CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-671

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-671	Submission Date: 7/18/03
	Review Date: 2/20/04
Submission Type; Code:	3S; 505(b)(2)
Brand/Code Name:	U.S. : To-be-determined
Generic Name:	SKY-0401 (Morphine Sulfate Sustained-Release Liposome Injection)
Primary Reviewer:	David Lee, Ph.D.
Secondary Reviewer	Suresh Doddapaneni, Ph.D.
OCPB Division:	DPE 2
ORM Division:	Division of Anesthetic, Critical Care and Addiction Drug Products
Applicant:	SkyePharma, Inc
Relevant IND(s):	52,113
Reference Listed Drug	Duramorph (morphine sulfate injection) – N 18-565 (Elkins-Sinn, Inc)
Formulation; Strength(s):	2-mL ready to use vial; 20 mg/2 mL; 15 mg/1.5 mL; 10 mg/mL
Proposed Indication:	[ ]
Proposed Dosage Regimen:	Single epidural injection at the initiation of surgery 5 mg -30 mg

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1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed the NDA submitted on 7/18/03.

From OCPB point of view, the information contained in the NDA is acceptable provided that (1) the sponsor commits to address the additional data required for the finalization of the in vitro release method and specifications as a post marketing commitment, and (2) a mutually satisfactory agreement can be reached between the Agency and Sponsor regarding the text in the package insert.

1.2 Phase IV Commitments

1. Before the in vitro release method and specifications can be finalized, additional data justifying the proposed method should be submitted. Specifically, release profiles in other media should be submitted justifying the selection of the proposed medium. In addition, quantifying the drug release in the medium rather than drug retained should be explored. Until the method and specifications are finalized, the proposed method can be used on an interim basis.

1.3 Summary of CPB Findings

SkyePharma has submitted NDA 21-671 for the morphine sulfate sustained-release liposome injection on 7/18/03. The pharmacokinetics (PK) of morphine have been studied extensively in the past and has been reported widely. The goal for developing a sustained-release formulation of morphine (also referred to as Skymorph in this NDA) for epidural use was to maintain morphine concentrations for a prolonged period at the epidural space, increasing analgesic duration of action. The Applicant submitted 7 PK studies in the Clinical Pharmacology section. Majority of PK studies measured morphine in the plasma; however, Study DTC96-003 also measured cerebrospinal fluid (CSF) morphine concentrations, although the CSF PK analysis was limited due to few subjects involved in the study (SkyePharma stated that there was considerable intersubject variability).

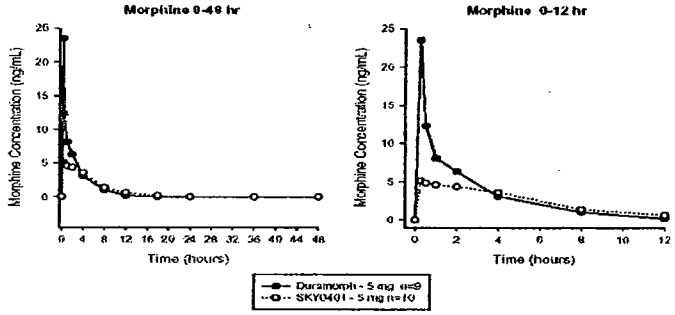
There are three distinct concepts associated with this product. Firstly, following epidural administration, the site of action is believed to be at the spinal level. Free morphine is eliminated from the epidural space, and plasma concentrations mainly reflect removal from the site of action following epidural injection. Thus, the systemic plasma concentrations do not indicate the actual morphine concentration at the epidural space. Additionally, the concentration-related adverse events at the site of action are not clear. It is noted that the concentration of morphine in the CSF has been observed to be 100 to 400 fold higher than the plasma concentration. Since the concentrations in plasma are at best an indirect measure of concentrations at the site of action, the concentration-effect relationships are speculative.

Secondly, in clinical practice, it is likely that morphine liposomes will be administered both with and without a test dose, a lidocaine/epinephrine solution, one of the methods used to rule out misplacement of the epidural needle/cathether. SkyePharma studied the effect of the test dose on the release of morphine from the liposomes by varying the time between the morphine liposome and test dose injections.

Thirdly, the analgesia obtained from epidural morphine is not dependent upon systemic morphine concentrations and the duration of analgesia continues beyond the time during which morphine may be detected in the plasma. Therefore, the relationship between systemic morphine concentration and pain intensity may be misleading.

Concentration-response Relationship: SkyePharma stated that formal pharmacokinetic /pharmacodynamic modeling was not conducted for two reasons. First, there are a limited number of patients with paired effectiveness and plasma pharmacokinetic data; and second, the concentrations in plasma are at best an indirect measure of concentrations at the site of action. However, the relationship between the plasma morphine pharmacokinetics and efficacy results from two pivotal Phase III clinical studies was examined. The results suggest an overall relationship between the dose of SKY0401 and reduction in pain as measured by postoperative fentanyl use or VAS pain intensity scales. The morphine AUC is observed to increase in a roughly dose-proportional fashion in a subset of patients in the same trials.

Relative Bioavailability : The relative bioavailability of Skymorph was compared to that of the reference listed drug, Duramorph (immediate-release morphine sulfate injection; NDA #18565; Elkins-Sinn, Inc.) in a Phase 3 study in patients undergoing lower abdominal surgery (Study SKY0401-012B). A 5 mg Skymorph and a 5 mg Duramorph were compared. Mean concentration-time curves for Duramorph 5 mg and SKY0401 5 mg are provided in the next figure, and a comparison of the pharmacokinetic results is presented in following table (2.7.1.6). (Figure Average Morphine Serum Concentrations Following Administration of Skymorph 5 mg or Duramorph 5 mg; the left-hand panel shows the 48-hr time course and the right-hand panel contains a zoom of the first 12 hr.



Variable	SKY0401 5 mg (n=10)	Duramorph 5 mg (n=9)
Cmax (ng/mL)	7.10 (3.40)	23.77 (12.81)
tmax (hr) [1]	1.00 (0.25–4.0)	0.25 (0.25–2.0)
AUC0-t (ng·hr/mL)	30.86 (11.82)	38.95 (8.03)
AUC (ng·hr/mL)[4]	38.80 (10.35)	42.76 (8.35)
λz (h-1)[4]	0.1813 (0.05)	0.3112 (0.067)
T1/2 (hr) [2,4]	3.82 (1.00)	2.23 (0.49)
Cmax [3]	6.39	20.27
AUC0-t [3]	28.74	38.34
AUC [3,4]	37.41	42.15
[1] Median (min-max)		
[2] Harmonic mean and pseudo standard deviation of the jackknife variance		
[3] Geometric mean of ln-transformed variables		
[4] n=8 for the SKY0401 and Duramorph groups.		

Skymorph's morphine early exposure was less than that of Duramorph (the mean Cmax and AUC of Skymorph morphine were 70 % and 10 % less than that of Duramorph, respectively).

Skymorph Dose proportionality/linearity: In all studies, the pharmacokinetics of SKY0401 appeared to be linear and dose-proportional (based on AUC) across the range of 5 mg to 30 mg. In contrast, Cmax did not always exhibit dose-proportionality and tended to increase by an amount less than the proportional change in dose. Results for the 2.5 mg and 40 mg doses of SKY0401 are not included in the following table because only 2 subjects received each of these doses.

Mean (SE) Morphine Pharmacokinetic Parameters: Pooled Analysis

Parameter	Unencapsulated Morphine 5 mg (n=26)	SKY0401 5 mg (n=14)	SKY0401 10 mg (n=36)	SKY0401 15 mg (n=71)	SKY0401 20 mg (n=63)	SKY0401 25 mg (n=32)	SKY0401 30 mg (n=25)
Cmax (ng/mL)	20.01 (10.08)	9.37 (5.67)	20.01 (9.51)	18.64 (10.43)	26.41 (18.57)	22.58 (15.36)	47.25 (28.87)
AUC0-t (ng hr/mL)	47.81 (39.41)	30.85 (11.82)	135.9 (116.7)	100.9 (43.64)	160.8 (76.34)	158.3 (55.73)	297.9 (134.8)
AUC0-∞(ng hr/mL)	51.67 (34.76)	40.98 (10.63)	124.89 (98.08)	131.62 (73.66)	185.94 (81.42)	207.26 (77.70)	341.51 (136.88)
t1/2 (hr)	5.81 (16.88)	4.244 (2.10)	16.17 (19.66)	19.97 (20.55)	23.90 (25.39)	32.90 (24.2-0)	25.75 (14.58)
λz (hr-1)	0.307 (0.101)	0.194 (0.078)	0.116 (0.096)	0.093 (0.10)	0.096 (0.15)	0.038 (0.03)	0.041 (0.035)
CL/F (mL/min/kg)	23.51 (6.96)	28.85 (9.70)	23.30 (13.53)	31.12 (21.83)	27.68 (12.09)	27.35 (10.63)	22.43 (8.75)
CL/F (mL/min)	1888.96 (520.47)	2190.67 (696.95)	1896.28 (1201.45)	2613.81 (2065.46)	2165.19 (1075.97)	2322.35 (925.98)	1779.10 (937.50)
Vz/F (L/kg)	6.39 (8.22)	9.85 (3.79)	24.24 (26.55)	38.20 (28.17)	46.33 (40.19)	62.02 (31.16)	42.93 (16.68)
Vz/F (L)	495.10 (552.49)	767.18 (341.10)	1766.57 (1562.62)	3026.43 (2105.95)	3641.11 (3217.03)	5346.45 (2903.98)	3262.18 (1429.60)

Skymorph Dose proportionality/linearity in patients: The Cmax and AUC of morphine appear to increase linearly with dose. A comparison of the pharmacokinetics between healthy subjects (Study DTC96-003) and patients undergoing surgery (Study SKY0401-008, -009. -011, -012B and -016) is presented below. The results of the comparison appear to demonstrate higher Cmax, lower AUC, and shorter half-life for healthy subjects compared to patients undergoing surgery. There were no apparent differences between healthy subjects and patients with respect to morphine CL/F, λz, and Vz/F. However, because of the small sample size of healthy subjects at each dose, these results should be interpreted with caution.

Comparison of Mean (SE) Morphine Pharmacokinetics between Healthy Subjects and Patients Undergoing Surgery: Pooled Analysis

	Cmax (ng/mL)	AUC0-∞ (ng·hr/mL)	t1/2 (hr)	λz (hr^{-1})	CL/F (mL/min/kg)	Vz/F (L/kg)
Healthy Subjects						
Unencapsulated MS (n=2)	26.0 (7.21)	39.37 (9.19)	3.34 (0.64)	0.21 (0.04)	25.91 (4.29)	7.62 (2.67)
5 mg SKY0401 (n=4)	15.07 (6.65)	45.33 (11.26)	4.37 (3.17)	0.22 (0.12)	29.91 (8.37)	10.00 (4.84)
10 mg SKY0401 (n=4)	34.25 (3.60)	86.30 (11.65)	9.56 (8.08)	0.11 (0.08)	27.45 (10.34)	19.53 (13.17)
20 mg SKY0401 (n=3)	52.633 (2.28)	171.43 (18.28)	11.27 (2.26)	0.06 (0.01)	30.51 (3.04)	29.94 (7.40)
30 mg SKY0401 (n=4)	58.85 (22.73)	281.15 (49.82)	20.88 (6.00)	0.04 (0.01)	25.82 (6.35)	44.42 (6.15)
Surgery Patients						
Unencapsulated MS (n=24)	19.56 (10.24)	52.84 (36.17)	6.04 (17.69)	0.32 (0.10)	23.28 (7.20)	6.28 (8.59)
5 mg SKY0401 (n=10)	7.10 (3.40)	38.80 (10.35)	4.18 (1.61)	0.18 (0.05)	28.32 (10.81)	9.77 (3.54)
10 mg SKY0401 (n=32)	18.23 (8.45)	131.91 (105.34)	17.37 (21.00)	0.12 (0.10)	22.55 (14.10)	25.10 (28.46)
20 mg SKY0401 (n=60)	25.10 (18.04)	186.77 (83.63)	24.62 (25.93)	0.10 (0.15)	27.51 (12.41)	47.28 (41.13)
30 mg SKY0401 (n=21)	45.04 (29.84)	355.71 (147.75)	26.89 (15.86)	0.04 (0.04)	21.64 (9.20)	42.58 (18.44)
Results presented in arithmetic means						

Skymorph interaction with test dose: Mean dose-normalized Cmax for subjects who received a test dose was approximately 63% higher than that for subjects who did not receive a test dose. However, the results indicated that a wait time of at least 10 minutes substantially mitigates the effect of the test dose on Cmax. As expected, AUC was not affected by administration of the test dose. Additionally, an examination of the effect of a test dose across all clinical studies confirmed the results of Study SKY0401-016.

Effect of Test Dose and Wait Interval on Cmax

		Cmax[1]		AUC0-∞
	n [2]	Mean (SE)	n	Mean (SE)
Test Dose	167	5.87 (0.28)	146	42.19 (1.79)
No Test Dose	**48**	**3.60 (0.32)**	**42**	**38.38 (3.03)**
Test Dose Interval				
≤3 minutes	21	8.70 (1.12)	20	36.96 (4.40)
4-9 minutes	7	5.98 (1.34)	7	42.14 (8.49)
10-14 minutes	**14**	**4.61 (0.73)**	**13**	**44.11 (6.52)**
15-30 minutes	44	5.76 (0.51)	43	40.04 (3.25)
>30 minutes	23	3.67 (0.45)	21	36.89 (4.29)
[1] Dose normalized to 5 mg				
[2] Wait interval information was unavailable for patients in Study SKY0401-008 and SKY0401-009. Therefore, the total n for the interval analysis is lower than that of the test dose group.				

Morphine CSF concentration: The Cmax and AUC of morphine CSF levels were 100 to 400 times that of the systemic morphine concentrations. Morphine was detected in the CSF as early as 5 minutes after injection. Following epidural administration of 2.5 and

5.0 mg of SKY0401, morphine concentrations in CSF were not detected after the 58-hour time point. Following epidural administration of 20 mg SKY0401, CSF concentrations of morphine stayed somewhat constant between 34 and 82 hours; however, at the 96-hour time point, morphine concentrations were not detected. For 10, 30, and 40 mg dosing cohorts, morphine concentrations in the CSF were measurable at 96 hours. In addition, two subjects who were dosed with 30 mg SKY0401 and one subject dosed with 40 mg SKY0401 had morphine CSF concentrations above 100 ng/mL at 96 hours.

Parameter	5 mg (n=2)	10 mg (n=2)	20mg (n=1)
AUC0-∞ (ng hr/mL)	7825.20	27406.11	50462.75
CL/F (L/hr)	0.65	0.53	0.40
Cmax (ng/mL)	3324.75	7035.00	8560.00
MRT (hr)	4.31	4.57	6.02
tmax (hr)	0.58	1.00	3.00
Vz/F (L)	5.55	4.19	3.53
t1/2 (hr)	6.13	10.29	6.17
Data Source: Table 12.3.2, Study DTC96-003			

This study indicated that there were no signs of spinal metabolism. M3G was not detected in CSF and only a trace of M6G was found in one CSF sample. Comparison of elimination profiles for morphine from CSF and plasma for subjects with indwelling catheters indicated that morphine was cleared with similar rates from CSF and plasma. Generally, t1/2 values were comparable for each subject if the values were determined over the same time period. The t1/2 and MRT values generally increased with increasing dose of SKY0401. CSF concentrations of morphine at 24 hours after the epidural dose appeared to be comparable to the minimal concentrations associated with analgesia (10.5-101 ng/mL), suggesting that SKY0401 has the potential to provide analgesia for extended periods, thereby reducing the need for repeated epidural doses.

Morphine-3-β-glucuronide: Plasma concentrations of inactive metabolite, M3G, were generally about 10-fold greater than plasma concentrations of morphine.

Morphine-6-β-glucuronide: Plasma concentrations of the pharmacologically active metabolite, M6G, peaked later than morphine and were also generally higher than plasma morphine concentrations, although peak concentrations of M6G were less than 50% of the morphine Cmax; overall mean AUC0-∞ values for M6G were approximately 1.5-fold higher than the corresponding AUC0-∞ values for morphine.

Metabolite-to-Parent Ratios: The pooled analysis of metabolite to parent (morphine) ratios demonstrated no appreciable dose-related differences in metabolite AUC ratios.

Morphine dose	Mean AUC M3G/M	Mean AUC M6G/M
5 mg	7.96	0.85
10 mg	7.77	1.02
15 mg	9.89	1.53
20 mg	9.79	1.45
25 mg	8.29	1.96
30 mg	10.4	1.38
5 mg Unencapsulated	8.15	0.97

Age and gender:

Cmax

Analysis of Mean (SD) Dose-Normalized Cmax by Gender and Age, All Studies

	Female	Male	≤65 years	>65 years
Parameter	n=128	n=117	n=183	n=62
Cmax (ng/mL)	6.45 (0.39)	5.15 (0.32)	5.87 (0.30)	5.58 (0.49)
Ratio[1]	1.25		1.05	
90% C.I.interval	1.09-1.45		0.89-1.24	
[1] Ratio of the geometric least square (LS) means of female to male/≤65 years to >65 years				

Female subjects exhibited a 25% higher Cmax than male subjects. This is likely due to the typical differences in body weight and body mass index between males and females. Subject age did not have an effect on mean Cmax. For subjects ≥75 years of age, due to the small sample size, statistical analysis was not performed.

CL/F

Analysis of Morphine Clearance (CL/F) by Gender: All Studies, All Doses

	Female	Male		90%	
Parameter	n=109	n=105	Ratio[1]	confidence interval	
CL/F (mL/min/kg)	23.651 (1.027)	26.147 (1.157)	0.9045	0.816	1.002
CL/F (mL/min)	1719.2 (78.089)	2283.3 (105.67)	0.7529	0.676	0.838
[1] Ratio of the geometric least square (LS) means of female to male					

When mean CL/F results were corrected for subject weight, no significant difference was observed between males and females.

Analysis of Morphine Clearance (CL/F) by Age: All Studies, All Doses

	≤65 years	>65 years		90%
Parameter	n=162	n=52	Ratio[1]	confidence interval
CL/F (mL/min/kg)	25.610 (0.911)	22.603 (1.420)	1.1330	1.006-1.277
CL/F (mL/min)	2066.4 (79.355)	1718.8 (116.50)	1.2023	1.057-1.367
[1] Ratio of the geometric least square (LS) means of female to male				

A slight effect of patient age was observed on SKY0401 CL/F. As the data show, clearance of SKY0401 was approximately 13% slower in subjects >65 years of age compared to those ≤65.

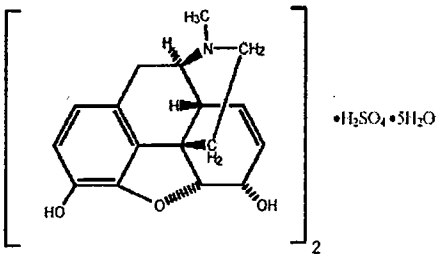
2 QBR

2.1 General Attributes of the Drug and Drug Product?

2.1.1 What is the description of the active drug?

International Nonproprietary Name:	Morphine Sulfate
Compendial Name:	Morphine Sulfate, USP
Chemical Name:	7,8-Didehydro-4,5á-epoxy-17-methylmorphinan-3,6á-diol sulfate (2:1) (salt), pentahydrate
Chemical Abstracts Service (CAS) registry number:	Pentahydrate 6211-15-0 Anhydrous 64-31-3
Molecular formula	(C17H19NO3)2 •H2SO4 •5H20
Formula weight	758.83

Structure of morphine sulfate:



2.1.2 What is the description and composition of the drug product?

SKY0401 (sustained-release encapsulated morphine) is a sterile, non-pyrogenic, white to off-white aqueous suspension of multivesicular lipid-based particles (DepoFoam®)drug delivery system) containing morphine sulfate, intended for local sustained release following epidural administration.

Component	Specification	Nominal Content per mL	Nominal Content per Vial (2 mL)	Molar Ratio (lipid:drug substance)	Weight Ratio (lipid:drug substance)
Morphine Sulfate (pentahydrate)	USP	10.0 mg	20.0 mg		
Dioleylphosphatidylcholine (DOPC)	in-house	4.2 mg	8.4 mg		
Dipalmitoylphosphatidyl-glycerol (DPPG)	in-house	0.9 mg	1.8 mg		
Cholesterol	NF	3.3 mg	6.6 mg		
Triolein	in-house	0.1 mg	0.2 mg		
Tricaprylin	in-house	0.3 mg	0.6 mg		
Sodium Chloride	USP				

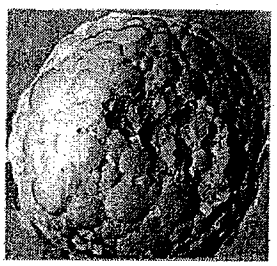
Role of Component in Formulation

Morphine Sulfate:	Active drug substance.
DOPC:	Zwitterionic phospholipid comprising the major constituent of the lipid membranes. The lipid layers, along with the triglycerides triolein and tricaprylin, provide the sustained-release properties of the product.
DPPG:	Negatively charged phospholipid included in the lipid membrane; helps prevent aggregation during and after manufacture.
Cholesterol:	Mechanical stabilization of the lipid membranes.
Triolein Tricaprylin:	Stabilization of membrane junctions in the multivesicular liposomal structure. Together with the lipid layers, provides the sustained-release properties of the product.
Sodium Chloride:	Tonicity adjustment (external phase / suspending medium).
Water for Injection:	

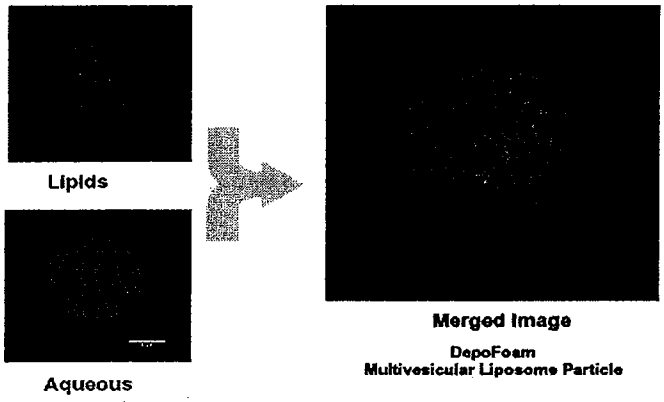
2.1.3 What are the highlights of the chemistry and physical-chemical properties of the liposome ?

The development plan of a sustained-release formulation of morphine for epidural administration, was to maintain morphine concentrations for a prolonged period at the epidural space, thereby increasing analgesic duration of action. The multivesicular liposome (MVL) that comprises the drug product is a lipid-based honeycomb of numerous non-concentric aqueous chambers containing dissolved drug. The sustained-release nature of the encapsulated morphine is imparted by the combination of lipids that form the walls of the MVL particles. Particles are generally in the 17–23 μm diameter size range. Lipids constitute approximately [ ] of the total particle volume. The particles are suspended in a 0.9% sodium chloride solution at a volume fraction (packed particle volume, or lipocrit) in the range of [ ] In the final product, the majority of the drug in the suspension is encapsulated within the MVLs, with less than [ ] of the total morphine appearing in the external phase.

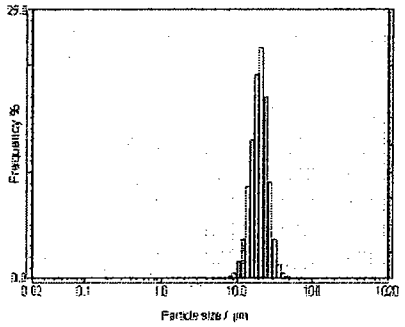
A typical scanning electron micrograph of an MVL particle is shown below:



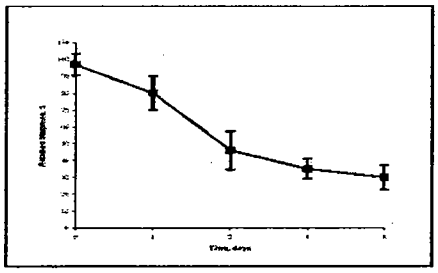
Confocal photomicrographs of an MVL particle are shown below. The lipid phase of the particle has been labeled with a red-fluorescent dye and the aqueous phase has been labeled with a green-fluorescent dye. The images clearly show the multivesicular nature of the particle.



A typical particle size distribution is shown below. The volume-weighted median diameter is on the order of 20 µm, with a d10 of 14 µm and a d90 of 28 µm.



A typical in-vitro release (retention) profile is shown below. In this procedure, MVLs are bathed in an aqueous BSA solution at 37°C with mild agitation. Samples are assayed at various times for the amount of morphine retained in the particles. This system exhibits a release profile over a 4-day period. From the clinical data, it appears that in vivo release (i.e., plasma concentrations) occurs somewhat more rapidly, generally over 24 to 48 hours. In all, the current in-vitro release system is being used only as a QC tool to characterize reproducibility of manufacture from lot to lot.



2.1.4 What are the highlights of the formulation development?

The Applicant stated that the chain length of the triglyceride has a significant impact on the release rate of drug from MVL systems. Based on this, a morphine MVL formulation

with tricaprylin and triolein were compared. The *in vivo* and *in vitro* tests were conducted with various ratios of the two triglycerides. Based on the *in vitro* and *in vivo* results, a triolein to tricaprylin mole ratio was selected as the lead formulation for preclinical and initial human clinical studies.

2.1.5 What are the proposed mechanism of action and therapeutic indication(s)?

It is speculated that epidural administration of morphine sulfate results in analgesia without general systemic adverse reactions (attendant loss of motor, sensory, or sympathetic function). It appears that, as compared to systemic administration of morphine at comparable doses, epidurally administered morphine results in improved analgesia with increased duration.

Morphine, a pure opioid agonist, is a μ-receptor, although it can interact with other opioid receptors at higher doses. Opiate receptors include μ (mu), kappa (kappa), and delta (delta), which have been reclassified by an International Union of Pharmacology subcommittee as OP1 (delta), OP2 (kappa), and OP3 (μ). In addition to analgesia, the widely diverse effects of morphine include drowsiness, changes in mood, respiratory depression, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous system.

Effects on the Central Nervous System (CNS): The principal therapeutic action of morphine is analgesia, although the precise mechanism of the analgesic action is unknown. Other therapeutic effects of morphine include anxiolysis, euphoria and feelings of relaxation. Throughout the brain and spinal cord, specific CNS opiate receptors and endogenous compounds with morphine-like activity have been identified and are likely to play a role in the expression and perception of analgesic effects. As with all opioids, morphine can cause respiratory depression, in part by a direct effect on the brainstem respiratory centers; opioids depress the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur at lower doses. Morphine may cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose; however, when asphyxia is present during opioid overdose, marked mydriasis occurs.

Effects on the Gastrointestinal Tract and on Other Smooth Muscle: Morphine reduces gastric, biliary and pancreatic secretions, and causes a reduction in motility. Digestion of food in the small intestine is delayed and propulsive contractions are decreased; propulsive peristaltic waves in the colon are decreased, while tone can be increased to the point of spasm, often resulting in constipation. Morphine can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi. Morphine may also cause spasm of the sphincter of the urinary bladder.

Effects on the Cardiovascular System: In therapeutic doses, morphine does not usually exert major effects on the cardiovascular system. Morphine produces peripheral vasodilatation that may result in orthostatic hypotension and fainting. Release of

histamine can occur, which may play a role in opioid-induced hypotension. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes and sweating.

2.1.6 What are the proposed dosage and route of administration?

The proposed dosage and route of administration is a liposomal solution and by epidural route, respectively. Plasma morphine concentration was measured as a surrogate to indicate exposure of cerebrospinal fluid to morphine.

2.1.7 What are the lots used in the clinical trials?

Clinical Study #	Phase	SKY0401 Lots Used	Scale
96-003	I	96-0085	Pilot
		97-0020	
C0401-008	II	97-0020	Pilot
		98-0007	
		98-0008	
		99-0010*	
C0401-009	II	97-0020	Pilot
		97-0021	
		98-0007	
		98-0008	
		99-0007	
SKY0401-011	III	00-4007	Commercial
		02-4004	
		02-4005	
		02-4007	
SKY0401-012	III	00-4007	Commercial
		02-4004	
		02-4005	
		02-4007	
SKY0401-015	II	02-4005	Commercial
		02-4007	
SKY0401-016	I	02-4005	Commercial
		02-4007	
SKY0401-017	II	02-4004	Commercial
		02-4005	
		02-4007	

* This lot was made with a different formulation, SKY0401.1, described in Section 3.2.P.2.2.1 (Formulation Development). It was tested in preclinical studies and used briefly in clinical study C0401-008, but not further pursued.

2.2 General Clinical Pharmacology

2.2.1 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

Pain intensity was rated by the patients using a Visual Analog Scale (VAS). As stated above, following epidural administration, the site of action is believed to be at the spinal

level. Due to limits on measuring morphine concentrations at spinal level, systemic plasma concentration of morphine was measured as a surrogate to indicate exposure of cerebrospinal fluid to morphine. It is should be noted that the pilot Study DTC96-003, measured CSF morphine concentrations. In this study, due to small number of subjects enrolled in the study, the results were variable. However, morphine CSF levels were 100 to 400 times the systemic morphine concentrations. No other CSF morphine concentrations were obtained in the remaining PK studies.

2.2.2 Exposure-response

2.2.2.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the pharmacological response or clinical endpoint.

The relationship between the plasma morphine pharmacokinetics and efficacy results from two pivotal Phase III clinical studies was examined (See below table; Studies SKY0401-011 and SKY0401-012B). The results suggest an overall relationship between the dose of SKY0401 and reduction in pain as measured by postoperative fentanyl use or VAS pain intensity scales. The morphine AUC is observed to increase in a roughly dose-proportional fashion in a subset of patients in the same trials.

The Applicant stated that formal pharmacokinetic /pharmacodynamic modeling was not conducted for two reasons. First, there are a limited number of patients with paired effectiveness and plasma pharmacokinetic data; and second, the concentrations in plasma are at best an indirect measure of concentrations at the site of action.

Mean (SD) Pharmacokinetic and Pharmacodynamic Measures

	Placebo	5 mg	10 mg	15 mg	20 mg	25 mg
SKY0401-011						
Total Fentanyl [1]	2091 (1803)			663 (715)	485 (715)	371 (675)
VAS 0-48 [2]	1462 (745)			946 (767)	737 (663)	654 (714)
AUC 0-∞ [3]				163 (102)	189 (98)	219 (84)
SKY0401-012B						
Total Fentanyl [1]		1213 (1079)	995 (907)	960 (770)	972 (982)	683 (620)
VAS 0-48 [2]		1125 (798)	1078 (784)	892 (686)	854 (725)	775 (602)
AUC 0-∞ [3]		39 (10)	93 (33)	128 (73)	176 (92)	189 (67)

[1] Total cumulative fentanyl dose 0 48 hours post-op (mcg) in all ITT patients
Study 011: N = 49, 50, 49, and 46 for placebo, 15, 20, and 25 mg doses, respectively
Study 012B: N = 86, 70, 84, 79, and 83 for 5, 10, 15, 20, and 25 mg doses, respectively
[2] Area under the effect versus time curve 0-48 hours for VAS pain intensity at rest in all ITT patients
Study 011: N = 48, 49, 47, and 45 for placebo, 15, 20, and 25 mg doses, respectively
Study 012B: N = 85, 66, 83, 75, and 82 for 5, 10, 15, 20, and 25 mg doses, respectively
[3] AUC0-(for serum morphine concentrations in PK evaluable patients
Study 011: N = 19, 21, and 19 for 15, 20, and 25 mg doses, respectively
Study 012B: N = 10, 12, 10, 12, and 10 for 5, 10, 15, 20, and 25 mg doses, respectively

Study 011

The endpoint measuring the total amount of fentanyl use 0-48 hours post-dose showed overall statistical significance ($p < 0.0001$). The mean (SD) amount of fentanyl used during the first 48 hours after surgery decreased with increasing SKY0401 dose. In addition, the mean (SD) area under the effect versus time curve for VAS pain intensity at rest (VAS0-48) decreased from 946 (767) in patients receiving SKY0401 15 mg to 371 (675). In the subset of patients with serum pharmacokinetic data, mean (SD) AUC0-∞ increased in approximate proportion to the dosage across the same dosage range.

