

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022496Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

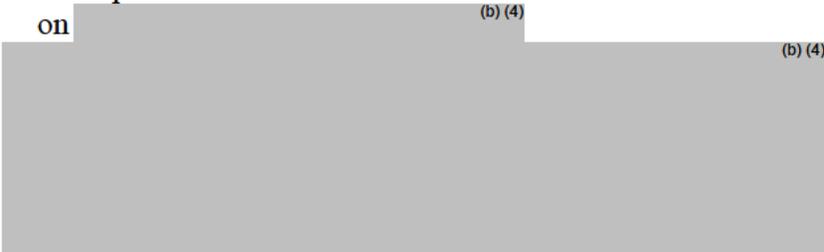
NDA 22-496
Submission Date: September 28, 2010
Brand Name: EXPAREL™
Generic Name: Bupivacaine extended-release liposome injection
Formulation/Strength: Extended-release liposome injection; 150 mg/10 mL and 300 mg/20 mL single use vials
OCP Reviewer: Zhihong Li, Ph.D.
OCP Team Leader: Yun Xu, Ph.D.
OCP Division: Division of Clinical Pharmacology 2
OND Division: Division of Anesthesia and Analgesia Products
Sponsor: Pacira Pharmaceuticals, Inc.
Submission Type; Code: New formulation, standard review; 3S
Dosing regimen: EXPAREL™ is intended for single-dose administration only. The Sponsor recommended the dose of EXPAREL™ is based on (b) (4)
 (b) (4)
Indication: Postsurgical analgesia

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1 EXECUTIVE SUMMARY

1.1 RECOMMENDATIONS

From the viewpoint of the Office of Clinical Pharmacology, NDA 22-496 submitted on September 28, 2010 is acceptable provided that a satisfactory agreement can be reached with the applicant regarding the Labeling for the product.

1.2 PHASE IV COMMITMENTS

None.

Labeling Recommendations

Please see Section 3 Detailed Labeling recommendations.

1.3 CLINICAL PHARMACOLOGY SUMMARY

The current submission is a 505(b)(2) application for SKY0402 (bupivacaine extended-release liposome injection, also referred to as EXPAREL™). SKY0402's active ingredient (bupivacaine) and inactive ingredient (DepoFoam) are each contained, though separately, in previously approved products. Bupivacaine has been marketed in the United States (US) for over 20 years as Marcaine®, which is also the reference listed drug (RLD) for this submission. DepoFoam is a liposomal extended-release formulation contained in the marketed products

DepoCyt[®] (NDA 21-041, 1999) and DepoDur[®] (NDA 21-671, 2004). The form of DepoFoam used in each of the three products – DepoCyt, DepoDur, and SKY0402 – has a (b) (4) different mixture of lipid components. However, unlike the other two products, SKY0402 employs a novel lipid excipient (dierucoylphosphatidylcholine [DEPC]) in its formulation.

As a 505(b)(2) application for a new formulation, the sponsor relies on Marcaine[®] extensively for clinical pharmacology related information. Labeling in related sections is based on approved Marcaine[®] label.

The clinical pharmacology/clinical database in this submission consists of 21 clinical studies (nine Phase 1, seven Phase 2, and five Phase 3 studies) and one observational follow-up study. This Clinical Pharmacology review focused on the five clinical studies which are in patients and have PK data, and also a PK study in subjects with hepatic impairment (SKY0402-C-110). The five studies are Phase 2 and 3 studies following four surgical procedures of inguinal hernia repair (SKY0402-C-201), bunionectomy (SKY0402-C-203 and SKY0402-C-317), (b) (4), (b) (4), and hemorrhoidectomy (SKY0402-C-316). The pharmacokinetic profile of SKY0402 varies with different surgical procedures.

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. (b) (4)

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 post-operative pain following inguinal hernia repair (SKY0402-C-201) and bunionectomy (SKY0402-C-203). (b) (4)

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. Reviewing 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 is not considered as clinically meaningful according to the review by IRT-QT group. A summary of the results is provided in section 4.3 Consult Review.

Overall, adequate Clinical Pharmacology information has been provided to support the current NDA submission.

2 QUESTION BASED REVIEW

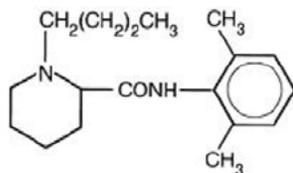
2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Drug substance: bupivacaine base

The chemical name for bupivacaine base is (*RS*)-1-butyl-N-(2,6-dimethylphenyl)piperidine-2-carboxamide or 1-butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide. Bupivacaine base is a racemic mixture, it is white to off-white crystalline powder, crystals or granules.

1. Structural formula:



2. Molecular formula: C₁₈H₂₈N₂O
3. Molecular weight: 288.43

Drug product: SKY0402

SKY0402 is a sterile, non-pyrogenic, white to off-white, preservative-free, aqueous suspension of multivesicular lipid-based particles (DepoFoam[®] drug delivery system) containing bupivacaine at a concentration of 15 mg/mL (expressed as anhydrous bupivacaine hydrochloride equivalent). SKY0402 is based on the DepoFoam technology, a proprietary injectable technology that provides for the sustained release of therapeutic compounds. The DepoFoam technology involves a non-classical, multivesicular liposome (MVL) system. Unlike traditional liposomes, the MVL particles have a non-lamellar honeycomb-like structure with numerous non-concentric aqueous chambers containing dissolved drug. (b) (4)

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Bupivacaine is related chemically and pharmacologically to the amide-type local anesthetics/analgesics. It is a homologue of mepivacaine and is related chemically to lidocaine. All three of these drugs contain an amide linkage between the aromatic nucleus and the amino or piperidine group. They differ in this respect from the procaine-type local anesthetics, which have an ester linkage.

Bupivacaine produces pharmacodynamic effects on the peripheral nervous system or central nervous system (CNS), i.e., at the level of terminal nerve endings and receptors by surface and infiltration anesthesia of nerve plexus, or discrete nerve blocks (peripheral nerve blocks), and into the subarachnoid or epidural space for spinal and epidural analgesia, respectively.

SKY0402 is an extended-release liposomal injection of bupivacaine, an amide-type local anesthetic/analgesic, indicated for single-dose local administration into the surgical wound to produce postsurgical analgesia.

2.1.3 What are the proposed dosage and route of administration?

The sponsor stated that SKY0402 is an extended-release liposome injection of bupivacaine, an amide-type local anesthetic/analgesic, indicated for single-dose local administration into the surgical wound to produce postsurgical analgesia.

The recommended dose of SKY0402 is based on (b) (4) The proposed dose of SKY0402 is (b) (4)

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor conducted five clinical studies in four surgical procedures to evaluate SKY0402 systemic PK and in some studies to compare SKY0402 with bupivacaine HCl to support cross-referencing to the RLD, dosing and claims. The key design features of these studies were summarized in Table 1.

Table 1. Design features of studies to support dosing and/or claims

Type of Study	CTD location, Study Identifier	Phase	Objectives of the Study	Study Design; Type of Control; and Procedure	Test Product(s) and Dosage Regimen; Route of Administration (Volume)	Number of Subjects	Subject Population	Duration of Treatment
Efficacy Safety PK	Section 5.3.5.1, SKY0402-C-201	2	Efficacy Safety PK	Randomized, double-blind, dose escalating, active-controlled	SKY0402 175 mg SKY0402 225 mg SKY0402 300 mg SKY0402 350 mg Bupi HCl 100 mg Local infiltration (40 mL)	12 12 12 14 26	Subjects with postsurgical pain following inguinal hernia repair	Single dose
(b) (4)								
Efficacy Safety PK	Section 5.3.5.1, SKY0402-C-316	3	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
Efficacy Safety PK	Section 5.3.5.1, SKY0402-C-317	3	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
Other	Section 5.3.5.4, SKY0402-C-203	2	Efficacy Safety PK	Randomized, double-blind, active-controlled	SKY0402 175 mg SKY0402 225 mg SKY0402 350 mg Bupi HCl 125 mg Perineural ankle nerve block (25 mL)	12 12 14 20	Subjects with postsurgical pain following bunionectomy	Single dose

The sponsor also conducted a PK study (SKY0402-C-110) to assess the PK and safety of SKY0402 in subjects with impaired hepatic function.

Type of Study	CTD location, Study Identifier	Phase	Objectives of the Study	Study Design; Type of Control; and Procedure	Test Product(s) and Dosage Regimen; Route of Administration (Volume)	Number of Subjects	Subject Population	Duration of Treatment
Intrinsic Factor PK	Section 5.3.3.3, SKY0402-C-110	1	Safety PK Comparison 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 with moderate hepatic impairment	Single dose

A total of 21 clinical studies including 12 clinical pharmacology studies were submitted in the NDA database. A complete list of all clinical studies is provided in Table 2. Studies not mentioned above are not reviewed in details, these include studies in healthy subjects with different dosing routes (e.g., S.C.) than that indicated in the proposed product label or studies with no PK information.

Table 2: Listing of clinical studies

Type of Study	CTD location, Study Identifier	Phase	Objectives of the Study	Study Design; Type of Control; and Procedure	Test Product(s) and Dosage Regimen; Route of Administration (Volume)	Number of Subjects	Subject Population	Duration of Treatment
PK/PD	Section 5.3.3.1, SKY0402-002	1	Safety PK/PD	Randomized, double-blind, active-controlled.	SKY0402 75 mg SKY0402 125 mg SKY0402 150 mg SKY0402 175 mg Bupi HCl 75 mg Perineural nerve block (15 mL)	6 7 6 6 12	Healthy subjects	Single dose
PK	Section 5.3.3.1, SKY0402-021	1	Efficacy Safety PK	Randomized, double-blind, placebo- and active-controlled crossover; 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 10 mg 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 9	Healthy subjects	Single dose
PK/PD	Section 5.3.3.1, SKY0402-C-103	1	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
Type of Study	CTD location, Study Identifier	Phase	Objectives of the Study	Study Design; Type of Control; and Procedure	Test Product(s) and Dosage Regimen; Route of Administration (Volume)	Number of Subjects	Subject Population	Duration of Treatment
PK/ Cardio-vascular	Section 5.3.3.1, SKY0402-C-105	1	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 Moxafloxacin Moxafloxacin-placebo tablet (one subject did not receive moxifloxacin-placebo)	47 47 47 49 48	Healthy subjects	Single dose of placebo or active drug per study period during two study periods
PK/PD	Section 5.3.3.1, SKY0402-C-108	1	PK/PD of 3 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
PK/ Cardio-vascular	Section 5.3.3.1, SKY0402-C-107	1	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

Type of Study	CTD location, Study Identifier	Phase	Objectives of the Study	Study Design; Type of Control; and Procedure	Test Product(s) and Dosage Regimen; Route of Administration (Volume)	Number of Subjects	Subject Population	Duration of Treatment
Intrinsic Factor PK	Section 5.3.3.3, SKY0402-C-110	1	Safety PK Comparison 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 with moderate hepatic impairment	Single dose
PD	Section 5.3.4.1, SKY0402-C-106	1	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 Bupi HCl 2.5 mg 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
PD	Section 5.3.4.1, SKY0402-C-109	1	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 received Bupi HCl in one arm and normal saline in the other arm on another day. Time to onset.	SKY0402 45 mg Bupi HCl 7.5 mg 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
Type of Study	CTD location, Study Identifier	Phase	Objectives of the Study	Study Design; Type of Control; and Procedure	Test Product(s) and Dosage Regimen; Route of Administration (Volume)	Number of Subjects	Subject Population	Duration of Treatment
Intrinsic Factor PK	Section 5.3.3.3, SKY0402-C-110	1	Safety PK Comparison 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 with moderate hepatic impairment	Single dose
PD	Section 5.3.4.1, SKY0402-C-106	1	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 Bupi HCl 2.5 mg 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
PD	Section 5.3.4.1, SKY0402-C-109	1	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 received Bupi HCl in one arm and normal saline in the other arm on another day. Time to onset.	SKY0402 45 mg Bupi HCl 7.5 mg 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

Type of Study	CTD location, Study Identifier	Phase	Objectives of the Study	Study Design; Type of Control; and Procedure	Test Product(s) and Dosage Regimen; Route of Administration (Volume)	Number of Subjects	Subject Population	Duration of Treatment
(b) (4)								
Efficacy and Safety	Section 5.3.5.1, SIMPLE Hemorrhoid-ectomy 312	3	Efficacy Safety	Randomized, double-blind, active-controlled	SKY0402 300 mg Bupi HCl 100 mg Local infiltration (40 mL)	101 103	Subjects with postsurgical pain following hemorrhoid-ectomy	Single dose
(b) (4)								
Efficacy and Safety PK	Section 5.3.5.1, SKY0402-C-316	3	Efficacy Safety PK	Randomized, double-blind, placebo-controlled	SKY0402 300 mg Saline (placebo) Local infiltration (30 mL)	95 94	Subjects with postsurgical pain following hemorrhoid-ectomy	Single dose
Efficacy and Safety PK	Section 5.3.5.1, SKY0402-C-317	3	Efficacy Safety PK	Randomized, double-blind; placebo-controlled	SKY0402 120 mg Saline (placebo) Local infiltration (8 mL)	97 96	Subjects with postsurgical pain following bunion-ectomy	Single dose
Type of Study	CTD location, Study Identifier	Phase	Objectives of the Study	Study Design; Type of Control; and Procedure	Test Product(s) and Dosage Regimen; Route of Administration (Volume)	Number of Subjects	Subject Population	Duration of Treatment
Other	Section 5.3.5.4, SKY0402-C-203	2	Efficacy Safety PK	Randomized, double-blind, active-controlled.	SKY0402 175 mg SKY0402 225 mg SKY0402 350 mg Bupi HCl 125 mg Perineural ankle nerve block (25 mL)	12 12 14 20	Subjects with postsurgical pain following bunionectomy	Single dose
(b) (4)								
(b) (4)								

Note: All studies are completed. Full clinical study reports were written for all studies, with the exception of SKY0402-C-211, for which a Synopsis only was written (the study was terminated early; only three subjects were enrolled).

