

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-671**

**Medical Review(s)**



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**  
**DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS**  
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**REVIEW AND EVALUATION OF CLINICAL DATA**

<b>NDA</b>	# 21-671
<b>Sponsor:</b>	SkyePharma, Inc
<b>Generic Name:</b>	Morphine
<b>Proprietary Name:</b>	SKY0401 (morphine sulfate sustained-release liposome injection)
<b>Pharmacologic Class</b>	Opiate, narcotic
<b>Proposed Indication</b>	Acute postoperative analgesia
<b>Submission Date</b>	July 18, 2003
<b>Dosage forms</b>	20mg/2mL, 15mg/1.5mL, 10mg/1mL
<b>Strengths</b>	10mg/mL, preservative free
<b>Route</b>	Epidural
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<b>Action Date</b>	May 18, 2004

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## Executive Summary

### 1.1 RECOMMENDATIONS

#### 1.1.1 Recommended Action

This reviewer recommends that SKY0401, (morphine sulfate sustained-release liposomal injection) be considered approvable, for lumbar epidural administration for the treatment of post-operative pain.

This reviewer does not agree with the sponsor's proposed dose of 20-mg SKY0401 for patients younger than 65 years having hip or lower abdominal surgery. My risk-benefit assessment of SKY0401 is based upon the clinical trial findings that the minimum effective doses had a safety profile for serious adverse events that was similar to unencapsulated epidural morphine. The incidence of patients with serious respiratory adverse events was dose-related. The incidence of opiate antagonist administration to reverse sedation or respiratory depression, another marker for the frequency of clinically important compromised ventilation, was related to the dose of SKY0401. This reviewer proposes a labeled SKY0401 dose for hip surgery patients of 15 mg. For lower abdominal surgery patients, this reviewer suggests a SKY0401 dose of 10 mg. Higher doses of SKY0401 are more effective in managing perioperative pain in these indications, but an increase in efficacy is outweighed by the nature and frequency of associated respiratory adverse events.

A 10-mg SKY0401 is appropriate for patients having cesarean section. By labeling the product at the 15-mg dose for hip surgery and the 10-mg dose for lower abdominal surgery and cesarean section, SKY0401 may be used to improve the duration of perioperative pain control at comparable risk to currently approved products. There was no apparent dose relationship to the incidence of serious adverse events among elderly patients studied in clinical trials so no additional reduction in dose based upon age alone is proposed.

#### 1.1.2 Recommended Phase IV Studies or Marketing Restrictions

None.

### 1.2 SUMMARY OF CLINICAL FINDINGS

#### 1.2.1 Overview of Clinical Program

SKY0401 is an extended-release liposome formulation of the active ingredient morphine sulfate designed for epidural administration, for the treatment of post-operative pain. Morphine, a pure opioid agonist, is relatively selective for the  $\mu$ -opioid receptor, although it can interact with other opioid receptors at higher doses. The SKY0401 formulation consists of a microscopic, lipid-based multivesicular matrix composed of adjacent chambers containing the encapsulated morphine in aqueous solution. *In vivo*, the

liposomal matrix is believed to release drug over an extended period of time by erosion and/or reorganization of the lipid membranes of the particles.

Subjects who received SKY0401 included 961 individuals in five randomized, double blind, placebo- or active-controlled, dose-ranging clinical studies (n=840), two open-label trials (n=65) and two volunteer studies (n=56). The comparator population was comprised of 234 patients exposed to either placebo (n=78), unencapsulated epidural morphine (n=101) or IV patient-controlled analgesia (n=55). The studies in volunteers were not included in the sponsor's Integrated Summary of Safety database also used in this review. The procedures studied in controlled trials were hip arthroplasty (SKY0401-009, -011), lower abdominal surgery (SKY0401-012B), cesarean section (SKY0401-015) and knee arthroplasty (SKY0401-017).

During the development of SKY0401, it was discovered that lidocaine displaces morphine out of DepoFoam™ particles *in vitro* and *in vivo* on a molar to molar basis. Study SKY0401-016 was designed and executed to assess the effects of an epidural placement "test dose" containing a small amount of lidocaine with epinephrine, administered at various time intervals, on the PK and PD profiles of SKY0401 in patients undergoing major upper abdominal surgery. Additional analyses were performed to define the clinical impact on use and timing of a test dose in the controlled clinical trials.

The sponsor conducted one study in volunteers (018) to assess the possible interaction of SKY0401 and a therapeutic dose of epidurally administered local anesthetic during the intra-operative period. This study was submitted as part of the 120-day safety update.

### 1.2.2 Efficacy

Efficacy of SKY0401 was demonstrated in four out of five adequate and well-controlled clinical trials of patients having various surgical procedures. Studies 009 and 011 were multicenter, randomized, double-blind, parallel group, dose-ranging trials in 314 patients having hip arthroplasty with epidural SKY0401 or epidural placebo. Study 012b was a randomized, double-blind, dose-controlled, parallel group, epidural dose-ranging study conducted in 487 patients having a variety of lower abdominal surgical procedures. Clinical trial 015 was a randomized, double-blind, active-controlled, epidural dose-ranging, parallel group study to evaluate the safety and efficacy of a single epidural dose of sustained-release encapsulated morphine (SKY0401) compared with IV patient controlled analgesia (PCA) morphine in the management of post-operative pain in 75 patients undergoing elective cesarean section under intrathecal anesthesia.

In each of these trials demonstrating efficacy of SKY0401 the primary endpoint was reduction of perioperative opiate requirements. In the placebo controlled trials of hip arthroplasty, the mean IV fentanyl requirement was reduced significantly by statistical and clinical criteria at all SKY0401 doses tested. In the clinical trial of abdominal surgery patients, 10-mg, 15-mg, 20-mg and 25-mg doses of SKY0401 were associated with a statistically significant reduction in median perioperative IV fentanyl administration compared with the 5-mg SKY0401 dose-control group. Patients having cesarean section

(Study 015) exhibited a significant reduction in IV morphine PCA when treated with SKY0401 in doses of 10 or 15 mg. The reduction in perioperative supplemental pain medication administered was, in most cases, related to the dose of SKY0401. A finding of efficacy in the primary endpoint was supported by various analyses of the secondary endpoints including visual analog and categorical pain scores and ratings of pain control by the surgeon and patient. Administration of all opiates used to supplement pain treatment was also analyzed by equipotent dosing with the same results of efficacy of SKY0401 as found for IV fentanyl or IV morphine, depending on the study. The timing of supplemental pain medication was analyzed to evaluate the duration of action of SKY0401. In some doses and settings, SK0401 improved pain control with respect to the comparator patients in the 24 to 48 hour period after administration of study drug. In the clinical trials where efficacy of SKY0401 was demonstrated, the duration of effect was longer than for 5-mg epidural unencapsulated morphine, a standard treatment.

One study (017) failed to demonstrate efficacy of SKY0401 greater than sham epidural with IV PCA in its primary endpoint. Study 017 was a randomized, double-blind, active-controlled, dose-ranging, parallel group study to evaluate the safety and efficacy of a single epidural 20-mg or 30-mg dose of SKY0401 compared with sham epidural (IV PCA) in the management of post-operative pain in 164 patients undergoing knee arthroplasty. Pain level recalled over a previous 4 hour period, with intensity measured as a visual analog score (VAS), defined a time-weighted pain recall score. The time-weighted pain recall score was assessed every 4 hours for 44 hours (following an initial 4 hour post-treatment assessment). There was no statistically significant difference in the time-weighted pain recall score between patients treated with SKY0401 or sham epidural (with IV PCA). The trial design may have interfered with demonstration of statistical significance. Analysis of supplemental pain medication as a secondary endpoint did suggest efficacy of SKY0401 compared to placebo.

In summary, efficacy of SKY0401 as an epidurally administered analgesic medication was demonstrated by analysis of the results of clinical trials in patients having hip, lower abdominal surgery and cesarean section.

### 1.2.3 Safety

The safety-related inclusion and exclusion criteria applied in the individual studies were generally consistent across the studies. The sponsor performed two pharmacokinetic studies in volunteers, three Phase 2 studies in patients undergoing hip surgery, upper abdominal surgery and cesarean section and three Phase 3 pivotal trials in patients undergoing hip surgery, lower abdominal surgery and in knee surgery. A total of 905 patients treated with SKY0401 and 230 patients treated with either epidural placebo, unencapsulated morphine or sham epidural (with IV PCA) alternatives were analyzed in the sponsor's Integrated Summary of Safety including a 30 day follow-up for adverse events. Patients over 75 years old and patients with serious concomitant medical conditions that increased surgical risk (ASA 3, see appendix for definition of ASA classification) were included. More women than men were included, but the number of each gender was sufficient. Most patients were Caucasians, but multiple racial groups were included and morphine is not associated with adverse events specific to race. All studies were performed in adults. Patients undergoing cesarean section were delivered before treatment so that there was no fetal exposure to SKY0401. Trial exclusions and

dropouts did not impair analysis of the safety of SKY0401. Perioperative monitoring, exposure to concomitant medication and duration of follow-up were sufficient to capture associated adverse events. The number and spectrum of patients studied and the quality of data is sufficient to render a premarket assessment of the safety of SKY0401.

There are three elements related to the use of this product that required examination for safety: morphine, the liposomal excipient and the epidural route of administration.

Morphine has been studied for many years and its systemic effects are well known. Patient monitoring was adequate to capture acute and delayed expression of systemic adverse events related to morphine.

The encapsulating lipid is a new excipient in the application of opioid epidural analgesia. Toxicity resulting from the close proximity of the drug product to the central nervous system was evaluated histologically in preclinical testing and further evaluated by 30-day postoperative assessment and comparison to baseline. There were no significant adverse findings.

Identification of the epidural space is often facilitated by the use of a small “test dose” prior to placement of a therapeutic dose of a drug to be administered epidurally. Many practitioners are likely to use a test dose containing lidocaine and epinephrine prior to administration of SKY0401. The sponsor’s performed pharmacokinetic studies revealing that administration of a lidocaine and epinephrine epidural test dose 10 minutes before SKY0401 administration was associated with higher blood levels of morphine, presumed to result due to its release from liposomal encapsulation. When SKY0401 was delayed for 15 minutes after test dose administration, blood levels of morphine were comparable to blood levels when a test dose was not used. Pharmacodynamic effects associated with the use of a test dose were not seen in clinical trials.

Five patients died during the conduct of clinical trials. One patient’s death (012-83-119) may have been related to SKY0401 as a consequence of vomiting and loss of airway protection. This patient was treated with SKY0401, but did not undergo surgery as planned because colonoscopy performed under anesthesia did not reveal a tumor. Later on the night of surgery the patient was treated for nausea (with ondansetron) and later was discovered in full cardiopulmonary arrest with emesis in the oral airway.

One or more SAEs were reported by 11% (96/905) of all SKY0401-treated patients in the Integrated Summary of Safety database, compared to 5% (4/78), 6% (6/97) and 9% (5/55) of epidural placebo, epidural unencapsulated morphine (MS) and sham epidural with IV PCA MS-treated patients respectively. Serious adverse events included paralytic ileus, respiratory depression, myocardial infarction, pulmonary embolism, hypoventilation, urinary retention, somnolence, cellulites gastrointestinal hemorrhage cardiac arrest, hypotension, postoperative wound infection, joint dislocation and pyrexia. These events were expected opioid effects of events expected for the patient population based upon the known pharmacology of morphine, collective clinical experience with unencapsulated morphine and this reviewer’s analysis of the reported adverse events associated with SKY0401.

With the exception of respiratory depression, there is no apparent dose-response across the dose levels of SKY0401 for any of these events. Of the cases of respiratory depression that did occur, 36 patients treated with SKY0401 (4%, 36/905) required treatment with a narcotic antagonist, but only one patient receiving unencapsulated morphine (1%, 1/97) and no patients treated with placebo, or sham epidural with IV PCA required a narcotic antagonist. Analysis of the SKY0401 patients who received a narcotic antagonist for respiratory depression revealed that the incidence of reversal treatment was related to the dose of SKY0401. Narcotic antagonist administration may be a conterminous finding for clinically significant respiratory depression.

Common adverse events included nausea, pruritis, pyrexia, vomiting, hypotension, anemia, headache, constipation, decreased oxygen saturation, urinary retention and dizziness. The only adverse events considered by the sponsor to be possibly related to the study medication involved known opioid effects. This reviewer agrees based upon the known pharmacology of morphine, collective experience with unencapsulated morphine and analysis conducted during review.

#### **1.2.4 Dosing**

The sponsor demonstrated efficacy of SKY0401 in doses of 10 mg, 20 mg and 30 mg in Study 009 of patients having hip surgery. Efficacy was also demonstrated in doses of 15 mg, 20 mg and 25 mg in the hip surgery patients of Study 011. The 15-mg dose was effectively bracketed in Study 009 even though it was not evaluated directly in that clinical trial. The clinical trial of abdominal surgery patients (Study 012b) also demonstrated a dose-response for efficacy, and evaluated 10-mg, 15-mg, 20-mg and 25-mg doses of SKY0401 collectively against a 5-mg comparator dose of SKY0401. Efficacy of SKY0401 is dose dependent, so that a 20-mg dose is more effective in general in reducing supplemental fentanyl usage than 15 mg. The sponsor suggested that a 20-mg dose in the setting of abdominal surgery and hip surgery was appropriate for patients less than 65 years old and suggested that older patients receive 15 mg. Their dosing suggestions were based primarily upon optimizing efficacy. The study of patients having cesarean section (015) demonstrated efficacy of SKY0401 in doses of 10 mg and 15 mg. The sponsor proposed 10-mg SKY0401 for use in cesarean section because the supplemental opiate requirements were indistinguishable between patients treated with 10-mg or 15-mg doses of SKY0401.

This reviewer also considered the clinical relevance of the treatment effect with increasing dose. The difference in median supplemental fentanyl used between hip surgery patients (Study 011) treated with 15-mg and 20-mg SKY0401 was only 150 mcg compared with a difference of 1205 mcg between placebo and 15 mg. In the study of lower abdominal surgery patients, the practical difference in treatment effect between doses was also small. For example, the median difference in supplemental fentanyl between patients treated with 10 mg compared with 25 mg of SKY0401 was only 145 mcg compared to a median difference of 220 mcg in supplemental fentanyl between patients treated with SKY0401 doses of 5 mg to 10 mg. A difference of 150-mcg in supplemental fentanyl administered over 48 hours is unlikely to have a significant clinical impact on patient care or comfort.

With a small improvement in treatment effect with higher doses, determination of an appropriate indicated dose must carefully weigh the relative dose-related safety of SKY0401. In particular, the incidence of serious respiratory adverse events was less than 1% (2/338) for patients treated with 10-mg or 15-mg SKY0401, comparable to the 1% (1/97) incidence with 5-mg unencapsulated morphine. In contrast, the incidence of serious respiratory adverse events was 1.8% (4/224) with 20-mg SKY0401. Further support for the use of the lowest effective dose of SKY0401 is found in the population of patients who required narcotic antagonism for opiate side effects. There was an increase in the use of narcotic antagonists to treat sedation, respiratory depression or similar reasons related to the dose of SKY0401. This incidence was 2% (2/97) for 5-mg unencapsulated morphine, about 4% (13/338) for 10 to 15-mg SKY0401 and about 9% (20/224) for 20-mg SKY0401.

After consideration of the magnitude of treatment effect with each dose in each population and the safety profile related to dose, this reviewer proposes a 15-mg SKY0401 dose for hip surgery and 10-mg SKY0401 for lower abdominal surgery and for cesarean section. Some patients may also benefit from higher doses, provided that vigilant monitoring is available for the perioperative period of risk from associated respiratory depression.

### 1.2.5 Special Populations

Of the total 905 patients exposed to SKY0401 (in the Integrated Summary of Safety), 600 were female and 305 were male. The predominant racial group was Caucasian with 723 exposures. Other races were represented in very limited numbers: 106 Black, 13 Asian, and 55 Hispanic patients and 8 patients of other races not specified were exposed to SKY0401. There were 253 patients exposed to SKY0401 who were 65 years old or older.

An age-related efficacy effect was shown in Study 011 of patients having hip surgery. Patients 65 years old or older had similar supplemental fentanyl requirements with a 15-mg dose of SKY0401 to patients younger than 65 years treated with 20 mg of SKY0401. This reviewer agrees with the sponsor's findings of comparable efficacy, but small difference in treatment effect between 15 and 20 mg dose of SKY0401 indicates that a 15-mg dose was also effective in the broad population. My own analysis of safety in patients by age group did not reveal a dose-response effect, so this reviewer proposes a lower dose for all age groups.

Study of SKY0401 in pediatric patients was deferred. This product may be given to infants by the caudal epidural route. Further study of in the pediatric population by the sponsor is pending approval of the drug in the adult population.

## Clinical Review

### 1.1 INTRODUCTION AND BACKGROUND

#### 1.1.1 Proposed Indications

SKY0401 is a sustained-release liposome injection of morphine sulfate for administration by the epidural route for the treatment of post-operative pain.

#### 1.1.2 Milestones in Product Development

The FDA discussed the sponsor's proposed clinical development plan with the sponsor on several occasions.

- The End of Phase 2 meeting took place on 13 January 2000. During the meeting, the agency agreed that the proposed endpoint (i.e., a reduction in fentanyl or total opioid use for the 48-hour post-dosing period) was an acceptable efficacy endpoint for the adequate and well-controlled Phase 3 studies. The agency recommended correlating this data with the pain scores. As an alternative to the placebo-controlled study, the agency recommended considering a dose-controlled study. The agency recommended extending the post-dose safety follow-up period for 30 days and not imposing an age limit in the proposed clinical studies. Also, the agency agreed to defer the pediatric studies until after NDA approval. A safety database of approximately 700 patients was recommended. It was stated that, according to 505(b)2 regulations, a comparative bioavailability study of SKY0401 versus the reference listed drug would be necessary.
- The sponsor was sent two letters (dated 10 April 2002 and 15 July 2002) from the agency regarding clinical study SKY0401-012B. The agency agreed with the inclusion of an unencapsulated morphine arm for comparison, advising to consider linear dose response as the primary efficacy analysis and concurred with the proposal to "start over" the randomisation after the amendment.
- During the teleconference held on 03 October 2002, SkyePharma agreed to amend the protocols for all ongoing studies instituting pulse oximetry monitoring for 24 hours post-dose and for 48 hours if surgery was cancelled after study drug administration.
- In the letter dated 14 February 2003 regarding clinical studies SKY0401-015 and -017, the agency reaffirmed its position that if a dose control or active control was utilized, then demonstrating efficacy superiority was required. The agency advised to administer the Neurological Assessment Questionnaire (NAQ) at baseline and use the questionnaire utilized in the pivotal studies in these studies. Also, the agency advised taking into account the amount of rescue medication used when analyzing the primary and secondary outcome measures in the study SKY0401-017.

- During the teleconference held on 21 February 2003, in addition to the topics discussed previously, the agency advised SkyePharma to provide a clear rationale supporting the recommended dose for each patient population.
- During the pre-NDA meeting held on 26 March 2003, the agency agreed with the NDA data format to be presented in the NDA.

### 1.1.3 Foreign Marketing

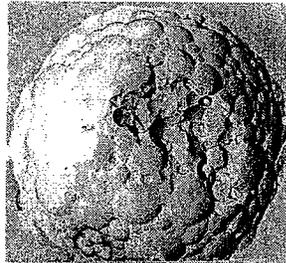
The product has not been marketed.

## 1.2 FINDINGS FROM OTHER REVIEW DIVISIONS OR CONSULTS

### 1.2.1 Chemistry

SKY0401 consists of morphine sulfate, USP formulated in a preservative free homogeneous suspension of multivesicular liposomes in NaCl 0.9% w/v in Water for Injection (WFI). Each vial contains morphine sulfate (expressed as the pentahydrate) at a nominal concentration of 10 mg/mL. Inactive ingredients include 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), cholesterol, 1,2-dipalmitoyl-sn-glycero-3-phospho-rac-(1-glycerol) (DPPG), tricaprylin, and triolein. The sustained-release nature of the encapsulated morphine is imparted by the combination of lipids that form nonconcentric walls of the liposome particles. Liposome particles are roughly spherical in the 17–23 µm diameter size range.

Figure 1.2-1 Electron Micrograph of Liposome Particle



From Sponsor's Summary of Quality, Figure 2.3.P.2.1, page 16

potential impurities have been identified in the active drug, Morphine Sulfate, USP (see DMF):

are potential impurities are not degradation products impurities, but derive from

The drug product includes various lipid components that facilitate an extended release profile for morphine in the epidural space. The ratio of DOPC (Dioleoylphosphatidylcholine), DPPC (Dipalmitoylphosphatidyl-glycerol), cholesterol, triolein and tricaprylin is related to the rate of morphine release. In particular, the length of the triglyceride has a significant impact on the release rate of active drug. Various preclinical formulations changing tricaprylin to triolein ratios were prepared and tested to

define an appropriate mixture of the two triglycerides to achieve the desired morphine release rate *in vitro* and *in vivo* (in serum and CSF).

In the *in vitro* release assay, formulations of the liposomal morphine suspension were bathed in an aqueous BSA solution at 37°C with mild agitation. Samples were assayed at various times for the amount of morphine retained in the particles. This system exhibited 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. The current *in-vitro* release system is being used as a QC tool to characterize reproducibility of manufacture from lot to lot.

Deficiencies remain in manufacturing quality assurance. Substrates used for manufacturing of the excipient require additional testing. The sponsor's proposed assay for retained morphine exhibited substantial variation and may not reflect *in vivo* conditions adequately. This means that it may be possible for clinically significant amounts of morphine to be released into the cerebrospinal fluid after the desired duration of analgesic efficacy. The adequacy of quality control, manufacturing and quality control is currently under discussion. The reader is referred to the detailed review by Dr. Michael Theodorakis.

### 1.2.2 Pharmacotoxicology

Preclinical studies focused on evaluation of the relative properties of unencapsulated morphine and morphine contained in the lipid delivery system. The pharmacokinetics of interaction of epidurally administered encapsulated morphine with lidocaine was examined. Disposition of the lipid matrix and evidence of local and systemic toxicity was studied in single and multiple dose models.

#### *Pharmacology*

The behavioral, physiological and antinociceptive activities of the encapsulated morphine were compared to those of unencapsulated morphine sulfate when administered intravenously (IV), intrathecally (IT), and epidurally (EPI) to adult beagle dogs. Mild to moderate decreases were observed in arousal state, muscle tone and coordination. After epidural injection, behavioral effects peaked earlier in most animals for 5-mg morphine sulfate administration (30 to 60 minutes) compared with 10- and 30-mg SKY0401 administration (5 and 10 hours, respectively). The animals recovered more quickly after 5-mg morphine sulfate administration; scores were back to near baseline by 10 hours. Behavioral scores returned to baseline by 24 and 48 hours after administration of 10- and 30-mg of SKY0401, respectively. Repeated weekly lumbar epidural injections SKY0401 appeared to result in a decrease in the magnitude of depression of arousal, muscle tone, coordination and body temperature.

#### *Pharmacokinetics*

The pharmacokinetics of single intravenous, intrathecal, or epidural injections of SKY0401 compared with unencapsulated morphine was studied in the beagle dog. Morphine concentrations in lumbar CSF reached their maximum earlier and declined later with SKY0401 than unencapsulated morphine. Peak morphine concentrations in CSF were approximately 3-fold lower after SKY0401 (30 mg) administration compared with

morphine sulfate administration at one-sixth the dose. Morphine pharmacokinetics in serum after SKY0401 or morphine sulfate administration were similar to those observed in lumbar CSF, except that serum concentrations were approximately 150- to 300-fold lower at the peak.

Morphine concentrations were also assessed in serum after repeated weekly lumbar epidural injections of 30 mg SKY0401 in beagle dogs. Morphine was not detected in the CSF of any animals euthanized 7 to 9 days after administration of the final (fourth) SKY0401 dose.

#### *Pharmacokinetic drug interactions*

Assessment of the *in vivo* interaction of lidocaine/epinephrine on the release of morphine sulfate from epidural administration of SKY0401 by evaluating serum pharmacokinetics of morphine was performed in beagle dogs (Study 033-00026). The administration of lidocaine/epinephrine immediately prior to dosing with SKY0401 resulted in a 2.5-fold to 3.0-fold increase in C<sub>max</sub>, of morphine occurring 5 minutes post-SKY0401 injection, compared to no lidocaine/epinephrine injection and flushing the catheter with saline after the lidocaine/epinephrine test dose and waiting 15 minutes. Flushing the epidural catheter with saline to remove residual lidocaine/epinephrine, then waiting 15 minutes prior to SKY0401 administration prevented the early release of morphine from SKY0401 in dogs.

#### *Disposition*

Morphine, injected into the epidural space, is rapidly absorbed into the general circulation. Absorption is so rapid that the plasma concentration-time profiles closely resemble those obtained after intravenous or intramuscular administration. Cerebrospinal fluid (CSF) concentrations of morphine, after epidural administration, are much higher than corresponding plasma concentrations even though a small fraction of the epidural dose actually reaches the CSF. The disposition of morphine in the CSF is known to follow a biphasic pattern, with an early half-life of 1.5 hours and a late phase half-life of about 6 hours.

Following epidural placement, some of the injected SKY0401 will leak from the intervertebral foramina. The remaining SKY0401 will be adjacent to the epidural fat. Clearance of lipid material is expected to occur by absorption into the fat where it will be metabolized along with similar endogenous compounds. Phagocytosis by local macrophages with clearance of breakdown products by local lymphatics is also anticipated. These mechanisms are fundamental to the clearance of blood administered therapeutically into the epidural space to manage headache associated with inadvertent dural puncture.

Preclinical study of rats injected intrathecally with a DepoFoam formulation of cytarabine in which DOPC (dioleoylphosphatidylcholine), the primary lipid constituent of DepoFoam, was <sup>14</sup>C and the cytarabine labeled with <sup>3</sup>H. provided supportive evidence that lipid excipients of SKY0401 will be excreted in a similar manner to endogenous compounds.

#### *Toxicity*

Review of the components of the liposomal excipient revealed differences in the composition (Triolein, Tricaprylin) compared with the liposomal excipient approved for the drug product DEPOCYT<sup>®</sup>, a chemotherapeutic agent for treatment of late stage lymphoma. Of the components in the liposome, neurotoxicity has only been related to tricapryline, however, the amount of tricapryline present in SKY0401 has a sufficient safety ratio to make neurotoxicity unlikely.

Single and repeated dose epidural administration of encapsulated morphine was associated with mild to moderate inflammatory reactions the at the injection site in dogs. Small localized hemorrhages of the meninges and focal degeneration of individual nerve roots near the spinal cord injection sites were believed to be related to local trauma. In a multiple-dose toxicity study of placebo depofoam administered via intrathecal injection to rhesus monkeys (SkyePharma Preclinical Report No. 033-00007) observed meningeal inflammation was minimal to slight in severity and diffusely observed throughout the spinal column. No inflammation was present in the peripheral nervous tissue or eyes of treated animals.

There was no evidence of pulmonary thrombosis or embolization after intravenous injection of liposomes in dogs.

Review of the clinical chemistry, hematology, cerebrospinal fluid and urinalysis results indicated no biologically meaningful effects associated with DepoFoam.

The safety of the DepoFoam drug delivery matrix was demonstrated in several animal species including rats, mice, guinea pigs, dogs, rabbits, and primates. Comprehensive multiple-dosing toxicity studies demonstrate that the DepoFoam matrix is associated with a very limited potential for producing significant local or systemic toxicity when administered either subcutaneously (mouse, dog), epidurally (dog), or by intrathecal injection (monkey). DepoFoam matrix is non-immunogenic (guinea pig), and is well tolerated in the vitreal cavity (rabbits), and biocompatible in subcutaneous tissues (rat).

The reader is referred to the detailed review by Dr. Mamata De.

### **1.2.3 Human Pharmacokinetics and Pharmacodynamics**

Following epidural administration of SKY0401, the site of action of morphine is believed to be at the spinal level. Free morphine moves from the epidural space to the CSF and to the systemic circulation, but not to the same degree. Systemic plasma concentrations also do not indicate the morphine concentration in the epidural space. The concentration of morphine in the CSF is 100 to 400 fold higher than the plasma concentration, so plasma measurements are an indirect measure of concentrations at the site of action. Analgesia resulting from epidural morphine is not dependent upon systemic morphine concentrations. The duration of analgesia also continues beyond the time when morphine may be detected in the plasma. Therefore, conclusions about efficacy of pain control may not be drawn based upon systemic morphine concentration.

Plasma concentrations of morphine are also used to detect drug interaction between lidocaine/epinephrine administered epidurally and SKY0401. A test dose comprised of about 45 mg of lidocaine and about 15 mcg of epinephrine in 3 mL is sometimes used to detect inadvertent placement of an epidural catheter into a blood vessel or the CSF. 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 (Study 016). The peak systemic concentration of morphine was elevated when

a test dose was administered within 10 minutes prior to administration of SKY0401. The systemic concentration of morphine falls to levels seen without a test dose within about an hour after SKY0401 administration. If the epidural catheter is flushed and a 10 to 15 minute delay is used between administration of the test dose and SKY0401, peak plasma concentrations are similar to those observed when no test dose was used.

Further study of the interaction of lidocaine/epinephrine with SKY0401 was conducted with therapeutic doses of local anesthetic in Study 018. In this setting, plasma levels of morphine were elevated unless 60 minutes was allowed to elapse between injection of the local anesthetic and SKY0401. Use of therapeutic doses of local anesthetics has not been proposed by the sponsor in the label.

In summary, systemic morphine levels are an indirect marker of morphine levels at the site of action in the spinal cord and may not reflect analgesic or other pharmacodynamic properties of SKY0401. Increased blood levels of morphine are observed when epidural injection of SKY0401 is preceded by epidural injection of lidocaine. When 15 minutes is allowed to elapse between epidural injection of lidocaine and epidural injection of SKY0401, blood levels of morphine are indistinguishable from SKY0401 injected without prior injection of lidocaine. The reader is referred to the detailed review by Dr. David Lee.

### **1.3 REVIEW METHODS**

#### **1.3.1 Conduct of Review**

The review began by determining that all applicable items of the clinical section were included and that the NDA was suitable for filing. During the review for filability of the initial submission, it was noted that the data tables included entries that were undefined and that there was no comprehensive database provided for the Integrated Summary of Safety analysis. The sponsor responded with complete definitions for the data entry tables and a comprehensive electronic dataset for analysis of safety. The 120-day safety review included a completed report of SKY0401-018, a study of pharmacokinetics of morphine after therapeutic and test dose administration of epidural lidocaine with epinephrine.

The 3 Phase 3 trials and 2 phase 2 trials were blinded, randomized and controlled studies of SKY0401 in patients. These studies were reviewed in detail for efficacy and safety. A Phase 1 study in volunteers, and the 3 open-label Phase 2 pharmacokinetic studies were reviewed for evidence of safety.

The sponsor's datasets included with the Integrated Summary of Safety (ISS) were the primarily source of safety data used in this review. Studies that were not included in the ISS dataset were evaluated individually from the adverse event tables provided with each study report.

All clinical trials used for purposes of review were conducted by the product sponsor. No other INDs, external consultants or advisory panels were used prior to submission and review of the application.

#### **1.3.2 Materials Consulted**

The sponsor submitted the application to the electronic document room under network path \\CDESUB\N21671\N-000\2003-07-18. The electronic database including

the Integrated Summary of Safety is filed under the network path \\CDESUB\N21671\N\_000\2003-08-25. The files for the 120-day Safety Update including the report of SKY0401-018 may be found under the network path \\CDESUB\N21671\N\_000\2003-11-07. The narrative was read from the pdf-formatted files and the electronic database was analyzed by individual study and using the submitted Integrated Summary of Safety datasets (xpt files). The studies used to evaluate efficacy are listed in Table 1.4-1 below. In addition, Study 008, an open-label study of pain in patients having hip arthroplasty and Study 016, a pharmacokinetic study in patients having upper abdominal surgery were included in the analysis of adverse events from the sponsor's integrated summary of safety database. The division file for IND 52,113 was also examined for reviews, minutes of meetings with the sponsor and correspondence with the sponsor.

### **1.3.3 Evaluation of Data Quality and Integrity**

Numbers and types of adverse events listed in the electronic database linked that was the stated source for the sponsor's analysis of safety were compared by this reviewer with the sponsor's tables of in the study reports. The narratives of all reported serious adverse events were read individually by this reviewer to evaluate the sponsor's medical conclusions. No discrepancies in the data were discovered. Dr. Dionne Price compared the sponsor's analysis efficacy to her own findings using the submitted electronic database. There were several ambiguities in the data definition tables that were explained satisfactorily by the sponsor early in the review process and the p-value calculated by Dr. Price differed slightly in one of the secondary analysis of the secondary endpoint in Study 015. These discrepancies were minor and did not affect the conclusion.

### **1.3.4 Compliance with Good Clinical Practices**

The protocol, written informed consent form, and Investigator's Brochure were reviewed by the Institutional Review Boards (IRBs) at the study sites. The Institutional Review Board (IRB) was properly constituted and operated in accordance with the requirements described in the Code of Federal Regulations (Title 21, Part 56) and the ICH Guideline for Good Clinical Practice. Each study was conducted in accordance with United States (US) Food and Drug Administration (FDA) Good Clinical Practice (GCP) guidelines and the tenets of the Declaration of Helsinki. All patients provided written informed consent, which was obtained at the screening visit. Prior to participation in the study, the investigator or designee, explained to each subject the study purpose and procedures, and the benefits and risks involved in study participation. Each subject was informed of his or her right to withdraw from the study anytime without prejudice. After this explanation, subjects voluntarily signed and dated an informed consent in the presence of a witness. Each subject was provided a copy of the informed consent.

