Although the two placebo-controlled studies demonstrated the superior efficacy of Exparel over placebo, the primary endpoint for the hemorrhoidectomy study, AUC_{0-72} for NRS of pain intensity, suggests that the duration of the superior efficacy is for the entire 72 hours. This is not the case. As described in Section 6.1.9, the analgesia derived from Exparel does not differ from placebo, at least not in a clinically meaningful way, beyond 24 hours.

Only two types of surgical procedures were evaluated in the pivotal studies that succeeded in demonstrating efficacy, and for each procedure a different dose of Exparel and a different technique of infiltration were used. This makes it impossible to extrapolate the dosing and infiltration methods to other surgical procedures with a reasonable expectation of efficacy.

(b) (4) They were successful in demonstrating Exparel is superior to placebo for providing up to 24 hours of postoperative analgesia following bunionectomy and hemorrhoidectomy when infiltrated into the surgical wound in a very specific manner.

6.1 Indication

The Applicant has proposed the following wording as the indication for Exparel:

> EXPAREL™ is an (b) (4) liposome injection of bupivacaine, an amide-type local anesthetic (b) (4) indicated for single-dose local administration into the surgical (b) (4) to produce postsurgical analgesia.

(b) (4)

6.1.1 Methods

The Phase 3 trials were appropriately designed for evaluating the analgesic properties of Exparel. The trials were all prospective, randomized, subject- and assessor-blinded, with controls - either bupivacaine HCl as an active control or normal saline as a placebo control. All the trials were designed to demonstrate that Exparel was superior to the comparator.

In the pivotal trials, the primary efficacy endpoint was the area under the curve (AUC) of the numerical rating scale (NRS) pain scores collected for different durations. Some of the pain scores were collected while the subject was at rest, others were collected while the subject was active, and others were collected regardless of the activity level (see Table 2. **Summary of pivotal trials for demonstrating the efficacy of Exparel** and the reviews of the individual studies in Section 9.4).

Numerous secondary endpoints were evaluated in the pivotal studies. Although the Applicant made statistical comparisons between treatment groups for these endpoints, they made no prespecified adjustments to the analyses to account for multiple comparisons. Therefore, at best, the findings for the comparisons of the secondary endpoints can be considered supportive, at best. The secondary efficacy endpoints from the pivotal studies include the following:

- AUC of pain intensity scores using the NRS at rest (NRS-R) for the Full Analysis set.
- AUC of pain intensity scores using the NRS-R – with worst observation carried forward and last observation carried forward (wWOCF+LOCF) - Intent-to-Treat population.
- Pain intensity scores at rest – wWOCF+LOCF – Intent-to-Treat.
- Percentage of pain free subjects.
- Percentage of subjects receiving opioid rescue medication.
- Total postoperative consumption of supplemental opioid medication.
- Time to first postoperative use of supplemental opioid medication.
- Subject's satisfaction with postoperative analgesia or blinded care provider's satisfaction with postoperative analgesia.

Other secondary endpoints related to opioid sparing were also evaluated by the Applicant, but were not included in all of the pivotal trials. These included:

- such as bowel movements
- postoperative nausea and vomiting (PONV)
- occurrence of constipation through 72 hours

The inclusion and exclusion criteria were similar across the pivotal trials. The following criteria applied to these trials:

1. Males and females (b) (4)) ≥18 years of age at the time of enrollment.
2. Non-pregnant females.
3. American Society of Anesthesiology (ASA) Physical Class 1-4 for each of the active controlled studies, 1-3 for the placebo-controlled hemorrhoidectomy study and not specified for the bunionectomy study.
4. Slated to electively undergo the specified procedure.
5. Clinical laboratory values that were within or not substantially outside the boundaries for normal limits.
6. Neurologically intact for peripheral sensation.
7. Without concurrent painful conditions or surgical procedures that require analgesic therapy.
8. Ability to provide informed consent, adhere to the study visit schedule and complete all study assessments and language specific questionnaires.

Current use of systemic glucocorticosteroids or use of glucocorticoids was not permitted for the placebo-controlled trials but was not an exclusion criterion for the active-controlled trials.

6.1.2 Demographics

The table below contains the summary subject demographic information for each of the pivotal trials. This table was constructed from the data available on subjects who received study drug and was based on actual drug administered not the assigned treatment. The data indicate that within each individual study there were no substantial differences between subjects in the two treatment groups for any of the demographic categories.

Due to the discrepancy in the findings of the pivotal trials (i.e., the placebo-controlled studies were wins for Exparel treatment, but the active-controlled studies were all losses for Exparel), subject demographics were reviewed from two additional perspectives. The first was whether there was a demographic difference between the subjects enrolled in the studies that failed to show efficacy for Exparel and those enrolled in the successful outcome studies. The second was whether the demographics of subjects in the successful studies adequately represent those of the patients likely to receive the product in the clinical setting if it is approved. Each perspective is considered below.

Comparing the characteristics for the subjects in the placebo-controlled studies to those in the active-controlled studies is relevant only for the two hemorrhoidectomy trials. In these two trials, the following observations regarding the subjects' demographics were noted:

1. The age distribution was similar in both studies.
2. The placebo-controlled study had approximately twice as many males as females compare to the more evenly distributed numbers in the active-controlled study.
3. All subjects in the placebo-control study were Caucasian whereas their counterparts in the active-controlled study were approximately 80% Caucasian.
4. There is a difference in the ASA-Physical Status distribution between the two studies with the active-control study being skewed toward subjects with more serious underlying medical conditions.

None of these differences were likely to have a substantial impact on the outcomes.

For the bunionectomy study, the demographics of the subjects reflect those of the general patient population with a predominance of females and age < 65 years old at the time of surgery. Similarly, the demographics of the subjects partaking in the hemorrhoidectomy study reflect those of the general population, in the United States, with males presenting more often than females for treatment, although no sex predilection has been reported, and age < 65 years old at the time of surgery.

Table 4. Subject demographics for the pivotal studies

Demographic		Study Type and Treatment Group						(b) (4)
		Placebo Control						
		Bunionectomy		Hemorrhoidectomy		Hemorrhoidectomy		
		Exparel (120 mg)	Saline	Exparel (300 mg)	Saline	Exparel (300 mg)	Bupivacaine (100 mg)	
Age (years)	18-64	96	91	86	84	95	93	
	≥65	1	5	9	10	6	10	
	≥75	0	0	2	2	2	3	
Gender	Male	22	12	63	67	53	53	
	Female	75	84	32	27	48	50	
Race	White	66	72	95	94	80	77	
	Black	25	21	0	0	13	10	
	Other	6	3	0	0	8	16	
ASA-PS	1	78	82	57	49	29	38	
	2	19	14	36	42	57	56	
	3	0	0	2	3	15	9	
	4	0	0	0	0	0	0	

6.1.3 Subject Disposition

The following table contains the subject disposition information from each of the pivotal studies.

Table 5. Subject disposition for the pivotal studies

Study	Screening Failures	Randomized	Received Treatment	Discontinued	Lost to follow-up	Excluded from analysis	Analyzed for efficacy
C-316	45	190	189	3	0	5	184
C-317	72	195	193	8	0	6	187
(b) (4)	30	251	245	15	3	27	218
C-312[1]	33	220	204	6	6	6	198
(b) (4)	5	146	136	54[2]	2	14	122

[1] These studies were identified by numbers that were contained in the protocol numbers:
(b) (4)
C-312: SIMPLE Hemorrhoidectomy 312
(b) (4)

[2] 45 subjects were discontinued for an "Administrative Reason."

The disposition of the subjects from screening through analysis for efficacy is unremarkable with the exception of the number of subjects discontinued (b) (4) (b) (4) This study less than three months after it began for "administrative reasons," not specified in the study report. The study report did state that it was not due to safety concerns.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint for each of the pivotal studies was the area under the curve (AUC) for the numeric rating scale (NRS) of pain intensity through various durations as indicated in Table 2. **Summary of pivotal trials for demonstrating the efficacy of Exparel** the endpoint was chosen as it reflects both magnitude and duration of effect for the treatments in relieving pain. This endpoint has been used as the primary endpoint in clinical trials of efficacy for other types of analgesics, and the Division concurred that this was an acceptable primary endpoint at the End-of-Phase 2 meeting which took place in 2006.

The design of the pivotal trials was appropriate for the indications sought and satisfied the regulations on well-controlled trials (21 CFR §314.126). The Applicant's efforts at minimizing the potential for bias were reasonable and appeared to be adequate; these included treatment randomization, protocol-specified methods for assuring the blinding of Investigators to the study drug administered, and protocol-specified statistical analysis plans.

Based on the study results for the primary endpoints, Exparel was demonstrated to be superior at providing post operative analgesia for two surgical procedures. The duration of that effect and the adequacy of dosing are discussed in Sections 6.9 and 6.8 below, respectively.

The table below presents the primary endpoints and outcomes for each of the pivotal studies.

Table 6. Pivotal study treatments, primary endpoints and outcomes

Study	Primary Endpoint	Treatment	Treatment Result [mean (SD)]	Outcome [win/loss] (p value)
(b) (4)				
C-312	AUC NRS pain intensity from 0-96[R] hours post-op	Exparel 300 mg	396 (213)	Loss (0.15)
		Bupivacaine HCl 150 mg	359 (194)	
(b) (4)				
C-316	AUC NRS pain intensity from 0-72[R] hours post-op	Exparel 300 mg	142 (101)	Win (<.0001)
		Normal saline	202 (104)	
C-317	AUC NRS pain intensity from 0-24[N] hours post-op	Exparel 120 mg	125 (48)	Win (0.001)
		Normal saline	146 (43)	

[A] Pain level with activity
[P] Pain level at rest
[N] Pain level at set time point regardless of activity level

6.1.5 Analysis of Secondary Endpoints(s)

In each of the pivotal studies, the Applicant included dozens of secondary endpoints (see the lists of these endpoints in the reviews of the individual studies in Section 9.4). These endpoints primarily assessed efficacy by comparing the AUC for pain scores at multiple time points, pain intensity scores at multiple time points, and the use of rescue analgesics (e.g., time to first rescue, total opioid usage during study period), Endpoints were also selected to assess the occurrence of adverse events related to opioid use (e.g., nausea, vomiting, constipation). The statistical analysis plan did not utilize a

hierarchical structure for analyzing these endpoints. Despite this shortcoming, only a few of the endpoints were reported by the Applicant to "significantly" differ between the treatment groups. (b) (4) those endpoints included:

- (b) (4)
- SIMPLE Hemorrhoidectomy 312 (with over 60 secondary endpoints)
  - adjusted mean NRS-R score at the 84 hour time point (p=0.04) [in favor of bupivacaine]
  - mean integrated NRS-R pain intensity scores and supplemental opioid pain medication consumption at the 84 hour time point (p=0.03) [in favor of bupivacaine]
- (b) (4)

It would not be appropriate to base a finding of efficacy on any of the secondary pain-related assessments in the two studies in which they favored Exparel. Aside from the statistical issues involved with the Applicant's analyses of these endpoints and the numbers of secondary endpoints that were evaluated in each of the studies, the findings were not consistent over time within the individual studies, (b) (4) Similarly, the integrated rank assessment using the NRS-A scores had favorable outcomes at 24 and 48 hours but not at 12, 36 and 60 hours.

For the placebo-controlled studies, the following secondary efficacy endpoints "significantly" differed between treatment groups, all favoring Exparel, as reported by the Applicant:

- SKY0402-C-317 [bunionectomy] (over 20 secondary endpoints)
  - mean pain intensity score [in the full analysis (FA) set]
    - before first use of rescue medication
    - at 2 hours
    - at 4 hours
  - percentage of subjects who were pain free [defined as an NRS of 0 or 1 (FA set)], at 2, 4, 8, and 48 hours
  - percentage of subjects who received no rescue pain medication through 8, 12, 16, 20, and 24 hours
  - total amount of postoperative Percocet use (FA set) at 24 hours
  - median time to first use of Percocet
- SKY0402-C-316 [hemorrhoidectomy] (over 20 endpoints)
  - median time to first opioid use (14 hours in the Exparel group versus 1 hour in the placebo group)
  - opioid use for through 72 hours (22 mg in the Exparel group compared to 29 mg in the placebo group)
  - percentage of subjects who required no opioids (opioid-free) up to 72 hours (28% for Exparel treated subjects versus 10% for placebo treated subjects

While the study results for the secondary endpoints in the placebo-controlled studies were supportive of the primary endpoint results, none would qualify for claims in the product labeling (b) (4) Furthermore, as was stated to the Applicant during the development program, claims related to opioid use (e.g., decreased opioid use with Exparel treatment) would need to be supported by demonstration of a clinically relevant benefit (e.g., reduced nausea, vomiting or constipation). (b) (4)

6.1.6 Other Endpoints

Exploratory endpoints were not included in the pivotal studies.

6.1.7 Subpopulations

Efficacy across subpopulations was performed by the Drs. Petullo and Price from the statistics review team. They conducted their assessment using data from the subjects who

were enrolled in the placebo-controlled pivotal trials and looked for differences in outcomes due to age, gender, race, and country where the study site was located.

For study C-316, all patients were classified as Caucasian so no analysis was performed for race. In this study, there was no significant treatment interaction for gender or age; however, there was a significant treatment interaction with country. The magnitude of the treatment effect in the Republic of Georgia was much larger than the treatment effect observed in Poland or Serbia. As there was a treatment effect observed in all countries and the study was not powered to detect treatment effects in individual countries, this finding was not considered to have a substantial impact on the efficacy findings.

For Study C-317, it was noted that there were more females enrolled than males, which is consistent with the patient populations presenting for bunionectomy. There were no significant interactions of treatment with any of the subgroups; however, it was noted that a treatment effect was not observed at the site in San Marcos, TX. As the Applicant did not provide an explanation, an exploratory analysis of baseline characteristics (age, gender, race, and baseline pain score) was performed by the statistics team, and no significant differences in this site from the other sites was found.

Lastly, in Study C-316, it was reported by the Applicant that nine patients had pain scores that were "completed with a hand of the investigator based on verbal interview with patients." As an exploratory analysis, these patients were removed from the primary analysis by the statistics team, and a significant treatment effect in favor of Exparel was still present.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Based on the pivotal studies, the Applicant has proposed (b) (4) doses of Exparel for clinical use:

(b) (4)

(b) (4)

For the two remaining dosing recommendations, there is a single study involving a single surgical procedure, which the Applicant relies upon for the evidence of dosing

efficacy. While the study findings were supportive of the dosing regimen, it is not clear how the findings can be extrapolated to incision lengths for other surgical procedures.

In the bunionectomy study, there was no stipulation as to the length of the surgical incision. Incision lengths are frequently longer than 3 cm for this procedure, yet that is the upper limit of incision size that this study is purported to support. Furthermore, the study drug was injected deep into the soft tissue around the osteotomy as well as the cut edges of the surgical wound, which confounds making a determination of the utility of this dose for other surgical procedures.

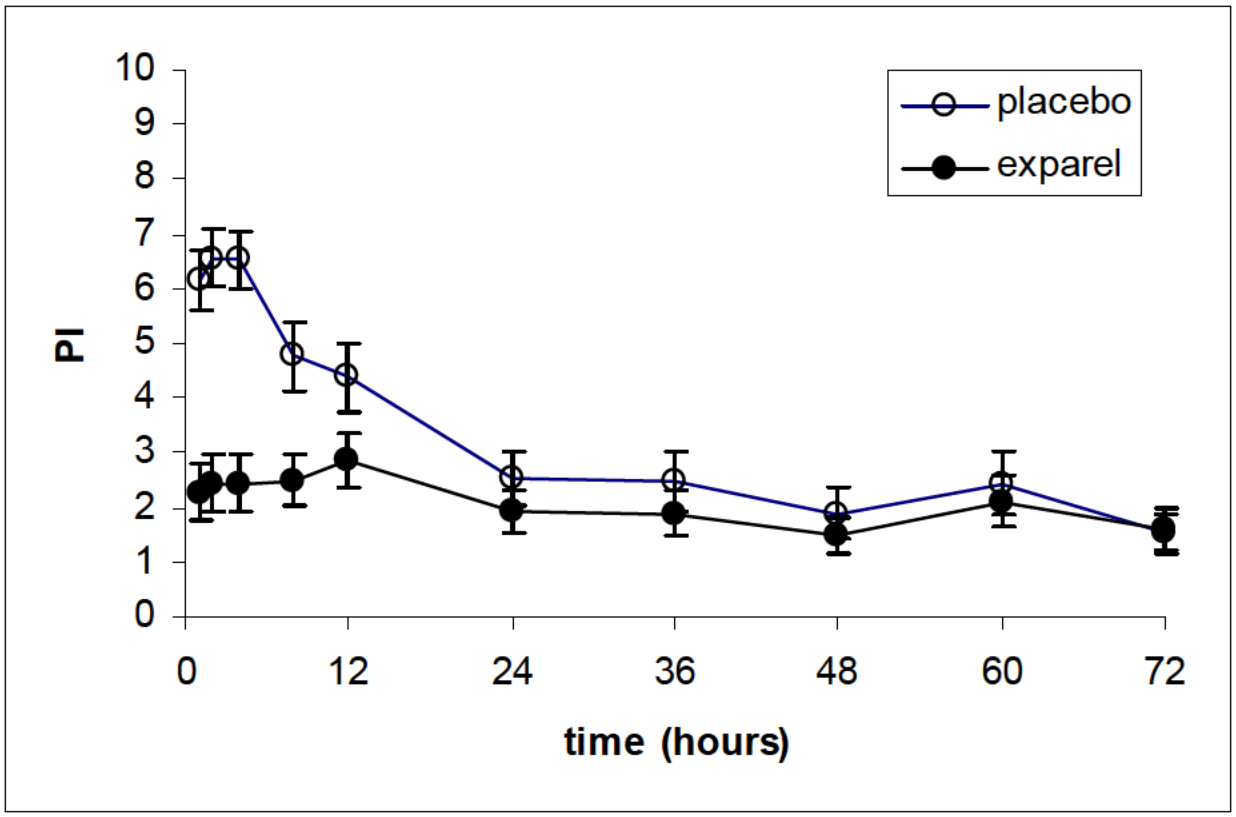
In the hemorrhoidectomy study, the entry criteria stipulated that the incision length had to be at least 3 cm and the protocol dictated that the Milligan-Morgan technique be used. However, this technique results in three triangular-shaped wounds that are left open to avoid abnormal narrowing of the anal canal as the wounds heal, and the protocol also dictated that 5 mL of the study drug should be infiltrated in six locations around the anal sphincter based on the even numbers of a clock face.