Definitions: Bupi HCl = bupivacaine HCl (commercially-available Marcaine® or Sensorcaine®); PD = pharmacodynamic; PK = pharmacokinetic; (b) (4)

(b) (4) TQT = thorough QT/QTc study.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Not applicable.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Plasma bupivacaine level was appropriately measured using validated LC-MS/MS methods for pharmacokinetic parameters. See section 2.4 Analytical Section for details.

2.2.4 Exposure-response

No Exposure-response relationship was assessed in this program.

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

Amide-type local anesthetics such as bupivacaine HCl are metabolized primarily in the liver via conjugation with glucuronic acid. Pipecolylxylylidine (PPX) is the major metabolite of bupivacaine HCl; approximately 5% of bupivacaine is converted to PPX.

2.2.5.1 What are the single dose and multiple dose PK parameters?

SKY0402 is intended for single-dose local administration only. PK characteristics are summarized in the following ADME sections.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

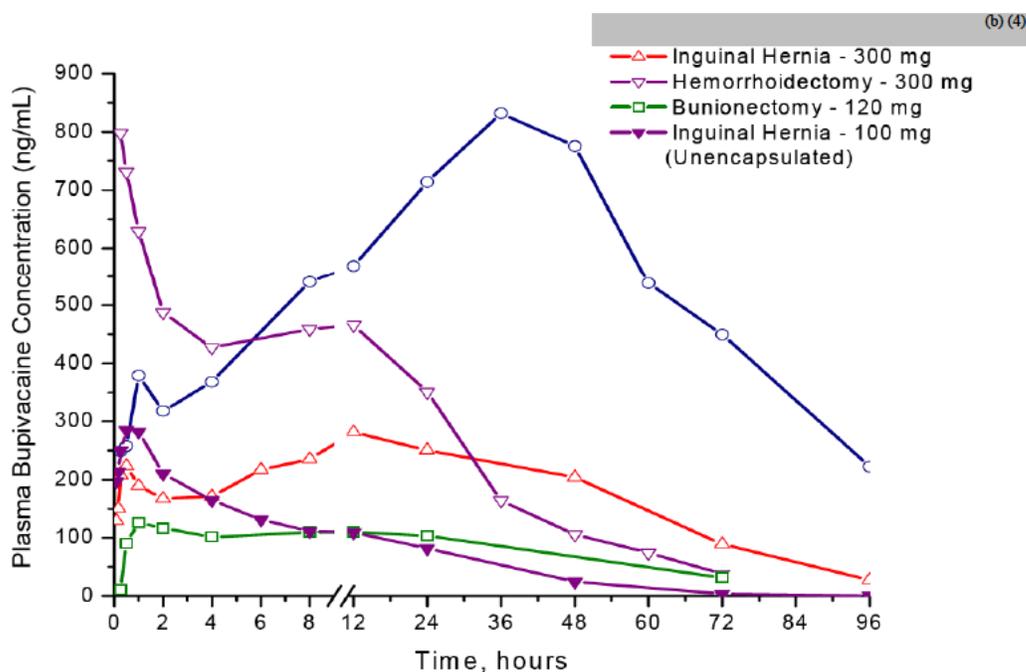
SKY0402 is intended for single-dose administration into the surgical wound. It is impossible and unethical to obtain PK samples in healthy volunteers with SKY0402 administered into surgical wounds. Therefore, only PK in patients with surgical wound is considered relevant and the PK studies in healthy volunteers are not reviewed in detail in the review.

2.2.5.3 What are the characteristics of drug absorption?

The rate of systemic absorption of bupivacaine is dependent upon the total dose of drug administered, the route of administration, and the vascularity of the administration site.

Mean plasma bupivacaine concentration–time curves by dose group in these four studies are presented in Figure 1.

Figure 1: Mean Plasma Concentrations of Bupivacaine After Administration of Single Doses of SKY0402 and Bupivacaine HCl (Unencapsulated)



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 that followed by a second peak that occurs at a median time of 12 to 24 hours.

Pharmacokinetic parameters were calculated using bupivacaine plasma concentrations obtained at various times after local administration of SKY0402 during several surgical procedures, including bunionectomy, inguinal hernia repair, hemorrhoidectomy, (b) (4). Descriptive statistics of PK parameters of representative SKY0402 doses in each study are provided in Table 3.

The sponsor submitted three studies that have head-to-head comparisons of bupivacaine immediate-release (IR) formulation and SKY0402 in systemic exposure. Compared to the unencapsulated IR formulation of bupivacaine, the plasma concentration-time profiles of SKY0402 are significantly different in two surgical procedures inguinal hernia repair (Study SKY0402-C-201) and bunionectomy (Study SKY0402-C-203). The T_{max} was significantly prolonged for SKY0402. (b) (4)

Based on only the systemic exposure profile, SKY0402 demonstrates the characteristics of delayed T_{max} for an extended-release product. (b) (4)

Table 3: Summary of Pharmacokinetic Parameters for Bupivacaine after Administration of Single Doses of SKY0402 and Bupivacaine HCl

Parameter [1]	Dose and Surgery/Incision Size			(b) (4)	Bupivacaine HCl	
	120 mg <3 cm	300 mg ≥3 cm				100 mg ≥3 cm
	SKY0402					Inguinal Hernia Study SKY0402-C-201 (N=27)
	Bunionectomy Study SKY0402-C-317 (N=26)	Hemorrhoidectomy Study SKY0402-C-316 (N=25)	Inguinal Hernia Study SKY0402-C-201 (N=12)			
C _{max} (ng/mL)	166 (92.7)	867 (353)	365 (128)		336 (156)	
T _{max} (h)	2	0.5	12		0.6	
AUC _(0-t) (h×ng/mL)	5864 (2038)	16,867 (7868)	16,028 (5455)		4360 (1559)	
AUC _(inf) (h×ng/mL)	7105 (2283)	18,289 (7569)	16,758 (6288)		4372 (1560)	
t _{1/2} (h)	34.1 (17.0)	23.8 (39.4)	14.6 (4.64)		8.47 (2.89)	

Source: Section 2.7.2, Table 11

[1] Arithmetic mean (standard deviation), except T_{max} (median).

2.2.5.4 What are the characteristics of drug distribution?

After bupivacaine has been released from SKY0402 and is absorbed systemically, bupivacaine distribution is expected to be the same as for other bupivacaine HCl solution formulations.

As described in Marcaine label, local anesthetics are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain. Local anesthetics appear to cross the placenta by passive diffusion. The rate and degree of diffusion is governed by (1) the degree of plasma protein binding, (2) the degree of ionization, and (3) the degree of lipid solubility. Fetal/maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding, because only the free, unbound drug is available for placental transfer. Bupivacaine, with a high protein binding capacity (95%), has a low fetal/maternal ratio (0.2 to 0.4). The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid soluble, non-ionized drugs such as bupivacaine readily enter the fetal blood from the maternal circulation.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

No mass balance study was conducted.

2.2.5.6 What are the characteristics of drug metabolism?

Amide-type local anesthetics such as bupivacaine HCl are metabolized primarily in the liver via conjugation with glucuronic acid. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics. Pipecolylxylidine (PPX) is the major metabolite of bupivacaine HCl; approximately 5% of bupivacaine is converted to PPX.

2.2.5.7 What are the characteristics of drug excretion?

After bupivacaine HCl has been released from SKY0402 and is absorbed systemically, bupivacaine excretion is expected to be the same as for other bupivacaine formulations. Elimination of bupivacaine depends largely upon the availability of plasma protein binding sites in the circulation to carry it to the liver where it is metabolized.

The kidney is the main excretory organ for most local anesthetics and their metabolites. About 6% of bupivacaine is excreted unchanged in the urine. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Acidifying the urine hastens the renal elimination of local anesthetics. Various PK parameters of the local anesthetics can be significantly altered by the presence of hepatic or renal disease, factors affecting urinary pH, renal blood flow, the route of drug administration, and the age of the patient. The half-life of bupivacaine HCl in adults is 2.7 hours and in neonates is 8.1 hours.

2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

Dose proportionality was evaluated in three surgical procedures. As shown in Table 11, SKY0402 showed reasonably dose-proportional increase in the mean values of C_{max} and AUC_{inf} in the management of post-operative pain following inguinal hernia repair (SKY0402-C-201) and bunionectomy (SKY0402-C-203). (b) (4)

2.2.5.9 How do the PK parameters change with time following chronic dosing?

SKY0402 is intended for single-dose administration only.

2.3 INTRINSIC FACTORS

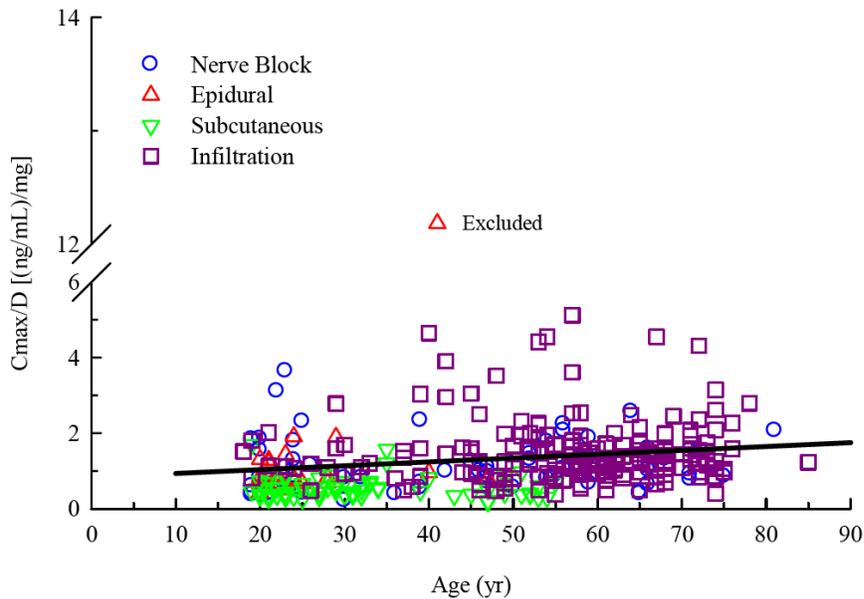
2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

As a 505(b)(2)NDA, the sponsor is cross referencing Marcaine[®] extensively for effects of intrinsic factors.