Study 012B

The endpoint measuring the total amount of fentanyl use 0-48 hours post-dose showed overall statistical significance ($p < 0.0015$). As was observed in Study 011, the amount of fentanyl used in the first 48 hours and the VAS0-48 decreased as the dosage of SKY0401 increased in Study 012B. Serum morphine AUC0-∞ also increased in a roughly dose-proportional fashion.

2.2.2.2 Does this drug prolong the QT or QTc interval?

QT study has not been studied. However, morphine is not known to prolong QT interval.

2.2.2.3 Is the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

It is well known that there is no predictable relationship between morphine serum levels and analgesic response. Additionally, an analgesic response is patient-specific, with a minimum effective analgesia plasma level. However, the minimum effective analgesia plasma concentration of morphine varies from patient to patient.

It is well known that several factors may affect a patient's response to a given opiate agonist including age, prior opiate therapy, medical condition, and emotions. Also, there is no relationship between morphine plasma levels and incidence of adverse events, although higher levels are associated with more adverse events than lower levels.

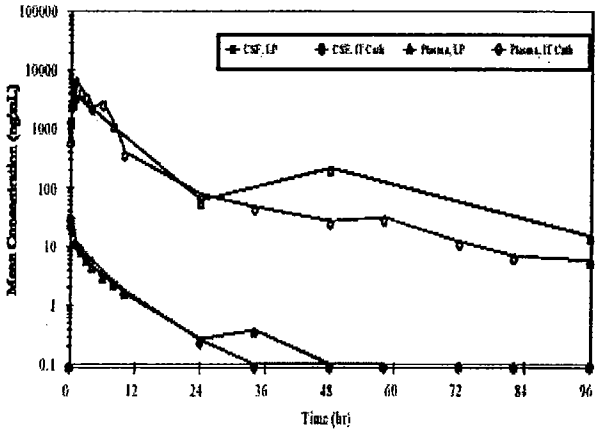
2.2.3 What are the PK characteristics of the drug and its major metabolite?

Morphine CSF

A pilot Study DTC96-003 measured CSF morphine concentrations. In this study, due to small number of subjects enrolled in the study, the results were variable. However, morphine CSF levels were 100 to 400 times that of the systemic morphine concentrations. Morphine was detected in the CSF as early as 5 minutes after injection.

Following epidural administration of 2.5 and 5.0 mg of SKY0401, morphine concentrations in CSF were not detected after the 58-hour time point. Following epidural administration of 20 mg SKY0401, CSF concentrations of morphine stayed somewhat constant between 34 and 82 hours; however, at the 96-hour time point, morphine concentrations were not detected. For 10, 30, and 40 mg dosing cohorts, morphine concentrations in the CSF were measurable at 96 hours. In addition, two subjects who were dosed with 30 mg SKY0401 and one subject dosed with 40 mg SKY0401 had morphine CSF concentrations above 100 ng/mL at 96 hours.

Mean CSF Morphine Concentrations for Subjects Who Received *20 mg* SKY0401 Epidurally: Study DTC96-003



Parameter	5 mg (n=2)	10 mg (n=2)	20mg (n=1)
AUC0∞ (ng hr/mL)	7825.20	27406.11	50462.75
CL/F (L/hr)	0.65	0.53	0.40
Cmax (ng/mL)	3324.75	7035.00	8560.00
MRT (hr)	4.31	4.57	6.02
tmax (hr)	0.58	1.00	3.00
Vz/F (L)	5.55	4.19	3.53
t1/2 (hr)	6.13	10.29	6.17
Data Source: Table 12.3.2, Study DTC96-003			

This study indicated that there were no signs of spinal metabolism. M3G was not detected in CSF and only a trace of M6G was found in one CSF sample.

Comparison of elimination profiles for morphine from CSF and plasma for subjects with indwelling catheters indicated that morphine was cleared with similar rates from CSF and plasma. Generally, t1/2 values were comparable for each subject if the values were determined over the same time period. The t1/2 and MRT values generally increased with increasing dose of SKY0401.

CSF concentrations of morphine at 24 hours after the epidural dose appeared to be comparable to the minimal concentrations associated with analgesia (10.5-101 ng/mL),

suggesting that SKY0401 has the potential to provide analgesia for extended periods, thereby reducing the need for repeated epidural doses.

Morphine

See below under single dose linearity and healthy vs. patients PK comparison sections.

Morphine-3-β-glucuronide

Plasma concentrations of inactive metabolite, M3G, were generally about 10-fold greater than plasma concentrations of morphine.

Morphine-6-β-glucuronide

Plasma concentrations of the pharmacologically active metabolite, M6G, peaked later than morphine and were also generally higher than plasma morphine concentrations, although peak concentrations of M6G were less than 50% of the morphine Cmax; overall mean AUC0-□ values for M6G were approximately 1.5-fold higher than the corresponding AUC0-□ values for morphine.

Metabolite-to-Parent Ratios

The pooled analysis of metabolite to parent (morphine) ratios demonstrated no appreciable dose-related differences in metabolite AUC ratios.

Morphine dose	Mean AUC M3G/M	Mean AUC M6G/M
5 mg	7.96	0.85
10 mg	7.77	1.02
15 mg	9.89	1.53
20 mg	9.79	1.45
25 mg	8.29	1.96
30 mg	10.4	1.38
5 mg Unencapsulated	8.15	0.97

2.2.3.1 What are the single dose PK parameters? (Provide tables to refer to in subsequent questions in this section). How does the PK of the drug in healthy volunteers compare to that in patients?

A comparison of the pharmacokinetics between healthy subjects (Study DTC96-003) and patients undergoing surgery (Study SKY0401-008, -009. -011, -012B and -016) is presented below. The results of the comparison appear to demonstrate higher Cmax, lower AUC, and shorter half-life for healthy subjects compared to patients undergoing surgery.

There were no apparent differences between healthy subjects and patients with respect to morphine CL/F, λz, and Vz/F. However, because of the small sample size of healthy subjects at each dose, these results should be interpreted with caution.

Comparison of Mean (SE) Morphine Pharmacokinetics between Healthy Subjects and Patients Undergoing Surgery: Pooled Analysis

	Cmax (ng/mL)	AUC0-∞ (ng·hr/mL)	t1/2 (hr)	λz (hr^{-1})	CL/F (mL/min/kg)	Vz/F (L/kg)
Healthy Subjects						
Unencapsulated MS (n=2)	26.0 (7.21)	39.37 (9.19)	3.34 (0.64)	0.21 (0.04)	25.91 (4.29)	7.62 (2.67)
5 mg SKY0401 (n=4)	15.07 (6.65)	45.33 (11.26)	4.37 (3.17)	0.22 (0.12)	29.91 (8.37)	10.00 (4.84)
10 mg SKY0401 (n=4)	34.25 (3.60)	86.30 (11.65)	9.56 (8.08)	0.11 (0.08)	27.45 (10.34)	19.53 (13.17)
20 mg SKY0401 (n=3)	52.633 (2.28)	171.43 (18.28)	11.27 (2.26)	0.06 (0.01)	30.51 (3.04)	29.94 (7.40)
30 mg SKY0401 (n=4)	58.85 (22.73)	281.15 (49.82)	20.88 (6.00)	0.04 (0.01)	25.82 (6.35)	44.42 (6.15)
Surgery Patients						
Unencapsulated MS (n=24)	19.56 (10.24)	52.84 (36.17)	6.04 (17.69)	0.32 (0.10)	23.28 (7.20)	6.28 (8.59)
5 mg SKY0401 (n=10)	7.10 (3.40)	38.80 (10.35)	4.18 (1.61)	0.18 (0.05)	28.32 (10.81)	9.77 (3.54)
10 mg SKY0401 (n=32)	18.23 (8.45)	131.91 (105.34)	17.37 (21.00)	0.12 (0.10)	22.55 (14.10)	25.10 (28.46)
20 mg SKY0401 (n=60)	25.10 (18.04)	186.77 (83.63)	24.62 (25.93)	0.10 (0.15)	27.51 (12.41)	47.28 (41.13)
30 mg SKY0401 (n=21)	45.04 (29.84)	355.71 (147.75)	26.89 (15.86)	0.04 (0.04)	21.64 (9.20)	42.58 (18.44)
Results presented in arithmetic means						

2.2.3.2 What are the characteristics of drug distribution?

Literature data: Morphine has an apparent volume of distribution ranging from 1.0 to 4.7 L/kg after *intravenous* dosage. Protein binding is low, about 36%, and muscle tissue binding is reported as 54%. A blood-brain barrier exists, and when morphine is introduced outside of the CNS (eg. *intravenously*), plasma concentrations of morphine remain higher than the corresponding CSF morphine levels. Conversely, when morphine is injected into the *intrathecal* space, it diffuses out into the systemic circulation slowly, accounting for the long duration of action of morphine administered by this route.

2.2.3.3 What are the characteristics of drug metabolism?

Literature data: Metabolism of morphine occurs in the primarily in the liver but also may occur in the brain and kidneys via cytochrome P450 2D6 enzymes. Morphine is conjugated with glucuronic acid to form 3-glucuronide (50%), 6-glucuronide (5—15%), and 3,6-glucuronide and other minor metabolites. Morphine 3-glucuronide antagonizes morphine and may cause hyperalgesia and myoclonus during high dose morphine therapy. In addition, the 3-glucuronide metabolite may be important in the development of tolerance to morphine. Morphine 6-glucuronide is a more potent analgesic than morphine and may significantly contribute to morphine's activity. With chronic dosing of morphine, the AUCs of the glucuronide metabolites are greater than that of morphine.

Active metabolite, morphine-6-glucuronide; t1/2 = 4.0 ± 1.5 hours. Steady-state ratio of active metabolite to parent after oral dosing = 4.9 ± 3.8.

2.2.3.3 What are the characteristics of drug excretion?

Literature data: Excretion is largely in the urine and bile as the morphine-3-β-glucuronide and 6-β-glucuronide metabolites, with smaller amounts as the secondary conjugate and unchanged drug. Morphine is eliminated by the kidneys, 2 to 12% being excreted unchanged in the urine. Within about 24 hours of the last dose given, total urinary elimination is approximately 90%. Between 7—10% is excreted in the feces, mainly via the bile. Terminal half-life is commonly reported to vary from 1.5 to 4.5 hours after parenteral administration.

With SKY0401, the terminal half-life increased with increasing epidural doses. See above table, section, 2.2.3.2.

2.2.3.4 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

In all studies, the pharmacokinetics of SKY0401 appeared to be linear and dose-proportional (based on AUC) across the range of 5 mg to 30 mg.

In contrast, Cmax did not always exhibit dose-proportionality and tended to increase by an amount less than the proportional change in dose. Results for the 2.5 mg and 40 mg doses of SKY0401 are not included in the following table because only 2 subjects received each of these doses.

Mean (SE) Morphine Pharmacokinetic Parameters: Pooled Analysis

Parameter	Unencapsulated Morphine 5 mg (n=26)	SKY0401 5 mg (n=14)	SKY0401 10 mg (n=36)	SKY0401 15 mg (n=71)	SKY0401 20 mg (n=63)	SKY0401 25 mg (n=32)	SKY0401 30 mg (n=25)
Cmax (ng/mL)	20.01 (10.08)	9.37 (5.67)	20.01 (9.51)	18.64 (10.43)	26.41 (18.57)	22.58 (15.36)	47.25 (28.87)
AUC0-t (ng hr/mL)	47.81 (39.41)	30.85 (11.82)	135.9 (116.7)	100.9 (43.64)	160.8 (76.34)	158.3 (55.73)	297.9 (134.8)
AUC0-∞(ng hr/mL)	51.67 (34.76)	40.98 (10.63)	124.89 (98.08)	131.62 (73.66)	185.94 (81.42)	207.26 (77.70)	341.51 (136.88)
t1/2 (hr)	5.81 (16.88)	4.244 (2.10)	16.17 (19.66)	19.97 (20.55)	23.90 (25.39)	32.90 (24.2-0)	25.75 (14.58)
λz (hr-1)	0.307 (0.101)	0.194 (0.078)	0.116 (0.096)	0.093 (0.10)	0.096 (0.15)	0.038 (0.03)	0.041 (0.035)
CL/F (mL/min/kg)	23.51 (6.96)	28.85 (9.70)	23.30 (13.53)	31.12 (21.83)	27.68 (12.09)	27.35 (10.63)	22.43 (8.75)
CL/F (mL/min)	1888.96 (520.47)	2190.67 (696.95)	1896.28 (1201.45)	2613.81 (2065.46)	2165.19 (1075.97)	2322.35 (925.98)	1779.10 (937.50)
Vz/F (L/kg)	6.39 (8.22)	9.85 (3.79)	24.24 (26.55)	38.20 (28.17)	46.33 (40.19)	62.02 (31.16)	42.93 (16.68)
Vz/F (L)	495.10 (552.49)	767.18 (341.10)	1766.57 (1562.62)	3026.43 (2105.95)	3641.11 (3217.03)	5346.45 (2903.98)	3262.18 (1429.60)

2.3 Intrinsic Factors

2.3.1.1 Pediatric patients. What is the status of pediatric studies and/or any pediatric plan for study?

Deferral of pediatric studies was discussed during the End of Phase 2 meeting held on Jan 13, 2000. The Division agreed, dated February 11, 2000, that pediatric studies should be deferred until after SKY0401 approval in the adult population.

2.3.1.2 Gender and age

In the current application, SKY was studied in over 900 subjects; 253 were 65 years of age and older and 53 of these patients were 75 years of age and over. With opioids, elderly patients (65 years of age or older) may have increased sensitivity to morphine. The Applicant stated that the efficacy and opioid adverse event profiles of these elderly patients at the same or lower dose of SKY were similar to younger adults. Since morphine liposome is intended for single dose usage, the morphine and its metabolites accumulation is not expected in elderly population

Across the six clinical studies described in this report, pharmacokinetic data are available for 282 male and female subjects 18 years of age or older who received SKY0401 or unencapsulated morphine. The mean (SD) age of all subjects was 53.4 (14.36) years, and ranged from 18-83 years. There were 139 males and 143 females. Of the 282 subjects, 69 were 65 years of age. The elderly population consisted of 41 males and 28 females with a mean (range) age of 71.6 (65-83) years.

The effect of age and gender on SKY0401 Cmax and clearance was assessed across all six clinical studies. For the analysis of Cmax, the Cmax of each dose across all studies was normalized to 5 mg and the pooled results were analyzed by gender and age.

Analysis of Mean (SD) Dose-Normalized Cmax by Gender and Age, All Studies

	Female	Male	≤65 years	>65 years
Parameter	n=128	n=117	n=183	n=62
Cmax (ng/mL)	6.45 (0.39)	5.15 (0.32)	5.87 (0.30)	5.58 (0.49)
Ratio[1]	1.25		1.05	
90% C.I.interval	1.09-1.45		0.89-1.24	
[1] Ratio of the geometric least square (LS) means of female to male/≤65 years to >65 years				

Female subjects exhibited a 25% higher Cmax than male subjects. This is likely due to the typical differences in body weight and body mass index between males and females.

Subject age did not have an effect on mean Cmax. For subjects ≥75 years of age, due to the small sample size, statistical analysis was not performed.

Analysis of Morphine Clearance (CL/F) by Gender: All Studies, All Doses

	Female	Male		90%
Parameter	n=109	n=105	Ratio[1]	confidence interval
CL/F (mL/min/kg)	23.65 (1.03)	26.15 (1.16)	0.90	0.82 - 1.00
CL/F (mL/min)	1719.2 (78.09)	2283.3 (105.67)	0.75	0.68 - 0.84
[1] Ratio of the geometric least square (LS) means of female to male				

When mean CL/F results were corrected for subject weight, no significant difference was observed between males and females.

Analysis of Morphine Clearance (CL/F) by Age: All Studies, All Doses

	≤65 years	>65 years		90%
Parameter	n=162	n=52	Ratio[1]	confidence interval
CL/F (mL/min/kg)	25.61 (0.91)	22.60 (1.42)	1.13	1.01-1.28
CL/F (mL/min)	2066.4 (79.35)	1718.8 (116.50)	1.20	1.06-1.37
[1] Ratio of the geometric least square (LS) means of female to male				

A slight effect of patient age was observed on SKY0401 CL/F. As the data show, clearance of SKY0401 was approximately 13% slower in subjects >65 years of age compared to those ≤65.

2.3.1.3 Renal impairment

Literature data: In patients with renal dysfunction, accumulation of the morphine-3 glucuronide and 6-glucuronide occurs leading to prolonged serum levels and increased toxicity. It is reported that in renal failure, t1/2 may increase to 50 ± 37 hours, resulting in significant accumulation of active glucuronide metabolite after parenteral administration. Since morphine liposome is intended for single dose usage, the morphine and its metabolites accumulation is not expected in elderly population

Additionally, morphine CL/F was not affected by age, where the renal function is known to decrease with age.

2.3.1.4 Hepatic impairment

Literature data: The half-life of morphine is significantly prolonged in patients with cirrhosis or hepatic disease. Therefore, the formation of morphine- 3-β-glucuronide and 6-β-glucuronide metabolites may decrease. Since morphine liposome is intended for single dose usage, the morphine and its metabolites accumulation is not expected in elderly population with impaired hepatic function.

2.4 Extrinsic Factors

2.4.1 Drug-Drug Interactions

2.4.1.1 Is the drug a substrate of CYP enzymes?

Literature data: Metabolism of morphine occurs in the primarily in the liver but also may occur in the brain and kidneys via cytochrome P450 2D6 enzymes. Morphine is conjugated with glucuronic acid to form 3-β-glucuronide (50%), 6-β-glucuronide (5—15%), and 3,6-glucuronide and other minor metabolites.

2.4.1.2 What other co-medications are likely to be administered to the target patient population?

In clinical practice, it is likely that morphine liposomes will be administered both with and without a test dose, a lidocaine/epinephrine solution, one of the methods used to rule out misplacement of the epidural needle/cathether. The Applicant studied the effect of the test dose on the release of morphine from the liposomes by varying the time between the morphine liposome and test dose injections.

Study SKY0401-016

Mean dose-normalized Cmax for subjects who received a test dose was approximately 63% higher than that for subjects who did not receive a test dose. However, the results indicated that a wait time of at least 10 minutes substantially mitigates the effect of the test dose on Cmax. As expected, AUC was not affected by administration of the test dose. Additionally, an examination of the effect of a test dose across all clinical studies confirmed the results of Study SKY0401-016.

Effect of Test Dose and Wait Interval on Cmax

		Cmax[1]		AUC0-∞
	n [2]	Mean (SE)	n	Mean (SE)
Test Dose	167	5.87 (0.28)	146	42.19 (1.79)
No Test Dose	**48**	**3.60 (0.32)**	**42**	**38.38 (3.03)**
Test Dose Interval				
≤3 minutes	21	8.70 (1.12)	20	36.96 (4.40)
4-9 minutes	7	5.98 (1.34)	7	42.14 (8.49)
10-14 minutes	**14**	**4.61 (0.73)**	**13**	**44.11 (6.52)**
15-30 minutes	44	5.76 (0.51)	43	40.04 (3.25)
>30 minutes	23	3.67 (0.45)	21	36.89 (4.29)
[1] Dose normalized to 5 mg				
[2] Wait interval information was unavailable for patients in Study SKY0401-008 and SKY0401-009.				
Therefore, the total n for the interval analysis is lower than that of the test dose group.				

2.5 General Biopharmaceutics

2.5.1 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The to-be-marketed formulation was used throughout the clinical studies.

2.5.2 What is the relative bioavailability of Skymorph modified-release liposomes?

The relative bioavailability of Skymorph was compared to that of the reference listed drug, Duramorph (immediate-release morphine sulfate injection; NDA #18565; Elkins-Sinn, Inc.) in a Phase 3 study in patients undergoing lower abdominal surgery (Study SKY0401-012B). A 5 mg Skymorph and a 5 mg Duramorph were compared. Mean concentration-time curves for Duramorph 5 mg and SKY0401 5 mg are provided in the next figure, and a comparison of the pharmacokinetic results is presented in following table.

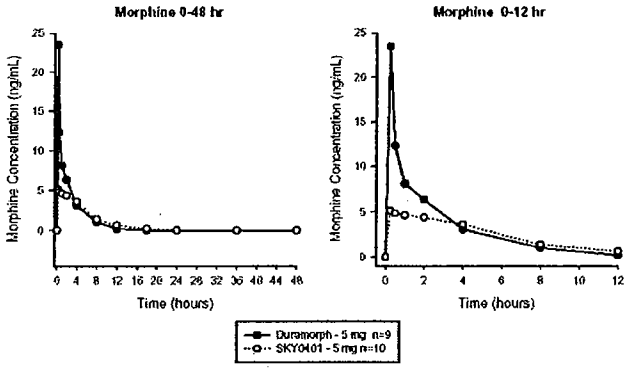


Figure Average Morphine Serum Concentrations Following Administration of Skymorph 5 mg or Duramorph 5 mg; the left-hand panel shows the 48-hr time course and the right-hand panel contains a zoom of the first 12 hr.

Variable	SKY0401 5 mg (n=10)	Duramorph 5 mg (n=9)
Cmax (ng/mL)	7.10 (3.40)	23.77 (12.81)
tmax (hr) [1]	1.00 (0.25–4.0)	0.25 (0.25–2.0)
AUC0-t (ng·hr/mL)	30.86 (11.82)	38.95 (8.03)
AUC (ng·hr/mL)[4]	38.80 (10.35)	42.76 (8.35)
λz (h-1)[4]	0.1813 (0.05)	0.3112 (0.067)
t1/2 (hr) [2,4]	3.82 (1.00)	2.23 (0.49)
Cmax [3]	6.39	20.27
AUC0-t [3]	28.74	38.34
AUC [3,4]	37.41	42.15
[1] Median (min-max)		
[2] Harmonic mean and pseudo standard deviation of the jackknife variance		
[3] Geometric mean of ln-transformed variables		
[4] n=8 for the SKY0401 and Duramorph groups.		

Morphine early exposure was less with Skymorph, with a mean Cmax of Skymorph which was 31.5% of Duramorph. Skymorph morphine mean AUC was 88.6% of that of Duramorph. Additionally, this study also looked at 10, 15, 20 and 25 mg Skymorph concentrations. The data indicated that ratios of M3G and M6G to that of the parent morphine was consistent throughout the dose levels. Thus, there did not appear to be any meaningful dose or dosage form-related differences in morphine metabolism based on molar ratios of metabolite AUC to parent (morphine) AUC.

Morphine dose	Mean AUC M3G/M	Mean AUC M6G/M
5 mg	7.96	0.85
10 mg	7.77	1.02
15 mg	9.89	1.53
20 mg	9.79	1.45
25 mg	8.29	1.96
30 mg	10.4	1.38
5 mg Unencapsulated	8.15	0.97

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? For all moieties measured, is free, bound or total measured? What bioanalytical methods are used to assess concentrations?

Yes, the total plasma concentrations of morphine and morphine metabolites were determined using [ ] methods developed at [ ]

2.6.1.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used? What are the lower and upper limits of quantification (LLOQ/ ULOQ)? What is the accuracy, precision and selectivity at these limits? What is the sample stability under the conditions used in the study? [ ] What is the QC sample plan?

A typical assay method is described below for morphine, M3G, and M6G. Morphine, M3G, M6G, and their respective internal standards, morphine-d3 (ISTD1), morphine-3-β-glucuronide-d3 (M3G-d3) (ISTD2), and morphine-6-β-glucuronide-d3 (M6G-d3) (ISTD3), were [ ]

Summary of Method Validation Results for Determination of Morphine, Morphine-3-β-glucuronide, and Morphine-6-β-glucuronide in Human Serum

Parameter	Morphine	M3G	M6G
Standard Concentrations (ng/mL)			
QC Concentrations (ng/mL)			
Linearity (mean r)			
Linear Range (ng/mL)			
LOQ (ng/mL)			
Intra-assay Precision (%CV)			
Intra-assay Accuracy (% difference from theoretical)			
Inter-assay Precision (%CV)[2]			
Inter-assay Accuracy [2] (% difference from theoretical)			
Recovery (%)			

[1] Analyzed after 5-fold dilution with analyte-free matrix
[2] Inter-assay precision and accuracy based on low, mid, and high controls only.
Note: Precision and accuracy results are based on replicate determinations of QC samples.
M3G = Morphine-3-β-glucuronide; M6G = Morphine-6-β-glucuronide; QC = Quality Control

3 Detailed Labeling Recommendations

Overall, the Applicant's proposal is acceptable. However, there are minor changes (~~strikeouts~~, and addition in *italics*) recommended for the Clinical Pharmacology section of the label. The Applicant's wording is in Font Arial.

CLINICAL PHARMACOLOGY

Mechanism of Action

1 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

4 Appendices

4.1 Proposed Package Insert

TRADEMARK™
(morphine sulfate sustained-release liposome injection)
CII
Rx Only

DESCRIPTION

12 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Protect from freezing. Store in the refrigerator at 2° to 8°C (36° to 46°F) until ready to use.

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

Manufactured by:
SkyePharma Inc.

San Diego, CA 92121

****

PCDoc#86775

4.2 Individual Study Review

Study DTC-96-003

A Phase 1 Dose Escalation Study of the Safety, Pharmacokinetics, and Pharmacodynamics of Sustained-Release Encapsulated Morphine (SKY0401) Administered Epidurally in Normal Volunteers

Note: The Applicant stated that this is a pilot Phase 1 study; the first study in which SKY0401 was administered to humans. Phase 1 safety study, a subgroup analysis was not planned.

Name of Investigational Product: SKY0401: Sustained-Release Encapsulated Morphine (formerly known as C0401)

Title of Study: A Phase I Dose Escalation Study of the Safety, Pharmacokinetics, and Pharmacodynamics of Sustained-Release Encapsulated Morphine (SKY0401) Administered Epidurally in Normal Volunteers

Principal Investigator: [redacted]
Study site: [redacted]

Objectives:
To assess the safety, pharmacokinetics, and pharmacodynamic profile of escalating single doses of sustained release encapsulated morphine (SKY0401) administered via epidural injection.

Methodology:
This was an open-label, dose escalation study evaluating single doses of SKY0401 (2.5, 5, 10, 20, 30, and 40 mg) and commercial unencapsulated morphine sulfate (2.5 or 5 mg) administered epidurally to healthy subjects. Subjects were followed for 96 hours after dosing to determine the safety, pharmacokinetic, and pharmacodynamic profile of SKY0401.

Note: Original Study design: Approximately 30 subjects were to be enrolled. Successive treatment groups of subjects (n = 2 per treatment group) were to receive SKY0401 at escalating doses of 5, 10, 20, 30, 40, 50, or 60 mg. Dose escalation was to continue until dose-limiting toxicity (DLT) occurred. As DLT was reached at 40mg, the 50- and 60-mg doses were not administered. A subsequent group (per Amendment 01) then received 2.5 mg SKY0401 in an effort to determine the 'no effect' dose. Amendment 01 also added two additional treatment groups (n = 2 per treatment group) of 2.5 and 5 mg of unencapsulated morphine sulfate. Amendment 01 permitted CSF samples to be obtained via lumbar

puncture instead of by an intrathecal catheter in order to characterize the adverse event profile of SKY0401 without potentially confounding adverse events due to the indwelling intrathecal catheter.

Study drug was administered epidurally (L2-L3 intervertebral space). The lumbar intervertebral space was first identified and anesthetized with 1% lidocaine (without epinephrine). An epidural needle was then advanced through the lumbar intervertebral space until the epidural space was identified using a loss of resistance technique. A test dose of 3 mL of 1.5% lidocaine with 1:200,000 epinephrine was injected to assure that the catheter was indeed in the epidural space (rather than positioned intrathecally or intravenously). Inadvertent intrathecal injection was ruled out by a lack of sensory block produced by the lidocaine within 5 minutes of injection. Inadvertent intravenous injection was ruled out by a lack of hypertensive and/or tachycardic response. Provided that both intrathecal and intravascular injection had been ruled out by the test dose, the full dose of SKY0401 was then administered via the epidural catheter as a bolus over 15 seconds.

Pharmacodynamic Analyses
The investigator was responsible for recording and analyzing pharmacodynamic evaluations. These analyses were not verified independently by the sponsor. The analysis of assessments was modified from the protocol (refer to Section 9.8). Pain tolerance and pain threshold were summarized separately for each dermatome. Stimulus response was fit to a logistic growth model for each timepoint and subject using SAS PROC NLIN. This model contained two parameters – a ceiling and slope parameter. For baseline data, the ceiling parameter was assumed to be 100, so that only the slope parameter was estimated. The means and standard errors for each timepoint and dose were calculated using PROC MIXED. An exchangeable correlation structure was assumed within each subject. Data from ARCI, VAS, and Maddox Wing were summarized as the mean value for each treatment group.

Protocol deviations on pharmacodynamic efficacy measures:

- ABGs were deleted at 12 and 18 hours post-dose.
- Mental Status assessments were deleted at 0.25, 0.75, 1, 2, 3, 4, 5, 6, 12, 18, 60, and 84 hours post-dose; assessments were added at 2.25, 3.75, 34, 58, and 82 hours post-dose.
- Trail Making Test was deleted.
- Experimental Pain Model assessments were deleted at 0.25, 0.75, 1, 2, 3, 4, 5, 6, 12, 18, 36, 60, and 84 hours post-dose; assessments were added at 2.25, 3.75, 5.75, 34, 58, and 82 hours post-dose.
- Arterial plasma PK samples were deleted at 12 and 18 hours post-dose. Venous plasma PK samples were deleted at 36, 60, and 84 hours post-dose; assessments were added at 34, 58, and 82 hours post-dose.
- CSF PK samples were deleted at 12, 18, 36, 60, 84 hours post-dose; assessments were added at 34, 58, and 82 hours post-dose.

The planned analysis for pharmacodynamic measurements was not performed as stated in the original protocol.

Number of subjects (planned and analyzed): Planned: 30 subjects
Total Enrolled: A total of 26 subjects were enrolled and received study treatment; 24 subjects completed the study. A total of 22 subjects were administered single doses of SKY0401 via epidural injection: 2.5 mg (n=2), 5 mg (n=4), 10 mg (n=4), 20 mg (n=4), 30 mg (n=6), or 40 mg (n=2). Four subjects received single doses of commercial unencapsulated morphine sulfate (Astramorph/PF.) via epidural injection: 2.5 mg (n=2) and 5 mg (n=2).

Diagnosis and main criteria for inclusion:
Male and female healthy subjects, aged 18 to 45 years, with no prior history of chronic use of analgesics (other than acetaminophen) were eligible for this study.

Investigational product, dose and mode of administration, batch number:

SKY0401 doses of 50 and 60 mg were also planned but were not administered. SKY0401 lot numbers 96-0085 (5, 10, 20, 30, and 40 mg) and 97-0020 (2.5 mg) were used.

Duration of treatment: A single epidural dose was injected over less than 15 seconds.

Reference therapy, dose and mode of administration, batch number:
Commercial unencapsulated morphine sulfate (Astramorph/PF™) was administered epidurally at single doses of 2.5 mg (n = 2) and 5 mg (n = 2) and was supplied by the study site. Astramorph/PF lot numbers 602090 (2.5 mg; Subjects 090 and 091) and 704030 (5 mg; Subjects 021 and 022) were used. The epidural dose of SKY0401 was prepared as a standardized **volume of 5 mL** (diluted as needed with saline). The drug suspension was to be gently mixed immediately prior to injection.