It is not clear how the results from either of these studies can be extrapolated to other surgical incisions either longer or shorter than 3 cm. However, the studies do support the use of Exparel for the surgical procedures evaluated using the techniques described in the protocols.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

It is important to note that the use of an AUC endpoint is helpful as it provides an assessment of both the magnitude and duration of the parameter assessed. However, the AUC value alone cannot represent the full clinical picture; examination of the plots of the raw data can provide a substantial insight into the meaning and relevance of the AUC finding. This is particularly true for the two placebo-controlled studies for Exparel. In the figures below, the mean pain intensity scores are plotted as a function of time. It was from these plots that the AUC values were determined.

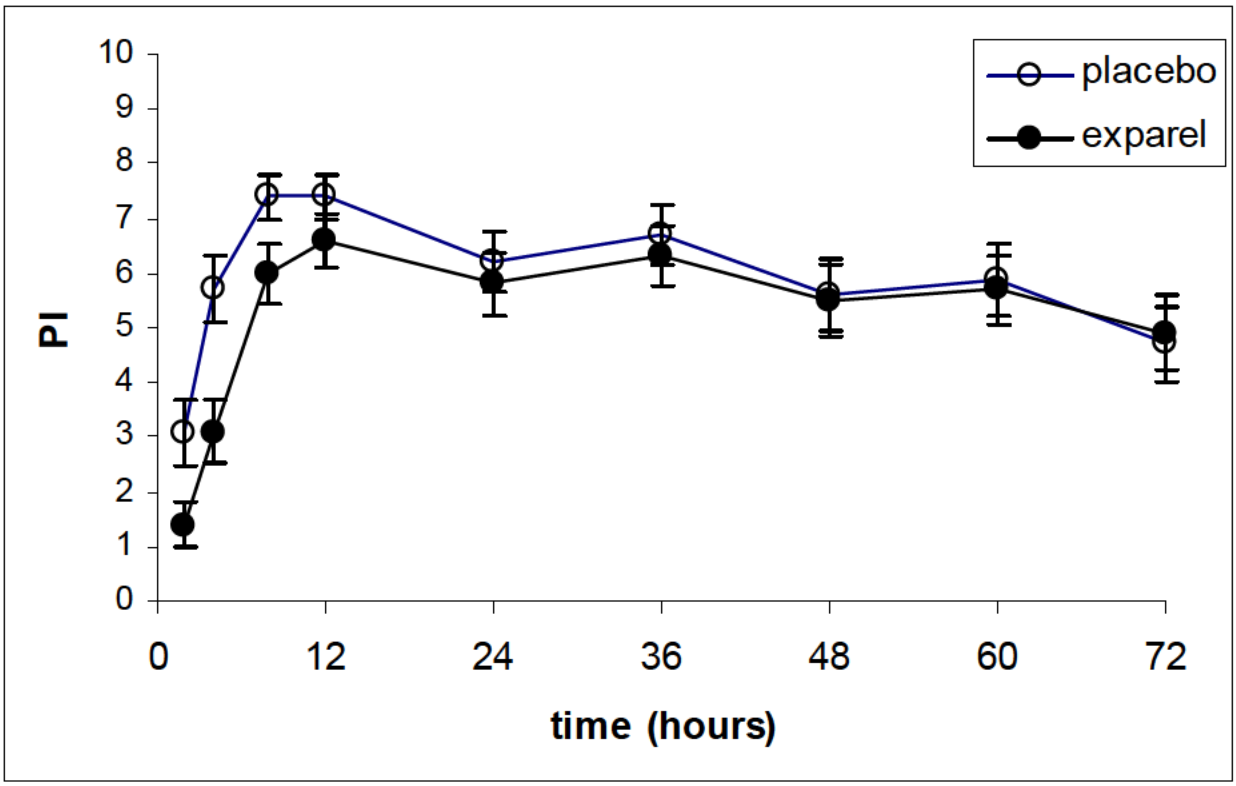
Figure 1. Mean Pain Intensity versus Time plot for hemorrhoidectomy study (C-316)



The plot for the hemorrhoidectomy study indicates that the difference between treatment groups occurs only during the first 24 hours following study drug administration. Between 24 and 72 hours, there is minimal to no difference between treatments; clearly there is no clinically relevant difference in the treatments for this time period. The plot makes it evident that the differences in AUCs for the two treatments over the 72-hour period is driven by the analgesic effects of Exparel during the first 24 hours following treatment, (b) (4)

The plot for the hemorrhoidectomy study, in the figure below, indicates that the efficacy of Exparel compared to placebo is superior only for the first 24 hours, which was the time period that the Applicant used for determining the AUCs. Had the AUCs been calculated out to 72 hours for this study, Exparel would likely still have significantly differed from placebo in a manner similar to that observed in the bunionectomy study.

Figure 2. Mean Pain Intensity versus Time plot for bunionectomy study (C-317)



In summary, the primary efficacy endpoints used in the pivotal studies were appropriate and support a finding of efficacy for Exparel (b) (4) Furthermore, the raw data used to calculate the primary endpoints for the placebo-controlled studies indicate that the analgesic effects of Exparel exceed those of placebo for up to 24 hours when administered following bunionectomy and hemorrhoidectomy procedures.

6.1.10 Additional Efficacy Issues/Analyses

There were no additional efficacy issues or analyses.

7 Review of Safety

Safety Summary

The safety of SKY0402 needs to be considered from two perspectives: toxicity related to systemic exposure and local toxicity. Each is considered separately below.

Systemic exposure includes not only bupivacaine absorbed from the tissues infiltrated with SKY0402 but also the absorption, and possible injection, of the bupivacaine-containing liposomes into the vasculature. Plasma bupivacaine levels were measured in several studies, and in a number of instances were found to be high enough that adverse events would be considered as likely to happen based on reports in the literature indicating severe toxicity occurring at levels of 1,000 mcg/L and higher. In the twelve studies where plasma bupivacaine levels were evaluated, there were 38 subjects who had bupivacaine levels > 750 mcg/L. These included a subject who was treated with placebo but had a plasma bupivacaine level measured at 867 mcg/L with no adverse events recorded. There were 25 subjects with bupivacaine levels measured at > 1,000 mcg/L, and 3 subjects with levels > 10,000 mcg/L recorded. These findings are further summarized in Section 7.3 below.
Not unexpectedly, higher doses of Exparel were associated with higher systemic exposures. The three highest plasma levels reported were 12,936 mcg/L, 34,331 mcg/L, and 42,662 mcg/L. In the review of the adverse events reported for these subjects, only one subject had an event suggestive of neurological or cardiac toxicity: mild lethargy. Review of the adverse events reported for the all of these subjects indicated that neurological or cardiac adverse events occurred only in subjects dosed with 450 mg (n=2) or 600 mg (n=12) of Exparel. All but three of the 22 adverse events for this group of subjects were reported as mild; two (confusion and hallucinations) were reported as moderate; and one (over sedation) was reported as severe and was associated with narcotic use in addition to Exparel. These adverse events are described and discussed in Section 7.3 below. It should be noted that none of the adverse events more commonly associated with the early stages of local anesthetic induced neurotoxicity (e.g., tinnitus, perioral numbness, metallic taste sensation) were reported by any subjects treated with Exparel.

While laboratory error may account for an occasional high value, the number seen in these studies suggest the possibility of another phenomenon, e.g. Exparel in the systemic circulation releasing its bupivacaine during sample preparation for the analysis. Regardless of the cause, the elevated plasma levels of bupivacaine were not associated with any adverse events that posed a substantial risk to patients.

In addition to the clinical experience described above, there were animal studies conducted which evaluated safety when the DepoFoam excipient or the final drug product, Exparel, were injected intravenously. As indicated in the Pharmacology-

Toxicology team's review, described below in Section 7.2.3, there is animal support for the safety of an inadvertent injection of up to 60 mg of Exparel in humans, which would represent a worse case scenario.

Local toxicity includes consideration of the effects of Exparel on the tissues into which it is injected, the wound healing process, (b) (4)

Wound healing was evaluated postoperatively in seven studies including both placebo-controlled pivotal studies (b) (4) study. In these studies, blinded care provider's satisfaction was assessed using a 0 to 10 numeric rating scale where 0 = completely unsatisfied with wound healing and 10 = completely satisfied with wound healing. The assessments were made at Day 8 or Day 10, and at Day 30 or Day 36 following treatment, depending on the study. At the Day 8/10 assessments, the blinded care provider's mean overall satisfaction with wound healing was 9 for all doses of Exparel, and 9 for the bupivacaine HCl group. There were no wound healing assessments made for placebo treated subjects at this time point. The blinded care provider's mean overall satisfaction with wound healing at the time of the Day 30/36 assessments was 8 for all the Exparel treated subjects. However, it was 7 for the subjects treated with ≤ 300 mg of Exparel and 9 for those treated with > 300 mg of Exparel. For bupivacaine treated subjects the mean score was 9, and for the placebo groups, the mean score was 5.

Wound status, i.e., erythema, edema, induration and drainage, were assessed on the same postoperative days as wound healing, but these assessments were made in a different set of studies. (b) (4) At the Day 8/10 assessment, most subjects in the Exparel dose groups and the bupivacaine HCl dose groups exhibited no erythema (39% to 53%) or very slight erythema (20% to 32%); no drainage (59% to 87%); no edema (26% to 39%) or very slight edema (28% to 37%); and no induration (32% to 59%) or minimal induration (23% to 27%).

Wound status was not assessed in the placebo group at the Day 8/10 time point. At the Day 30/36 assessment, most subjects in all treatment groups (Exparel, bupivacaine, and placebo) exhibited no erythema (57% to 63%) or very slight erythema (14% to 32%); no drainage (80% to 94%); no edema (35% to 54%) or very slight edema (17% to 44%); no induration (47% to 64%) or minimal induration (13% to 42%). There were no instances of "severe" assessments in any of these parameters for Exparel-treated subjects. There was a slightly higher incidence in the placebo group of very slight erythema, serous drainage, very slight and slight edema, and minimal to mild induration compared to the Exparel and bupivacaine treatment groups.

The overall level of satisfaction with wound healing, wound status, and wound scarring was similar between the Exparel and bupivacaine HCl groups

Exparel potential effects on orthopedic wound healing were examined by follow-up assessments of the subjects in study SKY0402-C-317 (bunionectomy). At the 4-6 week postoperative visit, follow-up radiographs and office notes were collected for 82% of the subjects. At that time, it was expected that evidence of improperly healing osteotomy leading to malunion or non-union would be manifest. No abnormal findings were noted in the subjects who received Exparel. This study suggests that Exparel does not have a toxic effect on tissues deeper than the cutaneous and subcutaneous layers of skin.

(b) (4)

In summary, the safety profile of Exparel does not appear to differ in a clinically significant way from bupivacaine. For the doses studied as part of the clinical development program, there is no evidence that Exparel produces tissue toxicity in the short or long term, that it adversely affects wound healing (b) (4), or that it is anymore likely than bupivacaine to cause neurological or cardiac toxicity with systemic absorption or inadvertent injection.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety database was derived from the 22 clinical studies conducted by the Applicant and listed in Table 1. **Summary of clinical studies (based on Table 5.2 in the Clinical Study Reports section of the NDA)** located in section 5. These consisted of eight controlled Phase 1 trials, which included two QTc and one hepatic impairment studies; seven controlled Phase 2 trials; five controlled Phase 3 trials and a single Phase 3 observational study.

All studies conducted with Exparel were by single dose administration. A total of 1307 subjects received a dose of Exparel. Doses administered ranged from 10 mg to 750 mg. All subjects who received a dose of study drug were included in the disposition tables for each study pool.

7.1.2 Categorization of Adverse Events

For the ISS, all adverse events (AEs) were coded by the Applicant using the Medical Dictionary for Regulatory Activities (MedDRA) version 12.1. Only treatment-emergent AEs (TEAEs), defined as an AE with an onset date and time on or after the start of study drug administration were included in the summaries. Treatment-emergent AEs were analyzed by the Applicant according to overall incidence, severity, relationship to study drug, classification as a serious adverse event (SAE), and related SAEs for each of the five study sets. Adverse events were also analyzed on the bases of age, gender, ethnicity, race, and ASA class for each of the sets.

The tabulations of AEs by severity included the categories 'severe,' 'moderate,' and 'mild.' Adverse events with missing severity had severity set to 'severe' by the Applicant. In the tabulations of AEs by relationship to study drug, "related" AEs were defined as those that had a relationship of 'possibly,' 'probably/related,' 'definitely,' 'related,' and 'Yes.' AEs with missing causal relationship were categorized as related by the Applicant.

The Applicant's categorization of neurological and cardiac adverse events were assessed by this reviewer by random comparisons of the verbatim terms to the preferred terms used by investigators and subjects, focusing on the events leading to dropouts or other changes in treatment.

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

In assembling their integrated safety database, the Applicant included any subject who received any portion of study drug. They reported that the pooled database was constructed from the CDISC SDTM migrated data for each study and put into their analysis dataset model. Migration to SDTM data before pooling was done to ensure that the data variable names, labels, and formats were consistent across the studies being pooled.

The Applicant noted that there were two subjects in Study SKY0402-C-316 and two in Study SKY0402-C-317 whose treatment could not be confirmed. Therefore, they elected to analyze these subjects based on the treatment group to which they were randomized. The Applicant also noted that in some of the other studies, there were subjects whose treatment was confirmed as different from that to which they were randomized. These subjects were analyzed based on the treatment they actually received.

The Applicant divided the safety dataset into five sets based on the use of their product within the study. These sets included the following:

1. All Wound Infiltration Studies (Phase 2 and 3 wound infiltration studies)
2. (b) (4)
4. Phase 1 Studies
5. All Studies (all Phase 1, 2, and 3 studies)

Throughout their Integrated Summary of Safety (ISS) and their Summary of Clinical Safety (SCS), the Applicant placed their emphasis on the All Wound Infiltration Studies data, as these were most relevant to the target population for the proposed indication. In addition to the All Wound Infiltration Studies pool, data from the All Studies pool were presented in the SCS. Safety data for the (b) (4) pool, and the Phase 1 Studies pool were provided in the ISS.

In the All Wound Infiltration Studies pool, the Applicant noted that a total of 823 subjects received SKY0402, which exceeded the minimum of 500 subjects requested by the. They also noted that there were 171 subjects ≥65 years of age and 135 subjects classified as ASA PS 3 or 4, which met the specifications of the Agency for at least 125 subjects for each of these groups.

The doses of SKY0402 ranged from 10 mg to 750 mg in the clinical studies; however, in the Phase 2 and Phase 3 studies, the highest dose of SKY0402 administered was 600 mg, (b) (4)

7.2 Adequacy of Safety Assessments

The timing and types of safety assessments made by the Applicant during the clinical development program were adequate to capture the potential toxicities related to the use of local anesthetics and liposomes both in the short and long term following administration of the drug product. The use of bupivacaine as an active comparator in several of the pivotal trials as well as some of the earlier studies

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exparel is intended as a single application product. Therefore, the relevant parameters for the safety assessments include dosing and demographics. The Applicant studied an adequate range of doses to cover the indications it is seeking, and has captured safety data for higher doses as well. The subject demographics sufficiently reflect the populations that will likely be treated with Exparel in the clinical setting. As this is a

locally infiltrated product, there are no demographics that would likely require special consideration.

7.2.2 Explorations for Dose Response

The Applicant conducted multiple dose exploration studies prior to selecting the doses used in the pivotal studies. (b) (4)

7.2.3 Special Animal and/or In Vitro Testing

Animal studies were conducted to support the doses and routes of administration for Exparel that were to be utilized in the clinical development program. Among these, there were animal studies conducted which evaluated safety when the DepoFoam excipient or the final drug product, Exparel, were injected intravenously. These were particularly important in assessing the potential risk for inadvertent intravascular injection. Regarding these studies, the Pharmacology-Toxicology team's review states:

> Intravenous SKY0402 (7.5 mg/kg) was not toxic at lethal doses of bupivacaine HCl (2.5 mg/kg) when injected into rats. However, the dose of SKY0402 tested (0.5 mL/kg and 1.2 mg/kg HED) was not high enough to be able to conduct a nonclinical-based human safety assessment for all the proposed clinical doses assuming inadvertent human intravenous injection is 100% of the total dose. However, this occurrence is not likely. Assuming inadvertent intravenous injection of 10% of the highest proposed human dose (b) (4) all proposed human doses would be supported for inadvertent intravenous dosing.
>
> Intravenous administration of SKY0402 Placebo resulted in clinical signs in one study and lethality in another at the dose volume of 1 mL/kg using the same batch of SKY0402 placebo. That would be 1 death in 28 rats and clinical signs in 3 of 28 including the one that died at a dose volume comparable to that of the highest proposed human dose of SKY0402. At a 10% inadvertent intravenous injection in the clinic, the inadvertent intravenous clinical dose would be equal to the NOAEL in the two nonclinical studies just mentioned (b) (4) SKY0402 Placebo).