2.3.1.1 Age

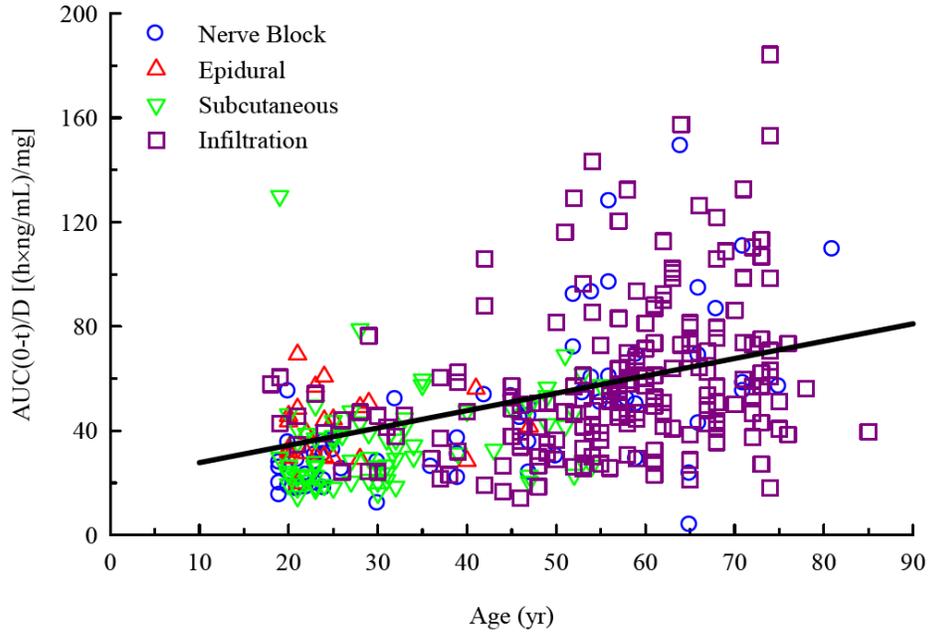
The age of the subjects in the PK studies ranged from 18 to 85 years. There were increases in C_{max}/D (Figure 2), $AUC_{(0-t)}/D$ (Figure 3), and $AUC_{(inf)}/D$ (Figure 4) with increasing age that were statistically significant (Table 4). This increase in exposure is suggestive of a decrease in clearance (CL) uncorrected for bioavailability (F) (CL/F) with increasing age. However, there was no trend toward an increase in $t_{1/2}$ with age and the regression was not significant (Table 4).

Figure 2: Relationship Between Dose-normalized Bupivacaine C_{max} and Age after Administration of SKY0402



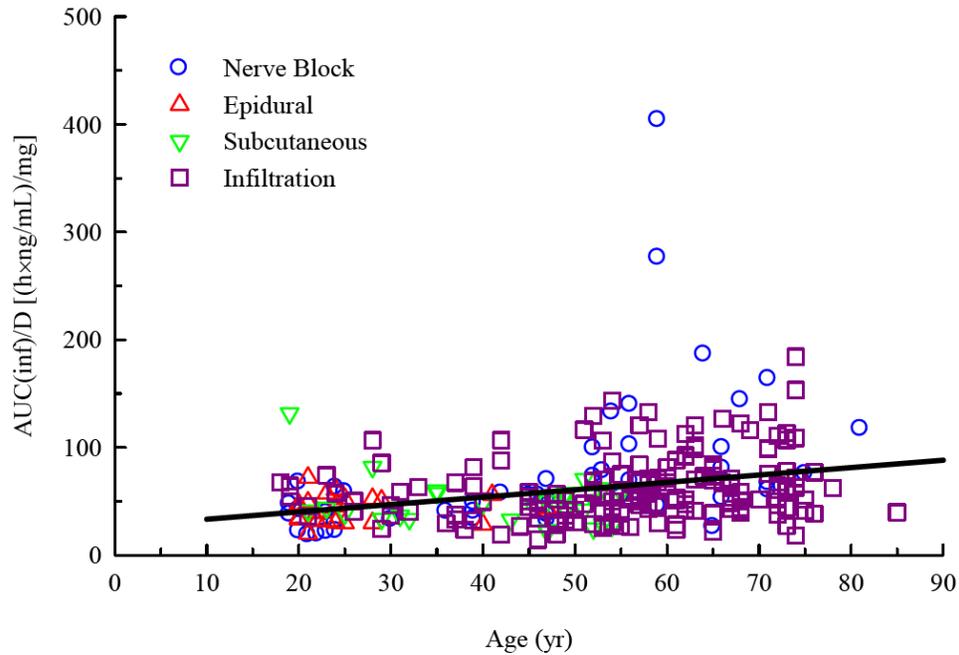
Source: [Section 5.3.5.3, Cross-study integrated PK analysis report](#)

Figure 3: Relationship Between Dose-normalized Bupivacaine $AUC_{(0-t)}$ and Age after Administration of SKY0402



Source: [Section 5.3.5.3, Cross-study integrated PK analysis report](#)

Figure 4: Relationship Between Dose-normalized Bupivacaine $AUC_{(inf)}$ and Age after Administration of SKY0402



Source: [Section 5.3.5.3, Cross-study integrated PK analysis report](#)

Table 4: Summary of the Regression Analyses of Pharmacokinetic Parameters versus Age

Dependent Variable	Parameter	Intercept	Slope	p-value [1]
Age	C_{max}/D	0.83	0.0102	0.0026
	$AUC_{(0-t)}/D$	21.10	0.6647	0.0000
	$AUC_{(inf)}/D$	26.42	0.6871	0.0000
	$t_{1/2}$	30.62	-0.1386	0.1505

Source: [Section 5.3.5.3, Cross-study integrated PK analysis report](#)

[1] p-value for the regression; values <0.05 are statistically significant.

Pediatric patients

[REDACTED] (b) (4)

- 1. [REDACTED]
- 2. [REDACTED]

[REDACTED] (b) (4)

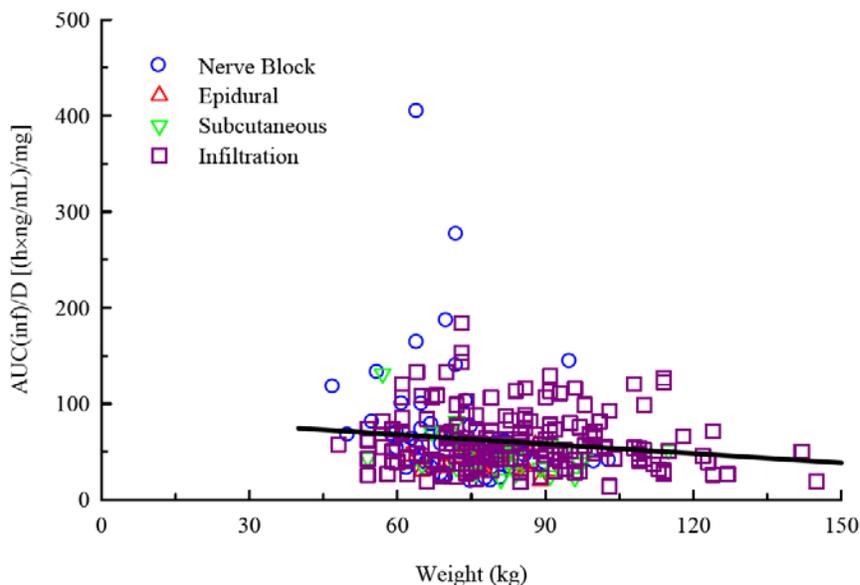
The sponsor requested a deferral for the age group sub sets of 2-5, 6-11 and 12- (b) (4) years. Since the younger age groups are considered more vulnerable and it is more difficult to assess response to therapy and doses, the sponsor proposed to determine the safety and efficacy of SKY0402 in older age groups first and then proceed to the younger patients. (1) For age group 12 to (b) (4) years, the sponsor believes that they currently have sufficient safety information from juvenile animals and clinical data in adults to initiate studies in pediatric patients. Older children/adolescents 12 to (b) (4) years would be considered at lower risk for systemic toxicity and will therefore be studied before young children to help define dosing. A clinical study protocol synopsis in the age group from 12 to (b) (4) years is submitted. The sponsor will rely on this study to provide useful data on possible dose adjustments required for the younger pediatric populations (i.e. 6-11 and 2-5). (2) For age group 6 to 11 years, the sponsor considers that a juvenile toxicity study is required in order to compliment the clinical data from adults and older children (12 to (b) (4) years). It is proposed to conduct such a study before undertaking clinical studies in pediatric patients younger than 12 years of age. Upon completion of the above pediatric older children/adolescents study, assuming no untoward safety concerns are found, and upon successful completion of the further juvenile rat study, initiation of the study of pediatric patients (Children 6 to 11 years) will

commence. (3) For age group 2 to 5 years, the sponsor decided that upon completion and careful evaluation of the study data from the pediatric study in children 6 to 11 years old and assuming no untoward safety concerns are found, initiation of the study of pediatric patients (Children 2 to 5 years) will commence.

2.3.1.2 Body Weight

There were no apparent relationships between C_{max}/D , $AUC_{(0-t)}/D$, or $t_{1/2}$ and body weight; none of those regression analyses were statistically significant (Table 5). There was a significant negative relationship between $AUC_{(inf)}/D$ and body weight (Figure 5, Table 5), suggesting a decrease in systemic exposure with an increase in body weight. However, examination of Figure 5 shows that comparable values of $AUC_{(inf)}/D$ are seen across the range of observed body weights. Consequently, although this relationship was statistically significant, it is not likely to be of clinical significance.

Figure 5: Relationship Between Dose-normalized Bupivacaine AUC(inf) and Weight after Administration of SKY0402



Source: [Section 5.3.5.3, Cross-study integrated PK analysis report](#)

Table 5: Summary of the Regression Analyses of Pharmacokinetic Parameters versus Weight

Dependent Variable	Parameter	Intercept	Slope	p-value [1]
Weight	C_{max}/D	1.75	-0.0050	0.1485
	$AUC_{(0-t)}/D$	64.75	-0.1266	0.2173
	$AUC_{(inf)}/D$	87.34	-0.3261	0.0204
	$t_{1/2}$	39.07	-0.1904	0.0512

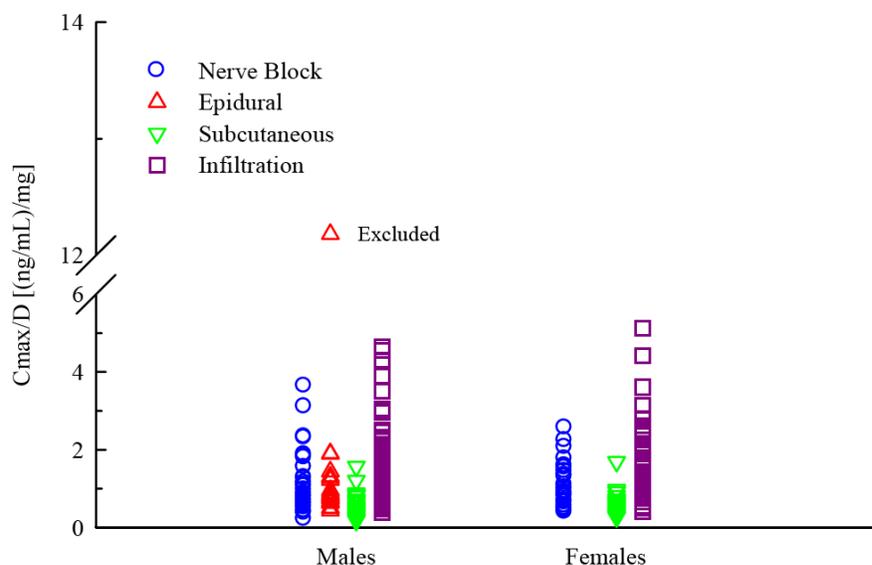
Source: [Section 5.3.5.3, Cross-study integrated PK analysis report](#)

[1] p-value for the regression; values <0.05 are statistically significant.

2.3.1.3 Gender

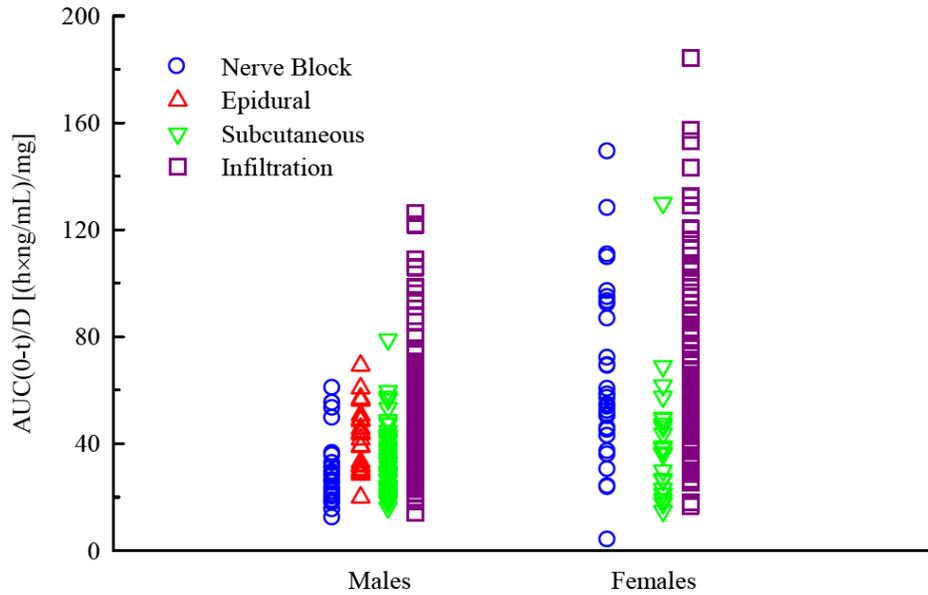
Values for C_{max}/D (Figure 6), $AUC_{(0-t)}/D$ (Figure 7), and $AUC_{(inf)}/D$ (Figure 8) were greater in females than in males and the differences were statistically significant (Table 6). The least squares means were 22%, 51%, and 64% higher for C_{max}/D , $AUC_{(0-t)}/D$, and $AUC_{(inf)}/D$, respectively, in females than in males (Table 6). Although the mean body weight for females (72 kg) was 11% lower than that in males (81 kg), this does not totally account for the difference, particularly for the AUCs, i.e. a higher exposure due to a higher per kilogram dose. There were no apparent differences in $t_{1/2}$ between males and females. Although the least squares mean was higher in females than in males, 28 hours vs. 22 hours, the difference was not statistically significant (Table 6). These results are based on cross study analysis, for the applied surgical procedure local infiltration only, exposure difference between male and females are not statistically significant.