Criteria for evaluation:
Pharmacodynamics: Pharmacodynamic ("efficacy") measurements included the following:
Antinociceptive activity – Cognitive/psychomotor evaluations – Tonic and Phasic Reaction Times, and Maddox Wing Ocular Test; Subjective effects of opioids - Addiction Research Center Inventory (ARCI) and Visual Analog Scales. No formal efficacy assessments were performed. Pharmacodynamic assessments were performed to characterize the antinociceptive activity, cognitive/psychomotor and subjective effects of escalating single doses of SKY0401. These assessments included the following: Antinociceptive activity – pain tolerance, pain threshold, and Stimulus Intensity-50 (SI50) were determined in three dermatomes (C2, L4, T10) using an experimental electrical pain model; Cognitive/psychomotor assessments – Tonic and Phasic Reaction Times and Maddox Wing Ocular Test; Subjective opioid effects - Addiction Research Center Inventory (ARCI) and Visual Analog Scales; Subjects received training during the screening visit for these assessments in an effort to ensure consistency and accuracy.

The **Visual Analog Scale** is a self-administered questionnaire used to measure the subjective effects of opioids. The checklist consisted of 20 symptoms that were rated on a 100 mm visual analog scale from 0 ("not at all") to 100 ("extremely"). Subjects completed the questionnaire following the ARCI. The symptoms rated were the following:

Sweaty	Floating	Carefree
Good Mood	Skin Itchy	Drunken
Sick	Turning of Stomach (Nauseous)	Energetic
High	Sleepy	Heavy or Sluggish Feeling
Any Drug Effect	Flushing	Confused
Good Effects	Dry Mouth	Lightheaded
Bad Effects	Coasting or Spaced Out	

Safety: Safety parameters included adverse event assessments, vital signs (heart rate, blood pressure, and respiratory rate), electrocardiography, arterial blood gases, hemoglobin oxygen saturation determined by pulse oximetry, physical examinations, and routine laboratory tests.

Pharmacokinetics: Morphine and morphine metabolites (morphine-3-glucuronide and morphine-6-glucuronide) concentrations were measured in plasma, CSF, and urine. **Arterial blood samples** were obtained pre-dose and at 5, 10, 15, and 30 minutes, and 1, 2, 3, 4, 6, 8, 10, and 24 hours post-dose. **Venous blood samples** were taken at 34, 48, 58, 72, 82, and 96 hours post-dose. CSF samples, obtained via an indwelling intrathecal catheter or lumbar puncture (per Amendment 01), were collected pre-dose and at 5, 10, 15, and 30 minutes, and 1, 2, 3, 4, 6, 8, 10, 24, 34, 48, 58, 72, 82, and 96 hours post-dose in some subjects. Urine was collected at the following time intervals post-dose: 0-6, 6-12, 12-24, 24-36, 36-48, 48-60, 60-72, 72-84, and 84-96 hours.

Drug Concentration Measurements
The pharmacokinetic profiles of morphine and its metabolites (morphine-3-glucuronide and morphine-6-glucuronide) were determined from plasma, CSF, and urine. All samples were analyzed using [ ] The lower limits of quantification (LLOQ) for the validated assay as noted below:

LLOQ (ng/mL)			
	Plasma	CSF	Urine
Morphine	[redacted]		
Morphine-3-glucuronide and morphine-6-glucuronide			

Time table of events:

TABLE 9.5.1 TIME AND EVENT SCHEDULE

Parameter	Screening[a]	Day 1 (0-24 hr post-dose)	Day 2 (48 hr post-dose)	Day 3 (72hr post-dose)	Day 4[b] 96 hr post-dose)
Written Informed Consent	X				
Medical History	X				
Physical Examination (including Oral Temp.)	X	Baseline[c]	X	X	X
Hematology, Serum Chemistry, and Urinalysis	X				X
HbsAg and HIV Testing	X				
Urine Drug Screen	X	Baseline[c]			
Psychophysical Training	X				
Pre-Dose[d] and Study Drug Administration		X			
Heart Rate, Blood Pressure, and Respiratory Rate (RR)	X	Baseline, upon admission, pre-dose[d], and post-dose: 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30 (RR only), 36, 42 (RR only), 48, 54 (RR only), 60, 66 (RR only), 72, 78 (RR only), 84, 90 (RR only), & 96 hours	X	X	X
Hemoglobin Oxygen Saturation via Pulse Oximetry	X	Baseline, upon admission, pre-dose[d], and post-dose: 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, & 96 hours	X	X	X
ECG (including Pulse Rate [PR])		Pre-dose[c] and post-dose: continuous for 4 hours; PR at 6, 8, 10, 12, 18, 24, 36, 48, 60, 72, 84, & 96 hours	X	X	X
Arterial Blood Gases		Pre-dose[c] and post-dose: 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, & 24 hours			
Electrical Pain Model, Reaction Time, and Madden Wing Choice Test	X	Pre-dose[c] and post-dose: 0.5, 1.25, 2.25, 3.75, 5.75, 8, 10, 24, 34, 48, 58, 72, 82, & 96 hours	X	X	X
ARCI and VAS	X	Pre-dose[c] and post-dose: 0.5, 1.25, 2.25, 3.75, 5.75, 8, 10, 24, 34, 48, 58, 72, 82, & 96 hours	X	X	X
Adverse Events		X	X	X	X
PK Samples		Arterial Blood: Pre-dose[c] and post-dose: 5, 10, 15, 30 minutes, 1, 2, 3, 4, 6, 8, 10, & 24 hours Venous Blood: Post-dose: 34, 48, 58, 72, 82, & 96 hours CSF: Pre-dose[c] and post-dose: 5, 10, 15, 30 minutes, 1, 2, 3, 4, 6, 8, 10, 24, 34, 48, 58, 72, 82, & 96 hours Urine: Post-dose: 0-6, 6-12, 12-24, 24-36, 36-48, 48-60, 60-72, 72-84, & 84-96 hours			

[a] Within 14 days prior to study drug administration

[b] All assessments performed at 96 hours post-dose

[c] Pre-dose = 5 to 15 min prior to study drug administration

[d] Hospital admission, and IT catheter and pulse oximeter placement

Statistical methods:

Data were summarized using frequency tables and descriptive statistics. No formal statistical tests were planned or performed.

Results Reported by the Applicant:

1. Demographics

Variable	SKY0401 (n=22)	Morphine Sulfate (n=4)
Age (years)		
Mean	31	26
SD	6.80	5.48
Range	22-43	20-32
Gender, n (%)		
Male	11 (50%)	4 (100%)
Female	11 (50%)	0
Race, n (%)		
Caucasian	4 (18%)	3 (75%)
African American	10 (45%)	1 (25%)
Asian	2 (9%)	0
Hispanic	6 (27%)	0
Height (in)		
Mean	67.2	71.8
SD	4.08	2.06
Range	60-73	69-74
Weight (lbs)		
Mean	156.2	177.0
SD	25.35	13.6
Range	122-200	160-193

Source: Appendix 16.2, Table 1

Table 1
Demographics
All Subjects (N=26)

		SKY0401 Treatment Groups									
		2.5 mg (n= 2)	5 mg (n= 4)	10 mg (n= 4)	20 mg (n= 4)	30 mg (n= 6)	40 mg (n= 2)	Total SKY0401 (n=22)	MS 2.5 mg (n= 2)	MS 5 mg (n= 2)	Total MS (n= 4)
Sex	Male	0(0%)	2(50%)	3(75%)	2(50%)	3(50%)	1(50%)	11(50%)	2(100%)	2(100%)	4(100%)
	Female	2(100%)	2(50%)	1(25%)	2(50%)	3(50%)	1(50%)	11(50%)	0(0%)	0(0%)	0(0%)
Race	Caucasian	1(50%)	0(0%)	1(25%)	1(25%)	1(17%)	0(0%)	4(18%)	1(50%)	2(100%)	3(75%)
	Black	0(0%)	2(50%)	1(25%)	2(50%)	3(50%)	2(100%)	10(45%)	1(50%)	0(0%)	1(25%)
	Asian	0(0%)	0(0%)	1(25%)	1(25%)	0(0%)	0(0%)	2(9%)	0(0%)	0(0%)	0(0%)
	Hispanic	1(50%)	2(50%)	1(25%)	0(0%)	2(33%)	0(0%)	6(27%)	0(0%)	0(0%)	0(0%)
Age (years)	Mean	37.50	26.75	24.50	37.00	30.67	29.50	31.23	24.50	27.50	26.00
	SD	7.78	5.19	7.85	4.55	6.22	7.78	6.00	6.36	6.36	5.48
	Min	32.00	22.00	23.00	33.00	23.00	24.00	22.00	20.00	23.00	20.00
	Max	43.00	33.00	40.00	43.00	39.00	35.00	43.00	29.00	32.00	32.00
	Median	37.50	26.00	25.50	36.00	29.50	29.50	31.00	24.50	27.50	26.00
Height (inches)	n	2(100%)	4(100%)	4(100%)	4(100%)	6(100%)	2(100%)	22(100%)	2(100%)	2(100%)	4(100%)
	Mean	61.50	65.75	69.00	69.00	67.30	68.00	67.17	71.50	72.00	71.75
	SD	2.12	4.99	0.82	2.94	4.26	7.07	4.00	3.54	0.00	2.06
	Min	60.00	61.00	68.00	66.00	63.00	63.00	60.00	69.00	72.00	69.00
	Max	63.00	71.00	70.00	72.00	73.00	73.00	73.00	74.00	72.00	74.00
	Median	61.50	65.50	69.00	69.00	66.00	68.00	67.50	71.50	72.00	72.00
Weight (pounds)	n	2(100%)	4(100%)	4(100%)	4(100%)	6(100%)	2(100%)	22(100%)	2(100%)	2(100%)	4(100%)
	Mean	165.00	142.75	156.25	156.25	150.50	147.50	156.23	170.00	184.00	177.00
	SD	11.31	9.00	12.44	13.50	30.79	20.51	25.35	14.14	12.73	13.64
	Min	157.00	130.00	122.00	125.00	126.00	133.00	122.00	160.00	175.00	160.00
	Max	173.00	151.00	168.00	197.00	200.00	162.00	200.00	180.00	193.00	193.00
	Median	165.00	145.00	172.50	161.50	155.50	147.50	154.00	170.00	184.00	177.50

2. Efficacy Results:

Data Sets Analyzed: A total of 22 subjects received protocol-specific doses of SKY0401 (2.5 mg, n=2; 5 mg, n=4; 10 mg, n=4; 20 mg, n=4; 30 mg, n=6; 40 mg, n=2). Four subjects received commercial unencapsulated morphine sulfate (Astramorph 2.5 mg, n=2; Astramorph 5 mg, n=2). Pharmacodynamic data were summarized for the 19 subjects that were administered SKY0401 correctly into the epidural space. The three subjects in whom SKY0401 was assumed to be inadvertently administered outside of the epidural space were excluded from this analysis. In addition, pharmacodynamic data were not analyzed for the four subjects who received unencapsulated morphine sulfate. Overall, dose-dependent trends were generally demonstrated for antinociceptive activity evaluations but were less readily observed with subjective and cognitive/psychomotor assessments. An increase for all antinociceptive activity evaluations (pain tolerance, pain threshold, SI50 values) in all three dermatomes was observed following 20, 30, and 40 mg SKY0401. Only minimal effect was observed following 2.5, 5, and 10 mg SKY0401. Time to peak effect for antinociceptive activity evaluations generally occurred between 5.75 to 10 hours post-dose.

3. Safety Results:

Adverse events observed following SKY0401 were pharmacologically predictable for an epidural opioid and no unexpected adverse events were reported. The adverse events most commonly reported were consistent with opioids (e.g., pruritus, nausea, vomiting, headache, somnolence, urinary retention). A dose response relationship was generally not observed for the most common opioid-related adverse events. No subjects were prematurely terminated from the study due to an adverse event. One serious adverse event (fever and chills) occurred in a subject who received 20 mg SKY0401 and was judged by the investigator not to be related to SKY0401. Two subjects treated with 40 mg SKY0401 experienced dose limiting toxicity, as defined per protocol (i.e., severe episodes of pruritus, oxygen desaturation, hypercapnia, and low systolic blood pressure). The 30 mg dose of SKY0401 was generally well tolerated by six subjects and was therefore determined to be the maximally tolerated dose.

4. Pharmacokinetic results

Pharmacokinetic analyses of plasma, CSF, and urine concentrations of morphine and morphine metabolites (morphine-6-glucuronide and morphine-3-glucuronide) are described in detail in a separate report (Report No. 042-00006). A brief summary of these results is provided here.

a) Summary of Pharmacokinetic Results

Following epidural administration of SKY0401, morphine was rapidly absorbed into the systemic circulation, and peak plasma concentrations were reached within 10 minutes. Overall, the mean Cmax, AUCinf, and t1/2 increased with escalating doses of SKY0401, as summarized below.

TABLE 13.1.1 MEAN PLASMA MORPHINE CONCENTRATIONS

Parameter (units)	SKY0401 (n=19)						5 mg Morphine Sulfate (n=2)
	2.5 mg (n=2)	5 mg (n=4)	10 mg (n=4)	20 mg (n=3)	30 mg (n=4)	40 mg (n=2)	
AUC_{inf} (ng x hr x mL^{-1})	21.1	45.3	86.3	171.4	281.2	394.2	39.4
C_{max} (ng/mL)	12.0	15.1	34.3	52.6	58.9	103.1	26.0
t_{max} (hr)	0.21	0.21	0.17	0.14	0.13	0.13	0.21
$t_{½}$ (hr)	2.6	4.4	9.6	11.3	20.9	20.9	3.34

Source: Report No. 042-00006
Excludes Subject 006, 007, and 008 [SKY0401] and Subjects 090 and 091 [2.5 mg MS]

Plasma concentrations of morphine-3-glucuronide were generally about 10-fold greater than plasma concentrations of morphine, while plasma concentrations of the pharmacologically active metabolite, morphine-6-glucuronide, peaked later than morphine but generally were lower than morphine concentrations (Table 13.1.2):

TABLE 13.1.2 MEAN PLASMA MORPHINE-6-GLUCURONIDE CONCENTRATIONS

Parameter (units)	SKY0401 (n=19)						5 mg Morphine Sulfate (n=2)
	2.5 mg (n=2)	5 mg (n=4)	10 mg (n=4)	20 mg (n=3)	30 mg (n=4)	40 mg (n=2)	
AUC_{inf} (ng x hr x mL^{-1})	n/a	58.5	102.8	270.4	510.3	736.6	450.9
C_{max} (ng/mL)	5.4	7.0	12.3	21.7	19.9	43.5	43.6
t_{max} (hr)	1.5	2.5	1.5	1.7	2.8	3.0	1.5
$t_{½}$ (hr)	n/a	4.6	3.7	11.8	28.3	23.6	9.5

Source: Report No. 042-00006
n/a – not available;
Excludes Subjects 006, 007, and 008 [SKY0401] and Subjects 090 and 091 [2.5 mg MS]

Morphine was detected in the CSF as early as 5 minutes post-dose. Mean CSF concentrations were 100 to 400-fold higher than plasma concentrations. The CSF peak concentrations occurred later than peak concentrations in plasma. Cmax was achieved between 0.58 to 3 hours for the 5 to 20 mg SKY0401 doses (Table 13.1.3). Even though very high concentrations of morphine were found in the CSF, there were no signs of metabolism in the CSF. Morphine-3-glucuronide was not detected in CSF and only a trace of morphine-6-glucuronide was found in one CSF sample.

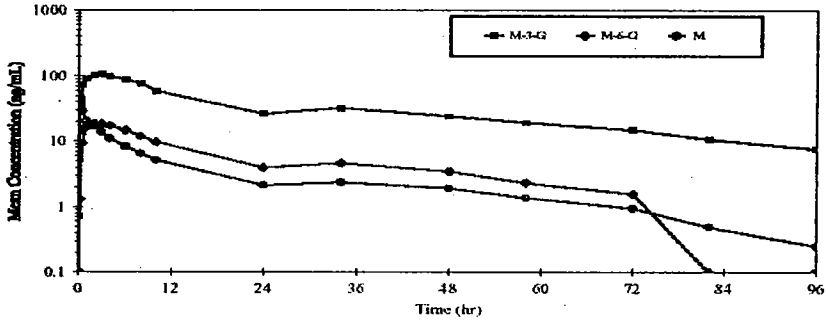
TABLE 13.1.3 MEAN CSF MORPHINE CONCENTRATIONS FOR SUBJECTS WITH AN INDWELLING INTRATHECAL CATHETER

Parameter (units)	SKY0401 (n=5)		
	5 mg (n=2)	10 mg (n=2)	20 mg (n=1)
AUC_{inf} (ng x hr x mL^{-1})	7,825.2	27,406.1	50,462.8
C_{max} (ng/mL)	3,324.8	7,035.0	8,560.0
t_{max} (hr)	0.58	1.0	3.0
$t_{½}$ (hr)	6.13	10.29	6.17

Source: Report No. 042-00006

The urinary excretion profile of morphine and morphine metabolites indicated that the majority of the dose was excreted within 96 hours following SKY0401. Only 5.6% to 7.3% of SKY0401 was excreted as morphine. Approximately 46% to 70% was excreted as morphine-3-glucuronide and approximately 10% to 14% was excreted as morphine-6-glucuronide.

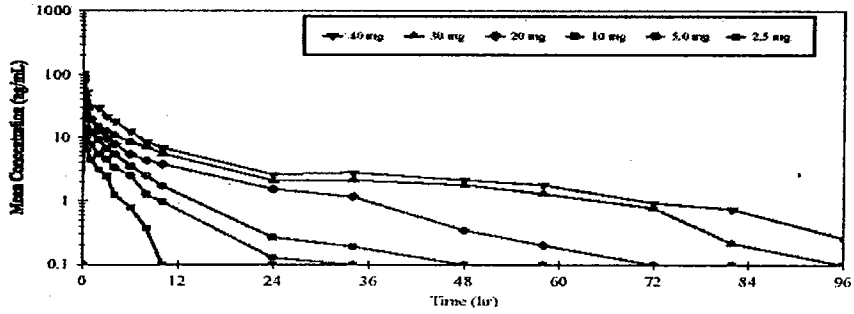
b) Plasma concentrations of M-3-G and M-6-G relative to those for morphine following epidural administration of 30 mg C0401:



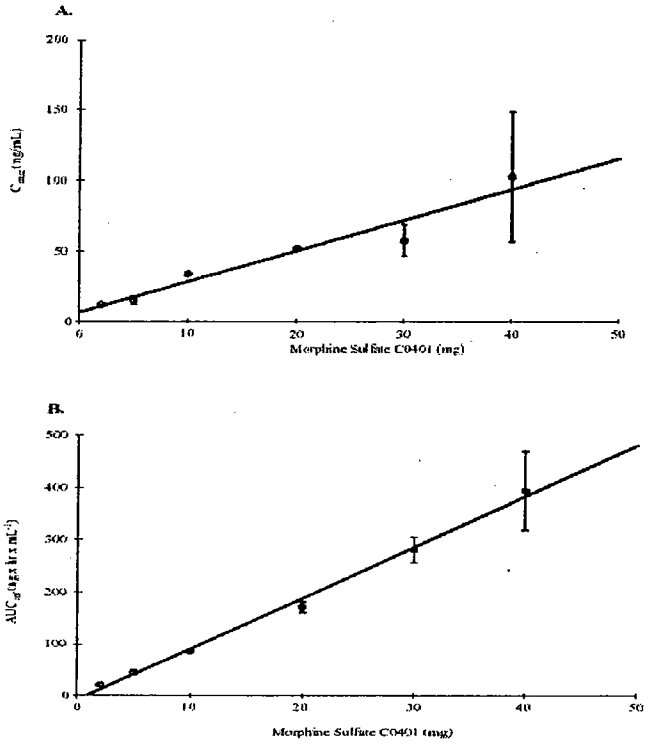
c) Relationship between Dose and Plasma Pharmacokinetics of Morphine

For all doses of SKY0401, morphine given epidurally appeared very rapidly in the systemic circulation. Within 5 minutes after administration, morphine was detected in blood.

Mean morphine plasma concentration-time curves following 2.5, 5, 10, 20, 30, and 40 mg epidural doses:



d) Cmax and AUCinf increased linearly with the dose



e) Mean Plasma Morphine Pharmacokinetics

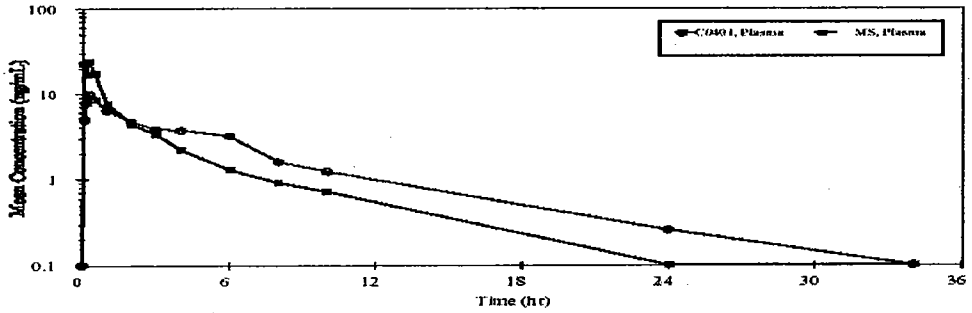
The rate of elimination of morphine from plasma was dose dependent. Morphine concentrations in plasma were measured beyond the 96 hour time point for both subjects administered 40 mg epidurally.

Mean pharmacokinetic parameters of morphine:

		2.5 mg C0401	5 mg C0401	10 mg C0401	20 mg C0401	30 mg C0401	40 mg C0401
Parameter	**Units**	**(n=2)**	**(n=4)**	**(n=4)**	**(n=3)**	**(n=4)**	**(n=2)**
AUCinf(+ SEM)	ng x hr x mL^{-1}	21.05	45.33(+ 5.63)	86.30(+ 5.83)	171.42(+ 10.55)	281.15(+ 24.91)	394.16
AUMCinf(+ SEM)	ng x hr^2 x mL^{-1}	68.17	259.94(+ 105.65)	855.47(+ 371.18)	2268.04(+ 654.52)	7379.68(+ 1341.84)	9106.28
Cl/F (+ SEM)	L/hr	121.82	115.32 (+ 13.62)	117.58 (+ 8.46)	117.52 (+ 6.90)	109.03 (+ 8.79)	105.50
Cmax (+ SEM)	ng/mL	12.00	15.07 (+ 3.32)	34.25 (+ 1.80)	52.63 (+ 1.31)	58.85 (+ 11.36)	103.10
MRTinf (+ SEM)	hr	3.08	5.29 (+ 1.53)	9.39 (+ 3.63)	12.89 (+ 2.87)	25.82 (+ 3.41)	24.36
tmax (+ SEM)	hr	0.21	0.21 (+ 0.02)	0.17 (+ 0.00)	0.14 (+ 0.03)	0.13 (+ 0.02)	0.13
Vz/F (+ SEM)	L	419.75	653.20 (+ 163.95)	1516.39 (+ 569.53)	1885.60 (+ 109.62)	3276.98 (+ 576.48)	3340.95
t1/2(+ SEM)	hr	2.56	4.37(+ 1.59)	9.56(+ 4.04)	11.27(+ 1.31)	20.88(+ 3.00)	20.92

f) Plasma Pharmacokinetics of Morphine after Doses of SKY0401 or Morphine Sulfate

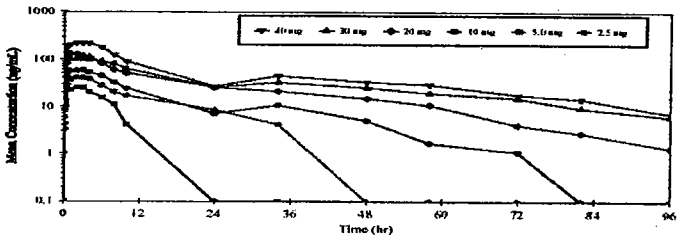
Subjects 01-021 and 01-022 were dosed epidurally with 5 mg of unencapsulated morphine sulfate and subjects 01-001 and 01-003 were dosed epidurally with 5 mg of SKY0401.



Parameter	Units	5 mg C0401 (n=4)	5 mg MS (n=2)
AUC_{inf}	ng x hr x mL^{-1}	45.33	39.37
$AUMC_{inf}$	ng x hr^2 x mL^{-1}	259.94	131.10
Cl/F	L/hr	115.32	130.56
C_{max}	ng/mL	15.07	26.00
MRT_{inf}	hr	5.29	3.41
t_{max}	hr	0.21	0.21
Vz/F	L	653.20	643.90
$t_{1/2}$	hr	4.37	3.34

g) Relationship between Dose and Plasma Pharmacokinetics of Morphine Metabolites

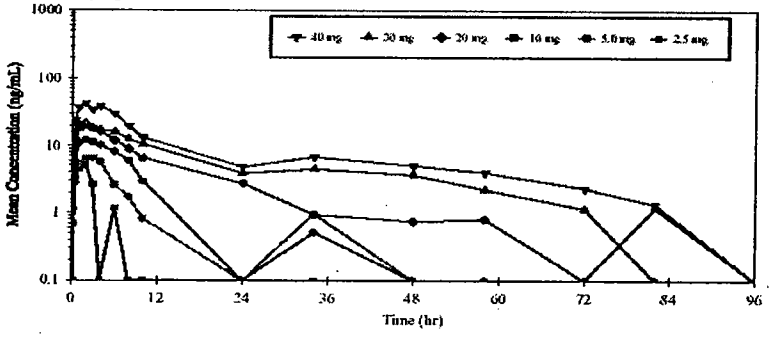
M-3-G was the predominant morphine-related compound circulating in plasma (mean plasma M-3-G concentrations as a function of time at 2.5, 5, 10, 20, 30, and 40 mg):



Mean Cmax and AUCinf values for M-3-G over the entire range of SKY0401 doses were 2-fold and 12-fold higher than corresponding values for morphine, respectively. Mean pharmacokinetic parameters for M-3-G are shown below:

Parameter	Units	2.5 mg C0401 (n=2)	5 mg C0401 (n=4)	10 mg C0401 (n=4)	20 mg C0401 (n=3)	30 mg C0401 (n=4)	40 mg C0401 (n=2)
AUC_{inf} (± SEM)	ng x hr x mL^{-1}	215.07	677.64 (± 37.00)	1101.24 (± 123.21)	2305.13 (± 188.40)	3266.94 (± 184.51)	4606.37
$AUMC_{inf}$ (± SEM)	ng x hr^2 x mL^{-1}	1455.08	14343.72 (± 2220.77)	31795.73 (± 4765.38)	57637.30 (± 13317.79)	141463.73 (± 12709.77)	147821.17
Cl/F (± SEM)	L/hr	11.63	7.44 (± 0.40)	9.47 (± 1.18)	8.80 (± 0.78)	9.26 (± 0.49)	8.94
C_{max} (± SEM)	ng/mL	26.10	43.93 (± 5.65)	61.60 (± 8.15)	132.67 (± 22.04)	106.28 (± 17.74)	223.50
MRT_{inf} (± SEM)	hr	6.76	20.85 (± 2.32)	28.61 (± 2.76)	24.71 (± 4.39)	43.11 (± 1.71)	33.88
t_{max} (± SEM)	hr	2.50	2.25 (± 0.63)	2.00 (± 0.58)	1.33 (± 0.33)	2.75 (± 0.48)	2.50
Vz/F (± SEM)	L	70.13	169.67 (± 17.86)	281.54 (± 7.56)	224.82 (± 47.77)	415.78 (± 30.29)	300.85
$t_{1/2}$ (± SEM)	hr	4.18	16.16 (± 2.38)	21.52 (± 2.48)	17.34 (± 2.05)	31.72 (± 4.18)	21.79

Below figure shows the mean plasma M-6-G concentration as a function of time following epidural administration:



Mean Plasma Morphine-6-Glucuronide Pharmacokinetic Parameters:

Parameter	Units	2.5 mg C0401 (n=2)	5.0 mg C0401 (n=4)	10.0 mg C0401 (n=4)	20.0 mg C0401 (n=3)	30.0 mg C0401 (n=4)	40.0 mg C0401 (n=2)
AUC_{inf} (± SEM)	ng x hr x mL^{-1}	NA	58.52 (± 6.20)	102.81 (± 16.52)	270.39 (± 21.24)	510.32 (± 22.09)	736.59
$AUMC_{inf}$ (± SEM)	ng x hr^2 x mL^{-1}	NA	449.28 (± 75.69)	693.61 (± 146.35)	5345.77 (± 2489.39)	20763.35 (± 2898.25)	23,634.45
CL/F (± SEM)	L/hr	NA	87.42 (± 9.44)	103.56 (± 19.61)	74.84 (± 5.59)	59.09 (± 2.36)	54.79
C_{max} (± SEM)	ng/mL	5.44	6.95 (± 1.09)	12.28 (± 0.95)	21.73 (± 0.64)	19.88 (± 2.16)	43.45
MRT_{inf} (± SEM)	hr	NA	7.79 (± 1.39)	6.61 (± 0.48)	18.65 (± 7.24)	40.41 (± 4.58)	32.83
t_{max} (± SEM)	hr	1.50	2.50 (± 0.50)	1.50 (± 0.29)	1.67 (± 0.33)	2.75 (± 1.11)	3.00
Vz/F (± SEM)	L	NA	606.61 (± 201.42)	546.31 (± 75.34)	1215.17 (± 271.59)	2382.22 (± 297.41)	1881.26
$t_{1/2}$ (± SEM)	hr	NA	4.63 (± 1.06)	3.72 (± 0.19)	11.76 (± 3.60)	28.34 (± 4.39)	23.60

h) CSF Pharmacokinetics of Morphine and Metabolites

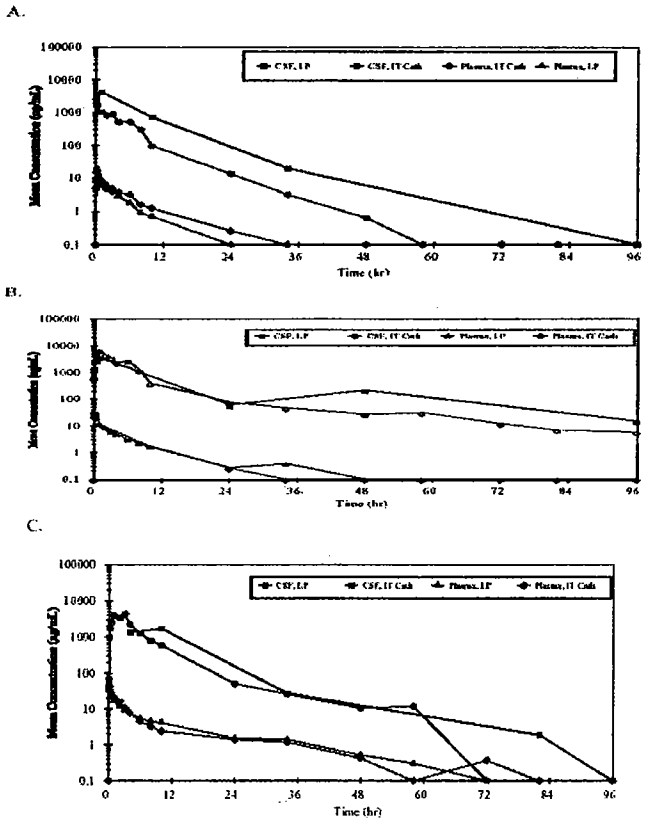
CSF Concentrations of Morphine

The first six subjects treated [01-001 and 01-003 (5 mg dose), 01-002 and 01-004 (10 mg dose), and 01-005 and 01-006 (20 mg dose)] had indwelling catheters for serial collection of CSF samples. Note that for Subject 01-006 (20-mg dose of C0401), the dose was not delivered into the epidural space, and the morphine concentrations in CSF were very low (<5 ng/mL) during the period from 1 to 10 hours after the dose. For the remaining 18 subjects, only 2 or 3 CSF samples were collected by LP during the 96 hour period. Concentrations of morphine in the CSF and plasma for subjects with an indwelling catheter, and the ratio of the CSF to plasma concentration for each sampling time for the first 24 hours after the dose are summarized below:

Time (hr)	Subject 01-001			Subject 01-002			Subject 01-003			Subject 01-004			Subject 01-005		
	CSF	Plasma	Ratio	CSF	Plasma	Ratio	CSF	Plasma	Ratio	CSF	Plasma	Ratio	CSF	Plasma	Ratio
0	0	0		0	0		0	0		0	0		0	0	
0.08	10.9	6.01	1.81	29.2	21.9	1.33	5040	3.89	1296	1260	25.4	49.6	137	54.5	2.514
0.17	108	10.5	10.3	210	30.8	6.82	6820	5.1	1337	2730	37	73.8	1940	52.6	36.88
0.25	263	14.3	18.4	581	26.6	21.8	3120	5.99	521	4740	31.6	150	3540	46.3	76.46
0.5	838	11.9	70.4	2480	19.1	130	1250	5.37	233	7480	22.5	332	4990	35.9	139
1	1520	6.82	223	3970	12	331	563	5.94	94.8	10100	12.3	821	7830	25.5	307.1
2	1430	4.52	316	2720	10.5	259	222	4.85	45.8	6430	8.84	727	6940	15.5	447.7
3	NS	4.04	NA	1820	7.34	248	883	3.68	240	5590	7.27	769	8560	10.7	800
4	NS	3.91	NA	1190	5.6	213	515	3.62	142	3570	6.44	554	4460	8.26	540
6	NS	3.16	NA	NS	3.57	NA	505	3.28	154	2830	4.13	685	2470	5.41	456.6
8	358	1.84	195	NS	2.35	NA	231	1.37	169	1220	2.84	430	1570	3.91	401.5
10	72.8	1.45	50.2	NS	1.47	NA	118	1.02	116	396	2.16	183	1160	3.09	375.4
24	10.5	0.52	20.3	NS	0	NA	16.6	0	NA	76.8	0.53	146	101	1.61	62.73
Mean			101			151			395			410			303.8

NA, not applicable; NS, no sample.