### **1.3.5 Financial Disclosure**

To comply with 21CFR §54.4, Certification and Disclosure Requirements, the Sponsor submitted certification on the financial interest and arrangements of the clinical investigators who enrolled subjects into the covered clinical studies of SKY0401. A list of investigators and sub-investigators in protocols SKY0401-008, SKY0401-009,

SKY0401-011, SKY0401-012, SKY0401-012B, SKY0401-015, SKY0401-016, and SKY0401-017 with no financial conflicts of interest was provided. Clinical Study DTC 96-003, which was a phase 1 study in normal volunteers, is not a covered clinical study as defined in 21 CFR Part 54 and certification was not provided. Studies SKY0401-008 and -009 were initiated prior to implementation of 21 CFR Part 54 and retrospective attempts were unsuccessful in obtaining a response from some investigators and subinvestigators. SkyPharma Inc. was unable to obtain the unformation required under 21 CFR Part 54 for one subinvestigator participating in study SKY0401-12b. The investigators who could not be contacted did not enroll a sufficient number of subjects to bias the outcome of the investigation. Furthermore the study design relied upon objective measurements of supplemental pain medication using patient controlled analgesia. The patients were able to administer supplemental pain medication at any hour of the day depending upon their symptoms. It would have been difficult for investigators to introduce bias into assessment of the primary efficacy variable.

## 1.4 DESCRIPTION OF DATA SOURCES

### 1.4.1 Sources of Clinical Data

The primary source data were the study reports and datasets submitted with the sponsor's new drug application.

The following table lists the studies primarily evaluated for determination of efficacy of SKY0401. Evaluation of safety was based primarily upon review and analysis of the sponsor's dataset submitted with the ISS, but the adverse event tables for the remaining studies were reviewed individually. Narratives of serious adverse events reported were also reviewed for each patient.

Table 1.4-1 Listing of Controlled Clinical Trials

Study	Study Design	Treatment Arms and Number of randomized patients (n)	Primary measure of efficacy
SKY0401-009	Hip Arthroplasty Pain, Phase 2, R/DB/PC	<ul style="list-style-type: none"> <li>•SKY0401 10 mg (35)</li> <li>•SKY0401 20 mg (32)</li> <li>•SKY0401 30 mg (26)</li> <li>•Placebo (27)</li> </ul>	Total intravenous fentanyl usage over 48 hours post-dose
SKY0401-011	Hip Arthroplasty Pain Phase 3, R/DB/PC	<ul style="list-style-type: none"> <li>•SKY0401 15 mg (50)</li> <li>•SKY0401 20 mg (49)</li> <li>•SKY0401 25 mg (46)</li> <li>•Placebo (49)</li> </ul>	Total intravenous fentanyl usage over 48 hours post-dose
SKY0401-12b	Lower Abdominal Surgery Pain, Phase 3, R/DB/DC	<ul style="list-style-type: none"> <li>•SKY0401 5 mg (86)</li> <li>•SKY0401 10 mg (70)</li> <li>•SKY0401 15 mg (84)</li> <li>•SKY0401 20 mg (79)</li> <li>•SKY0401 25 mg (83)</li> <li>•Unencapsulated morphine 5 mg (85)</li> </ul>	Total intravenous fentanyl usage over 48 hours post-dose
SKY0401-15	Cesarean Section Pain, Phase 2,	<ul style="list-style-type: none"> <li>•SKY0401 5 mg (19)</li> <li>•SKY0401 10 mg (19)</li> </ul>	Total supplemental opioid analgesic

Study	Study Design	Treatment Arms and Number of randomized patients (n)	Primary measure of efficacy
	R/DB/AC	•SKY0401 15 mg (19) •Unencapsulated morphine 5 mg (18)	medication (IV or PO) used through 48 hours post-dose
SKY0401-17	Knee Arthroplasty Pain, Phase 3, R/DB/AC	•SKY0401 20 mg (51) •SKY0401 30 mg (58) •IV PCA morphine (55)	Time weighted pain intensity recall score averaged over 44 hours

R/DB/PC: randomized, double-blinded, placebo controlled. DC: dose controlled. AC active controlled. The patients in group termed "IV PCA" by the sponsor in Study SKY0401 were treated with a sham epidural followed by IV PCA.

Reviews conducted of individuals studies submitted under IND 52,113 were used to confirm protocol amendments. A search of the Agency adverse event database between 1999 and 2003 was conducted for adverse events reported with use of epidural morphine.

#### 1.4.2 Literature Search

The medical literature was reviewed to confirm the sponsor's use of equivalent dose calculations for various opiates administered to patients as alternative forms of supplemental pain management.

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On Original

## 1.5 INDIVIDUAL REVIEW OF STUDIES FOR EFFICACY

### 1.5.1 Study 009, Hip arthroplasty:

This Phase 2, multicenter, randomized, double-blind, parallel group, dose-ranging study evaluated the safety, efficacy, and pharmacokinetic profile of a single epidural dose (10, 20, or 30 mg) of sustained-release morphine (SKY0401) compared with SKY0401 placebo (SKY0401 DepoFoam particles without encapsulated morphine) for the treatment of post-operative pain in patients undergoing hip arthroplasty under general anesthesia.

#### 1.5.1.1 Findings vs. Labeling Claims

See Section, "REVIEW OF PACKAGE INSERT".

#### 1.5.1.2 Study Plan

##### 1.5.1.2.1 Population, Design, and Objectives

###### Objectives

- To determine the efficacy and duration of post-operative analgesic effect of various doses (10, 20, or 30 mg) of SKY0401 in patients having hip surgery 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 profile of serum morphine and morphine metabolites following epidural SKY0401 administration (selected centers only).

**Population:** N= 126 randomized, 120 in efficacy analysis

###### • Inclusion Criteria

1. Candidates for total hip arthroplasty
2. Men and women, 18-75 years of age. Females of childbearing potential must have been using appropriate contraception and have a negative pregnancy test.
3. Free of significant cardiovascular, renal, hepatic, respiratory hematological, endocrine, or neurological disease that might be expected to alter the response to opioids or increase the risk from the procedure.
4. American Society of Anesthesiologists (ASA) Classification: Class 1, 2, or 3.
5. Weight > 45 kg
6. Must remain hospitalized for 72 hours following surgery.
7. Capable of using a PCA device.
8. Capable of speaking and understanding the English language and providing informed consent.

• **Exclusion Criteria**

1. Complicated hip fracture, defined as a hip fracture associated with another major fracture, other major injury, substantial soft-tissue trauma, infection, clinically significant hemorrhage, neurological complications, or any other conditions that could increase the risk of surgery or opiate therapy.
2. Documented history of allergic or idiosyncratic reactions to study medications.
3. Pregnant or breast-feeding.
4. AST, ALT or bilirubin > 3 x upper limit of normal.
5. BUN or creatinine >3 x upper limit of normal.
6. Clinical or laboratory evidence of any coagulopathy.
7. History of chronic narcotic therapy, controlled-substance abuse, or alcoholism.
8. Morbidly obese.
9. Administration of an investigational drug within 30 days of start of study.
10. Any contraindication to epidural administration of drugs.
11. Unwilling or unable to cooperate with the study procedures.
12. Any other condition which, in the opinion of the Investigator, would interfere with the evaluation of the subject.

**1.5.1.2.2 Design**

A minimum of 120 patients (30 per treatment group) undergoing hip arthroplasty performed under general anesthesia were randomized to be in a 1:1:1:1 ratio to receive one of the following: SKY0401 placebo (SKY0401 DepoFoam particles without morphine sulfate), or 10, 20, or 30 mg SKY0401. SKY0401 or SKY0401 placebo was administered epidurally prior to the induction of general anesthesia and approximately 30 minutes prior to the start of surgery.

Standardization of the general anesthetic technique was to include the use of intravenous (IV) etomidate, thiopental, or propofol for induction, IV fentanyl as narcotic, midazolam, oxygen, and isoflurane, and a muscle relaxant. The total amount of intra-operative IV fentanyl used during general anesthesia was to be limited to a maximum of 500 mcg and a bolus of IV fentanyl near the end of surgery was prohibited.

Post-operatively, all patients were instructed to initially request fentanyl when their pain changed from mild to moderate. At that time, a dose of 25-mcg fentanyl was to be administered to patients with moderate or severe pain and could be repeated until satisfactory pain relief was achieved. Subsequently, patients were permitted to self-administer IV fentanyl via a PCA pump (programmed to deliver boluses of 10 to 20 mcg per dose with a lockout time of 6 minutes) until satisfactory pain relief was achieved. The bolus dose was allowed to be increased, supplemented with additional doses, or if required, a basal infusion rate added for pain management.

Fentanyl usage was to have been quantified through 48 hours after study drug administration. Patient-rated assessments of pain intensity at rest and with activity (visual analog scale and categorical scale) were obtained at the time of first request for fentanyl (at rest only), and at 2, 3, 4, 6, 8, 10, 12, 18, 24, 30, 36, 48, and 72 hours post-dose.

Patient-determined overall rating of study medication was assessed at 24, 48, and 72 hours post-dose.

#### 1.5.1.2.3 Treatment Summary

- **Description of Study Drug**

SKY0401 was formulated as a sterile, non-pyrogenic, white to off-white, preservative-free, homogenous suspension of morphine encapsulated into multivesicular lipid-based particles (DepoFoam drug delivery system) intended for epidural use only. SKY0401 was provided in 2-mL single-use amber glass vials.

Placebo used for this study (referred to as SKY0401 placebo) contained DepoFoam particles in preservative-free 0.9% normal saline without the active ingredient, morphine, and was to have been supplied in 2-mL, single-use amber glass vials.

- **Treatment Assignment**

Patients were to be randomly assigned in a 1:1:1:1 ratio to one of the following four treatment groups: 10, 20, or 30 mg of SKY0401 or SKY0401 placebo. Randomization was blocked within each study site. Sealed envelopes with a description of the randomized treatment enclosed were provided to each pharmacy for each study site. Envelopes were labeled sequentially by patient number and were opened by the pharmacist prior to preparation of the study drug. The pharmacy provided the anesthesiologist with the appropriate blinded treatment assignment according to the contents of the randomization envelope.

- **Preparation of Study Drug**

Study drug was prepared by an unblinded pharmacist according to the randomization code provided. SKY0401 was diluted with injectable, preservative-free 0.9% normal saline to a total volume of 5 mL.

- **Blinding**

SKY0401 and SKY0401 placebo were visually identical. Study drug was prepared by an unblinded pharmacist not involved with performing patient assessments. Study patients and all study site personnel involved in the observation and reporting of patient responses, including the anesthesiologist and the individual conducting pain assessments, were blinded to patients' treatment assignments.

- **Administration of Study Drug**

The pharmacist provided the anesthesiologist with the appropriate dose prepared as described in the study protocol. The epidural dose of SKY0401 was prepared as a standardized volume of 5 mL. The drug suspension was to be gently mixed immediately prior to injection. Study drug was administered epidurally into a lumbar vertebral space in all patients, either via an epidural needle or catheter, within 30 minutes prior to the initiation of surgery. The lumbar vertebral space was first identified and anesthetized using 1-% lidocaine. An epidural needle or catheter was advanced through the lumbar

vertebral space until the epidural space was identified using a loss of resistance technique. If an epidural catheter was to be used, the catheter was inserted and advanced 3 to 4 cm into the epidural space. To assure that the needle or catheter was located in the epidural space (rather than positioned intrathecally or intravenously), a test dose of 3 mL of 2% lidocaine with 1:200,000 epinephrine was injected. Inadvertent intravascular injection was ruled out by a lack of a hypertensive and/or tachycardic response to epinephrine. Inadvertent intrathecal injection was ruled out by a lack of sensory block produced by the lidocaine within 3 to 5 minutes of injection. Provided that both intravascular and intrathecal injection had been ruled out by the test dose, the full dose of study drug was then administered via the epidural needle or catheter as a 5-mL bolus over 15 seconds.

- **Conduct of Anesthesia**

Intra-operative general anesthesia was to include the use of IV etomidate, thiopental, or propofol for induction, fentanyl as a narcotic, midazolam, oxygen, isoflurane, and a muscle relaxant. The total amount of fentanyl used intra-operatively was limited to a 500-mcg bolus. Administration near the end of surgery was discouraged.

Post-operatively, all patients were instructed to request analgesic medication when their pain changed from mild to moderate. At that time, an initial dose of 25 mcg of fentanyl was administered to patients with moderate or severe pain, and was repeated until satisfactory pain relief was obtained. The date, time, and first post-operative dose of fentanyl were recorded on the appropriate Case Report Form. Subsequent doses of fentanyl were administered by a PCA pump programmed to deliver fentanyl 10 to 20 mcg per dose with a lockout time of 6 minutes. The dose could be increased, supplemented with additional doses, or if required, a basal rate added to control pain.

The total fentanyl usage during each successive 6-hour interval following study drug administration was recorded through 48 hours. Patients were to receive supplemental IV fentanyl PCA as needed to control post-operative pain through 48 hours post-dose. At the discretion of the investigator, patients could receive alternative analgesic therapies after 48 hours. However, patients were to be maintained on IV PCA fentanyl if they still required a parenteral narcotic agent. Use of hypnotics or sedatives was permitted at bedtime only after all pain assessments had been completed for the day. Narcotic antagonists (e.g., naloxone) was to be used if non-narcotic agents failed in the management of the opiate-related adverse event. All medications were to be recorded on the Concomitant Medications Case Report Form. Prohibited medications included all analgesic or anti-inflammatory agents for 48 hours following study drug administration (except acetaminophen for fever or headache and aspirin up to 325 mg daily for platelet inhibition). The use of sedating antihistamines, tranquilizers, anti-anxiety agents, and antidepressant medications was discouraged but left to the discretion of the investigator.

1.5.1.2.4 Planned Assessments

Table 1.5.1-1 Schedule of Assessments Study 009

Parameter	Screening <sup>a</sup>	0 - <24 hr post-dose	≥ 24-47 hr post-dose	≥ 48-71 hr post-dose	≥ 72 hr post-dose
Informed Consent	X				
Medical History	X				
Physical Examination	X				
Hematology, Serum Chemistry, Urinalysis	X	Pre-dose <sup>b</sup>	24 hr	48 hr	72 hr
Temperature	X	Pre-dose <sup>b</sup>	24 hr	48 hr	72 hr
Respiratory Rate	X	Pre-dose <sup>b</sup> , 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18 hr	24, 30, 36 hr	48 hr	72 hr
Blood Pressure and Heart Rate	X	Pre-dose <sup>b</sup> , 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18 hr	24, 30, 36 hr	48 hr	72 hr
ECG		Pre-dose <sup>b</sup> , continuous during surgery, and 0.5, 1, 1.5 and 2 hr			
Pulse Oximetry		Pre-dose <sup>b</sup> , 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18 hr	24, 30, 36 hr	48 hr	72 hr
Capnometry		Pre-dose <sup>b</sup> , 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18 hr	24, 30, 36 hr	48 hr	72 hr
Pain Intensity Assessments (VAS and CAT)		2, 3, 4, 6, 8, 10, 12, 18 hr	24, 30, 36 hr	48 hr	72 hr
Overall Study Medication Rating			24 hr	48 hr	72 hr
Administer Study Drug		X			
Pain Meds		First request, IV PCA fentanyl and/or narcotic pain medications through 48 hours post-dose	X		
PK Samples		Pre-dose <sup>b</sup> , 0.5, 2, 4, 8, 12, 18 hr	24 h	48 hr	72 hr
Adverse Event Evaluation		X	X	X	X

<sup>a</sup> Within 14 days prior to study drug administration

<sup>b</sup> Pre-dose 5 to 15 minutes prior to study drug administration

From Sponsor's Protocol SKY0401-009, Time and Events Schedule, page 24

### 1.5.1.2.5 Analysis Plan

#### Efficacy Endpoints

- **Primary Efficacy Endpoint**

The primary efficacy variable for this study was the total fentanyl usage over 48 hours following administration of study drug. The total amount of fentanyl used by each patient was to be recorded by 6-hour intervals and the total amount used through 24 and 48 hours post-dose was to be calculated. Both “total fentanyl” (including that used during surgery), and “post-operative fentanyl” summations were to have been calculated.

To explore possible effects due to patients withdrawing prematurely from the study or due to the use of alternative pain control medications post-operatively, estimates of total narcotic use were also calculated. Total narcotic medication use through 48 hours post-dose was computed by first adjusting the actual fentanyl used during each 6-hour interval based on the use of any alternative narcotic medications during the period. For those patients who received an alternative opioid medication during a 6-hour interval the total amount of narcotic used was estimated by converting any alternative narcotic medications received to an equi-analgesic amount of fentanyl using standard conversion factors described by Reisine and Pasternak in Opioid Analgesics and Antagonists, in The Pharmacological Basis of Therapeutics (eds. Hardman, Limbird, Molinoff, Ruddon, Gilman), McGraw Hill, 1996, p.521-555.

- **Secondary Efficacy Endpoints**

- Proportion of patients receiving no fentanyl (or no narcotic medication) from 0-24, > 24-48, and 0-48 hours.
- Time between the dose of study drug and first dose of fentanyl (or first dose of narcotic medication).
- Time between recovery room arrival and first dose of fentanyl to control post-operative pain.
- Resting pain intensity (visual analog scale and categorical scale) at the time of the first dose of fentanyl (or other narcotic medication).
- Pain intensity at rest and with activity (using the visual analog scale and categorical scale) at 2, 3, 4, 6, 8, 10, 12, 18, 24, 30, 36, 48, and 72 hours post-dose.
- Patient-rated overall assessment of study medication at 24, 48, and 72 hours post-dose.

Evaluations made post-operatively were to be considered on-schedule if they were performed during the following windows post-dose:

Scheduled Time Points Window

2, 3, and 4 hours ± 30 minutes

6, 8, 10, and 12 hours ± 60 minutes

18, 24, 30, and 36 hours ± 120 minutes

48 and 72 hours ± 240 minutes

Any assessment obtained outside the above time windows was to be considered off-schedule. Data from missing or off-schedule assessments were to be handled as follows:

- Data for off-schedule or missing observations between two known values were to be interpolated linearly.
- Data at the end of a series (e.g., pain intensity scores at 72 hours post-dose) that were off schedule and early or that were missing were to be extrapolated using the last observation carried forward (LOCF).

- **Sample Size Calculation**

The study was to have the 30 patients per treatment group. The sample size for the study was based on two previous studies in post-surgical patients (protocol 9-10). A sample size of 30 patients per treatment group provides 89% power to detect a difference in means of 410 mcg (i.e., a 50% reduction in 24 hour fentanyl usage), assuming a SKY0401 placebo mean of 820 mcg fentanyl and a common standard deviation of 490 mcg, using a two group t-test with a 0.05 two-sided significance level.

- **Study Populations**

Analysis of efficacy was to have been based on the intent-to-treat population. Validity for each patient in the analysis was to have been determined solely by the availability of data for the parameter under analysis.

In the event that a patient did not complete the study, all study procedures listed for the 72-hour evaluation were to have been completed at the time of discontinuation along with the reason for the discontinuation.

Reasons for discontinuation specified by the protocol included:

1. Failure of study medications (C0401 and fentanyl PCA) to provide sufficient analgesic activity during the first 48 hours.
2. Adverse Event
3. Patient desire to withdraw; permitted at any time
4. Determination that continued participation in the study would not be in the best interest of the patient.

If any patient had withdrawn from the study prior to 24 hours post-dose, the projected total fentanyl use through 24 hours was to be computed. This estimate was to be calculated by computing the average narcotic used per hour over the final 6-hour interval in which narcotic use was recorded, multiplying this average by the difference between 24 hours and the actual number of hours for which narcotic use was recorded, and adding this to the total narcotic use through 24 hours. A similar procedure was to be used to calculate projected 48-hour fentanyl use for each patient.

- **Interim Analyses**

The protocol prespecified that one interim analysis was to be performed following completion of approximately 60 patients (approximately 15 patients per treatment group) solely to confirm the sample size for this study (per ICH Guideline E9) and to plan future studies. There were no intentions or plans for early termination of the study based upon achieving predefined criteria.

### **1.5.1.3 Amendments:**

#### **1.5.1.3.1 Amendment 01: 24 September 1998**

- The original protocol had specified that eligible patients were only those undergoing primary total hip arthroplasty. This amendment expanded eligibility to also include patients undergoing revisions of previous hip arthroplasty or hemiarthroplasty. These three pain models are considered to be similar.
- Administrative changes and statistical clarification

#### **1.5.1.3.2 Amendment 02: 8 July 1999**

- Serum sampling for pharmacokinetic analysis was deleted.
- Temperature was added to the Study Procedures and to the Time and Events Schedule.
- The major change to the planned statistical analysis was the following:  
Study sites were incorporated into the ANOVA models used to test the primary efficacy endpoints, resulting in the use of two-way ANOVA models instead of one-way models. Because many sites enrolled only small numbers of patients, 3 “pseudo-sites” were created for the purposes of the two-way ANOVA models. The ANOVA models used 7 sites total (3 pseudo-sites and 4 stand-alone sites). This pooling of sites was done in an unbiased way.
- Administrative changes and statistical clarification

### **1.5.1.4 Study Conduct**

#### **1.5.1.4.1 Patient Disposition**

A total of 126 patients were enrolled in the study between 29 June 1998 and 10 August 1999; data collection was completed on 17 September 1999. Sixteen study sites participated in the study; of the 16 sites, 13 enrolled at least one patient. The maximum number of patients enrolled at one site (site 04) was 25 patients. Of the 126 patients enrolled, 120 received study drug: SKY0401 (10 mg, n = 35; 20 mg, n = 32; and 30 mg, n = 26) and 27 received SKY0401 placebo. Six patients were randomised but did not

receive study drug. These patients were not included because they either had a surgical procedure different than that specified in the protocol or the study procedures could not be complied with.

One patient (03-004) was randomised to placebo but received 10-mg SKY0401 due to pharmacy error. This patient was analysed as part of the 10-mg SKY0401 group for all efficacy analyses except for the “intent-to-treat” primary efficacy analysis, in which he was analysed as part of his group of randomisation (placebo).

Six patients prematurely withdrew from the study after 48 hours, but prior to completing the entire 72-hour study period. The sponsor reported that none of these patients were withdrawn due to an adverse event. All of these patients were included in the efficacy analysis. Three patients were discontinued because of hospital administrative procedures and another patient was discharged before study procedures could be completed. One patient (2-004) was discontinued because of post-operative confusion attributed to preexisting post-traumatic stress disorder and claustrophobia and the remaining patient (2-007) because of inadequate pain control.

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Table 1.5.1-2 Disposition of Patients: Study 009

	Treatment Group					Total
	Placebo	SKY0401, 10 MG	SKY0401, 20 MG	SKY0401, 30 MG		
Patients Randomized	29	36	33	28	126	
Patients Randomized and Receiving Study Drug Dose	27	35	32	26	120	
Patients Included in Safety Analysis	27	35	32	26	120	
Patients Included in Efficacy Analyses:						
Per Protocol	27	35	32	26	120	
Intent to Treat	28	34	32	26	120	
Reason for Termination						
Study Completion	27 (96.4%)	31 (91.2%)	32 (100.0%)	24 (92.3%)	114 (95.0%)	
Insufficient Analgesic Effect	0	0	0	0	0	
Adverse Event	0	0	0	0	0	
Patient Request	1 (3.6%)	3 (8.8%)	0	1 (3.8%)	5 (4.2%)	
Other	0	0	0	1 (3.8%)	1 (0.8%)	

From sponsor's report on SKY0401-009, Section 15-2, Table 1.

#### Protocol Violations:

A few patients enrolled in the study underwent partial hip arthroplasty rather than a total hip arthroplasty prior to Amendment 01, which permitted these related hip procedures. Patients 06-006 and 04-014 were randomized and administered 10 and 20 mg SKY0401, respectively, but were noted during surgery to have an infected hip. Both patients did not undergo a revision to previous hip arthroplasty as planned; however, the orthopedic hardware was removed and both successfully completed the study. One patient (02-001, 20 mg SKY0401) with a history of narcotic abuse was enrolled, in violation of the exclusion criterion.

The protocol stated that study drug should be administered within 30 minutes of the start of surgery. However, the mean time from dosing to start of surgery was 0.8 hours and was > 30 minutes in 82% of all patients, usually because the surgery began slightly later than expected.

Patients requesting additional pain medication during the first 48 hours following study drug administration were only to receive IV fentanyl via PCA. In contradiction to the protocol, approximately 10% of patients (3, 6, 0, and 5 patients administered placebo, 10, 20 and 30 mg of SKY0401, respectively) received a narcotic pain medication other than fentanyl (e.g., oral oxycodone or hydrocodone) prior to 48 hours. The contribution of alternatives to fentanyl to the total supplemental narcotics received was small and did not appear to bias the conclusion. Conversion to a fentanyl equivalent dose was employed when alternative narcotics were used. (Reisine and Pasternak in Opioid Analgesics and Antagonists, in The Pharmacological Basis of Therapeutics (eds. Hardman, Limbird, Molinoff, Ruddon, Gilman), McGraw Hill, 1996, p.521-555.)

Evaluations at some time points may not have been performed if the patient was asleep, somnolent, or unavailable.

#### 1.5.1.4.2 Demographics/Group Comparability

A total of 120 patients, 62 (52%) men and 58 (48%) women received study drug. Their mean age was 56 years (range 18 to 75 years). Thirty-eight (32%) patients were at least 65 years of age. Of the patients receiving study drug, 96 (80%) were Caucasian, 19 (16%) were black, and 4 (3%) were Hispanic. Mean patient weight was 80.5 kg (range 45 to 123 kg). The majority of patients was ASA Class 2 (67%) and had degenerative joint disease as the reason for surgery (89%). Baseline characteristics were generally similar among treatment groups.

The majority of patients (72%) had a primary total arthroplasty performed. The mean duration of surgery was 2.2 hours (range 1 to 6 hours) and the mean time from study drug dosing to arrival in the recovery room was 3.3 hours (range 1 to 9 hours); these time periods were similar across treatment groups.

Study drug was administered epidurally into a lumbar interspace in all patients, either via epidural needle injection or epidural catheter, prior to the initiation of surgery.

An epidural catheter was used for study drug delivery in 53% of patients. These patients had an epidural catheter in place for a mean of 2.0 hours (range 0 to 21.6 hours). The epidural catheter tip was found to be intact after it was removed in all these patients. Study drug was administered at L2-L3 in 37% of patients, L3-L4 in 58% of patients, and at other locations in 5% of patients.

The most frequently used classes of concomitant medications were consistent with medications administered peri- and post-operatively. In addition to general anesthetics, those medications included the following: muscle relaxants (93%), cephalosporins (90%), laxatives and stool softeners (86%), anticoagulants (82%), local anesthetics (82%), mild analgesics (primarily acetaminophen) (70%), antiemetics (68%), antispasmodics and anticholinergics (57%), parasympathomimetics (53%), antianemic agents (50%), and antihistamines (primarily diphenhydramine) (50%).

The total duration of hospitalization and the time from dosing to discharge were comparable across the treatment groups. For all patients, the median duration of hospitalization was 5.0 days (range 4 to 54 days).

Exposure across demographic groups was a sufficient reflection of clinical practice to permit evaluation of efficacy of SKY0401. The distribution of racial groups was skewed because small numbers of patients from races other than Caucasians were studied, however neither the disease process, concurrent medical conditions nor the analgesic effect of morphine is expected to vary significantly according to racial groups.

#### **1.5.1.4.3 Interim Analysis**

An interim analysis was performed on 55 patients. A blinded interim analysis results summary, prepared by the third-party consulting group, was supplied to SkyePharma Inc. The results of the interim analysis confirmed the original sample size calculations; therefore, no changes were made to the study protocol or sample size based upon this interim analysis.

#### **1.5.1.5 Sponsor's Efficacy Results**

##### **1.5.1.5.1 Primary Efficacy Variables**

A single epidural dose of SKY0401 resulted in a dose-related reduction in the subsequent use of narcotic pain medication. A per protocol analysis (in which Patient 03-004 is analyzed as treated in the SKY0401 10-mg group) yielded comparable results to the ITT analysis.

Each of these analyses showed a progressive dose-related reduction in fentanyl use across the placebo, 10-, 20-, and 30-mg SKY0401 treatment groups. In every case, the ANOVA treatment effect analysis was statistically significant ( $p = 0.023$  to  $< 0.001$ ), as was the dose-response analysis by the Jonckheere-Terpstra test ( $p < 0.001$  for all showed statistically significant ( $p < 0.05$ ) differences between all three SKY0401 treatment groups and the placebo group for the 0 to 24-, and 0 to 48-hour intervals analyses of post-dose and post-operative fentanyl and total narcotic usage.

Total fentanyl and narcotic pain medication usage are summarized in Table 1.5.1-3, analyzed on an intent-to-treat basis, with Patient 03-004 analyzed as part of the placebo group.

Table 1.5.1-3 Total Fentanyl and Narcotic Usage (mcg) Intent-to-Treat Analysis, Study 009.

Time	Placebo (n = 28)	10 mg SKY0401 (n = 34)	20 mg SKY0401 (n = 32)	30 mg SKY0401 (n = 26)	P-value <sup>3</sup>
<i>Fentanyl Usage</i>					
Mean Usage 0 to 24 h	1548.4	599.3	395.5	361.3	<0.001
Mean Usage > 24 to 48 h	885.3	721.9	509.7	290.8	0.023
Mean Usage 0 to 48 h	2433.7	1321.2	905.2	652.1	<0.001
<i>Total Narcotic Usage<sup>2</sup></i>					
Mean Usage 0 to 24 h	1548.4	599.3	395.5	361.3	<0.001
Mean Usage > 24 to 48 h	897.2	772.5	509.7	345.5	0.025
Mean Usage 0 to 48 h	2445.6	1371.7	905.2	706.8	<0.001

1. Patient 03-004 is analyzed as part of the placebo group (group of randomization) for this "intent-to-treat" analysis.

2. Adjusted for use of other narcotic medications

3. Two-way analysis of variance (ANOVA) where main effects are treatment group and study site.

From Sponsor's Study Report SKY0401-009, Table 11.2.1.1, Efficacy Analysis, page 34.

### 1.5.1.5.2 Secondary Efficacy Variables

- Proportion of patients receiving no fentanyl (or no narcotic medication) from 0-24, > 24-48, and 0-48 hours.

The sponsor evaluated the percentage of patients using no post-operative fentanyl with increasing SKY0401 dose.

Table 1.5.1-4 Patients Receiving No Postoperative Fentanyl, Study 009

Post-operative Time	Placebo (n=27)	10 mg SKY0401 (n=35)	20 mg SKY0401 (n=32)	30 mg SKY0401 (n=26)	p-value <sup>1</sup>
0-24 hours	1 (3.7%)	7 (20.0%)	13 (40.6%)	11 (42.3%)	0.001
0-48 hours	1 (3.6%)	2 (5.7%)	5 (15.6%)	7 (26.9%)	0.042

\* Fisher's Exact Test

From sponsor's Table 11.2.2.1, Study report SKY0401-009, page 35.

- Time between the dose of study drug and first dose of fentanyl (or first dose of narcotic medication).

The time to first use of fentanyl to control post-operative pain was significantly longer for patients administered SKY0401 compared to placebo.

Table 1.5.1-5 Time to First Dose of Post-Operative Fentanyl (Hours), Study 009

	Placebo (n = 27)	10 mg SKY0401 (n = 35)	20 mg SKY0401 (n = 32)	30 mg SKY0401 (n = 26)	p-value*
<i>Time Post-Dose for First Post-Operative Fentanyl Usage</i>					
Median	3.2	13.5	24.8	16.1	<0.001
Range	1.6-6.2	2.1-41.7	31.5-45.5	3.3-45.5	
<i>Time Between Recovery Room Arrival and First Fentanyl Usage</i>					
Median	0.3	10.0	21.1	12.8	<0.001
Range	0.0-1.7	0.1-38.3	0.0-42.6	0.4-41.9	

\*p-value based on Log-Rank test for equality of product-limit survival curves.

From sponsor's Table 11.2.3.1, Study report SKY0401-009, page 35.

- Time between recovery room arrival and first dose of fentanyl to control post-operative pain.

The time to first use of fentanyl to control post-operative pain was significantly longer for patients administered SKY0401 compared to placebo. See Table 1.5.1-5.

- Resting pain intensity (visual analog scale and categorical scale) at the time of the first dose of fentanyl (or other narcotic medication).

Mean VAS and CAT pain intensity (resting) at the time of the first request for pain medication were lower for patients administered SKY0401 compared to placebo (p < 0.001). VAS was scored from 0= no pain to 100= most severe pain possible. CAT scores were coded as 0=1 to 1= mild, 2=moderate and 3= severe.

Table 1.5.1-6: Pain Intensity Score at First Request (Rest), Study 009

1 <sup>st</sup> Request	Placebo (=27)	10 mg SKY0401 (n=35)	20 mg SKY0401 (n=32)	30 mg SKY0401 (n=26)
VAS Mean	75	49	38	51
N	19	27	23	12
CAT Mean	2.5	1.8	1.7	1.7
N	26	30	26	16

Data was abstracted from the sponsor's Table 11.3.1, Study report SKY0401-009, page 36

- Pain intensity at rest and with activity (using the visual analog scale and categorical scale) at 2, 3, 4, 6, 8, 10, 12, 18, 24, 30, 36, 48, and 72 hours post-dose.

The sponsor reported that VAS and CAT pain intensity ratings were also lower for SKY0401 patients compared to placebo patients from 3 through 18 hours post-dose (p ≤ 0.003 at each time point). Differences in resting VAS scores after 18 hours were not significantly different among treatment groups. Resting CAT scores at 24 hours were

significantly lower for SKY0401 groups than the placebo patients ( $p = 0.032$ ); the differences after 24 hours were not significant.

Relative mean VAS and CAT pain intensity values with activity showed similar results to the results seen at rest. Both the VAS and CAT scores with activity were significantly lower in the SKY0401 treatment groups than the placebo group.

Patients in all treatment groups were permitted to self-titrate supplemental pain medication to optimize pain relief, therefore pain intensity ratings reflect the level of pain in patients having post-operative narcotic essentially available *ad lib* with or without SKY0401 pretreatment in the background.