Figure 6: Distribution of Dose-normalized Bupivacaine C_{max} by Gender after Administration of SKY0402



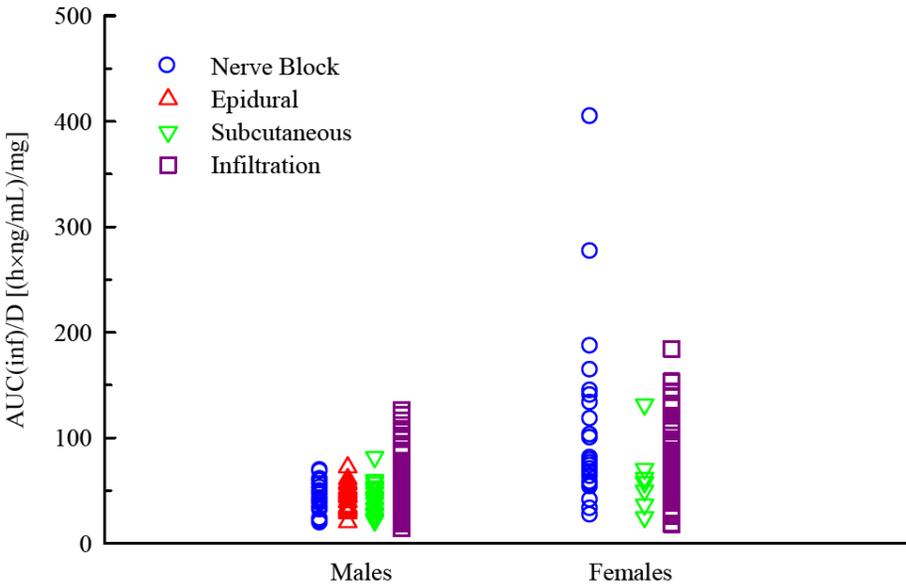
Source: [Section 5.3.5.3, Cross-study integrated PK analysis report](#)

Figure 7: Distribution of Dose-normalized Bupivacaine AUC(0-t) by Gender after Administration of SKY0402



Source: [Section 5.3.5.3, Cross-study integrated PK analysis report](#)

Figure 8: Distribution of Dose-normalized Bupivacaine AUC(inf) by Gender after Administration of SKY0402



Source: [Section 5.3.5.3, Cross-study integrated PK analysis report](#)

Table 6: Summary of the Analyses of Pharmacokinetic Parameters by Gender

Parameter	Least Squares Mean		p-value [1]
	Males	Females	
C_{max}/D	1.13	1.38	0.0136
$AUC_{(0-t)}/D$	42.40	63.84	0.0000
$AUC_{(inf)}/D$	48.82	80.15	0.0000
$t_{1/2}$	22.03	27.98	0.0942

Source: [Section 5.3.5.3, Cross-study integrated PK analysis report](#)

[1] p-value for the regression; values <0.05 are statistically significant.

2.3.1.4 Hepatic impairment

The sponsor evaluated the PK profile of SKY0402 in subjects with moderate hepatic impairment (Child-Pugh Score 7-9, Class B). 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 the product is local acting and the systemic exposure does not have direct relationship with local efficacy, no dose adjustment is recommended in patients with mild to moderate hepatic impairment. However, the drug should be used cautiously in patients with hepatic disease, consistent with the Marcaine label.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

No dosage regimen adjustment is recommended. As a 505(b)(2) submission, labeling languages in specific population sections are consistent with the Marcaine label. Same as in the Marcaine label, this drug should be used cautiously in patients with hepatic disease. This product is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function and geriatric patients. As indicated in Marcaine label, care should be taken in dose selection, and it may be useful to monitor renal function in geriatric patients and patients with impaired renal function.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

SKY0402 is a local anesthetic/analgesic, indicated for single-dose local administration into the surgical wound. There were no specific studies or analyses designed to evaluate the effects of

factors such as herbal products, diet, smoking or alcohol use on the PK or PD of SKY0402.

2.4.2 Drug-drug interactions

No drug-drug interaction (DDI) study was conducted. DDI information is adopted from the RLD, Marcaine®.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Not applicable.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-market formulation was used in the pivotal clinical trial.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not applicable. SKY0402 is a local anesthetic/analgesic, indicated for single-dose local administration into the surgical wound.

2.5.4 Are the commercial and clinical formulations used during development adequately linked?

The commercial formulation was used in the submitted studies.

2.6 ANALYTICAL SECTION

The LC-MS/MS method for bupivacaine evolved during the SKY0402 development program due to changes in the analytical range, change in instrumentation, and the inclusion of a metabolite, pipecolylxylidine (PPX). Each change was validated and the specific method used for each study is shown in Table 7.

Table 7. Bioanalytical Methods Used for the SKY0402 Clinical Pharmacology Studies

Study	Test Method No.	(b) (4) Validation No.
SKY0402-C-110	(b) (4) SOP-5-77.0	V/PPX/HP
SKY0402-C-201	(b) (4) SOP-5-45.1	V/BUP/HP/Amend No. 1
SKY0402-C-203	(b) (4) SOP-5-45.1	V/BUP/HP/Amend No. 1

(b) (4)	(b) (4) SOP-5-45.2	V/BUP/HP/Amend No. 2 & V/BUP/HP/Amend No. 3
SKY0402-C-316	(b) (4) SOP-5-77.0	V/PPX/HP
SKY0402-C-317	(b) (4) SOP-5-77.0	V/PPX/HP

V/BUP/HP/Amend No. 1 (SOP 5-45.1)

The assay had a validated linear range for the assay of bupivacaine in plasma of 0.1 to 500 ng/mL. The QC concentrations, within- and between-day coefficients of variation and accuracy are summarized in Table 8.

Table 8: Intra- and Inter-assay Coefficients of Variation and Accuracy for the Assay of Bupivacaine in Human Plasma (V/BUP/HP/Amend No. 1)

Conc (ng/mL)	Precision		Accuracy (% bias)
	Intra-Assay	Inter-Assay	
0.1	3.45	8.32	0.27
0.3	4.25	8.36	-3.13
75	8.26	7.61	0.56
300	3.33	10.55	-1.68
500	5.45	8.18	-8.62
750 [1]	5.03	8.63	-4.90

Source: SKY0402-C-103, SKY0402-C-105, SKY0402-C-107, SKY0402-C-108, SKY0402-C-201, SKY0402-C-203, (b) (4) Clinical study reports

[1] Diluted 1:2 with blank plasma.

(b) (4)

V/PPX/HP (SOP 5-77.0)

The assay had a validated linear range for the assay of bupivacaine in plasma of 1 to 500 ng/mL. The QC concentrations, within- and between-day coefficients of variation, and accuracy for the assay are summarized in Table 10.

Table 10: Intra- and Inter-assay Coefficients of Variation and Accuracy for the Assay of Bupivacaine in Human Plasma (V/PPX/HP)

Conc (ng/mL)	Precision		Accuracy (% bias)
	Intra-Assay	Inter-Assay	
1	2.42	4.19	1.69
3	4.69	3.66	2.38
75	3.70	3.13	3.12
300	3.88	3.75	5.23
500	1.97	2.81	-0.36
1500 [1]	2.10	3.15	6.15

Source: SKY0402-C-110, SKY0402-C-316, SKY0402-C-317 Clinical study reports

[1] Diluted 1:5 with blank plasma.

3 DETAILED LABELING RECOMMENDATIONS

Recommended changes by this reviewer are indicated by strikethrough for deleted text and additions by underlined text, as follows:

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

4 APPENDICES

4.1 PROPOSED PACKAGE INSERT (ORIGINAL AND ANNOTATED)

See attached draft annotated label at the end of this document.

4.2 INDIVIDUAL STUDY REVIEW

4.2.1 SKY0402-C-201: A Phase 2, Multicenter, Randomized, Double-Blind, Dose-Escalating/De-Escalating Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of a Single Dose of Sustained-Release Encapsulated Bupivacaine (SKY0402) in the Management of Postoperative Pain in Subjects Undergoing Inguinal Hernia Repair

Objectives:

The primary objective of this study was to determine the appropriate dose of SKY0402 for the management of post-operative pain following inguinal hernia repair. Secondary objectives were to evaluate the safety, efficacy, and PK of various doses of SKY0402 compared to a single 100 mg dose of bupivacaine HCl.

Study design and sample size:

This was a Phase 2, multicenter, randomized, double-blind, dose-escalating study. SKY0402 was administered in a dose escalating fashion with a starting dose of 175 mg in Cohort 1. The dose levels were 175 mg, 225 mg, 300 mg, and 350 mg. The 100 mg dose of bupivacaine HCl remained constant for all cohorts. Study drug was given as single administration consisting of two SC infiltrations with what was expected to be a slight nerve block component due to several nerves which travel in the area of infiltration.

Seventy-six (76) male subjects undergoing inguinal hernia repair were enrolled and all completed the study. Thirteen (13) subjects in Cohort 1 (175 mg), twelve subjects in Cohort 2 (225 mg), twelve subjects in Cohort 3 (300 mg), and 14 subjects in Cohort 4 (350 mg) received SKY0402. Twelve (12) subjects in Cohort 1 and four subjects in Cohorts 2 through 3 and five subjects in Cohort 4 received bupivacaine HCl. Blood samples were collected for 96 hours after dosing and analyzed for bupivacaine using an LC-MS/MS method.

PK evaluations:

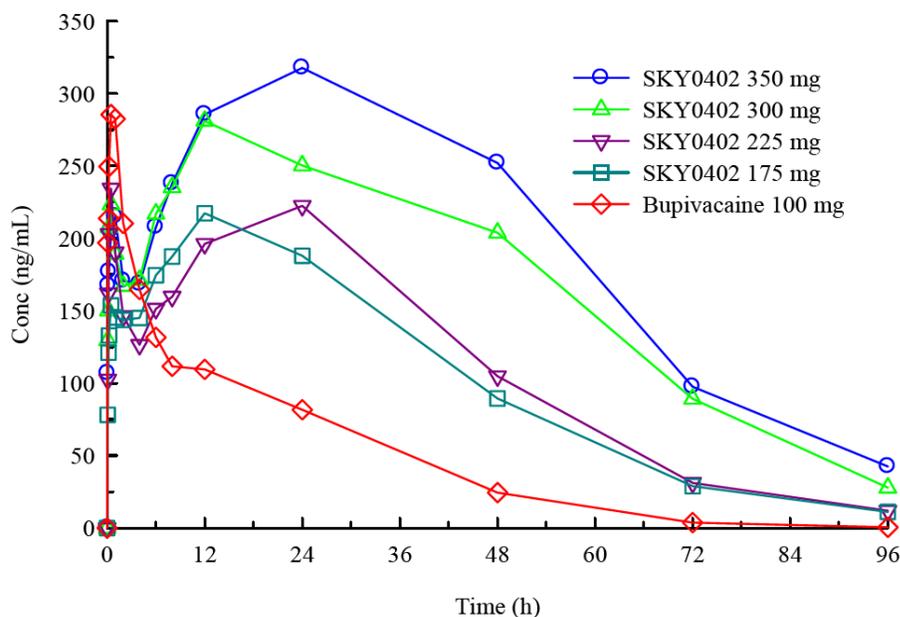
Blood samples to determine plasma bupivacaine concentrations were obtained before dosing and every 5 minutes during the wound infiltration process and at the following time points after the last wound infiltration injection: 5 (± 2) minutes, 10 (± 2) minutes, 15 (± 2) minutes, 30 (± 5) minutes, 1 hour (± 10 minutes), 2 hours (± 10 minutes), 4 hours (± 15 minutes), 6 hours (± 15 minutes), 8 hours (± 15 minutes), 12 hours (± 15 minutes), 24 hours (± 30 minutes), 48 (± 2) hours, 72 (± 2) hours, and 96 (± 2) hours.