7.2.4 Routine Clinical Testing

Appropriate routine clinical testing was performed throughout the clinical development program. The findings of these evaluations indicated no areas of special safety concerns.

7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolism, clearance and interaction of Exparel are not expected to differ from that of DepoFoam or bupivacaine HCl. The clinical studies provided no evidence that such a difference exists.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The two types of toxicities of major concern related to the use of local anesthetics are neurological and cardiac; both of which result from elevated systemic exposures due to either inadvertent intravascular administration or absorption of the drug product. The 0.5% Marcaine label states the following:

> Local anesthetics should also be used with caution in patients with hypotension or heart block. Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be performed after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.
>
> Because amide-local anesthetics such as MARCAINE are metabolized by the liver, these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations. Local anesthetics should also be used with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by these drugs.
>
> Injection of repeated doses of local anesthetics may cause significant increases in plasma levels with each repeated dose due to slow accumulation of the drug or its metabolites, or to slow metabolic

degradation. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with their age and physical status.

7.3 Major Safety Results

The table below provides a summary of the doses of Exparel and comparators evaluated in the studies that constitute the safety database. The table also includes the reasons for the subects' early termination from the study.

Table 7. Summary of study drug doses and subject dispositions for the safety database

Study Drug	**SKY0402**																				**Bupiv. HCl**	**Pla-cebo**
Dose (mg)	10	15	45	50	75	100	105	120	125	150	175	180	225	300	345	350	450	600	750	All		
Safety Population [1]	9	161	129	6	31	8	25	97	7	55	38	24	49	381	25	28	73	229	16	1307	622	239
Subjects Who Terminated Early [n (%)]	0 (0)	5 (3)	4 (3)	0 (0)	2 (7)	0 (0)	1 (4)	4 (4)	1 (14)	1 (2)	0 (0)	2 (8)	0 (0)	5 (1)	1 (4)	0 (00)	0 (0)	34 (15)	0 (0)	60 (5)	54 (9)	7 (3)
Death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)
Adverse Event [2]	0 (0)	4 (3)	3 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	8 (1)	3 (1)	1 (0)
Lost to Follow-up	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	2 (1)	0 (0)	5 (4)	13 (2)	0 (0)
Withdrawal by Subject	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	5 (1)	0 (0)	0 (0)	0 (0)	3 (1)	0 (0)	12 (19)	8 (1)	6 (3)
Other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	3 (3)	1 (14)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	26 (11)	0 (0)	32 (2)	27 (4)	0 (0)
Not Reported	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	3 (0)	2 (0)	0 (0)

7.3.1 Deaths

Two deaths were reported during the clinical development program. These included subject 208-032-7002, who was treated with 600 mg of SKY0402 and subject 208-005-3030 who was treated with a 150 mg dose of bupivacaine HCl.

Subject 208-032-7002
Subject 208-032-7002 was a 69 year old Caucasian female who presented on (b) (6) (b) (6), for total knee arthroplasty (TKA). She had a past medical history significant for hypertension, bipolar depression, hypothyroidism, osteoporosis, osteoarthritis, status-post two cerebral vascular accidents, obesity and a rash. Her medications at the time of entry into the study were lisinopril, amlodipine, ziprasidone, divalproex sodium, benzotropine, levothyroxine, ibandronate sodium, Vitamin D, propoxyphene, acetaminophen, and clobetasol cream.

The subject received a 600-mg dose of SKY0402 via wound infiltration at the end of her surgical procedure. In the post-anesthesia care unit, the subject received 16 mg of morphine and was reported to have used her morphine PCA. She became "unresponsive," but when treated with naloxone and 3 L/m oxygen, she became responsive.

Two days after her surgery, the subject was reported to have "altered mental status" that was classified as an SAE as it was considered immediately life-threatening. At that time she was discontinued from the study by the Investigator. The CRF states that "due to the subject's altered mental status, the subject can not continue to give adequate consent, therefore all further study procedure will be discontinues. This is due to a pre-existing condition in which was stable at screening." The CRF also notes that, on Day 4 postdose, her mentation cleared, and she was alert and oriented to time, place, and person.

Three days following surgery and study drug administration, the subject was found to be anemic, hematocrit was reported at 20%, which was attributed to intraoperative blood loss. Two units of packed red blood cells were administered and the hematocrit was noted to have increased to 25%.

The subject's remaining hospital course was complicated by urinary retention that was treated with insertion of a Foley catheter. The narrative states that "urological studies (not specified) were evaluated" and that the subject was eventually "weaned from her Foley when her cognition improved." At an unspecified time thereafter, the subject developed bladder and bowel distention. A CT scan was done, which indicated "some genitourinary problems as well as a mild ileus." After having a bowel movement, the subject was prepared for discharge. On September 29, 2008, the study site was notified by the subject's surgeon that she had died on (b) (6) An autopsy

conducted at the time concluded that the cause of death was "complications of marked haemorrhagic cystitis." The Investigator assessed the cause of death as not related to study treatment; the Applicant concurred with the assessment.

After reviewing the CRF and narrative for this subject, I concur with the Applicant that the cause of death was not related to study treatment.

Subject 208-005-3030
Subject 208-005-3030 was a 71-year old Caucasian female subject who died on postdose Day 4. Her medical history included degenerative joint disease, hypertension, hyperlipidemia, edema, left total knee replacement four months earlier, hysterectomy, sleep apnea managed with CPAP, anxiety, obesity, and fractures of the leg and thumb. The subject received 150 mg bupivacaine HCl via wound infiltration during TKA surgery on (b) (6) Her initial course was uneventful, and she was weaned from morphine PCA on (b) (6) The next morning, while ambulating in the hall, the subject became dizzy, lost consciousness, and fell back striking her head. Initially she was semi-conscious, hypotensive, and had low oxygen saturation. She was transferred to the Intensive Care Unit where she rapidly deteriorated and required cardiopulmonary resuscitation for several minutes. A pulmonary angiogram was performed, which confirmed the diagnosis of bilateral pulmonary emboli. The subject received thrombolytic therapy with tissue plasminogen activator (TPA) at the time of resuscitation from the initial arrest in the ICU.

The subject's course continued to decline over the next several days with hypotension, bradycardia, pulseless electrical activity requiring resuscitation, status epilepticus requiring induction of a coma with propofol and subsequent anoxic encephalopathy. Interventions were limited at the request of the subject's family to comfort care. The subject died on post-dose Day 4.

The Investigator assessed the cause of death as unlikely related to study treatment. The Applicant's assessment was that the event was not related to study treatment.

After reviewing the CRF and narrative for this subject, I concur with the Applicant that the cause of death was not related to study treatment.

7.3.2 Nonfatal Serious Adverse Events

There were 51 serious adverse events (SAEs) across all studies. Of these, 25 occurred in subjects treated with Exparel, 24 occurred in subjects treated with bupivacaine HCl, and 2 occurred in subjects treated with placebo.

With one exception, the Investigators and Applicant concurred that all of the SAEs for Exparel-treated subjects were unrelated to study drug. After reviewing the CRF and narrative for these subjects, I concur with the Applicant and Investigators that the SAEs were not related to study treatment. The SAE where the Investigator and Applicant differed is summarized below:

The subject (Subject 105-001-0030) was a 29-year-old White (not Hispanic or Latino) female healthy subject, who experienced an SAE of acute hepatitis. She had no relevant medical history. There were no abnormalities found on the screening physical exam and the drug screen was negative. The subject was a non-smoker. Relevant concomitant medications included ibuprofen for headache and an antihistamine for hay fever.

The subject received 450 mg SKY0402 via subcutaneous injection on Day 1 as part of a thorough QT study. On Day 48 postdose, the subject was found to have acute hepatitis. The follow-up laboratory tests performed on Day 73 postdose showed a slight increase in aminotransferases: AST 40 IU/L (normal 0-31 IU/L) and ALT 38 IU/L (normal 10-35 IU/L). The other biochemistry parameters were within their normal ranges including bilirubin, alkaline phosphatase, GGT, and CK.

The subject was recalled on Day 76 postdose, for a repeat biochemistry test. At this time, she did not report any adverse events; however, the results of biochemistry tests showed that she had worsening liver function tests indicating possible acute hepatitis:

- Bilirubin 71 µmol/L (normal 0-20 µmol/L)
- Indirect Bilirubin 17 µmol/L (normal <15 µmol/L)
- Direct Bilirubin 54 µmol/L (normal 0-5 µmol/L)
- ALP 245 IU/L (normal 35-104 IU/L)
- AST 405 IU/L (normal 0-31 IU/L)
- ALT 981 IU/L (normal 10-35 IU/L)
- GGT 239 IU/L (normal 9-35 IU/L)
- Fasting glucose 6.9 mmol/L (normal 3.9-5.8 mmol/L)

Additional extensive testing was done while supportive therapy was provided. No cause for the hepatitis was identified. By Day 81 postdose, the subject's physical examination and laboratory assessments were all within normal limits, and the SAE was considered fully resolved.

The Investigator consulted a toxicologist, who believed it was unlikely that Exparel or DepoFoam was responsible for causing the hepatitis.

On review of the CRF and the narrative, I do not think it is possible to rule out Exparel as the cause of the hepatitis based on the information available; however, I would consider it possibly related rather than probably related.

In the bupivacaine HCl group, 24 subjects experienced one or more SAEs. Seven of the SAEs (scar, hypoglycemia, hemarthrosis, joint swelling, arthrofibrosis [n=2 subjects], and knee arthroplasty) were assessed by an Investigator as related to study drug. After reviewing the related documents, I concur with the Investigators.

In the placebo group, two subjects experienced an SAE. Both SAEs were assessed by the Investigator as not related to study drug. I concur with their conclusions.

7.3.3 Dropouts and/or Discontinuations

Among subjects who received any study drug, there were 13 subjects who withdrew from a study due to an adverse event. Eight of the subjects were enrolled in a Phase 1 study; two subjects were enrolled in a Phase 2 study; and three subjects were enrolled in a Phase 3 study. In addition to these, there was one subject who was withdrawn from a study due to a pretreatment adverse event.

Three of the 13 subjects had received both Exparel and bupivacaine HCl, four subjects had received Exparel alone (with or without saline control), four subjects had received bupivacaine HCl alone (with or without saline control), and one subject had received placebo.

Review of the documentation provided for each of the subjects who withdrew failed to indicate a clinically relevant safety issue related to the use of Exparel.

7.3.4 Significant Adverse Events

Table 8. Elevated plasma bupivacaine levels reported in the clinical trials

Exparel Dose	Plasma Bupivacaine Concentration (mcg/L)			
	750-999 n	1,000-1,999 n	2,000-9,999 n	> 10,000 n
150		1	1	
300	6	8	1	
350	1			
450	1			2
600	4	11		1
Total	12	20	2	3

Table 9. Cardiac and neurological adverse events associated with systemic bupivacaine levels ≥ 750 mcg/L

Treatment Emergent Adverse Events		**Exparel Dose**		
System	**MedDRA Code**	**450 mg [N=26] n (%)**	(b) (4)	**Total [N=239]**
Neurological	Anxiety	1 (4)		1 (<1)
	Confusion or Hallucination			3 (1)
	Dizziness			3 (1)
	Lethargy, Sedation or Fatigue			4 (2)
	Headache	1 (4)		1 (<1)
Cardiac	Bradycardia			2 (1)
	Tachycardia			7 (3)
	Ventricular Tachycardia			1 (<1)

7.3.5 Submission Specific Primary Safety Concerns

The special safety concerns related to neurological and cardiac toxicity are described above in the Summary of Safety.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The common adverse events associated with Exparel were similar in nature and frequency to those associated with bupivacaine.

7.4.2 Laboratory Findings

No laboratory finding indicated a special concern for the safety of Exparel.

7.4.3 Vital Signs

None of the vital sign assessments of subjects receiving Exparel indicated a special concern for safety.

7.4.4 Electrocardiograms (ECGs)

None of the ECG assessments of subjects receiving Exparel indicated a special concern for safety.

7.4.5 Special Safety Studies/Clinical Trials

Two studies were conducted to assess the effect of Exparel on QT prolongation. These studies were reviewed by the Interdisciplinary Review Team for QT Studies. They concluded that no apparent QT prolongation effect of Exparel for 300 mg, 450 mg, 600 mg and 750 mg was detected in the two thorough QT studies (Study SKY0402-C-105 and Study SKY0402-C-107). Bupivacaine appeared to be associated with concentration-dependent QTc interval shortening, and a similar negative concentration-QT relationship was observed for all tested dose groups across two QT studies. The review team also noted the following:

> Conclusions on the QT prolongation effect of SKY0402 up to 750 mg based on Study SKY0402-C-105 and Study SKY0402-C-107 are drawn without assay sensitivity being demonstrated in either of the two QT studies. 1.) Study SKY0402-C-107 did not include a positive control arm (e.g., 400 mg moxifloxacin) to demonstrate assay sensitivity. 2.) Assay sensitivity was not established in the second stage of Study SKY0402-C-105, where the QT effect of SKY0402 was assessed. Even though assay sensitivity in the first stage of Study SKY0402-C-105 was established, as evident by the 24-hour moxifloxacin ECG profile (Figure 4) and the largest lower bound of the two-sided 90% CI of $\Delta\Delta$QTcI greater that 5 ms, using the first stage assay sensitivity to claim assay sensitivity in the second stage is not valid. The conclusions on “no apparent QT

prolongation effect" are drawn mainly because SKY0402 shortens QT interval in a concentration-dependent manner. To establish assay sensitivity using 400 mg moxifloxacin is only important to quantify small increases in QT interval. Because QT prolongation is not anticipated for drugs shorten QT interval, to demonstrate assay sensitivity is not critical in the QT studies.

7.4.6 Immunogenicity

There were no immunogenicity issues related to the use of Exparel.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

(b) (4)

For the pooled analyses, there were fewer TEAEs reported for Exparel doses ≤ 300 mg compared with the >300-750 mg group. It should be noted that the incidence of TEAEs in the bupivacaine HCl group falls between these combined dose groups.

When the Exparel All Doses group is compared to the bupivacaine HCl group, the TEAE rates are similar. (b) (4)

A noteworthy difference is that some of the TEAEs potentially associated with neurotoxicity occurred with greater frequency for Exparel then bupivacaine. These included anxiety (5% versus 1%), confusional state (2% versus 1%), lethargy (3% versus 0%), and dizziness (8% versus 5%). There was no such difference for cardiac TEAEs.

7.5.2 Time Dependency for Adverse Events

The time dependency of TEAEs for Exparel should be considered from three perspectives based on when they occur:

1. Immediately following injection

2. When systemic exposure reaches C_{max}
3. Long enough after the surgical procedure that the healing process would be expected to be complete

The TEAEs related to the first perspective would include neurological and cardiac toxicity related to intravascular injection of the drug product and anaphylactic reactions. Neither was observed in the clinical trials. The TEAEs of concern occurring at T_{max} would be the same as those related to intravascular injection, i.e., neurological and cardiac toxicity. Such adverse events were not reported for the clinical studies. In addition, TEAEs related to Exparel did not appear substantially different than those for bupivacaine for both of these time periods.

TEAEs of concern that occur during the healing process include reactions at the incision site (e.g., infection, dehiscence, irritation, inflammation and edema), delayed healing due to interactions between the drug product and deeper tissues (e.g., delayed or incomplete healing at the osteotomy site for the bunionectomy) as well as reactions between the drug product (b) (4) In these regards, there was no clinically significant difference between Exparel and bupivacaine.

7.5.3 Drug-Demographic Interactions

The safety of Exparel did not appear to grossly differ from bupivacaine among subjects based their age, gender, and race. It should be noted that >90% of subjects were less than 60 years of age, > 85% were Caucasian; and > 80% were classified as ASA-PS 1 and 2.

7.5.4 Drug-Disease Interactions

Exparel is administered to provide local analgesia. It is not intended to treat any disease condition. Exparel is not indicated for infiltration related to the excision of superficial skin lesions, e.g., skin cancers. It is not know what effect, if any, it would have on these diseases.

7.5.5 Drug-Drug Interactions

No clinical drug-drug interaction studies were conducted for this NDA. The Applicant intends to incorporate the bupivacaine-drug interactions noted in

the Marcaine label into the Exparel label. In addition to those interactions, there is a known lidocaine-DepoFoam interaction that will also be included in the product labeling. This interaction was noted in a mini-pig model that demonstrated increased systemic exposure to bupivacaine when local administration of lidocaine with epinephrine was followed within 5 or 10 minutes by a dose of Exparel. The exposure was affected by the doses of the two drugs as well as the time interval separating their administration. Bupivacaine exposure was substantially reduced when doses were separated by 20 or 40 minutes. The Applicant concluded from the study that the potential risk of a clinically relevant interaction can be minimized by allowing 20 minutes to elapse between infiltration of lidocaine and administration of Exparel. This interaction is described in the DepoDur label.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Exparel is intended as an acute use product; therefore, evaluation of its carcinogenicity potential was not required and is not necessary to fully assess the product's safety.