- Patient-rated overall assessment of study medication at 24, 48, and 72 hours post-dose. Patient ratings were statistically significantly higher in the SKY0401 treatment groups compared to the placebo group at 24 and 48 hours post-dose ( $p < 0.001$  and  $p = 0.021$  at 24 and 48 hours, respectively), but not at 72 hours ( $p=0.303$ ).

#### **Additional Analysis:**

A subgroup analysis was performed looking at the primary endpoint of fentanyl usage at the 4 highest enrolling clinical sites (04, 08, 06, 12). A dose-dependent reduction in the post-operative use of fentanyl for SKY0401 compared to placebo was generally observed.

#### **1.5.1.6 REVIEWER'S COMMENTS**

This Phase 2 study in 120 patients was designed to evaluate the analgesic efficacy of 10 mg-, 20-mg and 30-mg SKY0401 compared with placebo in the setting of hip arthroplasty. The protocol amendment September 24, 1998 expanded inclusion criteria to accept patients undergoing revisions of previous hip arthroplasty or hemiarthroplasty. One patient who was treated with a hemiarthroplasty before the amendment was approved was included in the analysis, but did not affect the conclusion. Statistical amendment (July 8, 1999) to the protocol was made before the blind was broken and did not affect the analysis. Of the 126 patients enrolled, 6 patients did not receive study drug and were not included in the efficacy analysis. Six additional patients withdrew from the protocol after completing the first 48 hours. These patients were included in the efficacy analysis. This reviewer determined that the study conduct reflected the protocol despite minor variances and was adequate to analyze efficacy of SKY0401.

The sponsor was able to demonstrate a statistically significant reduction in supplemental fentanyl, the primary efficacy endpoint, among each of the dose groups treated with SKY0401 compared with placebo. The study was powered to detect a 410 mcg difference in supplemental fentanyl with an anticipated mean dose of 820 mcg to be given to the placebo group. Moreover, the difference in fentanyl administered was also clinically relevant. For example, in the first 48 hours the mean fentanyl received by patients treated with placebo was 2434 mcg compared with a mean of 1321 mcg in the group treated with 10 mg of SKY0401. This is a reduction of 22 mL of fentanyl at 50mcg/mL, a very large dose in clinical practice.

The amount of supplemental fentanyl was reduced in a manner that was dependent on the dose of SKY0401 administered. Statistically significant differences were reported by the sponsor between 10-mg, 20-mg and 30-mg doses of SKY0401, but the difference in supplemental fentanyl was smaller with increasing dose. For example, the mean difference in supplemental fentanyl between 10-mg and 20-mg doses of SKY0401 was 416mcg (8.3 mL) given over 48 hours, but the difference between 20 mL and 30 mL of SKY0401 was about 253 mcg (5 mL).

Analysis of secondary endpoints supported a finding of efficacy for SKY0401. A small, increasing number of patients with increasing dose of SKY0401 required no supplemental fentanyl. Patients treated with SKY0401 exhibited a longer latency before requiring supplemental fentanyl than patients treated with placebo for treatment of postoperative pain. Pain scores (VAS and CAT) were lower in patients treated with SKY0401 than placebo at the first request for supplemental pain medication and remained lower for 18 hours. Patients rated pain control with SKY0401 better than with placebo at 24 and 48 hours, but not 72 hours after administration. This finding further supports the sponsor's contention that SKY0401 has a therapeutic effect from 0 to 48 hours.

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### 1.5.2 Study 011, Hip arthroplasty:

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

#### 1.5.2.1 Findings vs. Labeling Claims

See Section, "REVIEW OF PACKAGE INSERT".

#### 1.5.2.2 Study Plan

##### 1.5.2.2.1 Population, Design, and Objectives

**Objective:** To confirm the efficacy of SKY0401 in the management of post-operative pain following hip arthroplasty.

**Population:** N=200 randomized, 194 in efficacy analysis

- **Inclusion Criteria:**

1. Males and females aged  $\geq 18$  years at Screening.
2. Females of child-bearing potential must have a negative urine beta-hCG pregnancy test performed during Screening. Females are eligible only if they are not pregnant or lactating, are either post-menopausal or surgically sterile, or, if of child-bearing potential, using an acceptable means of contraception for  $\geq 1$  month prior to Screening, including any of the following:
  - Oral contraceptives
  - Implantable (e.g., Norplant) or injectable contraceptive (e.g., Depo-Provera)
  - Barrier methods (e.g., condoms with spermicide)
  - IUD
  - Lifestyle with a personal choice of abstinence
  - Non-heterosexual lifestyle
  - Vasectomy of sexual partner.
3. Undergoing unilateral hip arthroplasty (indications may include, but are not limited to, the following: osteoarthritis, rheumatoid arthritis, avascular necrosis, non-pathologic fracture) under general or regional (intrathecal) anesthesia including:
  - Primary total arthroplasty
  - Hemiarthroplasty
  - Revision of a previous hip arthroplasty.
4. American Society of Anesthesiology (ASA) Physical Class 1, 2, or 3
5. Willing and able to use a PCA pump.
6. Willing to only receive IV fentanyl for 48 hours post-dose to control post-operative pain.
7. Expected and willing to remain hospitalized for a minimum of 48 hours post-dose.

8. Capable of speaking and understanding English sufficiently to provide written informed consent and responses to pain assessment scales and neurological assessment questionnaires.

• **Exclusion Criteria**

1. Morbid obesity, defined as a body mass index (BMI) =40. BMI is calculated as follows:  
(weight [lbs.] ÷ height [inches]<sup>2</sup>) x 704.5.
2. Undergoing any of the following:
  - Bilateral hip arthroplasty
  - Current or previous hip arthroplasty secondary to metastatic cancer of the bone or Paget's Disease
  - Other concurrent surgical procedures (such as knee arthroplasty or vascular surgery) in addition to hip arthroplasty. (Note: bone grafting is allowed.)
3. Any complication following a previous hip arthroplasty and/or current risk factors (e.g., septic hip joint) which, in the opinion of the investigator, might increase the risk of surgery or complicate the patient's post-operative course.
4. Patients undergoing hip arthroplasty under epidural anesthesia.
5. Current or historical evidence of any clinically significant disease or condition that, in the opinion of the investigator, might increase the risk of surgery or complicate the patient's post-operative course.
6. Suspected or documented history of sleep apnea, narcolepsy, or excessive daytime sleepiness.
7. Female who is pregnant or lactating.
8. History of hypersensitivity or idiosyncratic reaction to opioid medications.
9. Any contraindication for the epidural administration of study drug (e.g., coagulopathy, local infection).
10. Administration of an investigational drug within 30 days prior to Screening.
11. Suspected or documented history of substance abuse and/or alcoholism.
12. Unwilling or unable to provide written informed consent and/or to comply with study procedures, including use of a PCA pump, completion of all patient-rated scales, and 30-day follow-up assessments.

**Design:**

The enrolled patients were to have undergone hip arthroplasty performed under general or regional (intrathecal) anesthesia randomized in a 1:1:1:1 ratio to receive one of the following: placebo (injectable, preservative-free 0.9% normal saline without DepoFoam particles), or 15, 20, or 25 mg SKY0401. SKY0401 or placebo was to have been administered epidurally prior to the induction of general or regional anesthesia at approximately 30 minutes prior to the start of surgery.

For both general and regional anesthesia patients, the total amount of intra-operative IV fentanyl use was to be recommended at a maximum of 250 mcg. A bolus of IV or IM fentanyl, or IM ketorolac near the end of surgery was to have been prohibited. Use of ketorolac was to have been prohibited through 48 hours after study drug administration. Patients were to have had a PCA pump set up within 30 minutes after

completion of surgery, and were not to be given control of the PCA pump until after the first request for pain medication. If a member of the study personnel (i.e., the blinded study coordinator or blinded Investigator) who was trained to perform assessments (VAS-R and CAT-R), confirmed that the patient initially had moderate to severe pain, the investigator was to administer an initial (25 mcg) bolus of IV fentanyl. After the first bolus dose of IV fentanyl, the PCA pump (equipped with a printer) was to have been connected to the patient's IV line and programmed to deliver on-demand boluses of IV fentanyl of 10 to 20 mcg per bolus, with a lockout interval of six minutes. A continuous infusion that delivered a background or basal rate of IV fentanyl was prohibited. If pain control was deemed inadequate by the Investigator or the patient, alteration of the bolus dose was to have been permitted as appropriate. Conversely, if pain control was deemed sufficient by the Investigator or the patient, the dose of 10 to 20 mcg per bolus could be titrated downwards. Narcotic medications other than IV fentanyl were not to be permitted intra-operatively through 48 hours post-dose. Concomitant medications were to be recorded for 48 hours post-dose.

Fentanyl usage was to have been be quantified through 48 hours after study drug administration. Pain intensity at rest was to have been assessed using both a Visual Analog Scale (VAS-R) and Categorical Scale (CAT-R) at the time of first request for fentanyl and at 4, 8, 12, 18, 24, 30, 36; and 48 hours post-dose. Activity scores and patient-rated evaluation of pain intensity with activity (VAS-A and CAT-A) were to have been assessed at 24 and 48 hours post-dose. Patient and surgeon ratings of pain control were to have been assessed on the mornings of Day 2 and Day 3.

#### **1.5.2.2.2 Treatment Summary**

- **Study Drug:**

SKY0401 was a sterile, non-pyrogenic, white to off-white, preservative-free, homogenous suspension of morphine encapsulated into multivesicular lipid-based particles (DepoFoam drug delivery system). SKY0401 was intended for epidural use only. Placebo was to have been injectable preservative-free 0.9% normal saline without DepoFoam particles or the active ingredient, morphine, and was to have been supplied (for use as both placebo and as diluent for SKY0401) by the hospital pharmacy.

- **Treatment Assignment**

Patients were to have been randomly assigned in a 1:1:1:1:1 ratio on Day 1 to one of the following four treatment groups: placebo, or 15, 20, or 25 mg of SKY0401. This randomization was to have been stratified by both type of anesthesia (regional and general) and by site. Study sites were to randomize each patient by calling a telephone-based computerized Central Randomization System. Once patient eligibility was confirmed, the patient was to have been randomized by the system, assigned a patient number, and assigned to a treatment group.

- **Preparation of Study Drug**

Study drug was to have been prepared by an unblinded pharmacist according to the treatment assignment. SKY0401 was to be prepared by dilution with injectable, preservative-free 0.9% normal saline to a total volume of 5 mL.

- **Blinding**

As SKY0401 and placebo were visually distinguishable, study drug was to have been administered by an unblinded anesthesiologist uninvolved with patient assessments and data collection. The clinical staff involved with the conduct of the study, and the patient was to remain blinded to the assigned treatment group.

- **Administration of Study Drug**

Study drug was to have been administered prior to induction of general anesthesia and regional (intrathecal) anesthesia and approximately 30 minutes prior to the start of surgery (defined as the time of the first incision).

A 3 mL test dose of local anesthetic (e.g., 3 mL of 1.5% lidocaine with 1:200,000 epinephrine) was to have been administered through the epidural needle or catheter (catheter inserted prior to test dose) followed by a 3 to 5 minutes period of observation to rule out an inadvertent intravascular or intrathecal injection.

- **Conduct of Anesthesia**

Except for narcotics there were no restrictions on administration of agents used for general anesthesia. A strong recommendation was to be given that long-acting pain medication was to be avoided 24 hours prior to incision. Neuromuscular blockade was to have been reversed as deemed appropriate by the anesthesiologist.

Regional (intrathecal) anesthesia was to have been managed by the intrathecal administration of bupivacaine (at a dose of 12.5 to 17 mg, with or without dextrose) in a lumbar intervertebral space different from that used to administer study drug.

For general and regional (intrathecal) anesthesia, the total amount of intra-operative analgesics administered was to have been no more than 250 mcg of IV fentanyl. No more than 100 mcg of fentanyl was to have been used during induction with subsequent boluses doses of 25-50 mcg to be given only as needed. Other intraoperative opioid analgesics were to be prohibited. A bolus of IV fentanyl or IM ketorolac "near the end of surgery" were to be prohibited.

SKY0401 was a slow-release formulation of morphine with effects due to continued release of morphine that could potentially persist for several days.

Patients were to have a PCA pump containing IV fentanyl set up within 30 minutes after completion of surgery. The patient was not to be given control of the PCA pump until after their first request for pain medication. Narcotic medications other than IV fentanyl were not to be permitted for 48 hours post-dose. Additionally, the following medications were to be prohibited through 48 hours post-dose:

- Formulations of fentanyl other than IV fentanyl (e.g., Duragesic<sup>®</sup>)
- Anti-inflammatory agents (e.g., ketorolac [Toradol<sup>®</sup>]) except for the following:
  - Acetaminophen - maximum of 650 mg/24 hours for fever or headache only;
  - Aspirin - maximum of 325 mg/24 hours for platelet inhibition.

- Cyclo-oxygenase inhibitor agents, including COX-2 specific inhibitors (e.g., celecoxib [Celebrex®] and rofecoxib [Vioxx®]).

The use of following medications were discouraged but were left to the discretion of the investigator:

- Benzodiazepines and other anti-anxiolytics;
- Anti-depressants (including tricyclics and serotonin-specific uptake inhibitors);
- Sedating anti-histamines;
- Any other medication that might cause sedation.

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#### **1.5.2.2.4 Analysis Plan**

##### **Primary Efficacy Endpoint**

The primary efficacy endpoint was stipulated to be the total amount of IV fentanyl usage through 48 hours post-dose.

##### **Secondary Efficacy Endpoints**

1. Time to first post-operative fentanyl use.
2. Proportion of patients receiving no fentanyl post-operatively.
3. Activity score: Captured at 24 and 48 hours (1 = sit up on bedside (feet hanging) with assistance. 2 = sit up on bedside (feet hanging) without assistance. 3 = stand with assistance. 4 = stand without assistance. 5 = walk with assistance. 6 = walk freely without assistance.)
4. Pain intensity evaluation using the visual analog scale: VAS ( 0 = no pain; 100 = most severe pain possible)
5. Pain intensity evaluation using the category scale: CAT (pain level = none, mild, moderate, or severe) scales
6. Patient rating of pain medication. (very good, good, fair, or poor)
7. Surgeon rating of pain medication. (very good, good, fair, or poor)

##### **Sample Size Calculation**

This study was designed to enroll at least 50 patients in each of the 4 treatment groups (placebo, or 15, 20, or 25 mg of SKY0401) for a total of at least 200 patients in the study. Based upon results from Phase 2 studies, it was estimated that IV fentanyl usage for 48 hours following study drug administration for the placebo group would be at least 900 mcg, and the pooled standard deviation would be approximately 600 mcg. To estimate the study sample size, the following assumptions were made: 1) two-sided hypothesis test; 2) Type I error of 0.05; 3) power of 90%; and 4) t-test for the difference between two independent means. The minimum sample size needed to detect a difference of 400 mcg of total IV fentanyl usage over 48 hours was calculated as at least 50 patients per treatment group.

##### **Study Populations**

The safety population was to have included all randomized patients who received any study drug whether or not they underwent the planned surgical procedure. The intent-to-treat (ITT) population was to consist of all randomized patients who underwent the planned surgical procedure regardless of whether they received their assigned study drug according to the randomization procedure. The ITT population was to have been used in the analysis of primary and secondary efficacy variables.

##### **Handling Patient Dropouts and Discontinuations**

All randomised patients were to be followed through Day 30, whether or not they received study drug. If a patient withdrew from the study prior to Day 30, they were not to

be replaced with another randomised patient. Every attempt was to be made to follow these patients through Day 30. If a patient died, withdrew from the study, or was lost to follow-up before 48 hours, their 48-hour total IV fentanyl usage was to have been a projected amount of fentanyl usage. The projected amount was to be the average amount of post-operative fentanyl administered per hour over the last 6 hours (or available number of hours if less than 6 hours) in which IV fentanyl use was quantified (whether or not it was actually given), multiplying this amount by the number of hours remaining in the 48-hour periods, and adding this to the amount of IV fentanyl actually used.

### 1.5.2.3 Amendments

#### Amendment 01: 01 June 2001

1. The total amount of intra-operative IV fentanyl use was changed to a recommended maximum of 250 mcg, rather than an absolute maximum. A bolus of IV or IM fentanyl (rather than just IV) or IM ketorolac near the end of surgery was prohibited. Use of ketorolac was prohibited through 48 hours after study drug administration.
2. Chronic daily narcotic medication usage was added as an exclusion criterion.
3. In keeping with local practice standards, to verify proper epidural needle or catheter placement, either a test dose of preservative free lidocaine or aspiration to check for absence of blood or CSF was permitted. If a test dose was to be used, the time prior to study drug administration was changed to be 15 minutes instead of 3-5 minutes.
4. The post-operative maximum dose of 650 mg acetaminophen in a 24-hour period was changed to be a maximum recommended dose rather than an absolute maximum dose.
5. The definition of hypoxia as moderate with O<sub>2</sub> sat of <94% on room air (RA) for 6 minutes, and severe as <85%, was replaced by "Hypoxia: clinically significant reduction in O<sub>2</sub> saturation, documented by oximetry and requiring intervention (such as supplemental O<sub>2</sub>)."
6. Demographic and baseline measurement variables were to be compared to evaluate the effect of randomization. Age, sex, ASA class and use of test dose and/or flush were to be considered candidates for inclusion in the analysis due to anticipated correlation with outcome variables, as requested by FDA.
7. Administrative changes were also incorporated.

### 1.5.2.4 Study Conduct

#### 1.5.2.4.1 Patient Disposition

The original protocol planned for an enrollment of 200 patients, with approximately 50 patients in each of 4 treatment groups. In the completed study, two hundred patients were randomized with 51, 50, and 49 patients assigned to receive 15-mg, 20-mg, and 25-mg SKY0401 and 50 patients to receive placebo. One hundred ninety-four patients were included in the efficacy analysis. This population included 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 not followed for their use of fentanyl or other opioid medication. Of the 6 patients

not included in the efficacy population, 5 were not followed for fentanyl or opioid usage and the remaining 1 did not have surgery.

The type of anesthesia was similar between treatment groups with 105 patients (54%) having received a general technique and 89 patients (46%) having received a regional anesthetic. Data on opioid usage through 48 hours post-dose was collected for 189 patients (97%) in the ITT population.

Table 1.5.2-2 Disposition of Patients, Study 011

	Placebo	SKY0401				Total
		15 mg	20 mg	25 mg	All	
Randomized	50	51	50	49	150	200
Randomized and Received Study Drug (Safety Population)	47 (94%)	48 (94%)	45 (90%)	43 (88%)	136 (91%)	183 (92%)
Randomized and Received Planned Surgical Procedure (ITT Population)	49 (98%)	50 (98%)	49 (98%)	46 (94%)	145 (97%)	194 (97%)
Type of Anesthesia (ITT Population)						
General	28 (57%)	27 (54%)	25 (51%)	25 (54%)	77 (53%)	105 (54%)
Regional	21 (43%)	23 (46%)	24 (49%)	21 (46%)	68 (47%)	89 (46%)
Opioid Usage Collected Through 48 Hours (ITT Population)						
No	1 (2%)	0 (0%)	3 (6%)	1 (2%)	4 (3%)	5 (3%)
Yes	48 (98%)	50 (100%)	46 (94%)	45 (98%)	141 (97%)	189 (97%)

From sponsor's report SKY0401-011, Section 10.1, page 45

Twenty-seven clinical sites in the United States participated in this study with patients enrolled at 23 sites. The number of patients randomized by clinical site ranged from one to 34.

**Unplanned exclusions:**

Of the 6 patients not included in the ITT analyses, 5 were not followed for use of fentanyl or opioid medication and 1 did not undergo surgery. (Table 1.5.2-2)

Seventeen patients did not receive study drug and were not included in the safety analyses. Four patients terminated treatment due to noncompliance/lost to follow-up and one patient withdrew consent, but were included in the safety population until withdrawal.

**1.5.2.4.2 Demographics/Group Comparability**

Overall, the mean age was 61 years for all SKY0401-treated patients and 59 years for the placebo-treated patients. One hundred and two of the 200 randomized patients (51%) were males. One hundred seventy-five patients (88%) were Caucasian. The treatment groups were also similar in terms of height, weight, BMI, and ASA Classification. Demographic characteristics were also evaluated for the patients included in the safety and ITT analyses, and for safety patients who received no test dose, received test dose < 15 minutes prior to study drug, and received test dose =15 minutes prior to

study drug. The demographic and baseline characteristics of the ITT and safety populations were similar across all treatment groups. In addition, the distribution of demographic characteristics between all randomized patients and the ITT and safety populations were similar.

#### 1.5.2.4.3 Unplanned Analyses/Protocol Deviations

Seven patients (4%) received an inclusion or exclusion waiver. Protocol deviations includes a patient 1007 (25 mg SKY0401 treatment group) who received the test dose 2 minutes after the study drug was administered and patient 17006 (25 mg SKY040 treatment group) who received the study drug after the start of surgery.

No interim analyses were conducted.

#### 1.5.2.5 Sponsor's Efficacy Results

##### 1.5.2.5.1 Primary Efficacy Variable

The primary efficacy endpoint was the total amount of IV fentanyl used through 48 hours post-dose. The mean total fentanyl usage in the 15, 20, and 25-mg SKY0401 treatment groups was 663 mcg, 485 mcg, and 370 mcg, respectively, compared with 2091 mcg in the placebo treatment group. The efficacy of the 20 and 25 mg SKY0401 treatment groups was comparable, as indicated by the median fentanyl values of 250 mcg in both groups. Moreover, there were no differences ( $p > 0.05$ ) at any time point observed between the 20 and 25-mg SKY0401 groups. The mean total fentanyl usage was highly significantly reduced in all SKY0401 treatment doses compared with placebo ( $p < 0.0001$ ), and there was a 75% reduction in the need for IV fentanyl with SKY0401 treatment (510 mcg) compared with placebo (2091 mcg). Overall, through 48 hours post-dose, there was a dose-related reduction in the need for post-operative IV fentanyl.

Table 1.5.2-3: Total Fentanyl Usage Through 48 hours Post-Dose, Study 011

	Placebo	SKY0401				Total
		15 mg	20 mg	25 mg	All	
Patients (n)	49	50	49	46	145	194
Total Fentanyl Usage (mcg) Through 48 Hours Post-Dose						
Mean	2091.4	663.0	485.4	370.6	510.2	909.6
Median	1605.0	400.0	250.0	250.0	275.0	426.5
Min - Max	195 - 9510	0 - 3321	0 - 4301	0 - 4422	0 - 4422	0 - 9510
p-value: SKY0401 dose vs. placebo <sup>1</sup>	-	< 0.0001	< 0.0001	< 0.0001		

P-values were determined using ANOVA with terms for treatment group and type of anesthesia. Pairwise comparisons were evaluated only if the overall treatment group effect was significant.

<sup>1</sup>p-value < 0.0001 for overall test among the treatment groups.

Min = Minimum; Max = Maximum.

From Sponsor's Table 11.4.1.1-1, Clinical Study Report; Protocol No SKY0401-011, Page 51.

**1.5.2.5.2 Secondary Efficacy Variables**

• **Time to First Post-Operative Fentanyl Usage**

The median time to first post-operative fentanyl usage was 3.6 hours for the placebo-treated patients and 21.3 hours for all SKY0401-treated patients. The difference was significantly shorter for the placebo group compared with any of the SKY0401 groups ( $p < 0.0001$ ).

Table 1.5.2-4 Time to First Post-Operative Fentanyl Usage, Study 011

	Placebo	SKY0401			
		15 mg	20 mg	25 mg	All
Time (Hours) to First Post-Operative Fentanyl Usage					
n	49	50	49	46	145
Median	3.6	15.4	22.7	22.8	21.3
Min - Max	1.6 - 48+	1.8 - 48+	2.1 - 48+	2.0 - 48+	1.8 - 48+
p-value (SKY0401 vs. placebo) <sup>1,2</sup>		< 0.0001	< 0.0001	< 0.0001	

<sup>1</sup>p-values were determined using Log-Rank test stratified by type of anesthesia. Pairwise evaluations were evaluated only if the overall treatment group effect was significant.

<sup>2</sup>p-value < 0.0001 for overall test among the treatment groups.

Min = Minimum; Max = Maximum; +. indicates that the largest value was censored.

Sponsor's Study Report 11, Efficacy Evaluation, From Sponsor's Table 11.4.1.2-2

• **Proportion of patients receiving no Post-Operative Fentanyl**

The sponsor did not present an analysis of the proportion of patients who did not receive supplementary fentanyl in the 48-hour period after administration of the study drug. Instead, the sponsor presented an analysis of the proportion of patients who did not receive fentanyl in successive 12-hour intervals after receiving study drug.

Table 1.5.2-5: Proportion of Patients Receiving No Post-Operative Fentanyl by 12-Hour Intervals, Study 011

	Placebo	SKY0401			
		15 mg	20 mg	25 mg	All
Proportion Receiving No Post-Operative Fentanyl by 12-Hour Intervals					
n	49	50	49	46	145
0 -12 hours	2%	52%	57%	63%	57%
> 12 to 24 hours	8%	42%	59%	70%	57%
> 24 to 36 hours	6%	24%	49%	50%	41%
> 36 to 48 hours	8%	22%	35%	54%	37%

Sponsor's Study Report 11, Efficacy Evaluation, From Sponsor's Table 11.4.1.2-2

- **Activity Score**

There were no significant differences between treatment groups. The activity level at 24 and 48 hours post-dose was assessed by using a Six-Grade Mobilization Score, where 1 = sit up on bedside (feet hanging) with assistance, 2 = sit up on bedside (feet hanging) without assistance, 3 = stand with assistance, 4 = stand without assistance, 5 = walk with assistance, and 6 = walk freely without assistance. At 24 hours post-dose, the mean activity scores for SKY0401-treated and placebo-treated patients were 3.0 and 2.7, respectively. At 48 hours post-dose, the mean activity scores were 3.8 and 4.2, respectively.

- **Pain Intensity Evaluation using Visual Analog Scale**

The VAS-R (Rest) scores for pain intensity at rest showed the reduction of pain ( $p < 0.05$ ) at 48 hours in the all SKY0401 treatment groups compared with the placebo treatment group.

Table 1.5.2-6: Pain Evaluation at Rest Over 48 Hours Using VAS (AUC) Score, Study 011

	Placebo	SKY0401			
		15 mg	20 mg	25 mg	All
VAS-R Scores 0 – 48 Hours (AUC)					
n	48	49	47	45	141
Mean (mm)	1462.4	945.7	736.8	653.5	782.8
p-value (SKY0401 vs. placebo) <sup>1</sup>	---	0.0005	<0.0001	<0.0001	---
VAS-A Scores at 24 Hours Post-Dose					
n	45	48	46	43	137
Mean (mm)	52.2	33.3	31.6	23.3	29.6
p-value (SKY0401 vs. placebo) <sup>2</sup>	---	0.0013	0.0006	<0.0001	---
VAS-A Scores at 48 Hours Post-Dose					
n	46	47	42	44	133
Mean (mm) <sup>3</sup>	39.2	32.4	31.5	23.4	29.1

P-values were determined using ANOVA including terms for treatment groups and type of anesthesia. Pairwise comparisons were evaluated only if the overall treatment group effect was significant.

1p-value < 0.0001 for overall test among the treatment groups.

2p-value < 0.0001 for overall test among the treatment groups.

3Overall test among the treatment groups was not significant and therefore pairwise comparisons were not performed.

AUC = Area under the curve; VAS = Visual Analog Scale: 100 mm length line (0 = no pain and 100 = the most severe pain); VAS-R = pain assessment using VAS while patients was at rest; VAS-A = pain assessment using VAS while patient was active; mm = millimeter.

From Sponsor's Study 11, Efficacy Evaluation, Analysis of Efficacy, Table 11.4.1.2-3, page 58

The sponsor presented their analysis of pain intensity with activity (VAS-A), measured as AUC at 24 hours indicating that all doses of SKY0401 (15 mg, 20 mg and 25 mg) were associated with reductions when compared with placebo ( $< 0.05$ ). (Table 1.5.2-6)

- **Pain Intensity Evaluation using a Categorical Scale**

Pain intensity evaluated hours at rest (CAT-R) and with activity (CAT-A) at 48 was not different from placebo ( $p = 0.059$  and  $P = 0.53$  respectively). In contrast, the sponsor reports that the means of both CAT-A and CAT-R at 24 hours at each SKY0401

dose (15 mg, 20 mg and 25 mg) were lower than the means calculated for placebo (p<0.05). (See Table 1.5.2-7).

Table 1.5.2-7 Sponsor’s Pain Intensity Evaluation Using Categorical Scale, Study 011

	Placebo	SKY0401			
		15 mg	20 mg	25 mg	All
<b>CAT-R Scores at 24 Hours Post-Dose</b>					
n	49	50	49	46	145
Mean	1.4	0.8	0.6	0.6	0.7
p-value (SKY0401 v. placebo) <sup>1</sup>	--	0.0004	< 0.0001	< 0.0001	--
<b>CAT-R Scores at 48 Hours Post-Dose</b>					
n	49	50	49	46	145
Mean <sup>2</sup>	0.9	0.8	0.6	0.6	0.7
<b>CAT-A Scores at 24 Hours Post-Dose</b>					
n	49	50	49	46	145
Mean	1.9	1.3	1.2	1.0	1.2
p-value (SKY0401 vs. placebo) <sup>3</sup>	--	0.0052	0.0014	< 0.0001	--
<b>CAT-A Scores at 48 Hours Post-Dose</b>					
n	49	50	49	46	145
Mean <sup>2</sup>	1.6	1.2	1.3	1.0	1.2

P-values were determined using the CMH (row-mean-score) test stratified by type of anesthesia. Pairwise comparisons were evaluated only if the overall treatment group effect was significant.

<sup>1</sup>p-value < 0.0001 for overall test among the treatment groups.

<sup>2</sup>Overall test among the treatment groups was not significant and therefore pairwise comparisons were not performed.

<sup>3</sup>p-value = 0.0003 for overall test among the treatment groups.

CAT = Categorical Scale: 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain. CAT-R = pain assessment using CAT while patient was at rest; CAT-A = pain assessment using CAT while patient was active.

From Sponsor’s study 11, Efficacy Analysis, Table 11.4.1.2-4, pg. 59.

**• Patient Ratings of Pain Control**

At 48 hours post-dose, the proportion of patients who rated their pain control as good or very good was greater in the SKY0401 groups (83%) compared with the placebo group (67%) particularly for the 25 mg SKY0401 group (p= 0.0030). At 24 hours after study drug, the proportion of SKY0401 patients rating their pain as good or very good (90%) was greater than placebo (65%) for patient groups treated with 15-mg, 20-mg and 25-mg SKY0401 (p= 0.0054, 0.0002, 0.0010 respectively).

**• Surgeon Ratings of Pain Control**

The proportion of patients rated by the surgeon rated as having good or very good pain control at 24 hours was 87% for the SKY0401 group compared with 61% for the placebo group. At 48 hours, 75% of the SKY0401 patients compared with 57% of the placebo patients were rated as having good or very good pain control. These differences were statistically significant (p<0.05).

**1.5.2.5.3 Sponsor’s Additional Analysis**

- Secondary analysis of primary efficacy endpoint: supplemental fentanyl use, evaluated by successive intervals

The sponsor reported a consistent dose-related reduction in fentanyl usage ( $p < 0.05$ ) in all SKY0401 groups compared with the placebo group through 24 hours post-dose, from 24 to 48 hours post-dose, and through 48 hours post-dose. It is important to note that the sponsor did not extrapolate the amount of fentanyl used for subjects that did not complete the study as was required for primary efficacy analysis.

Table 1.5.2-8 Fentanyl Supplementation by 24-Hour Intervals in the First 48 Hours, Study 011

	Placebo	SKY0401			
		15 mg	20 mg	25 mg	All
<b>Fentanyl Usage (mcg) 0 to 24 Hours Post-Dose<sup>1</sup></b>					
n	49	50	49	46	145
Mean	1282.2	294.9	210.0	201.0	236.4
p-value (SKY0401 vs. placebo) <sup>3</sup>	--	< 0.0001	< 0.0001	< 0.0001	--
<b>Fentanyl Usage (mcg) &gt; 24 to 48 hours Post-Dose<sup>1</sup></b>					
n	49	50	48	46	144
Mean	788.1	368.1	274.8	166.8	272.7
p-value (SKY0401 vs. placebo) <sup>4</sup>	--	0.0025	0.0002	< 0.0001	--
<b>Fentanyl Usage (mcg) 0 to 48 hours Post-Dose<sup>1</sup></b>					
n	49	50	49	46	145
Mean	2070.3	663.0	479.2	367.8	507.2
p-value (SKY0401 vs. placebo) <sup>5</sup>	--	< 0.0001	< 0.0001	< 0.0001	--
<b>Post-Operative Fentanyl Usage (mcg) Through 48 Hours Post-Dose<sup>2</sup></b>					
n	49	50	49	46	145
Mean	1959.1	571.0	393.4	269.2	415.3
p-value (SKY0401 vs. placebo) <sup>6</sup>	--	< 0.0001	< 0.0001	< 0.0001	--

For subjects who died, withdrew from the study, or were lost to follow-up before 48 hours post-dose, his/her total fentanyl usage through 48 hours was the actual amount reported and not a projected amount as for the primary efficacy Intra-operative usage not included. P-values were determined using ANOVA with terms for treatment group and type of anesthesia. Pairwise comparisons were evaluated only if the overall treatment group effect was significant. <sup>3</sup> p-value < 0.0001 for overall test among treatment groups. <sup>4</sup> p-value < 0.0001 for overall test among treatment groups. <sup>5</sup> p-value < 0.0001 for overall test among treatment groups. <sup>6</sup> p-value < 0.0001 for overall test among treatment groups.

From Sponsor's Study Report 11, Efficacy Evaluation, Table 11.4.1.2-1, page 55.

The sponsor reported similar findings of dose-related reduction in fentanyl administration for successive 4-hour intervals after administration of SKY0401 compared with placebo.

- Time to First Post-Operative Opioid Usage (all opiate analgesics administered)

The secondary analysis of the time to first fentanyl usage was also conducted in terms of the time to first opioid dosage received. These results were consistent with those for fentanyl usage, and demonstrated a marked delay to first opioid usage with SKY0401 administration (3.4 hours versus 18.2 hours for placebo and total SKY0401 groups, respectively;  $p < 0.0001$  for each SKY0401 group).