Study results:

There was a dose-related and reasonably dose-proportional increase in the mean plasma bupivacaine concentrations after administration of SKY0402 (Figure 9) and in the mean values of C_{max} and $AUC_{(inf)}$ (Table 11). Although mean plasma concentrations after administration of bupivacaine HCl 100 mg were higher than after all doses of SKY0402 during the initial few hours, from approximately 12 hours onward exposure to bupivacaine from SKY0402 was greater. The mean (standard deviation [SD]) C_{max} for bupivacaine HCl 100 mg, 336 (156) ng/mL, was comparable to those for the 225 mg and 300 mg doses of SKY0402 [303 (83.8) ng/mL and 365 (130) ng/mL, respectively; Table 11]. The $AUC_{(inf)}$ after the bupivacaine HCl 100 mg dose was 4374 (1561) h×ng/mL (Table 11); assuming linear PK, a 300 mg dose would have an $AUC_{(inf)}$ of ~13,000 h×ng/mL, similar to those observed for the 225 mg and 300 mg doses of SKY0402 [10,295 (4486) h×ng/mL and 16,758 (6288) h×ng/mL, respectively; Table 11]. This suggests that the bioavailability of bupivacaine is comparable whether derived from SKY0402 or from bupivacaine HCl.

The apparent terminal elimination half-life ($t_{1/2}$) was similar across SKY0402 dose groups and approximately twice that of bupivacaine HCl (Table 11). This observed difference in the $t_{1/2}$ is likely due to the slow absorption of bupivacaine from the administration site due to the extended release properties of the SKY0402 formulation.

Figure 9: Mean Plasma Concentrations of Bupivacaine after Administration of SKY0402 and Bupivacaine HCl by Local Administration Into the Surgical Wound Into Subjects Undergoing Inguinal Hernia Repair



Source: [Section 5.3.5.1, SKY0402-C-201 Clinical study report](#)

Table 11: Summary of Pharmacokinetic Parameters for Bupivacaine from the Clinical Pharmacology Studies

Study No.	Study Objective [2]	Dose Route Formulation [3]	Subjects No. (M/F) Type	Treatment [3] [SKY0402 Lot No.]	Pharmacokinetic Parameters [1]			
					C _{max} (ng/mL)	T _{max} (h)	AUC _(inf) [4] (h×ng/mL)	t _{1/2} (h)
SKY0402-C-110	To evaluate the PK profile of SKY0402 in subjects with moderate hepatic impairment.	300 mg SC SKY0402	18 (14/4) Healthy Volunteers (9 [7/2] with normal hepatic function, 9 [7/2] with hepatic impairment)	SKY0402 [07-2701]				
				Normal Hepatic Impairment	103 (37.7) 149 (42.6)	48.0 24.0	11,051 (4499) 17,976 (2447)	37.6 (9.80) 46.5 (26.3)
SKY0402-C-201	To evaluate the PK of various doses of SKY0402 compared to a single 100 mg dose of bupivacaine HCl.	175 mg Infiltration SKY0402	76 (76/0) Subjects Undergoing Inguinal Hernia Repair	SKY0402 [04-2502]				
				175 mg	241 (88.6)	12.0	9597 (4370)	15.9 (6.69)
				225 mg	303 (83.8)	10.1	10,295 (4486)	14.1 (5.14)
				300 mg	365 (130)	12.1	16,758 (6288)	14.6 (4.64)
				350 mg	415 (122)	12.1	19,476 (8015)	18.9 (6.20)
				Bupivacaine 100 mg	336 (156)	0.61	4374 (1561)	8.47 (2.89)
SKY0402-C-203	To evaluate the PK of various doses of SKY0402 compared to a single 125 mg dose of bupivacaine HCl.	175 mg Nerve Block SKY0402	58 (10/48) Subjects Undergoing Bunionectomy	SKY0402 [04-2502; 05-2502]				
				175 mg	241 (84.0)	24.1	19,811 (11,475)	38.6 (32.0)
				225 mg	213 (69.7)	48.0	15,399 (7021)	31.3 (19.5)
				350 mg	365 (241)	36.2	33,729 (37,002)	66.8 (107)
				Bupivacaine 125 mg	542 (230)	0.58	8074 (2883)	11.0 (2.74)
				125 mg Nerve Block SKY0402				
(b) (4)								

SKY0402-C-316	To assess the PK of bupivacaine.	300 mg Infiltration SKY0402	25 (17/8) Subjects Undergoing Hemorrhoid- ectomy (Only subjects in the PK subgroup.)	SKY0402 [08-2507] 300 mg	867 (353)	0.50	18,289 (7569)	23.8 (39.4)
SKY0402-C-317	To assess the PK of bupivacaine.	120 mg Infiltration SKY0402	26 (6/20) Subjects Undergoing First Metatarsal Osteotomy (Only subjects in the PK subgroup.)	SKY0402 [08-2505] 120 mg	166 (92.7)	2.00	7105 (2283)	34.1 (17.0)

[1] Arithmetic mean ± standard deviation except Tmax for which the median is reported. Values are rounded for consistency between studies and tables.

[2] Only the pharmacokinetic objectives of the study are included in this table.

[3] Bupivacaine is used to represent bupivacaine HCl.

[4] AUC_(0-inf) for SKY0402-C-110, SKY0402-C-201, SKY0402-C-203, and (b) (4)

(b) (4)

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4.2.3 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:

The primary objective of this study was to evaluate the magnitude and duration of the effect of a single intraoperative administration of 300 mg of SKY0402 compared with placebo (0.9% sodium chloride for injection) in the reduction of postoperative pain. The primary endpoint was the $AUC_{(0-72)}$ of the numeric rating scale at rest (NRS-R) pain intensity scores through 72 hours, NRS-R $AUC_{(0-72)}$, for subjects receiving SKY0402 versus placebo. The secondary objectives of this study were to evaluate additional efficacy parameters, characterize the safety profile of SKY0402 in comparison with placebo, and to assess the PK of clearance of bupivacaine from the blood plasma.

Study design and sample size:

This was a Phase 3, multicenter, parallel-group, placebo-controlled, randomized, double-blind study to evaluate the efficacy and safety of SKY0402 compared with placebo. Each subject in this study underwent 2- or 3-column excisional hemorrhoidectomy for internal or internal/external hemorrhoids under general anesthesia, using the Milligan-Morgan technique. A single dose of study drug was administered intraoperatively via local infiltration. Approximately 180 subjects were to be enrolled to receive 300 mg SKY0402 or placebo in a 1:1 ratio (90 subjects per treatment group).

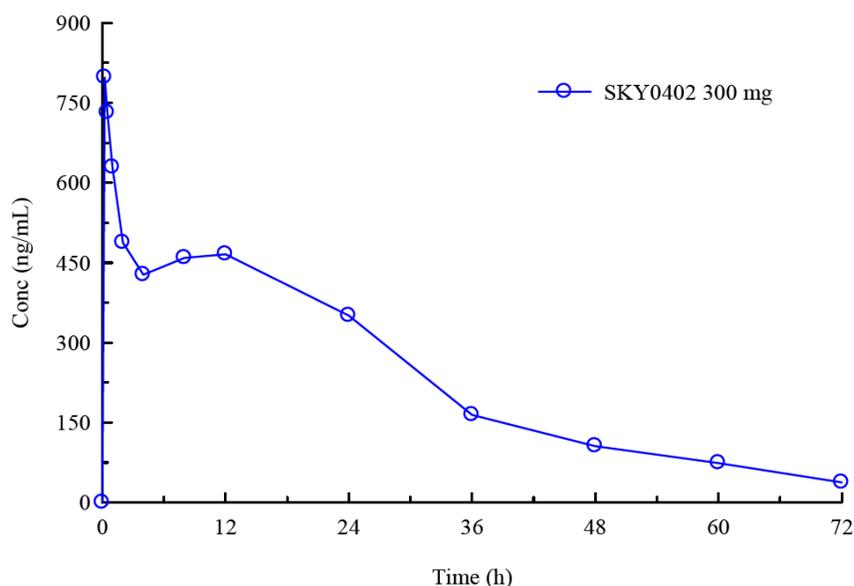
Blood samples for PK analysis were only collected from subjects from selected sites. Blood samples were available for 25 subjects in the SKY0402 arm through 72 hours after surgery and comprised the PK analysis population. Samples were analyzed for bupivacaine using an LC-MS/

MS method. Placebo samples sent to the bioanalytical assay laboratory were not analyzed but were collected to ensure the double-blind treatment.

Study results:

The mean plasma concentrations of bupivacaine are illustrated in Figure 12. A mean C_{max} of 867 (353) ng/mL was reached at a median T_{max} of 0.50 h and the mean $t_{1/2}$ was 23.8 (39.4) h (Table 11).

Figure 12: Mean Plasma Concentrations of Bupivacaine after Administration of Single 300 mg Doses of SKY0402 via Local Infiltration to Subjects Undergoing Hemorrhoidectomy



Source: [Section 5.3.5.1, SKY0402-C-316 Clinical study report](#)

4.2.4 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:

The primary objective of this study was to 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. The primary endpoint was the $AUC_{(0-24)}$ of the NRS pain intensity scores through 24 hours for subjects receiving SKY0402 vs. placebo. The secondary objectives were to evaluate additional efficacy parameters, characterize the safety profile of SKY0402 in comparison with placebo, and assess the PK of clearance of bupivacaine from the blood plasma.

Study design and sample size:

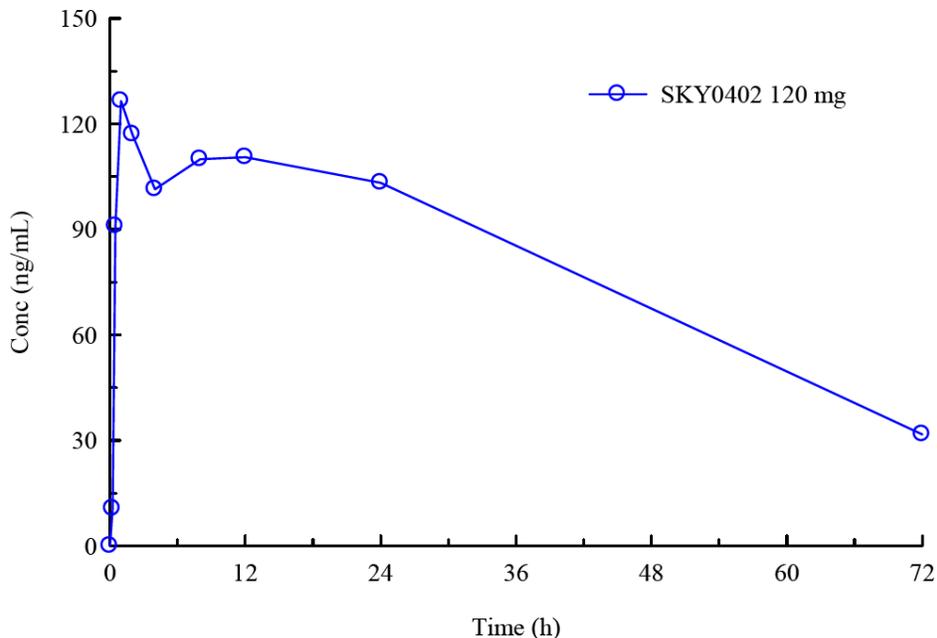
This was a Phase 3, multicenter, parallel-group, placebo-controlled, randomized, double-blind study to evaluate the efficacy and safety of SKY0402 compared with placebo. On Day 1, each subject in this study underwent bunionectomy under midazolam (up to a total of 10 mg intravenously [IV]) and/or propofol sedation followed by a Mayo block utilizing a maximum of 25 mL of 2% lidocaine without epinephrine. At least 30 minutes after the lidocaine was injected, a single dose of study drug was administered intraoperatively by local infiltration. Approximately 186 subjects were to be enrolled to receive 120 mg SKY0402 or placebo in a 1:1 ratio.

Blood samples for PK analysis were only collected from subjects from selected sites. Blood samples were available for 26 subjects in the SKY0402 arm through 72 hours after surgery and comprised the pharmacokinetic analysis population. Samples were analyzed for bupivacaine using an LC-MS/MS method. Placebo samples sent to the bioanalytical assay laboratory were not analyzed but samples were collected to ensure the double-blind treatment.

Study results:

The mean plasma concentrations of bupivacaine are illustrated in Figure 13. A mean C_{max} of 166 (92.7) ng/mL was reached at a median T_{max} of 2.00 h and the mean $t_{1/2}$ was 34.1 (17.0) h (Table 11).