As early as 5 minutes after the epidural dose, morphine was detected in CSF. Peak concentrations of morphine in CSF occurred in 1 to 3 hours. Overall, the morphine concentrations in CSF greatly exceeded corresponding concentrations in plasma. Mean CSF to plasma ratios for each subject ranged from 100 to 400. CSF mean morphine concentrations are similar for the subjects that received the 10 or 20 mg doses, but substantially different for the subjects that received the 5 mg dose.



A) 5 mg SKY0401 B) 10 mg SKY0401 C) 20 mg SKY0401; Mean CSF morphine concentrations. CSF was sampled by either LP or IT catheter

Maximum Observed Morphine CSF Concentrations for Subjects Who Were Sampled By Using Lumbar Puncture:

Subject	Time (hr)	Dose (mg)	Concentration (ng/mL)	Formulation
01-023	3.0	2.5	1210	C0401
01-024	10.0	2.5	196	C0401
01-019	1.0	5.0	4240	C0401
01-020	10.0	5.0	719	C0401
01-021	4.0	5.0	1160	MS
01-022	1.0	5.0	1750	MS
01-017	0.5	10.0	2860	C0401
01-018	1.0	10.0	3630	C0401
01-015	10.0	20.0	1700	C0401
01-016	4.0	20.0	1330	C0401
01-007	10.0	30.0	2.63*	C0401
01-008	8.0	30.0	8.01*	C0401
01-011	4.0	30.0	7360	C0401
01-012	8.0	30.0	2660	C0401
01-013	4.0	30.0	6030	C0401
01-014	6.0	30.0	3300	C0401
01-009	2.0	40.0	8010	C0401
01-010	6.0	40.0	4400	C0401

* Subject apparently did not receive the dose in the epidural space.

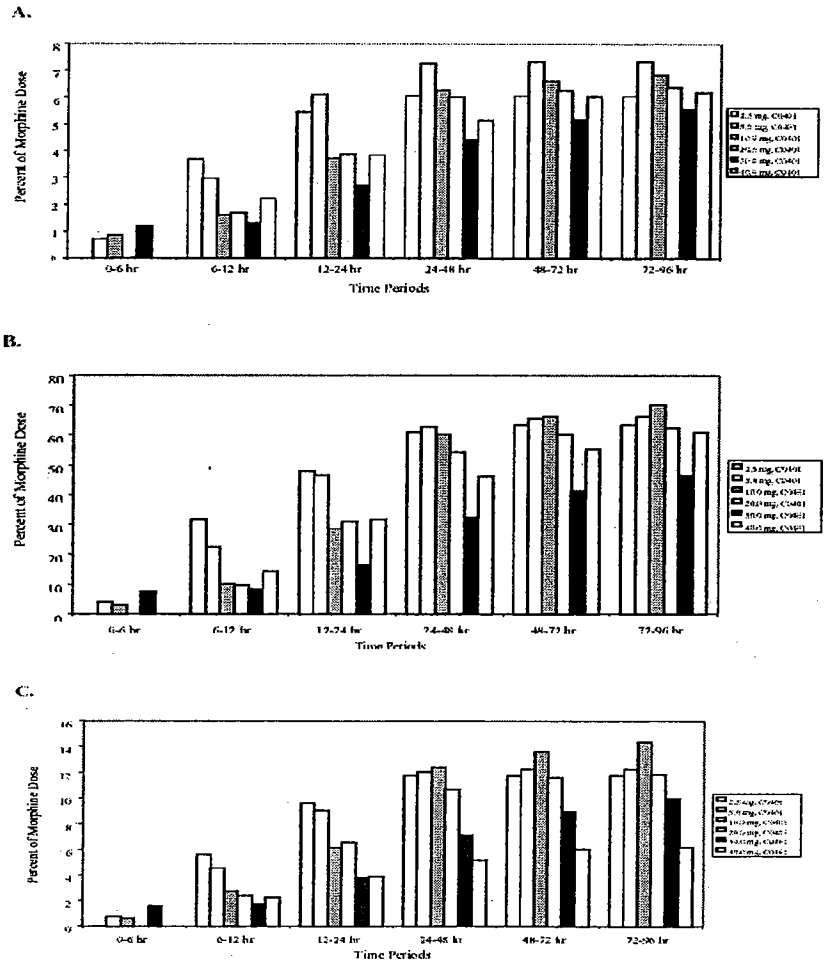
i) Urinary Excretion of Morphine and Metabolites

The following table summarizes the cumulative urinary excretion of morphine, M-3-G, and M-6-G within 96 hours following epidural injection of SKY0401. Overall, a high percentage of the dose (62 to 91%) was recovered in the urine. Only 5.6 to 7.3% of the dose was excreted as morphine. Approximately 46 to 70% and 10 to 14% of SKY0401 was excreted as M-3-G and M-6-G, respectively. At the lower doses of SKY0401, the majority of morphine and metabolites was excreted within 48 hrs following C0401 administration.

Cumulative Urinary Excretion of Morphine, M-3-G and M-6-G:

C0401 Dose	Percent of Dose Excreted in 96 hr			
	Morphine	M-3-G	M-6-G	Total
2.5 mg C0401	6.05	63.28	11.77	81.10
5.0 mg C0401	7.34	66.40	12.26	86.00
10 mg C0401	6.82	70.27	14.36	91.45
20 mg C0401	6.37	62.47	11.86	80.70
30 mg C0401	5.56	46.36	9.96	61.88
40 mg C0401	6.18	60.91	12.29	79.38

The following figure illustrates the percent of dose that was excreted as morphine, M-3-G, and M-6-G, respectively, in the urine for various intervals during the 96 hour study period.



Study SKY0401-016

Title of Study: A Randomized, Open-Label, Parallel Group Study to Evaluate the Effects of Lidocaine/Epinephrine Test Dose Administration on the Pharmacokinetic (PK) and Pharmacodynamic (PD) Profiles of a Single Epidural Dose of Sustained-Release Encapsulated Morphine (SKY0401) in Patients Undergoing Major Upper Abdominal Surgery
Investigators / Study Centers:: Multicenter study in the United States
Study Period: 06 May 2002 to 18 February 2003 **Clinical Phase:** Phase 1
Primary Objective: To evaluate the effects of lidocaine/epinephrine test dose administration on the PK profile of a single epidural dose of SKY0401 in patients undergoing major upper abdominal surgery.
Secondary Objective: To evaluate the safety and efficacy profile of SKY0401, with and without a lidocaine/epinephrine test dose, in patients undergoing major upper abdominal surgery.
Methodology: This was a Phase 1, multicenter, randomized, open-label, parallel group study to evaluate a single epidural dose of SKY0401 (15 mg) in a 5-mL volume, administered with or without a preceding 3-mL test dose containing lidocaine (1.5%) with epinephrine (1:200,000) in patients undergoing major upper abdominal surgery via a midline incision.
No. of Patients (Planned and Analyzed): Planned enrollment was for a total of 50 patients. Patients were randomized to one of five treatment arms: Group 1 received no test dose prior to administration of study drug, followed immediately by 1 mL administration of normal saline to flush the epidural line. Groups 2, 3 and 4 received a test dose followed by a1-mL flush with normal saline and then, after a waiting period (3 minutes for Group 2, 10 minutes for Group 3, and 15 minutes for Group 4), received SKY0401 immediately followed by 1 mL of normal saline to flush the epidural line. Group 5 received a test dose without a saline flush and then, after a 3-minute wait, received SKY0401 immediately followed by a flush with 1 mL of normal saline. All patients received a 15 mg dose of SKY0401. Thirty-nine patients were enrolled. Of these, 8, 8, 7, 8, and 8, patients, respectively, were randomized to Groups 1 through 5. The 39 patients were included in both the intent-to-treat (ITT) and the safety analyses.
Diagnosis and Main Criteria for Inclusion: Males or females ☐18 years of age, scheduled for major upper abdominal surgery via an upper abdominal midline incision under general anesthesia, American Society of Anesthesiology (ASA) Class 1, 2, or 3, willing and able to use a patient-controlled analgesia (PCA) pump, to receive only IV fentanyl for 72 hours to control post-operative pain, and to remain hospitalized for a minimum of 72 hours post-dose.
Test Product: SKY0401 (Sustained-Release Encapsulated Morphine) **Lot Numbers:** 02-4005 and 02-4007
Dosage: A single dose of SKY0401 (15 mg) in a 5-mL volume
Duration of Treatment: Approximately 30 minutes prior to the start of surgery, a single 5-mL dose of 15 mg SKY0401 was administered by epidural injection at a controlled rate over 15 seconds.

Criteria for Evaluation:
Pharmacokinetics: Blood samples for serum concentration measurements of morphine and morphine metabolites were collected prior to study drug administration and for 72 hours post-dose. Pharmacokinetic parameters ($AUC_{0\rightarrow tlast}$, $AUC_{0\rightarrow\infty}$, C_{tlast}, C_{max}, t_{max}, k_{el}, λ_z, $t_{1/2el}$) were then determined. Efficacy: Efficacy was evaluated by the assessment of the total amount of IV fentanyl used through 72 hours post-dose, the time to first post-operative IV fentanyl usage, and pain intensity evaluations. Safety: Safety was assessed by recording vital signs, including respiratory rate (RR), heart rate (HR), and blood pressure (BP), and conducting brief neurological checks and sedation scores through 72 hours post-dose. Additional safety data were collected by conducting physical and neurological examinations at Screening (i.e., ≤ 21 days prior to study drug administration) and on Day 4 (where Day 1 is the day of study drug administration), and by recording all AEs following study drug administration through Day 7 and selected AEs (to identify any potential neurological sequela[e] of epidural analgesia) and serious AEs (SAEs) through Day 30.

Statistical Methods:
Efficacy Analyses: Efficacy analyses were conducted on the ITT population, which consisted of all randomized patients who received any study drug and who underwent the planned surgical procedure. Patients were analyzed according to the dosing regimen received. Analysis of variance (ANOVA) was used to compare the average amount of total IV fentanyl among the treatment groups. The time from study drug administration to the first post-operative use of IV fentanyl was summarized with medians and Kaplan-Meier curves and compared among treatment groups using logrank tests. Pain intensity evaluations using scores from a Visual Analog Scale (VAS) were analyzed using ANOVA. Pain intensity evaluations using scores from a categorical scale (CAT) were analyzed using the Mantel-Haenszel test. All other analyses were conducted using ANOVA or Fisher.s exact test.

Safety Analyses: Safety analyses were conducted on the safety population, which included all randomized patients who received any study drug whether or not they underwent the planned surgical procedure. Patients were analyzed according to the dosing regimen received. Summary tables and individual patient listings were provided for all safety measurements. Descriptive statistics were used to summarize safety data where appropriate. All AEs were listed, documenting the course, outcome, severity, and causality to study drug. Verbatim terms on CRFs were mapped to preferred terms and related system organ classes using the Medical Dictionary of Regulatory Activities (MedDRA). The percentage of patients with AEs and the severity of AEs were displayed by body system for each study group. The numbers and incidence of SAEs (including those that resulted in death) by study group was also displayed. Incidences of AE and SAEs among study groups were compared using Fisher.s exact test. Pharmacokinetics Analyses: The methods used in the analysis of the PK data are presented in a separate report.

RESULTS
Efficacy Results (ITT Population, N = 39):
Mean total fentanyl usage through 72 hours post-dose in Groups 1 through 5 was 1258.8, 860.6, 1718.9, 1000.3, and 1001.3 mcg, respectively. There were no statistically significant differences observed among treatment groups.

No significant differences were observed among the treatment groups in terms of total fentanyl usage from 0 to 24, > 24 to 48, or > 48 to 72 hours post-dose. Similarly, mean opioid usage (converted to fentanyl equivalents) through 72 hours post-dose was similar

among the treatment groups.

No significant differences were observed among the treatment groups in terms of the time to first post-operative fentanyl usage.

No significant differences were observed among the treatment groups at any time point in terms of VAS and CAT assessments of pain intensity at rest (VAS-R and CAT-R, respectively) and with activity (VAS-A and CAT-A, respectively). The one exception was the VAS-R scores at the first request for pain medication. In Groups 1 through 5, the mean VAS-R scores were 69.7, 23.5, 30.5, 55.0, and 59.5, respectively, with a significant differences noted among the treatment groups ($p = 0.0425$).

Safety Results (Safety Population, N = 39):

Adverse events from Days 1 to 7 were reported by all patients in each treatment group. The total number of AEs reported was 146, including 29, 24, 17, 37, and 39 in Groups 1 through 5, respectively. The most frequently reported AEs were hypotension, nausea, pruritus, and pyrexia, the majority of which were related to opioid administration. There were no significant differences observed among the treatment groups. The majority of AEs (> 90%) in each treatment groups were mild to moderate in severity. Seven severe AEs were reported, including 1 (3%), 2 (5%), and 4 (10%) in Groups 1, 4, and 5, respectively. Fifty-nine AEs (40%) were considered related (possibly or probably) to study drug, with the most frequently reported including hypotension, pruritus, and nausea. Neurological AEs from Days 8 to 30 were reported by 3 patients (8%), including 1 patient each (13%) in Groups 2, 3, and 4, respectively. All of the neurological AEs were mild or moderate, none were considered related to study drug, and there were no significant differences reported among the treatment groups.

□

Pharmacokinetic Results: The results of the analyses of the PK data are presented in a separate report.

CONCLUSIONS: This Phase 1, parallel-group study was designed to evaluate the effects of a lidocaine/epinephrine test dose on the PK profile of morphine following the administration of SKY0401. Although increasing the time between test dose administration and SKY0401 administration does flatten the PK profile of morphine, these PK changes have no clear effect on the PD profile of SKY0401. Overall, the limited data presented in this report indicate that the use of dosing regimens designed to modulate the PK profile of morphine following the administration of SKY0401 have no clear effect on either the safety or efficacy of SKY0401. Moreover, any differences observed among the groups should be interpreted with caution, due to the very small number of patients in each of the treatment groups.

Patients were to be randomized in a 1:1:1:1:1 ratio to one of the following dosing regimens:

. Group 1: No test dose + SKY0401 + flush with 1 mL normal saline

. Group 2: Test dose + flush with 1 mL normal saline + 3-minute wait + SKY0401 + flush with 1 mL normal saline

. Group 3: Test dose + flush with 1 mL normal saline + 10-minute wait + SKY0401 + flush with 1 mL normal saline

. Group 4: Test dose + flush with 1 mL normal saline + 15-minute wait + SKY0401 + flush with 1 mL normal saline
. Group 5: Test dose + No flush + 3-minute wait + SKY0401 + flush with 1 mL normal saline

Results

1) Demographics

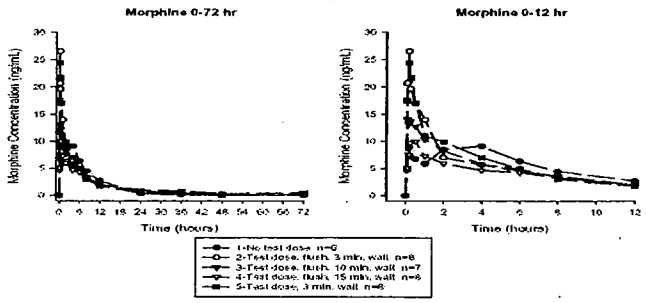
	Treatment Group Number[1]					Total
	1	2	3	4	5	
Patients (n)	8	8	7	8	8	39
Age (years)						
Mean (SD)	48.9 (16.8)	61.4 (16.0)	56.0 (10.9)	59.5 (11.0)	64.3 (12.4)	58.1 (14.1)
Median	50.0	59.5	58.0	59.0	64.0	59.0
Min-Max	26 – 72	39 – 82	41 – 70	46 – 75	45 – 78	26 – 82
Age Group (years)						
< 65	7 (88%)	5 (63%)	5 (71%)	5 (63%)	5 (63%)	27 (69%)
65 - 75	1 (13%)	0 (13%)	2 (29%)	3 (38%)	0 (0%)	7 (18%)
> 75	0 (0%)	2 (25%)	0 (0%)	0 (0%)	3 (38%)	5 (13%)
Gender						
Male	3 (38%)	4 (50%)	2 (29%)	6 (75%)	5 (63%)	20 (51%)
Female	5 (63%)	4 (50%)	5 (71%)	2 (25%)	3 (38%)	19 (49%)
Race						
Caucasian	7 (88%)	8 (100%)	6 (86%)	6 (75%)	8 (100%)	35 (90%)
Black	0 (0%)	0 (0%)	1 (14%)	2 (25%)	0 (0%)	3 (8%)
Asian	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hispanic	1 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
ASA						
Class 1	1 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Class 2	4 (50%)	6 (75%)	6 (86%)	4 (50%)	6 (75%)	26 (67%)
Class 3	3 (38%)	2 (25%)	1 (14%)	4 (50%)	1 (25%)	12 (31%)

[1]Treatment Groups: 1 = No test dose; 2 = Test dose, flush, 3 minute wait; 3 = Test dose, flush, 10 minute wait; 4 = Test dose, flush, 15 minute wait; 5 = Test dose, no flush, 3 minute wait.
SD = Standard deviation; ASA = American Society of Anesthesiology.
Source: Section 14.1, Tables 3.a and Appendix 16.2, Listing 4.

2) PK Results

a. Morphine Results

Mean morphine concentration-time curves for each SKY0401 treatment group are plotted:



Mean (SD) PK Parameters for Morphine by Treatment Group

Variable	Group 1 (n=6)	Group 2 (n=8)	Group 3 (n=7)	Group 4 (n=8)	Group 5 (n=8)
C_{max} (ng/mL)	11.47 (7.347)	30.24 (8.485)	15.58 (9.287)	11.38 (6.401)	25.56 (10.061)
t_{max} (hr) [1]	2.00 (0.17–6.0)	0.17 (0.08–0.25)	0.25 (0.08–2.0)	0.50 (0.17–1.0)	0.21 (0.08–2.0)
AUC_{0-t} (ng•hr/mL)	85.62 (31.419)	98.52 (44.206)	100.88 (52.213)	81.03 (43.589)	92.37 (29.183)
$AUC_{0-\infty}$ (ng•hr/mL) [4]	120.23 (40.816)	114.35 (46.490)	142.46 (77.460)	97.64 (51.446)	111.80 (40.842)
λ_z (hr^{-1}) [4]	0.1062 (0.0719)	0.0884 (0.0811)	0.0507 (0.0439)	0.1206 (0.1544)	0.1215 (0.1305)
$t_{1/2}$ (hr) [2,4]	6.53 (4.732)	7.84 (8.649)	13.66 (13.859)	5.75 (10.805)	5.71 (8.045)
CL/F (mL/min/kg) [4]	27.67 (7.032)	33.14 (14.675)	25.42 (11.374)	50.25 (52.019)	30.38 (8.857)
CL/F (mL/min) [4]	2288.0 (753.17)	2512.5 (954.16)	2357.3 (1430.88)	4507.9 (4818.71)	2519.7 (923.74)
V_z/F (L/kg) [4]	25.76 (19.768)	38.12 (23.329)	43.84 (21.752)	41.89 (29.844)	46.06 (51.440)
V_z/F (L) [4]	1904.05 (1196.833)	3019.5 (1974.33)	3588.3 (1250.43)	3686.2 (2645.70)	3177.1 (3154.90)
C_{max} [3]	9.59	29.01	13.70	9.24	24.05
AUC_{0-t} [3]	80.39	89.97	87.58	63.32	88.52
$AUC_{0-\infty}$ [3,4]	114.56	106.50	123.56	78.87	105.34

[1] Median (min-max)

[2] Harmonic mean and pseudo standard deviation of the jackknife variance

[3] Geometric mean of ln-transformed variables

[4] n=6 for Group 3

Group 1 = No test dose, Group 2 = Test dose + flush + 3 min wait, Group 3 = Test dose + Flush + 10 min wait, Group 4 = Test dose + Flush + 15 min wait, Group 5 = Test dose + 3 min wait

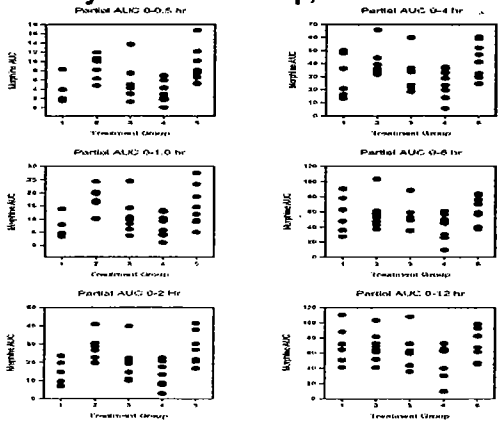
Early Systemic Drug Exposure by Treatment Group

Partial AUC Ratio (%) [1]	Group 1 (n=6)	Group 2 (n=8)	Group 3 (n=7)	Group 4 (n=8)	Group 5 (n=8)
AUC_{0-t} (0-0.5hr)	3.6	9.1	5.5	4.3	9.7
AUC_{0-t} (0-1hr)	7.3	17.0	10.9	9.3	17.3
AUC_{0-t} (0-2hr)	15.7	27.6	19.3	17.4	28.5
AUC_{0-t} (0-4hr)	35.9	40.4	32.4	30.4	46.9
AUC_{0-t} (0-8hr)	66.5	58.0	50.3	50.6	68.3
AUC_{0-t} (0-12hr)	83.2	69.2	60.3	62.8	78.4

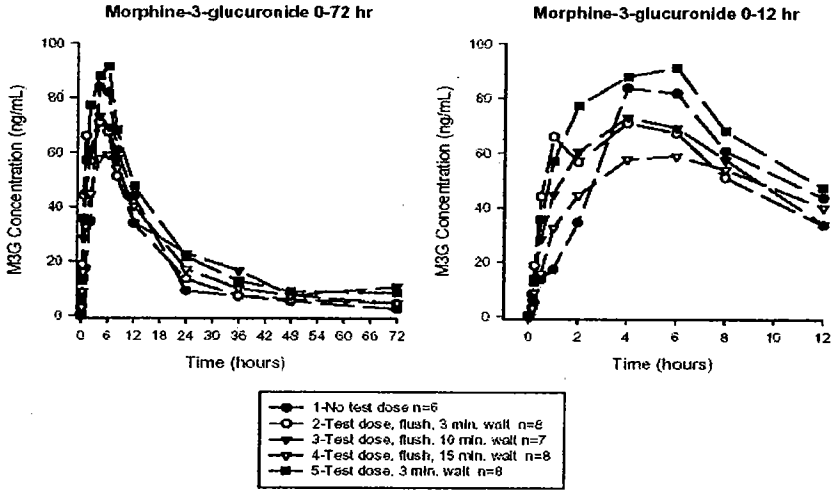
[1] Percentage of morphine AUC measured during indicated time interval relative to AUC_{0-t} (measured from time 0 to the last concentration > the LOQ). Calculated as partial AUC $_{0-t}$/Total AUC_{0-t} x 100.

Group 1 = No test dose, Group 2 = Test dose + flush + 3 min wait, Group 3 = Test dose + Flush + 10 min wait, Group 4 = Test dose + Flush + 15 min wait, Group 5 = Test dose + 3 min wait

Individual Partial AUC by Treatment Group, 0-12 hr



b) Metabolite Pharmacokinetic Results



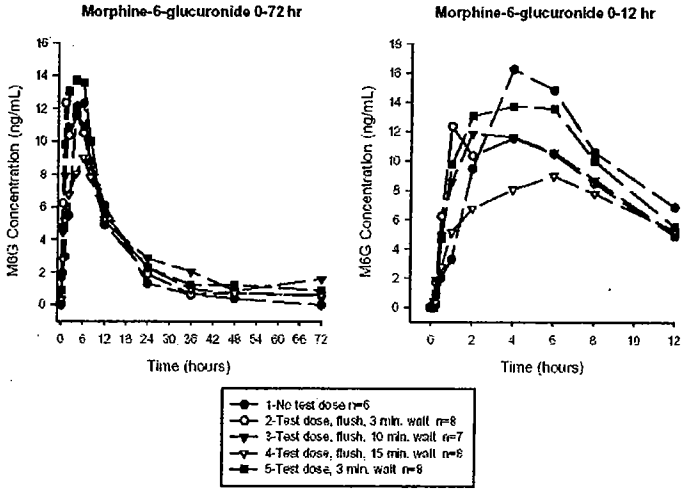


Table 6:	Mean (SD) PK Parameters for M3G by Treatment Group				
	Group 1	Group 2	Group 3	Group 4	Group 5
Variable	(n=6)	(n=8)	(n=7)	(n=8)	(n=8)
Cmax (ng/mL)	92.25 (45.320)	87.53 (16.534)	78.60 (12.201)	63.88 (25.355)	101.80 (25.118)
tmax (hr) [1]	6.0 (4.0–12.0)	4.0 (1.0–6.0)	4.0 (2.0–6.0)	4.0 (2.0–12.0)	6.0 (2.0–8.0)
AUC0-t (ng□hr/mL)	1306.55 (616.960)	1327.30 (386.209)	1497.86 (466.613)	1302.22 (447.011)	1707.71 (583.361)
AUC0-□ (ng□hr/mL)[4]	1460.09 (709.184)	1670.20 (563.747)	2102.64 (1245.98)	1679.92 (743.035)	2232.68 (1030.446)
(hr-1) [4]	0.0344 (0.0149)	0.0223 (0.0112)	0.0311 (0.0164)	0.0258 (0.0101)	0.0307 (0.0256)
□z					
t (hr) [2,4]	20.153 (9.004)	31.07 (15.554)	22.26 (12.604)	26.87 (10.121)	22.57 (23.109)
1/2					
Cmax [3]	83.17	86.15	77.73	58.13	99.10
AUC0-t [3]	1214.10	1273.39	1424.37	1212.77	1606.11
[3,4]	1344.82	1582.55	1829.59	1504.22	2003.64
AUC0-□					

[1] Median (min-max)
[2] Harmonic mean and pseudo standard deviation of the jackknife variance
[3] Geometric mean of ln-transformed variables
[4] n=6 for Group 3
Group 1 = No test dose, Group 2 = Test dose + flush + 3 min wait, Group 3 = Test dose + Flush +10 min wait,
Group 4= Test dose + Flush + 15 min wait, Group 5 = Test dose + 3 min wait
Data Source: Appendix A, Table 6

Table 7:	Mean (SD) PK Parameters for M6G by Treatment Group				
	Group 1	Group 2	Group 3	Group 4	Group 5
Variable	(n=6)	(n=8)	(n=7)	(n=8)	(n=8)
Cmax (ng/mL)	13.61 (6.469)	15.68 (4.216)	13.32 (2.232)	9.83 (4.013)	16.20 (4.720)
tmax (hr) [1]	6.0 (4.0–12.0)	1.0 (1.0–4.0)	4.0 (2.0–6.0)	6.0 (2.0–8.0)	4.0 (1.0–8.0)
AUC0-t (ng□hr/mL)	158.84 (98.901)	194.81 (103.491)	209.23 (89.326)	170.87 (85.733)	210.95 (113.720)
(ng hr/mL) [4]	225.90 (118.066)	286.89 (167.148)	317.61 (115.076)	230.98 (155.95)	315.63 (221.821)
AUC0-□					
(hr-1) [4]	0.0927 (0.0414)	0.0443 (0.0397)	0.0338 (0.0295)	0.0566 (0.0466)	0.0835 (0.0738)
T1/2 (hr) [2,4]	7.48 (3.429)	15.63 (17.202)	20.48 (25.118)	12.24 (11.489)	8.30 (8.651)
Cmax [3]	12.22	15.21	13.15	9.03	15.61
AUC0-t [3]	138.68	167.30	187.42	148.71	186.42
[3,4]	207.68	245.97	291.56	190.79	254.27
AUC0-□					

[1] Median (min-max)
[2] Harmonic mean and pseudo standard deviation of the jackknife variance
[3] Geometric mean of ln-transformed variables
[4] n=5, 6, 7, and 7 for Groups 1, 3, 4, and 5, respectively
Group 1 = No test dose, Group 2 = Test dose + flush + 3 min wait, Group 3 = Test dose + Flush +10 min wait,
Group 4= Test dose + Flush + 15 min wait, Group 5 = Test dose + 3 min wait
Data Source: Appendix A
, Table 7

Study SKY0401-008

Title of Study: A Phase 2, Open-Label, Dose Escalation/De-Escalation Study of Sustained-Release Encapsulated Morphine (SKY0401) Administered Epidurally for the Treatment of Post-Operative Pain in Patients Undergoing Total Hip Arthroplasty

Note: The Applicant stated that this is a Phase 2 pilot study to assess efficacy and safety.

Study Centers: Multicenter – 6 study sites located in the United States. One site did not enroll patients.

Studied period (years): 2 years; First patient enrolled: 19 June 1998; Last patient completed: 10 June 2000

Objectives: To assess the safety, antinociceptive activity and pharmacokinetics of various doses of sustained-release encapsulated morphine (SKY0401) following epidural administration in patients undergoing hip surgery under regional (intrathecal) anesthesia in comparison to unencapsulated morphine.

Additionally the protocol was amended to also assess an alternate formulation of sustained-release encapsulated morphine (SKY0401.1) and unencapsulated morphine.

Methodology: Open-label, dose-ranging study evaluating single epidural doses of SKY0401, SKY0401.1 and unencapsulated morphine at various doses in serial cohorts of patients undergoing total hip arthroplasty under regional anesthesia with intrathecal bupivacaine.

This Phase 2 study was the first study in which SKY0401 was administered to patients undergoing surgical procedures. The subject population comprised patients undergoing total hip arthroplasty under regional (intrathecal) anesthesia. This study was initially designed to investigate the efficacy, safety, and pharmacokinetics of SKY0401 administered epidurally. The protocol was subsequently amended to also evaluate an alternate formulation of SKY0401 (referred to as SKY0401.1) and an active control (unencapsulated morphine).