Table 1.5.2-9 Time to First Post-Operative Opioid Usage, Study 011

	Time to First Post-Operative Fentanyl and First Opioid Usage Within 48 Hours ITT Population					
	Treatment Groups					
	Placebo	15 mg SKY0401	20 mg SKY0401	25 mg SKY0401	All SKY0401	Total
Number of Patients	49	50	49	46	145	194
Time from Study Drug Administration to First Post-Operative Fentanyl Usage (hours)						
n	49	50	49	46	145	194
Number of Censored Patients	1	8	14	14	36	37
Median**	3.6	15.4	22.7	22.8	21.3	6.5
95% C.I. for Median	(3.1, 4.2)	(6.1, 26.5)	(8.1, 36.8)	(9.0, 42.3)	(9.0, 27.6)	(5.1, 14.9)
Min - Max	1.6 - 48.0+	1.8 - 48.0+	2.1 - 48.0+	2.0 - 48.0+	1.8 - 48.0+	1.6 - 48.0+
Time from Study Drug Administration to First Post-Operative Opioid Usage (hours)						
n	49	50	49	46	145	194
Number of Censored Patients	1	5	11	13	29	30
Median**	3.4	8.8	10.3	22.8	18.2	5.4
95% C.I. for Median	(3.0, 3.9)	(5.1, 23.0)	(4.1, 29.6)	(9.0, 42.3)	(8.0, 23.2)	(4.3, 8.2)
Min - Max	1.4 - 48.0+	1.4 - 48.0+	2.0 - 48.0+	2.0 - 48.0+	1.4 - 48.0+	1.4 - 48.0+

\* P-values are determined using Log-Rank Test stratified by type of anesthesia. Pairwise comparisons of each SKY0401 dose to placebo should be evaluated only if the overall treatment group effect is significant.  
 \*\* Medians are obtained using the Kaplan-Meier product limit estimates.  
 + indicates that the largest value is censored.

(Sponsor's Study 11, Section 14.2, Table 11, page 213)

- **Integrated Rank Assessment Using Visual Analog Scale and Total Fentanyl Usage**

To account for the effect of the amount of fentanyl on pain intensity, the pain intensity data were analysed by the sponsor as an integrated rank at rest and with activity using the VAS scores and total IV fentanyl usage. Integrated Ranks were calculated as follows: Both VAS scores and total fentanyl usage scores are ranked in the combined treatment groups (the average of the respective ranks will be used in case of ties). Each patient's VAS rank and total fentanyl usage rank were then subtracted from the mean overall rank  $[(n + 1) / 2]$  and expressed as a percentage difference of the mean overall rank. Patient's integrated ranks are the sum of the percentage difference for the VAS score and the percentage difference for the total fentanyl usage score. P-values were determined using ANOVA including terms for treatment groups and type of anesthesia. Pairwise comparisons of each SKY0401 dose to placebo should be evaluated only if the overall treatment group effect is significant. The sponsor reports a significant reduction in pain intensity with SKY0401 treatment (except for the pain intensity evaluation at rest for the first request for pain medication).

#### 1.5.2.6 REVIEWER'S COMMENTS

This Phase 3 study in 194 patients was designed to evaluate the analgesic efficacy of 15-mg, 20-mg and 25-mg SKY0401 compared with placebo in the setting of hip arthroplasty. The amendment to the protocol (June 1, 2001) was made after 44 patients had been studied, however the amendment did not change the patient population or the type of analysis to be performed. The changes to the protocol are not expected to affect the conclusions. Of the 6 patients not included in the efficacy population, 5 were not followed for fentanyl or opioid usage and the remaining patient did not have surgery. This reviewer determined that the study conduct reflected the protocol despite minor variances and was adequate to analyze efficacy of SKY0401.

The sponsor was able to demonstrate a statistically significant reduction in supplemental fentanyl, the primary efficacy endpoint, among each of the dose groups treated with SKY0401 compared with placebo. The reduction in supplemental fentanyl between patients treated with SKY0401 was also clinically relevant when compared with placebo. For example, the median supplemental fentanyl dose over 48 hours was 1605 mcg (32mL) among placebo patients compared with 400 mcg of fentanyl (8mL) among the patients treated with 15 mg of SKY0401. In comparing the relative benefit of each dose of SKY0401 it is striking how little difference there appears to be in amount of supplemental fentanyl required. For example, there was only 150-mcg difference in the median supplemental fentanyl needed between the 15-mg and 25 mg doses of SKY0401 and no difference at all between the median supplemental fentanyl required for the 20-mg and 25-mg SKY0401 doses. It is questionable that a difference of 150 mcg (3 mL) of fentanyl administered over 48 hours is of real practical significance. The data were not normally distributed so median values were used for this discussion, but similar differences were reported for mean values of supplementary fentanyl.

Analysis of the secondary efficacy endpoints supported the finding of efficacy for SKY0401. The median time to first post-operative fentanyl usage was shorter than for

SKY0401 patients, indicating delayed onset of postoperative pain among the patients receiving SKY0401. The median latency of pain onset was dose-dependent, but there was substantial variation within each dose group. The sponsor's analysis of time to first use of any opiate produced similar findings to the analysis of the time to first fentanyl usage, but the dose-dependent differences for SKY0401 treatment was smaller than for fentanyl alone.

There was a dose-dependent increase in the number of patients who did not receive additional fentanyl in the first 48 hours among patients treated with SKY0401 compared with placebo. This suggests that SKY0401 patients were more comfortable than placebo and that higher doses of SKY0401 improved comfort.

There was no significant difference in "activity score" between placebo and SKY0401 patients. This is an important negative result because early activity is a clinical goal to minimize complications of major surgery. To this reviewer, this finding indicates that disabling effects related to the drug offset some of the dose-dependent benefit of reduced pain. SKY0401 did not appear to worsen patient activity compared with placebo, but it did not result in improved physical activity, as this reviewer would have expected with reduced postoperative pain.

VAS scores at rest and with activity in the first 48 hours were reduced in a dose-dependent manner among patients treated with SKY0401 compared with placebo. Categorical pain scores were lower at 24 hours, but not 48 hours among patients treated with SKY0401 compared with placebo. Patient rated their pain control as good or very good at 24 hours more frequently when treated with 15-, 20- or 25-mg doses of SKY0401 compared with patients who received placebo. At 48 hours however, only patients treated with 25-mg of SKY0401 continued to rate their pain control as better than placebo. The proportion of patients the surgeon rated as having good or very good pain control at 24 and 48 hours was reported by the sponsor to be higher for all SKY0401 treatment groups compared with the placebo group. These findings using various pain assessment tools support the sponsor's contention that SKY0401 was more efficacious than placebo in reducing perioperative pain. To account for the effect of the amount of fentanyl on pain intensity, the sponsor calculated an integrated rank score incorporating VAS and IV fentanyl usage. This analysis supported the sponsor's contention that pain intensity was reduced by treatment with SKY0401. The degree and duration of pain reduction measured was dependent upon the measurement tool used.

An additional analysis by the sponsor provided a breakdown of the supplemental fentanyl administered by 24-hour intervals in the first 48 hours. This analysis departed from methodology used in the primary efficacy analysis because there was no extrapolation of fentanyl usage for patients who did not complete the study. Despite modification to the analysis, the data indicates that supplemental fentanyl was reduced in the 24 to 48 hour period as well as in the first 24 hours.

### 1.5.3 Study 012b, Lower abdominal surgery:

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

#### 1.5.3.1 Findings vs. Labeling Claims

See Section, "REVIEW OF PACKAGE INSERT".

#### 1.5.3.2 Study Plan

##### 1.5.3.2.1 Population, Design, and Objectives

###### Objectives:

To compare the efficacy and safety of different (single bolus) epidural doses of SKY0401 to placebo in relieving perioperative pain after abdominal surgery.

**Population:** N= 546 randomized, 487 in efficacy analysis

###### • Inclusion Criteria

1. Males and females aged  $\geq 18$  years at the Screening Visit.
2. Females of childbearing potential must have a negative urine beta-hCG pregnancy test performed during screening. Females are eligible only if they are not pregnant or lactating, are either post-menopausal or surgically sterile, or, if of child-bearing potential, using an acceptable means of contraception for = 1 month prior to Screening, including any of the following:
  - Oral contraceptives
  - Implantable (e.g., Norplant) or injectable contraceptive (e.g., Depo-Provera)
  - Barrier methods (e.g., condoms with spermicide)
  - IUD
  - Lifestyle with a personal choice of abstinence
  - Non-heterosexual lifestyle
  - Vasectomy of sexual partner.
3. Undergoing lower abdominal surgery (i.e., surgeries via an abdominal incision below the umbilicus), under general or regional (intrathecal) anesthesia. Note that transverse, midline, or Pfannensteil incisions are permitted. The types of procedures to be enrolled include, but are not limited to, the following:
  - General Surgery – sigmoid colon resection
  - Gynecological – total abdominal hysterectomy, salpingoophorectomy, or myomectomy
  - Urological – radical prostatectomy, or cystectomy.
4. American Society of Anesthesiology (ASA) Physical Class 1, 2, or 3

5. Willing and able to use a PCA pump.
6. Willing to only receive IV fentanyl for 48 hours post-dose to control post-operative pain.
7. Expected and willing to remain hospitalized for a minimum of 48 hours post-dose.
8. Capable of speaking and understanding English sufficiently to provide written informed consent and responses to pain assessment scales and neurological assessment questionnaires.

• **Exclusion Criteria**

1. Morbid obesity, defined as a body mass index (BMI) = 40. BMI is calculated as follows: (weight [lbs.] / height [inches]<sup>2</sup>) x 704.5.
2. The following surgical procedures:
  - Cesarean section
  - Herniotomy
  - Appendectomy
  - Low abdominal vascular surgery
3. Any lower abdominal surgical procedure in which the incision is above the umbilicus (e.g., upper abdominal incision) or does not involve an abdominal incision (i.g., laparoscopic surgery, vaginal hysterectomy, nephrectomy, transurethral prostatectomy).
4. Any current risk factors (e.g., peritonitis) which, in the opinion of the investigator, might increase the risk of surgery or complicate the patient's post-operative course.
5. Patients undergoing lower abdominal surgery under epidural anesthesia.
6. Current or historical evidence of any clinically significant disease or condition that, in the opinion of the investigator, might increase the risk of surgery or complicate the patient's post-operative course.
7. Suspected or documented history of sleep apnea, narcolepsy, or excessive daytime sleepiness.
8. Female who is pregnant or lactating.
9. History of hypersensitivity or idiosyncratic reaction to opioid medications.
10. Any contraindication for the epidural administration of study drug (e.g., coagulopathy, and local infection).
11. Administration of an investigational drug within 30 days prior to Screening.
12. Suspected or documented history of substance abuse and/or alcoholism.
13. Unwilling or unable to provide written informed consent and/or to comply with study procedures, including use of a PCA pump, completion of all patient-rated scales, and 30-day follow-up assessments.

**Design:**

The enrolled patients were to have been randomized in a 1:1:1:1:1 ratio to receive one of the following: placebo (injectable, preservative-free 0.9% normal saline without DepoFoam particles), or 10-, 15-, 20-, or 25-mg SKY0401. SKY0401 or placebo was to have been administered epidurally prior to the induction of general or regional anesthesia at approximately 30 minutes prior to the start of surgery. For both general and regional anesthesia patients, the advocated maximum total amount of intra-operative IV fentanyl use was limited to 250 mcg. A bolus of IV or IM fentanyl near the end of surgery was prohibited. Use of ketorolac was to have been prohibited through 48 hours after study

drug administration. Patients were to have had a PCA pump set up within 30 minutes after completion of surgery, and were not to be given control of the PCA pump until after the first request for pain medication. If a member of the study personnel (i.e., the blinded study coordinator or blinded Investigator) who was trained to perform assessments (VAS-R and CAT-R), confirmed that the patient initially had moderate to severe pain, the investigator was to administer an initial (25 mcg) bolus of IV fentanyl. After the first bolus dose of IV fentanyl, the PCA pump (equipped with a printer) was to have been connected to the patient's IV line and programmed to deliver on-demand boluses of IV fentanyl of 10 to 20 mcg per bolus, with a lockout interval of six minutes. A continuous infusion that delivered a background or basal rate of IV fentanyl was prohibited. If pain control was deemed inadequate by the Investigator or the patient, alteration of the bolus dose was to have been permitted as appropriate. Conversely, if pain control was deemed sufficient by the Investigator or the patient, the dose of 10 to 20 mcg per bolus could be titrated downwards. Narcotic medications other than IV fentanyl were not to be permitted intra-operatively through 48 hours post-dose. Concomitant medications were to be recorded for 48 hours post-dose.

Fentanyl usage was to have been quantified through 48 hours after study drug administration. Pain intensity at rest and with activity were to have been assessed using both a Visual Analog Scale (VAS-R and VAS-A) and Categorical Scale (CAT-R and CAT-A) at the time of first request for fentanyl and at 4-, 8-, 12-, 18-, 24-, 30-, 36-, and 48-hours post-dose. Patient and surgeon ratings of pain medication were to have been assessed on the mornings of Day 2 and 3.

#### 1.5.3.2.2 Treatment Summary

- **Description of Study Drug**

SKY0401 is formulated as a sterile, non-pyrogenic, white to off-white, preservative-free, homogenous suspension of morphine encapsulated into multivesicular lipid-based particles (DepoFoam drug delivery system intended for epidural use only. The placebo was injectable preservative-free 0.9% normal saline without DepoFoam particles or the active ingredient, morphine, and was to have been supplied (for use as both placebo and as diluent for SKY0401) by the hospital pharmacy.

- **Treatment Assignment**

Patients were to have been randomly assigned in a 1:1:1:1:1 ratio on Day 1 to one of the following five treatment groups: placebo, or 10, 15, 20, or 25 mg of SKY0401. This randomization was to have been stratified by both type of anesthesia (regional or general) and by site. Study sites were to randomize each patient by calling a telephone-based computerized Central Randomization System. Once patient eligibility was confirmed, the patient was to have been randomized, assigned a patient number, and assigned to a treatment group. Administration of dosages of SKY0401 other than 10, 15, 20, and 25 mg was prohibited.

- **Preparation of Study Drug**

Study drug was to have been prepared by an unblinded pharmacist according to the treatment assignment. SKY0401 was to be diluted with injectable, preservative-free 0.9% normal saline to a total volume of 5 mL.

- **Blinding**

As SKY0401 and placebo are distinguishable, study drug was to have been administered by an unblinded anesthesiologist who was not involved with patient assessments and data collection. The clinical staff involved with the conduct of the study and the patient were to remain blinded to the assigned treatment group.

- **Administration of Study Drug**

Study drug was to have been administered prior to induction of general anesthesia and regional (intrathecal) anesthesia and approximately 30 minutes prior to the start of surgery (defined as the time of the first incision).

Study drug was to have been administered via an epidural needle or catheter. When using an epidural catheter, a 3-mL test dose of local anesthetic (e.g., 3 mL of 1.5% lidocaine with 1:200,000 epinephrine) was to have been administered before the study drug to detect incorrect identification of the epidural space.

- **Conduct of Anesthesia**

Except for narcotics, there were no restrictions on administration of agents used for general anesthesia. Neuromuscular blockade was to be reversed as deemed appropriate by the anesthesiologist.

Regional (intrathecal) anesthesia was to be managed by the intrathecal administration of bupivacaine (at a dose of 12.5 to 17 mg, with or without dextrose) in a lumbar intervertebral space different from that used to administer study drug.

For both general and regional (intrathecal) anesthesia, the total amount of intra-operative analgesics administered was to be no more than 250 mcg of IV fentanyl.

SKY0401 is a slow-release formulation of morphine with effects due to continued release of morphine that could potentially persist for several days.

Patients were to have a PCA pump containing IV fentanyl set up within 30 minutes after completion of surgery. The patients were not to be given control of the PCA pump until after their first request for pain medication. Narcotic medications other than IV fentanyl were not to be permitted for 48 hours post-dose. Additionally, the following medications were to be prohibited through 48 hours post-dose:

- Formulations of fentanyl other than IV fentanyl (e.g., Duragesic®)
- Anti-inflammatory agents (e.g., ketorolac [Toradol<sup>®</sup>]) except for the following:
  - “Acetaminophen [Sic]- maximum of 650 mg/24 hours for fever or headache only”;
  - Aspirin - maximum of 325 mg/24 hours for platelet inhibition.
  - Cyclo-oxygenase inhibitor agents, including COX-2 specific inhibitors (e.g., celecoxib [Celebrex®] and rofecoxib [Vioxx®]).

The use of following medications were discouraged but were left to the discretion of the investigator:

- Benzodiazepines and other anti-anxiolytics;

- Anti-depressants (including tricyclics and serotonin-specific uptake inhibitors);
- Sedating anti-histamines;
  - Any other medication that might cause sedation.

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Sustained-Release Encapsulated Morphine)

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1.5.3.2.3 Planned Assessments: Table 1.5.3-1 Schedule of Assessments, Study 012b

Assessment	Screening (Up to 21d prior to dosing)	Pre-Dose	Time of Dose	15 min. Post-Dose	30 min. Post-Dose	1 hr Post-Dose	2 hr Post-Dose	q 1 hr for hrs 1-24						24 hr Post-Dose	30 hr Post-Dose	36 hr Post-Dose	48 hr Post-Dose	Day 7 Follow-Up	Day 30 (+4d) Follow-Up		
								4 hr Post-Dose	8 hr Post-Dose	12 hr Post-Dose	18 hr Post-Dose	24 hr Post-Dose	30 hr Post-Dose							36 hr Post-Dose	48 hr Post-Dose
Informal Consent	X																				
Medical History	X																				
Oral Temperature	X																				
Respiratory Rate	X																				
Heart Rate and Blood Pressure	X						X		X		X		X		X		X				
Physical Exam (neurological exam)	X																				
12-Lead ECG	X																				
Pt. Training (Scales & Use of PCA Pump)	X																				
Routine Lab Tests (urine pregnancy test at Screening, if required)	X																				
Randomize Pt and Prepare Study Drug		X																			
PK Samples <sup>2</sup>			X			X		X		X		X		X		X		X			
Admin. Study Drug <sup>3</sup>				X																	
Setup PCA Pump <sup>4</sup>						X															
Pain Intensity at Rest <sup>5</sup> (VAS-R & CAT-R)							X		X		X		X		X		X				
Pain Intensity with Activity (VAS-A & CAT-A) <sup>5a</sup>							X		X		X		X		X		X				
Sedation Score							X		X		X		X		X		X				
Brief Neuro Check							X		X		X		X		X		X				
Pt & Surgeon Rating of Pain Medication							X		X		X		X		X		X				
Concomitant Meds																					
PO Intake <sup>6</sup>																					
Adverse Events																					
NAQ	X																				

1 Scales and use of the PCA pump: 2 Urine pregnancy test at Screening; 3 Conducted anytime on Day 3; 4 Performed by selected study sites only. If an IV line was used, the line was flushed prior to collecting the PK sample. Pain intensity assessments were performed prior to blood draw; 5 Study drug was administered by an unblinded anesthesiologist not involved in other study procedures; 6 The PCA pump was set up within 30 minutes after completion of surgery. Patients were not to be given control of the PCA pump until after the first request for IV fentanyl/PCA. The first dose of IV fentanyl was to be administered by study personnel after pain assessments; 7 Was also conducted at the time of first request for pain medication; 8 Activity consisted of the patient taking a deep breath followed by a forceful cough; 9 Conducted in the morning of a) Day 2 and b) Day 3; 10 Selected AEs for potential neurological sequelae (e) of epidural analgesia were assessed using a standardized neurological assessment questionnaire (NAQ).

Record concomitant medications (including fentanyl) taken 24 hours prior to surgery, intra- and post-operatively through 48 hours post-dose.

Record the time the patient is able to first tolerate clear liquid diet

All adverse events will be recorded from time of dose through Day 7. SAEs (and deaths) will be recorded through Day 30.

From Clinical Protocol SKY0401-12b, 1/7/2000, Appendix A, page 38, "Time and Events Schedule".

#### 1.5.3.2.4 Analysis Plan

##### Efficacy Endpoints

- **Primary Efficacy Endpoint**

The primary efficacy endpoint was to be the average of the total amount of IV fentanyl usage through 48 hours post-dose of study drug. The protocol stipulated that fentanyl was to have been the only perioperative narcotic used to supplement the epidural analgesic for 48 hours.

The protocol allowed for an analysis of average total narcotic usage in the event that a “a clinically meaningful number of protocol violations occur in which other narcotics are administered”. (Study Report SKY0401-12b, 16: Appendices, Clinical Protocol December 7, 2000, page 903) A common total narcotic dose was to have been calculated using standard conversion factors such as those described by Reisine and Pasternak in *Opioid Analgesics and Antagonists*, in The Pharmacological Basis of Therapeutics (eds. Hardman, Limbird, Molinoff, Ruddon, Gilman), McGraw Hill, 1996, p.521-555.

- **Secondary Efficacy Endpoints**

1. Time to first post-operative fentanyl use.
2. Proportion of patients receiving no fentanyl post-operatively.
3. Pain intensity evaluation using the visual analog scale, VAS ( 0 = no pain; 100 = most severe pain possible).
4. Pain intensity evaluation using the categorical scale, CAT (pain level = none, mild, moderate, or severe).
5. Patient rating of pain medication. (very good, good, fair, or poor)
6. Surgeon rating of pain medication. (very good, good, fair, or poor)

- **Sample Size Calculation**

This study was designed to enroll at least 100 patients in each of the 5 treatment groups (placebo, or 10, 15, 20, or 25 mg of SKY0401) for a total of at least 500 patients in the study. Based upon results from Phase 2 studies in patients undergoing hip surgery, it was estimated that IV fentanyl usage for 48 hours following study drug administration for the placebo group would be at least 900 mcg and the pooled standard deviation is approximately 600 mcg. To estimate the study sample size, the following assumptions were made: 1) two-sided hypothesis test; 2) Type I error of 0.05; 3) power of 90%; and 4) t-test for the difference between two independent means. A sample size of 100 patients per treatment group was to allow detection of a difference of 400 mcg of total IV fentanyl usage over 48 hours when the pooled standard deviation was at most 870 mcg. It was assumed that the pooled standard deviation of IV fentanyl usage over 48 hours would be larger in patients undergoing different types of abdominal surgery than in patients undergoing same type of surgery.

- **Study Populations**

The safety population was to have included all randomized patients who received study drug whether or not they underwent the planned surgical procedure. The intent-to-

treat (ITT) population was to consist of all randomized patients who underwent the planned surgical procedure regardless of whether they received their assigned study drug according to the randomization procedure. The ITT population was to be used in the analysis of primary and secondary efficacy variables.

All randomized patients were to be followed through a planned Day 30 follow-up, regardless of the reason for withdrawal and whether or not a study drug was administered. If a patient withdrew from the study because of a clinically significant laboratory abnormality or adverse event, the patient was to be followed until satisfactory resolution of the event.

If a patient withdrew from the study before 48 hours post-dose, all study procedures noted for 48 hours post-dose or Day 3 were to be completed at the time of withdrawal. In addition, all Day 7 and Day 30 assessments were to be conducted.

All randomized patients were to be followed through Day 30, whether or not they received study drug. If a patient withdrew from the study prior to Day 30, they were not to be replaced with another randomized patient.

If a patient died, withdrew from the study, or was lost to follow-up before 48 hours, their 48-hour total IV fentanyl usage was to be a projected amount of fentanyl usage. The projected amount was to be calculated as the sum of the IV fentanyl actually used and the average amount of post-operative fentanyl administered extrapolated over the remaining time in 48 hours. The extrapolation consisted of the average quantified IV fentanyl dose per hour over the previous 6 hours multiplied by the number of hours remaining.

The primary efficacy endpoint was the total amount of IV fentanyl usage for 48 hours following study drug administration. It was to be analyzed on an intent-to-treat basis using an analysis of variance (ANOVA).

### **1.5.3.3 Amendments**

#### **1.5.3.3.1 Amendment 01: 11 June 2001**

1. The total amount of intra-operative IV fentanyl use was changed to a recommended maximum of 250 mcg, rather than an absolute maximum. A bolus of IV or IM fentanyl (rather than just IV) or IM ketorolac near the end of surgery was prohibited. Use of ketorolac was prohibited through 48 hours after study drug administration.
2. Chronic daily narcotic medication usage was added as an exclusion criterion.
3. In keeping with local practice standards, to verify proper epidural needle or catheter placement, either a test dose of preservative free lidocaine or aspiration to check for absence of blood or CSF was permitted. If a test dose was to be used, the time prior to study drug administration to be 15 minutes instead of 3-5 minutes.

4. The post-operative maximum dose of 650 mg acetaminophen in a 24-hour period was changed to be a maximum recommended dose rather than an absolute maximum dose.
5. The definition of hypoxia as moderate with O<sub>2</sub> sat of <94% on room air (RA) for 6 minutes, and severe as <85%, was replaced by “Hypoxia: clinically significant reduction in O<sub>2</sub> saturation, documented by oximetry and requiring intervention (such as supplemental O<sub>2</sub>).”
6. Demographic and baseline measurement variables were to be compared to evaluate the effect of randomization. Age, sex, ASA class and use of test dose and/or flush were to be considered candidates for inclusion in the analysis due to anticipated correlation with outcome variables, as requested by FDA.
7. Administrative changes were also incorporated.

#### **1.5.3.3.2 Amendment 02: 19 January 2002**

1. Study SKY0401-012 was amended due to slow enrollment and requests by European regulatory authorities for comparison to an active drug. The placebo arm was changed to a 5-mg SKY0401 dose control arm. A 5-mg unencapsulated morphine arm was added also. The primary comparison was to be between any of the original doses and the 5-mg SKY0401 dose, using Dunnett’s test.
2. The ITT population was to consist of all randomized patients enrolled after Amendment 2 who underwent the planned surgical procedure regardless of whether they received their assigned study drug according to the randomization procedure. Data from patients enrolled before Amendment 2 was to be included in the data listings only, without analysis of efficacy performed for these patients.
3. All patients who received study drug pre- and post-Amendment 2 were to be included in safety analyses, and analyzed according to the study treatment actually received. In addition, a safety analysis of patients enrolled post-Amendment 2 was also to be performed.

#### **1.5.3.3.3 Amendment 03 :21 October 2002**

1. Mandatory, continuous pulse oximetry for 24 hours post-dose (48 hours post-dose if patients receive study drug but did not undergo surgery) was added.
2. Administrative changes were incorporated.

#### **1.5.3.4 Study Conduct**

##### **1.5.3.4.1 Patient Disposition**

The original protocol design involved a placebo-treatment group and four SKY0401-treatment groups, with a planned enrollment of 500 patients. The protocol was amended (Amendment 02) to change the design from a placebo-controlled study to a dose-controlled study with an active comparator. Consequently, enrollment to the placebo group was halted, and a 5-mg SKY0401, dose-control group was added and an MS-group was added as an active comparator.

In the completed study, five hundred and forty-six patients were randomized with 91, 88, 92, 91, and 90 patients assigned to receive SKY0401 at 5-, 10-, 15-, 20-, and 25-mg, respectively. A further 89 patients were randomized to receive 5 mg of MS. In addition, 5 patients had been randomized to receive placebo prior to Amendment 02. Four hundred and eighty-seven patients were included in the efficacy analyses. The 487 patients (89%) in the efficacy analyses included all patients who were randomized after Amendment 02 (498 patients) and who underwent their planned surgical procedure (ITT population) except for 11 patients who withdrew consent or were not followed postoperatively. Evaluation of the distribution of the patients between treatment groups indicated that the withdrawals did not significantly impact on the efficacy analysis. This included 0, 85, 86, 70, 84, 79, and 83 patients in the placebo, 5-mg MS and 5-, 10-, 15-, 20-, and 25-mg SKY0401 groups, respectively.

In the ITT population, the majority of patients (> 82%) in each of the treatment groups received general anesthesia, with opioid usage data collected through 48 hours post-dose for 482 patients (99%).

Table 1.5.3-2 Disposition of Patients, Study 012b

	Placebo	5 mg MS	SKY0401							Total
			5 mg	10 mg	15 mg	20 mg	25 mg	Combined 10, 15, 20, 25 mg	All	
Randomized	5	89	91	88	92	91	90	361	452	546
Safety Population	4 (80%)	66 (74%)	102 (112%)	84 (96%)	91 (99%)	84 (92%)	88 (98%)	NA	449 (99%)	519 (95%)
ITT Population	0 (0%)	85 (96%)	86 (95%)	70 (80%)	84 (91%)	79 (87%)	83 (92%)	316 (88%)	402 (89%)	487 (89%)
Type of Anesthesia (ITT Population)										
General	-	74 (87%)	71 (83%)	62 (89%)	73 (87%)	67 (85%)	71 (86%)	273 (86%)	344 (86%)	418 (86%)
Regional		11 (13%)	15 (17%)	8 (11%)	11 (13%)	12 (15%)	12 (14%)	43 (14%)	58 (14%)	69 (14%)
Opioid Usage Collected Through 48 Hours? (ITT Population)										
No	-	1 (1%)	0 (0%)	2 (3%)	0 (0%)	2 (3%)	0 (0%)	4 (1%)	4 (1%)	5 (1%)
Yes		84 (99%)	86 (100%)	68 (97%)	84 (100%)	77 (97%)	83 (100%)	312 (99%)	398 (99%)	482 (99%)
AE Information Collected Through Day 7? (Safety Population)										
No	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	NA	2 (< 1%)	2 (< 1%)
Yes	4 (100%)	66 (100%)	102 (100%)	84 (100%)	91 (100%)	82 (98%)	88 (100%)	NA	447 (> 99%)	517 (> 99%)
Patients Followed Through Day 30 for SAE and NAQ? (Safety Population)										
No	0 (0%)	1 (2%)	0 (0%)	0 (0%)	3 (3%)	4 (5%)	2 (2%)	NA	9 (2%)	10 (2%)
Yes	4 (100%)	65 (98%)	102 (100%)	84 (100%)	88 (97%)	80 (95%)	86 (98%)	NA	440 (98%)	509 (98%)
Reason for Early Termination (Safety Population)										
Noncompliance/ Lost to Follow-up	0 (0%)	1 (2%)	0 (0%)	0 (0%)	2 (2%)	1 (1%)	1 (1%)	NA	4 (1%)	5 (1%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	3 (4%)	1 (1%)	NA	5 (1%)	5 (1%)

Safety population = patients randomized and received study drug including patients studied before amendment 2. Note that the number of patients listed as randomized in the table includes patients randomized before amendment 2. The number of patients randomized after amendment 2 and who underwent the planned surgery was 498. Patients were included in the treatment group of the study drug actually received. Eighteen patients were dosed incorrectly and, for the safety analyses, were re-assigned to the treatment group of the actual dose received. Seventeen patients were randomized to the MS group, but actually received 5 mg SKY0401 (patients 1108, 6106, 6111, 6122, 12102, 12126, 16101, 19102, 36120, 63101, 66101, 73107, 73113, 73115, 74106, 74118, and 84109). One patient was randomized to the 5 mg

SKY0401 group, but actually received 25 mg SKY0401 (patient 1109). The percentage of patients in the 5 mg SKY0401 treatment group is greater than 100% because more patients received this dose than were randomized to the treatment group.

ITT population = Randomized after Amendment 02 and received planned surgical procedure. Patients were included in the treatment group to which they were randomized. Eleven patients were excluded even though they had surgery (patients 7103, 7105, 42105, 42113, 42114, 45105, 70123, 72105, 73125, 83107, and 83118). These patients withdrew consent or were not followed post-operatively.

MS = Unencapsulated morphine sulfate; ITT = Intent-to-treat; AE = Adverse event; SAE = Serious adverse event; NAQ = Neurological Assessment Questionnaire; NA = Not applicable.

From sponsor's study report SKY040112b, Section 10.1, page 56.

Fifty-five clinical sites in the United States and an additional 8 clinical sites in Australia participated in this study, with patients enrolled at 45 and 6 sites, respectively. The number of patients randomized by clinical site ranged from 1 to 63.

#### **Unplanned exclusions:**

Eleven patients were excluded from the ITT population even though they had surgery. These patients withdrew consent and/or were not followed post-operatively. Five patients (1%) terminated treatment early as a result of other reasons, including patient 74132 in the SKY0401 15-mg group (death prior to Day 30 follow-up visit), patients 12106, 70106, and 83119 in the SKY0401 20-mg group (unknown reason, inadequate pain control, and death prior to 24 hours post-dose, respectively), and patient 19103 in the SKY0401 25-mg group (site unable to contact the patient via telephone for the Day 30 assessment).

#### **1.5.3.4.2 Demographics/Group Comparability**

Overall, the mean age was 52 years for the SKY0401-treated patients, 52 years for the 10-, 15-, 20-, and 25-mg SKY0401-treated patients combined, 50 years for the 5-mg SKY0401-treated patients, 52 years for the MS- treated patients, and 55 years for the placebo-treated patients. Four hundred and fifteen of 519 patients (80%) were in the <65 years of age group and 387 of the 519 (75%) were females. Four hundred patients (77%) were Caucasian, with a further 68 patients (13%) Black. Sixty-two percent (324 of 519 patients) and 22% (112 of 519 patients) were ASA Class 2 and 1, respectively. The treatment groups were also similar in terms of height, weight, and BMI.

All patients in the ITT population underwent abdominal surgery. There were no significant differences among the treatment groups regarding the surgical procedure, with 260 and 174 of 487 patients (53% and 36%, respectively) undergoing a midline or Pfannensteil, respectively. The incision was extended above the umbilicus in 51 patients (11%), and the mean duration of surgery was 127 minutes.

Two hundred and one patients (39%) and 318 patients (61%) received study drug via a catheter or a needle, respectively, and the mean time from test dose to study drug administration was 23 minutes. There were no differences observed among treatment groups. Use of a test dose to assist in epidural placement of the drug was different among the treatment groups ( $p = 0.0015$ ).