Figure 13: Mean Plasma Concentrations of Bupivacaine after Administration of Single 120 mg Doses of SKY0402 via Local Infiltration to Subjects Undergoing First Metatarsal Osteotomy



Source: [Section 5.3.5.1, SKY0402-C-317 Clinical study report](#)

4.2.5 SKY0402-C-203: A Phase 2, Multicenter, Randomized, Double-Blind, Dose-Escalating/De-Escalating Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Sustained-Release Encapsulated Bupivacaine (SKY0402) Administered as a Nerve Block in the Management of Postoperative Pain in Subjects Undergoing Bunionectomy

Objectives:

The primary objective of this study was to determine the appropriate dose of SKY0402 administered as a nerve block for the management of post-operative pain following a bunionectomy. The secondary objectives were to evaluate the safety, efficacy, and PK of various doses of SKY0402 compared to a 125 mg dose of bupivacaine HCl.

Study design and sample size:

This was a Phase 2, multicenter, randomized, double-blind, dose-escalating study. SKY0402 was administered in a dose escalating fashion, with a starting dose of 175 mg in Cohort 1. The dose levels were 175 mg, 225 mg, and 350 mg. The 125 mg dose of bupivacaine HCl remained constant for all cohorts. Study drug was administered as a single nerve block infiltration.

Fifty-eight (58) healthy male and female volunteers undergoing bunionectomy were enrolled and all subjects completed the study. Twelve (12) subjects in Cohort 1 (175 mg), 12 subjects in Cohort 2 (225 mg), and 14 subjects in Cohort 3 (350 mg) received SKY0402. Twelve (12) subjects in Cohort 1, four subjects in Cohort 2, and four subjects in Cohort 3 received bupivacaine HCl. Blood samples were collected every 5 minutes during the ankle block procedure and for 96 hours after the last ankle block injection. Samples were analyzed for bupivacaine using an LC-MS/MS method.

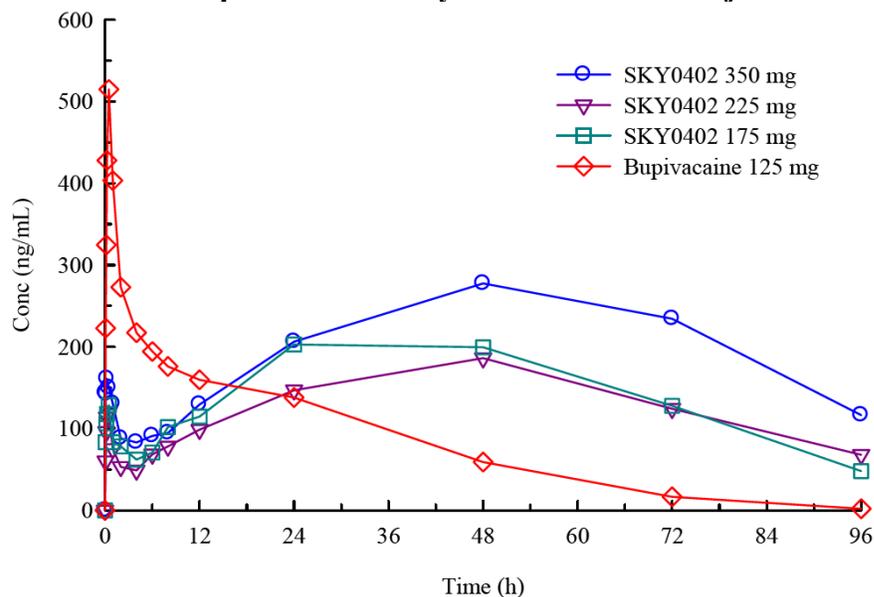
Study results:

There was a dose-related increase in the mean plasma bupivacaine concentrations after administration of SKY0402 (Figure 14) and in the mean values of C_{max} and $AUC_{(inf)}$ (Table 11). Although mean plasma concentrations after administration of bupivacaine HCl were higher than after SKY0402 during the initial few hours, from approximately 16 hours onward exposure to bupivacaine from SKY0402 was greater. The mean C_{max} for bupivacaine HCl 125 mg, 542 (230) ng/mL, was higher than those for all doses of SKY0402 (Table 11). The $AUC_{(inf)}$ after the bupivacaine HCl 125 mg dose was 8074 (2883) h×ng/mL (Table 11); assuming linear PK, a 225 mg dose would have an $AUC_{(inf)}$ of ~14,533 h×ng/mL, similar to that observed for the 225 mg dose of SKY0402 [15,399 (7021) h×ng/mL; Table 11]. This suggests that the bioavailability of bupivacaine is comparable from SKY0402 and bupivacaine HCl.

The $t_{1/2}$ was similar across SKY0402 dose groups and approximately four times longer than that of bupivacaine HCl (Table 11). This observed difference in the $t_{1/2}$ is likely due to the slow absorption of bupivacaine from the administration site due to the extended-release properties of the SKY0402 formulation.

Figure 14: Mean Plasma Concentrations of Bupivacaine after Administration of

SKY0402 and Bupivacaine HCl by Nerve Block to Subjects Undergoing Bunionectomy



Source: [Section 5.3.5.4, SKY0402-C-203 Clinical study report](#)

4.2.6 SKY0402-C-110: An Open-Label, Phase 1 Study to Assess the Pharmacokinetics and Safety of SKY0402 in Subjects with Impaired Hepatic Function

Objectives:

The objectives of this study were a) to evaluate the PK profile of SKY0402 in subjects with moderate hepatic impairment (Child-Pugh Score 7-9, Class B) compared with age-, gender-, and weight-matched control subjects with normal hepatic function, b) to evaluate the safety profile of SKY0402 in subjects with moderate hepatic impairment and in healthy volunteers, and c) to determine if the PK profile of SKY0402 (i.e. the PK of bupivacaine and its major metabolite) is altered in subjects with impaired liver function to the extent that an adjustment of the labeled dosage would be indicated.

Study design and sample size:

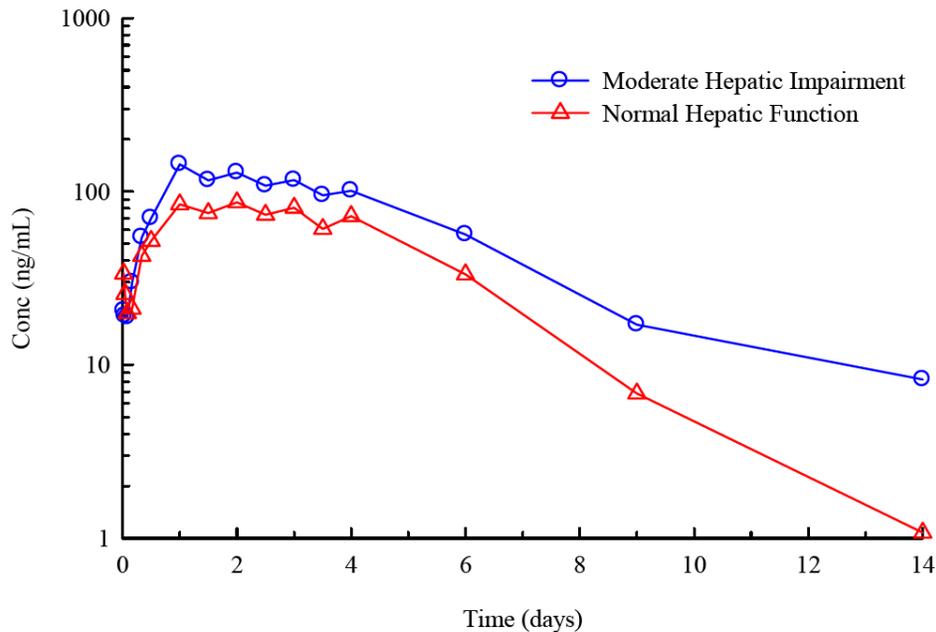
This was a Phase 1, single-center, open-label, parallel-group study in which SKY0402 300 mg was administered via subcutaneous (SC) injection to nine volunteers with moderate hepatic impairment and to nine control subjects with normal hepatic function matched for gender, age ($\pm 15\%$), and weight ($\pm 20\%$). All 18 subjects completed the study.

Blood samples were collected for 24 hours on an in-patient basis. After being discharged, subjects returned to the study facility for outpatient blood sampling at 36, 48, 60, 72, 84, and 96 hours, and then 7, 10, 14, and 21 days after receiving study treatment. Blood samples were analyzed for bupivacaine and pipecolylxylidine (PPX), a major metabolite of bupivacaine, using a liquid chromatography tandem mass spectrometry (LC-MS/MS) method. In addition, the free (unbound) fractions of bupivacaine and PPX were measured in the 24-hour sample.

Study results:

Consistent with the hepatic clearance of bupivacaine, mean plasma concentrations were higher in subjects with moderate hepatic impairment than in healthy controls (Figure 15) with approximate 1.5- and 1.6-fold increases in the mean values for C_{max} and area under the plasma concentration extrapolated to infinity [$AUC_{(inf)}$] (Table 11) time curve. There was a corresponding increase in apparent terminal elimination half life ($t_{1/2}$) of about 20%, from 37.6 (9.80) hours in healthy controls to 46.5 (26.3) hours in subjects with moderate hepatic impairment.

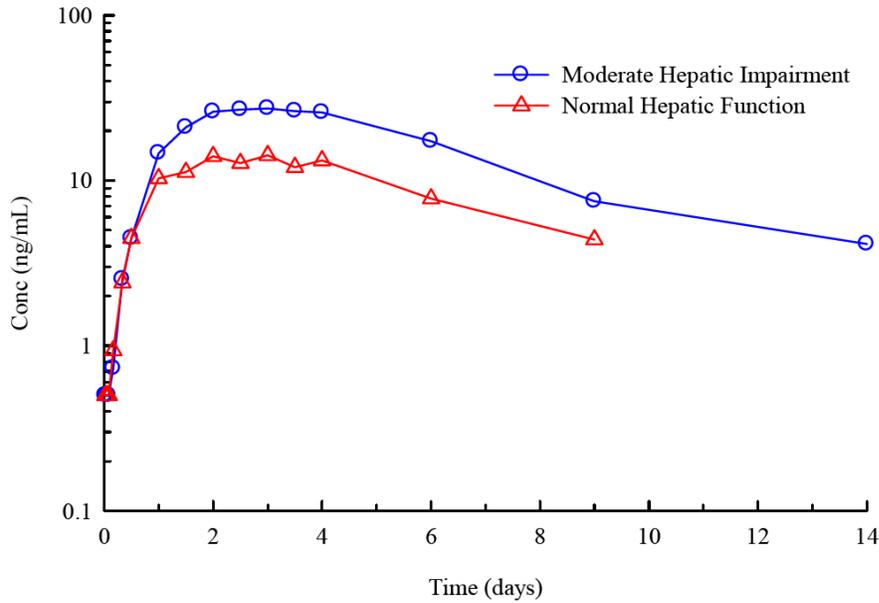
Figure 15: Mean Plasma Concentrations of Bupivacaine after Subcutaneous Administration of 300 mg of Bupivacaine to Subjects with Normal Hepatic Function and Subjects with Moderate Hepatic Impairment



Source: [Section 5.3.3.3, SKY0402-C-110 Clinical study report](#)
Abbreviation: Conc=concentration

Mean plasma concentrations of PPX were also higher in subjects with moderate hepatic impairment (Figure 16) with an approximate 1.9-fold increase in C_{max} and 1.6-fold increase in $AUC_{(inf)}$ (Table 15).

Figure 16: Mean Plasma Concentrations of PPX after Subcutaneous Administration of 300 mg of Bupivacaine to Subjects with Normal Hepatic Function and Subjects with Moderate Hepatic Impairment



Source: Section 5.3.3.3, SKY0402-C-110 Clinical study report

Table 15: Summary of Pharmacokinetic Parameters for Pipecolylxylidine from the Clinical Pharmacology Studies

Study No.	Study Objective [2]	Dose Route Formulation	Subjects No. (M/F) Type	Treatment	Pharmacokinetic Parameters [1]			
					C _{max} (ng/mL)	T _{max} (h)	AUC _(inf) (h×ng/mL)	t _{1/2} (h)
SKY0402-C-110	To evaluate the PK profile of SKY0402 in subjects with moderate hepatic impairment.	300 mg SC SKY0402	18 (14/4) Healthy Volunteers (9 [7/2] with normal hepatic function, 9 [7/2] with hepatic impairment)	SKY0402 Normal Hepatic Impairment	16.2 (9.90) 31.2 (18.9)	65.3 72.0	2760 (1319) 4507 (2747)	154 (205) 57.4 (28.1)

[1] Arithmetic mean (standard deviation) except T_{max} for which the median is reported. Values are rounded for consistency between studies and tables.

[2] Only the PK objectives of the study are included in this table.