Number of patients (planned and analyzed):
Planned: Approximately 45 patients; Enrolled: 51 patients were enrolled:
- 26 received SKY0401 (n=4 [10 mg], n=1 [15 mg], n=12 [20 mg], n=1 [25 mg] and n=8 [30 mg])
- 13 patients received 5 mg unencapsulated morphine sulfate
- 11 patients received an alternate sustained release morphine formulation SKY0401.1 (n=1 [20 mg] and n=10 [30 mg])
- 1 patient assigned to the SKY0401.1 dosing group did not receive study drug.

The study drug administered was as follows:
- Part 1: cohorts of patients received a single epidural dose of SKY0401 at one of the following doses: 10, 15, 20, 25, or 30 mg.
- Part 2: cohorts of patients received either SKY0401.1 (an alternate formulation of SKY0401) at 20 or 30 mg or an active control (5 mg of unencapsulated morphine sulfate). (A sub-objective of this Part of the study was to evaluate if SKY0401.1 would result in significantly lower serum morphine peak levels or extended duration of morphine release compared to that observed for SKY0401.)

Diagnosis and main criteria for inclusion: Men and women, aged 18-65 years, undergoing total hip arthroplasty under regional anesthesia and who were capable of using a patient-controlled analgesia (PCA) device were enrolled. Following surgery, patients were permitted to self-administer IV fentanyl via a patient-controlled analgesia (PCA) device if needed for pain management; fentanyl usage was quantified through 48 hours post-dose.

Test product, dose and mode of administration, batch number: SKY0401 at doses of 10, 15, 20, 25 and 30 mg was administered as a single epidural dose approximately 30 minutes prior to surgery. Lot numbers 97-0020, 98-0007, and 98-0008 were used. SKY0401.1 at a dose of either 20 mg or 30 mg was administered as a single epidural dose Approximately 30 minutes prior to surgery. Lot number 99-0010 was used. After epidural administration of study drug, regional anesthesia was to be induced via intrathecal administration of bupivacaine in the lumbar region.

SKY0401 and SKY0401.1 contained the following other ingredients in the concentrations indicated:

	SKY0401	SKY0401.1
Cholesterol	3.3 mg/mL	mg/mL
Triolein	0.1 mg/mL	mg/mL
Tricaprylin	0.3 mg/mL	mg/mL
DOPC	3.9 mg/mL	mg/mL
DPPG	0.85 mg/mL	mg/mL
	≤ 2.0 mg/mL	mg/mL

Duration of treatment: Single epidural dose was administered over a 15-second period within 30 minutes prior to surgery.

Reference therapy: Controlled patients received 5 mg unencapsulated morphine (Astromorph/PFTM or Duramorph) supplied by the hospital pharmacy.

Criteria for evaluation:
Efficacy: Fentanyl consumption over 24 and 48 hours post-dose, time to first post-operative narcotic analgesic medication post-dose and after recovery room arrival, pain intensity ratings at rest and with activity by visual analog and categorical scales through 72 hours post-dose; global patient ratings of pain medication at 24, 48 and 72 hours.
Safety: Adverse events and changes in physical examination, vital signs, capnometry, pulse oximetry, laboratory tests and electrocardiograms. (The primary efficacy endpoint was fentanyl usage through 24 and 48 hours following study drug administration. The additional efficacy endpoints were: time between dosing and first dose of fentanyl for post-operative pain and time from recovery room arrival to first dose of fentanyl for postoperative pain. Pain intensity was assessed by two methods (Visual Analog Scale [VAS] and global categorical ratings [CAT]), at the time of first dose of fentanyl for post-operative pain and at 2, 3, 4, 6, 8, 10, 12, 18, 24, 30, 36, 48 and 72 hours (NONE, MILD, MODERATE, SEVERE). The patients performed an overall rating of the study medication at 24, 48 and 72 hours post-dose (POOR, FAIR, GOOD, VERY GOOD, EXCELLENT). Safety parameters were followed through 72 hours. Serum morphine levels were also assessed at baseline and at 0.5, 2, 4, 8, 12, 18, 24, 48, and 72 hours following dosing as well as at the time any significant opioid toxicity was observed.)

Statistical methods: Data were summarized using frequency tables and descriptive statistics. Four way comparisons of morphine sulfate, 10 mg, 20 mg and 30 mg of SKY0401 were made. P-values for the categorical counts were determined using Fisher's Exact test. P-values for the mean scores were determined by the Kruskal-Wallis test. Median time-to-event analyses were calculated by the Kaplan-Meier product limit estimates.

Pharmacokinetics
Blood samples were drawn from patients for serum determination of free morphine and morphine metabolites levels at baseline (just prior to study drug administration) and at 0.5, 2, 4, 8, 12, 18, 24, 48 and 72 hours following study drug administration. In addition, a blood sample was to be drawn for determination of morphine and morphine metabolites levels at any time a significant opioid toxicity was observed. PK parameters were listed and summarized by means of descriptive statistics (n, arithmetic mean, standard deviation, minimum, median, maximum). In addition, for t1/2el, harmonic means were calculated, and for AUC and Cmax, geometric means and between-subject variability (CVb) were also calculated. PK analysis was performed by SkyePharma AG using WinNonlin Software, Professional 3.1 version (Pharsight Corp., CA, USA).

Results:
1. Efficacy Results:

See medical review regarding the fentanyl usage. The pain intensity scores were comparable among the treatment groups. This is not unexpected, since patients in all treatment groups were permitted to self-titrate supplemental pain medication to optimize pain relief. At 48 hours, pain control medication was rated as "excellent" by 15.4% of unencapsulated morphine patients and by 46.2% of SKY0401 patients.

2. Safety Results:

SKY0401 was generally well tolerated by this population of patients undergoing hip surgery under regional (intrathecal) anesthesia. The adverse events most commonly observed were consistent with events often observed following surgery, intrathecal anesthesia and/or opioid administration. The incidence of most adverse events following SKY0401 administration did not show a dose-response pattern, except for hypoxia. For SKY0401 patients, adverse events related to alterations in respiratory function, such as hypoxia, hypercapnia or hypoventilation, tended to be mild-to-moderate in severity and either required no intervention or were treated with supplemental oxygen: no SKY0401 patients required naloxone for the treatment of respiratory depression. All significant respiratory adverse events had an onset during the first 24 hours following study drug administration. No serious/unexpected events, deaths, or premature study

terminations due to adverse events occurred in the study. The adverse event profile of the alternate formulation of encapsulated morphine SKY0401.1 did not show any advantages over SKY0401. In fact, SKY0401.1 exhibited increased incidence of respiratory depression required naloxone administration and hypotension compared to SKY0401.

3. Pharmacokinetic Results:

Note: Not all patients with PK samples drawn were included in all PK analyses. No baseline corrections were done for 3 patients who had quantifiable pre-dose levels of morphine and/or metabolites. Extrapolated PK parameters (i.e. AUC and MRT) should be interpreted with care because of the significant number of values for which extrapolation exceeded 20%.

Summary:

- From the mean profiles, roughly proportional pharmacokinetics over the dose range of 10-30 mg were observed for the SKY0401 formulation, extended and confirmed over the dose range of 5-30 mg by the results obtained for 5 mg unencapsulated morphine sulfate and the alternate SKY0401.1 formulation.
- Results of the PK analysis for the control unencapsulated morphine sulfate are in good agreement with those previously observed in the literature. Average peak morphine serum levels of 13.9 ng/ml occurred at ~0.5 h, and then declined monoexponentially with an average t1/2el value of 2.14 h (range 1.48–2.70 h, when excluding 1 patient with t1/2el = 83.2 h).
- Whatever the SKY0401 or SKY0401.1 dose, morphine Cmax occurred on average very early (median of ~0.5 h). For the two metabolites, Cmax occurred at about 4 h (except for 2 patients dosed with the 10 mg SKY0401 showing a higher Cmax at 72 h than at 4 h, for the M3G), and both the up- and downslope of the concentration-time curve were more prolonged than for morphine.
- Point estimates for the ratio of sustained-release encapsulated to control unencapsulated morphine formulation AUC (based on average AUC0-t) were superior for SKY0401 (102% for 30 mg and 88% for 20 mg) compared to SKY0401.1 (85% for 30 mg and 74% for 20 mg). The decrease in Cmax when comparing SKY0401.1 to SKY0401 was 24% for 30 mg and 14% for 20 mg.

TABLE 3
DEMOGRAPHICS
PAGE 1 OF 1

Variable	Morphine Sulfate N=12	10 mg SKY0401 N= 4	20 mg SKY0401 N=12	30 mg SKY0401 N= 8	SKY0401 (All Doses) N=24	SKY0401.1 (All Doses) N=11	All Patients Receiving Study Drug N=50
Age							
Mean (SEM)	51.5 (3.32)	52.8 (5.45)	45.6 (3.38)	53.4 (2.93)	49.3 (2.16)	51.8 (2.33)	50.4 (1.49)
Range	34 - 72	38 - 61	25 - 64	42 - 64	25 - 64	43 - 64	25 - 72
n	13	4	12	8	24	11	50
Sex							
Male	5 (38.5%)	0 (0.0%)	3 (25.0%)	4 (50.0%)	7 (29.2%)	8 (72.7%)	22 (44.0%)
Female	8 (61.5%)	4 (100.0%)	9 (75.0%)	4 (50.0%)	17 (70.8%)	3 (27.3%)	28 (56.0%)
Race							
Caucasian	12 (92.3%)	4 (100.0%)	11 (91.7%)	7 (87.5%)	24 (92.3%)	11 (100.0%)	47 (94.0%)
Black	1 (7.7%)	0 (0.0%)	1 (8.3%)	1 (12.5%)	2 (7.7%)	0 (0.0%)	3 (6.0%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hispanic	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Height (cm)							
Mean (SEM)	165.6 (2.43)	167.3 (1.67)	167.6 (1.98)	171.1 (5.47)	168.2 (1.90)	177.7 (2.56)	170.2 (1.42)
Range	147.9 - 175.3	162.6 - 170.2	154.9 - 177.8	149.9 - 190.5	149.9 - 190.5	160.0 - 193.6	147.9 - 193.0
n	13	4	12	8	24	11	50
Weight (kg)							
Mean (SEM)	73.6 (4.30)	78.4 (6.17)	72.8 (3.54)	78.8 (6.91)	75.8 (2.79)	95.3 (6.32)	79.6 (2.52)
Range	52.1 - 107.1	59.9 - 84.9	56.8 - 98.5	49.9 - 104.4	49.9 - 104.4	72.0 - 135.7	49.9 - 135.7
n	13	4	12	6	24	11	50

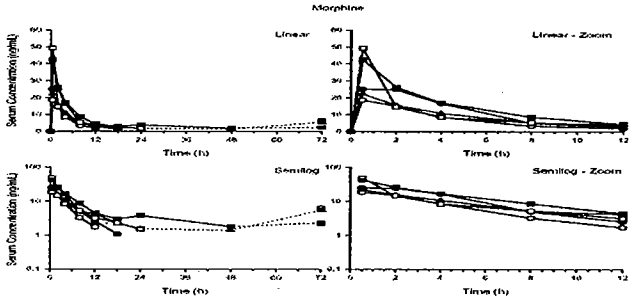
a) Demographics

	Summary of Demographic Data of All Patients Receiving Study Drug in Parts 1 and 2.		
	Age (years)	Weight (kg)	Height (cm)
N	50	50	50
Mean	50.4	79.6	170
Range	25 - 72	49.9 - 136	147 - 193

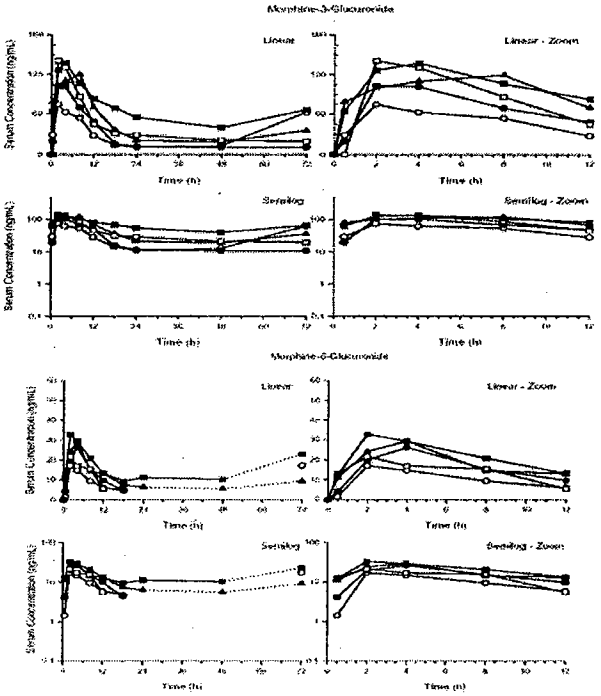
morphine sulfate. The present results do not show a significant reduction of morphine serum peak concentrations or extension of duration of the serum morphine availability with the alternate formulation SKY0401.1.

b) Figures

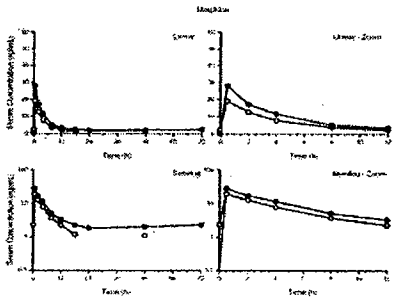
Part 1:



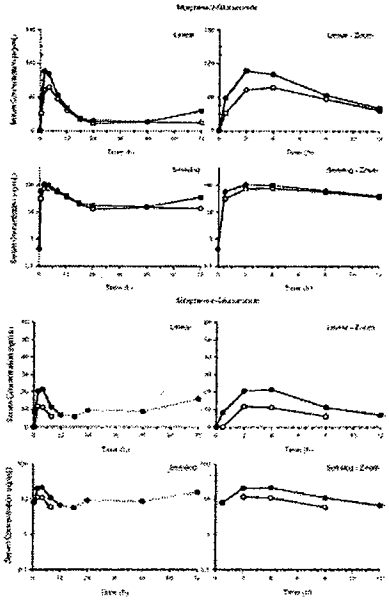
Mean morphine serum concentration vs. time curves following epidural SKY0401 administration (Part 1). Open circle 10mg; Closed c 15; Closed tri 20; Open sq 25; Closed sq 30



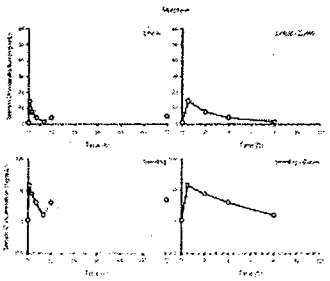
Part 2:



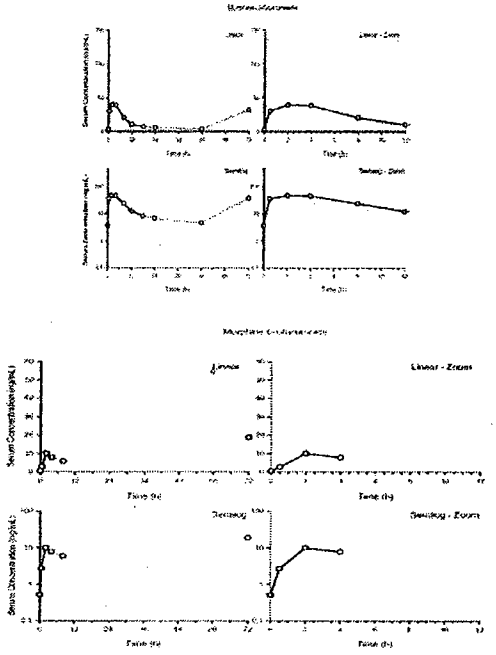
Mean morphine serum concentration vs. time curves following epidural SKY0401.1 administration (Part 2). Open circle) 20 mg and (closed circle) 30 mg doses.



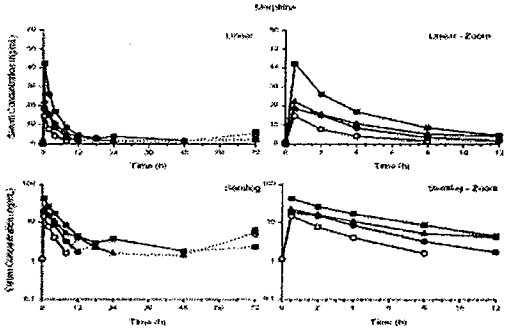
Part 2 unencapsulated morphine sulfate



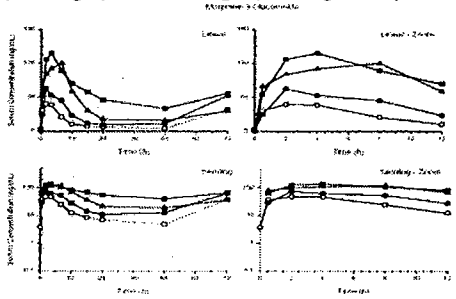
Mean morphine serum concentration vs. time curves following epidural administration of unencapsulated morphine sulfate (Part 2). (open circle) 5 mg dose.

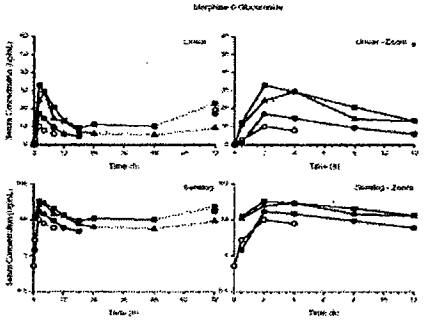


Comparison Part 1 and part 2

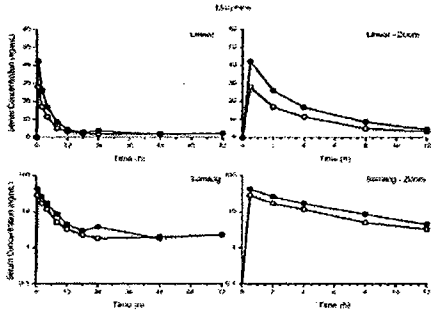


Mean morphine serum concentration vs. time curves following epidural SKY0401 administration at 10, 20 and 30 mg (Part 1) versus following epidural administration of 5 mg unencapsulated morphine sulfate (Part 2). Symbol types refer to: (open circle) 5 mg unencapsulated morphine sulfate (closed circle) 10 mg, (closed triangle) 20 mg, and (closed square) 30 mg doses.

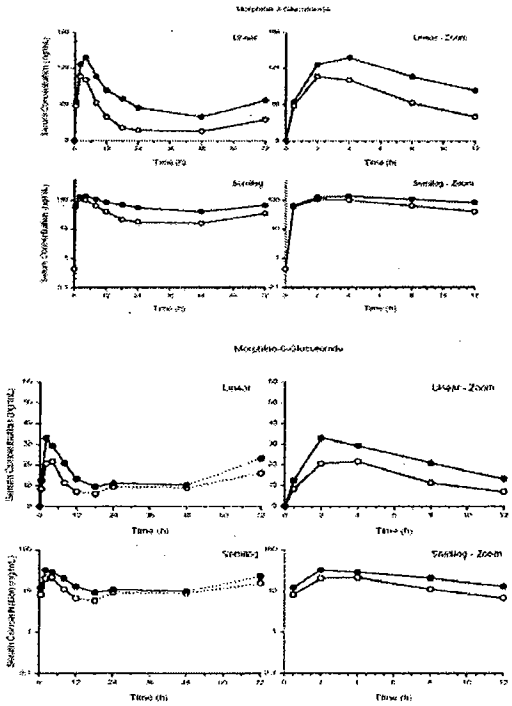




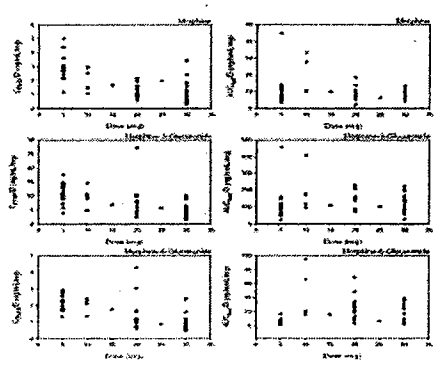
Formulation comparison 401 vs 401.1



Mean morphine serum concentration vs. time curves following epidural SKY0401 (Part 1) versus SKY0401.1 (Part 2) administration at 30 mg each. Symbol types refer to: (closed circle) SKY0401 30 mg, (open circle) SKY0401.1 30 mg. When less than half of the values were below LOQ mean is shown as a dotted line.



c) Individual Cmax AUC dose normalized



Individual Cmax and AUC dose-normalised versus dose for morphine and its metabolites. Symbol types refer to: (open circle) SKY0401 (Part 1), (closed circle) to SKY0401.1 (Part 2) and (closed triangle) to unencapsulated morphine sulfate.

d) Summary of Pharmacokinetic Parameters for Morphine after Epidural Administration of the SKY0401 Formulation (Part 1).

Parameter (unit)	Dose	Mean	Coefficient of variation, %	Minimum	Maximum
Cmax (ng/ml)	10 MG	18.5	50.2		
	15 MG	25.0			
	20 MG	22.2	42.1		
	25 MG	49.3			
	30 MG	34.5	88.5		
tmax (h)	10 MG	0.525			
	15 MG	0.450			
	20 MG	0.525			
	25 MG	0.533			
	30 MG	0.542			
AUC0–tlast	10 MG	177	69.1		
(ng/ml □ h)	15 MG	148			
	20 MG	154	55.8		
	25 MG	155			
	30 MG	268	42.9		
(h)	10	3.08 1	0.654 a		
t1/2el	MG				
	15	4.43 2			
	MG				
	20	8.31 3	5.19 a		
	MG				
	25	8.28 2			
	MG				
	30	13.8 4	18.7 a		
	MG				
	10	112 1	3.82		
AUC0–□	MG				
	15	155 2			
(ng/ml □ h)	MG				
	20	180 3b	41.8		
	MG				
	25	172 2			
	MG				
	30	326 4b	54.3		
	MG				
MRT0–tlast (h)	10 MG	21.0	96.7		
	15 MG	4.53			
	20 MG	13.1	90.4		
	25 MG	6.05			
	30 MG	14.2	48.5		
	10	4.45 1	10.4		
MRT0–□ (h)	MG				
	15	5.40 2			
	MG				
	20	18.8 3b	115		
	MG				
	25	9.16 2			
	MG				
	30	28.5 4b	74.4		

	MG				

'Mean' refers to geometric mean for Cmax, AUC0-tlast, AUC0-∞, to harmonic mean for t1/2el, to median for tmax and to arithmetic mean for MRT0–tlast, MRT0–∞. Sample size = 4 for the 10 mg, 1 for the 15 mg, 12 for the 20 mg, 1 for the 25 and 8 for the 30 mg doses. 1: n=2 patients, 2: n=1 patients, 3: n=8 patients, 4: n=7 patients. apseudo standard deviation, bincluding values for which AUC and/or AUMC extrapolation exceed 20%.

Summary of Pharmacokinetic Parameters for Morphine-3-Glucuronide after Epidural Administration of the SKY0401 Formulation (Part 1).

Parameter (unit)	Dose	Mean	Coefficient of variation, %	Minimum	Maximum
max (ng/ml)	10 MG	90.1	48.4		
	15 MG	103			
	20 MG	133	70.7		
	25 MG	141			
	30 MG	137	34.4		
max (h)	10 MG	40.1			
	15 MG	2.10			
	20 MG	3.04			
	25 MG	2.33			
	30 MG	6.02			
AUC0–tlast	10 MG	1686	70.2		
(ng/ml □ h)	15 MG	1648			
	20 MG	2596	48.7		
	25 MG	2552			
	30 MG	3962	44.8		
t1/2el (h)	10 MG	58.8 [1]			
	15	2			
	MG				
	20	30.7 [3]	14.6 [a]		
	MG				
	25 MG	78.4 [1]			
	30 MG	25.5 [4]	5.81 [a]		
AUC0–□	10 MG	1422 [1b]			
	15	2			
(ng/ml □ h)	MG				
	20 MG	3135 [3b]	47.0		
	25 MG	4760 [1b]			
	30 MG	4049 [4b]	51.8		
MRT0–tlast (h)	10 MG	35.3	46.9		
	15 MG	20.7			
	20 MG	23.8	31.5		
	25 MG	25.2			
	30 MG	27.5	27.6		
MRT0–□ (h)	10 MG	65.2 [1b]			
	15	2			
	MG				
	20 MG	39.7 [3b]	32.1		
	25 MG	99.7 [1b]			
	30 MG	36.4 [4b]	25.5		

'Mean' refers to geometric mean for Cmax, AUC0-tlast, AUC0-∞, to harmonic mean for t1/2el, to median for tmax and to arithmetic mean for MRT0–tlast, MRT0–∞. Sample size = 4 for the 10 mg, 1 for the 15 mg, 12 for the 20 mg, 1 for the 25 and 8 for the 30 mg doses. 1: n=1 patients, 2: n=0 patients, 3: n=7 patients, 4: n=3 patients. apseudo standard deviation, bincluding values for which AUC and/or AUMC extrapolation exceed 20%.

Summary of Pharmacokinetic Parameters for Morphine-6-Glucuronide after Epidural Administration of the SKY0401 Formulation (Part 1).

Parameter (unit)	Dose	Mean	Coefficient of variation, %	Minimum	Maximum
C_{max} (ng/ml)	10 MG	19.8	26.9		
	15 MG	26.3			
	20 MG	26.2	59.3		
	25 MG	21.6			
	30 MG	32.5	51.5		
t_{max} (h)	10 MG	3.01			
	15 MG	4.00			
	20 MG	4.02			
	25 MG	2.33			
	30 MG	4.01			
$AUC_{0-tlast}$	10 MG	378	105		
(ng/ml □ h)	15 MG	234			
	20 MG	472	67.2		
	25 MG	172			
	30 MG	506	106		
$t_{1/2el}$ (h)	10 MG	6.48 [1]			
	15 MG	5.39 [1]			
	20 MG	5.69 [2]	3.32 [a]		
	25 MG	5.49 [1]			
	30 MG	8.14 [3]	4.86 [a]		
$AUC_{0-□}$	10 MG	240 [1]			
(ng/ml □ h)	15 MG	268 [1]			
	20 MG	484 [2]	115		
	25 MG	216 [1b]			
	30 MG	436 [3b]	114		
$MRT_{0-tlast}$ [(h)]	10 MG	27.3	89.4		
	15 MG	7.26			
	20 MG	20.8	69.6		
	25 MG	5.44			
	30 MG	19.9	72.3		
$MRT_{0-□}$ [(h)]	10 MG	10.5 [1b]			
	15 MG	9.60 [1b]			
	20 MG	13.5 [2b]	65.7		
	25 MG	8.40 [1b]			
	30 MG	19.8 [3b]	70.7		

e) Summary of Pharmacokinetic Parameters for Morphine after Epidural Administration of the SKY0401.1 Formulation (Part 2).

Parameter (unit)	Dose	Mean	Coefficient of variation, %	Minimum	Maximum
C_{max} (ng/ml)	20 MG	19.2			
	30 MG	26.2	50.7		
t_{max} (h)	20 MG	0.500			
	30 MG	0.517			
$AUC_{0-tlast}$	20 MG	129			
(ng/ml □ h)	30 MG	224	30.5		
(h)	20	1			
$t_{1/2el}$	MG				
	30 MG	27.3 [2]	28.4 [a]		
	20	1			
$AUC_{0-□}$	MG				
(ng/ml □ h)	30 MG	261 [2b]	41.6		
$MRT_{0-tlast}$ [(h)]	20 MG	13.2			
	30 MG	21.9	31.0		
	20	1			
$MRT_{0-□}$ [(h)]	MG				
	30 MG	39.3 [2b]	87.3		

'Mean' refers to geometric mean for Cmax, AUC0-tlast, AUC0-∞, to harmonic mean for t1/2el, to median for tmax and to arithmetic mean for MRT0–tlast, MRT0–∞. Sample size = 1 for the 20 mg and 10 for the 30 mg doses. 1: n=0 patient, 2: n=2 patients. apseudo standard deviation, bincluding values for which AUC and/or AUMC extrapolation exceed 20%.

Summary of Pharmacokinetic Parameters for Morphine-3-Glucuronide after Epidural Administration of the SKY0401.1 Formulation (Part 2).

Parameter (unit)	Dose	Mean	Coefficient of variation, %	Minimum	Maximum
C_{max} (ng/ml)	20 MG	77.3			
	30 MG	103	64.4		
T_{max} (h)	20 MG	4.00			
	30 MG	3.96			
$AUC_{0-tlast}$	20 MG	1607			
(ng/ml □ h)	30 MG	2061	43.7		
(h)	20	1			
$T_{1/2el}$	MG				
	30	1			
	MG				
	20	1			
$AUC_{0-□}$	MG				
	30	1			
(ng/ml □ h)	MG				
$MRT_{0-tlast}$ [b]	20 MG	25.3			
	30 MG	28.1	33.1		
	20	1			
$MRT_{0-□}$ [b]	MG				
	30	1			
	MG				

Summary of Pharmacokinetic Parameters for Morphine-6-Glucuronide after Epidural Administration of the SKY0401.1 Formulation (Part 2).

Parameter (unit)	Dose	Mean	Coefficient of variation, %	Minimum	Maximum
C_{max} (ng/ml)	20 MG	11.7			
	30 MG	22.4	33.2		
T_{max} (h)	20 MG	2.00			
	30 MG	3.96			
$AUC_{0-tlast}$	20 MG	65.2			
(ng/ml □ h)	30 MG	253	116		
$T_{1/2el}$ (h)	20 MG	6.03			
	30 MG	5.82 [1]	3.67 [a]		
$AUC_{0-□}$	20 MG	118 [b]			
(ng/ml □ h)	30 MG	263 [1b]	82.0		
$MRT_{0-tlast}$ [b]	20 MG	4.30			
	30 MG	16.0	109		
$MRT_{0-□}$ [b]	20 MG	9.87 [b]			
	30 MG	24.4 [1b]	159		

f) Summary of Pharmacokinetic Parameters for Morphine after Epidural Administration of the Morphine Sulfate Unencapsulated Formulation (Part 2).

Parameter (unit)	Dose	Mean	Coefficient of variation, %	Minimum	Maximum
C_{max} (ng/ml)	5 MG	13.9	36.9		
T_{max} (h)	5 MG	0.500			
$AUC_{0-tlast}$	5 MG	43.8	68.7		
(ng/ml □ h)					
$T_{1/2el}$ (h)	5 MG	2.14 [1]	0.824 [a]		
$AUC_{0-□}$	5 MG	51.4 [1b]	57.0		
(ng/ml □ h)					
$MRT_{0-tlast}$ [b]	5 MG	5.39	189		
$MRT_{0-□}$ [b]	5 MG	13.5 [1b]	254		

Summary of Pharmacokinetic Parameters for Morphine-3-Glucuronide after Epidural Administration of the Morphine Sulfate Unencapsulated Formulation (Part 2).

Parameter (unit)	Dose	Mean	Coefficient of variation, %	Minimum	Maximum
C_{max} (ng/ml)	5 MG	51.7	44.5		
T_{max} (h)	5 MG	3.83			
$AUC_{0-tlast}$	5 MG	499	78.2		
(ng/ml □ h)					
$T_{1/2el}$ (h)	5 MG	5.09 [1]	2.40 [a]		
$AUC_{0-□}$	5 MG	458 [1b]	47.3		
(ng/ml □ h)					
$MRT_{0-tlast}$ [b]	5 MG	13.0	127		
$MRT_{0-□}$ [b]	5 MG	9.22 [1b]	42.4		

Summary of Pharmacokinetic Parameters for Morphine-6-Glucuronide after Epidural Administration of the Morphine Sulfate Unencapsulated Formulation (Part 2).