There were no significant differences among the treatment groups receiving general, 445 patients (86%), or regional anesthesia, 74 patients (14%). The mean time from the administration of study drug to the administration of general anesthesia was 20.9 minutes. For those patients who received regional anesthesia, the mean time from the administration of study drug to anesthesia administration was 13.8 minutes.

#### **1.5.3.4.3 Unplanned Analyses**

Three patients received the study drug after the start of surgery.

The protocol was amended (Amendment 02) to change the design from a placebo-controlled study to a dose-controlled study with an active comparator. Consequently, enrollment to the placebo group was halted, and a 5-mg SKY0401 dose-control group was added and an MS group was added as an active comparator.

No interim analyses were conducted.

#### **1.5.3.5 Sponsor's Efficacy Results**

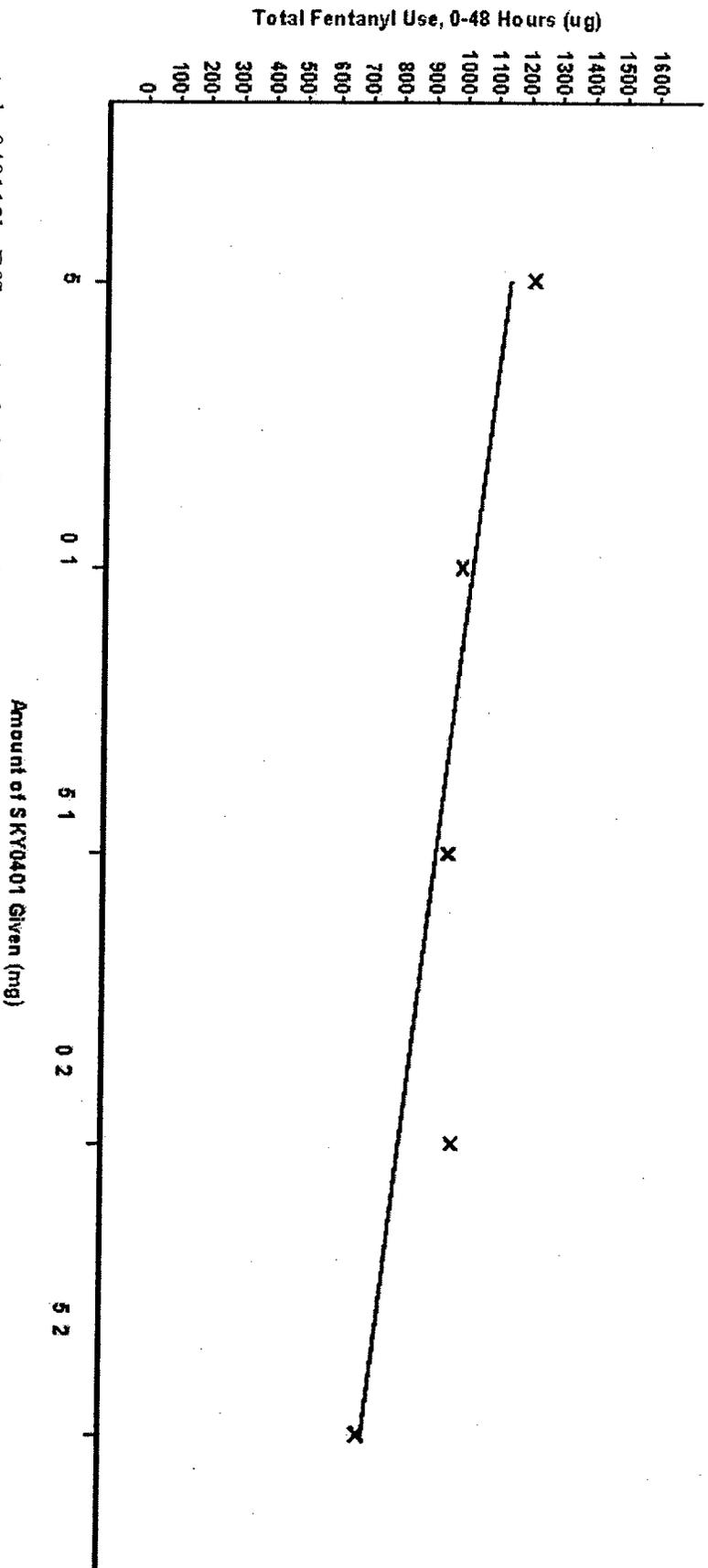
##### **1.5.3.5.1 Primary Efficacy Variable**

The primary efficacy endpoint defined in the study protocol was an assessment of the reduction in the average use of IV fentanyl through 48 hours post-dose. The sponsor reported two assessments that were used to analyze IV fentanyl use. First, the sponsor performed a linear regression analysis of dose-related reduction in the need for post-operative IV fentanyl through 48 hours based on advice following Agency Biometric review of the study protocol. Next, the sponsor presented an analysis of the mean total IV fentanyl usage comparing 10-, 15-, 20-, and 25-mg dose groups treated with SKY0401 to the group treated with 5-mg SKY0401. An ANOVA was performed on the ranked data as allowed by the study protocol because the data followed a non-normal distribution.

The sponsor's regression analysis of mean dose of IV fentanyl (Figure 12b-01) indicates a reduction in patient usage with an increasing dose of epidural SKY0401 administered before incision.

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Figure 1.5.3-1: Sponsor's Regression Analysis of Mean Fentanyl Usage Through 48 hours and SKY0401 Treatment Groups in ITT Population, Study 12b



From Study-report-sky040112b, Efficacy Analysis, Page 148.

Note that numerical labels associated with tick marks on the abscissa have tens and ones digits transposed, i.e. 52 should read 25.

P-value using rank-transformed data (slope different from zero)= 0.0004

95% Confidence Interval of Slope (-34.5030,-9.8657)

Estimate of slope (dose response parameter)=-22.2

The sponsor also reports that reduction in the use of IV fentanyl through 48 hours was demonstrated in terms of mean total IV fentanyl usage by ANOVA. The sponsor states that the mean total IV fentanyl usage through 48 hours post-dose in the 10-, 15-, 20, and 25-mg SKY0401 treatment groups was 995-, 959-, 972-, and 683-mcg, respectively, compared with 1213-mcg in the 5-mg SKY0401.

No adjustment was used for between-group measures of statistical significance to account for repeated measures artifact despite protocol specification that Dunnett's adjustment was to have been used to determine statistical significance between treatment groups. The sponsor did, however, report  $p < 0.05$  associated with IV fentanyl usage lower in the 10-, 20, and 25-mg SKY0401 groups, but not in the 15-mg SKY0401 group compared with the 5-mg SKY0401 group.

A similar between group analysis of the reduction in IV fentanyl use through 48 hours was also performed comparing SKY0401 with epidural 5-mg unencapsulated morphine. All dose groups (10, 15, 20, and 25 mg) of SKY0401 exhibited reductions ( $p < 0.05$ ) in IV fentanyl compared with the MS-dose group.

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Table 1.5.3-3: Sponsor's Fentanyl Usage Post-Dose ITT Population, Study 012b

Number of Patients	Treatment Groups										Overall Treatment P-Value*
	5 mg Urethecapsulated Morphine	5 mg SKY0401	10 mg SKY0401	15 mg SKY0401	20 mg SKY0401	25 mg SKY0401	10, 15, 20, 25 mg SKY0401	All SKY0401	Total		
Total IV Fentanyl Usage Through 48 Hours**											
n	85	86	70	84	79	83	316	402	487		
Mean (SD)	1217.7 (894.0)	1213.3 (1078.7)	995.1 (986.7)	959.0 (770.3)	972.0 (982.4)	682.5 (619.6)	897.6 (851.6)	965.2 (912.8)	1009.2 (913.7)		
Median	1005.0	955.0	645.0	760.0	590.0	500.0	614.5	668.9	745.0		
Min - Max	0 - 4577	0 - 6854	85 - 5518	0 - 3870	0 - 5033	0 - 3053	0 - 5518	0 - 6854	0 - 6854		
Pairwise p-value vs 5 mg SKY0401			0.1185	0.0599	0.0820	0.0001	0 - 5518	0 - 6854	0 - 6854		
Pairwise p-value vs 5 mg morphine		0.9811	0.1212	0.0621	0.0856	0.0001				0.0052	0.0012

\* P-values are determined using ANOVA including classification terms for treatment group and type of anesthesia. Pairwise comparisons vs 5 mg SKY0401 for each of the 10, 15, 20 and 25 mg SKY0401 treatment groups and pairwise comparisons of each SKY0401 treatment group vs 5 mg unencapsulated morphine should be evaluated only if the overall treatment group effect is significant.  
 \*\* If a patient discontinued before 48 hours, their 48-hour total IV fentanyl usage is projected by taking the average amount of post-operative IV fentanyl administered per hour over the 6 hours preceding discontinuation (or available number of hours if less than 6 hours) and multiplying that average amount by the number of hours remaining in the 48-hour period, and adding this to the amount of IV fentanyl actually used.

From sponsor's "Study Report SKY04012b, End of Text Tables and Figures, Efficacy Results, Section 14.2, Table 9, Page 216."

Narcotics other than fentanyl were used to supplement analgesia in the first 48 hours after epidural study drug administration. This deviation from strict execution of the protocol was anticipated and the protocol outlined a plan to calculate the total narcotic dose as a fentanyl-equivalent dose per patient. The same statistical techniques applied to analysis of average total fentanyl usage were applied to total narcotic usage.

Statistically significant differences were reported by the sponsor among SKY0401 treatment groups and between 5-mg MS and higher doses (15 mg to 25 mg) of SKY0401 treatment groups. The sponsor further reported differences in supplemental narcotic usage ( $p < 0.05$ ) between 5-mg SKY0401 and each of 15-, 20- and 25- mg, but in contradiction to the protocol, no adjustment for repeated measures was used. The sponsor also reported  $p < 0.05$  between 5-mg MS and each of 15-, 20- and 25-mg SKY0401 groups.

Table 1.5.3-4 Sponsor's Reported Total Fentanyl-Equivalent Narcotic Supplement in 48 Hours After Study Drug, Study 012b

	MS	SKY0401					
	5 mg	5 mg	10 mg	15 mg	20 mg	25 mg	All
Patients (n)	85	86	70	84	79	83	402
Total opioid usage through 48 hours post-dose (mcg)							
Mean	1312.5	1283.5	1041.0	962.7	1008.0	703.1	1000.3
Median	1210.0	994.0	743.7	767.5	622.6	520.0	747.5
Min - Max	0 - 4577	0 - 7857	85 - 5518	0 - 3870	0 - 5033	0 - 3053	0 - 7857
p-value vs. 5 mg SKY0401 <sup>1</sup>	-	-	NS	0.0194	0.0499	< 0.0001	-
p-value vs. 5 mg MS <sup>2</sup>	-	NS	NS	0.0130	0.0358	< 0.0001	-

For patients who discontinued prior to 48 hours, his/her 48-hour opioid analgesic usage was a projected amount. P-values were determined using ANOVA including classification terms of treatment group and type of anesthesia after a rank-transformation of the data. Pairwise comparisons were evaluated only if the overall treatment group effect was significant.

<sup>1</sup>p-value = 0.0016 for overall test among SKY0401 treatment groups.

<sup>2</sup>p-value = 0.0001 for overall test among all treatment groups (SKY0401 and MS).

MS = Unencapsulated morphine sulfate; Min = Minimum; Max = Maximum; NS = Not significant.

### 1.5.3.5.2 Secondary Efficacy Variables

- **The time to first post-operative IV fentanyl usage**

The average time to first post-operative IV fentanyl usage by treatment group is summarized in Table 1.5.3-5 below.

Table 1.5.3-5. Sponsor's Findings of Average Time to First IV Fentanyl Administration, Study 012b

	MS	SKY0401					
	5 mg	5 mg	10 mg	15 mg	20 mg	25 mg	All
Patients (n)	85	86	70	84	79	83	402
Time to First Post-Operative IV Fentanyl							
Median <sup>1,2</sup>	3.6	3.7	3.6	3.4	3.7	4.0	3.7
Min - Max <sup>3</sup>	1.4 - 48.0	1.5 - 48.0	1.9 - 48.0	0.7 - 48.0	1.6 - 48.0	1.3 - 48.0	0.7 - 48.0

P-values were determined using a logrank test stratified by type of anesthesia. Pairwise comparisons were evaluated only if the overall treatment group effect was significant.

<sup>1</sup>Medians were obtained using the Kaplan-Meier product limit estimates.

<sup>2</sup>p-values for overall test among SKY0401 treatment groups and among all treatment groups (SKY0401 and MS) were not significant.

<sup>3</sup>largest value was censored in all treatment groups.

MS = Unencapsulated morphine sulfate; IV = Intravenous; Min = Minimum; Max = Maximum.

From Sponsor's study-report-sky040112b, Efficacy Analysis, page 72.

The sponsor found no statistically significant differences in the median time to first post-operative IV fentanyl requirement between treatment groups 5-, 10-, 15-, 20-, and 25-mg SKY0401 and the 5-MS group. They found that evaluation by gender (male or female), age group (< 65 or =65 years of age), race (Caucasian or non-Caucasian), type of anesthesia (general or regional), ASA Classification (Class 1, 2, or 3). The sponsor reported that an analysis of use of test dose usage and timing of test dose administration failed to reveal statistically significant differences.

• **Proportion of Patients Receiving No Post-Operative IV Fentanyl**

The sponsor reports that through the first 24 hours post-dose there were no significant differences among the treatment groups in the proportion of patients that did not require IV fentanyl for post operative pain relief.

In contrast, when considering the entire 48 hour post-dose interval, they noted a significant difference among the treatment groups (p = 0.0096), with a higher proportion of patients (p<0.05) receiving no fentanyl in the 10-, 15-, 20-, and 25-mg SKY0401 groups compared with the MS. When analyzed between > 24 to 48 hours, the sponsor indicated that higher numbers of patients receiving no post-operative IV fentanyl were also observed in the 10-, 15-, 20-, and 25-mg SKY0401 groups compared with the MS group (p <0.05). The sponsor states that similar findings were noted between > 36 to 48 hours.

The proportion of patients receiving no post-operative IV fentanyl is summarized in Table 1.5.3-6 below.

Table 1.5.3-6: Sponsor's Reported Proportion of Patients Receiving No Post-Operative IV Fentanyl, Study 012b

	MS	SKY0401					
	5 mg	5 mg	10 mg	15 mg	20 mg	25 mg	All
Patients (n)	85	86	70	84	79	83	402
Proportion Receiving No Post-Operative IV Fentanyl							
Through 24 hours <sup>1</sup>	6%	14%	20%	20%	18%	18%	18%
Through 48 hours <sup>2,3</sup>	2%	6%	17%	16%	13%	16%	13%
p-value vs. 5 mg MS	-	NS	0.0015	0.0029	0.0121	0.0028	-
0 to 12 hours <sup>1</sup>	20%	19%	27%	25%	18%	24%	22%
> 12 to 24 hours <sup>1</sup>	19%	23%	34%	32%	35%	37%	32%
> 24 to 36 hours <sup>2,4</sup>	12%	16%	27%	23%	32%	35%	26%
p-value vs. 5 mg MS	-	NS	0.0155	NS	0.0019	0.0004	-
> 36 to 48 hours <sup>2,3</sup>	14%	20%	31%	27%	39%	33%	30%
p-value vs. 5 mg MS	-	NS	0.0104	0.0343	0.0002	0.0043	-

P-values were determined using the CMH test stratified by type of anesthesia. Pairwise comparisons were evaluated only if the overall treatment group effect was significant.

<sup>1</sup>p-values for overall test among SKY0401 treatment groups and all treatment groups (SKY0401 and MS) were not significant.

<sup>2</sup>p-value for overall test among SKY0401 treatment groups was not significant.

<sup>3</sup>p-value = 0.0096 for overall test among all treatment groups (SKY0401 and MS).

<sup>4</sup>p-value = 0.0027 for overall test among all treatment groups (SKY0401 and MS).

<sup>5</sup>p-value = 0.0039 for overall test among all treatment groups (SKY0401 and MS).

MS = Unencapsulated morphine sulfate; IV = Intravenous.

From sponsor's Study Report SKY04012b "Efficacy Evaluation, Analysis of Efficacy, Table 11.4.1.2-4, page73.

• **Pain Intensity Evaluations: Visual Analog Scale**

The mean VAS scores for pain intensity at rest (VAS-R) over 48 hours in the 15-, 20-, and 25-mg SKY0401 treatment groups were lower than those in both the 5-mg SKY0401 and the 5-mg MS group. VAS-R was also evaluated using area under the curve (AUC) analysis including terms for treatment groups and type of anesthesia. Improved pain scores were achieved with SKY0401 doses of 15-, 20-, and 25-mg in a setting where all patients were self-treating (PCA) their post-operative pain with supplemental fentanyl.

At the first request for pain medication, there were no significant differences observed among the treatment groups, with mean VAS-R scores of 58 and 57 in the SKY0401-treated and MS-treated patients, respectively. The 15-, 20-, and 25-mg SKY0401 groups consistently demonstrated lower VAS-R scores when compared with the 5-mg MS group at the 12- (p <0.05), 18- (p <0.05), 24- (15- and 25-mg groups only; p <0.05), 30- (p <0.05), and 36-hours (p <0.05) time points.

Analysis of pain with activity (VAS-A) by AUC demonstrated a reduction in pain intensity over 48 hours with 10-, 15-, 20-, and 25-mg SKY0401 compared with 5-mg SKY0401 and with 20- and 25-mg SKY0401 compared with 5-mg MS.

Table 1.5.3-7: Sponsor’s Reported Summary of Pain Response at Rest and with Activity, Study 12b

	MS	SKY0401					
	5 mg	5 mg	10 mg	15 mg	20 mg	25 mg	All
Number of Patients	85	86	68	83	77	82	396
AUC (0-48 Hours) at Rest (VAS-R)							
Mean	1174.2	1125.2	1078.1	891.6	853.8	774.7	942.8
p-value vs. 5 mg SKY0401 <sup>1</sup>	–	–	NS	0.0265	0.0141	0.0013	–
p-value vs. 5 mg MS <sup>2</sup>	–	NS	NS	0.0107	0.0056	0.0004	–
Number of Patients	85	86	67	84	77	82	396
AUC (0-48 Hours) with Activity (VAS-A)							
Mean	1998.0	2027.3	1716.7	1706.6	1666.6	1601.5	1748.4
p-value vs. 5 mg SKY0401 <sup>3</sup>	–	–	0.0448	0.0299	0.0202	0.0052	–
p-value vs. 5 mg MS <sup>4</sup>	–	NS	NS	NS	0.0384	0.0106	–

P-values were determined using ANOVA including terms for treatment groups and type of anesthesia. Pairwise comparisons were evaluated only if the overall treatment group effect was significant.

<sup>1</sup>p-value = 0.0068 for overall test among SKY0401 treatment groups.

<sup>2</sup>p-value = 0.0008 for overall test among all treatment groups (SKY0401 and MS).

<sup>3</sup>p-value = 0.0490 for overall test among SKY0401 treatment groups.

<sup>4</sup>p-value = 0.0139 for overall test among all treatment groups (SKY0401 and MS).

MS = Unencapsulated morphine sulfate. AUC = Area under the curve.

VAS = Visual Analog Scale, i.e., pain assessment on a 100 mm length line, where 0 = no pain and 100 = the most severe pain possible; VAS-R = pain assessment using VAS while patient was at rest; VAS-A = pain assessment using VAS with activity.

From sponsor’s Study Report SKY04012b “Efficacy Evaluation, Analysis of Efficacy”, Sponsor’s Table 11.4.1.2-5, page 75.

• **Pain Intensity Evaluations: Categorical Scale**

Pain intensity ratings at rest and with activity were evaluated using a categorical scale (CAT-R and CAT-A) (where 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain). With exceptions, the data demonstrated lower pain scores with SKY0401 10 to 25-mg compared with SKY0401 5-mg.

Table 1.5.3-8 Number of Patients Having No Pain or Mild Pain vs. Moderate or Severe Pain at Rest by Treatment Group, Study 012b

	5 MS	5 SKY	10 SKY	15 SKY	20 SKY	25 SKY	10-25 SKY	5-25 SKY	Total	p value SKY 5, MS
N	85	84	70	84	79	83	316	402	487	
1 <sup>st</sup> request	11	8	7	13	10	7	37	45	56	0.59
	71	72	51	58	58	63	230	302	373	0.63
	3	6	12	13	11	13	49	55	58	
4 hrs	31	28	29	36	28	42	135	163	194	0.18
	35	37	27	30	30	21	118	145	180	0.21
	19	21	14	18	21	20	73	94	113	

	<b>5 MS</b>	<b>5 SKY</b>	<b>10 SKY</b>	<b>15 SKY</b>	<b>20 SKY</b>	<b>25 SKY</b>	<b>10-25 SKY</b>	<b>5-25 SKY</b>	<b>Total</b>	<b>p value SKY 5, MS</b>
<b>N</b>	<b>85</b>	<b>84</b>	<b>70</b>	<b>84</b>	<b>79</b>	<b>83</b>	<b>316</b>	<b>402</b>	<b>487</b>	
<b>8 hrs</b>	62 20 3	59 24 3	50 15 5	65 14 5	56 19 4	70 9 4	241 57 18	300 81 21	362 101 24	0.002 0.004
<b>12 hrs</b>	59 22 4	70 15 1	51 15 4	75 6 3	65 9 5	74 7 2	265 37 14	335 52 15	394 74 19	0.006 0.0001
<b>24 hrs</b>	62 22 1	64 22 6	47 20 3	69 24 1	65 10 4	69 13 1	250 57 9	314 79 9	276 101 10	0.0004 0.0001
<b>30 hrs</b>	54 28 3	62 24 0	49 20 2	75 8 1	62 14 3	74 7 2	260 48 8	322 72 8	376 100 11	0.0006 0.0000
<b>36 hrs</b>	57 23 5	66 18 2	50 17 3	66 17 1	65 10 4	69 12 2	250 56 10	316 74 12	373 97 17	0.024 0.003
<b>48 hrs</b>	69 14 2	67 18 1	51 16 3	74 8 2	62 13 4	72 10 1	259 47 10	326 64 11	395 79 13	0.06 0.08

Data was abstracted from sponsor's study report SKY041012b, Section 14.2 Table 19 Pages 259-263.

N indicates number of patients. "1<sup>st</sup> Request" indicates data collected at patient's first request for supplemental pain medication. "4-48 hrs" indicates data collected 4 to 48 hours after study drug administration. "5 MS" refers to treatment group that received 5-mg epidural unencapsulated morphine. 5 SKY refers to treatment group that received 5-mg SKY0401. "10-25 SKY" refers to patients treated with from 10-mg SKY0401 to 25-mg SKY0401. 5-25 SKY refers to patients treated with from 5-mg SKY0401 to 25-mg SKY0401. "Total" refers to the sum of all patients in each category. "p value SKY, MS" refers to the calculated p value from ANOVA of ranked data used to compare the group treated with 5-mg SKY0401 to the groups treated with from 10- to 25-mg SKY0401 and the group treated with 5-mg MS to the groups treated with from 10- to 25-mg SKY0401. The vertical column of three numbers in each cell under the various treatment groups indicates (from top to bottom) the number of patients having no or mild pain, moderate or severe pain and the number of missing values. Emboldened numbers in the cells in treatment group columns are used to identify doses the sponsor indicated were significant in between group analysis.

The sponsor presented the results of multiple comparison between each of 10-, 15-, 20 and 25-mg SKY0401 treatment groups the 5-mg SKY0401 group. A similar analysis was also presented by the sponsor comparing between each of 10-, 15-, 20 and 25-mg SKY0401 treatment groups the 5-mg MS group. In neither between-group analysis were adjustments made for repeated measurements.

When SKY0401 groups were compared with 5-mg MS, reduced CAT-R scores were observed at 8 hours (25 mg; p = 0.0043), 12 hours (15, 20, and 25 mg; p<0.05), 18 hours (15, 20, and 25 mg; p <0.05), 24 hours (15, 20, and 25 mg; p<0.05), 30 hours (15, 20, and 25 mg; p<0.05), and 36 hours (20 and 25 mg; p<0.05).

The sponsor reported similar results from their analysis of CAT-A (categorical scale with activity).

• **Patient and Surgeon Rating of Pain Control**

The control of pain was rated by patients and surgeons as very good, good, fair, or poor. See Table 1.5.3-9. On Day 2, more patients had higher ratings of pain control in the 15-, 20-, and 25-mg SKY0401 groups compared with 5-mg SKY0401 (p<0.05). Pain control was also better for 15- and 25-mg SKY0401 than 5-mg MS on day 2. The

proportion of patients who rated their pain control as good or very good was higher in the 15- and 25-mg SKY0401 groups compared with the 5-mg SKY0401 group ( $p < 0.05$ ). At Day 3, there were no significant differences observed among the treatment groups in terms of overall ratings of pain control or in the proportion of patients who rated their pain control as good or very good.

When pain control was rated by the surgeon, more patients had higher ratings at Day 2 for the 25-mg SKY0401 group compared with the 5-mg SKY0401 group ( $p = 0.0021$ ). Pain control was better for 10, 15 and 25 mg SKY0401 when compared with 5-mg MS. on day 2 and for 15- and 25-mg SKY0401 on day 3. There were no differences among the treatment groups at either Day 2 or 3 in terms of the proportion of patients, as rated by the surgeon, with pain ratings of good or very good.

Table 1.5.3-9: Sponsor's Reported Patient and Surgeon Ratings of Pain Control, Study 012b

Overall Ratings of Pain Control	MS	SKY0401					
	5 mg	5 mg	10 mg	15 mg	20 mg	25 mg	All
Patient Rating at Day 2							
p-value vs. 5 mg SKY0401 <sup>1</sup>	-	-	NS	0.0033	0.0493	0.0001	-
p-value vs. 5 mg MS <sup>2</sup>	-	NS	NS	0.0473	NS	0.0030	-
Patient Rating at Day 3 <sup>3</sup>							
Surgeon Rating at Day 2							
p-value vs. 5 mg SKY0401 <sup>4</sup>	-	-	NS	NS	NS	0.0021	-
p-value vs. 5 mg MS <sup>5</sup>	-	NS	0.0197	0.0473	NS	0.0002	-
Surgeon Rating at Day 3 <sup>6</sup>							
p-value vs. 5 mg MS <sup>7</sup>	-	NS	NS	0.0408	NS	0.0024	-

P-values were determined using the CMH (row-mean-score) test stratified by type of anesthesia. Pairwise comparisons were evaluated only if the overall treatment group was significant.

<sup>1</sup>p-value = 0.0015 for overall test among SKY0401 treatment groups.

<sup>2</sup>p-value = 0.0015 for overall test among all treatment groups (SKY0401 and MS).

<sup>3</sup>p-values for overall test among SKY0401 treatment groups and all treatment groups (SKY0401 and MS) were not significant.

<sup>4</sup>p-value = 0.0205 for overall test among SKY0401 treatment groups.

<sup>5</sup>p-value = 0.0028 for overall test among all treatment groups (SKY0401 and MS).

<sup>6</sup>p-value for overall test among SKY0401 treatment groups was not significant.

<sup>7</sup>p-value = 0.0225 for overall test among all treatment groups (SKY0401 and MS).

NS = Not significant; MS = Unencapsulated morphine sulfate.

From sponsor's Study Report SKY04012b "Efficacy Evaluation, Efficacy Results", Sponsor's Table 11.4.1.2-7, page 78.

### 1.5.3.5.3 Additional Efficacy Analyses Presented by Sponsor

- Secondary analysis of primary efficacy endpoint: supplemental fentanyl use, evaluated by successive intervals

The sponsor performed a secondary analysis of the primary efficacy endpoint comparing the 10-, 15-, 20-, and 25- mg SKY0401 groups with the 5-mg SKY0401 group in terms of IV fentanyl usage by successive intervals of time through 48 hours following

the administration of study drug. The results were consistent with those reported above for the primary efficacy analyses. For patients that did not complete the study, the amount of fentanyl used was the amount actually used rather than a calculated projection as performed in the primary efficacy analysis. Compared with the 5-mg SKY0401 treatment group, fentanyl usage in the 10-, 20- and 25-mg SKY0401 treatment groups was reduced from > 24 to 48 hours post-dose (20 and 25 mg groups only; p<0.05), 0 to 48 hours post-dose (p<0.05), and post-operatively through 48 hours post-dose (p<0.05). When evaluated by successive 4-hour intervals, mean IV fentanyl usage at each interval after 8 hours post-dose was consistently lower in the 10-, 15-, 20-, and 25-mg SKY0401 groups compared with the 5-mg SKY0401 treatment group.

Compared with the MS treatment group, fentanyl usage in the 10-, 15-, 20- and 25-mg SKY0401 treatment groups was also reduced from > 24 to 48 hours post-dose (p<0.05), 0 to 48 hours post-dose (p<0.05), and post-operatively through 48 hours post-dose (p<0.05). When evaluated by successive 4-hour intervals, mean IV fentanyl usage at each interval after 8 hours post-dose was also consistently lower in the 10-, 15-, 20-, and 25-mg SKY0401 groups when compared with the 5-mg MS treatment group.

Table 1.5.3-10 Sponsor's Reported Summary of Secondary Analysis of Primary Efficacy Endpoint, Study 012b

	MS	SKY0401					
	5 mg	5 mg	10 mg	15 mg	20 mg	25 mg	All
IV fentanyl usage (mcg) 0 to 24 hours post-dose							
n	85	86	70	84	79	83	402
Mean	677.3	662.4	559.1	591.5	598.9	404.0	563.8
p-value vs. 5 mg SKY0401 <sup>1</sup>	-	-	NS	NS	NS	0.0003	-
p-value vs. 5 mg MS <sup>2</sup>	-	NS	NS	NS	NS	0.0001	-
IV fentanyl usage (mcg) > 24 to 48 hours post-dose							
n	85	86	69	84	78	83	400
Mean	540.3	550.9	401.2	366.9	322.3	277.5	385.1
p-value vs. 5 mg SKY0401 <sup>3</sup>	-	-	NS	NS	0.0042	0.0005	-
p-value vs. 5 mg MS <sup>4</sup>	-	NS	0.0066	0.0077	0.0001	< 0.0001	-
IV fentanyl usage (mcg) 0 to 48 hours post-dose							
n	85	86	70	84	79	83	402
Mean	1217.6	1213.3	954.6	958.4	917.1	681.4	947.0
p-value vs. 5 mg SKY0401 <sup>5</sup>	-	-	0.0237	NS	0.0143	< 0.0001	-
p-value vs. 5 mg MS <sup>4</sup>	-	NS	0.0042	0.0311	0.0023	< 0.0001	-
Post-Operative IV fentanyl usage (mcg) through 48 hours post-dose							
n	85	86	70	84	79	83	402
Mean	1029.4	1020.8	761.8	751.1	704.2	517.0	753.1
p-value vs. 5 mg SKY0401 <sup>6</sup>	-	-	0.0271	NS	0.0092	0.0001	-
p-value vs. 5 mg MS <sup>4</sup>	-	NS	0.0021	0.0097	0.0005	< 0.0001	-

For patients who died, withdrew from the study, or were lost to follow-up before 48 hours post-dose, his/her fentanyl usage was the actual amount reported and not a projected amount as for the primary efficacy.

P-values were determined using ANOVA including classification terms of treatment group and type of anesthesia after a rank-transformation of the data. Pairwise comparisons were evaluated only if the overall treatment group effect was

significant.

\*p-value = 0.0049 for overall test among SKY0401 treatment groups.

\*p-value = 0.0016 for overall test among all treatment groups (SKY0401 and MS).

\*p-value = 0.0067 for overall test among SKY0401 treatment groups.

\*p-value < 0.0001 for overall test among all treatment groups (SKY0401 and MS)

\*p-value = 0.0011 for overall test among SKY0401 treatment groups.

\*p-value = 0.0025 for overall test among SKY0401 treatment groups.

MS = Unencapsulated morphine sulfate; IV = Intravenous; NS = Not significant.

From sponsor's "Study Report SKY04012b, Efficacy Evaluation, Analysis of Efficacy, Table 11.4.1.2-1", page 70.

- Time to First Post-Operative Opioid Usage (all opiate analgesics administered)

This secondary efficacy endpoint was also analyzed by the sponsor in terms of the time to first post-operative opioid usage. The results were consistent with those above, with the median time of 3.5 hours in the SKY0401 groups and 3.4 hours in the MS group. No p values less than 0.05 were observed among the treatment groups.

- Pain Intensity Evaluations: Integrated Rank Assessment Using VAS Scores and Total IV Fentanyl Usage

In an effort to account for the effect of opioid analgesic medication usage on pain intensity, the sponsor analyzed the data as an integrated rank at rest and with activity using the VAS scores and total IV fentanyl usage data. In this analysis, lower scores were reflective of combined lower pain scores and lower IV fentanyl usage. The results demonstrated a reduction ( $p < 0.05$ ) in combined pain intensity scores at rest and total IV fentanyl usage over the entire 48-hour time period (using the AUC) for 15-, 20-, and 25-mg SKY0401 compared with 5-mg SKY0401 and with 10-, 15-, 20-, and 25-mg SKY0401 compared with 5-mg MS treatment. Similar results were noted in combined pain intensity scores with activity and total IV fentanyl usage, with reductions ( $p < 0.05$ ) observed over the entire 48-hour period (using the AUC) with 10-, 15-, 20-, and 25-mg SKY0401 dose groups compared with both the 5-mg SKY0401 and 5-mg MS groups.

- Total Opioid Use in 48 hours

Total opioid usage (total usage through 48 hours post-dose and at successive intervals of time through 48 hours post-dose) was also evaluated, with opioid usage converted to fentanyl equivalents. These results were consistent with those for IV fentanyl usage, and demonstrated a decreased usage of opioids with SKY0401 treatment compared with both 5-mg SKY0401 and 5-mg MS use. Patients in the 15-, 20-, and 25-mg SKY0401 groups demonstrated lower total opioid usage ( $p < 0.05$ ) through 48 hours post-dose compared with patients in the 5-mg SKY0401 group. In addition, lower usage ( $p < 0.05$ ) was also reported in the 15-, 20-, and 25-mg SKY0401 groups compared with 5-mg MS group.