4.3 CONSULT REVIEW

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

SUMMARY

No apparent QT prolongation effect of bupivacaine (SKY0402) (300, 450, 600, and 750 mg) was detected in two QT studies (Study SKY0402-C-105 and Study SKY0402-C-107). Bupivacaine appears to be associated with concentration-dependent QTc interval shortening. Similar negative concentration-QT relationships were observed in all tested dose groups across two QT studies (Figure 18 and Figure 19). As shown in Study SKY0402-C-107, the smallest lower bounds of the 2-sided 90% confidence intervals (CI) for the mean differences between SKY0402 (600 and 750 mg) and placebo, per ICH E14 analysis, were -9.1 and -11.9 ms, respectively. The detected QTc interval shortening is not considered as clinically meaningful.

The QT effect following the administration of SKY0402 was evaluated in two QT studies - Study SKY0402-C-105 and Study SKY0402-C-107. Study SKY0402-C-107 is an extension of Study SKY0402-C-105. The overall findings were summarized as follows:

- No apparent QT prolongation effect of 300 mg and 450 mg SKY0402 was detected in Study SKY0402-C-105. Study SKY0402-C-105 was a single center, randomized, 2-stage (placebo/moxifloxacin stage and bupivacaine stage), double-blind, placebo (to moxifloxacin)- and positive-controlled, five-way cross-over trial. A total of 48 healthy subjects received SKY0402 300 mg, SKY0402 450 mg, placebo, and a single oral dose of 400 mg moxifloxacin. The study results for the largest upper bounds of placebo adjusted, baseline-corrected QTcI ($\Delta\Delta\text{QTcI}$) were summarized in Table 16.
- No apparent QT prolongation effect of 600 mg and 750 mg SKY0402 was detected in Study SKY0402-C-107. Study SKY0402-C-107 was a phase I, single center, sequential dose and open-label study. A total of 16 healthy subjects, who were previously enrolled in Study SKY0402-C-107, received SKY0402 600 mg and 750 mg. The study results for the largest upper bounds of $\Delta\Delta\text{QTcI}$ were summarized in Table 15.
- 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 17) and the largest lower bound of the two-sided 90% CI of $\Delta\Delta\text{QTcI}$ greater than 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.

Table 16: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds $\Delta\Delta\text{QTcI}$ for SKY0402 (300mg, 450 mg, 600 mg and 750 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (h)	$\Delta\Delta\text{QTcI}$ (ms)	90% CI (ms)
SKY0402 300 mg	96	1.1	(-1.3, 3.5)
SKY0402 450 mg	0	1.4	(-0.9, 3.6)
SKY0402 600 mg	0	3.6	(-0.9, 8.1)
SKY0402 750 mg	0.5	-1.2	(-6.4, 3.9)
Moxifloxacin 400 mg	3	11.0	(9.0, 12.9) *

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 8.1 ms.

Using 750 mg as suprathreshold dose yields 40% increase in maximum exposure. In patients with moderate hepatic impairment, the C_{max} increases by 50-60%. The suprathreshold dose tested in the trial is slightly (10~ 20%) lower than the maximum exposure achieved in patients with moderate hepatic impairment. Because bupivacaine demonstrates concentration-dependent QTc interval shortening, the maximum exposure in patients with moderate hepatic impairment is unlikely to be associated with meaningful QTc interval prolongation. Because bupivacaine is administered directly into the surgical wound, inadvertent intra-vascular drug administration is possible. However, intravascular administration of bupivacaine changes the intended route of administration. Exposure increase due to overdose or change in route of administration does not need to be covered / investigated by using suprathreshold exposure in a TQT study.

Figure 17: Mean and 90% CI $\Delta\Delta\text{QTcI}$ Time Course for SKY0402 Treatment Group and Moxifloxacin 400 mg (SKY0402-C-105)

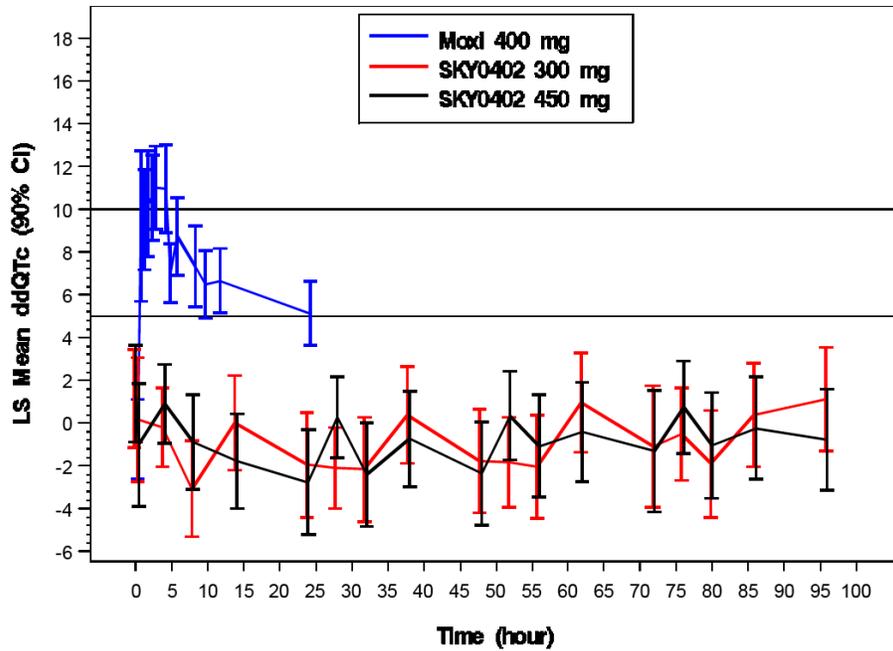


Figure 18: Scatter Plot Showing the Relationship Between $\Delta\Delta QTcI$ (ms) and Bupivacaine Concentrations (ng/mL) in Studies SKY0402-C-105 and SKY0402-C-107 (Shown also are the Population Predicted Line Based on Linear Model for Both Studies)

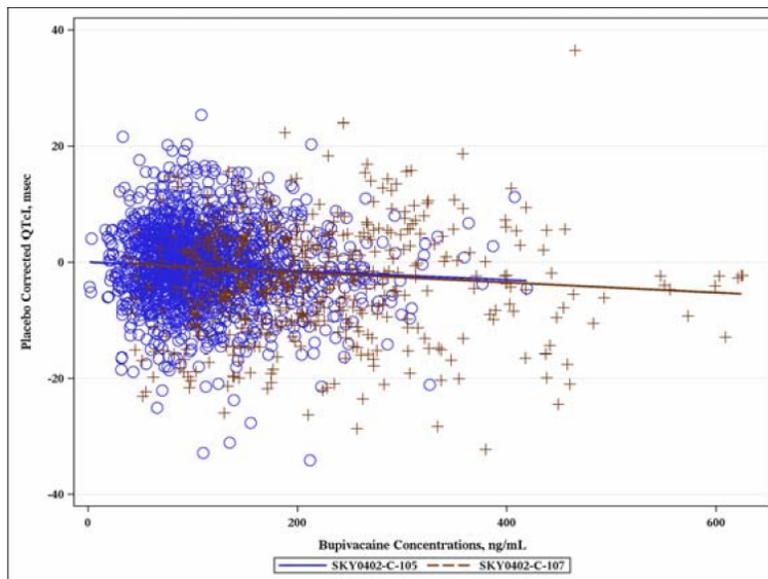
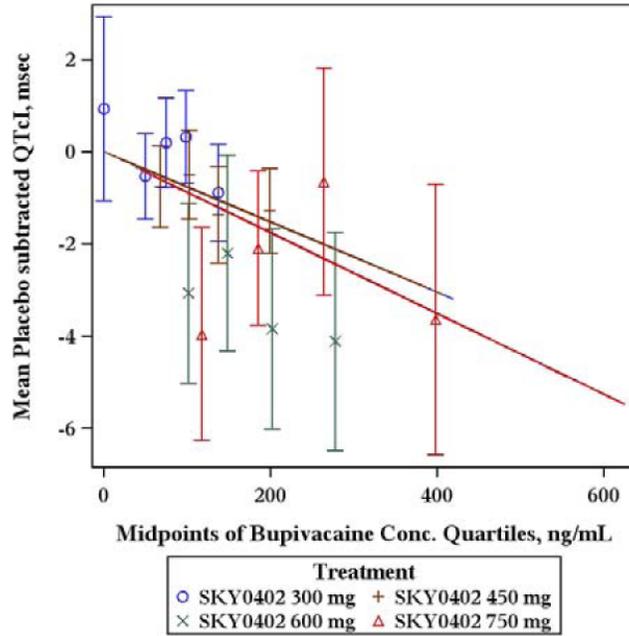


Figure 19: Relationship $\Delta\Delta QTcI$ (ms) and Bupivacaine Concentrations (ng/mL) by Midpoints of Concentration Quartiles (Shown also are the Population Predicted Line Based on Linear Model for Both Studies)



4.4 CLINICAL PHARMACOLOGY FILING MEMO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		Clinical Pharmacology & Biopharmaceutics (HFD 870) Tracking/Action Sheet for Formal/Informal Consults	
From: Zhihong Li, Ph.D.		To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission	
DATE: 12/02/2010	IND No.: Serial No.:	NDA No. 22496	DATE OF DOCUMENT 9/28/2010
NAME OF DRUG SKY0402	PRIORITY CONSIDERATION Standard	Date of informal/Formal Consult: 10/06/2010	
NAME OF THE SPONSOR: [Pacira Pharmaceuticals Inc.]			
TYPE OF SUBMISSION			
CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE			
<input type="checkbox"/> PRE-IND	<input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE	<input type="checkbox"/> FINAL PRINTED LABELING	
<input type="checkbox"/> ANIMAL to HUMAN SCALING	<input type="checkbox"/> BIOAVAILABILITY STUDIES	<input type="checkbox"/> LABELING REVISION	
<input type="checkbox"/> IN-VITRO METABOLISM	<input type="checkbox"/> IN-VIVO WAIVER REQUEST	<input type="checkbox"/> CORRESPONDENCE	
<input type="checkbox"/> PROTOCOL	<input type="checkbox"/> SUPAC RELATED	<input type="checkbox"/> DRUG ADVERTISING	
<input type="checkbox"/> PHASE II PROTOCOL	<input type="checkbox"/> CMC RELATED	<input type="checkbox"/> ADVERSE REACTION REPORT	
<input type="checkbox"/> PHASE III PROTOCOL	<input type="checkbox"/> PROGRESS REPORT	<input type="checkbox"/> ANNUAL REPORTS	
<input type="checkbox"/> DOSING REGIMEN CONSULT	<input type="checkbox"/> SCIENTIFIC INVESTIGATIONS	<input type="checkbox"/> FAX SUBMISSION	
<input type="checkbox"/> PK/PD- POPPK ISSUES	<input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): [Filing Meeting]	
<input type="checkbox"/> PHASE IV RELATED			
REVIEW ACTION			
<input checked="" type="checkbox"/> NAI (No action indicated)	<input type="checkbox"/> Oral communication with Name: []	<input type="checkbox"/> Formal Review/Memo (attached)	
<input type="checkbox"/> E-mail comments to: <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others (Check as appropriate and attach e-mail)	<input type="checkbox"/> Comments communicated in meeting/Telecon. see meeting minutes dated: []	<input type="checkbox"/> See comments below <input type="checkbox"/> See submission cover letter <input type="checkbox"/> OTHER (SPECIFY BELOW):	
REVIEW COMMENT(S)			
<input type="checkbox"/> NEED TO BE COMMUNICATED TO THE SPONSOR		<input type="checkbox"/> HAVE BEEN COMMUNICATED TO THE SPONSOR	
RECOMMENDATIONS:			
This NDA application is fileable from a clinical pharmacology perspective.			
BACKGROUND:			
Pacira Pharmaceuticals, Inc. has submitted this original New Drug Application (NDA 22-496) for SKY0402 (bupivacaine extended-release liposome injection) to be marketed under the proposed proprietary name EXPAREL™ in accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and 21 CFR Part 314.50 and 314.54.			
SKY0402 is an extended-release liposome injection of bupivacaine, an amide-type local anesthetic/analgesic, indicated for single-dose local administration into the surgical wound to produce postsurgical analgesia. The drug product has two strengths, 150 mg in a 10 mL single use vial and 300 mg in a 20 mL single use vial. SKY0402's active ingredient (bupivacaine) has been marketed in the US for over 30 years as Marcaine® (bupivacaine HCl			

<p>injection) and is listed as the Reference Listed Drug (NDA 16-964). The sponsor also reference published literature for historic and supporting information on the compound.</p> <p>A total of 21 Clinical studies including 12 Clinical Pharmacology studies are submitted in the NDA database. The sponsor requests (b) (4) deferral of pediatric studies for the age group of 2 to (b) (4). The conducted Clinical Pharmacology/Biopharmaceutics studies meet the regulatory requirements for filing and this application is fileable from a clinical pharmacology perspective. The Clinical Pharmacology filing check list and slides presented at the filing meeting on 11/03/2010 are attached as attachment-1 and attachment-2, respectively to this tracking sheet.</p>	
<p>SIGNATURE OF REVIEWER: <u>Zhihong Li, Ph.D.</u></p> <p>SIGNATURE OF TEAM LEADER: <u>Suresh Doddapaneni, Ph.D.</u></p>	<p>Date: 12/02/2010</p> <p>Date: 12/02/2010</p>
<p>CC.: HFD # []; TL: []</p>	<p>Project Manager: Date:</p>

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
11	Has the applicant made an appropriate attempt to	X			

2	determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?				
1 3	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
1 4	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
1 5	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Sponsor is requesting a (b) (4) deferral for 2- (b) (4) yrs
1 6	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
1 7	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
1 8	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
1 9	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

None.