Parameter (unit)	Dose	Mean	Coefficient of variation, %	Minimum	Maximum
C_{max} (ng/ml)	5 MG	10.4	24.5		
T_{max} (h)	5 MG	2.12			
$AUC_{0-tlast}$ (ng/ml □ h)	5 MG	26.9	71.3		
$T_{1/2el}$ (h)	5 MG	1.99 [1]	1.51 [a]		
$AUC_{0-□}$ (ng/ml □ h)	5 MG	54.7 [b]	43.6		
$MRT_{0-tlast}$ [(h)]	5 MG	2.74	31.6		
$MRT_{0-□}$ [(h)]	5 MG	5.36 [b]	45.2		

g) Individual Pharmacokinetic Parameter Values Gathered per Treatment for Morphine after Epidural Administration of the SKY0401 Formulation (Part 1).

Dose	Subject Number	Subject Initials	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2el}$ (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-□}$ (ng.h/mL)	MRT_{0-t} (h)	$MRT_{0-□}$ (h)
10	01-016		14.7	0.433	a	276	a	36.2	a
10	01-011		10.7	0.550	a	333	a	40.7	a
10	03-001		29.6	0.500	2.69	102	109	3.38	4.12c
10	01-019		25.3	1.97	3.61	105	115	3.57	4.77c
15	01-012		25.0	0.450	4.43	148	155	4.53	5.40
20	02-003		31.4	0.533	a	368	a	44.2	a
20	02-005		17.8	1.15	6.42	154	166	7.47	9.27c
20	02-004		43.2	0.450	6.74	214	224	4.99	6.26c
20	01-004		11.3	2.25	58.0	181	280b	24.3	70.3b
20	02-002		21.6	2.00	14.9	272	307	14.0	20.4c
20	01-017		21.1	0.467	a	168	a	21.0	a
20	01-003		14.3	0.533	4.08	46.3	92.7b	2.03	6.04b
20	01-002		16.4	0.500	a	106	a	7.42	a
20	01-005		27.7	0.500	13.7	136	194b	7.67	18.4b
20	01-013		39.2	0.517	11.0	106	127	4.33	9.37c
20	02-001		25.8	0.483	a	173	a	10.9	a
20	01-001		18.1	2.00	6.07	145	154	8.61	10.1
25	01-014		49.3	0.533	8.28	155	172	6.05	9.16c
30	02-006		37.8	0.517	18.9	378	424	15.2	21.8c
30	01-009		10.2	7.98	8.40	125	142	9.17	12.5c
30	01-006		54.5	0.517	20.7	346	406	13.3	22.8c
30	01-018		71.7	0.533	4.54	190	197	3.59	4.33c
30	01-010		20.7	0.550	32.7	223	288b	13.2	32.0b
30	01-015		102	0.433	51.4	409	499	11.6	36.1c
30	01-007		19.0	2.07	a	259	a	24.5	a
30	01-008		33.5	1.97	56.6	360	560b	23.1	69.8b

h) Assay Validation

SkyePharma Inc.
Validation Report

Document Number: [ ]
Page 1 of 20

Validation Report for Quantitation of Morphine and its Metabolites in Human Serum by [ ]

Effective Date: DEC 0 9 1999

1. Scope:

1.1. The assay validated is an HPLC method that is used to determine the concentration of Morphine and Morphine glucuronides, Morphine-3-β-glucuronide, Morphine-6-β-glucuronide (M3G, M6G) in Serum using [redacted]

2. Associated Document:

2.1. 044-20003 - Quantitation of Morphine and its Metabolites in Human Serum by

3. References:

3.1. NA

4. Results:

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2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Study 009

CLINICAL PHARMACOKINETIC REPORT PROTOCOL NO. SKY0401-009
IND No. 52,113

A Phase 2, Randomized, Placebo-Controlled, Dose-Finding, Double-Blind Study of Sustained-Release Encapsulated Morphine (SKY0401) Administered Epidurally for the Treatment of Post-Operative Pain in Patients Undergoing Hip Arthroplasty Procedures

Objectives:

- To determine the efficacy and duration of post-operative analgesic effect of various doses (10, 20, or 30 mg) of SKY0401 compared to SKY0401 placebo.
- To evaluate the safety profile of various doses (10, 20, or 30 mg) of SKY0401 compared to SKY0401 placebo.
- To establish an appropriate dose range for future Phase 3 clinical studies.
- To determine the pharmacokinetic (PK) profile of morphine and its metabolites following epidural SKY0401 administration (selected centers only).

Rationale for study design

The three doses of SKY0401 selected for this study were based on the results of the initial Phase 1, dose-escalation study. In that study, doses less than 10 mg were not associated with any significant antinociceptive activity and a dose of 40 mg was associated with dose-limiting opioid toxicity. Thus, SKY0401 doses of 10, 20, and 30 mg were selected for this study. The use of a placebo control group was ethical, as an opioid analgesic (i.e., IV fentanyl PCA) was available to all patients post-operatively through 48 hours post-dose. SKY0401 placebo (SKY0401 DepoFoam particles without morphine sulfate) was

utilized as placebo since its appearance was identical to SKY0401, thereby preserving the double-blind of the study.

Number of patients:
Planned: 120 patients
Total Enrolled: Of the 126 patients enrolled, 120 received study drug: SKY0401 (10 mg, n = 34; 20 mg, n = 32; and 30 mg, n = 26) and 28 received SKY0401 placebo.
Total Sampled for PK: Of the 120 patients dosed, 54 had samples drawn for PK SKY0401: n = 16 for 10 mg, n = 14 for 20 mg, n = 13 for 30 mg, and n = 11 for SKY0401 placebo).
Diagnosis and main criteria for inclusion:
Eligible patients included males and females aged 18 to 75 years undergoing a hip arthroplasty (total primary arthroplasty, hemiarthroplasty, or revision of a previous hip arthroplasty).
Investigational product, dose and mode of administration, batch number
SKY0401 (sustained-release encapsulated morphine) at a single dose of 10, 20, or 30 mg was administered epidurally at a lumbar intervertebral space. Lot numbers 97-0020, 97-0021, 98-0007, 98-0008, and 99-0007 were used.
Duration of treatment
A single 5 mL dose was injected epidurally at a controlled rate over 15 seconds.
Reference therapy:
SKY0401 placebo (DepoFoam particles without morphine sulfate) was administered epidurally at a lumbar intervertebral space. Lot number 98-0005 was used.
Criteria for evaluation:
Efficacy: The primary efficacy parameter was the total amount of fentanyl used over 48 h post-dose. Secondary efficacy parameters included the time of the first use of narcotic pain medication post-operatively, patient-rated evaluations of pain intensity (visual analog scale and categorical scale) at rest and with activity, and patient-rated evaluation of study medication (categorical scale).
Safety: Safety was assessed by recording: vital signs (temperature, respiratory rate, heart rate, and blood pressure), physical examinations, electrocardiograms, pulse oximetry (to determine oxygen hemoglobin saturation), capnometry (to determine PETCO2), routine clinical laboratory tests, and adverse events.
Pharmacokinetics: Blood samples for determination of serum concentration-time profiles of free morphine and its metabolites, morphine-3-glucuronide and morphine-6-glucuronide, were drawn predose and at 0.5, 2, 4, 8, 12, 18, 24, 48 and 72 h post-dose. PK parameters were estimated from those data for each patient receiving SKY0401, using only concentrations above LOQ.
Statistical Methods:
Efficacy and Safety: See separate report.
Pharmacokinetics: PK parameters were listed and summarized by means of descriptive statistics (n, arithmetic mean, standard deviation, minimum, median, maximum). In addition, for t1/2el, harmonic means were calculated, and for AUC and Cmax geometric means and between-subject variability (CVb) were also calculated. PK analysis was performed by SkyePharma AG using WinNonlin Software, Professional 3.1 version (Pharsight Corp., CA, USA).

Results:

1. Demographics and Baseline Characteristics (N = 120)

Measure	Placebo (n = 27)	10 mg SKY0401 (n = 35)	20 mg SKY0401 (n = 32)	30 mg SKY0401 (n = 26)	P-value
Age (years)					
Mean	57.7	54.1	56.4	54.6	0.079[1]
Range	26-75	29-75	18-75	27-73	
□ 65 years n (%)	11 (40.7%)	8 (22.9%)	11 (34.4%)	8 (30.8%)	0.381[2]
Sex					
Male	12 (44.4%)	20 (57.1%)	17 (53.1%)	13 (50.0%)	0.871[2]
Female	15 (55.6%)	15 (42.9%)	15 (46.9%)	13 (50.0%)	
Race					
Caucasian	22 (81.5%)	25 (71.4%)	27 (84.4%)	22 (84.6%)	0.514[2]
Black	5 (18.5%)	8 (22.9%)	3 (9.4%)	3 (11.5%)	
Hispanic	0	1 (2.9%)	2 (6.3%)	1 (3.8%)	
Other	0	1 (2.9%)	0	0	
Height (cm)					
Mean	170.0	171.0	169.3	170.6	0.938[1]
Range	150-185	150-188	147-193	152-188	
Weight (kg)					
Mean	78.6	79.6	81.6	82.6	0.604[1]
Range	45-113	60-113	48 -118	45-123	

2. Efficacy

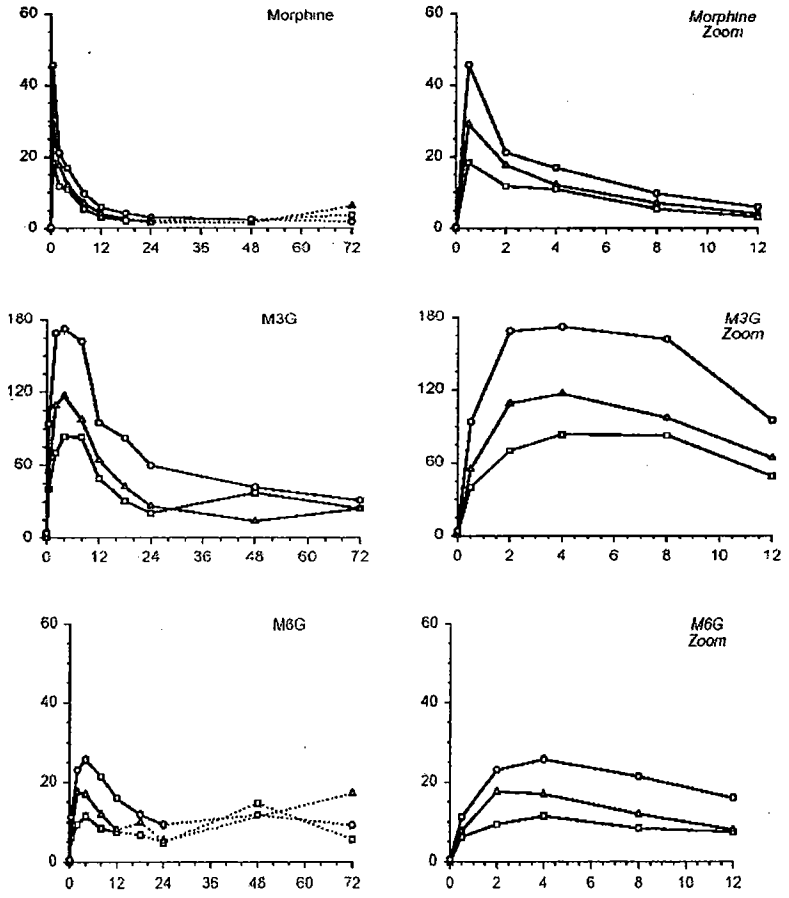
The epidural administration of a single dose of SKY0401 resulted in dose-related post-operative analgesia, as evidenced by a reduction in use of supplemental narcotic pain medication, an increased time to use of additional narcotics, and improved overall pain intensity ratings compared to placebo. Mean fentanyl usage through 48 hours post-dose was 2434 mcg for placebo patients and 1321, 905, and 652 mcg in the 10, 20, and 30 mg SKY0401 dose groups, respectively ($p < 0.001$). Through 48 hours post-dose, 4% of SKY0401 placebo patients and 6%, 16%, and 27% of patients in the 10, 20, and 30 mg SKY0401 treatment groups did not use supplemental fentanyl ($p = 0.042$). The median time to the first post-operative fentanyl use was 3.2 hours for placebo patients and 13.5, 24.8, and 16.1 hours for the 10, 20, and 30 mg SKY0401 dose groups, respectively ($p < 0.001$). Pain intensity scores (rest and with activity) were significantly higher (i.e., worse) in the placebo group than in the SKY0401 treatment groups throughout 18 hours post-dose; thereafter, pain scores were comparable across groups, as would be expected as patients self-titrated PCA fentanyl as needed to comparable levels of pain relief.

3. Safety

SKY0401 exhibited a side-effect profile typical for an opioid analgesic agent. The side effects that tended to be observed more frequently with SKY0401 than with placebo were common opioid side effects, such as headache, constipation, nausea, vomiting, somnolence, hypoxia, hypoventilation, pruritus, and urinary retention. The incidence of these events was not obviously dose-related. The onset of opioid adverse events, such as respiratory depression, usually occurred 2.5 to 18 hours post-dose and were reversible with opioid antagonist therapy. Five (5%) of the 97 patients receiving SKY0401 experienced respiratory depression that was rated as severe and lasted for 20 to 66 hours. For these patients, the onset of respiratory depression was at 3 to 5 hours following study drug administration. No patient exhibited the late initial onset of respiratory depression (i.e., after 24 hours) with no preceding evidence of respiratory depression or somnolence at earlier timepoints. As SKY0401, like other narcotic analgesics, can reduce blood pressure and respiratory drive, patients should be observed for at least 24 hours following SKY0401 administration. Patients exhibiting evidence of respiratory depression or excessive somnolence during the first 24 hours should be followed closely until all evidence of opioid toxicity has resolved. SKY0401 should only be administered by personnel experienced in the administration of epidural agents and familiar with the use of narcotic antagonists. No new adverse events were observed which were not consistent with opioid profile. Other safety variables, including clinical laboratory evaluations, ECGs, or physical examination findings, did not reveal any findings of clinical concern. No deaths occurred in the study. No patients terminated from the study prematurely because of an adverse event.

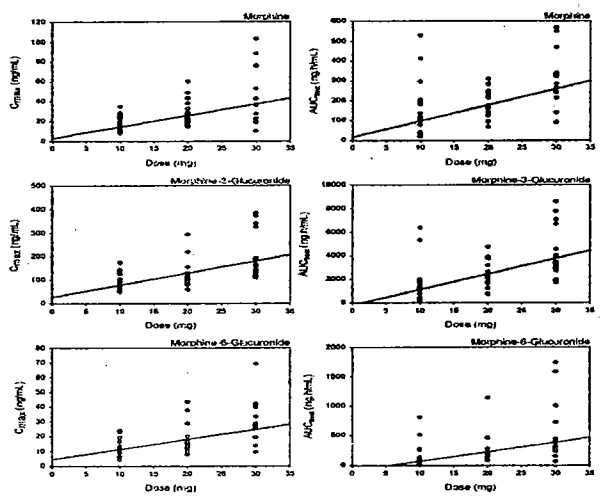
4. PK

a. Figure 1: Mean morphine and its metabolites serum concentration vs. time curves following epidural SKY0401 administration.



Symbol types refer to: (•) 30 mg dose, (.) 20 mg dose, and ( ) 10 mg dose. When less than half of the values were below LOQ, mean is shown as a dotted line.

b. SKY0401 formulation exhibited roughly proportional pharmacokinetics over the dose range of 10-30 mg.



c. Summary of Pharmacokinetic Parameters for Morphine and its metabolites after Epidural Administration of the SKY0401 Formulation

Morphine:

Parameter (unit)		SKY0401 Dose	Mean	Coefficient of variation, %	Minimum	Maximum
Cmax (ng/ml)		10 MG	17.4	51.7		
		20 MG	27.1	44.3		
		30 MG	36.8	81.2		
tmax (h)		10 MG	0.558			
		20 MG	0.500			
		30 MG	0.500			
AUC0 tlast (ng/ml □	h)	10 MG	119	112		
		20 MG	170	44.9		
		30 MG	263	66.4		
t (h) 1/2el		10 MG	5.19[1]	5.99 [a]		
		20 MG	8.90[2]	5.34 [a]		
		30 MG	19.1[3]	18.3 [a]		
AUC[0] □ (ng/ml □	h)	10 MG	135[1b]	108		
		20 MG	180[2b]	35.1		
		30 MG	318[3b]	55.4		
MRT0 tlast (h)		10 MG	13.6	79.7		
		20 MG	10.3	70.0		
		30 MG	14.0	47.1		
MRT[0] □ (h)		10 MG	25.3[1b]	131		
		20 MG	15.3[2b]	78.3		
		30 MG	25.5[3b]	48.7		

Mean refers to geometric mean for Cmax, AUC0-tlast, AUC[0-inf], to harmonic mean for t1/2el, to arithmetic mean for MRT0 tlast, MRT[0] and to median for tmax. Sample size = 16 for the 10 mg, 14 for the 20 mg, and 13 for the 30 mg dose. na for not applicable.[1]: n=9 patients, [2]: n=11 patients, [3]: n=10 patients. [a]pseudo standard deviation, [b]including values for which AUC and AUMC extrapolation exceed 20%.

Morphine-3-glucuronide

Parameter (unit)	SKY0401 Dose	Mean	Coefficient of variation, %	Minimum	Maximum
Cmax (ng/ml)	10 MG	91.9	45.5		
	20 MG	116	43.5		
	30 MG	188	48.8		
tmax (h)	10 MG	4.01			
	20 MG	4.00			
	30 MG	3.92			
AUC0 tlast (ng/ml □ h)	10 MG	1255	121		
	20 MG	2171	53.5		
	30 MG	3917	55.4		
t (h) 1/2el	10 MG	8.08[1]	6.41 [a]		
	20 MG	25.3[2]	14.6 [a]		
	30 MG	25.1[3]	6.48 [a]		
AUC[0] □ (ng/ml □ h)	10 MG	1592[1b]	85.6		
	20 MG	2585[2b]	40.5		
	30 MG	4947[3b]	55.3		
MRT0 tlast (h)	10 MG	17.5	67.0		
	20 MG	20.0	31.7		
	30 MG	21.2	33.0		
MRT[0] □ (h)	10 MG	25.5[1b]	75.4		
	20 MG	36.5[2b]	42.0		
	30 MG	33.1[3b]	33.7		

Morphine-6-glucuronide

Parameter (unit)	SKY0401 Dose	Mean	Coefficient of variation, %	Minimum	Maximum
Cmax (ng/ml)	10 MG	12.1	46.5		
	20 MG	16.5	52.8		
	30 MG	25.4	54.8		
tmax (h)	10 MG	4.03			
	20 MG	4.00			
	30 MG	4.00			
AUC0 tlast (ng/ml □ h)	10 MG	86.4	179		
	20 MG	194	97.4		
	30 MG	409	114		
t (h) 1/2el	10 MG	5.47[1]	2.87 [a]		
	20 MG	8.09[2]	4.81 [a]		
	30 MG	18.5[3]	14.5 [a]		
AUC[0] □ (ng/ml □ h)	10 MG	162[1b]	37.1		
	20 MG	293[2b]	84.6		
	30 MG	634[3b]	82.4		
MRT0 tlast (h)	10 MG	10.5	113		
	20 MG	12.4	113		
	30 MG	16.7	65.5		
MRT[0] □ (h)	10 MG	11.8[1b]	31.3		
	20 MG	31.5[2b]	187		
	30 MG	43.6[3b]	86.3		

Study 011

Title of Study:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Ranging Study to Evaluate the Safety and Efficacy of a Single Epidural Dose of Sustained-Release Encapsulated Morphine (SKY0401) in the Management of Post-Operative Pain in Patients Undergoing Hip Arthroplasty

Analytical Study Site:
[ ]

Study Period:
First Patient Enrolled: 29 January 2001
Last Patient Observed: 29 July 2001

Objectives:
The primary objective of this study was to confirm the efficacy of post-operative analgesic effect of various doses (15, 20 or 25 mg) of SKY0401 compared to placebo.

Secondary objectives were to (1) evaluate the safety and efficacy profile of various doses (15, 20 or 25 mg) of SKY0401 compared to placebo; (2) assess the effects of SKY0401 on post-operative pain intensity, patient activity, and patient/surgeon ratings of pain control, and, (3) gain additional information on serum morphine and morphine metabolites pharmacokinetics (PK) following epidural SKY0401 administration (selected centers only).

This report is limited to the pharmacokinetic analyses of the PK evaluable population.

Methodology:
This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study comparing the safety, efficacy, and pharmacokinetic profile of single epidural doses of SKY0401 (15, 20, or 25 mg) compared to placebo for the treatment of post-operative pain in patients undergoing hip arthroplasty performed under general or regional (intrathecal) anesthesia. Study drug administration occurred prior to induction of general or regional (intrathecal) anesthesia and approximately 30 minutes prior to the start of surgery. Patients were permitted post-operatively to self-administer intravenous (IV) fentanyl via a patient-controlled analgesia (PCA) pump. Opioid medications other than IV fentanyl PCA were not permitted through 48 hours post-dose. Patients were assessed for efficacy, safety, and PK parameters (selected centers only) for a total of 48 hours post-dose while hospitalized.

Number of Patients:
Planned: 200 patients (at least 50 patients per treatment group)

Total Enrolled: 200 patients were enrolled, 150 received study drug: SKY0401 (15 mg, n = 51; 20 mg, n = 50; and 25 mg, n = 49), and 50 received placebo.

Total Sampled for PK: Of the 200 patients enrolled, 92 had blood samples drawn for PK analysis. Twenty-four patients were not analyzed for PK because they were randomized to receive placebo. Of the 68 patients who received SKY0401, 66 were evaluated for PK (15 mg, n = 23; 20 mg, n = 22; 25 mg, n = 21). Two patients were excluded from all PK analyses because they had insufficient serum data.

Diagnosis and Main Criteria for Inclusion:
Males or females ≥18 years of age, scheduled for unilateral hip arthroplasty (primary total arthroplasty, hemiarthroplasty, or revision of a previous hip arthroplasty), willing and able to use a patient-controlled analgesia (PCA) pump, to receive only IV fentanyl for 48 hours to control post-operative pain, and to remain hospitalized for a minimum of 48 hours post-dose.

Investigational Product, Dose and Mode of Administration, Batch Number:
SKY0401 (sustained-release encapsulated morphine) single doses of 15, 20, or 25 mg were

administered epidurally into a lumbar intervertebral space. Lot numbers 00-4007, 02-4004, 02-4005, 02-4007, and were used.

Duration of Treatment:
A single 5-mL dose was injected epidurally at a controlled rate over 15 seconds. Treatment Group Dilutions :
15 mg SKY0401 Dilute 1.5 mL SKY0401 with 3.5 mL normal saline
20 mg SKY0401 Dilute 2 mL SKY0401 with 3 mL normal saline
25 mg SKY0401 Dilute 2.5 mL SKY0401 with 2.5 mL normal saline
Placebo 5 mL of 0.9% normal saline

Reference Therapy:
Placebo (injectable, preservative-free, 0.9% normal saline without DepoFoam. particles) was administered epidurally at a lumbar intervertebral space at a controlled rate over 15 seconds.

Criteria for Evaluation:
Efficacy: The primary efficacy endpoint was the total amount of IV fentanyl usage through 48 hours post-dose. Secondary efficacy endpoints included the time to first use of IV fentanyl post-operatively, the proportion of patients receiving no fentanyl post-operatively, patient-rated evaluations of pain intensity at rest and with activity using the visual analog scale (VAS) and a categorical scale (CAT), activity scores, and patient and surgeon ratings of pain control.
Safety: Safety was assessed by recording vital signs, including respiratory rate (RR), heart rate (HR), and blood pressure (BP), and conducting brief neurological checks and sedation scores through 48 hours post-dose. Additional safety data were collected by conducting physical and neurological examinations and routine clinical laboratory tests at Screening (i.e., ≤ 21 days prior to study drug administration) and on Day 3 (where Day 1 is the day of study drug administration), and by recording all adverse events (AEs) following study drug administration through Day 7 and neurological AEs (to identify any potential neurological sequela[e] of epidural analgesia) and serious AEs (SAEs) through Day 30.

Statistical Methods:
Efficacy Analyses: Efficacy analyses were conducted on the ITT population, which consisted of all randomized patients who underwent the planned surgical procedure, regardless of whether they received their assigned study drug according to the randomization procedure, and who were followed for use of fentanyl or other opioid medications. Analysis of variance (ANOVA) on ranked data was used to compare the average amount of total IV fentanyl among the treatment groups. If the primary analysis revealed a significant effect among treatment groups, Dunnett.s test, a multiple comparison procedure, was then used to compare each dose of SKY0401 with placebo. The linear model included terms for treatment group and type of anesthesia. For secondary analyses, the time from study drug administration to the first post-operative use of IV fentanyl and time to first post-operative opioid usage were summarized with medians and Kaplan-Meier curves, and logrank tests was used to compare treatment groups. All other secondary endpoints were analyzed using ANOVA or Fisher.s exact test, followed by pairwise tests with placebo if the overall effect was significant.
Safety Analyses: Safety analyses were conducted on the safety population, which included all randomized patients who received any study drug whether or not they underwent the planned surgical procedure. Summary tables and individual patient listings were provided for all safety measurements, and the results were presented separately by treatment (analyzed according to the study treatment actually received), as well as for all SKY0401 groups combined. Descriptive statistics were used to summarize safety data where appropriate. In addition, laboratory values were summarized with shift tables (i.e., low-normal-high at baseline versus low-normal-high at Day 3 or a 3-by-3 contingency table) to assess changes in laboratory values from baseline to Day 3. All AEs were listed, documenting the course, outcome, severity, and causality to study drug. Verbatim terms on Case Report Forms (CRFs) were mapped to preferred terms and related system organ classes using the Medical Dictionary of Regulatory Activities (MedDRA). The percentage of patients with AEs and the severity of AEs were displayed by body system for each study group. The numbers and incidence of SAEs (including those that resulted in death) by study group was also displayed. Incidences of AE and SAEs among study groups were compared using Fisher.s exact test.

Pharmacokinetics: Blood samples for determination of serum concentrations of morphine and its metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), were collected predose and at 0.25, 0.5, 1, 2, 4, 8, 12, 18, 24, 36, and 48 hours post-dose. PK parameters were estimated from data for each patient receiving SKY0401, using only concentrations above LOQ. PK parameters except t1/2 were listed and summarized by descriptive statistics (n, arithmetic mean, standard deviation, CV%, median, minimum, maximum). Summary statistics for t1/2 included n, harmonic mean, pseudo standard deviation of the jackknife variance, CV%, median, minimum and maximum. In addition, for AUC and Cmax geometric means were also calculated. PK analysis was performed by [redacted] SAS version 8.2 was used to calculate all parameters except λz and t1/2, where Kinetica 2000. software (InnaPhase Corp., Philadelphia, PA, USA) was used.

Results:

1. Efficacy Results (ITT Population, N = 194):

- Patients treated with SKY0401 at 15, 20, and 25 mg demonstrated a significant reduction in the need for IV fentanyl through 48 hours post-dose compared with patients receiving placebo ($p < 0.0001$). With increasing doses of SKY0401 (15, 20, and 25 mg), a decrease in the mean total fentanyl usage through 48 hours was observed (663.0, 485.4, and 370.6 mcg, respectively).
- In patients ≥ 65 years of age, pain control (as evidenced by a decreased requirement for post-operative fentanyl) was achieved with 15 mg SKY0401 and was comparable with that achieved with 20 mg SKY0401 in younger (< 65 years of age) patients.
- Secondary analyses of the primary endpoint comparing fentanyl usage at 4- and 24-hour intervals consistently demonstrated a significant reduction of fentanyl usage with SKY0401 at all doses compared with placebo.
- There was a significant delay in the time to first fentanyl usage with SKY0401 treatment at all doses compared with placebo ($p < 0.0001$).
- There was a significant decrease in the proportion of patients requiring post-operative fentanyl with SKY0401 treatment at all doses compared with placebo.
- Mean VAS and CAT pain intensity ratings at rest and with activity were generally lower for SKY0401-treated patients. Importantly, the VAS-R in terms of AUC through 48 hours was significantly decreased in all SKY0401 treatment groups compared with placebo ($p = 0.0005$, < 0.0001, and < 0.0001 for SKY0401 15, 20, and 25 mg, respectively).
- Although all patients were allowed to self-administer IV fentanyl via a PCA pump, more SKY0401-treated patients (83%) rated their pain control as good or very good compared with placebo-treated patients (67%) at 48 hours post-dose. These ratings were consistent with those of the surgeons (75% and 57%, respectively).
- There were no clear effects of test dose administration (no test dose, test dose administered < 15 minutes prior to study drug, or test dose administered ≥ 15 minutes prior to study drug) on the efficacy of SKY0401 in terms of total fentanyl usage.

2. Safety Results (Safety Population, N = 183):

- The most frequently reported AEs in the SKY0401-treated patients were consistent with opioid treatment. Adverse events other than those expected for opioid agents were comparable among the treatment groups, indicating the absence of AEs that were related to DepoFoam. The most common AEs from Days 1 to 7 in the SKY0401 and placebo treatment groups were nausea, pyrexia, hypotension, vomiting, pruritus, and anemia, with the incidence of vomiting, pruritus, and urinary retention increased with SKY0401 treatment.
- The majority of AEs were mild to moderate in severity.
- There was no clear relationship between the dose of SKY0401 and the number, severity, or relationship to treatment of AEs reported.
- There were no differences in the neurological AEs reported among the SKY0401 and placebo treatment groups. Few neurological events were reported from Days 8 to 30, and all were mild and not serious.
- There were three SAEs, hypotension (SKY0401 25 mg), hypoventilation (SKY0401 25 mg), and somnolence (SKY0401 20 mg), that were related to SKY0401 treatment. All were related to the opioid profile of SKY0401.
- There were no deaths or study discontinuations due to AEs.

There were no clinically significant hematology or biochemistry abnormalities related to SKY0401 treatment.

Following the administration of study drug, statistically significant decreases were noted in RR, systolic BP, and diastolic BP in all treatments groups, including placebo. The decreases in the SKY0401 treatment groups were dose related, with the most consistent decreases over time observed in the SKY0401 25 mg dose group. These effects may have been the result of drug effects upon the respiratory and cardiovascular centers, or reflective of enhanced pain control achieved with SKY0401.

Compared with patients who received 15 or 20 mg, the administration of 25 mg SKY0401 resulted in longer periods of sedation.

Thirteen percent of SKY0401-treated patients had saturated oxygen monitoring in response to an AE compared with 4% of placebo-treated patients. Within the 13% of SKY0401-treated patients, there were 4 (8%), 9 (20%), and 6 (12%) patients in the 15, 20, and 25 mg treatment groups, respectively.

An opioid antagonist was administered to 17 SKY0401-treated patients (13%) and 0 placebo-treated patients (0%), including 4 (8%), 4 (9%), and 9 (21%) in the 15, 20, and 25 mg SKY0401 groups, respectively. For the majority of SKY0401-treated patients (88%) who received an opioid antagonist, the initial administration time occurred with 24 hours post-dose. No SKY0401-treated patients received an opioid antagonist after 48 hours.

There were no apparent effects of test administration (no test dose, test dose administered < 15 minutes prior to study drug, or test dose administered ≥ 15 minutes prior to study drug) on the safety profile of SKY0401.