7.6.2 Human Reproduction and Pregnancy Data

Exparel was not evaluated for use in pregnant subjects. Its use in this population should not be recommended, and it should be labeled the same as bupivacaine HCl in this regard.

7.6.3 Pediatrics and Assessment of Effects on Growth

Exparel has not been administered to pediatric subjects. The Applicant has requested that a pediatric program be deferred until the product has been approved for use in adults. At that time, the Applicant will initiate its pediatric development program conducting clinical studies in older children, 12 (b) (4) years of age, first and then evaluating Exparel in children 6-11 years of age followed by studies in children 2-5 years of age. (b) (4)

It is appropriate that the pediatric program be deferred at this time. Evaluating Exparel in pediatric patients in an age-wise progression from older to younger is also appropriate. (b) (4) Bupivacaine is currently used in this age group, and Exparel may be suitable for these patients as well. If studies in older children indicate that Exparel poses no greater risk than bupivacaine, and Exparel is found to be efficacious in older patients, studies in the youngest group of patients should be conducted.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The potential for overdose with Exparel exists if the drug is injected intravascularly. As indicated in sections above, small doses injected intravenously are not likely to result in harm. Labeling the product to require frequent aspiration with the syringe as the product is being administered will help to reduce that risk. Bupivacaine, the active ingredient of Exparel, is not associated with any abuse; therefore, the risk with Exparel is expected to be equally as low. Exparel is intended for single dose application; therefore, withdrawal and rebound are not issues of concern.

7.7 Additional Submissions / Safety Issues

There were not addition safety issues.

8 Postmarket Experience

Exparel is not currently marketed in the United States or elsewhere in the world.

9 Appendices

9.1 Literature Review/References

The Applicant did not submit a comprehensive literature review as part of this NDA. Such a review was not requested or required by the Division.

9.2 Labeling Recommendations

The following changes to the proposed labeling are recommended based on the findings in this review:

1. Indications should be modified to postoperative analgesia following hemorrhoidectomy or bunionectomy.
2. Dosing and Administration should be modified to reflect the methods and doses of Exparel that were used in the two placebo-controlled pivotal studies.
3. Warnings and Precautions should be limited to those apropos the use of a local anesthetic for infiltration into surgical wounds. (b) (4)
4. Warnings and Precautions should be modified to clearly reflect that Exparel is not recommended for administration by any method other than local infiltration and for any other surgical procedures other than hemorrhoidectomy and bunionectomy.

9.3 Advisory Committee Meeting

An Advisory Committee was not convened to review data or provide input regarding any issue related to this application.

9.4 Reviews of Individual Clinical Studies

9.4.1 SKY0402-C-316

A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Local Administration of SKY0402 for Prolonged Postoperative Analgesia in Subjects Undergoing Hemorrhoidectomy

Objectives

Primary Objective

To evaluate the magnitude and duration of the effect of a single intraoperative administration of 300 mg SKY0402 compared with placebo (0.9% sodium chloride for injection) in the reduction of postoperative pain.

Secondary Objectives

1. To evaluate additional efficacy parameters
2. To characterize the safety profile of SKY0402 in comparison with placebo
3. To assess the pharmacokinetics of clearance of bupivacaine from the blood plasma.

Study Design

This was a Phase 3, multicenter, placebo-controlled, randomized, double-blinded, study designed to evaluate the efficacy and safety of 300 mg SKY0402 compared to placebo (normal saline) administered by local infiltration for postoperative analgesia in subjects undergoing hemorrhoidectomy under general anesthesia.

Study Population

Subjects were enrolled from the population of patients presenting for hemorrhoidectomy that was to be performed under general anesthesia who met the criteria listed below, copied from the final study report.

Inclusion Criteria

1. ≥18 years of age at the Screening Visit.
2. American Society of Anesthesiology (ASA) Physical Class 1-3.
3. Scheduled to undergo 2- or 3-column excisional hemorrhoidectomy for internal or internal/external hemorrhoids, under general anesthesia using the Milligan-Morgan technique, including modified approaches with specialized instruments, such as LigaSure™ or harmonic scalpel, with a cumulative incision length of a minimum 3 cm.
4. Applies to female subjects only: Postmenopausal, surgically sterile, or willing to use acceptable means of contraception for at least 30 days after surgery including any of the following: hormonal contraceptives (e.g., oral, injectable, implantable starting at least 30 days before study drug administration), effective double-barrier methods (e.g., condoms with spermicide), intrauterine device, lifestyle with a personal choice of abstinence, nonheterosexual lifestyle, or a strictly monogamous relationship with a partner who has had a vasectomy.
5. Clinical laboratory values less than twice the upper limit of normal or, if abnormal, deemed not clinically significant per the Investigator.
6. Ability to provide informed consent, adhere to the study visit schedule and complete all study assessments and language specific questionnaires.

Exclusion Criteria

1. Currently pregnant, nursing, or planning to become pregnant during the study or within one month after study drug administration.
2. Use of any of the following medications within the times specified before surgery:
    a. NSAID including selective COX-2 inhibitor, opioid, SSRI, tricyclic antidepressant, gabapentin, pregabalin within three days of surgery.
    b. Use of acetaminophen/paracetamol within 24 hours of surgery.
3. Concurrent painful physical condition or concurrent surgery that may require analgesic treatment (such as NSAID, opioid, SSRI, tricyclic antidepressant, gabapentin, pregabalin) in the postoperative period for pain that is not strictly related to the hemorrhoidectomy procedure and may confound the postoperative assessments (e.g., rheumatoid arthritis, chronic neuropathic pain, concomitant vasectomy, fissurectomy).

4. Chronic user of analgesic medications, including taking opioid medications for more than 14 days in the last 3 months, or non-opioid pain medications more than 5 times per week.
5. Current use of systemic glucocorticosteroids (e.g. Decadron) or use of glucocorticoids within one month of enrollment into this study.
6. History of hepatitis (other than hepatitis A).
7. History of, suspected, or known addiction to or abuse of illicit drug(s), prescription medicine(s), or alcohol within the past 2 years.
8. Failure of presurgical drug and alcohol screen.
9. Body weight less than 50 kilograms (110 pounds).
10. History of hypersensitivity or idiosyncratic reactions to amide-type local anesthetics, opioids, or propofol.
11. Administration of an investigational drug within 30 days prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study.
12. Previous participation in an SKY0402 study.
13. Uncontrolled anxiety, schizophrenia, or other psychiatric disorder that, in the opinion of the Investigator, may interfere with study assessments or compliance.
14. Significant medical conditions or laboratory results that, in the opinion of the Investigator indicate an increased vulnerability to study drug and procedures, and expose subjects to an unreasonable risk as a result of participating in this clinical trial.
15. Single-column hemorrhoidectomy or hemorrhoidectomy without an internal component.
16. Concurrent fissurectomy.
17. Any clinically significant event or condition uncovered during the surgery (e.g., excessive bleeding, acute sepsis) that might render the subject medically unstable or complicate the subject's postoperative course.
18. A cumulative incision length of less than 3 cm.

Stopping Criteria

This study involved a single dose of study medication; therefore, individual stopping criteria were not related to continued administration of study drug, but rather the ability of subjects to continue to participate in the follow-up evaluations. The following clinical situations and the methods of follow-up to deal with them were included in the protocol:

1. If a subject experienced an adverse event (AE) that rendered him or her incapable of continuing with the remaining study visits and assessments, a

final evaluation visit was to have been performed, so that the subject's study participation could be terminated in a safe and orderly manner.

2. Subjects were to be free to discontinue from the study at any time, without prejudice to future treatment. These subjects were to have been encouraged to complete at least the study safety assessments.
3. A subject may have been discontinued from the study if he or she refused either study drug administration or to comply with study procedures. Reasons for discontinuation from the study were to be documented on the case report form (CRF).
4. A subject could be discontinued from the study by the Investigator, if it was considered to be in the best interest of the subject. If the discontinuation occurred after administration of the study drug, a final evaluation visit was to be performed, so that the subject could be terminated in a safe and orderly manner.

The protocol did not specify any study stopping criteria.

Efficacy Endpoints

Primary Efficacy Endpoint

The area under the curve of numeric rating scale at rest (NRS-R) pain intensity scores through 72 hours (NRS-R AUC_{0-72}) for subjects receiving SKY0402 versus placebo.

Secondary Efficacy Endpoints

1. Area under the curve of NRS-R through 12, 24, 36, 48, and 60 hours. (NRS-R AUC0-xx, where xx = 12, 24, 36, 48, and 60).
2. The proportion of subjects who were pain free (defined as an NRS-R of 0 or 1) at 72 hours and other time points.
3. Average daily pain with NRS-BM.
4. Proportion of subjects who received no supplemental opioid pain medication.
5. Total postoperative consumption, in mg, of supplemental opioid pain medication through 12, 24, 36, 48, 60, and 72 hours.
6. Time to first postoperative use of opioid medication.
7. Brief Pain Inventory.
8. PONV-free time through 72 hours.
9. Percentage of subjects with postoperative constipation through 72 hours.
10. Use of antiemetic medication (i.e., any medication given postoperatively to treat nausea and/or vomiting) administered through 12, 24, 36, 48, 60, and 72 hours.
11. Time to first bowel movement through 72 hours.

12. Subject's satisfaction with postoperative analgesia.
13. Date subject returns to work or normal daily activities.

Safety Assessments

1. Clinical laboratories at Baseline and Day 8.
2. AEs and SAEs through Day 30.
3. Vital signs (temperature, resting heart rate, and blood pressure) at Screening, Baseline, 0.5, 1, 1.5, and 2 hours following study drug administration and on Days 8 and 30.
4. Caregiver's satisfaction with wound healing at Day 30.

Pharmacokinetic Measurements

Blood samples for the determination of plasma bupivacaine concentrations were to be collected from approximately 50 subjects at specified sites at Baseline and at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after the start of study drug infiltration.

Methods

Subjects were to have been screened within 30 days of study drug administration. The assessments that were to have been made during the screening process are listed in the schedule of study procedures in the section below.

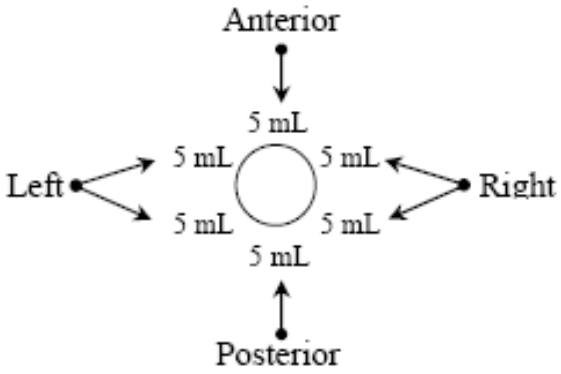
Prior to the surgical procedure, baseline assessments, also listed in the schedule of study procedures in the section below, were to have been conducted. The surgical procedure was to have been performed while the subjects were under general anesthesia with standard monitoring as determined by the individual study sites. At the end of the surgical procedure, continuing eligibility was to have been assessed based on exclusion criteria 17 and 18 (i.e., verify that no serious intraoperative complications have occurred and that the incision is at least 3 cm in length).

For those subjects who were still eligible to partake in the study, the study drug was then to have been administered by a member of the surgical team. The

study drug was to have been prepared in the syringe covered with a finger cot, to assure blinding, and administered using the following infiltration method:

1. All injections were to be performed with an infiltrative *moving needle* technique, with frequent aspirations to reduce the chance for accidental intravascular injection. If blood was aspirated into the syringe, the needle was to have been moved to a different location and aspiration was to be performed again. This process was to be repeated until no blood was aspirated.
2. Study drug was to have been injected in small increments at any given location and only after negative aspiration.
3. A gauze pad was to have been placed on the skin over the needle insertion site to absorb any fluid that might be expelled onto the skin as the needle was withdrawn to avoid inadvertent unblinding.
4. The total volume of study drug to have been used for infiltration was to be 30 mL.
5. A standard anal block procedure was to have been performed by infiltrating the perianal tissues (just outside the external sphincter) with 5 mL of study drug injected at the 2, 4, 6, 8, 10 and 12 o'clock positions as indicated in the figure below.

Figure 3 Anal block procedure for infiltration of study drug. The circle in the center represents the anal sphincter. (From p. 27 of final study report)



The start of administration of study drug was to have served as the reference time point for all further assessments through 72 hours; the day of study drug administration was to have been used to mark Day 1 of the study. Subjects were to have been hospitalized for at least 72 hours after surgery thereby allowing postoperative analgesia and the collection of study data to take place under the supervision of study staff.

For the first 3 hours after study drug administration, the following procedures and assessments were to have been executed:

1. Measure vital signs (temperature, resting heart rate, and blood pressure) at 0.5, 1, 1.5, and 2 hours.
2. Conduct NRS-R at the end of general anesthesia, before the first dose of rescue morphine, if applicable, and at 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours.
3. Draw blood samples for plasma bupivacaine from approximately 50 subjects at specified centers at 0.25, 0.5, 1, and 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after beginning of administration of study drug.
4. Record all rescue morphine and other concomitant medications (including antiemetics).
5. Record occurrence and duration (start and stop times) of any nausea and vomiting.
6. Record date and time of first and every bowel movement or occurrence and duration of constipation and conduct NRS-BM, if applicable.
7. Record all AEs and SAEs.
8. Administer BPI questionnaire at 24 and 72 hours.
9. Record subject's satisfaction with postoperative analgesia at 24 and 72 hours.

During the postoperative period, subjects were to have been instructed to avoid constipation by eating a high fiber diet and drinking plenty of non-caffeinated liquids. Stool softeners and laxatives were to have been prescribed as necessary. At the discretion of the surgeon, the surgical area could be cleaned using shallow warm baths (sitz baths) three times a day and after each bowel movement for the first week after surgery. The use of topical or intrarectal medication was not to have been permitted unless necessary to treat an adverse event.

On Day 8, subjects were to have returned to the study site for assessments of vital signs, performing clinical laboratory assessments, and recording of adverse events, particularly those suggestive of local toxicity, including sensory or motor impairment and signs of nerve or tissue irritation.

At the 30 day visit the final assessments were to have been made including:

1. The caregiver's satisfaction with wound healing was to have been assessed. The caregiver was to respond to the following question, "On a scale of 0 to 10, where 0 = completely satisfied and 10 = completely unsatisfied, how satisfied are you with the subject's wound healing?"
2. Subject productivity was to have been recorded as the date on which the subject was able to return to work or, if the subject did not work outside the home or had a strenuous job, was able to return to normal daily activities (e.g., care for one's self, get dressed, prepare meals,

short trips outside the home). Normal daily activities were not to necessarily include all activities that the subject was able to accomplish before surgery (e.g., participation in sports; heavy lifting or cleaning).

Schedule

(Schedule begins on next page.)

Table 10. Schedule of study procedures (based on Table 1; p. 39 of Clinical Study Report)

Procedure					After Study Drug Administration										
						4-72 Hours								Site Visit	Site Con-tact
						4	8	12	24	36	48	60	72		
	Study Day	Day -30 to -1	Day -1 to 1	1	1	1	1	1	2	2	3	3	5	8	30
	Time Window (±h)					0.25	.5	.5	1	2	2	4	4	24	96
Informed consent		X													
Drug Screen		X													
Clinical Labs[B]		X												X	
Assess/confirm eligibility		X	X												
Medical history, demographics and baseline characteristics		X	X												
Train self-assessments		X	X												
Pregnancy test (women of childbearing potential)			X												
Physical examination			X												
Randomize subject & prepare study drug			X												
Vital signs[C]		X	X		0.5, 1, 1.5, & 2									X	X
Study drug administration				X											
NRS-R[D]			X		1 & 2	X	X	X	X	X	X	X	X		
Subject's satisfaction with postoperative analgesia									X				X		

Procedure					After Study Drug Administration										
						4-72 Hours								Site Visit	Site Con-tact
						4	8	12	24	36	48	60	72		
	Study Day	**Day -30 to -1**	**Day -1 to 1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**3**	**5**	**8**	**30**
	Time Window (±h)					**0.25**	**.5**	**.5**	**1**	**2**	**2**	**4**	**4**	**24**	**96**
Brief Pain Inventory		X							X				X		X
Record occurrence and duration of nausea/vomiting					X	X	X	X	X	X	X	X			
Record occurrence and duration of constipation					X	X	X	X	X	X	X	X			
Record date/time of each BM and conduct NRS-BM					X	X	X	X	X	X	X	X			
Caregiver's satisfaction with wound healing															X
Subject productivity (date subject returned to work or normal daily activities)															X
Concomitant medications[E]		X[F]	X[F]	X	X	X	X	X	X	X	X	X	X		
Record AEs and SAEs (starting at signing of ICF)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood draw for pharmacokinetics at specified center only			X		0.25, 0.5, 1 and 2h	X	X	X	X	X	X	X	X		

[A] Screening was to be conducted within 30 days before the administration of study drug.
[B] Clinical labs were to include Chem-12 and CBC
[C] Temperature, heart rate, and blood pressure were to be measured after the subject had rested for at least 5 minutes in the supine position.
[D] In addition to scheduled assessments, NRS-R was to be assessed at the end of the anesthetic and before the first dose of rescue IM morphine.