Zhihong Li, Ph.D.

12/02/2010

Reviewing Clinical Pharmacologist

Date

Suresh Doddapaneni, Ph.D.

12/02/2009

Team Leader/Supervisor

Date

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/s/

ZHIHONG LI
09/19/2011

YUN XU
09/19/2011

ONDQA BIOPHARMACEUTICS REVIEW SUPPLEMENT

NDA#:	22-496/S-000
Submission Date:	7/27/2011
Brand Name:	Exparel
Generic Name:	Bupivacaine (SKY0402)
Formulation:	Extended release liposome injection
Stengths:	150 mg/10 mL and 300 mg/20 mL vials
Sponsor:	Pacira Pharmaceuticals
Reviewer:	John Duan, Ph.D.
Submission Type:	Original NDA

SKY0402 is an extended-release liposomal injection of bupivacaine, an amide-type local anesthetic/analgesic, indicated for single-dose local administration into the surgical wound to produce postsurgical analgesia. The current review is a supplement for a previous review, in which comments and recommendations were made for the proposed in vitro release specifications.

COMMENTS

The applicant accepted the Agency's recommendations for the acceptance criteria of the in vitro release testing with minor modifications agreed by the Agency. The method and acceptance criteria are summarized below.

Medium:	0.5 % bovine serum albumin (BSA)/50 mM pH 7 phosphate buffered saline (PBS) and 0.05% sodium azide.
Temperature:	37 °C
Dilution:	17-fold dilution and aliquoted in 1.80-mL portions
Rotation Speed:	12 RPM.
Sampling:	0, 4, 24, 48, and 168 hours
Analysis:	HPLC with UV detection at 263 nm.

The acceptance criteria:

4 h:	(b) (4)	released
24 h:	(b) (4)	released
48 h:	(b) (4)	released
168 h:	(b) (4)	released

RECOMMENDATION

An amendment has been submitted to update the new acceptance criteria. No further action is necessary at this time.

John Duan, Ph.D.
Reviewer
ONDQA Biopharmaceutics

Date

Patrick Marroum, Ph.D.
ONDQA Biopharmaceutics

Date

cc: NDA 22-496
Angelica Dorantes, Patrick Marroum, John Duan

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FOLLOWING THIS PAGE



The acceptance criteria are shown below.

- 4 h: (b) (4) released
- 24 h: (b) (4) released
- 48 h: (b) (4) released
- 168 h: NLT (b) (4) released

As discussed during the teleconference and subsequent communications, the method and acceptance criteria are acceptable.

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/s/

JOHN Z DUAN
08/05/2011

PATRICK J MARROUM
08/11/2011

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	22-496/S-000
Submission Date:	9/28/2010, 2/1/2011
Brand Name:	Exparel
Generic Name:	Bupivacaine (SKY0402)
Formulation:	Extended release liposome injection
Stengths:	150 mg/10 mL and 300 mg/20 mL vials
Sponsor:	Pacira Pharmaceuticals
Reviewer:	John Duan, Ph.D.
Submission Type:	Original NDA

SKY0402 is an extended-release liposomal injection of bupivacaine, an amide-type local anesthetic/analgesic, indicated for single-dose local administration into the surgical wound to produce postsurgical analgesia.

RECOMMENDATION

The following comment should be conveyed to the sponsor:

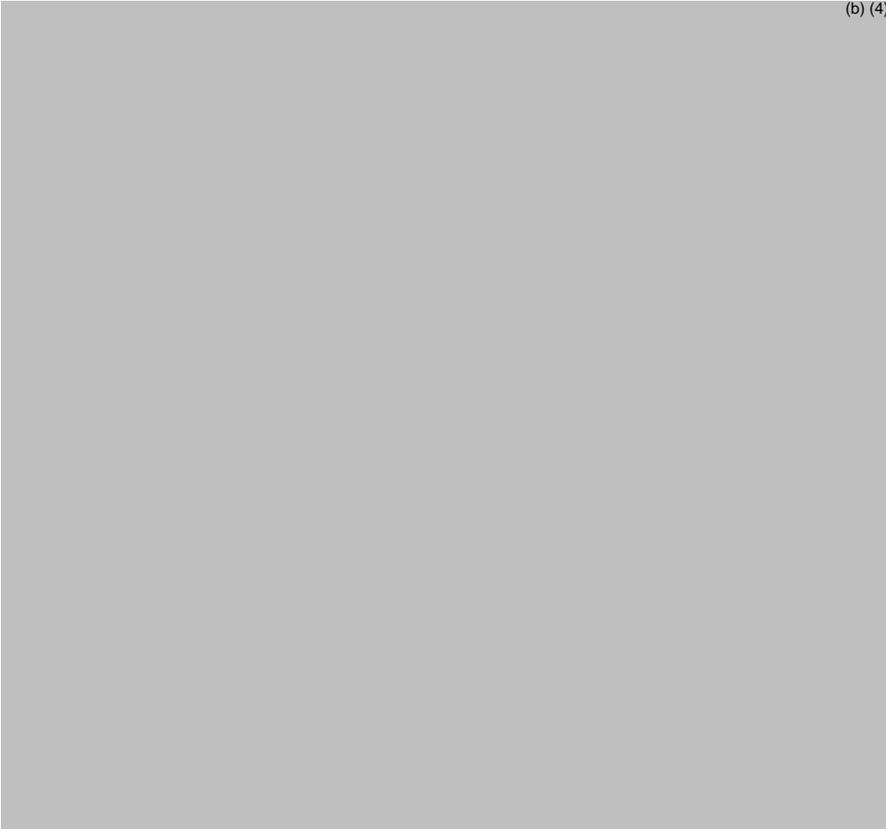


4 hours:	(b) (4)
24 hours:	(b) (4)
48 hours:	(b) (4)

COMMENTS

Agency's Comment #11 – 74-Day Letter (Dec 10, 2010)

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FOLLOWING THIS PAGE



John Duan, Ph.D.
Reviewer
ONDQA Biopharmaceutics

Date

Patrick Marroum, Ph.D.
ONDQA Biopharmaceutics

Date

cc: NDA 22-496
Angelica Dorantes, Patrick Marroum, John Duan

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

/s/

JOHN Z DUAN
06/01/2011

PATRICK J MARROUM
06/03/2011

From: Zhihong Li, Ph.D.

To: DOCUMENT ROOM (LOG-IN and LOG-OUT)
Please log-in this consult and review action for the specified IND/NDA submission

DATE: 12/02/2010

IND No.:
Serial No.:

NDA No.
22496

DATE OF DOCUMENT
9/28/2010

NAME OF DRUG
SKY0402

PRIORITY CONSIDERATION
Standard

Date of informal/Formal Consult:
10/06/2010

NAME OF THE SPONSOR: [Pacira Pharmaceuticals Inc.]

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

- | | | |
|--|--|--|
| <input type="checkbox"/> PRE-IND | <input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> ANIMAL to HUMAN SCALING | <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> IN-VITRO METABOLISM | <input type="checkbox"/> IN-VIVO WAIVER REQUEST | <input type="checkbox"/> CORRESPONDENCE |
| <input type="checkbox"/> PROTOCOL | <input type="checkbox"/> SUPAC RELATED | <input type="checkbox"/> DRUG ADVERTISING |
| <input type="checkbox"/> PHASE II PROTOCOL | <input type="checkbox"/> CMC RELATED | <input type="checkbox"/> ADVERSE REACTION REPORT |
| <input type="checkbox"/> PHASE III PROTOCOL | <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> ANNUAL REPORTS |
| <input type="checkbox"/> DOSING REGIMEN CONSULT | <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS | <input type="checkbox"/> FAX SUBMISSION |
| <input type="checkbox"/> PK/PD- POPPK ISSUES | <input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others) | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> PHASE IV RELATED | | [Filing Meeting] |

REVIEW ACTION

- | | | |
|---|---|--|
| <input checked="" type="checkbox"/> NAI (No action indicated) | <input type="checkbox"/> Oral communication with | <input type="checkbox"/> Formal Review/Memo (attached) |
| <input type="checkbox"/> E-mail comments to: | Name: [] | <input type="checkbox"/> See comments below |
| <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox | <input type="checkbox"/> Comments communicated in | <input type="checkbox"/> See submission cover letter |
| <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others | meeting/Telecon. see meeting minutes | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| (Check as appropriate and attach e-mail) | dated: [] | |

REVIEW COMMENT(S)

- NEED TO BE COMMUNICATED TO THE SPONSOR HAVE BEEN COMMUNICATED TO THE SPONSOR

RECOMMENDATIONS:

This NDA application is fileable from a clinical pharmacology perspective.

BACKGROUND:

Pacira Pharmaceuticals, Inc. has submitted this original New Drug Application (NDA 22-496) for SKY0402 (bupivacaine extended-release liposome injection) to be marketed under the proposed proprietary name EXPAREL™ in accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and 21 CFR Part 314.50 and 314.54.

SKY0402 is an extended-release liposome injection of bupivacaine, an amide-type local anesthetic/analgesic, indicated for single-dose local administration into the surgical wound to produce postsurgical analgesia. The drug product has two strengths, 150 mg in a 10 mL single use vial and 300 mg in a 20 mL single use vial. SKY0402's active ingredient (bupivacaine) has been marketed in the US for over 30 years as Marcaine® (bupivacaine HC1

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	NDA 22496	Brand Name	EXPAREL™
OCP Division (I, II, III, IV, V)	II	Generic Name	SKY0402
Medical Division	DAAP	Drug Class	Amide-type local anesthetics/analgesics
OCP Reviewer	Zhihong Li	Indication(s)	Postsurgical analgesia
OCP Team Leader	Suresh Doddapaneni	Dosage Form	Liposomal injection
Pharmacometrics Reviewer	N/A	Dosing Regimen	Single-dose
Date of Submission	9/28/2010	Route of Administration	Local administration into the surgical wound
Estimated Due Date of OCP Review	3/28/2010	Sponsor	Pacira Pharmaceuticals Inc.
Medical Division Due Date		Priority Classification	Standard
PDUFA Due Date	7/28/2011		

Clin. Pharm. and Biopharm. Information

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	4		
I. Clinical Pharmacology		12		
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	X	12		
Healthy Volunteers-		6		
single dose:	X	6		
multiple dose:	X	0		
Patients-		6		
single dose:		6		
multiple dose:	X	0		
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	X	1		

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PD -				
	Phase 2:			
	Phase 3:			
PK/PD -				
	Phase 1 and/or 2, proof of concept:	X	5	
	Phase 3 clinical trial:	X	2	
Population Analyses -				
	Data rich:			
	Data sparse:			
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
	solution as reference:	X	1	
	alternate formulation as reference:			
Bioequivalence studies -				
	traditional design; single / multi dose:			
	replicate design; single / multi dose:			
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies			16	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	<input type="checkbox"/>	<input type="checkbox"/>	X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	<input type="checkbox"/>	<input type="checkbox"/>	X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X	<input type="checkbox"/>	<input type="checkbox"/>	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X	<input type="checkbox"/>	<input type="checkbox"/>	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	<input type="checkbox"/>	<input type="checkbox"/>	X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	<input type="checkbox"/>	<input type="checkbox"/>	X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	<input type="checkbox"/>	<input type="checkbox"/>	X	Sponsor is requesting a (b) (4) deferral for 2 (b) (4) yrs
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	<input type="checkbox"/>	<input type="checkbox"/>	X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	<input type="checkbox"/>	<input type="checkbox"/>	X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X	<input type="checkbox"/>	<input type="checkbox"/>	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?	<input type="checkbox"/>	<input type="checkbox"/>	X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

None.

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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Zhihong Li, Ph.D.	12/02/2010
Reviewing Clinical Pharmacologist	Date
Suresh Doddapaneni, Ph.D.	12/02/2009
Team Leader/Supervisor	Date

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

/s/

ZHIHONG LI
12/07/2010

SURESH DODDAPANENI
12/07/2010