3. Pharmacokinetics:

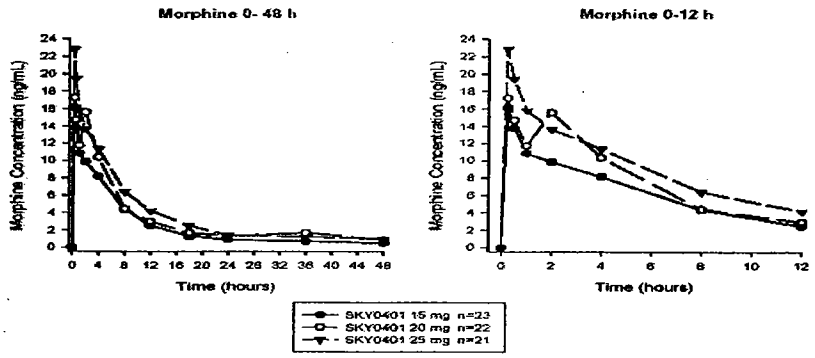
a. Sample analyses were performed by [redacted] Serum morphine and morphine metabolite concentrations were determined using [redacted] The lower limit of quantitation (LLOQ) for morphine in human serum was [redacted] ng/mL, with linearity demonstrable to [redacted] ng/mL (upper limit of quantitation, ULOQ). The LLOQ for M3G in human serum was [redacted] ng/mL, with linearity demonstrable to [redacted] ng/mL. The LLOQ for M6G in human serum was [redacted] ng/mL, with linearity demonstrable to [redacted] ng/mL. The LLOQ and ULOQ of M3G were changed to [redacted] ng/mL in a subsequent method validation

Demographic Data for Pharmacokinetic Population Receiving Study Drug

Demographic	Overall n=66
Gender	
Female	33 (50.0%)
Male	33 (50.0%)
Race	
Caucasian	58 (87.9%)
Black	7 (10.6%)
Hispanic	1 (1.5%)
Age (years)	
Mean (SD)	58.1 (12.8)
Median	58.5
(Min-Max)	(19 83)
Height (in.)	
Mean (SD)	67.95 (4.1)
Median	68.0
(Min-Max)	(60.0 77.0)
Weight (lb)	
Mean (SD)	183.84 (37.0)
Median	185.1
(Min-Max)	(113.5 253.8)
BMI (kg/m^2)	
Mean (SD)	27.97 (4.9)
Median	27.0
(Min-Max)	(19.0 40.0)

b. Morphine Results

Mean morphine concentration-time curves for each SKY0401 dose group are plotted:



An overall summary of the individual and mean morphine PK results by treatment group is provided

	Mean (SD) PK Parameters for Morphine by SKY0401 Dose		
	15 mg	20 mg	25 mg
Variable	n=23	n=22	n=21
Cmax (ng/mL)	17.40 (10.563)	23.35 (17.331)	24.91 (16.816)
tmax (hr)[1]	0.50 —	0.75 —	0.50 —
AUC0-t (ng□hr/mL)	112.97 (47.447)	149.58 (84.582)	168.87 (60.569)
AUC0-□ (ng□hr/mL)[4]	162.57 (101.546)	189.42 (98.125)	218.74 (84.294)
□z (hr-1)[4]	0.0568 (0.0585)	0.0364 (0.0285)	0.0327 (0.0246)
t1/2 (hr)[2,4]	12.20 (13.849)	19.02 (15.552)	21.20 (16.800)
CL/F (mL/min/kg)[4]	25.06 (13.888)	27.05 (12.830)	26.50 (10.166)
CL/F (mL/min)[4]	2171.62 (1457.646)	2279.40 (1344.803)	2217.23 (913.837)
Vz/F (L/kg)[4]	42.52 (23.899)	69.25 (45.503)	62.75 (25.877)
Vz/F (L)[4]	3559.51 (2037.161)	5588.33 (3595.906)	5180.11 (2151.430)
Cmax [3]	14.16	18.61	20.60
AUC0-t [3]	102.84	130.54	159.47
AUC0-□ [3,4]	137.13	167.26	203.09

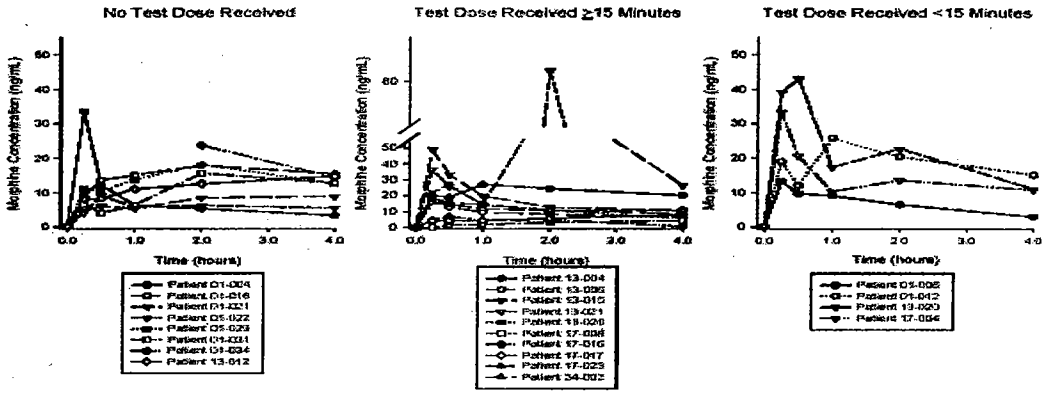
[1] Median (min-max)
[2] Harmonic mean and pseudo standard deviation of the jackknife variance
[3] Geometric mean of ln-transformed variables
[4] n=19, 21, 19 for the 15, 20, and 25 mg SKY0401 dose groups, respectively.
Data source: Appendix A,
Table 5

The results for Cmax and AUC demonstrated dose-proportional pharmacokinetics of SKY0401 across the dose range of 15 to 25 mg. The relationship between dose and CL/F was analyzed using a fixed effects analysis of variance (ANOVA). In the analysis, no statistically significant dose-related differences in CL/F were observed (p=0.8742).

c. Effect of Lidocaine/Epinephrine on SKY0401

The mean concentration-time curves by test dose administration illustrate that Cmax is blunted and that tmax appears to be shifted to the right, as would be expected with a sustained-release delivery system, when no test dose is administered. The highest mean Cmax values and most rapid tmax values were observed in those patients who received the test dose within 15 minutes of study medication.

Mean Morphine Serum Concentration-Time Curves by Dose Group and Test Dose Administration

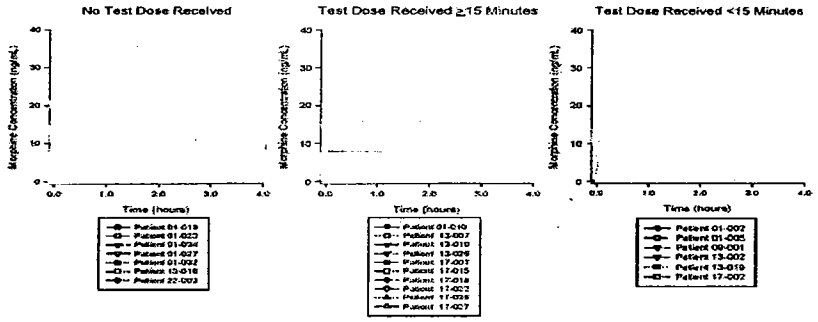


Across all three dose groups, Cmax was greater than 20 ng/mL in 16.7% (3/18) of patients who did not receive a test dose compared with 37.5% (12/32) of patients who received a test dose at least 15 minutes prior to study medication and 66.7% (10/15) of patients who received a test dose within 15 minutes of study medication (Table 4). The individual patient plots demonstrate the variability between.

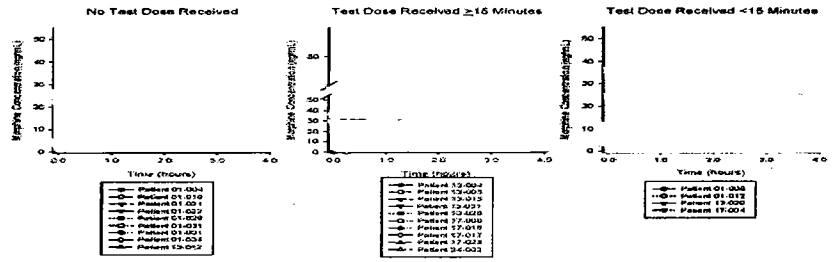
Effect of Test Dose on Individual Cmax after SKY0401 Administration

Dose	No Test Dose Cmax >20	(Cmax Range)	Test Dose ≥15 Minutes Cmax >20	(Cmax Range)	Test Dose <15 Minutes Cmax >20	(Cmax Range)
15 mg	1/7		2/10		5/6	
20 mg	2/8		4/10		3/4	
25 mg	0/3		6/12		2/5	

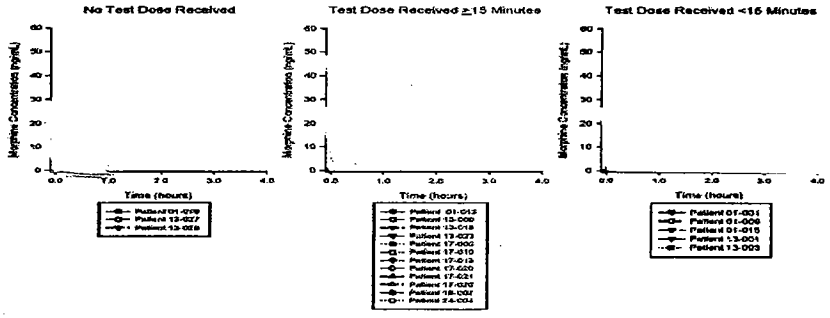
Individual Morphine Serum Concentration-Time Curves Through 4 Hours Post-Dose: 15 mg Dose Group



Individual Morphine Serum Concentration-Time Curves Through 4 Hours Post-Dose: 20 mg Dose Group



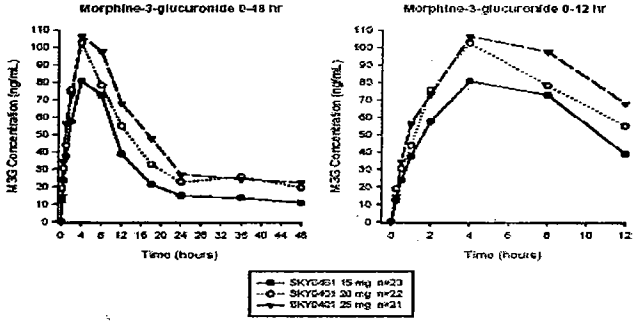
Individual Morphine Serum Concentration-Time Curves Through 4 Hours Post-Dose: 25 mg Dose Group



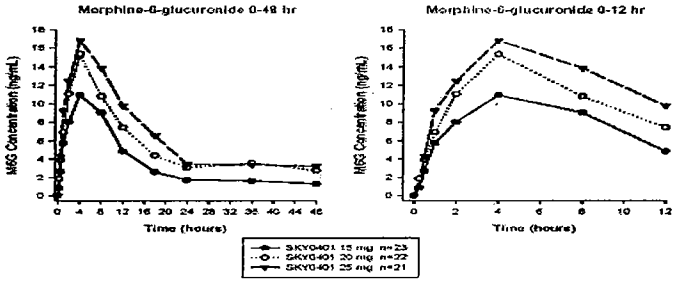
d. Metabolite Pharmacokinetic Results

Mean concentration-time curves for the morphine metabolites, M3G and M6G, are plotted :

Average Morphine-3-Glucuronide Serum Concentrations by SKY0401 Treatment and Time



Average Morphine-6-Glucuronide Serum Concentrations by SKY0401 Treatment and Time



The serum concentration profiles of both metabolites were comparable across all three doses. For the two metabolites, median tmax for all three doses occurred at 4 hours.

A summary of the individual and mean serum concentrations for M3G is provided below.

Mean (SD) PK Parameters for M3G by SKY0401 Dose

	15 mg	20 mg	25 mg
Variable	n=23	n=22	n=21
Cmax (ng/mL)	91.56 (49.085)	109.55 (56.772)	120.54 (60.032)
tmax (hr)[1]	4.0	4.0	4.0
AUC0-t (ng□hr/mL)	1272.23 (663.361)	1814.04 (1084.201)	2062.46 (1470.931)
AUC0-□ (ng□hr/mL)[4]	1890.11 (1223.841)	3072.95 (2371.174)	3290.86 (2183.347)
□z (hr-1)[4]	0.0393 (0.0282)	00.0316(0.0331)	0.0318 (0.0274)
t1/2 (hr)[2,4]	17.66 (13.152)	21.96 (227.374)	21.81 (20.062)
Cmax [3]	81.01	93.56	107.92
AUC0-t [3]	1136.73	1506.71	1746.76
AUC0-□ [3,4]	1625.23	2364.28	2767.05

[1] Median (min-max)

[2] Harmonic mean and pseudo standard deviation of the jackknife variance

[3] Geometric mean of ln-transformed variables

[4] n=21, 20, and 20 for the 15 mg, 20 mg, and 25 mg SKY0401 dose groups, respectively.

Data source: Appendix A, Table 6

Table 6: Mean (SD) PK Parameters for M6G by SKY0401 Dose

	15 mg	20 mg	25 mg
Variable	n=23	n=22	n=21
Cmax (ng/mL)	11.75 (4.968)	16.47 (8.898)	18.51 (9.089)
tmax (hr)[1]	4.0	4.0	4.0
AUC0-t (ng□hr/mL)	162.85 (90.707)	257.42 (167.797)	299.06 (203.063)
AUC0-inf (ng□hr/mL)[4]	290.13 (168.842)	454.70 (316.821)	526.51 (279.632)
□z (hr-1)[4]	0.0496 (0.0481)	0.029 (0.034)	0.0226 (0.0201)
t1/2 (hr)[2,4]	13.97 (14.851)	23.66 (34.621)	30.64 (32.530)
Cmax [3]	10.77	13.89	16.70
AUC0-t [3]	141.28	206.53	254.91
AUC0-inf [3,4]	242.93	374.49	455.77

[1] Median (min-max)
[2] Harmonic mean and pseudo standard deviation of the jackknife variance
[3] Geometric mean of ln-transformed variables
[4] n=10, 18, and 13 for the 15 mg, 20 mg, and 25 mg SKY0401 dose groups, respectively.
Data source: A ppendix A, Table 7

Study 12B

Title of Study:
A Phase 3, Randomized, Double-Blind, Dose-Controlled, Parallel Group, Dose-Ranging Study to Evaluate the Safety and Efficacy of a Single Epidural Dose of Sustained-Release Encapsulated Morphine (SKY0401) in the Management of Post-Operative Pain in Patients Undergoing Lower Abdominal Surgery

Study Centers:
Multicenter – 50 study sites located in the United States and Australia

Analytical Study Site:
[ ]

Study Period:
First Patient In: 8 April 2002
Last Patient Observed: 9 January 2003

Objectives:
The primary objective of this study was:
- To confirm the efficacy of SKY0401 in the management of post-operative pain following lower

abdominal surgery. The primary efficacy parameter was an assessment of the reduction in the use of IV fentanyl for 48 hours following study drug administration for patients receiving 10, 15, 20, and 25 mg SKY0401 compared with 5 mg SKY0401 (dose control arm).
Secondary objectives were:
• To evaluate further the safety and efficacy profile of various doses (5, 10, 15, 20, or 25 mg) of SKY0401 compared with 5 mg of unencapsulated morphine and investigate the dose-response relationship among the SKY0401 doses.
• To assess the effects of SKY0401 on post-operative pain intensity, patient/surgeon ratings of pain control.
• To gain additional information on serum morphine and morphine metabolites pharmacokinetics (PK) following epidural administration (selected centers only).

Methodology:

This Phase 3, multicenter, randomized, double-blind, dose-controlled, parallel group, dose-ranging study evaluated the safety, efficacy, and pharmacokinetic profile of single epidural doses of SKY0401 (5, 10, 15, 20, or 25 mg) compared with unencapsulated morphine (5 mg) for the treatment of postoperative pain in patients undergoing lower abdominal surgery performed under general or regional (intrathecal) anesthesia. Lower abdominal surgery was defined as surgery via an abdominal incision below the umbilicus excluding laparoscopic surgery, transurethral prostatectomy, cesarean section, hernial repair, appendectomy, and lower abdominal vascular surgery. Study drug administration occurred prior to induction of general or regional (intrathecal) anesthesia and approximately 30 minutes prior to the start of surgery. Patients were permitted post-operatively to selfadminister intravenous (IV) fentanyl via a patient-controlled analgesia (PCA) pump. Opioid medications other than IV fentanyl PCA were not permitted through 48 hours post-dose. Patients were assessed for efficacy, safety, and PK parameters (selected centers only) for a total of 48 hours post-dose while hospitalized. While originally designed as a placebo-controlled trial (SKY0401-012), the study protocol was amended (SKY0401-012B) to change the placebo arm of the study and include additional treatment arms of a single 5 mg dose of SKY0401 (dose control arm) and a single 5 mg dose of unencapsulated epidural morphine.

***Number of Patients*:**

Planned: 504 patients (at least 84 patients per treatment group)
Total Enrolled: Of the 546 patients enrolled, 5 were randomized to receive placebo (under the originally planned placebo control design) and 541 were randomized to receive active study drug; 452 received SKY0401 (5 mg, n=91; 10 mg, n=88; 15 mg, n=92; 20 mg, n=91; and 25 mg, n=90), and 89 received unencapsulated morphine (5 mg).
Total Sampled for PK: Of the 546 patients enrolled in this study, 69 had blood samples drawn for PK analysis, including 1 patient who received placebo. Of the 68 patients who received active treatment and who had blood samples collected, 65 had sufficient samples and/or data for PK analysis: (SKY0401: 5 mg, n=10; 10 mg, n=12; 15 mg, n=10; 20 mg, n=12; 25 mg, n=10; and unencapsulated morphine 5 mg, n=11).

Treatment Group	Dilutions
5 mg SKY0401	Dilute 0.5 mL SKY0401 with 4.5 mL normal saline
10 mg SKY0401	Dilute 1 mL SKY0401 with 4 mL normal saline
15 mg SKY0401	Dilute 1.5 mL SKY0401 with 3.5 mL normal saline
20 mg SKY0401	Dilute 2 mL SKY0401 with 3 mL normal saline
25 mg SKY0401	Dilute 2.5 mL SKY0401 with 2.5 mL normal saline
5 mg unencapsulated morphine	5 mL of 0.1% Duramorph/Astramorph/PF

Diagnosis and Main Criteria for Inclusion:

Eligible patients included males and females ε18 years of age undergoing lower abdominal surgery via an abdominal incision below the umbilicus.

Investigational Product, Dose and Mode of Administration, Batch Number:

SKY0401 (sustained-release encapsulated morphine) at a single dose of 5, 10, 15, 20, or 25 mg was administered epidurally at a lumbar intervertebral space. Lot numbers 00-4007, 02-4004, 02-4005, and 02-4007 were used. The 5 mg SKY0401 dose also functioned as a dose control arm.

Duration of Treatment:
A single, 5-mL dose was injected epidurally at a controlled rate over 15 seconds.
Reference Therapy:
Unencapsulated morphine 5 mg (Duramorph®/Astramorph/PF™) at a single, 5-mL dose was injected epidurally at a lumbar intervertebral space.

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was an assessment of the reduction in the use of IV fentanyl used through 48 hours post-dose. Secondary efficacy endpoints included the time to the first use of IV fentanyl post-operatively, the proportion of patients receiving no fentanyl post-operatively, patient-rated evaluations of pain intensity at rest and with activity using the visual analog scale (VAS) and a categorical scale (CAT), and patient and surgeon ratings of pain control.
Safety: Safety was assessed by monitoring continuous pulse oximetry for 24 hours post-dose (48 hours post-dose for those patients who received study drug, but did not undergo surgery), by recording vital signs, including respiratory rate (RR), heart rate (HR), and blood pressure (BP) through 48 hours post-dose, and by conducting physical and neurological examinations at Screening (i.e., ≤ 21 days prior to study drug administration) and on Day 3 (where Day 1 was the day of study drug administration). Additional safety data were collected by performing brief neurological checks and sedation scores through 48 hours post-dose, by conducting routine laboratory tests at Screening and on Day 3, and by recording all adverse events (AEs) following study drug administration through Day 7 and neurological AEs (to identify any potential neurological sequela[e] of epidural analgesia), serious AEs (SAEs), and deaths through Day 30.

Pharmacokinetics: At selected centers, blood samples for the determination of serum concentration measurements of morphine and morphine metabolites were collected at pre-dose and through 48 hours post-dose. Pharmacokinetic parameters, including Cmax, AUC, t1/2, and tmax were subsequently determined.

Statistical Methods:
Efficacy Analyses: Efficacy analyses were conducted on the ITT population, which consisted of all randomized patients who were enrolled after Amendment 02 who underwent the planned surgical procedure regardless of whether or not they received study drug. All efficacy analyses were performed according to the treatment group assigned. A linear dose-response relationship comparing the total IV fentanyl used for 48 hours following study drug administration was assessed using a least-squares regression analysis adjusted for type of anesthesia. Analysis of variance (ANOVA) on ranked data was used to compare the average amount of total IV fentanyl used through 48 hours post-dose among the treatment groups. The linear model included terms for treatment group and type of anesthesia. If the primary analysis revealed a
significant effect among the treatment groups, a multiple comparisons procedure was then used to compare 10, 15, 20, and 25 mg doses of SKY0401 to 5 mg of SKY0401, according to a dose-control study design. In addition, each dose of SKY0401 was compared to MS.
For secondary analyses, the time from study drug administration to the first post-operative use of IV fentanyl was summarized with medians and Kaplan-Meier curves, and a logrank test was used to compare treatment groups. All other secondary endpoints were analyzed using ANOVA or Cochran-Mantel-Haenzsel (CMH) tests, followed by pairwise tests of the 10, 15, 20, and 25 mg SKY0401 groups with the 5 mg SKY0401 group if the overall effect was significant.
Safety Analyses: Safety analyses were conducted on the safety population, which included all randomized patients who received study drug (pre-and post-Amendment 02) according to the study treatment actually received. Summary tables and individual patient listings were provided for all safety measurements, and the results were presented separately by treatment (analyzed according to the study treatment actually received), as well as for combined SKY0401groups. Differences among treatment groups were compared using ANOVA with treatment and type of anesthesia terms, the CMH test stratified by type of anesthesia,

or Fisher.s exact test, as appropriate. Descriptive statistics were used to summarize safety data where appropriate. In addition, laboratory values were summarized with shift tables (i.e., low-normal-high at baseline versus low-normal-high at Day 3 or a 3-by-3 contingency table) to assess changes in laboratory values from baseline to Day 3. All AEs were listed, documenting the course, outcome, severity, and causality to study drug. Verbatim terms on Case Report Forms (CRFs) were mapped to preferred terms and related system organ classes using the Medical Dictionary of Regulatory Activities (MedDRA). The percentage of patients with AEs and the severity of AEs were displayed by body system for each study group. The numbers and incidence of SAEs (including those that resulted in death) by study group were also displayed. Incidences of AE and SAE among study groups were compared using Fisher.s exact test. Pharmacokinetic Analyses: The methods used in the analyses of the PK data are presented in a separate report.

Results:

1. Efficacy Results (ITT Population, N = 487):

- Mean total IV fentanyl usage though 48 hours post-dose in the 10, 15, 20, and 25 mg SKY0401 treatment groups was 995.1, 958.4, 972.0, and 682.5 mcg, respectively, compared with 1213.3 and 1217.7 mcg in the5 mg SKY0401 and MS treatment groups, respectively. The need for fentanyl through 48 hours was significantly reduced in patients treated with 10, 20, and 25 mg SKY0401 compared with 5 mg SKY0401 ($p = 0.0447$, 0.0222, and < 0.0001, respectively) and in the 10, 15, 20, and 25 mg SKY0401 treatment groups compared with the MS group ($p = 0.0094$, 0.0320, 0.0040, and < 0.0001, respectively).
- There were no significant differences among the treatment groups in terms of the time to the first post-dose usage of IV fentanyl.
- Through 48 hours post-dose, a significantly higher proportion of patients received no IV fentanyl in the 10, 15, 20, and 25 mg SKY0401 groups compared with MS ($p = 0.0015$, 0.0029, 0.0121, and 0.0028, respectively).
- Mean pain intensity ratings at rest (VAS-R) were significantly lower through 48 hours (using AUC) with 15, 20, and 25 mg SKY0401 treatment compared to both 5 mg SKY0401 ($p = 0.0265$, 0.0141, and 0.0013, respectively) and MS ($p = 0.0107$, 0.0056, and 0.0004, respectively). It is important to note that these significant differences were observed even though patients in all treatment groups had IV PCA fentanyl available at all times to self-treat pain.
- Pain intensity ratings with activity (VAS-A) were also reduced with SKY0401 treatment through 48 hours (using AUC), with significantly lower scores demonstrated in 10, 15, 20, and 25 mg SKY0401 compared with 5 mg SKY0401 ($p = 0.0448$, 0.0299, 0.0202, and 0.0052, respectively) and in the 20 and 25 mg SKY0401 groups compared with the MS group ($p = 0.0384$ and 0.0106, respectively). It is important to note that these significant differences were observed even though patients in all treatment groups had IV PCA fentanyl available at all times to self-treat pain.
- When the pain intensity data were analyzed as an integrated rank at rest using the VAS scores and IV fentanyl usage data, there was a significant reduction in combined pain intensity at rest and IV fentanyl usage over the entire 48-hour time period (using AUC) in the 15, 20, and 25 mg SKY0401 treatment groups compared with the 5 mg SKY0401 group ($p = 0.0395$, 0.0052, and 0.0001, respectively) and in the 10, 15, 20, and 25 mg SKY0401 groups compared with the MS group ($p = 0.0282$, 0.0045, 0.0004, and $<$ 0.0001, respectively). The integrated analysis of the VAS scores with activity and the IV fentanyl usage demonstrated significantly lower scores over the entire 48-hour period (using AUC) in the 10, 15, 20, and 25 mg SKY0401 groups compared with both the 5 mg SKY0401 ($p = 0.0202$, 0.0332, 0.0108, and 0.0002, respectively) and MS groups ($p = 0.0071$, 0.0120, 0.0036, and < 0.0001, respectively). Ratings of pain intensity using the CAT scale demonstrated generally lower scores with SKY0401 treatment. CAT-R scores were significantly lower in the 15, 20, and 25 mg SKY0401 groups compared with the 5 mg SKY0401 at 8 (15 and 25 mg; $p = 0.0270$ and 0.0001, respectively), 12 ($p = 0.0313$, 0.0252, and 0.0035, respectively), 24 ($p = 0.0033$, 0.0013, and 0.0003, respectively), 30 ($p = 0.0024$, 0.0148, and 0.0009, respectively), and 36 hours (20 and 25 mg; $p = 0.0078$ and 0.0061, respectively) post-dose. Compared with the MS group, CAT-R scores were significantly lower in the 15, 20, and 25 mg SKY0401 groups at 8 (25 mg only; $p = 0.0043$), 12 ($p = 0.0012$, 0.0012, and 0.0001, respectively), 18 ($p = 0.0012$, 0.0081, and 0.0015, respectively), 24 ($p = 0.0137$, 0.0045, and 0.0015, respectively), 30 ($p = 0.0001$, 0.0016, and $<$ 0.0001, respectively), and 36 hours (20 and 25 mg only; $p = 0.0006$ and 0.0004, respectively) post-dose.

2. **Safety Results (Safety Population, N = 519):**

- Five hundred and seven patients (98%) reported an AE from Days 1 to 7, including 96%, 95%, 96%, 100%, 99%, and 100% of patients in the 5 mg MS and 5, 10, 15, 20, and 25 mg SKY0401 treatment groups, respectively. A total of 2421 AEs were reported. The most common AEs were nausea (344 patients, 66%), pruritus (267 patients, 51%), pyrexia (171 patients, 33%), vomiting (130 patients, 25%) and hypotension (113 patients, 22%), the majority of which were consistent with epidural opioid treatment. Significant differences were demonstrated among the treatment groups in terms of flatulence ($p = 0.0122$), pruritus ($p = 0.0301$), urinary retention ($p = 0.0346$), anemia ($p = 0.0395$), and allergy to chemicals (allergy to surgical occlusive dressing; $p = 0.0468$). The highest incidence of pruritus was observed in the 20 mg SKY0401 group (51 patients, 61%), with the highest incidence of urinary retention in the 25 mg SKY0401 group (12 patients, 14%). The majority of AEs (97%) were mild to moderate in severity.
- Nine hundred and four AEs (42%) in the SKY0401-treated patients and 115 AEs (45%) in the MS-treated patients were considered possibly or probably related to study drug.
- Forty-four SKY0401-treated patients (10%) and 5 MS-treated patients (8%) reported neurological AEs. Of the 81 total neurological AEs, 74 (91%) were mild to moderate in severity. Of the 7 severe neurological AEs, 5 (39%) were in the 20 mg SKY0401 group, with 1 each in the MS group (5%) and 15 mg SKY0401 group (17%). Seven neurological AEs (10%) in the SKY0401-treated patients and 1 (9%) in the MS-treated patients were regarded as possibly or probably related to study drug, including weakness, back pain, paraesthesia, headache, muscle cramps, and hypoaesthesia.
- There were no significant differences among treatment groups in terms of neurological status at Day 30.
- There were 2 deaths during the study. The death of patient 74132 (15 mg SKY0401), the result of myocardial infarction exacerbated by respiratory distress secondary to pneumonia, was not related to study drug. Patient 83119 (20 mg SKY0401) died as the result of a cardiac arrest and, in the absence of an autopsy, this was classified as related to study drug. A third death occurred after the Day 30 time point and was not considered part of the study. This involved patient 11106 (5 mg SKY0401) who died as a result of renal, respiratory, and multi-organ failure, and this death was not related to study drug.