[E] At each scheduled NRS-R assessment, all postoperative medication the subject had used was to be recorded.
[F] All medication the subject used within 3 days before the scheduled surgery was to be recorded; was to include medication name, date, and time.

Amendments to the Protocol

No amendments to the protocol were made and no changes to the planned analyses were made prior to breaking the blind.

Post Hoc Changes

What was described as an “exploratory post hoc analysis” was conducted in which the NRS pain intensity scores were summarized at each time point using a wWOCF+LOCF imputation.

Conduct of the Study

The first subject was screened on May 11, 2009, and the last subject underwent the final evaluation on August 18, 2009.

The Applicant reported 114 protocol deviations involving 53 subjects. Of these deviations, five qualified as protocol violations by the Applicant and resulted in the exclusion of the four subjects from the per-protocol population.

Most of the deviations were relatively minor, e.g., completing assessments outside of the allowed time range. The table below describes the violations as reported by the Applicant.

Table 11. Protocol violations resulting in exclusion from the per-protocol population.

Subject ID	Protocol Violation
020-0004	Patient received Paracetamol (Perfalgan) within 72 hours after study drug administration (20 Aug 2009, 14:00) due to fever 37.5 C.
020-0004	PK concentrations don't fit the profiles (i.e. assignment either to active drug or placebo) for subjects 020-0004 randomized on 17 AUG 2009 at 15:54:20 and 020-0008, randomized on 17 AUG 2009 at 16:08:23
020-0005	Patient received 5 mg of MF during the surgery, approximately 10 min. before the start of study drug administration.
020-0008	PK concentrations don't fit the profiles (i.e. assignment either to active drug or placebo) for subjects 020-0004 randomized on 17 AUG 2009 at 15:54:20 and 020-0008, randomized on 17 AUG 2009 at 16:08:23
031-0002	NRS-R patient diary card for this patient is lost

It should be noted that four of the five deviations and three of the four exclusions from the per-protocol population occurred at site 020. At the same site, there were eight deviations reported as pain scores "completed with a hand of Investigator based on verbal interview with patients." This deviation occurred only once at a different site. The subjects from site 020 included:

0001, 0004, 0005, 0008, 0009, 0013, 0015, and 0020

The other subject with whom this deviation occurred was 024-0001.

Results as Reported by the Applicant

Primary Efficacy Analysis

The primary endpoint was the area under the curve of NRS-R pain intensity scores through 72 hours (NRS-R AUC_{0-72}). SKY0402 demonstrated a statistically significant reduction in pain through 72 hours compared with placebo ($p<0.0001$). The mean (standard deviation) values of NRS-R AUC_{0-72} for SKU0402 and placebo were 142 (101) and 202 (104), respectively.

Secondary Efficacy Analyses

Multiple secondary endpoint results also demonstrated a significant advantage for SKY0402:

1. The median time to first opioid use was 14 hours in the SKY0402 group ($p<0.0001$) and was 1 hours in the placebo group.
2. At all time points up to 72 hours, there was a statistically significant reduction in opioid use for the SKY0402 treated subjects compared with placebo; through 72 hours, this difference was 22 mg in the SKY0402 group compared to 29 mg in the placebo group ($p=0.0006$).
3. The percentage of subjects who required no opioids (opioid-free) up to 72 hours was 28% for SKY0402 treated subjects versus 10% for placebo treated subjects ($p=0.0007$).

Pharmacokinetic Findings

Plasma bupivacaine concentrations following administration of 300 mg SKY0402 were assessed with individual and summary parameter estimates.

1. The mean C_{max} value was 867 ng/mL.
2. The median T_{max} value was 0.5 hours for 25 subjects.
3. The T_{max} occurred at 36 hours in 1 subject, 24 hours in 1 subject, and 12 hours in 2 subjects.

4. Half-life values had a mean of 24 hours.
5. Plasma clearance was 19 L/hr for 24 subjects.
6. A PK/PD relationship could not be established in this study.

Brief Summary of Safety
The Applicant reported the following safety outcomes for this study.

The adverse event incidence for SKY0402 was similar to placebo. The incidence of gastrointestinal treatment emergent adverse events (TEAEs) was higher in the placebo group than in the SKY0402 group.

The gastrointestinal AEs more frequently reported in the placebo group were anal hemorrhage, vomiting, and painful defecation. The Applicant stated his may be related to the increased opioid use in the patients receiving placebo.

There were no deaths or withdrawals due to adverse events. There was one SAE of mild thrombophlebitis in the placebo group, which resolved the next day after treatment.

There were no clinically meaningful shifts in any of the chemistry or hematology values from Screening to the Day 8 visit. Vital signs (temperature, heart rate, blood pressure) did not change in a clinically significant manner from baseline to the last visit in either treatment group.

Mean scores for overall satisfaction with the subject's wound healing were not statistically significantly different between treatment groups.

Discussion of Results

There was concern for how the study was designed and whether or not bias may have been introduced. Specifically, the use of a finger cot to mask the content of the syringes containing study drug was a novel approach to blind the Investigator from the study treatment; however, the Investigator was charged with aspirating this same syringe and assessing whether blood was present in its barrel mixed with the study drug. This raised the concern that the Investigator was able to discern whether the original content of the syringe was clear, i.e., placebo, or milky white, i.e., SKY0402, and therefore, was not blinded. This would have possibly introduced bias into the study. To assess this possibility, the Division requested, and the Applicant submitted, a sample of the drug product for evaluation. Using a latex finger cot, it was noted, by this reviewer and the Cross Disciplinary Team Leader, that blinding was not likely jeopardized provided the study was conducted as per the protocol.

In addition to the above, the number of incidents in which data that were to have been recorded by the subjects but were actually recorded by the Investigator was disconcerting. Whether the Investigator accurately entered the subjects' responses raises the concern that the results may not be accurate. This concern was partially mitigated when the possibility for unblinding the Investigators at the time of study drug administration was determined to be low.

The Division of Scientific Investigations agreed to investigate the sites used for this study. Their investigation revealed no irregularities in the data collection process.

To further assure that the results were not biased by these deviations, Dr. David Petullo, the statistical reviewer, analyzed the data from this study with and without the results reported from site 20 where all but one of the Investigator entries of data to be recorded by the subjects occurred. He found that SKY0402 continued to demonstrate a statistically significant reduction in pain through 72 hours compared with placebo when data from site 20 was excluded from the analysis. This information is useful only if it can be demonstrated that the methods used in the study did not result in unblinding the Investigators.

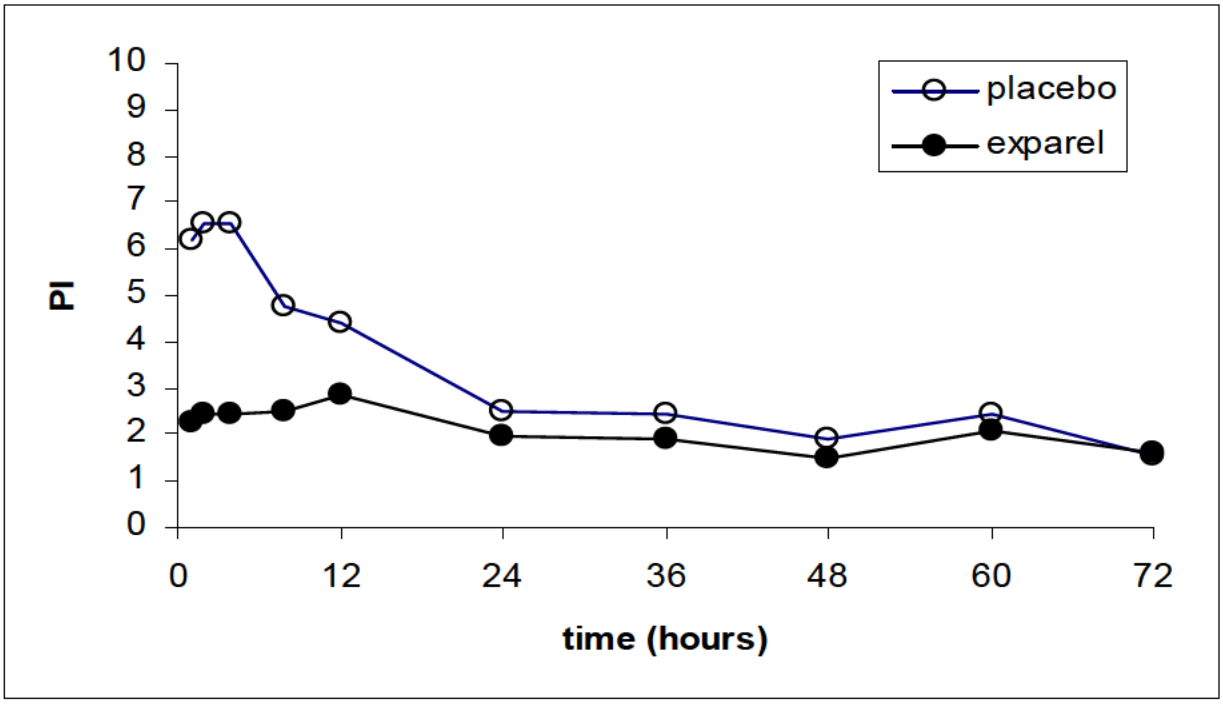
With the above concerns can be laid to rest, it appears that SKY0402 was superior to placebo based on the primary endpoint, NRS-R AUC_{0-72}. This finding was supported by some of the more than 30 secondary efficacy endpoints, most notably narcotic usage, although it was not tied to a clinically relevant benefit.

While the study results for the primary endpoint demonstrated a superior effect for SKY0402 versus placebo, that superiority was due only to the differences observed within the first 12-24 hours following study drug administration. The statistical review team generated a graph (shown below) of pain intensity as a function of time. The graph is important for two reasons:

1. It demonstrates that by 24 hours after study drug administration there is no difference between treatment groups.
2. The protocol specified combination of analgesics and SKY0402 kept average pain scores in the mild range (0-3) throughout the 72 hour observation period; whereas, the combination of analgesics and placebo resulted in moderate levels of pain during the first 24 hours of observation. This suggests a clinically relevant difference between treatments during this time period, provided analgesic use was equivalent between the treatment groups or less for the SKY0402-treatment group.

The apparent lack of efficacy after 24 hours should be an important consideration for labeling, if the product is approved, especially, as the primary endpoint for this pivotal study was the AUC for pain intensity over the first 72 hours following study drug administration.

Figure 4. Mean Pain Intensity Scores versus Time (Figure 1 from the Statistics review)



The maximum plasma levels of bupivacaine following the 300 mg dose of SKY0402 ranged from 144 ng/mL to 1535 ng/mL with a mean value (standard deviation) of 867 (353) ng/mL. C_{max} occurred 4 hours (range: 0.5 h to 36 h) following injection. It should be noted that neurotoxicity related to bupivacaine has been reported to occur at plasma levels on the order of 1 mcg/mL.[1] Convulsions have been reported at levels of ≥ 4 mcg/mL.[2]

Conclusions

This study has demonstrated that a 300 mg dose of SKY0402 is effective, compared to placebo, at reducing post-operative hemorrhoidectomy pain. Although the primary endpoint was the AUC for pain intensity during the first 72 hours postoperatively, the two treatments differed significantly and clinically only during the first 24 hours.
The Applicant has also demonstrated that a 300 mg dose of SKY0402, when used by the prescribed method of administration for hemorrhoidectomy; can result in plasma concentrations of bupivacaine that have been associated with literature-reported neurotoxic outcomes.

9.4.2 SKY0402-C-317

A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Safety and Efficacy of a Single Administration of SKY0402 for Prolonged Postoperative Analgesia in Subjects Undergoing First Metatarsal Osteotomy (Bunionectomy)

Objectives

Primary Objective

Evaluate the magnitude and duration of the effect of a single intraoperative administration of SKY0402 120 mg, compared with placebo (0.9% sodium chloride for injection) in the reduction of postoperative pain following bunionectomy

Secondary Objectives

1. Evaluate additional efficacy parameters
2. Characterize the safety profile of SKY0402 in comparison with placebo
3. Assess the pharmacokinetics of clearance of bupivacaine from the blood plasma

Study Design

This was a Phase 3, randomized, placebo-controlled, double-blinded, multicenter study to evaluate the efficacy and safety of intraoperative administration of SKY0402, compared to normal saline, administered by local infiltration when used for post-operative analgesia following a first metatarsal osteotomy.

Study Population

Subjects were enrolled from the population of patients presenting for first metatarsal osteotomy (bunionectomy) that was to be performed under Mayo block and intraoperative sedation who met the criteria listed below, copied from the final study report.

Inclusion Criteria

1. Age ≥18 years of age at the Screening Visit.
2. Scheduled to undergo primary unilateral first metatarsal osteotomy without hammertoe.
3. Ability to receive Mayo block for intraoperative local analgesia.
4. Ability to receive propofol and/or midazolam for intraoperative sedation.
5. Female subjects must have been surgically sterile or at least two years menopausal, or using an acceptable method of birth control. If of childbearing potential, there must have been a documented negative blood or urine pregnancy test within 24 hours before surgery.
6. Clinical laboratory values less than or equal to twice the upper limit of normal or, if abnormal, deemed not clinically significant per the Investigator.
7. Ability to provide informed consent, adhere to the study visit schedule, and complete all study assessments.

Exclusion Criteria

1. Currently pregnant, nursing, or planning to become pregnant during the study or within one month after study drug administration.
2. Chronic users of analgesic medications, including taking opioid medications for more than 14 days in the last 3 months, or non-opioid pain medications more than 5 times per week.
3. Use of any NSAID including selective COX-2 inhibitor within three days of surgery.
4. Use of selective serotonin reuptake inhibitors (SSRIs), gabapentin, pregabalin (Lyrica), or duloxetine (Cymbalta) within three days of surgery
5. Use of acetaminophen within 24 hours of surgery.
6. Use of systemic glucocorticosteroids or use of systemic glucocorticoids within one month of enrollment into this study.
8. Peripheral neuropathy including diabetic neuropathy, chemotherapy-induced neuropathy, or HIV neuropathy.
9. History of hepatitis.
10. History of suspected or known addiction to or abuse of drugs or alcohol within the past two years.
11. Failure to pass drug screen.
12. Current evidence of alcohol abuse (greater than 4 units of alcohol per day: 1 unit = ½ pint of beer, 1 glass of wine, or 1 oz. of spirits).
13. Evidence of peripheral ischemic disease.
14. Type I or Type II diabetes.
15. Current acute or chronic medical or major psychiatric disease that, in the opinion of the Investigator, would interfere with the evaluation of study drug efficacy or safety.
16. Malignancy in the last 2 years, with the exception of non-metastatic basal cell or squamous cell carcinoma of the skin or localized carcinoma in situ of the cervix.

17. History of hypersensitivity or idiosyncratic reactions to amide-type local anesthetics or to opioid medication.
18. Administration of an investigational drug within 30 days prior to study drug administration or planned administration of another investigational product or procedure during the subject's participation in this study.
19. Previous participation in an EXPAREL study.
20. Significant medical conditions or laboratory results that, in the opinion of the Investigator, indicated an increased vulnerability to study drugs and procedures.
21. Current painful physical conditions or concurrent surgery other than bunionectomy that may require analgesic treatment (such as NSAID or opioid) in the postoperative period for pain that is not strictly related to the bunionectomy procedure and may confound the postoperative assessments.

In addition, the subject was to be ineligible to receive study drug if he or she met the following criteria during surgery:

22. Any clinically significant event or condition uncovered during the surgery (e.g., excessive bleeding, acute sepsis) that might render the subject medically unstable or complicate the subject's postoperative course.

Stopping Criteria

This study involved a single dose of study medication; therefore, individual stopping criteria were not related to continued administration of study drug, but rather the ability of subjects to continue to participate in the follow-up evaluations. The following clinical situations and the methods of follow-up to deal with them were included in the protocol:

1. If a subject experienced an adverse event (AE) that rendered him or her incapable of continuing with the remaining study visits and assessments, a final evaluation visit was to have been performed, so that the subject's study participation could be terminated in a safe and orderly manner.
2. Subjects were to be free to discontinue from the study at any time, without prejudice to future treatment. These subjects were to have been encouraged to complete at least the study safety assessments.
3. A subject may have been discontinued from the study if he or she refused either study drug administration or to comply with study procedures. Reasons for discontinuation from the study were to be documented on the CRF.
4. A subject could be discontinued from the study by the Investigator, if it was considered to be in the best interest of the subject. If the discontinuation occurred after administration of the study drug, a final evaluation visit was to be performed, so that the subject could be terminated in a safe and orderly manner.

The protocol did not specify any study stopping criteria.

Efficacy Endpoints

Primary Efficacy Endpoint

Area under the curve (AUC) of NRS through 24 hours (NRS AUC_{0-24}).

Secondary Efficacy Endpoints

1. AUC of NRS through 36, 48, 60, and 72 hours. (NRS AUC0-xx , where xx = 36, 48, 60, 72).
2. Proportion of subjects who were pain free (defined as an NRS of 0 or 1) at 24 hours and other time points.
3. Proportion of subjects who received no rescue pain medication (Percocet or ketorolac).
4. Total postoperative consumption, in mg, of Percocet through 24, 36, 48, 60, and 72 hours.
5. Total amount of postoperative Percocet use through 24, 36, 48, 60, and 72 hours.
6. Time to first use of Percocet.
7. Time to first use of IV ketorolac.
8. Subject's satisfaction with postoperative analgesia at 24 and 72 ±8 hours.