From 0 to 24 hours post-dose, opioid usage in the 25-mg SKY0401 group was reduced ( $p < 0.05$ ) compared with both the 5-mg SKY0401 and MS groups.

From > 24 to 48 hours post-dose, the 10-, 15-, 20-, and 25-mg SKY0401 groups demonstrated lower opioid usage ( $p < 0.05$ ) compared to both the 5-mg SKY0401 and MS groups.

### 1.5.3.6 REVIEWER'S COMMENTS

This Phase 3 study in 487 patients was designed to evaluate the analgesic efficacy of 10-mg, 15-mg, 20-mg and 25-mg SKY0401 compared with placebo in the setting of lower abdominal surgery. The study design was amended January 19, 2002 to replace the placebo arm with a 5-mg SKY0401 dose-control arm and a 5-mg unencapsulated morphine arm was added also. The efficacy analysis was performed on data collected from patients enrolled after the protocol was amended and the conclusion reflects this analysis. The safety population included patients studied both before and after the amendment. The protocol amendments of June 11, 2001 and October 21 2002 did not impact the analyses or conclusions.

The primary comparison was between 10-mg, 15-mg, 20-mg and 25-mg SKY0401 and the 5-mg SKY0401 dose. Of the 16 patients not included in the efficacy population, 11 withdrew consent or were not followed postoperatively. Five other patients terminated treatment early. This reviewer determined that the study conduct reflected the protocol despite minor variances and was adequate to analyze efficacy of SKY0401.

The sponsor was able to demonstrate a statistically significant reduction in supplemental fentanyl, the primary efficacy endpoint, that SKY0401 in doses of 10 mg, 15 mg, 20 mg and 25 mg were collectively superior to a 5-mg dose of SKY0401. To differentiate efficacy between doses of SKY0401 the sponsor presented a linear regression model. The model indicates a trend toward improved efficacy with increasing dose, but the slope of the regression line was not acute. Taken together, these findings support a conclusion of efficacy for SKY0401, but suggest that differences in efficacy between doses above 5 mg may be minor.

My clinical interpretation of the 145 mcg median difference (less than 3 mL) in supplemental fentanyl administered over 48 hours for patients treated with SKY0401 doses ranging from 10 mg to 25 mg is that it is too small to be of practical significance. In other words, despite the statistical significance of SKY0401 doses (10 mg, 15 mg, 20 mg and 25 mg) compared collectively to 5 mg SKY0401, the clinical impact of increasing the dose from 10 mg to 25 mg was small, in terms of the median amount of supplemental fentanyl given to patients. (The median rather than the mean was used for this assessment because the data were not normally distributed.)

Analysis of some of the secondary efficacy endpoints supported the finding of efficacy for SKY0401. Analysis of all the supplemental narcotic administered over 48 hours, calculated in fentanyl equivalent units demonstrated a dose-related reduction for SKY0401. These findings are consistent with the sponsor's analysis reported for IV fentanyl. They suggest that use of alternative opiates for pain control did not bias the finding that SKY0401 reduced patient requirements for additional pain control measures for 48 hours after administration. A reduction in supplemental fentanyl and opioid (in

fentanyl equivalent units) over 48 hours associated with SKY0401 treatment was also observed in comparison to the supplemental fentanyl requirements of patients treated with a 5-mg dose of epidural unencapsulated morphine. The sponsor's analysis suggested that for 15-mg, 20-mg or 25-mg doses of SKY0401, the VAS at rest was lower than when 5 mg of SKY0401 was given. With activity a SKY0401 dose as low as 10 mg reduced VAS compared with a 5-mg dose of SKY0401. The assessment of pain with activity, clinically the more important measurement, did not demonstrate striking dose-dependent improvement with a SKY0401 dose above 10 mg compared with 5-mg SKY0401.

Findings of efficacy demonstrated mixed success for some of the secondary endpoints. There appeared to be a general trend of increasing frequency of patients reporting no pain or mild pain with increasing dose of SKY0401. SKY0401 doses of 15 mg, 20 mg and 25 mg appeared to be similar and superior when compared with 5 mg SKY0401. The 10-mg dose of SKY0401 did not appear to be better than the 5-mg dose using this measure. The impressions of patients and surgeons in interpreting the quality of pain control on the second postoperative day was mixed except for the highest dose of SKY0401 (25 mg). At the 25-mg dose, patients and surgeons, blinded to treatment group appeared to identify better pain control compared to the 5-mg dose of SKY0401.

The sponsor attempted to demonstrate that SKY0401 was effective between 24 and 48 hours after administration. The sponsor's analysis reported a statistically significant reduction in IV fentanyl in patients treated with SKY0401 doses as small as 10 mg compared with 5 mg of unencapsulated morphine, but not compared with 5 mg SKY0401. In the sponsor's analysis, only 20-mg and 25 mg doses of SKY0401 were statistically superior to 5-mg SKY0401 in reducing IV fentanyl in the 24 hour to 48-hour period after surgery. The sponsor's analysis of total opioid usage indicated that between 24 and 48 hours post-dose, the 10-, 15-, 20-, and 25-mg SKY0401 groups demonstrated lower opioid usage compared to both the 5-mg SKY0401 and unencapsulated morphine groups.

No adjustments were made for statistical multiple comparisons testing in the efficacy analyses, however the data trends support the sponsor's conclusion.

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#### **1.5.4 Study 015, Cesarean section:**

A Randomized, Double-Blind, Active-Controlled, Dose-Ranging, Parallel Group 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 Elective Cesarean Section under Intrathecal Anesthesia

##### **1.5.4.1 Findings vs. Labeling Claims**

See Section, "REVIEW OF PACKAGE INSERT".

##### **1.5.4.2 Study Plan**

###### **1.5.4.2.1 Population, Design, and Objectives**

**Objectives:** The primary objective of this study is to compare the analgesic efficacy of SKY0401 versus unencapsulated morphine for the management of post-operative pain following cesarean section. The secondary objective of this study is to compare the safety profile of SKY0401 versus unencapsulated morphine for the management of post-operative pain following cesarean section.

**Population:** N= 79 randomized, 75 in efficacy analysis

- **Inclusion Criteria:**

1. Females  $\geq$  18 years of age at the Screening Visit
2. Undergoing elective cesarean section under intrathecal anesthesia
3. American Society of Anesthesiology (ASA) Physical Class 1 or 2
4. Willing to receive PO acetaminophen with codeine or IV morphine for 48 hours post-dose to control post-operative pain
5. Expected and willing to remain hospitalized for a minimum of 48 hours post-dose
6. Capable of speaking and understanding English sufficiently to provide written informed consent and responses to pain assessment scales and neurological assessment questionnaires

- **Exclusion Criteria:**

1. Morbid obesity at the beginning of the pregnancy, defined as a body mass index (BMI)  $\geq$  40. BMI is calculated as follows: (weight [lbs.]  $\div$  height [inches]<sup>2</sup>) x 704.5
2. More than 40 pounds weight gain during the pregnancy
3. Current or historical evidence of any clinically significant disease or condition that, in the opinion of the investigator, might increase the risk of surgery or complicate the patient's post operative course
4. Patients undergoing emergency cesarean section
5. Patients undergoing cesarean section under epidural or general anesthesia
6. Suspected or documented history of sleep apnea, narcolepsy, or excessive daytime sleepiness

7. History of hypersensitivity or idiosyncratic reaction to opioid medications
8. Any contraindication for the epidural administration of study drug (e.g., coagulopathy, local infection)
9. Administration of an investigational drug within 30 days prior to Screening
10. Suspected or documented history of substance abuse and/or alcoholism
11. Chronic narcotic medication usage (defined as daily narcotics for more than the 7 days prior to enrollment)
13. Unwilling or unable to provide written informed consent and/or to comply with study procedures, completion of all patient-rated scales, and 30-day follow-up assessments

Patient who have been enrolled and randomized were to have been excluded for the following adverse events or protocol violations:

13. Dural puncture with epidural needle
14. Experienced any clinically significant complications (e.g., excessive bleeding) during the surgery, which rendered the patient medically unstable or might complicate the patient's post-operative course
15. Received any local anesthetic agent (such as bupivacaine, lidocaine, etc.) through the epidural catheter prior to the study drug administration
16. Received general anesthesia due to failure of intrathecal anesthesia

### **Design**

Enrolled patients were to have been randomized in a 1:1:1:1 ratio to receive one of the following: 5, 10, or 15 mg of SKY0401 or 5 mg of unencapsulated morphine. SKY0401 or unencapsulated morphine will be administered epidurally following delivery and clamping of the umbilical cord.

Post-operatively, all patients were to have been permitted to receive oral acetaminophen with codeine, IV morphine as an intermittent bolus or IV morphine administered via a PCA pump, if supplemental pain medication is needed. Narcotic medications other than PO acetaminophen with codeine or IV morphine was not to have been permitted postoperatively through 48 hours post-dose.

Narcotic analgesic medication usage was to have been be quantified through 48 hours after study drug administration. Pain intensity at rest and with activity (cough) will be assessed using both a Visual Analog Scale (VAS-R and VAS-A) and Categorical Scale (CAT-R and CAT-A) at the time of first request for analgesic medication and at 4, 8, 12, 24, 30, 36, and 48 hours post-dose. Functional ability was to have been assessed at 24 and 48 hours postdose. Patient ratings of pain control was also to have been assessed at 24 and 48 hours post-dose.

#### **1.5.4.2.2 Treatment Summary**

##### **Description of Study Drug**

SKY0401 is formulated as a sterile, non-pyrogenic, white to off-white, preservative-free, homogenous suspension of morphine encapsulated into multivesicular lipid-based particles (DepoFoam drug delivery system). SKY0401 is intended for epidural use only. It is supplied as a 2-ml single-use vial. Each vial contains 10 mg/ml of sustained-release encapsulated morphine.

##### **1.5.4.2.3 Treatment Assignment**

Patients will be randomly assigned in a 1:1:1:1 ratio stratified by site on Day 1 to one of the following four treatment groups: 5 mg of unencapsulated morphine, or 5, 10 or 15 mg of SKY0401. Once patient eligibility is confirmed, the patient will be randomized to a treatment group by utilizing randomization envelopes provided by the sponsor. The next sequential randomization envelope should be opened for each patient.

##### **1.5.4.2.4 Preparation of Study Drug**

Study drug will be prepared by an unblinded pharmacist according to the treatment assignment.

##### **Blinding**

As SKY0401 and unencapsulated morphine are visually distinguishable, study drug must be administered by an unblinded anesthesiologist uninvolved with post-operative patient assessments and data collection. The principal investigator, all study staff (including the surgeon) involved with the conduct of the study, and the patient will remain blinded to the assigned treatment group.

The study drug will be prepared by the pharmacist, placed in a sealed opaque bag and transported to the operating room. Since syringes used for SKY0401 and unencapsulated morphine are of different sizes, two syringes (3-cc and 5-cc) will be placed in the opaque bag, with one of them being empty, to help maintain the blind.

The blinded investigator or designee will be permitted to insert the epidural needle and catheter. However, in order to preserve the blind, it is important that the blinded investigator not be permitted to view the prepared syringes of study drug. Study drug must only be removed from the opaque bag and be visible to and injected by an unblinded anesthesiologist who is not involved in study assessments.

##### **Administration of Study Drug**

Study drug must be administered through an epidural catheter following delivery and clamping of the umbilical cord. Study drug will be administered as part of a combined spinal epidural anesthesia technique. The full dose of study drug was to have been injected via the epidural catheter. Following injection of the study drug, the epidural catheter was to have been flushed with 1 mL of preservative-free 0.9% normal saline. Study

medication was not to have been co-administered or mixed with any other medications. No other epidural agents were allowed after study drug administration.

### Conduct of Anesthesia

Regional (intrathecal) anesthesia will be induced via the intrathecal administration of the combination of bupivacaine (at a dose of 12 to 15 mg, with or without dextrose) and fentanyl (10 mcg) in a lumbar intervertebral space. Bupivacaine must not be co-administered or mixed with study drug or any other medications except 10 mcg of fentanyl. Use of anesthetics other than 12 to 15 mg of bupivacaine (with or without dextrose) in combination with 10 mcg of fentanyl is prohibited. All intra-operative opioid analgesics or pain medications, except fentanyl, are prohibited, including ketorolac (Toradol).

At the time of the first request for pain medication, the trained study personnel member will perform the pain intensity assessments at rest (VAS-R and CAT-R) and with activity (VAS-A and CAT-A). Then at the discretion of the investigator, the patient is to receive PO acetaminophen with codeine, IV morphine as an intermittent bolus, or IV morphine via PCA pump depending on pain intensity and patient's ability to tolerate oral medication. For patients receiving PCA morphine, the PCA pump (equipped with a printer) will be programmed to deliver on-demand boluses of IV morphine of 1 mg per bolus with a lockout interval of 10 minutes. A continuous infusion (background or basal rate) of IV morphine PCA is prohibited. If pain control is deemed inadequate by the investigator and/or the patient, the bolus dose may be altered as appropriate; however, adding a basal rate is prohibited. Conversely, if pain control is deemed sufficient by the investigator and/or the patient, the rate of 1 mg per bolus may be titrated downwards or patient can be switched to acetaminophen with codeine. Printouts from the PCA pump must be retained as a source document. The date and time of the first dose of analgesic medication administered post-operatively will be recorded on the appropriate Case Report Form. All analgesic medication usage will be recorded on the appropriate page of the Case Report Form, from time zero (defined as the time of the beginning of study drug administration) through 48 hours post-dose.

- Anti-inflammatory agents (e.g., ketorolac [Toradol]) except for the following:
  - "Acetaminophen [Sic]- maximum of 650 mg/24 hours for fever or headache only";
  - Aspirin - maximum of 325 mg/24 hours for platelet inhibition.
  - Cyclo-oxygenase inhibitor agents, including COX-2 specific inhibitors (e.g., celecoxib [Celebrex®] and rofecoxib [Vioxx®]).

The use of following medications were discouraged but were left to the discretion of the investigator:

- Benzodiazepines and other anti-anxiolytics;
- Anti-depressants (including tricyclics and serotonin-specific uptake inhibitors);
- Sedating anti-histamines;
- Any other medication that might cause sedation.

1.5.4.2.5 Assessments

Table 1.5.4-1: Schedule of Assessments

	Screening (Up to 21d prior to dosing)	Pre-Dose	Time of Dose	Time Post-Dose										Follow-Up				
				1 hr	2 hrs	4 hrs	8 hrs	12 hrs	24 hrs	30 hrs	36 hrs	48 hrs	Day 7	Day 30 (+4 d)				
Informed Consent	X																	
Medical History	X																	
Respiratory Rate		X																
Heart Rate and Blood Pressure	X	X																
Physical Exam (incl. Neurological Exam)	X			X	X	X	X	X	X	X	X	X	X	X				
Pt. Training (Scales & Use of PCA Pump)	X																	
Randomize Pt and Prepare Study Drug		X																
Admin. Study Drug <sup>2</sup>			X															
Pain Intensity at Rest <sup>3</sup> (VAS-R & CAT-R)					X	X	X	X	X	X	X	X	X	X				
Pain Intensity with Activity (VAS-A & CAT-A) <sub>3,4</sub>					X	X	X	X	X	X	X	X	X	X				
Sedation Score					X	X	X	X	X	X	X	X	X	X				
Brief Neuro Check					X	X	X	X	X	X	X	X	X	X				
Functional Ability																		
Patient Rating of Pain Control																		
Concomitant Medications		Record concomitant medications (including analgesic medications) taken 24 hours prior to surgery, intra- and post-operatively through 48 hours post-dose.																
PO Intake		Record the time the patient is able to first tolerate clear liquid diet																
Adverse Events		All adverse events will be recorded from time of dose through Day 7. SAEs and deaths will be recorded through Day 30.																
Abbreviated NAO																		X <sup>5</sup>

- To be conducted anytime on Day 3.
  - Study drug will be administered by an unblinded anesthesiologist not involved in other study procedures following delivery and clamping of the umbilical cord.
  - Should also be conducted at the time of first request for pain medication.
  - Activity will consist of the patient taking a deep breath followed by a forceful cough.
  - Selected AEs for potential neurological sequelae of epidural analgesia will be assessed using an abbreviated standardized neurological assessment questionnaire (NAO).
- From Sponsor's Protocol SKY0401-105, Amendment #1, Appendix A, Time and Events Schedule Page 248.

#### 1.5.4.2.6 Analysis Plan

##### Efficacy Endpoints

- **Primary Efficacy Endpoint**

The primary efficacy endpoint was the total amount of supplemental opioid analgesic medications (IV and PO) used through 48 hours post-dose. All opioid medications used were converted to IV morphine equivalents.

- **Secondary Efficacy Endpoints**

- The amount of IV opioid analgesic medication used;
- The time to first post-operative opioid analgesic medication use;
- The proportion of patients receiving no IV opioid analgesic medication post-operatively;
- The proportion of patients receiving no opioid analgesic medication post-operatively;
- Pain intensity evaluations using the VAS;
- Pain intensity evaluations using the CAT;
- Functional ability scores;
- Patient ratings of pain control.

- **Sample size Calculation**

The primary efficacy endpoint is the total amount of all narcotic analgesic medications used during the 48 hours following study drug administration, measured in morphine equivalents (mg). Based on a prior study in hip surgery (SKY0401-008), the standard deviation of these measurements is estimated to be approximately 78 mg. The same study indicated a mean 0-48 hour analgesic requirement of 117 mg (morphine-equivalent) in the active control group (unencapsulated morphine). With a two-tailed test at a significance level of  $p=0.05$  and 80% power ( $\alpha=0.20$ ), the sample size of  $n=20$  patients per group should enable detection of a difference of at least 69 mg between the SKY0401 and control groups. This represents a 59% decrease assuming a control mean of 117 mg, which is within clinical expectation based on previous results.

- **Study Populations**

The intent-to-treat (ITT) population consists of all randomized patients. The population to be included in all primary and secondary efficacy analyses includes all ITT patients unless they did not receive study drug due to exclusion criteria.

Patients experiencing the following medical complications and protocol failures were also excluded:

1. Dural puncture with epidural needle
2. Clinically significant complications (e.g., excessive bleeding) during the surgery, which rendered the patient medically unstable or might complicate the patient's post-operative course
3. Treatment with any local anesthetic agent (such as bupivacaine, lidocaine, etc.) through the epidural catheter prior to the study drug administration
4. Treatment with general anesthesia due to failure of intrathecal block.

**Amendment 1: 26 April 2002**

This amendment clarified that the protocol would use the intent-to-treat population for analysis of the primary and secondary efficacy variables with exceptions for medical complications or administration of local anesthetic through the epidural catheter prior to administration of study drug. The statistical section was expanded to included detailed information on management of missing data.

**1.5.4.3 Study Conduct**

**1.5.4.3.1 Patient Disposition**

Seventy-nine patients were enrolled in the study with 19, 19, 21, and 20 patients randomized to receive MS, and SKY0401 5, 10, and 15 mg, respectively, study drug was received by 18 (95%), 19 (100%), 18 (86%), and 18 (90%) patients, respectively.

Four patients were excluded from efficacy analysis after randomization because of medical complications or pretreatment with epidural local anesthetic as prespecified in the protocol (exclusion criteria 13-16). Two patients who did not receive study drug because of protocol violations were included in analysis of efficacy because they met the inclusion criteria of the protocol.

Seventy-five patients randomized to receive either 5-mg unencapsulated morphine or SKY0401 at 5-, 10- and 15-mg, (with 18, 19, 19 and 19 patients assigned to each group respectively), comprised the ITT population used in the analysis of primary and secondary efficacy variables. All 75 patients analyzed for efficacy received the entire dose of study drug and completed the required 48-hour evaluation period.

Table 1.5.4-2 Disposition of Patients, Study 015

	MS	SKY0401				Total
	5 mg	5 mg	10 mg	15 mg	All	
Randomized	19	19	21	20	60	79
Safety Population	18 (95%)	19 (100%)	18 (86%)	18 (90%)	55 (92%)	73 (92%)
Efficacy Population	18 (95%)	19 (100%)	19 (91%)	19 (95%)	57 (95%)	75 (95%)
AE Data Collected Through Day 7 (Safety Population)?						
Yes	17 (94%)	19 (100%)	18 (100%)	17 (94%)	54 (98%)	71 (97%)
No	1 (6%)	0 (0%)	0 (0%)	1 (6%)	1 (2%)	2 (3%)
Patient Followed Through Day 30 For SAEs and NAQ (Safety Population)?						
Yes	15 (83%)	19 (100%)	17 (94%)	16 (89%)	52 (95%)	67 (92%)
No	3 (17%)	0 (0%)	1 (6%)	2 (11%)	3 (5%)	6 (8%)

From sponsor's study report SKY0401-015, Section 10.1, page 43.

Table 1.5.4-3 Randomized Patients Who Did Not Receive Study Drug, But Were Included In The Efficacy Analysis, Study 015

Patient ID #	Treatment Group	Reason Study Drug Was Not Administered
5202 SKY0401	15 mg	Fentanyl was not given in spinal.
6207 SKY0401	10 mg	Leakage of IT dose of bupivacaine and fentanyl. Investigator was concerned about adequate analgesia for surgery. Second IT dose given in new site. Potential need for epidural catheter for intra-operative medication. Study abandoned.

From sponsor's study report SKY0401-015, Section 10.1, page 43.

#### 1.5.4.3.2 Demographics/Group Comparability

There were no significant differences among the treatment groups regarding the surgical procedure, with the majority of patients (72 of 75; 96%) undergoing a transverse (Pfannensteil) incision. The mean duration of surgery was 43.5 minutes and the mean time from umbilical cord clamping to the end of surgery was 32.2 minutes. The distribution of demographic and baseline characteristics was similar among treatment groups. Overall, the mean age was 31.0 years for both the SKY0401-treated and the MS-treated patients. Forty-seven of the 73 patients (64%) were Caucasian, with a further 12 patients (16%) Hispanic. Seven investigational sites participated in this study, and all 7 enrolled patients.

#### 1.5.4.3.3 Unplanned Analyses

No interim analyses were conducted.

For those patients who did not receive study drug, the surgery start time plus 20 minutes was used as the study drug administration time for the purposes of the primary and secondary analyses.

No patient died, withdrew from the study, or was lost to follow-up before 48 hours post-dose, so actual opioid usage by patients was used instead of projected usage based on adjustment specified by the protocol. All ITT patients were followed for 48 hours post-dose.

For patients who did not receive any opioid during the first 48 hours, they were censored using a value of 48 hours to determine the time to first post-operative opioid medication usage and the time to first post-operative IV opioid usage.

Patient 4215 did not have a valid time recorded for morphine administered via a PCA pump. For the purposes of analyzing the secondary endpoints, this time was arbitrarily assigned to within the first 24 hours.

Visual analog scale values were imputed for patients who discontinued prior to the 48-hour assessment for the analysis of AUC only. Each missing assessment occurring after the patient's last non-missing assessment was imputed using the average values at the time point from all the other patients in the corresponding treatment group.

#### 1.5.4.4 Sponsor's Efficacy Results

##### 1.5.4.4.1 Primary Efficacy Variables

The primary efficacy endpoint was the total amount of supplemental opioid analgesic medication (IV and PO in morphine equivalent units) used through 48 hours post-epidural dose. A total of 72 of the 75 patients (96%) in the ITT population received an opioid analgesic medication of some type through 48 hours post-dose, with natural opium alkaloids (including panadeine, morphine, oxycocet, morphine sulfate, and Vicodin®) being the most common class administered. Narcotic medications other than PO acetaminophen with codeine or IV morphine were not stipulated by the protocol.

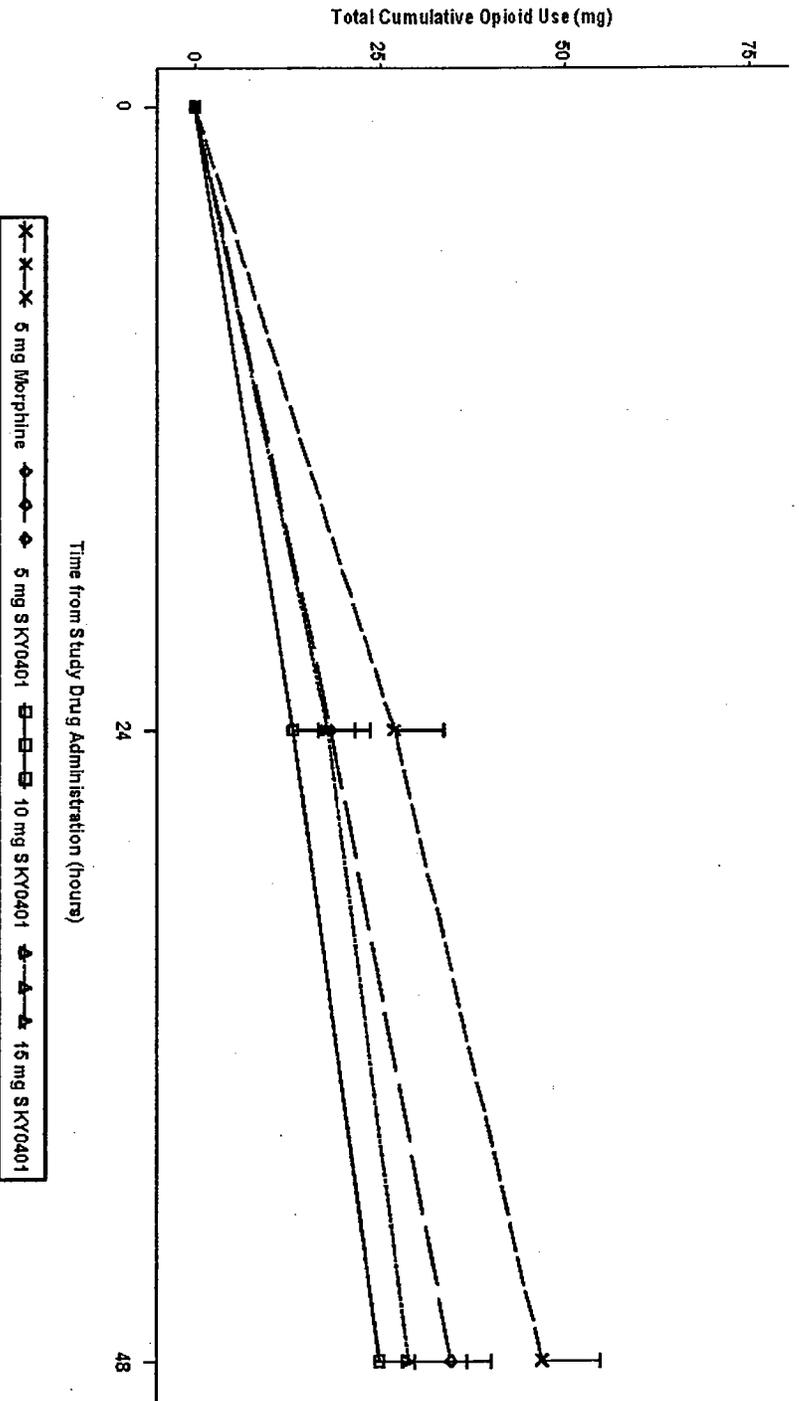
The data did not follow a normal distribution, and therefore, so an ANOVA was performed on the ranked data as stipulated in the Statistical Plan of the protocol. There was a significant difference among the treatment groups in total opioid analgesic medication usage ( $p = 0.0209$ ).

The mean total opioid analgesic medication usage through 48 hours post-dose in the 5, 10, and 15 mg SKY0401 treatment groups was 34.7 mg, 25.1 mg, and 28.9 mg, respectively, compared with 47.0 mg in the MS group. The usage in both the 10 and 15 mg groups was significantly less than in the MS treatment group ( $p = 0.0289$  and  $0.0178$ , respectively). The efficacy of the 10 and 15-mg SKY0401 groups was comparable, as indicated by the median opioid analgesic usage values of 19.0 and 18.0 mg, respectively.

Overall, through 48 hours post-dose, there was a dose-related reduction in the need for post-operative opioid analgesic medication, as demonstrated by the graphical representation of the cumulative usage by treatment group.

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Figure 1.5.4-1 Cumulative Opioid Usage Over 48 hours, Study 015



Sponsor's Figure 1, Clinical Study Report; Protocol No. SKY0401-015 page 209

Subgroup analyses revealed a significant difference in total opioid medication usage among treatment groups in terms of race (Caucasians vs. all other races,  $p = 0.0048$ ) and ASA Classification (Class 2,  $p = 0.0338$ ). No significant differences were noted with respect to age (younger than 30 years vs. at least 30 years old) or weight (less than 200 pound vs. at least 200 pounds).

#### 1.5.4.4.2 Secondary Efficacy Variables

- **Secondary Analyses Of The Primary Efficacy Endpoint**

The secondary analyses of the primary efficacy endpoint compared SKY0401 and MS treatment groups in terms of opioid analgesic medication usage by successive 24-hour intervals through 48 hours following the administration of study drug. See Table 1.5.4-4 below. The sponsor indicated that results were consistent with those reported above for the primary efficacy analyses, with both the 10 and 15 mg dose groups. The sponsor also presented a subgroup analysis of total supplementary opioid administration by successive 24-hour intervals. Statistically significant differences were reported by the sponsor for the 24-48 hour interval, but not for the initial 24 hours post-epidural treatment.

Table 1.5.4-4 Sponsor's Summary of Secondary Analysis of the Primary Efficacy Endpoint, Study 015

	MS	SKY0401			
	5 mg	5 mg	10 mg	15 mg	All
Number of Patients	18	19	19	19	57
Opioid Analgesic Medication Usage (mg) 0 to 24 Hours Post-Dose Mean <sup>1</sup>	27.0	18.5	13.4	18.0	16.6
Opioid Analgesic Medication Usage (mg) > 24 to 48 hours Post-Dose Mean <sup>2</sup> p-value (Each SKY0401 Dose vs. MS)	19.9	16.2 NS	11.7 0.0134	10.9 0.0001	12.9
Opioid Analgesic Medication Usage (mg) 0 to 48 Hours Post-Dose Mean <sup>3</sup> p-value (Each SKY0401 Dose vs. MS)	47.0	34.7 NS	25.1 0.0108	28.9 0.0065	29.6

P-values were determined using one-way ANOVA after rank-transformation of the data. Pairwise comparisons of each SKY0401 dose to MS were evaluated only if the overall treatment group effect was significant.

Actual opioid usage, with no adjustment made for patients discontinuing the study prior to 48 hours.

1p-value for overall test among treatment groups was not significant (therefore no pairwise evaluations performed).

2p-value = 0.0008 for overall test among treatment groups.

3p-value = 0.0209 for overall test among treatment groups.

MS = Unencapsulated morphine sulfate; NS = Not significant.

From sponsor's Table 11.4.1.2-1, Clinical Study Report; Protocol No. SKY0401-015, page 49

- **Time To First Post-Operative Opioid Medication Usage**

The median time to first post-dose opioid analgesic medication usage was similar between all the treatment groups, with a median time of 2.8 hours for all SKY0401 treatment groups and 3.0 hours for the MS-treated patients. This suggests that there were no differences among the treatment groups in terms of the onset of analgesic activity. The sponsor also analyzed the secondary efficacy endpoint in terms of the time to first post-dose IV opioid analgesic medication usage with no significant differences observed between the treatment groups.

Subgroup analyses by the sponsor revealed no significant differences for age (comparing patients younger than 30 to patients at least 30 years old), race (comparing Caucasians to other all other races combined) or body weight (comparing patients weighing less than 200 pounds to those over 200 pounds).

• **Proportion Of Patients Receiving No Opioid Analgesic Medication Post-Operatively**

Overall, the sponsor reports that there were no significant differences among the treatment groups through 24 and 48 hours post-dose. There was, however, a significant difference observed from > 24 to 48 hours post-dose ( $p = 0.0383$ ). A subgroup analysis by the sponsor indicated that the proportion of patients receiving no IV opioid medication was significantly higher in the 10 and 15 mg SKY0401 groups (17/19, 90% and 17/19 90%, respectively) compared with the MS treatment group (10/19, 56%;  $p = 0.0293$  and  $0.0293$ , respectively). The sponsor’s analysis by age, race and weight using the using the same subgroup divisions as in earlier subgroup analysis revealed no significant differences.

• **Pain Intensity Evaluations**

• **Visual Analog Scale**

At the first request for pain medication, the mean VAS-R scores in the SKY0401 5, 10, and 15-mg groups, and the 5-mg MS group were 39.2, 34.1, 38.8, and 42.9, respectively, with no significant differences demonstrated among the treatment groups. At the subsequent time points, the mean VAS-R scores were consistently lower in the SKY0401-treated patients compared with the patients in the MS group.

The analysis of VAS scores by area under the curve (AUC) demonstrated a significant reduction in pain intensity over 48 hours with 10 mg SKY0401 ( $p = 0.0008$ ) and 15 mg SKY0401 ( $p < 0.0001$ ) compared with MS treatment. Similarly significant results were obtained when a covariate for opioid analgesic medication use was incorporated into the analysis.

Table 1.5.4-5 Sponsor’s Summary Of VAS Pain Scores (AUC) At Rest And With Activity, Study 015

	MS	SKY0401			
	5 mg	5 mg	10 mg	15 mg	All
Number of Patients	18	19	19	19	57
AUC (0 to 48 Hours) at Rest (VAS-R)					
Mean <sup>1</sup>	1186.3	840.9	454.4	484.0	593.1
p-value (Each SKY0401 dose vs. MS)		NS	0.0003	0.0005	
AUC (0 to 48 Hours) with Activity (VAS-A)					
Mean <sup>2</sup>	2085.7	1825.7	1235.2	1035.7	1365.5
p-value (Each SKY0401 dose vs. MS)		NS	0.0008	< 0.0001	

P-values were determined using one-way ANOVA. Pairwise comparisons of each SKY0401 dose to MS were evaluated only if the overall treatment group effect was significant.