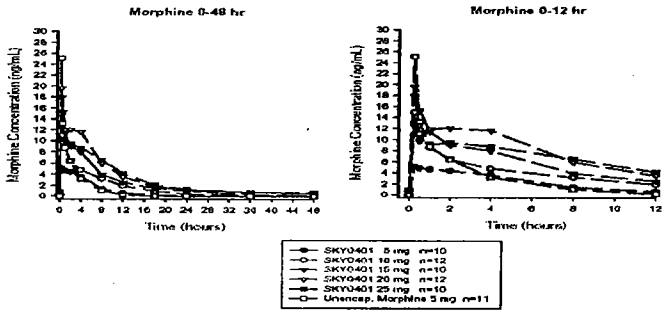
3. **Demographic Data for Pharmacokinetic Population Receiving Study Drug**

Demographic	Overall n=65
Gender	
Male	31 (47.7%)
Female	34 (52.3%)
Race	
Caucasian	46 (70.8%)
Black	13 (20.0%)
Hispanic	6 (9.2%)
Age (years)	
Mean (SD)	54.1 (13.41)
Median	51.0
(Min-Max)	(27–81)
Height (in.)	
Mean (SD)	67.46 (4.165)
Median	67.0
(Min-Max)	(59.0–77.0)
Weight (lb)	
Mean (SD)	186.28 (44.397)
Median	180.1
(Min-Max)	(100.0–305.8)
BMI (kg/m^2)	
Mean (SD)	28.57 (5.059)
Median	28.0
(Min-Max)	(18.0–43.0)

4. Morphine Results

Mean morphine concentration-time curves for each SKY0401 dose group and the 5 mg unencapsulated morphine group are plotted:

Average Morphine Serum Concentrations by Treatment and Time



Mean (SD) Morphine Pharmacokinetic Results

Variable	5 mg unencapsulated (n=11)	SKY0401 5 mg (n=10)	SKY0401 10 mg (n=12)	SKY0401 15 mg (n=10)	SKY0401 20 mg (n=12)	SKY0401 25 mg (n=10)
Cmax (ng/mL)	25.35 (12.005)	7.10 (3.399)	16.24 (8.764)	18.25 (7.753)	24.25 (28.726)	15.01 (5.326)
tmax (hr) [1]	0.25 ([redacted])	1.00 ([redacted])	0.25 [redacted]	0.50 [redacted]	1.50 [redacted]	0.25 [redacted]
AUC0-t (ng□hr/mL)	39.24 (8.095)	30.86 (11.821)	73.26 (22.765)	102.14 (45.705)	142.59 (56.131)	136.48 (41.884)
AUC0-□ (ng□hr/mL)[4]	44.07 (7.954)	38.80 (10.347)	92.77 (33.220)	127.66 (73.213)	175.85 (91.526)	188.97 (66.731)
□z (hr-1)[4]	0.3084 (0.0612)	0.1813 (0.0485)	0.0814 (0.0568)	0.1323 (0.1430)	0.0825 (0.0991)	0.0426 (0.0379)
t (hr) [2,4] 1/2	2.25 (0.451)	3.82 (0.998)	8.52 (6.107)	5.24 (7.627)	8.40 (13.251)	16.27 (16.324)
CL/F (mL/min) [4]	1941 (312.2)	2325 (783.0)	2043 (781.5)	2545 (1351.7)	2325 (1111.3)	2512 (1014.0)
CL/F (mL/min/kg)[4]	22.05 (5.229)	28.32 (10.805)	25.39 (8.376)	32.97 (12.951)	29.08 (12.904)	28.35 (12.285)
Vz/F (L)[4]	385 (67.5)	824 (354.4)	2410 (1677.7)	1948 (1362.0)	3466 (2726.6)	6023 (3987.5)
Vz/F (L/kg)[4]	4.32 (0.789)	9.77 (3.544)	36.66 (35.223)	27.99 (21.985)	44.54 (37.543)	64.45 (40.261)
Cmax [3]	22.08	6.39	14.08	16.47	17.74	14.03
AUC0-t [3]	38.59	28.74	70.19	93.74	131.07	130.82
AUC [3,4]	43.48	37.41	87.13	111.53	158.33	177.57

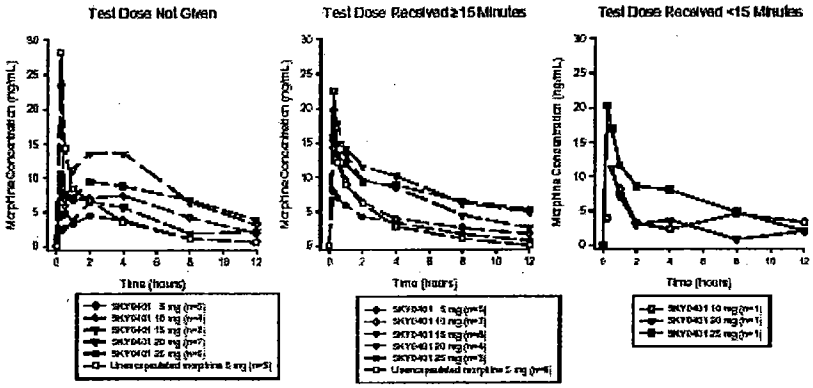
[1] Median (min-max)
[2] Harmonic mean and pseudo standard deviation of the jackknife variance
[3] Geometric mean of ln-transformed variables
[4] n=10, 8, and 11, for the 5 mg unencapsulated, 5 mg SKY0401 and 10 mg SKY0401 groups, respectively.

The relationship between dose and CL/F was analyzed using a fixed effects analysis of variance (ANOVA). In the analysis, no significant dose-related differences in CL/F were observed (p=0.6882), demonstrating that the pharmacokinetics of SKY0401 were linear. A summary of this analysis is provided in Appendix A, Table 9.

5. Effect of Lidocaine/Epinephrine on SKY0401

Of the 65 patients evaluated for PK, 36 (55.4%) received a lidocaine with epinephrine test dose and 29 (44.6%) did not receive a test dose. The majority (33/36, 91.7%) of patients who received a test dose received it at least 15 minutes prior to the administration of study medication. Examination of the effect of test dose on morphine PK was not originally planned, and thus, no formal statistical analyses were performed.

Summary of Mean Morphine Serum Concentration (ng/mL) by Treatment, Time, and Test Dose



In the 5 mg unencapsulated morphine treatment group (immediate release), mean Cmax was similar between the patients who received a test dose and those who did not (22.5 ng/mL [test dose] and 28.2 ng/mL [no test]); however, in the SKY0401 5 mg group, the mean Cmax was 8.0 ng/mL for patients who received a test dose and 4.5 ng/mL for those who did not.

Effect of Test Dose on Individual Cmax after SKY0401 Administration

	No Test Dose		Test Dose ≤15 Minutes	
Dose	C_{max} >20	(C_{max} Range)	C_{max} >20	(C_{max} Range)
Unencapsulated 5 mg	4/5		4/6	
5 mg SKY0401	0/5		0/5	
10 mg SKY0401	1/4		4/7	
15 mg SKY0401	0/2		3/8	
20 mg SKY0401	2/7		3/4	
25 mg SKY0401	1/6		0/3	

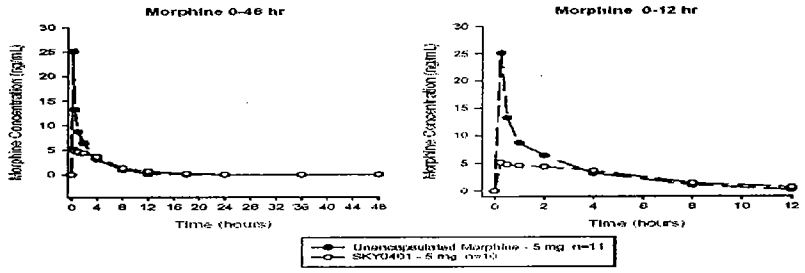
Data are presented as th e number of patients with C_{max} >20 ng/mL (C_{max} range, ng/mL)
Data Source: Appendix A, Table 2.1 and Table 5.

6. Relative Morphine Bioavailability

The design of this study was amended to include an active control arm for a comparison of morphine bioavailability following administration of SKY0401 relative to an approved, immediate-release epidural morphine product (Duramorph/Astramorph/PF).

Mean concentration-time curves for unencapsulated morphine 5 mg and SKY0401 5 mg are provided:

Average Morphine Serum Concentrations Following Administration of SKY0401 5 mg or Unencapsulated Morphine 5 mg



Mean (SD) Morphine Pharmacokinetic Results, 5 mg Treatment Groups

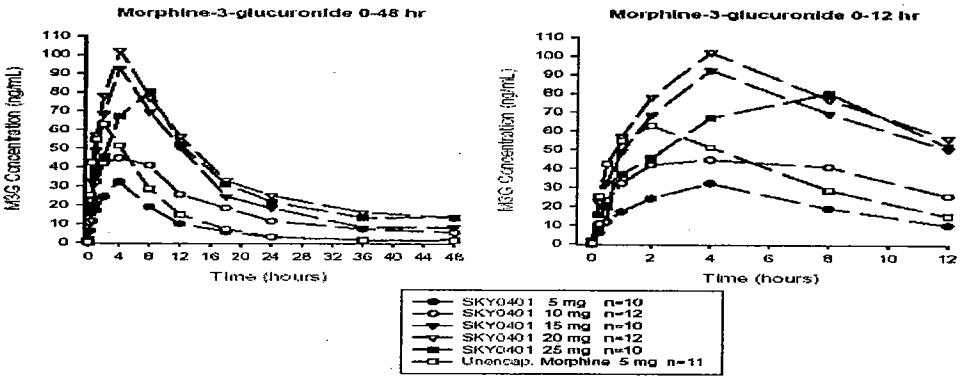
Variable	SKY0401 5 mg (n=10)		Unencapsulated MS 5 mg (n=11)	
Cmax (ng/mL)	7.10	(3.399)	25.35	(12.005)
tmax (hr) [1]	1.00	([redacted])	0.25	([redacted])
AUC0-t (ng□hr/mL)	30.86	(11.821)	39.24	(8.095)
AUC0-□ (ng□hr/mL)[4]	38.80	(10.347)	44.07	(7.954)
□z (hr-1)[4]	0.1813	(0.0485)	0.3084	(0.0612)
(hr) [2,4]	3.82	(0.998)	2.25	(0.451)
t1/2				
Cmax [3]	6.39		22.08	
AUC0-t [3]	28.74		38.59	
[3,4]	37.41		43.48	
AUC0-□				

[1] Median (min-max)
[2] Harmonic mean and pseudo standard deviation of the jackknife variance
[3] Geometric mean of ln-transformed variables
[4] n=8 and 10 for the SKY0401 and unencapsulated morphine groups, respectively.
Data Source: Appendix A,
Table 5

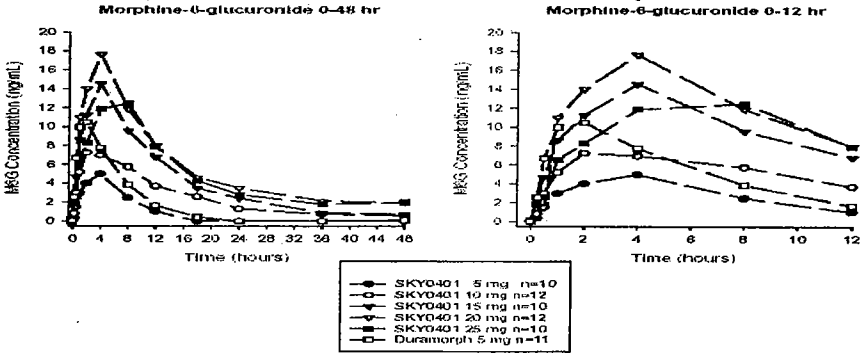
7. Metabolite Pharmacokinetic Results

Mean M3G and M6G concentration-time curves for all treatment groups are plotted

Average Morphine-3-Glucuronide Serum Concentrations by Treatment and Time



Average Morphine-6-Glucuronide Serum Concentrations by Treatment and Time



Mean (SD) PK Parameters for M3G by Treatment Group

Variable	5 mg unencapsulated (n=11)	SKY0401 5 mg (n=10)	SKY0401 10 mg (n=12)	SKY0401 15 mg (n=10)	SKY0401 20 mg (n=12)	SKY0401 25 mg (n=10)
Cmax (ng/mL)	66.1 (20.85)	33.9 (13.55)	57.8 (13.12)	99.9 (49.46)	129.9 (113.46)	81.5 (24.98)
tmax (hr) [1]	2.0	4.0 ([redacted])	4.0 ([redacted])	4.0 ([redacted])	6.0 ([redacted])	8.0 ([redacted])
AUC0-t (ng□hr/mL)	601.6 (219.76)	361.3 (109.40)	852.3 (322.28)	1442.8 (675.57)	1722.0 (928.66)	1482.5 (432.38)
AUC (ng□hr/mL)[4]	656.1 (243.37)	452.3 (146.80)	1074.6 (458.48)	1616.4 (842.33)	2809.6 (1610.84)	2153.0 (860.31)
□z (hr^{-1})[4]	0.102 (0.0594)	0.051 (0.0365)	0.048 (0.0235)	0.058 (0.0291)	0.051 (0.0626)	0.033 (0.0118)
t (hr) [2,4] 1/2	6.8 (3.92)	13.6 (10.63)	14.4 (7.07)	12.0 (6.44)	13.5 (23.92)	21.1 (7.26)
Cmax [3]	63.4	31.5	56.4	90.8	105.8	77.0
AUC0-t [3]	569.0	345.5	804.9	1322.4	1543.1	1426.7
AUC [3,4]	616.6	429.6	993.8	1454.8	2466.1	2019.3

[1] Median (min-max)
[2] Harmonic mean and pseudo standard deviation of the jackknife variance
[3] Geometric mean of ln-transformed variables
[4] n=10, 8, 11, 9, 9, and 8 for the unencapsulated morphine 5 mg, SKY0401 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg groups, respectively.
Data Source: Appendix A, Table 6

Mean (SD) PK Parameters for M6G by Treatment Group

Variable	5 mg unencapsulated (n=11)	SKY0401 5 mg (n=10)	SKY0401 10 mg (n=12)	SKY0401 15 mg (n=10)	SKY0401 20 mg (n=12)	SKY0401 25 mg (n=10)
Cmax (ng/mL)	11.2 (2.88)	5.4 (2.27)	9.4 (2.15)	15.4 (5.21)	22.3 (22.39)	13.3 (3.67)
tmax (hr) [1]	2.0 ([redacted])	4.0 ([redacted])	2.0 ([redacted])	4.0 ([redacted])	4.0 ([redacted])	6.0 ([redacted])
AUC0-t (ng□hr/mL)	72.7 (31.25)	32.6 (17.33)	118.9 (71.82)	193.4 (75.73)	263.3 (147.61)	233.4 (49.77)
AUC (ng□hr/mL)[4]	92.1 (24.81)	59.9 (N/A)	175.2 (120.76)	297.0 (182.70)	406.8 (264.07)	642.9 (681.48)
□z (hr^{-1})[4]	0.182 (0.0404)	0.162 (N/A)	0.090 (0.0563)	0.075 (0.0561)	0.074 (0.0940)	0.028 (0.0204)
t (hr) [2,4] 1/2	3.8 (0.86)	4.3 (N/A)	7.7 (4.95)	9.3 (7.38)	9.4 (16.45)	25.1 (19.11)
Cmax [3]	10.9	5.0	9.1	14.7	17.2	12.7
AUC0-t [3]	67.1	27.3	104.3	181.2	233.7	227.8
AUC [3,4]	89.2	59.9	144.0	254.3	338.9	462.0

[1] Median (min-max)
[2] Harmonic mean and pseudo standard deviation of the jackknife variance
[3] Geometric mean of ln-transformed variables
[4] n=5, 1, 9, 9, 10, and 9 for the unencapsulated morphine 5 mg, SKY0401 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg groups, respectively.
Data Source: Appendix A, Table 7

Study 018

Effect of the Time between Administrations on the Potential Interaction between a Single Therapeutic Dose of Lidocaine/Epinephrine Administered Epidurally and a Single Dose of Sustained-Release Encapsulated Morphine (SKY0401) Administered Epidurally to Healthy Volunteers

PROTOCOL SKY0401-018

Title of Study:
Effect of the Time between Administrations on the Potential Interaction between a Single Therapeutic Dose of Lidocaine/Epinephrine Administered Epidurally and a Single Dose of Sustained-Release Encapsulated Morphine (SKY0401) Administered Epidurally to Healthy Volunteers
Investigator: [redacted]
Study Center: [redacted]

Publication (reference): None
Study Period (years): July 21 to August 29, 2003 **Phase of Development:** 1
Objectives: The objective of this study was to assess the effect of the inter-dose interval (i.e., the time between administrations) on the potential interaction between a single, fixed therapeutic dose of lidocaine/epinephrine administered epidurally and a single, fixed dose of SKY0401 administered

epidurally. This potential interaction was assessed by measuring the serum concentrations of morphine after dosing.

Methodology:

In this Phase 1, single center, randomized, open-label, cohort-sequential study, each healthy subject received the following sequence of treatments:

1. Test dose of 3 mL of 1.5% lidocaine with epinephrine (1:200,000) administered epidurally
2. Anesthesia of 20 mL of 1.5% lidocaine with epinephrine (1:200,000) administered epidurally (manually over 1 minute) followed by 1-mL normal saline flush 3. 15 mg SKY0401 in a 5 mL volume administered epidurally (manually over 15 seconds) followed by a 1-mL normal saline flush

Treatment groups were defined by the time interval between the administration of the lidocaine/epinephrine anesthesia and SKY0401. The 15 subjects in Cohort 1 were randomized to one of five inter-dose interval groups: 3, 15, 30, 60, and 120 minutes. If an inter-dose interval group had no more than 1 subject with a Cmax >20 ng/mL, it was evaluated again in Cohort 2. (A serum concentration threshold of >20 ng/mL was chosen based on data from Study 0401-016.) Based on the results in Cohort 1 and Protocol Amendment No. 1, 18 subjects were randomized in Cohort 2 to one of three inter-dose interval groups: 60, 90, and 120 minutes. Naltrexone 50 mg was administered during the trial to block the opioid effects of SKY0401. Subjects were followed for pharmacokinetic (PK) parameters for 72 hours post-dose. Following confinement at the [ ] clinic the evening prior to treatment, subjects were transported to the [ ] Center for the epidural procedure. When released by the anesthesiologist, subjects were transported to the [ ] clinic by ambulance to complete the trial.

Duration of Treatment:

Subjects received a single dose of SKY0401 and two doses of lidocaine/epinephrine (test dose and anesthetic dose) on Day 1.

Criteria for Evaluation:

Efficacy: Not applicable in this study.

Pharmacokinetics:

The serum concentrations of morphine and morphine metabolites were assessed pre-dose and 5, 10, 15, and 30 minutes and 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72 hours after SKY0401 administration. PK parameters were calculated for morphine, morphine-3-glucuronide, and morphine-6-glucuronide for each inter-dose interval across both cohorts.

Safety:

Safety assessments included the monitoring of adverse events, vital signs, and oxygen saturation.

Statistical Methods:

Efficacy: Not applicable in this study.

Pharmacokinetics:

Using standard non-compartmental methods, PK parameters were calculated for all subjects who received SKY0401 and had adequate (i.e., above the lower limit of quantification) serum concentration data. The pharmacokinetic parameters for serum morphine were calculated for each inter-dose interval group across both cohorts (combined for the two cohorts). Serum concentrations and PK variables were summarized by inter-dose interval group using the following descriptive statistics: mean, standard deviation, coefficient of variance percent, median, minimum, and maximum. Categorical variables were tabulated by inter-dose interval group using the number and percentage of subjects by category. Ninety-five percent confidence intervals were calculated for mean values. There was no imputation of missing data. All analyses were performed using SAS®, Version 8.2 (SAS Institute).

Safety:

All subjects who received SKY0401 were included in the summaries of safety data. Safety data was combined for the two cohorts. Adverse events were classified using the Medical Dictionary for Regulatory Activities Version 6.0. Concomitant medications and the frequency of adverse events were summarized by

inter-dose interval group. Descriptive statistics for blood pressure, heart rate, respiration rate, and oxygen saturation were provided at each time point for each inter-dose interval group.

Analytical Methodology

Sample analyses were performed at [redacted]

[redacted] Serum morphine and morphine metabolite concentrations were determined using [redacted] assay (Method [redacted] The lower limit of quantitation (LLOQ) for morphine in human serum was [redacted] ng/mL with linearity demonstrable to [redacted] ng/mL (upper limit of quantitation, ULOQ). The LLOQ for morphine-3-glucuronide (M3G) in human serum was [redacted] ng/mL with linearity demonstrable to [redacted] ng/mL. The LLOQ for morphine-6-glucuronide (M6G) in human serum was [redacted] ng/mL with linearity demonstrable to [redacted] ng/mL. Table 8-3 below provides details about the analytical method.

Table 8-3 Analytical Method Validation for Morphine and its Metabolites

	Morphine	M3G	M6G
Assay range (ng/mL)			
Linearity (correlation coefficient)	[redacted]		
Intrabatch precision (% CV)			
Intrabatch accuracy (%RE)			
Interbatch precision (%CV)			
Interbatch accuracy (%RE)			
Accuracy and precision of QC samples			
morphine concentrations = [redacted]			
M3G concentrations =			
M6G concentrations =			

Results

1. Efficacy Results: Not applicable in this study.

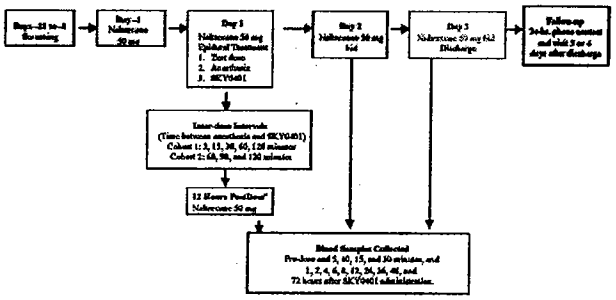
2. Pharmacokinetic Results:

a. Using Cmax >20 ng/mL as a threshold, this study qualitatively assessed the effects of 3-, 15-, 30-, 60-, 90-,and 120-minute intervals between epidural doses of 20 mL of 1.5% lidocaine with epinephrine (1:200,000) and 15 mg of SKY0401. As previously demonstrated in other studies, the incidence of subjects with Cmax >20 ng/mL generally decreased as the interval increased.

b. The incidence of subjects with Cmax >20 ng/mL in the 60-, 90-, and 120-minute inter-dose interval groups was less than the incidence of subjects with Cmax >20 ng/mL in the 3-, 15-, and 30-minute inter-dose interval groups.

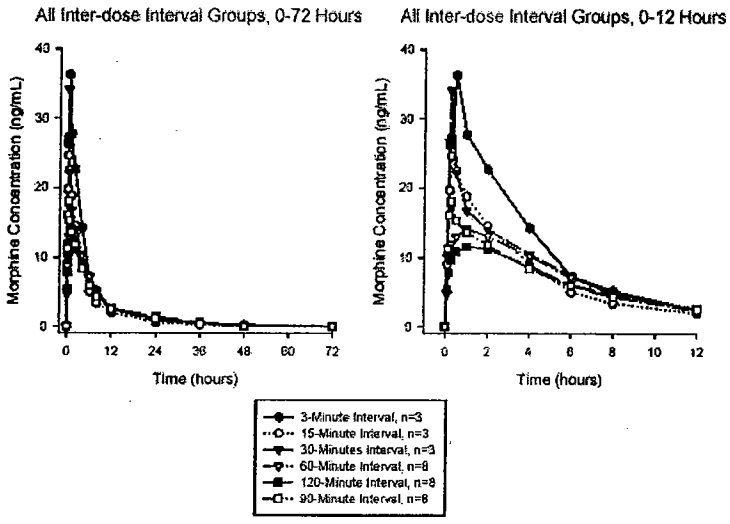
Sequence of Medication	Details of Administration	
	Cohort 1	Cohort 2
Test Dose: Lidocaine/Epinephrine	3 mL 1.5% lidocaine with epinephrine (1:200,000) administered epidurally	3 mL 1.5% lidocaine with epinephrine (1:200,000) administered epidurally
↓ 6-Minute Interval	To rule out intrathecal or intravascular placement of epidural catheter	To rule out intrathecal or intravascular placement of epidural catheter
Anesthesia: Lidocaine/Epinephrine	20 mL 1.5% lidocaine with epinephrine (1:200,000) administered epidurally (manually over 1 minute) followed by 1-mL normal saline flush	20 mL 1.5% lidocaine with epinephrine (1:200,000) administered epidurally (manually over 1 minute) followed by 1-mL normal saline flush
↓ Assigned Inter-dose Interval	Randomized inter-dose intervals of 3, 15, 30, 60, or 120 minutes after completion of lidocaine/epinephrine anesthetic dose	Randomized inter-dose intervals of 60, 90, or 120 minutes after completion of lidocaine/epinephrine anesthetic dose
Study Medication: SKY0401	15 mg (in 5 mL) administered epidurally (manually over 15 seconds) followed by 1-mL normal saline flush	15 mg (in 5 mL) administered epidurally (manually over 15 seconds) followed by 1-mL normal saline flush

Note: Inter-dose intervals studied in Cohort 2 were determined by results from Cohort 1.



[a] The 12-hour dose of naltrexone was administered 12 hours after the previous dose of naltrexone.
Note: Treatment on Day 1 consisted of the following epidural administrations: (1) test dose of 3 mL 1.5% lidocaine with epinephrine (1:200,000), (2) anesthesia, 20 mL 1.5% lidocaine with epinephrine (1:200,000) 6 minutes after test dose followed by a 1-mL normal saline flush; and (3) the study medication, 15 mg of SKY0401 (in a 5-mL volume), administered at the inter-dose intervals specified for each of the two cohorts and followed by a 1-mL normal saline flush.

C. Mean Morphine Serum Concentrations by Treatment Group

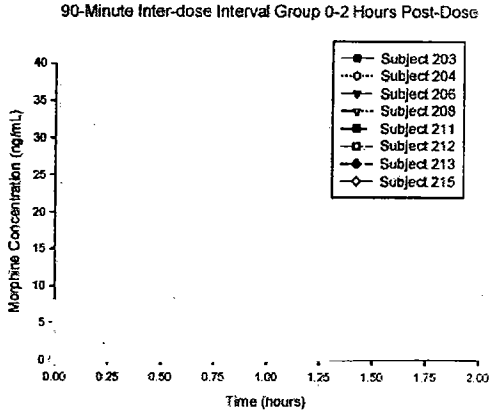


d. Mean (SD) Morphine PK Parameters by Inter-dose Interval Treatment Group

	Inter-dose Interval Treatment Group (Mean SD)					
Variable	3 Minutes (n=3)	15 Minutes (n=3)	30 Minutes (n=3)	60 Minutes (n=8)	90 Minutes (n=8)	120 Minutes (n=8)
C_{max} (ng/mL)	37.03 (4.591)	24.76 (8.908)	34.10 (21.969)	14.91 (4.324)	19.71 (10.768)	12.45 (2.979)
T_{max} (hr)[a]	0.50 (—)	0.25 (—)	0.25 (—)	1.00 (—)	0.63 (—)	1.50 (—)
AUC_{0-t} (ng hr/mL)	172.02 (61.390)	109.60 (12.929)	132.30 (39.416)	124.91 (43.859)	112.52 (31.301)	117.44 (24.756)
$AUC_{0-\infty}$ (ng hr/mL)	189.01 (62.613)	119.14 (15.925)	142.71 (42.930)	135.28 (46.088)	124.56 (29.136)	128.99 (25.416)
$\lambda_{z\,(KE)\,(hr^{-1})}$	0.0649 (0.0522)	0.1023 (0.0456)	0.1101 (0.0943)	0.1055 (0.1204)	0.0719 (0.0179)	0.0638 (0.0111)
T½ (hr)	15.85 (10.302)	7.96 (4.107)	10.03 (7.140)	10.73 (5.026)	10.23 (2.770)	11.23 (2.388)
Cl (mL/min)	1411.58 (404.746)	2122.03 (266.140)	1872.49 (609.910)	2131.16 (1037.26)	2145.65 (692.261)	1999.91 (360.649)
V_z (L)	1876.11 (1404.52)	1404.60 (541.476)	1385.69 (674.905)	1674.08 (656.469)	1988.90 (1207.83)	1927.58 (435.677)

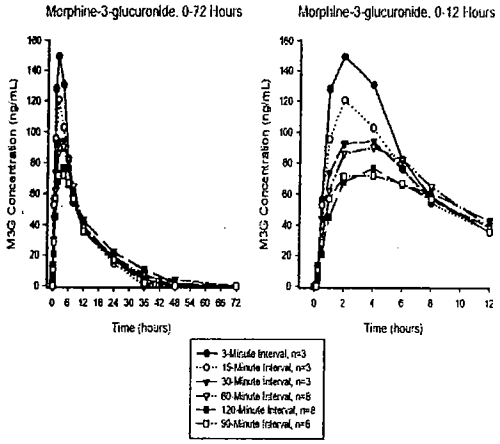
Data Source: Appendix 16.2.2, Table 6
[a]Median (minimum-maximum)

e. Morphine Serum Concentration by Subject in 90-Minute Inter-dose Interval Group, 0-2 Hours Post-Dose

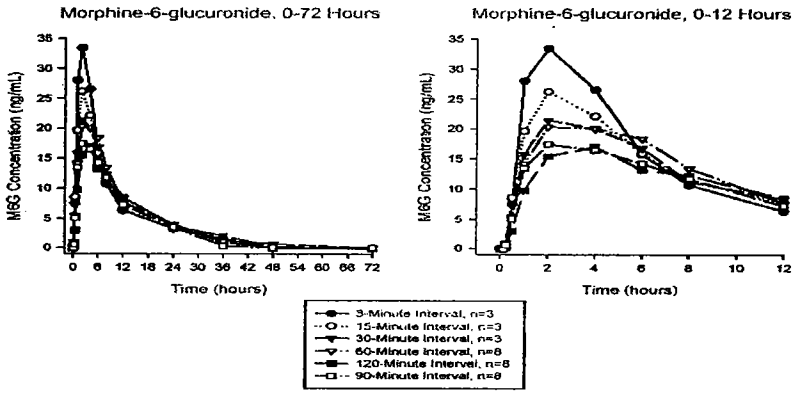


f. Metabolite Pharmacokinetic Results

Mean Morphine-3-glucuronide Serum Concentrations by Treatment Group:



Mean Morphine-6-glucuronide Serum Concentrations by Treatment Group:



Mean (SD) Morphine-3-glucuronide PK Parameters by Inter-dose Interval Treatment Group

	Inter-dose Interval Treatment Group (Mean ± SD)				
Variable	3 Minutes (n=3)	15 Minutes (n=3)	30 Minutes (n=3)	60 Minutes (n=8)	90 Minutes (n=8)
^{C}max (ng/mL)	149.27 (42.531)	120.58 (28.797)	95.15 (28.396)	95.13 (18.930)	77.05 (27.889)
^{T}max (hr)[a]	2.00 —	2.00 —	4.00 —	4.00 —	4.00 —
^{AUC}0-t (ng hr/mL)	1390.9 (318.600)	1168.3 (77.199)	1260.9 (281.528)	1253.9 (244.448)	1013.3 (431.818)
^{AUC}0-∞ (ng hr/mL)	1680.5 (194.461)	1363.4 (40.202)	1594.4 (371.354)	1544.9 (319.629)	1288.5 (491.769)
λ_{z} (KE) (hr -1)	0.0616 (0.0365)	0.0799 (0.0217)	0.0598 (0.0348)	0.0592 (0.0168)	0.0682 (0.0109)
T½ (hr)	13.65 (6.108)	9.09 (2.324)	15.22 (9.878)	12.71 (4.216)	10.42 (1.887)

Data Source: Appendix 16.2.2, Table 7
[a]Median (minimum-maximum)

Mean (SD) Morphine-6-glucuronide PK Parameters by Inter-dose Interval Treatment Group

	Inter-dose Interval Treatment Group (Mean ± SD)				
Variable	3 Minutes (n=3)	15 Minutes (n=3)	30 Minutes (n=3)	60 Minutes (n=8)	90 Minutes (n=8)
^{C}max (ng/mL)	33.40 (7.435)	26.18 (3.077)	21.45 (5.623)	22.01 (6.631)	18.28 (6.59)
^{T}max (hr)[a]	2.00 —	2.00 —	2.00 —	3.00 —	2.00 —
^{AUC}0-t (ng hr/mL)	283.18 (16.936)	262.45 (46.882)	272.20 (57.172)	259.14 (74.105)	216.7 (90.94)
^{AUC}0-∞ (ng hr/mL)	333.94 (12.090)	303.63 (41.380)	337.13 (51.328)	314.34 (80.794)	272.4 (98.09)
λ_{z} (KE) (hr -1)	0.0573 (0.0303)	0.0705 (0.0167)	0.0564 (0.0222)	0.0623 (0.0139)	0.07 (0.01)
T½ (hr)	14.14 (5.750)	10.18 (2.251)	13.56 (4.991)	11.85 (3.849)	10.55 (1.80)

Data Source: Appendix 16.2.2, Table 8
[a]Median (minimum-maximum)

4.3 Consult Review (including Pharmacometric Reivews) – Not applicable.

4.4 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-671	**Brand Name**	**TBD**
OCPB Division (I, II, III)	II	**Generic Name**	**Morphine Sulfate sustained-release liposome injection**
Medical Division	HFD-170	**Drug Class**	**Opioid**
OCPB Reviewer	David Lee	**Indication(s)**	**For post-operative pain**
OCPB Team Leader	Suresh Doddapaneni	**Dosage Form**	**Injection**
		Dosing Regimen	**Single dose**
Date of Submission	7/18/03	**Route of Administration**	**Epidural**
Estimated Due Date of OCPB Review	4/20/04	**Sponsor**	**SkyePharma, Inc**
Medical Division Due Date	4/26/04	**Priority Classification**	**S**
PDUFA Due Date			

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			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:				
Patients-				
single dose:	X	5		
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	6		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2		**Comparison with test dose (lidocaine/epinephrine)**
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				

gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X			
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		7		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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

/s/

David Lee
5/6/04 11:41:56 AM
BIOPHARMACEUTICS
FYI : 11/17/03 submission contains Study 018 (test dose of 20 mL of lido). One Phase 4 Commitment comment.

Suresh Doddapaneni
5/6/04 01:16:01 PM
BIOPHARMACEUTICS