Safety Assessments

1. Vital signs (temperature, resting heart rate, and blood pressure) at Baseline and at 24 hours and 72 ± 8 hours and Day 30 ±4 after study drug administration.
2. Wound healing and status at 30 ± 4days.
3. Clinical laboratory values at Baseline and the 72 ± 8 hour visit.
4. Treatment Emergent AEs (TEAE) and SAEs were to be collected during the timeframe noted in Methodology.

Methods

Screening was to have occurred up to 30 days prior to the scheduled surgical procedure and was to have required that the following assessments be performed:

- Obtain written informed consent
- Assess subject eligibility (inclusion/exclusion criteria)
- Obtain relevant medical/surgical history; record demographic and baseline characteristics
- Train subject on use of self-assessment measures (e.g., NRS scores)
- Conduct alcohol screen
- Instruct subject to discontinue excluded medications

- Obtain clinical laboratory samples

All subjects who were screened but did not meet eligibility criteria or who declined to participate were to have the reasons for the failure to be enrolled documented.

On the day of the surgical procedure, Day 1, the following procedures were to have been conducted before administration of the study drug and initiation of the surgical procedure:

- Reconfirm eligibility
- Review medical history
- Record adverse events that have occurred since the subject signed the informed consent document and the actions taken to treat the events
- Record the date and time of all medications taken within 3 days before the scheduled surgery
- Conduct a pregnancy test for female subjects of childbearing potential
- Conduct a urine drug screen
- Measure vital signs (temperature, resting heart rate, and blood pressure)
- Verify laboratory values are within appropriate range
- Perform a physical examination
- Review subject training for use of self-assessment measures
- Randomize subject and prepare study drug
- Conduct NRS for pain
- Obtain blood sample for plasma bupivacaine quantitation from approximately 50 subjects from selected sites; the combined number of subjects to comprise the PK population was capped at approximately 50

At the time of the surgical procedure, the following assessments and procedures were to have been performed:

- Sedate the subject using midazolam and/or propofol.
- Perform a Mayo block using lidocaine recording the start time.
- Monitor the subject intraoperatively according to the site's standard procedures.
- Record the date and time of the start of surgery.
- Confirm eligibility based on exclusion criteria (i.e., verify that no serious intraoperative complications have occurred).
- Administer study drug; record the start time of study drug administration. (At least 30 minutes must elapse between the start time of the lidocaine Mayo block and the start time of the administration of study drug.)
- Record the time of the end of surgery.
- Record all concomitant medications administered intraoperatively.
- Record all AEs.

Preparation of the study drug took into account that SKY0402 and 0.9% sodium chloride are visually distinguishable, therefore, an unblinded pharmacist (or other unblinded

member of the study team) was to have prepared 2 syringes as a sterile preparation (fitted with an 18-gauge to a 21-gauge needle) of study drug. Each syringe was to have contained 4 mL of the study drug, for a total of 8 mL. Then, the needle of each syringe was to have been replaced with a 22 gauge to a 25 gauge injection needle. An opaque, non-powdered sterile glove was to have been obtained to cover the barrel of each syringe. A small circular opening (3-5 mm diameter) was to have been cut in the tip of the finger of the opaque sterile glove to allow the connector of the syringe (e.g. Luer lock) to pass through the opening without exposing the bottom of the barrel. The study staff preparing the syringes was to have ensured that the content of each syringe was completely concealed and that the finger of the glove fitted tightly around the barrel, so that it would not slide during the injection procedure. The glove was to have been trimmed appropriately allowing enough length to maintain the blind. The individuals preparing and administering study drug were to have performed all injections, with frequent aspirations to reduce the chance of accidental intravascular injection. If an aspiration drew blood, it should have been seen through the sterile glove covering the syringe, and the needle was to then have been moved and placed into a different location until the aspiration was negative. A sterile gauze pad was to have been placed over the needle insertion site to absorb any fluid that could be expelled as the needle was withdrawn to avoid inadvertent unblinding.

The time of administration of study drug was to have served as the reference time for all subsequent assessments and procedures. The study drug injection was to have occurred using the following technique.

Immediately prior to closure of the surgical wound, the soft tissue around the osteotomy as well as the cut edges of the soft tissue for the surgical wound were to have been infiltrated with study drug. All injections were to have been performed with an infiltrative moving needle technique, with frequent aspirations to reduce the chance of accidental intravascular injection. A total volume of 8 ml was to have been infiltrated using two syringes containing 4 mL of study drug in each. In order to ensure the study drug was adequately mixed, the syringes were to have been gently inverted and reverted prior to drug administration. The first syringe, filled with 4 ml of study drug, was to have been used to infiltrate into the soft tissue immediately medial to the cut bone in a fan pattern, ensuring that the infiltrated tissue extends 2 cm both distal and proximal to the wound, into the tissue, about 1 cm deep, immediately dorsal to the cut bone and into the soft tissue on the sole aspect of the cut bone, extending distal and proximal to the wound. Care was to have been taken to infiltrate around the cut bone surface as this was the most highly concentrated area for pain receptors on c-fibers. After this infiltration was completed, the next syringe was to have been used to infiltrate into the tissue lateral to the osteotomy and into the surface of the cut tissue, again extending 2 cm proximal and distal to the wound, and making sure that both the dorsal and ventral (or sole) aspect of the soft tissues were well infiltrated, especially around the periosteum. The final ml or so of study drug from this syringe was to have been administered to the subcutaneous tissue overlying the wound.

At least 30 minutes was to have passed between the end of the Mayo block and the start of study drug administration. The Mayo block was not to have included infiltration of medicine just under the incision itself, and the study drug was not to have been held in the syringe for more than four hours after preparation for administration.

During the first 24 hours following study drug administration, the following were to have been done:

- Measure vital signs (temperature, resting heart rate, and blood pressure) at 24 hours.
- Conduct NRS for pain at 2, 4, 8, 12, and 24 hours.
- Conduct NRS for pain at the first use of rescue pain medication, if applicable.
- Draw blood samples for plasma bupivacaine from approximately 50 subjects from selected sites at 0.25, 0.5, 1, 2, 4, 8, 12, 24, and 72+8 hours after beginning of administration of study drug; the combined number of subjects to comprise the PK population were capped at approximately 50.
- Record all rescue pain medication (Percocet and/or ketorolac).
- Administer subject's satisfaction with postoperative analgesia at 24 hours.
- Record all AEs.
- Record all concomitant medications.
- Record the date and time that subject is discharged from the surgical center.

From 24 through 72 hours post study drug administration, the subject was to conduct the following assessments and procedures:

- Record NRS at 36, 48, 60, and 72 hours; a staff member from the study center was to call subject at each time point to remind the subject of the need to assess and record in the subject diary the pain intensity using the 0-10 NRS scale and record the use of and rescue and other concomitant medications. The 72 hour pain assessment was to have occurred prior to traveling to study center for the 72 + 8 hour study center follow up visit. The 72 hour pain assessment and the 72+8 hour study center visit were not to be combined.
- Conduct NRS for pain at the first use of rescue pain medication, if applicable.
- Record rescue pain medication (Percocet).
- Record all concomitant medications.
- Record all AEs and SAEs in the subject diary.

At 80 hours after study drug administration, the subject was to have returned to the study site at which time, the following assessments were to have been made:

- Measure vital signs (temperature, resting heart rate, and blood pressure).
- Draw blood samples for plasma bupivacaine from approximately 50 subjects from selected sites; the combined number of subjects to comprise the PK population was capped at approximately 50.

- Record subject's satisfaction with postoperative analgesia.
- Obtain clinical laboratory samples.
- Retrieve subject diaries.
- Record all Investigator-reported and/or subject-reported AEs and SAEs. To elicit AEs pertinent to potential local toxicity, the subjects were particularly questioned about any residual sensory/motor impairment, or signs of nerve and/or tissue irritation.
- Record rescue pain medication (Percocet).
- Record all concomitant medications.

On Day 30 (±4 days), subjects were to have returned to the study site for assessment of the following:

- Vital signs (temperature, resting heart rate, and blood pressure).
- Wound healing and status score.
- Any adverse events that occurred since the Day 3 visit.

On Day 30, wound healing was also to have been assessed using the grading system in the table below.

Table 12. Wound Status Scoring Grades (Table 2 from Final Study Report, p. 45)

Parameter	Score	Scoring Criteria
Erythema	0	No erythema
	1	Very slight erythema (barely perceptible)
	2	Well defined erythema
	3	Moderate to severe erythema
	4	Severe erythema (beet redness) to slight eschar formation (injuries in depth)
Drainage	0	None
	1	Serous
	2	Serosanguinous
	3	Bloody
	4	Purulent
Edema	0	No edema
	1	Very slight edema (barely perceptible)
	2	Slight edema (edges well defined)
	3	Moderate edema (raised approx. 1 mm)
	4	Severe edema (raised >1 mm and beyond area of exposure)
Induration	0	None
	1	Minimal
	2	Mild (spongy tissue)
	3	Moderate (firm, warm)
	4	Severe (hard, red, hot or crepitus)

Schedule

(Schedule begins on next page.)

Table 13. Schedule of study procedures (based on Table 1; p. 41 of Clinical Study Report)

Procedure					After Study Drug Administration													
					In-Patient								At Home				On Site	On Site
	Time post-drug				.25 h	.5h	1h	2h	4h	8h	12 h	24 h	36h	48h	60h	72h	80h	720h
	Study Day	Day -30 to -1	Day -1 to 1	Day 1	1	1	1	1	1	1	1	2	2	3	3	4	4+ 8 h	30
	Time Window (±)								.25	.5	.5	1	1 h	1 h	1 h	1 h		4 d
Informed consent		X																
Assess/confirm eligibility		X	X															
Medical history, demographics and baseline characteristics[A]		X	X															
Pregnancy test (women of childbearing potential)			X															
Urine Drug Screen			X															
Clinical Labs[B]		X														X		
Physical examination			X															
Vital signs			X									X					X	X
Randomize subject & prepare study drug			X															
Study drug administration				X													X	X

Procedure					After Study Drug Administration													
					In-Patient								At Home				On Site	On Site
	Time post-drug				.25 h	.5h	1h	2h	4h	8h	12 h	24 h	36h	48h	60h	72h	80h	720h
	Study Day	Day -30 to -1	Day -1 to 1	Day 1	1	1	1	1	1	1	1	2	2	3	3	4	4+ 8 h	30
	Time Window (±)								.25	.5	.5	1	1 h	1 h	1 h	1 h		4 d
Pain Intensity NRS				X				X	X	X	X	X	X	X	X	X		
Reminder call to subject												X	X	X	X	X		
Blood draw for pharmacokinetics[C]				X								X					X	
Subject satisfaction with postoperative analgesia												X					X	
Retrieve subject diaries																	X	
Wound healing and status																		X
Concomitant medications			X	X	X			X	X	X	X	X	X	X	X	X	X	
Record AEs and SAEs (starting at signing of ICF)		X	X	X	X			X	X	X	X	X	X	X	X	X	X	X

[A] Demographics and alcohol screening were performed a screening only.
[B] Laboratory assessments consisted of Chem-12 and CBC.
[C] PK samples were taken for all subjects at selected sites only.

Amendments to the Protocol

No amendments were made to the protocol; although protocol clarifications were issued to the Investigators on May 4 and July 13, 2009. These were not of a nature that would be expected to substantially impact on the conduct or findings of the study.

Post Hoc Changes

A post-hoc analysis was conducted in which the primary efficacy endpoint was reassessed when data from a particular study site, San Marcos (site 200), was noted to substantially differ from that of the other sites. In the reanalysis, data from this study site were excluded. The findings from this analysis are described, as reported by the Applicant, below.

In addition to the above, an analysis of the percentage of subjects who received no rescue medication through 8, 12, 16, and 20 hours was added, and "pain free" was additionally defined as an NRS score of 0 and as an NRS score of 0, 1, or 2.

Conduct of the Study

The first subject was enrolled in the study on April 27, 2009, and the last subject completed the study on September 17, 2009. According to the Applicant, the study was conducted in accordance with the clinical research guidelines.

There were a total of 193 subjects enrolled (randomized and treated) in this study: 97 subjects received 120 mg SKY0402 and 96 subjects received placebo. Two subjects were randomized, but not treated: one subject was found to have elevated blood pressure after randomization, and one did not have surgery due to unstable vital signs.

Eight subjects did not complete the study: 4 subjects in the SKY0402 group and 4 subjects in the placebo group. Only one of these was due to an adverse event: hypotension that occurred on Day 2, in a subject treated with placebo.

The applicant reported a total of 74 protocol deviations: 25 in the SKY0402-treatment group and 48 in the placebo-treatment group. Most of these were related to missed assessments, assessments made outside the allotted timeframe, missed PK samples and PK samples taken outside of the allotted timeframe. Seven of the deviations were also considered as violations, which resulted in exclusion of the subjects from the Per Protocol analysis. Five of the violations were in the SKY0402-treatment group and 2

were in the placebo-treatment group. Of these, the only ones of note were one subject from each treatment group that was classified as "mis-randomized; actual treatment administered cannot be confirmed."

Results as Reported by the Applicant

Primary Efficacy Analysis
The primary efficacy endpoint, AUC of pain intensity scores through 24 hours using the wWOCF+LOCF imputation for NRS scores, was statistically different between SKY0402 and placebo (p=0.0005). The mean value for the SKY0402-treated subjects was 125; it was 146 for subjects treated with placebo.

Secondary Efficacy Analyses
The secondary endpoint results supported the primary endpoint finding. The AUC of pain intensity continued to be statistically significant through 36 hours (p=0.02).

The following secondary endpoints favored SKY0402:

1. The difference between treatment groups in the mean pain intensity score [in the full analysis (FA) set]
    - before first use of rescue medication
    - at 2 hours
    - at 4 hours
2. The difference between treatment groups in the percentage of subjects who were pain free [defined as an NRS of 0 or 1 (FA set)], at 2, 4, 8, and 48 hours.
3. The difference between treatment groups in the percentage of subjects who received no rescue pain medication through 8, 12, 16, 20, and 24 hours.
4. The difference between treatment groups in the total amount of postoperative Percocet use (FA set) at 24 hours.
5. The difference between the median time to first use of Percocet.

PK Analysis
The bupivacaine concentrations following administration of 120 mg of SKY0402 were assessed with individual and summary pharmacokinetic figures and parameter estimates. The mean Cmax value was 166 ng/mL and the median Tmax value was 2.0 hours for 26 subjects. The Tmax occurred at 24 hours in 4 subjects. Half-life values had a mean of 34 hours and plasma clearance was 19 L/hr for 22 subjects.

Exploratory analyses of possible PK/PD relationships were examined with regression analyses and graphical presentations. Regression analyses did not elucidate meaningful correlations between PK and PD variables.

Post Hoc Analysis

Examination of the data by site revealed that the mean value for the SKY0402 group in primary endpoint analysis (AUC of pain intensity scores through 24 hours using the wWOCF+LOCF imputation for NRS scores) from site 200 (San Marcos) was higher than the other sites, whereas the mean values in the placebo groups were similar among the sites such that there was no difference between the SKY0402 group and the placebo group at the San Marcos site. Thus, a post hoc exploratory analysis was performed excluding data from this site and including data from sites 100, 300, and 400 only. When results from this site were excluded and the results from the other three sites were reanalyzed, the primary endpoint remained statistically significant, and the AUC of the pain intensity was statistically significant through 48 hours (p=0.04).

Brief Summary of Safety

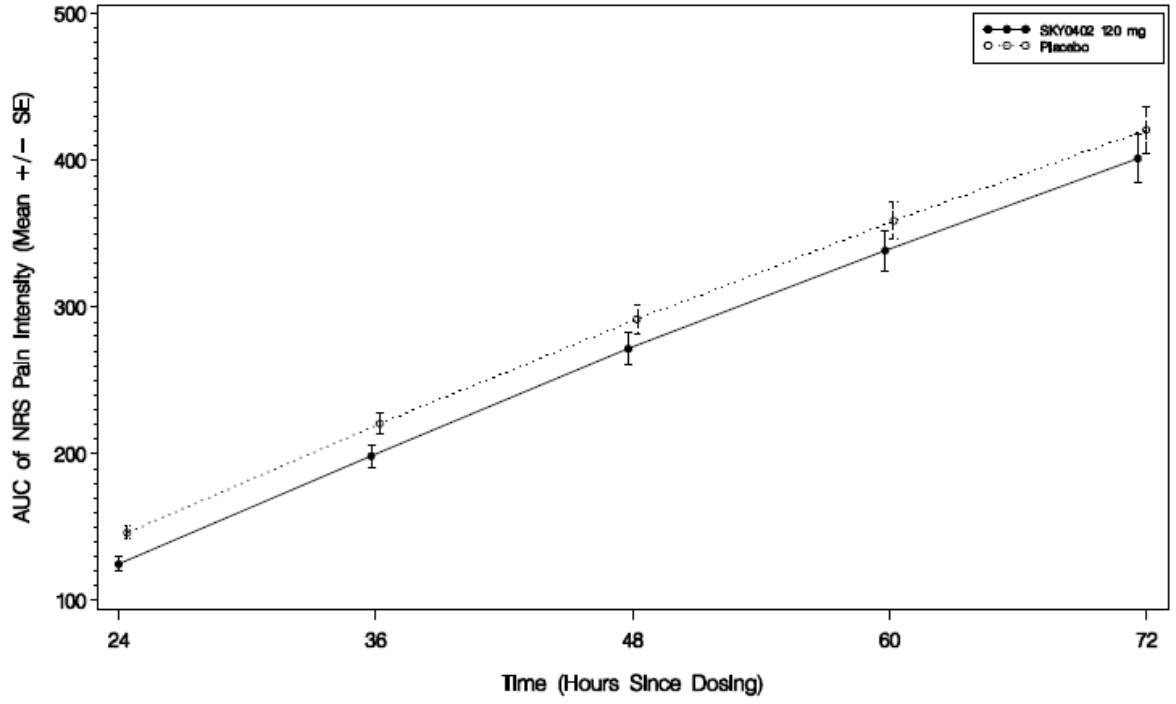
1. The incidence of systemic TEAEs was lower in the SKY0402 group (58%) compared with the placebo group (66%). This difference was largely accounted for by the higher incidence of dizziness in the placebo group (26%) compared with the SKY0402 group (11%).
2. The incidence of vomiting was higher in the SKY0402 group (27.8%) compared with the placebo group (18%).
3. Most TEAEs were reported as not related to study medication and were mild or moderate in severity.
4. The incidence of related systemic TEAEs was higher in the SKY0402 group (9%) compared with the placebo group (5%).
5. The incidence of severe TEAEs was higher in the SKY0402 group (11%) compared with the placebo group (5%); the incidence of moderate TEAEs was higher in the placebo group (21%) compared with the SKY0402 group (12%).
6. Severe vomiting was observed in 9% of subjects in the SKY0402 group compared with 2% of subjects in the placebo group.
7. There were no clinically meaningful shifts in any of the chemistry or hematology values from Screening to the 80 hour visit.
8. Vital signs (temperature, heart rate, blood pressure) did not change in a clinically significant manner from baseline to the last visit in either treatment group.
9. There was no statistically significant difference between treatment groups in the distribution of subjects across the assessment categories for any of the wound assessments (erythema, drainage, edema, and induration). Mean scores for overall satisfaction with the subject's wound healing were not statistically significantly different between treatment groups.
10. No subjects demonstrated any evidence of malunion or non-union on their routine podiatric follow-up visits.