<sup>1</sup>p-value = 0.0007 for overall test among treatment groups.

<sup>2</sup>p-value = 0.0001 for overall test among treatment groups.

MS = Unencapsulated morphine sulfate; AUC = Area under the curve; VAS = Visual Analog Scale: 100 mm length line (0 = no pain and 100 = the most severe pain); VAS-R = pain assessment using VAS while patient was at rest; VAS-A = pain assessment using VAS while patient was active.

From sponsor's table 11.4.1.2-3, Clinical Study Report; Protocol No. SKY0401-015, page 52

• **Integrated Rank Assessment Using VAS Scores And Opioid Analgesic Usage Data**

To account for the effect of opioid analgesic medication usage on pain intensity, the data were also analyzed, by the sponsor, as an integrated rank at rest and with activity using the VAS scores and opioid analgesic usage data. In this analysis, lower scores (with negative numbers lower than positive numbers) were reflective of combined lower pain scores and lower opioid analgesic medication usage. The results demonstrated a significant reduction in pain intensity at rest with the 10 and 15 mg SKY0401 dose groups over the entire 48-hour time period (using the analysis of AUC) and at the 24, 30, and 36 hour time points post-dose. The assessment of the pain intensity with activity (using VAS-A and opioid analgesic usage) demonstrated significant reductions with the 10 and 15 mg SKY0401 dose groups over the entire 48-hour time period (using the analysis of AUC) and at the 12 (15 mg SKY0401 only), 24, 30, 36, and 48 hour time points post-dose.

Table 1.5.4-6 Sponsor's Summary Of Integrated Rank Assessment Of Pain Intensity Evaluations Based On The AUC Analysis Using Visual Analog Scale And Total Opioid Analgesic Medication Usage, Study 015

	MS	SKY0401			
	5 mg	5 mg	10 mg	15 mg	All
Number of Patients	18	19	19	19	57
AUC (0 to 48 Hours) at Rest					
Mean <sup>1</sup>	60.7	29.3	- 42.4	- 44.5	- 19.2
p-value (Each SKY0401 dose vs. MS)		NS	0.0010	0.0008	
AUC (0 to 48 Hours) with Activity					
Mean <sup>2</sup>	65.7	34.6	- 39.3	- 57.5	- 20.8
p-value (Each SKY0401 dose vs. MS)		NS	0.0003	< 0.0001	

P-values were determined using one-way ANOVA. Pairwise comparisons of each SKY0401 dose to MS were evaluated only if the overall treatment group effect was significant.

<sup>1</sup>p-value = 0.0009 for overall test among treatment groups.

<sup>2</sup>p-value < 0.0001 for overall test among treatment groups.

MS = Unencapsulated morphine sulfate; AUC = Area under the curve; VAS = Visual Analog Scale: 100-mm length line

(0 = no pain and 100 = the most severe pain).

From Sponsor's table 11.4.1.2-4 Clinical Study Report; Protocol No. SKY0401-015, page 53.

• **Categorical Scale**

Pain intensity ratings at rest and with activity were evaluated using the categorical scale (where 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain). At rest, only the evaluation at 24 hours post-dose demonstrated a significant reduction in pain intensity with SKY0401 treatment compared with MS treatment, with no patients having moderate to severe pain in the 10 and 15 mg groups (0% and 0%, respectively) compared with 5 patients (28%) in the MS group (p = 0.0492 and 0.0123, respectively). The CAT-A scores demonstrated significantly lower pain intensity in the SKY0401 10 and 15 mg dose groups at 24 hour (p = 0.0064 and 0.0140, respectively) and 30 hour (p = 0.0304 and 0.0018, respectively) time points and for the SKY0401 15 mg group alone at the 36 hour (p = 0.0030) and 48 hour (p = 0.0186) time points compared with the MS treatment group.

Table 1.5.4-7 Sponsor's Summary Of Pain Intensity Evaluations With Rest And With Activity Using The Categorical Scale, Study 015

	MS	SKY0401			
	5 mg	5 mg	10 mg	15 mg	All
Number of Patients	18	19	19	19	57
CAT-R scores at 24 Hours Post-Dose Mean <sup>1</sup> p-value (Each SKY0401 dose vs. MS)	1.2	0.9 NS	0.7 0.0492	0.6 0.0123	0.8
CAT-R scores at 48 hours Post-Dose Mean <sup>2</sup>	0.9	0.8	0.7	0.6	0.7
CAT-A scores at 24 hours Post-Dose Mean <sup>3</sup> p-value (Each SKY0401 dose vs. MS)	1.8	1.6 NS	1.2 0.0064	1.2 0.0140	1.3
CAT-A scores at 48 hours Post-Dose Mean <sup>4</sup> p-value (Each SKY0401 dose vs. MS)	1.8	1.7 NS	1.3 NS	1.2 0.0186	1.4

P-values were determined using the CMH (row-mean-score) test. Pairwise comparisons of each SKY0401 dose to MS were evaluated only if the overall treatment group effect was significant.

<sup>1</sup>p-value = 0.0360 for overall test among treatment groups.

<sup>2</sup>p-value for overall test among treatment was not significant (therefore no pairwise evaluations performed).

<sup>3</sup>p-value = 0.0043 for overall test among treatment groups.

<sup>4</sup>p-value = 0.0461 for overall test among treatment groups.

MS = Unencapsulated morphine sulfate; CAT = Categorical Scale: 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain; CAT-R = pain assessment using CAT scale while patient was at rest; CAT-A = pain assessment using CAT scale while patient was active; NS = Not significant.

- Functional Ability Scores

Functional ability was assessed at 24 and 48 hours post-dose for each of 4 functions (resting on the bed, sitting, walking, and using the restroom) by assigning scores to reflect the level of difficulty of each function (0 = not difficult at all, 1 = minimally difficult, 2 = somewhat difficult, 3 = fairly difficult, 4 = very difficult, 5 = unable to do, and 6 = unable to do for a reason other than pain). In addition, an overall functional ability score was generated based on the sum of the scores over all 4 functions. At both 24 and 48 hours post-dose, the 10- and 15-mg SKY0401-treated patients had significantly lower overall mean functional scores compared to MS-treated patients. The 10- and 15-mg SKY0401 mean scores were both significantly lower (p = 0.0001 and 0.0002, respectively) compared with the MS group score. When the functional ability scores

among treatment groups for each of the 4 functions were analyzed, the 10- and 15- mg SKY0401 dose groups were consistently significantly lower at 24 and 48 hours post-dose than those of the MS treatment group (with the exception of the value for sitting at 48 hours post-dose for the 15-mg SKY0401 group).

• **Patient Ratings Of Pain Control**

The control of pain was rated by patients as very good, good, fair, or poor. At 48 hours post-dose, the rating of pain control was significantly higher in the 10- and 15-mg SKY0401-treated patients compared with MS-treated patients. The difference was largely the result of the percentage of patients who rated their pain control as very good (32%, 53%, and 74% in the 5-, 10-, and 15-mg SKY0401 groups compared with 22% in the MS group). There were no significant differences among the treatment groups in terms of patient-rated pain control at 24 hours when the proportion of patients with pain control ratings of good or very good were calculated and analyzed.

Table 1.5.4-8 Sponsor’s Analysis of Patient Rating of Pain Control at 48 Hours Post-Dose, Study 015

	MS	SKY0401			
	5 mg	5 mg	10 mg	15 mg	All
Number of Patients	18	19	19	19	57
Rating of Pain Control, Mean (%)					
1 (Poor)	2 (11%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
2 (Fair)	3 (17%)	2 (11%)	2 (11%)	0 (0%)	4 (7%)
3 (Good)	9 (50%)	9 (47%)	5 (26%)	4 (21%)	18 (32%)
4 (Very Good)	4 (22%)	6 (32%)	10 (53%)	14 (74%)	30 (53%)
Missing	0 (0%)	2 (11%)	2 (11%)	1 (5%)	5 (9%)
Mean <sup>†</sup>	2.8	3.2	3.5	3.8	3.5
p-value (Each SKY0401 Dose vs. MS)		NS	0.0321	0.0009	

P-values were determined using the CMH (row-mean-score) test. Pairwise comparisons of each SKY0401 dose to MS were evaluated only if the overall treatment group effect was significant.

<sup>†</sup>p-value = 0.0026 for overall test among treatment groups.

MS = Unencapsulated morphine sulfate; NS = Not significant.

From Sponsor’s table 11.4.1.2-7 Clinical Study Report; Protocol No. SKY0401-015, page 56.

**1.5.4.5 REVIEWER’S COMMENTS**

This Phase 2 study in 75 patients was designed to evaluate the analgesic efficacy of 5-mg, 10 mg-and 15-mg SKY0401 compared with 5-mg unencapsulated epidural morphine in the setting of cesarean section. Of the 79 patients enrolled, 4 patients were withdrawn because of medical complications or pretreatment with therapeutic doses of local anesthetic. The rationale for these withdrawals was specified in the protocol amendment April 26, 2002 and did not affect the analysis of efficacy or the conclusions. Two other patients who did not receive study drug were included in analysis of efficacy because they met the inclusion criteria of the protocol. This reviewer determined that the

study conduct reflected the protocol despite unpredictable and often unavoidable events in medical practice and was adequate to analyze efficacy of SKY0401.

The sponsor's primary analysis of efficacy was based upon the mean supplementary opiate received by patients over 48 hours converted to a median equivalent cumulative dose of morphine. Patients treated with 10- or 15-mg SKY0401 demonstrated a comparable and significant reduction in the need for opioid analgesic medications (IV and PO) through 48 hours post-dose compared with patients treated with 5-mg unencapsulated epidural morphine.

Analysis of the secondary endpoints supported the finding of efficacy for SKY0401. There was no difference in latency to first supplemental opiate treatment between unencapsulated epidural morphine and SKY0401 indicating that the encapsulating excipient did not delay onset of analgesia, nor did higher doses of SKY0401 provide a longer period of analgesia immediately after surgery. The sponsor's subgroup analysis of supplemental opiate administration demonstrated improved efficacy of SKY0401 in the 24-hour to 48-hour period for doses of 10- and 15-mg SKY0401 compared with 5-mg unencapsulated epidural morphine. The sponsor's p values exhibited in Table 1.5.4-4 compared with the p values exhibited in the sponsor's primary analysis of efficacy for total supplementary opioid administration are different although the data are identical. In both the primary and secondary analysis, the sponsor's the p values are small enough to be considered statistically significant. This reviewer's examination of the statistical analysis of the same data by Dionne Price (Biostatistics reviewer), indicates that the median supplementary opioid received by patients in the 10- and 15-mg SKY0401 groups was significantly lower than in the 5-mg dose unencapsulated morphine group. Dr. Price's analysis also confirmed the sponsor's contention that there was no significant difference between the 10- and 15-mg dose groups in median supplementary use of opioids. In summary, while the sponsor's calculations are incorrect, the conclusion is valid.

The sponsor reported that patients treated with 10-mg and 15-mg of SKY0401 exhibited a smaller dose of supplemental morphine between 24 and 48 hours compared with 5-mg unencapsulated morphine. Mean VAS scores at rest and with activity were lower over 48 hours than 5-mg unencapsulated epidural morphine. Similar analysis of an integrated rank assessment using VAS and opioid analgesic usage had similar findings. Analysis of pain using a categorical scale at rest was notable for reduction in assessed pain at 24 hours but not at 48 hours associated with 10- and 15-mg doses of SKY0401 compared with unencapsulated morphine. At 48-hours post-dose, only the 15-mg SKY0401 group for CAT pain intensity with activity appeared to be lower than the unencapsulated morphine treatment group. At both 24- and 48-hours post-dose, the 10- and 15-mg SKY0401-treated patients had significantly lower overall mean functional scores compared to unencapsulated morphine treated patients. At 48 hours post-dose, the percentage of patients rating their pain control very good or good was higher in the 10- and 15-mg SKY0401-treated patients compared with MS-treated patients.

### 1.5.5 Study 017, Knee arthroplasty:

A Randomized, Double-Blind, Active-Controlled, Dose-Ranging, Parallel Group 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 Knee Arthroplasty

#### 1.5.5.1 Findings vs. Labeling Claims

See Section, "REVIEW OF PACKAGE INSERT".

#### 1.5.5.2 Study Plan

**Objectives:** To evaluate the efficacy of SKY0401 (20 or 30 mg) in managing post-operative pain following knee arthroplasty.

**1.5.5.2.1 Population:** N = 168 randomized, 164 in efficacy analysis

#### 1.5.5.2.2 Study Design:

- **Inclusion Criteria**

- 1) Males and females at least 18 years of age at Screening.
- 2) Females of child-bearing potential with a negative urine or blood ®-human chorionic gonadotropin ( $\beta$ -hCG) pregnancy test performed during Screening. Females were eligible only if they were not pregnant or lactating, were either post-menopausal or surgically sterile, or, if of child-bearing potential, using an acceptable means of contraception for at least 1 month prior to Screening, including any of the following:
  - a) Oral contraceptives;
  - b) Implantable (e.g., Norplant®) or injectable (e.g., Depo-Provera®) contraceptives;
  - c) Barrier methods (e.g., condoms with spermicide);
  - d) Intrauterine device;
  - e) Lifestyle with a personal choice of abstinence;
  - f) Non-heterosexual lifestyle;
  - g) Vasectomy of sexual partner.
- 3) Scheduled for elective unilateral knee arthroplasty under general or regional (intrathecal) anesthesia.
- 4) American Society of Anesthesiology (ASA) Physical Class 1, 2, or 3.
- 5) Willing and able to use a PCA pump.
- 6) Willing to receive only IV morphine via PCA pump or IV hydromorphone for 48 hours post-dose to control post-operative pain.
- 7) Expected and willing to remain hospitalized for a minimum of 48 hours post-dose.
- 8) Capable of speaking and understanding English sufficiently to provide written informed consent and responses to pain assessment scales and neurological assessment questionnaires.

• **Exclusion Criteria**

- 1) Morbid obesity, defined as a body mass index (BMI) > 40, where BMI = (weight /height<sup>2</sup>) x 704.5; where weight was expressed in pounds and height in inches.
- 2) Current or historical evidence of any clinically significant disease or condition that, in the opinion of the Investigator, might have increased the risk of surgery or complicated the patient's post-operative course.
- 3) Undergoing any of the following:
  - a) Bilateral knee arthroplasty;
  - b) Current or previous knee arthroplasty secondary to metastatic cancer of the bone or Paget's Disease;
  - c) Other concurrent surgical procedures (such as hip arthroplasty or vascular surgery) in addition to knee arthroplasty (bone grafting was allowed).
- 4) Undergoing knee arthroplasty under epidural anesthesia.
- 5) Administered of any kind of regional blocks (except intrathecal anesthesia) for intra-operative or post-operative analgesia/anesthesia.
- 6) Suspected or documented history of sleep apnea, narcolepsy, or excessive daytime sleepiness.
- 7) Female who was pregnant or lactating.
- 8) History of hypersensitivity or idiosyncratic reaction to opioid medications.
- 9) Any contraindication for the epidural administration of study drug (e.g., coagulopathy, local infection).
- 10) Administered of an investigational drug within 30 days prior to Screening.
- 11) Suspected or documented history of substance abuse and/or alcoholism.
- 12) Chronic opioid medication usage (defined as daily opioids for more than the 7 days prior to enrollment).
- 13) Unwilling or unable to provide written informed consent and/or to comply with study procedures, including use of a PCA pump, completion of all patient-rated scales, and follow-up assessments at Day 30.

**1.5.5.2.3 Study Design**

Patients scheduled to undergo knee arthroplasty under general or regional (intrathecal) anesthesia were to have been randomized in a 1:1:1 ratio to one of the following treatment groups: SKY0401 at 20 or 30 mg, or sham epidural with IV PCA morphine. Study drug was to have been administered by epidural injection prior to the induction of general or regional anesthesia at approximately 30 minutes prior to the start of surgery. Patients randomized to the IV PCA morphine group were to have received a sham epidural injection i.e. the epidural needle entered the skin but not the epidural space.

All patients were to have access to additional post-operative medications to ensure adequate pain control. For patients in the SKY0401 treatment groups, IV hydromorphone was to have been administered at the first request for pain medication until "No Pain" status was achieved and then patients were to be set up with a PCA pump that administered saline. If pain control was inadequate following this initial administration, the PCA regimen was to have been increased and at the same time, the patient was stipulated to receive an IV injection of hydromorphone (0.2 mg/mL). At the first request

for pain medication, patients in the sham epidural “IV PCA morphine” treatment group were to receive IV morphine until “No Pain” status was achieved, and then were to have been set up with a PCA pump and permitted to self-administer IV morphine until satisfactory pain relief was achieved. If pain control was inadequate following this initial administration, the IV morphine PCA regimen was to have been increased and patients were also to receive an IV saline injection (mimicking 0.2 mg/mL hydromorphone).

The maximum recommended amount of intra-operative analgesics was to have been 250 mcg of IV fentanyl per patient, regardless of whether anesthesia was general or regional. All other intra-operative opioid analgesics or pain medications, except fentanyl, were prohibited. Opioid medications other than IV morphine or hydromorphone were not to have been permitted throughout the 48-hour period post-dose. All other concomitant medications administered during this 48-hour period were to have been recorded. Time-weighted pain intensity recall scores were to have been assessed over 44 hours following the 4-hour post-dose assessment. Current pain intensity was to be assessed at rest and with activity using both a Visual Analog Scale (VAS-R and VAS-A) and Categorical Scale (CAT-R and CAT-A) at the time for first request for analgesic medication and at 4, 8, 12, 24, 30, 36, and 48 hours post-dose. Patient ratings of pain control were to have been assessed at 24 and 48 hours post-dose. Range-of-motion evaluations were to have been performed at 48 hours post-dose and at discharge. At discharge, the use of physical support required at home was also to have been assessed. Through 48 hours post-dose, total opioid usage was to have been assessed, in addition to the time to first post-operative opioid usage and the proportion of patients receiving no post-operative opioid medications.

#### 1.5.5.2.4 Treatment Summary

- **Description of Study Drug**

SKY0401 is formulated as a sterile, non-pyrogenic, white to off-white, preservative-free, homogenous suspension of morphine encapsulated into multivesicular lipid-based particles (DepoFoam® drug delivery system). SKY0401 is intended for epidural use only. It is supplied as a 2-mL single-use vial. Each vial contains 10 mg/mL of sustained-release encapsulated morphine. Morphine, hydromorphone, and saline placebo were to have been supplied by the hospital pharmacy.

- **Treatment Assignment**

Patients were to be randomly assigned in a 1:1:1 ratio stratified by site on Day 1 to one of the following three treatment groups:

- IV PCA morphine. (sham epidural)
- 20 mg SKY0401 epidurally.
- 30 mg SKY0401 epidurally.

Once patient eligibility was confirmed, the patient was to have been randomized to a treatment group by utilizing randomization envelopes provided by SkyePharma. The next sequential randomization envelope was to have been opened for each patient. A patient is stipulated to be considered enrolled once they have been randomized.

- **Preparation of Study Drug**

Study drug was to have been prepared by an unblinded pharmacist (not involved in direct patient care).

- **Blinding**

As patients assigned to the IV PCA arm were to receive a sham epidural injection (skin penetration only), study drug administration procedures were stipulated to be performed by an unblinded anesthesiologist uninvolved with post-operative patient care, post-operative assessments and data collection. All personnel (including the surgeon) involved in the patient's post-operative care and the patient were to remain blinded to the assigned treatment group. The study drug was to have been prepared by the pharmacist, placed in a sealed opaque bag and transported to the operating room. If a patient was assigned to the IV PCA (sham epidural) arm, an empty syringe was to have been placed in the bag. Study drug was required to be removed from the opaque bag and be visible to and injected only by an unblinded anesthesiologist who is not involved in study assessments. Separate bags with the post-operative pain control medications will be provided as follows:

- For patients assigned to the IV PCA (sham epidural) morphine arm – morphine for pain control at the first request for pain medication, morphine for PCA pump and normal saline as a rescue medication.
- For patients assigned to the SKY0401 arms – hydromorphone for pain control at the first request for pain medication, saline for PCA and hydromorphone as a rescue medication.

These were to have been labeled so as to maintain the double-blind.

- **Administration of Study Drug**

Study drug was to have been administered according to the randomized treatment group at the desired lumbar intervertebral space. Study drug have been administered prior to anesthesia and approximately 30minutes prior to the start of surgery (defined as the time of the first incision).

Proper placement of a needle or a catheter in the epidural space was to have been verified before the study drug administration. Acceptable techniques for verifying proper placement include:

- Aspiration to check for absence of blood or cerebrospinal fluid, or
- Administration of a 3 mL test dose of 1.5% preservative-free lidocaine with 1:200,000 epinephrine through the epidural needle or catheter.
- Following test dose administration, flush the catheter/needle with 1 mL of preservative free 0.9% normal saline. Observation of the patient for at least 15 minutes for a hypertensive and/or tachycardic response to epinephrine, to rule out an inadvertent intravascular injection. Inadvertent intrathecal injection was too have been ruled out by a lack of sensory block produced by test dose within 15 minutes of injection.

Note: If a lidocaine/epinephrine test dose is administered, SKY0401 was stipulated not be administered for at least 15 minutes.

Dosages of SKY0401 other than 20 or 30 mg are prohibited.

- For patients receiving regional (intrathecal) anesthesia, the intrathecal anesthesia was stipulated to be administered through an intervertebral space different from that used to administer study drug.
- Local anesthetic to be used for the regional anesthesia was to have been limited to bupivacaine (with or without dextrose) at a dose of 12.5 to 17 mg only. Bupivacaine was not to be co-administered or mixed with study drug or any other medications.

No other medications were to be permitted to be administered through the epidural catheter and/or needle.

If the patient is assigned to the IV PCA (sham epidural) morphine arm, the study procedures were to be performed as follows:

1. Identify the desired lumbar intervertebral space and create a skin wheal using lidocaine to anesthetize.
2. Mimic epidural injection and perform skin penetration, without advancing to the epidural space.
3. Remove the empty syringe from the opaque bag labeled "**Study Medication**".
4. Remove the needle from the patient's back.

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On Original*

APPENDIX A:  
TIME AND EVENTS SCHEDULE

	Screening (Up to 21 days prior to dosing)	Pre- Dose	Time of Dose	Time Post-Dose							Discharge	Follow-Up			
				4 hrs	8 hrs	12 hrs	24 hrs	30 hrs	36 hrs	48 hrs		Day 7 (+2 days)	Day 30 (+4 days)		
Informed Consent	X														
Medical History	X														
Pr. Training (Scales & Use of PCA Pump)	X														
Respiratory Rate		X					q 2 hr at 24-36 hrs				q 4 hr at 36-48 hrs				
Pulse Oximetry		X					q 2 hr at 24-36 hrs				q 4 hr at 36-48 hrs				
Capnometry		X					q 2 hr at 24-36 hrs				q 4 hr at 36-48 hrs				
Heart Rate and Blood Pressure	X	X					q 2 hr at 24-36 hrs				q 4 hr at 36-48 hrs				
Physical Exam (incl. Neurological Exam)	X	X					q 2 hr at 24-36 hrs				q 4 hr at 36-48 hrs				
Randomize Patient and Prepare Study Drug		X													
Admin. Study Drug			X												
Pain Intensity at Rest (VAS & CAT-R)				X			X				X				
Pain Intensity with Activity (VAS-A & CAT-A)				X			X				X				
Reassessed Pain Intensity (VAS)				X			X				X				
Sedation Score				X			X				X				
Brief Neuro Check				X			X				X				
Physical Therapist's Rating of Patient's Ability to Tolerate Physical Therapy				X			X				X				
Patient's Rating of Overall Pain Control							X				X				
Range-of-motion Evaluation											X				
Use of Physical Support											X				
Concomitant Medications											X				
PO intake															
Adverse Events															
Abbreviated NAO															X <sup>1</sup>

- To be conducted anytime on Day 3.
- To be conducted anytime on Day 3.
- Study drug will be administered by an unblinded anesthesiologist not involved in other study procedures. Should also be conducted at the time of first request for pain medication.
- To be conducted anytime on Day 2 and Day 3.
- Selected AEs for potential neurological sequelae(e) of epidural analgesia will be assessed using an abbreviated standardized neurological assessment questionnaire (NAO). From Clinical Protocol SKY0401-017, 2/13/2002, Appendix A, page 36, "Time and Events Schedule".

#### 1.5.5.2.6 Analysis Plan

- **Primary Efficacy Endpoint**

The primary efficacy endpoint is the time-weighted pain intensity recall score averaged over 48 hours following randomization. The score was to have been obtained using the Visual Analog Scale (VAS) to answer the question “ How much pain have you had since your last assessment”.

- **Secondary Efficacy Endpoints**

1. Pain intensity at rest evaluation using the Visual Analog Scale at Rest (VAS-R).
2. Pain intensity at rest evaluation using the Categorical Scale at Rest (CAT-R).
3. Pain intensity with activity evaluation using the Visual Analog Scale with Activity (VAS-A).
4. Pain intensity with activity evaluation using the Categorical Scale with Activity (CAT-A).
5. Physical therapist’s rating of patient’s ability to tolerate physical therapy.
6. Patient’s rating of overall pain control.
7. Range-of-motion evaluation.
8. Use of physical support.

- **Sample Size Calculation**

The sample size calculation for this study was based on the difference in mean time-weighted pain intensity recall VAS over 48 hours, using the primary comparison of SKY0401 30 mg versus sham epidural with IV PCA morphine. A mean difference in mean weighted pain intensity recall VAS score of 10 mm was considered to be clinically significant. Using a standard deviation of 15 mm, with  $\alpha=0.05$  (2-tailed) and  $\beta= 0.1$  (90% power), a total of 50 patients per treatment group would detect a 10 mm treatment difference in pain intensity recall VAS over 48 hours post-treatment, at a 0.05% significance level. Thus, the sample size for this study was to be approximately 150 randomized patients (50 per treatment group).

- **Study Populations**

All randomized patients who underwent the procedures for study drug administration and received drug were to have been included in the safety analysis. Safety analysis was to be performed according to the drug actually received, regardless of randomization.

There was to be one patient population for the purposes of efficacy analysis: the ITT population. All randomized patients who underwent the procedures to prepare for study drug administration (epidural or sham epidural), regardless if drug was administered, and had at least one scheduled post-randomization assessment on the primary efficacy variable were to have been included in the ITT population.

If a patient withdrew after receiving study drug and prior to Day 30, they were not to be replaced with another randomized patient.

The last observation carried forward (LOCF) approach was to have been used for missing efficacy data. The value of the variate was to be replaced by the value from the previous post-randomization assessment.

### 1.5.5.3 Amendments:

**Amendment:** 01: 21 October 2002

#### Changes In Study Conduct

- To add stratification details for randomization;
- To delete time-weighted analysis of pain intensity at rest (VAS-R) scores;
- To add continuous pulse oximetry monitoring for all patients;
- To include interim analysis.

#### Changes To Planned Analyses Prior To Unblinded Data Availability

- The definition of the ITT population was changed to consist of all randomized patients, regardless if drug was administered, who have at least two scheduled post-randomization pain intensity recall assessments. Patients were to be analyzed according to their randomization procedure assignment.
- The definition of the safety population was changed to include all randomized patients who received any study drug whether or not they underwent the planned surgical procedure.
- The primary efficacy variable was changed from the time-weighted pain intensity recall score averaged over 48 hours following randomization to the time-weighted pain intensity recall score averaged over 44 hours following the 4-hour post-dose assessment. This change was made because the score from the first pain recall assessment could not be used in the analysis. Patients were to have been asked to indicate the amount of pain they had experienced since the last pain assessment. Since the first assessment did not have a reference time point, it was not appropriate to use it in the analysis. However, the time of the first assessment was used as the baseline for the time-weighting of this endpoint.
- Time-weighted current pain intensity scores at rest and with activity (VAS and CAT) were not included in the analysis plan and were not analyzed.
- The protocol specified that the analysis of demographic continuous variables was to be performed using a one-way ANOVA. The analysis plan specified that the analysis would be performed using an ANOVA with terms for treatment group and type of anesthesia.
- The protocol specified that the analysis of demographic categorical variables was to be performed using a Fisher's exact test or Pearson chi-square test. The analysis plan specified that the analysis would be performed using a CMH test stratified by type of anesthesia.
- The protocol specified that the last observation carried forward approach would be used to impute missing data. The analysis plan specified other methods for the primary and secondary variables

- The analysis plan specified that for patients who did not receive study drug or for whom the time of study drug administration was not reported, the surgery time minus 30 minutes would be used as the study drug administration time.
- The protocol specified that the primary efficacy variable would be analyzed using an ANOVA with terms for treatment and investigational site as factors. Treatment-by-center interaction would also be examined in this model. The analysis plan specified that the difference among sites and treatment-by-site interactions for the primary parameter would be investigated in an exploratory manner.
- The analysis of total opioid usage through 48 hours was added.
- The analysis of the proportion of patients receiving no post-operative opioid was added.
- The protocol was not clear on the analyses to use for the secondary efficacy variables.

The analyses to be used were detailed in the analysis plan.

The changes to the statistical analysis plan (amended on 10 April 2003) after the interim analysis and prior to the availability of unblinded data are outlined below:

- An analysis of an integrated assessment of pain intensity VAS and total opioid usage with patients at rest and with activity (VAS-R and VAS-A) was added.
- The use of the term “narcotic” was changed to “opioid” throughout the analysis plan.

#### Changes To Analyses After Data Availability

An analysis of an integrated assessment of time-weighted pain intensity recall scores and total opioid usage was added.

**Amendment:** 02: 6 January 2003. Administrative changes only

### 1.5.5.4 Study Conduct

#### 1.5.5.4.1 Patient Disposition

A total of 168 patients were enrolled in this study. One hundred and twelve patients were randomized to the SKY0401 treatment groups and 56 patients to the IV PCA morphine treatment (sham epidural) group. Fifty-one and 61 patients were randomized to the 20 and 30 mg SKY0401 treatment groups, respectively. One hundred and sixty-four of the 168 randomized patients (98%) had at least two post-randomization assessments of the primary efficacy variable and were included in the ITT analyses. This included 55 (98%), 51 (100%), and 58 (95%) patients in the IV PCA morphine (sham epidural) and 20 and 30 mg SKY0401 treatment groups, respectively.

Nineteen clinical sites, 17 in the United States and 2 in Australia, participated in this study with patients enrolled at 14 sites in the United States and 2 sites in Australia. The number of patients randomized by clinical site ranged from one to 34.

Table 1.5.5-2 Disposition of Patients, Study 017

	IV PCA Morphine	SKY0401			Total
		20 mg	30 mg	All	
Randomized	56	51	61	112	168
Safety Population	55 (98%)	51 (100%)	56 (92%)	107 (96%)	162 (96%)
ITT Population	55 (98%)	51 (100%)	58 (95%)	109 (97%)	164 (98%)
AE Data Collected Through Day 7 (Safety Population)?					
Yes	55 (100%)	51 (100%)	56 (100%)	107 (100%)	162 (100%)
No	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Patient Followed Through Day 30 For SAEs and NAQ (Safety Population)?					
Yes	50 (91%)	49 (96%)	54 (96%)	103 (96%)	153 (94%)
No	5 (9%)	2 (4%)	2 (4%)	4 (4%)	9 (6%)
Type of Anesthesia (ITT Population)					
General	14 (25%)	15 (29%)	21 (36%)	36 (33%)	50 (30%)
Regional	41 (75%)	36 (71%)	37 (64%)	73 (67%)	114 (70%)
Opioid Usage Collected Through 48 Hours Post-Dose (ITT Population)?					
Yes	55 (100%)	50 (98%)	57 (98%)	107 (98%)	162 (99%)
No	0 (0%)	1 (2%)	1 (2%)	2 (2%)	2 (1%)

From sponsor's Study Report SKY0401-17, Section, 10.1, page 53.

**Unplanned Exclusions:**

Four patients were not included in the ITT population.

Table 1.5.5-3 Patients Excluded From ITT Population, Study 017

Patient ID Number	Treatment Group	Reason Not Included in ITT Population
2454	30 mg SKY0401	Surgery cancelled; no assessments of primary efficacy
3477	30 mg SKY0401	Positive test dose (wet tap); no assessments of primary efficacy
12402	IV PCA morphine	Patient withdrew consent; no assessments of primary efficacy
12405	30 mg SKY0401	Patient withdrew consent; no assessments of primary efficacy

IV = Intravenous; PCA = Patient-controlled analgesia; ITT population = patients who were randomized and had two post-randomization assessments of the primary efficacy variable. Patients are included in the treatment group to which they were randomized.

From Sponsor's Study Report SKY0401-17, Section, 10.1 Table 10.1-3, page 54

#### 1.5.5.4.2 Demographics/Group Comparability

The distribution of demographic and baseline characteristics were similar among treatment groups, with the exception of race (p = 0.0392).

Table 1.5.5-4 Variation in ITT Population by Race, Study 017

Characteristic	IV PCA Morphine	SKY0401			Total
		20 mg	30 mg	All	
Patients (n)	55	51	58	109	164
Caucasian	54 (98%)	49 (96%)	46 (79%)	95 (87%)	149 (91%)
Black	1 (2%)	1 (2%)	5 (9%)	6 (6%)	7 (4%)
Asian	0 (0%)	0 (0%)	1 (2%)	1 (1%)	1 (1%)
Hispanic	0 (0%)	1 (2%)	6 (10%)	7 (6%)	7 (4%)

From Sponsor's Clinical Study Report Protocol No. SKY0401-017, Efficacy Evaluation Table 11.2-2, page 60.

All patients in the ITT population underwent knee surgery and there were no significant differences among treatment groups regarding the surgical procedure. The majority of patients (84%) required the surgery for osteoarthritis and underwent a primary total arthroplasty (95%). A tourniquet was used during surgery in 155 patients (95%), with a mean duration of tourniquet use of 72.4 minutes and a mean duration of surgery of 100.3 minutes.