Discussion of Results

The concerns regarding study drug blinding techniques that were raised in Study SKY0402-C-316, described above, applied to this study as well. The steps taken by the Division to evaluate the adequacy of the blinding technique also apply, and therefore, the issue is not one of concern. In addition, there were no issues related to protocol deviations in obtaining subject pain scores for this study, as there were with the previous one, which also reduced the concern for potential bias.

In terms of efficacy, SKY0402 was demonstrated to be superior to placebo for providing analgesia following a bunionectomy when used directed in the protocol and in conjunction with oxycodone, acetaminophen and ketorolac. This analgesic effect persisted up to 24 hours post-operatively, and depending on how the data are interpreted, the effect may persist up to 36 hours post-operatively. In the figure below, is a plot, by the Applicant, of AUC of NRS pain intensity as a function of time as determined using the full analysis set. In this plot, the AUC for SKY0402 nearly parallels that of placebo for the entire study period. Furthermore, the two are only minimally disparate at the first two time points, i.e., at 24 and 36 hours following study drug administration.

Figure 5. AUC of NRS Pain Intensity Scores Time Plot (Figure 14.2-1.1, p. 136 of the Final Study Report)

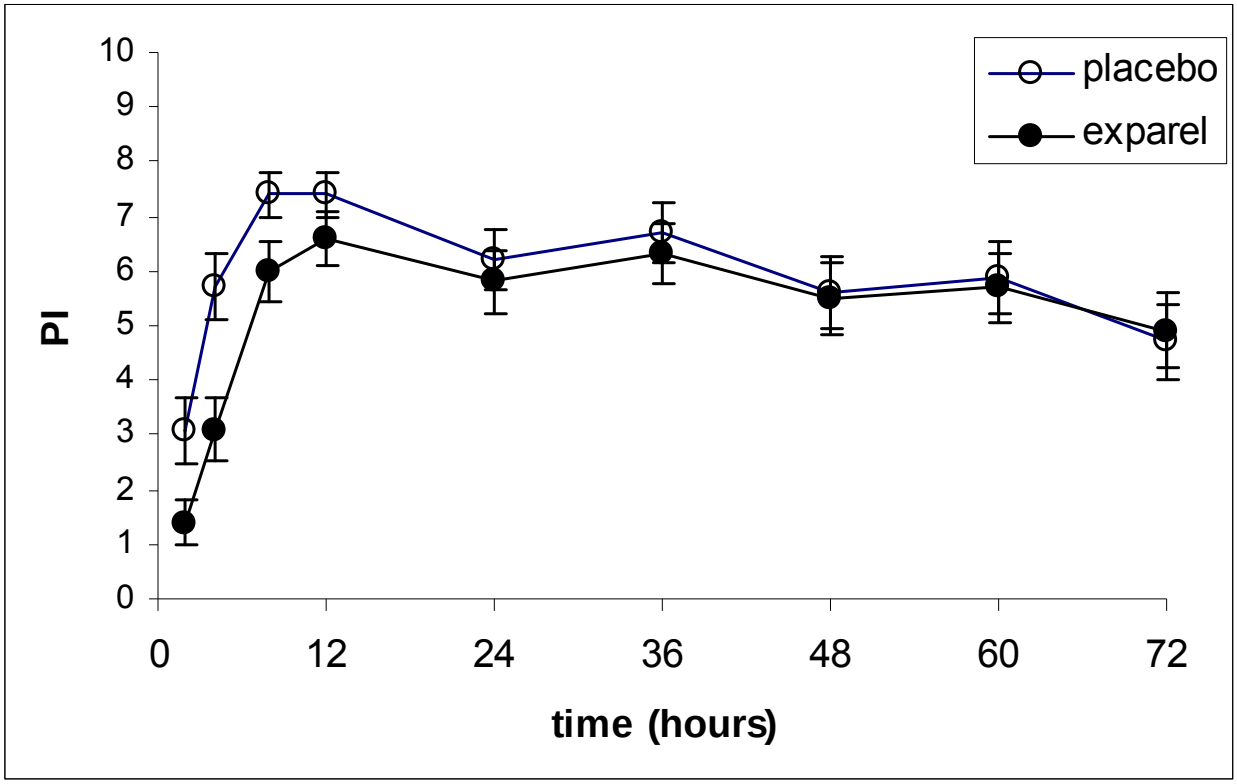


A better appreciation of the differences in analgesic effects of the two treatments may be obtained by examining the mean NRS pain intensity scores collected over the entire

study period. The Applicant has produced such a plot, which is reproduced in the figure below. In this figure, the differences between treatments are distinct from each other only up to the 12-hour post-administration assessment. After that the pain intensity for the two treatments are indistinguishable. The data from this plot indicate the following:

1. The analgesic effects of SKY0402 exceed that of placebo for somewhere between 12 and 24 hours.
2. At 2 hours following injection of the study drug, patients in both treatment groups are experiencing mild pain (defined as a pain score of 0-3), or are pain free based on the Applicant's revised definition of a pain score of 0-2. This is likely due to residual analgesia from the Mayo block. Nonetheless, there is a clear distinction between treatments favoring SKY0402.
3. By 4 hours after study drug injection, placebo-treated patients are experiencing moderate levels of pain (defined as a pain score of 4-7) as are SKY0402-treated patients, although to a substantially less extent.
4. At 8 hours after study drug administration, both treatment groups have mean scores that are indicative of moderate levels of pain, and by the Applicant's computation, are indistinguishable.
5. The moderate levels of pain that are experienced by both treatment groups persist until at least 48 hours, and for some subjects, until the end of the study period.

Figure 6. Mean Pain Intensity Scores versus Time (Figure 3 from the Statistics review)



To further assess the analgesic effects of the two treatment groups, the Applicant compared the percentages of subjects who received no rescue medication at nine time points. In the table below, this data, from the full analysis group, has been modified to show the number and percentages of subjects who did require rescue medication.

Table 14. Times to requirement of rescue pain medications for each treatment group.

	Subjects Who Required Rescue Medication N (%)								
Time After Study Drug Administration (hours)	8	12	16	20	24	36	48	60	72
Treatment									
SKY0402 (n = 97)	57 (59)	77 (79)	87 (90)	90 (93)	90 (93)	94 (97)	95 (98)	95 (98)	95 (98)
Placebo (n = 96)	87 (91)	93 (97)	94 (98)	95 (99)	95 (99)	95 (99)	95 (99)	95 (99)	95 (99)

The data in the table indicate that by 16 hours after administration of SKY0402, the need for rescue pain medications has reached the level that would be expected had the treatment been ineffective, i.e., at 16 hours after administration of SKY0402, the level of pain is such that patients will require rescue medication to the same extent as if they had not been treated at all.

Thus, while the study showed a significant difference between AUC of NRS pain intensity scores at 24 hours for the two treatment groups, it appears that the clinical utility of SKY0402 is greatest during the first 12 hours, for bunionectomy, and requires that rescue medication be available throughout that period.

In terms of its safety for use following a bunionectomy, SKY0402 appeared to be well tolerated. The maximum plasma level observed in the study was 530 ng/mL, which was substantially less than that observed in the hemorrhoidectomy study.

Conclusions

SKY0402 was demonstrated to be superior to placebo for providing analgesia following a bunionectomy when used in conjunction with oxycodone, acetaminophen and ketorolac. This analgesic effect persisted up to 12 hours and no more than 24 hours post-operatively. SKY0402 appears to pose little risk when used as described in this study and for this indication.

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9.4.4 SIMPLE Hemorrhoidectomy 312

A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Active-Control Study to Evaluate the Safety and Efficacy of a Single Administration of SKY0402 for Prolonged Postoperative Analgesia in Subjects Undergoing Hemorrhoidectomy

Objectives

Primary Objective

To demonstrate the superiority of SKY0402 compared with bupivacaine HCl, with respect to the extent and duration of the analgesic effect achieved by a single administration of the study drug via local infiltration in subjects undergoing hemorrhoidectomy under general or spinal anesthesia.

Secondary Objectives

1. To evaluate additional efficacy parameters.
2. To characterize the safety profile of SKY0402 in comparison with bupivacaine HCl.

Study Design

This was a Phase 3, multicenter, parallel-group, active-control, randomized, double-blind study designed to evaluate the efficacy and safety of 300 mg of SKY0402 compared to 100 mg of bupivacaine HCl administered as a local infiltration for postoperative analgesia in subjects undergoing hemorrhoidectomy under general or spinal anesthesia.

Study Population

The study population was drawn from patients presenting for either an internal or combination internal and external hemorrhoidectomy under either a general or a spinal anesthetic. The eligibility for enrollment was based on the criteria listed below.

Inclusion Criteria

1. Male or female, ≥ 18 years of age at the Screening Visit.
2. Female subjects only: Postmenopausal, surgically sterile, or willing to use acceptable means of contraception for at least 30 days after surgery including any of the following:
    a. hormonal contraceptives (e.g., oral, injectable, implantable starting at least 30 days before study drug administration)
    b. effective double-barrier methods (e.g., condoms with spermicide)
    c. intrauterine device
    d. lifestyle with a personal choice of abstinence
    e. non-heterosexual lifestyle
    f. a strictly monogamous relationship with a partner who has had a vasectomy
3. Scheduled to undergo 2- or 3-column excisional hemorrhoidectomy for internal or internal/external hemorrhoids, under general or spinal anesthesia, using Milligan-Morgan or Ferguson-type techniques, including modified approaches with specialized instruments, such as LigaSure™ or harmonic scalpel, with a cumulative incision length of a minimum 3 cm.
4. American Society of Anesthesiology (ASA) Physical Classification System class 1-4.
5. Able and willing to comply with all study visits and procedures.
6. Able to speak, read, and understand the language of the Informed Consent, study questionnaires, and other instruments used for collecting subject-reported outcomes, in order to enable accurate and appropriate responses to pain scales and other required study assessments.
7. Willing and capable of providing written informed consent.

Exclusion Criteria

1. Pregnancy, nursing, or planning to become pregnant during the study or within one month after dosing.
2. Use of any of the following medications within the times specified before surgery:
    a. Long-acting opioid medication within 3 days.
    b. Any opioid medication within 24 hours.
3. Concurrent painful physical condition or concurrent surgery that may require analgesic treatment in the postoperative period for pain that is not strictly related to the hemorrhoidectomy procedure and may confound the postoperative assessments (e.g., rheumatoid arthritis, chronic neuropathic pain, concomitant vasectomy) confound the postoperative study assessments.
4. Single-column hemorrhoidectomy or hemorrhoidectomy without an internal component.
5. Body weight less than 50 kilograms (110 pounds).

6. History of hypersensitivity or idiosyncratic reactions to amide-type local anesthetics, opioid medication, or any ingredients of the medications administered in this study (e.g., sulfites in Marcaine with epinephrine).
7. Contraindication to epinephrine, such as concurrent administration of ergot-type drugs, monoamine oxidase (MAO) inhibitors or antidepressants of triptyline or imipramine types, conditions where the production or exacerbation of tachycardia could prove fatal (e.g., poorly controlled thyrotoxicosis or severe heart disease), or any other pathological conditions that might be aggravated by the effects of epinephrine.
8. Contraindication to any of the pain-control agents planned for postoperative use (e.g., acetaminophen, morphine, oxycodone, morphine, ketorolac, ketoprofen, diclofenac, etc.).
9. Administration of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study.
10. Suspected, or known addiction to or abuse of illicit drug(s), prescription medicine(s), or alcohol within the past 2 years.
11. Uncontrolled anxiety, schizophrenia, or other psychiatric disorder that, in the opinion of the Investigator, may interfere with study assessments or compliance.
12. Significant medical conditions or laboratory results that, in the opinion of the Investigator, indicate an increased vulnerability to study drugs and procedures, and expose the subject to an unreasonable risk as a result of participating in this clinical trial, such as: debilitating diseases, acute illnesses, hypotension, partial or complete conduction block, impaired cardiac function, untreated hypertension, advanced arteriosclerotic heart disease, cerebral vascular insufficiency, pre-existing abnormal neurological or neuromuscular disease (e.g., epilepsy, myasthenia gravis), advanced liver disease, severe renal impairment, advanced diabetes, comorbid conditions associated with an immunocompromised status, such as blood dyscrasias, HIV/AIDS, or recent chemotherapy.
13. Any clinically significant event or condition uncovered during surgery (e.g., excessive bleeding, acute sepsis) that might render the subject medically unstable or complicate the subject's postoperative course.
14. A cumulative incision length less than 3 cm.

Stopping Criteria

This study involved a single dose of study medication; therefore, individual stopping criteria were not related to continued administration of study drug, but rather the ability

of subject's to continue to participate in the follow-up evaluations. The following clinical situations and the methods of follow-up to deal with them were included in the protocol:

1. If a subject experienced an adverse event (AE) that rendered him or her incapable of continuing with the remaining study visits and assessments, the subject was to be discontinued from further participation in the study. A final evaluation visit was to have been performed, so that the subject's study participation could be terminated in a safe and orderly manner.
2. Subjects were to be free to discontinue from the study at any time, without prejudice to future treatment. These subjects were to have been encouraged to complete at least the study safety assessments.
3. A subject may have been discontinued from the study if he or she refused either study drug administration or to comply with study procedures.
4. A subject could be discontinued from the study by the Investigator, if it was considered to be in the best interest of the subject. If the discontinuation occurred after administration of the study drug, a final evaluation visit was to be performed, so that the subject could be terminated in a safe and orderly manner.

Every effort was to be made to follow any ongoing AEs or serious adverse events (SAEs) until satisfactory resolution was obtained or further follow-up was otherwise no longer warranted.

The protocol specified only the following study stopping criteria:

> If Pacira, an Investigator, or officials from regulatory authorities discover conditions during the study that indicate that the study or study site should be terminated, this action may be taken after Pacira has notified the Investigator(s).

Efficacy Endpoints

Primary Efficacy Endpoint

Area under the curve of pain scores with activity, using the NRS-R through 96 hours.

Secondary Efficacy Endpoints

1. Total postoperative consumption of supplemental opioid pain medication through 12, 24, 36, 48, 60, 72, 84, and 96 hours.
2. Proportion of subjects receiving no supplemental opioid pain medication postoperatively through 12, 24, 36, 48, 60, 72, 84, and 96 hours.
3. AUC of NRS-R through 12, 24, 36, 48, 60, 72, and 84 hours.
4. Pain intensity evaluations on NRS-R at each assessed time point.
5. Pain with first bowel movement (NRS-BM).

6. Average daily pain with bowel movement (NRS-BM).
7. Time to first postoperative use of opioid medications.
8. Integrated rank assessment using the NRS-R scores and total postoperative opioid usage through 12, 24, 36, 48, 60, 72, 84, and 96 hours.
9. QOL questionnaire (EQ-5D).
10. Pharmacoeconomic questionnaire.
11. Time to first occurrence of PONV.
12. PONV-free time through 96 hours.
13. Postoperative use of antiemetic medication administered through 12, 24, 36, 48, 60, 72, 84, and 96 hours.
14. Discharge readiness.
15. Time to first bowel movement through 96 hours.
16. Subject's overall satisfaction with postoperative analgesia.
17. Blinded care provider's satisfaction with postoperative analgesia.
18. Time to return to work or normal daily activities.

Safety Assessments

1. AEs through Day 8 and SAEs and deaths through Day 30.
2. Vital signs (temperature, heart rate, and blood pressure) at Baseline, 0.5, 1, 1.5 and 2 hours and on Day 8.
3. Incidence of urinary retention, if reported by >5% of subjects.
4. Incidence of local hemorrhagic complications, if reported by >5% of subjects

Methods

Subjects were to be randomized in a 1:1 ratio to receive either 300 mg SKY0402 or 100 mg bupivacaine HCl with epinephrine 1:200,000. The randomization was to be stratified by site and modality of anesthesia (spinal or general anesthesia). Subjects who were randomized, but withdrew from the study before receiving study drug or did not undergo the planned surgical procedure were to be replaced.

The study drug (i.e., SKY0402 or bupivacaine HCl) was to be administered during surgery by an unblinded member of the surgical team. The unblinded study personnel were not to perform postoperative study assessments. If the adequate assignment of blinded and unblinded study personnel was not practical due to personnel shortages or other objective circumstances, alternative blinding arrangements could be implemented if mutually agreed upon by the Investigator and Pacira. For example, opaque syringes could be used to keep the person administering study drug blinded and enable him/her

to participate in postoperative study assessments. These alternative procedures were to be documented in writing and approved by Pacira.

The protocol for the study was broken down into three time periods: preoperative, intra-operative and postoperative. The procedures for each are described below.

Preoperative Procedures
Screening assessments were to be performed within 30 days before the scheduled surgical procedure. All subjects who were screened for enrollment, but did not meet eligibility criteria or who declined to participate, were to be documented on a screening log with a precise reason for non-participation.

On the day of the surgical procedure, Day 1, after the subject had arrived at the clinic, the subject's eligibility was to have been reconfirmed; a repeat pregnancy test was to have been performed on female subjects of child-bearing potential, a physical exam was to have been performed, baseline values for vital signs and responses to the Quality of Life (QOL) assessment were to have been obtained; and the subject was to have been randomized.

Intraoperative Procedures
The following assessments and procedures were to have been performed during surgical anesthesia, study drug administration, and surgery:

1. Administer general or spinal anesthesia to the subject.
2. Confirm eligibility based on exclusion criteria 13 and 14 (i.e., verify that no serious intraoperative complications had occurred and the incision was greater than 3 cm in length).
3. Administer study drug; record the start time of study drug infiltration.
4. Administer ketorolac IV(or appropriate alternative) at end of surgery.

Postoperative Procedures
All procedures were to have been timed from the start of the study drug administration. During the first three hours after the drug was administered, the following assessments and procedures were to have been performed:

1. Vital signs (temperature, resting heart rate, and blood pressure) were to have been measured at 0.5, 1, 1.5, and 2 hours.
2. NRS-R was to have been assessed at the time that the first dose of opioids were given, regardless of route of administration as well as at Hours 1 and 2.
3. As soon as a subject was able to tolerate oral medication, treatment with acetaminophen 1000 mg orally was to have been initiated and continued three times daily for four days.
4. Assessments of readiness for discharge at were to have been performed at Hours 1 and 2 and again at Hour 3, if the subject was still at the surgical facility at that point and his or her overall score was less than 9 at 2 hours.

5. All supplemental pain medications and other concomitant medications (including antiemetics) were to have been recorded.
6. The occurrence and duration (start and stop times) of any episodes of nausea and vomiting were to have been recorded.
7. The date and time of the first and every bowel movement and conduct NRS-BM, if applicable were to have been recorded.
8. The date and time that subject is discharged from the surgical center was to have been recorded.

From Hours 3 through 96 following study drug administration, each subject was to have undergone the following additional assessments and procedures:

1. NRS-Rs were to have been obtained at 4, 8, 12, 24, 36, 48, 60, 72, 84, and 96 hours.
2. Assessments of pain intensity during bowel movements using a numeric rating scale (NRS-BM) were to have been conducted.
3. The QOL questionnaire was to have been administered at 48, 72, and 96 hours.
4. The subject's overall satisfaction with postoperative analgesia was to have been assessed at 96 hours.

On Day 8 (± 24 hours), subjects were to have returned to the study site so that the following assessments and procedures could be conducted:

1. Measurement of vital signs (temperature, resting heart rate, and blood pressure).
2. Assessment of the blinded care provider's satisfaction with postoperative analgesia.
3. Recording subject's responses to the pharmacoeconomic questionnaire (region specific).
4. Recording all Investigator-reported and/or subject-reported AEs and SAEs, for which the subjects were to be particularly questioned about any residual sensory/motor impairment, or signs of nerve and/or tissue irritation.

On Day 30 (± 48 hours), the following actions were to have been taken:

1. Record the date the subject returned to work or normal daily activities.
2. Record any SAEs that occurred since the Day 8 visit and report to Pacira, as appropriate.
3. If subjects were unable to report to the study site or if this visit could not be otherwise conducted in person, the information listed above was to have been obtained through a phone interview with the subject.

The various assessments of the subjects for their levels of pain, use of analgesic products, vital signs, level of satisfaction and occurrence of treatment-emergent adverse reactions were to have been made in accordance with the study procedure schedule that follows.

Schedule

Table 18. Schedule of Study Procedures (taken from Table 1 on page v of the final study report)

Procedure		Screen	Base-line	Surgery	After Study Drug Administration												
						4-96 Hours											
						4	8	12	24	36	48	60	72	84	96		
	Study Day	-30 - 1	1	1	1	1	1	1	2	2	3	3	4	4	5	8	30
	Time Window (±h)				0.16	0.25	.5	.5	1	2	2	3	3	4	4	24	48
Informed consent		X															
Assess/confirm eligibility		X	X	X													
Medical history, demographics and baseline characteristics		X															
Pregnancy test (women of childbearing potential)		X	X														
Physical examination			X														
Train self-assessments		X	X														
Vital signs[B]		X	X		0.5, 1, 1.5, & 2											X	
Randomize subject & prepare study drug			X														
Study drug administration				X													
Ketorolac 30 mg (or equivalent) at end of surgery				X													
NRS-R assessment					1 & 2[C]	X	X	X	X	X	X	X	X	X	X		
Acetaminophen 1000mg TID					X	X	X	X	X	X	X	X	X	X	X		
Assessment for discharge readiness					1, 2 & 3[D]												
Subject's overall satisfaction															X		

Procedure		Screen	Base-line	Surgery	After Study Drug Administration												
						4-96 Hours											
						4	8	12	24	36	48	60	72	84	96		
	Study Day	**-30 - 1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**4**	**5**	**8**	**30**
	Time Window (±h)				**0.16**	**0.25**	**.5**	**.5**	**1**	**2**	**2**	**3**	**3**	**4**	**4**	**24**	**48**
with postoperative analgesia																	
Blinded care provider's satisfaction with postop analgesia																X	
Quality of life questionnaire			X								X		X		X		
Record occurrence and duration of nausea/vomiting					X	X	X	X	X	X	X	X	X	X	X		
Record date/time of each BM and related pain (NRS-BM)					X	X	X	X	X	X	X	X	X	X	X		
Retrieve diaries and or worksheets																X	
Pharmacoeconomic questionnaire (region specific)																X	
Document return to work or basic daily activities																	X
Concomitant medications		X[E]	X[F]	X	X	X	X	X	X	X	X	X	X	X	X		
Record AEs (starting at signing of ICF)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record SAEs (starting at signing of ICF)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[A] Screening must be conducted within 30 days before the administration of study drug.
[B] Measure temperature, heart rate, and blood pressure after the subject has rested for at least 5 minutes in the supine position.
[C] In addition to the 1 and 2 hour assessments, assess NRS-R at the first dose of opioids (regardless of route of administration).
[D] Assess discharge readiness at 3 hours if the subject is still at the surgical facility at that point and his or her overall score was less than 9 at 2 hours.
[E] Instruct the subject to discontinue prohibited medications.
[F] Record all medication the subject used within 3 days before the scheduled surgery.

Amendments to the Protocol

The original protocol was not amended, but there were three "protocol clarification notes" distributed to the study centers and a change in the Medical Monitor. The Medical Monitor was changed from (b) (4) on July 28, 2008.

The protocol clarifications sent to the Investigators during the study included two pertaining to maintaining the double-blind during study drug administration, dated June 25, 2008, and August 1, 2008, and one pertaining to the use of antibiotics and intraoperative local administration of medication (e.g., epinephrine), dated June 27, 2008.

Post Hoc Changes

Prior to unblinding the study, the Applicant decided to pool all sites that enrolled fewer than 10 subjects.

It was also determined that only one site used spinal anesthesia; therefore, the mode of anesthesia was not used in the model.

The BMI data were calculated using an incorrect formula in the database, therefore the BMI data were removed from all tables and listings.

Conduct of the Study

The first subject was screened for enrollment into the study on July 28, 2008, and the last follow-up evaluation of a subject was conducted on February 24, 2009.

The Applicant stated that the clinical aspects of this study were conducted in accordance with the study protocol. Protocol waiver requests (not specified) were granted for the following three subjects: 28-1074, 28-1117, and 61-1170.

The following protocol deviations that were reported:

1. At Site 067, five subjects received 4000 mg of acetaminophen and three subjects received 5000 mg of acetaminophen during the 0-24 hour postoperative period. A corrective action plan was initiated at the site.
2. At Site 067, study drug for two subjects was inadvertently switched.

3. Site 020 failed to record vital signs in the recovery room per the protocol. However, the subjects were safely observed in the post-anesthesia recovery unit. Therefore, the lack of recorded vital signs did not create a safety concern.
4. Subject 057-1119 was randomized but did not give his consent to participate in the study. This subject did not receive any study drug.

These deviations were considered by the Applicant as minor and deemed inconsequential with respect to study results.

Results as Reported by the Applicant

Primary Efficacy Analysis
For the primary efficacy endpoint, AUC of the NRS-R pain intensity scores through 96 hours, SKY 0402 was compared to bupivacaine HCl using ANOVA with treatment and site as the main effects. As shown in the table below, the adjusted mean difference in the AUC of the NRS-R pain intensity scores through 96 hours was not statistically significantly different between the two treatment groups (p=0.15).

It was noted that the treatment groups were similar in their demographics for age, gender, race, ASA classification, weight and height.

Table 19. Primary Efficacy Analysis: NRS-R AUC0-96 hours (based on Table 7, p.55 of the Clinical Study Report)

Statistic	SKY0402	Bupivacaine HCl
N	99	99
Mean	396	359
Standard Deviation	213	194
Median	393	329
Minimum, Maximum Values	18, 866	3, 903
Adjusted Mean (Standard Error)	393 (20)	352 (21)
Difference of Adjusted Mean (Standard Error)	41 (28)	
95% CI for Difference of Adjusted Means	(-15, 6)	
p-value	0.15	

Secondary Efficacy Analyses
There were over 60 secondary endpoints evaluated by the Applicant when the analyses for individual endpoints at multiple timepoints during the study are taken into account, e.g., proportion of subjects receiving no supplemental opioid pain medication postoperatively through 12, 24, 36, 48, 60, 72, 84, and 96 hours. Of these, only 2 differed significantly between treatment groups, and in both cases, the difference

favored bupivacaine HCl over SKY0402. These differences included the adjusted mean NRS-R score at the 84 hour time point (p=0.04) and the mean integrated NRS-R pain intensity scores and supplemental opioid pain medication consumption at the 84 hour time point (p=0.03). There were no other statistically significant differences between the two treatment groups in any other efficacy variable at any time point. The table below summarizes the differences observed for this assessment.

Table 20. Secondary Efficacy Analysis: NRS-R Score at 84 Hours (based on Table 14.2.2.2, p.127 of the Clinical Study Report)

Statistic	**SKY0402** (N=99 enrolled)	**Bupivacaine HCl** (N=99 enrolled)
N (evaluable at this timepoint)	98	96
Mean	4	4
Standard Deviation	3	2
Median	4	3
Minimum, Maximum Values	0, 10	0, 10
Adjusted Mean (Standard Error)	4 (0.3)	4 (0.3)
Difference of Adjusted Mean (Standard Error)	0.7 (0.3)	
95% CI for Difference of Adjusted Means	(0, 1.4)	
p-value	0.04	

Table 21. Secondary Efficacy Analysis: NRS-R AUC0-84 (based on Table 14.2.2.7, p.142 of the Clinical Study Report)

Statistic	**SKY0402** (N=99 enrolled)	**Bupivacaine HCl** (N=99 enrolled)
N (evaluable at this timepoint)	98	96
Mean	-14	14
Standard Deviation	95	87
Median	-23	36
Minimum, Maximum Values	-190, 176	-182, 176
Adjusted Mean (Standard Error)	-16 (9)	13 (9)
Difference of Adjusted Mean (Standard Error)	-28 (13)	
95% CI for Difference of Adjusted Means	(-53, -3)	
p-value	0.03	

Table 22. Secondary Efficacy Analysis: Resumption of Work or Normal Daily Activities by Day 30 (based on Table 14.2.2.18, p. 162 of the Clinical Study Report)

Number of Days from Surgery	SKY0402 (N=99 enrolled)	Bupivacaine HCl (N=99 enrolled)
≤ 7 days (Day 8) [n (%)]	17 (17)	9 (9)
> 7 days - ≤ 14 days (Day 15) [n (%)]	39 (39)	38 (38)
> 14 days - ≤ 21 days (Day 22) [n (%)]	19 (19)	31 (31)
> 21 days [n (%)]	12 (12)	13 (13)
Not reported or did not return [n (%)]	12 (12)	8 (8)
p-value	0.06 (rounded from 0.0576)	

Brief Summary of Safety

The Applicant summarized the safety findings as follows:

1. There were no deaths in the study.
2. Three SAEs were reported during this study. In the SKY0402 group, one subject experienced an SAE of fecal impaction and one subject experienced an SAE of chronic postoperative pain. In the bupivacaine HCl group, one subject experienced an SAE of bleeding peptic ulcer. None of the SAEs was assessed by an Investigator as related to study drug.
3. Perioperative administration of SKY0402 via local infiltration was well tolerated in subjects undergoing hemorrhoidectomy under general or spinal anesthesia. The incidence of treatment emergent adverse events (TEAEs) was similar between the SKY0402 group (66%) and the bupivacaine HCl group (63%).
4. TEAEs common to both treatment groups with an incidence ≥5% were nausea, constipation, vomiting, In the SKY0402 treatment group alone, flatulence, abdominal pain, pyrexia, pruritus, and urinary retention also occurred with an incidence ≥5%. In the bupivacaine HCl treatment group, headache was the only other TEAE with an incidence ≥5%.
5. Headache and dizziness were the only two TEAEs (preferred terms) reported in the Nervous System Disorders system organ class (SOC). Three subjects in each treatment group experienced dizziness. The incidence of headache was lower in the SKY0402 group than in the bupivacaine HCl group. There was only one TEAE reported in the Cardiac Disorders SOC: one subject in the bupivacaine HCl group experienced tachycardia. There were no TEAEs in the Cardiac Disorders SOC reported in the SKY0402 group.

Discussion of Results

The study failed to show a difference between SKY0402 and the currently approved and marketed formulation of bupivacaine HCl. This failure was not only for the primary endpoint of AUC of the NRS of pain intensity scores, at rest, through 96 hours after

surgery, but for 36, 48, 60, 72, and 84 hours as well where the AUCs for SKY0402-treated subjects were greater than those for bupivacaine-treated subjects. At 12 and 24 hours after surgery, the mean AUCs for SKY0402-treated subjects did exceed those of the bupivacaine treated subjects but the differences were 1 and 4 units, respectively, that would have no clinical significance. Further lack of superiority of SKY0402 over bupivacaine was demonstrated by a lack of difference in the following assessments:

- Total postoperative consumption of supplemental opioid pain medication through 12, 24, 36, 48, 60, 72, 84, and 96 hours.
- Proportion of subjects receiving no supplemental opioid pain medication postoperatively through 12, 24, 36, 48, 60, 72, 84, and 96 hours.
- Time to first postoperative use of opioid medications.
- Integrated rank assessment using the NRS-R scores and total postoperative opioid usage through 12, 24, 36, 48, 60, 72, 84, and 96 hours.
- Time to first bowel movement.
- Pain with first bowel movement (NRS-BM).
- Average daily pain with bowel movement (NRS-BM).
- QOL questionnaire (EQ-5D).
- Time to first occurrence of PONV
- Postoperative use of antiemetic medication administered through 12, 24, 36, 48, 60, 72, 84, and 96 hours.
- Discharge readiness.
- Subject's overall satisfaction with postoperative analgesia.
- Blinded care provider's satisfaction with postoperative analgesia.
- Time to return to work or normal daily activities.

Based on the safety assessments made, the two treatments appeared to be equally well tolerated. Of particular interest for these study drugs were the incidents of neurological and cardiac toxicity. The protocol did not include continuous ECG monitoring or specify assessments of neurotoxicity, which limits it utility for characterizing the risk profile of SKY0402; however, no serious adverse events related to these toxicities were reported, which provides some reassurance. It should be noted that the adverse events reported included 3% incidence of dizziness in both treatment groups, and a 1% incidence of moderate anxiety, mild tinnitus and mild blurred vision for SKY0402-treated (subjects 051-1102, 028-1154 and 063-2014, respectively), but not bupivacaine-treated subjects. Each of the neurological adverse events was considered "not related" to study drug by the Investigator. This issue is addressed in the safety section of this review.

Conclusions

This study failed to show any statistically or clinically meaningful advantage of SKY0402 over bupivacaine HCl when used following hemorrhoidectomy despite a systematic

assessment of over 60 different efficacy endpoints. Overall, SKY0402 appeared to be tolerated as well as bupivacaine.

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/s/

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