#### 1.5.5.4.3 Unplanned Analyses

Definition of the ITT population was changed from "all randomized patients who underwent the procedures to prepare for study drug administration (epidural or sham epidural), regardless if drug was administered, and had at least one scheduled post-randomization assessment on the primary efficacy variable" to consist of all randomized patients, regardless if drug was administered, who have at least two scheduled post-randomization pain intensity recall assessments. Patients were to be analyzed according to their randomization procedure assignment.

The primary efficacy variable was changed from the time-weighted pain intensity recall score averaged over 48 hours following randomization to the time-weighted pain intensity recall score averaged over 44 hours following the 4-hour post-dose assessment. This change was made because the score from the first pain recall assessment could not be used in the analysis.

Time-weighted current pain intensity scores at rest and with activity (VAS and CAT) were not included in the analysis plan and were not analyzed.

An analysis of total opioid usage through 48 hours was added.

An analysis of the proportion of patients receiving no post-operative opioid was added.

An analysis of an integrated assessment of pain intensity VAS and total opioid usage with patients at rest and with activity (VAS-R and VAS-A) was added after the interim analysis and prior to unblinding of the data.

An analysis of an integrated assessment of time-weighted pain intensity recall scores and total opioid usage was added after the data became available.

#### Changes in Quantitative and Statistical Procedures:

- The protocol specified that the analysis of demographic continuous variables was to have been performed using a one-way ANOVA. The analysis plan specified that the analysis would be performed using an ANOVA with terms for treatment group and type of anesthesia.
- The protocol specified that the analysis of demographic continuous variables was to have been performed using a one-way ANOVA. The analysis plan specified that the analysis would be performed using an ANOVA with terms for treatment group and type of anesthesia.
- The protocol specified that the last observation carried forward approach would be used to impute missing data. The analysis plan specified other methods for the primary and secondary variables.
- The analysis plan specified that for patients who did not receive study drug or for whom the time of study drug administration was not reported, the surgery time minus 30 minutes would be used as the study drug administration time.
- The protocol specified that the primary efficacy variable would be analyzed using an ANOVA with terms for treatment and investigational site as factors. Treatment-by-center interaction would also be examined in this model. The analysis plan specified that the difference among sites and treatment-by-site interactions for the primary parameter would be investigated in an exploratory manner.

#### 1.5.5.5 Sponsor's Efficacy Results

##### 1.5.5.5.1 Primary Efficacy Variable

The primary efficacy endpoint was the time-weighted pain intensity recall score using the VAS averaged over 44 hours following the 4-hour post-dose assessment. At 4, 8, 12, 24, 30, 36, and 48 hours post-dose, patients answered the question: "How much pain have you had since your last pain assessment?" A 100 mm scale was used to score VAS (0 = no pain; 100 = most severe pain possible). Since the 4-hour post-dose assessment did not have a reference time point, it was not used in the analysis. The mean VAS scores over 44 hours (4 to 48 hour time period) were 39, 35, and 32 for the IV PCA morphine (sham epidural) and 20 and 30 mg SKY0401 treatment groups, respectively. Although pain intensity scores were reduced in a dose-dependent manner with SKY0401 treatment

compared with sham epidural with IV PCA morphine, the overall test among the groups did not achieve statistical significance ( $p = 0.09$ ).

#### 1.5.5.5.2 Secondary Efficacy Variables

1. Pain intensity at rest evaluation using the Visual Analog Scale at Rest (VAS-R). Not analyzed as per Amendment: 01: 21 October 2002.

The VAS scores for pain intensity at rest (VAS-R), when evaluated using an analysis of area under the curve (AUC) including terms for treatment groups and type of anesthesia, demonstrated that pain was significantly reduced over 48 hours with SKY0401. Mean VAS-R scores over 48 hours in the 20 and 30 mg SKY0401 groups (1182.5 and 1040.1, respectively) were significantly lower than that in the sham epidural with IV PCA morphine group (1560.0) ( $p = 0.0094$  and  $0.0002$ , respectively). Significantly reduced pain scores were achieved in the SKY0401-treated patients despite the fact that all patients had unlimited access to SKY0401 medications to manage their post-operative pain (hydromorphone for the SKY0401 patients or morphine for the sham epidural with IV PCA morphine patients). Significantly reduced pain scores at rest were also demonstrated with SKY0401 treatment at the patient's first request for pain medication, with mean VAS-R scores of 52.7 and 50.7 in the 20 and 30 mg SKY0401 groups, respectively, and 65.5 in the sham epidural with IV PCA morphine group ( $p = 0.0039$  and  $0.0001$ , respectively). In addition, significantly lower VAS-R scores were achieved at the 4 ( $p < 0.0001$  for both SKY0401 groups), 8 ( $p < 0.0001$  for both SKY0401 groups), and 12 ( $p = 0.0024$  and  $0.0012$ , respectively) hour post-dose time points in the 20 and 30 mg SKY0401 groups compared with the sham epidural with IV PCA morphine group.

2. Pain intensity at rest evaluation using the Categorical Scale at Rest (CAT-R). Not analyzed as per Amendment: 01: 21 October 2002.

At rest, significantly lower pain scores were observed with the 20 and 30 mg SKY0401 groups compared with sham epidural with IV PCA morphine at the first request for medication ( $p = 0.0188$  and  $0.0021$ , respectively), 4 hours ( $p < 0.0001$  for both SKY0401 groups), 8 hours ( $p < 0.0001$  for both SKY0401 groups), and 12 hours ( $p = 0.0057$  and  $0.0006$ , respectively). The 30 mg SKY0401 group was also significant at 24 hours post-dose ( $p = 0.0385$ ).

3. Pain intensity with activity evaluation using the Visual Analog Scale with Activity (VAS-A).

Not analyzed as per Amendment: 01: 21 October 2002.

The analysis of AUC demonstrated a significant reduction in pain intensity over 48 hours with 20 and 30 mg SKY0401 compared with sham epidural with IV PCA morphine ( $p = 0.0360$  and  $0.0007$ , respectively). As with the VAS-R scores, it is important to stress that all patients had unlimited access to either hydromorphone or morphine post-operatively to manage their pain. The VAS-A scores in the 20 and 30 mg SKY0401 groups were also both significantly reduced compared with the sham epidural with IV PCA morphine group at 4 ( $p < 0.0001$  for both SKY0401 groups), 8 ( $p = 0.0002$  and  $< 0.0001$ , respectively), 12 ( $p = 0.0045$  and  $0.0013$ , respectively), and 24 (30 mg SKY0401 only;  $p = 0.0039$ ) hours post-dose. In addition, at the first request for pain medication, a significant difference

among the treatment groups was almost achieved ( $p = 0.0550$ ), with the mean VAS-A scores in both SKY0401 groups lower than that in the sham epidural with IV PCA morphine group.

4. Pain intensity with activity evaluation using the Categorical Scale with Activity (CAT-A).

Not analyzed as per Amendment: 01: 21 October 2002.

The CAT-A also demonstrated lower pain intensity in the SKY0401 treatment groups. Compared with the sham epidural with IV PCA morphine group, statistically significantly lower CAT-A scores were achieved at 4 hours ( $p < 0.0001$  for both SKY0401 groups), 8 hours ( $p < 0.0001$  for both SKY0401 groups), 12 hours (20 and 30 mg;  $p = 0.0055$  and  $0.0022$ , respectively), and 24 hours (30 mg;  $p = 0.0031$ ).

5. Physical therapist's rating of patient's ability to tolerate physical therapy.

On Days 2 and 3, the patient's ability to tolerate physical therapy was improved in the 20 and 30-mg SKY0401 treatment groups compared with the sham epidural with IV PCA morphine group, although statistical significance was achieved only for the 30 mg SKY0401 group ( $p = 0.0121$  and  $0.0106$  at Days 2 and 3, respectively).

6. Patient's rating of overall pain control.

Pain control, as rated by the patient, was significantly improved at 24 hours post-dose in the 20 and 30-mg SKY0401 groups compared with the sham epidural with IV PCA morphine group ( $p = 0.0249$  and  $0.0008$ , respectively). In addition, the proportion of patients at 24 hours post-dose who rated their pain control as good or very good was significantly higher in the 20 and 30-mg SKY0401 groups compared with the sham epidural with IV PCA morphine group ( $p = 0.0328$  and  $0.0018$ , respectively). No significant differences were observed among the treatment groups at 48 hours post-dose.

7. Range-of-motion evaluation.

There were no significant differences among the treatment groups in terms of a passive knee range-of-motion evaluation (at 48 hours and at discharge).

8. Use of physical support.

There were no significant differences among the treatment groups and in terms of the need for physical support for home use (at discharge).

Added by Amendment: 01: 21 October 2002:

- Total opioid usage through 48 hours.

Total post-operative opioid usage in the 20 and 30-mg SKY0401 groups was significantly reduced from 0 to 48 hours (44.0 and 38.9 mg, respectively) compared with the sham epidural with IV PCA morphine group (132.2 mg) using rank-transformed data ( $p < 0.0001$  for both groups). Total opioid usage was also significantly reduced in the 20 and 30-mg SKY0401 groups compared with the sham epidural with IV PCA morphine group from 0 to 24 hours ( $p < 0.0001$  for both groups), > 24 to 48 hours ( $p < 0.0001$  for both

groups), post-operatively through 48 hours post-dose ( $p < 0.0001$  for both groups), and at all 4-hour intervals from 0 to 48 hours.

- The proportion of patients receiving no post-operative opioid. The proportion of patients receiving no post-operative opioid medication was significantly higher in both the 20 and 30 mg SKY0401 groups compared with the sham epidural with IV PCA morphine group through 24 ( $p = 0.0041$  and  $< 0.0001$ , respectively) and 48 hours ( $p = 0.0294$  and  $0.0019$ , respectively) post-dose, and at all other intervals examined (through 12 hours, > 12 to 24 hours, > 24 to 36 hours, > 24 to 48 hours, and > 36 to 48 hours).

### **Additional Efficacy Analysis**

An analysis of the primary efficacy variable between among demographic and test-dose treated groups was also conducted:

Time-weighted pain intensity recall scores averaged over 44 hours (4 to 48 hours) were also evaluated by gender (male or female), age group ( $< 65$  or  $\geq 65$  years), race (Caucasian or non-Caucasian), type of anesthesia (general or regional), ASA Classification (Class 1, 2, or 3), and test dose (none,  $< 15$  minutes prior to study drug, or  $\geq 15$  minutes prior to study drug). No significant differences were observed among the treatment groups in terms of time-weighted pain intensity recall scores in any of these subgroups (Sponsor's Study Report SKY0401-17, section 14.2, Table 43), with the exception of patients who received a test dose  $\geq 15$  minutes prior to study drug administration ( $p = 0.0234$ ). In this subgroup of patients, the mean VAS scores over 44 hours (4 to 48 hour time period) were 56.4, 44.3, and 27.1 for the sham epidural with IV PCA morphine and 20 and 30 mg SKY0401 treatment groups, respectively.

### **1.5.5.6 REVIEWER'S COMMENTS**

This Phase 3 study in 164 patients was designed to evaluate the analgesic efficacy of 20-mg or 30-mg SKY0401 compared with sham epidural with IV PCA in the setting of knee arthroplasty. Four patients out of 168 randomized were not included. Of the 4 patients not included in the efficacy population, 2 patients withdrew consent, one patient did not have surgery and one patient experienced a mechanical complication of epidural placement before administration of study drug. Protocol amendments of October 21, 2002 and January 6, 2003 consisted primarily of changes to the proposed statistical analysis. They do not change the conclusions of this review. This reviewer determined that the study conduct reflected the protocol despite these variances and was adequate to analyse efficacy of SKY0401.

The sponsor's primary analysis of efficacy was the time-weighted pain intensity recall score averaged over 44 hours following an initial 4-hour post-dose assessment. A VAS score was used to quantify recalled pain. Analysis of the primary efficacy endpoint indicates that the study did not demonstrate a statistically significant reduction in mean

VAS scores associated with SKY0401 treatment compared with sham epidural with IV PCA. This failure may be a result in part of patients' difficulty in quantifying recalled pain.

Analysis of total post-operative opioid usage as a secondary efficacy endpoint demonstrated a reduction in 20 and 30-mg SKY0401 groups from 0 to 48 hours compared with the sham epidural with IV PCA morphine group. Post-operative opioid usage was cut by about 2/3 in the patient groups receiving SKY0401 compared with the IV PCA group. These findings are consistent with the results of the sponsor's other pivotal trials and probably reflect efficacy of the SKY0401. These results may be considered supportive of other trials, but cannot stand by themselves because this study was not specifically designed and powered to test a hypothesis of reduced postoperative opioid usage.

Other analyses of secondary endpoints also tended to support efficacy of SKY0401. The VAS scores for pain intensity at rest and with activity, when evaluated using an analysis of area under the curve (AUC) including terms for treatment groups and type of anesthesia, indicated that pain was significantly reduced over 48 hours with SKY0401. The proportion of patients receiving no post-operative opioid medication was higher in both the 20 and 30-mg SKY0401 groups compared with the sham epidural with IV PCA morphine group through 24 and 48 hours.

Analysis of other secondary endpoints did not support or weakly supported efficacy of SKY0401. No significant differences were observed among the treatment groups in terms of time-weighted pain intensity recall scores. There were no significant differences among the treatment groups in terms of a passive knee range-of-motion evaluation (at 48 hours and at discharge). There were no significant differences among the treatment groups and in terms of the need for physical support for home use (at discharge). No significant differences were observed among the treatment groups in pain control as rated by the patient and in the proportion of patients describing good or very good pain control at 48 hours post-dose, however patients treated with 20 mg or 30 mg of SKY0401 did report better pain control than patients treated with sham epidural with IV PCA at 24 hours.

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*The following studies (008, 003 and 016) were primarily PK/PD trials. They will be presented in an abbreviated format.*

### **1.5.6 Study 008, Hip arthroplasty, (open-label):**

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

#### **1.5.6.1 Summary**

This, the first study in which SKY0401 was administered to patients undergoing surgery was a Phase 2, open-label, serial cohort, dose-ranging design to assess the safety, efficacy and pharmacokinetics of administering a single epidural injection of SKY0401 to patients undergoing total hip arthroplasty under regional anesthesia. Fifty patients received a single dose of study medication: 10 mg SKY0401 (n=4), 15 mg SKY0401 (n=1), 20 mg SKY0401 (n=12), 25 mg SKY0401 (n=1), 30 mg SKY0401 (n=8), 20 mg SKY0401.1 (n=1) or 30 mg SKY0401.1 (n=10) with 13 patients in the comparator group treated with 5 mg unencapsulated morphine.

Each patient was to receive a single epidural dose of study medication administered just prior to the administration of spinal anesthesia and within 30 minutes prior to the start of surgery. The protocol was amended 5 times. Changes were made in the number of patients permitted in each dose group and in the permitted dose of study drug. The doses that were studied were 5-, 10-, 15-, 20-, 25- and 30-mg doses of study drug. The protocol was revised to include patients undergoing total abdominal hysterectomy or total knee replacement, but this change was reversed in a subsequent amendment. The formulation of the study drug was changed from SKY0401 to SKY0401.1 (content of excipient constituents in SKY0401.1 is lower than in SKY0401) that revealed a lower C<sub>max</sub> and an extended period of morphine availability with the newer formulation. The maximum dose was lowered from 30 mg to 20 mg of SKY0401.1 following incidents of respiratory depression. The Drug Administration section was updated to reflect addition of an active control drug commercially available unencapsulated morphine sulfate.

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 level at any time a significant opioid toxicity was observed.

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. The primary efficacy endpoint was fentanyl usage through 24 and 48 hours following study drug administration.

In this Phase 2 open-label pilot study, epidural administration of a single dose of SKY0401 resulted in post-operative analgesia, as evidenced by a reduction in the need for supplemental narcotic pain medication required to achieve the adequate pain control, and by an increased time to use any additional narcotics compared to unencapsulated morphine. The SKY0401 and SKY0401.1 formulations appeared to perform similarly with regards to efficacy measurements.

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### 1.5.7 Study 003, PK analysis, volunteers:

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

#### 1.5.7.1 Summary

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.

Of the 30 subjects originally anticipated, 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).

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. Overall, dose-dependent trends were generally demonstrated. 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.

Following epidural administration of SKY0401, peak plasma concentrations (C<sub>max</sub>) of morphine were observed within approximately 10 minutes for all SKY0401 doses. The mean plasma C<sub>max</sub> ranged from 12 to 103 ng/mL for the 2.5 to 40 mg doses of SKY0401. The mean plasma AUC<sub>inf</sub> also increased linearly with escalating doses of SKY0401. The mean t<sub>1/2</sub> increased from 2.6 to 20.9 hours, respectively, for the 2.5 to 40 mg doses. Peak CSF concentrations of morphine were achieved 5 minutes post-dose and C<sub>max</sub> was achieved between 0.58 to 3 hours for the 5 to 40 mg SKY0401 doses. The inactive metabolite, morphine-3-glucuronide, was not detected in the CSF; however, it was the primary metabolite found in plasma and urine. The active metabolite, morphine-6-glucuronide, was detected in trace amounts in only one CSF sample, but was present in plasma and urine at similar concentrations as morphine.

SKY0401 at doses of 20, 30, and 40 mg administered epidurally resulted in antinociceptive activity (including increases in measurements of pain tolerance, pain threshold, and SI50 compared to baseline); lower doses of SKY0401 exhibited minimal effects. The 40-mg dose of SKY0401 elicited protocol-defined dose limiting toxicity, while doses of 30 mg or below were well tolerated. Therefore, 30 mg was determined to

be the maximum tolerated dose of SKY0401. As minimal effects were observed even at the lowest dose of SKY0401 investigated (2.5 mg), a “no effect” dose was not identified. No unusual or unexpected adverse events were reported and no subjects were prematurely terminated from the study due to an adverse event.

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### 1.5.8 Study 016, Upper abdominal surgery, (open label):

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

#### 1.5.8.1 Summary

The primary objective was 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. The 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.

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 a 1-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.

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 ( $AUC_{0-t_{last}}$ ,  $AUC_{0-\infty}$ ,  $C_{t_{last}}$ ,  $C_{max}$ ,  $t_{max}$ ,  $k_{el}$ ,  $\lambda_z$ ,  $t_{1/2el}$ ) were then determined.

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.

#### Summary:

Examination of the early exposure data indicated that, during the first hour, the rate of morphine delivery to the systemic circulation was faster for all patients who received a test dose 3 minutes before administration of the SKY0401 dose (Groups 2 and 5) relative to those who did not receive a test dose (Group 1) or who received a test dose 10 or 15 minutes prior to SKY0401 administration (Groups 3 and 4, respectively).

Among the groups that received a test dose prior to SKY0401 administration, the percentage of total morphine  $AUC_{0-t}$  delivered in the first hour was lower when the catheter was flushed with saline and SKY0401 administration was delayed by 10 or 15 minutes (Groups 3, 4). In the first hour, the partial  $AUC_{0-t}$  ratios to total  $AUC_{0-t}$  for Groups 1, 3, and 4 were 7.3%, 10.9% and 9.3%, respectively. Over the same time period, the partial  $AUC_{0-t}$  ratios were 17.0% in Group 2 and 17.3% in Group 5. Among the patients who did not receive a test dose, 1/6 had a peak serum concentration of  $>20$  ng/mL. In contrast, among the patients who received a test dose 3 minutes before SKY0401 administration, 13/16 had a  $C_{max}$  of  $>20$  ng/mL. With a 10-minute interval between test dose and SKY0401 administration, 2/7 patients had a  $C_{max}$  of  $>20$  ng/mL, while with a 15-minute interval, 0/8 patients had a  $C_{max}$  of  $>20$  ng/mL.

The results of this study confirmed prior data that concomitant administration of lidocaine with epinephrine results in an increase in the rate of systemic morphine delivery from SKY0401. The effect was substantially mitigated by flushing the epidural catheter with normal saline after administration of lidocaine with epinephrine and delaying the administration of SKY0401 by at least 15 minutes.

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.

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## 1.6 INTEGRATED REVIEW OF SAFETY

### 1.6.1 Brief Statement of Findings

Based upon analysis of the data presented and evaluation of the case report forms, the following findings were made with regards to the safety of SKY0401.

1. A total of 967 patients and volunteers were exposed to SKY0401. The ISS included 905 patients exposed to SKY0401 and did not include subjects participating in two volunteer studies.
2. There were five patient deaths during conduct of clinical trials with one patient death possibly related to SKY0401.
3. In the ISS there were 96 patients with serious adverse events out of 905 patients (11%) treated with SKY0401 compared with 4/78 (5%) patients treated with placebo, 6/97 (6%) treated with unencapsulated morphine and 5/55 (9%) treated with sham epidural with IV PCA.
4. Serious adverse events were typical of adverse events associated with opiates or the surgical procedure and included paralytic ileus, respiratory depression, myocardial infarction, pulmonary embolism, hypoventilation, urinary retention, somnolence, cellulitis, gastrointestinal hemorrhage, atrial fibrillation, cardiac arrest, hypotension, post-operative wound infection, joint dislocation, and pyrexia.
5. Respiratory adverse events occurred more frequently with SKY0401 than in the comparator population. Opiate antagonists were used more frequently in SKY0401 patients than in comparator groups, particularly for respiratory adverse events.
6. Common adverse events were typical of opiate adverse events or the surgical procedure including nausea, pruritus, pyrexia, vomiting, hypotension, anemia, headache, constipation, decreased oxygen saturation, urinary retention, and dizziness.

### 1.6.2 Adequacy of Exposure and Safety Assessment

Nine clinical trials were conducted under IND 52,113 in which, 961 subjects were exposed to SKY0401. The table below is reproduced from the NDA and details the exposures from 8 of the clinical trials. Study 018 was submitted with the 120 day safety update and included 34 volunteers exposed to SKY0401 in addition to the 927 individuals listed in the table below. The sponsor's integrated summary of safety (ISS) database did not include volunteer subjects in Study 003 or 018. There were no serious adverse events in Study 003. A narrative was provided for the single serious adverse event occurring in Study 018. Overall the exposure in Phase 2 and 3 clinical trials appears adequate for meaningful review.

Table 1.6-1 Exposure to SKY0401 and Comparators In Clinical Trials

Study No.	Indication	SKY0401- Number of Subjects Evaluable for Safety									Controls - Number of Subjects			
		2.5 mg	5 mg	10 mg	15 mg	20 mg	25 mg	30 mg	40 mg	Total SKY 0401	MS 2.5 mg	MS 5 mg	MS PCA	Plac.
003*	Vols	2	4	4		4		6	2	22	2	2		
008**	Hip			4	1	12	1	8		26		13		
009	Hip			35		32		26		93				27
011	Hip				48	45	43			136				47
017	Knee					51		56		107			55	
012B	Lower Abdo		102	84	91	84	88			449		66		4
015	C-sect		19	18	18					55		18		
016	Upper Abdo				39					39				
<b>Total Evaluable for Safety</b>		<b>2</b>	<b>125</b>	<b>145</b>	<b>197</b>	<b>228</b>	<b>132</b>	<b>96</b>	<b>2</b>	<b>927</b>	<b>2</b>	<b>99</b>	<b>55</b>	<b>78</b>
<b>Total included in ISS tables*</b>		<b>0</b>	<b>121</b>	<b>141</b>	<b>197</b>	<b>224</b>	<b>132</b>	<b>90</b>	<b>0</b>	<b>905</b>	<b>0</b>	<b>97</b>	<b>55</b>	<b>78</b>

\*Data from this Phase 1 volunteer study was not included in the integrated safety tables

\*\* Excludes patients who received the alternative SKY0401.1 formulation

Table is from sponsor's Summary of Safety 2.7.4, page 7.

### 1.6.3 Methods for Review of Safety

The review of safety consisted primarily of a review of the sponsor's Summary of Safety and electronic Integrated Summary of Safety (ISS) database with selected review of narratives of case report narratives for serious adverse events. The Agency adverse event reporting system (AERS) database was examined for adverse events associated with epidural morphine reported between 1999 and 2003 for qualitative comparison to the adverse events reported with SKY0401.

### 1.6.4 Subject Demographics

The demographic characteristics for all subjects who were included in the Integrated Summary of Safety database are summarized in the table below. Overall, the subjects were predominantly female and Caucasian. Of the patients treated with SKY0401, 66% were female compared with 54% in the placebo group, 55% treated with sham epidural with IV PCA and 76% treated with unencapsulated morphine. Caucasians, comprised 80% of the SKY0401 treatment population compared with 88%, 78% and 98% of the placebo, unencapsulated morphine and sham epidural with IV PCA treatment groups.

Table 1.6-2 Demographic Distribution of Patients Evaluated for Safety

	Placebo	5 mg Unencapsulated Morphine	IV PCA Morphine	5 mg SKY0401	10 mg SKY0401	15 mg SKY0401	20 mg SKY0401	25 mg SKY0401	30 mg SKY0401	All SKY0401	Total
Number of Patients	78	97	55	121	141	197	224	132	90	905	1135
Age (Years)											
n	78	97	55	121	141	197	224	132	90	905	1135
Mean (SD)	59.0 (12.3)	47.7 (14.7)	68.0 (9.2)	47.3 (13.4)	49.5 (15.3)	53.7 (15.9)	57.1 (12.9)	55.2 (14.0)	61.5 (12.4)	54.0 (14.7)	54.5 (14.8)
Median	61.0	48.0	69.0	45.0	48.0	54.0	58.0	53.5	63.0	54.0	55.0
Min-Max	26 - 85	18 - 87	43 - 85	18 - 91	19 - 84	19 - 90	18 - 81	25 - 99	27 - 88	18 - 99	18 - 99
Age Group (Years)											
< 65	47 (60.3%)	83 (85.6%)	16 (29.1%)	105 (86.8%)	116 (82.3%)	143 (72.6%)	146 (65.2%)	92 (69.7%)	50 (55.6%)	652 (72.0%)	798 (70.3%)
65 - 75	26 (33.3%)	12 (12.4%)	28 (50.9%)	14 (11.6%)	18 (12.8%)	38 (19.3%)	68 (30.4%)	31 (23.5%)	31 (34.4%)	200 (22.1%)	266 (23.4%)
> 75	5 (6.4%)	2 (2.1%)	11 (20.0%)	2 (1.7%)	7 (5.0%)	16 (8.1%)	10 (4.5%)	9 (6.8%)	9 (10.0%)	53 (5.9%)	71 (6.3%)
Sex											
Male	36 (46.2%)	23 (23.7%)	25 (45.5%)	34 (28.1%)	34 (24.1%)	63 (32.0%)	92 (41.1%)	42 (31.8%)	40 (44.4%)	305 (33.7%)	389 (34.3%)
Female	42 (53.8%)	74 (76.3%)	30 (54.5%)	87 (71.9%)	107 (75.9%)	134 (68.0%)	132 (58.9%)	90 (68.2%)	50 (55.6%)	600 (66.3%)	746 (65.7%)
Race											
Caucasian	69 (88.5%)	76 (78.4%)	54 (98.2%)	82 (67.8%)	108 (76.6%)	162 (82.2%)	188 (83.9%)	110 (83.3%)	73 (81.1%)	723 (79.9%)	922 (81.2%)
Black	8 (10.3%)	12 (12.4%)	1 (1.8%)	21 (17.4%)	20 (14.2%)	22 (11.2%)	21 (9.4%)	13 (9.8%)	9 (10.0%)	106 (11.7%)	127 (11.2%)
Asian	0 (0.0%)	1 (1.0%)	0 (0.0%)	2 (1.7%)	3 (2.1%)	3 (1.5%)	4 (1.8%)	0 (0.0%)	1 (1.1%)	13 (1.4%)	14 (1.2%)
Hispanic	1 (1.3%)	8 (8.2%)	0 (0.0%)	14 (11.6%)	9 (6.4%)	8 (4.1%)	9 (4.0%)	8 (6.1%)	7 (7.8%)	55 (6.1%)	64 (5.6%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)	1 (0.7%)	2 (1.0%)	2 (0.9%)	1 (0.8%)	0 (0.0%)	8 (0.9%)	8 (0.7%)

Table is from sponsor's Summary of Safety 2.7.4, page 30

### 1.6.5 Subject Disposition

Patients treated with SKY0401 or epidural unencapsulated morphine or placebo received a single dose. The table on the next page presents the various reasons that patients were discontinued during conduct of clinical trials.

Patients withdrawn before study completion "Administrative" for non-completion included premature discharge from hospital before completion of study procedures, patient non-compliance or loss to follow-up. Inadequate pain control requiring alternative treatment was the reason patients were listed as dropouts for "lack of efficacy". Among patients receiving SKY0401 there was no apparent dose relationship to any reason for non-completion. Also, there is no apparent difference for non-completion between SKY0401 and any of the control medications except that a disproportionately high number of dropouts for unexplained reasons (listed as "other") occurred in the sham epidural with IV PCA MS treatment group. All four of the unexplained dropouts in the sham epidural with IV PCA MS group were treated on 3/11/03 and discontinued on 4/11/03 after 24 days in the trial.

The timing of unexplained dropouts occurred long after the pharmacodynamic period of activity of the study drug and there were no associated adverse events.

*Appears This Way  
On Original*

Table 1.6-3 Distribution of Patient Who Did Not Complete Clinical Trials by Treatment Group and Reason for Dropout.

Treatment Group	Number of Dropouts	Total Exposure in ISS	% Dropout/Exposure	Number of Dropouts for AE	Number of Dropouts for Lack of Efficacy	Number of Administrative Dropouts	Number of Unexplained Dropouts
5 mg SKY0401	0	121	0.0%	0	0	0	0
10 mg SKY0401	4	141	2.8%	1	1	2	0
15 mg SKY0401	13	197	6.6%	3	0	10	0
20 mg SKY0401	13	224	5.8%	2	1	7	3
25 mg SKY0401	2	132	1.5%	0	0	2	0
30 mg SKY0401	4	90	4.4%	0	0	2	2
ALL SKY0401	36	905	4.0%	0	0	0	0
5 mg Unencap. MS	5	97	5.2%	0	1	4	0
IV PCA MS (sham epidural)	5	55	9.1%	0	0	1	4
Placebo epidural	1	78	1.3%	0	0	1	0
<b>Totals</b>	<b>47</b>	<b>1135</b>	<b>4.1%</b>	<b>6</b>	<b>3</b>	<b>29</b>	<b>9</b>

Data was abstracted from verbatim explanations in sponsor's Summary of Safety, Appendix 2.7.4.7, Listing 1, pages 421-426.

## 1.6.6 Findings

### 1.6.6.1 Deaths

Five patients died during the conduct of the clinical trials including the follow-up period. These patients are identified in Table 1.6-4 below.

Table 1.6-4 Patients Who Died During Conduct of Clinical Trials

Study	Patient No.	A/G/R	Treatment Group	Cause of Death
SKY0401-012B	012-11-106	62/f/C	No Study Medication	Multi-organ Failure
	012-74-132	79/f/C	SKY0401 15 mg	Myocardial infarction, Respiratory distress, Pneumonia
	012-83-119	74/m/C	SKY0401 20 mg	Cardiac Arrest
SKY0401-016	016-01-333	60/m/C	SKY0401 15 mg	Asystole, Pulmonary Embolus
SKY0401-107	017-23-404	67/f/C	SKY0401 20 mg	Myocardial infarction

A/G/R refers to age in years, gender (male, M or female, f), race (Caucasian, Black, Asian)

Data was abstracted from sponsor's case report form narratives.

Patient 012-83-119 may have died because of adverse events related to the study drug. This 74-year-old Caucasian man was administered 20 mg of SKY0401 according to protocol for SKY0401-12b. The patient did not have a lower abdominal operation as expected because the pre-incision colonoscopy under anesthesia revealed that there was no tumor. The patient was recovered in a post anesthesia care unit and evaluated with hourly assessment of vital signs following discharge to a hospital room for overnight observation. At about 10 hours after administration of study drug the patient developed symptoms of nausea and vomiting which were treated with ondansetron (4 mg). The nausea and vomiting resolved within 30 minutes. At about 21 hours after study drug administration the patient was observed to be snoring in a lateral decubitus position. Another observation 20 minutes later revealed the patient to be unresponsive with emesis in the airway. Cardiopulmonary resuscitation was unsuccessful. No autopsy was performed, but the reporting physician listed myocardial infarction as the cause of death with secondary emesis in the oral airway.

It is possible that the patient's cause of death was acute myocardial infarction. Approximately 25% of myocardial infarctions are the initial presentation of ischemia and infarction during sleep is not uncommon. In this particular case however, the patient's earlier symptoms of nausea and vomiting, symptoms common with posterior wall ischemia, appeared to resolve after treatment with ondansetron. This would not be expected if the patient's symptoms resulted from myocardial ischemia. The interval between apparently untroubled sleep and cardiac arrest was only 20 minutes suggesting that the precipitating event was rapid and profound such as a malignant ventricular dysrhythmia or airway obstruction. While malignant ventricular dysrhythmia is common with myocardial ischemia, there is no evidence submitted to support that this occurred.

The documented findings are most consistent with emesis aspiration into the airway as the cause of death. Epidural morphine can provoke nausea and vomiting, just as this patient exhibited earlier, and can also cause respiratory depression within 24 hours of administration. The absence of surgical stimulation is likely to have contributed to respiratory depression, somnolence and vomiting. In the absence ECG data or other evidence of cardiac ischemia before cardiac arrest, it seems likely that the study drug was primarily responsible the death of this patient.

Patient 12-74-132 was a 79-year-old Caucasian woman with a history of inferior myocardial infarction. She received 15 mg of SKY0401 in accordance with study protocol and underwent subtotal colectomy as planned. The patient was removed from the study protocol on the night of surgery because of inadequate pain control and she was treated with additional epidural morphine. On postoperative day 14 the patient developed an exacerbation of shortness of breath and expired. The cause of death was attributed by the sponsor's reporter to myocardial infarction exacerbated by pneumonia.

The elapsed time between administration of the study drug and the patient's death was much too long for the study drug to have been a likely cause of death. Failure of the study drug to provide pain control precipitated additional epidural morphine administration. It is possible that this additional central axis narcotic inhibited clearance of pulmonary secretions and enabled pneumonia to develop. The relationship of inadequate efficacy of study drug to this patient's death is too remote to consider causal.

Patient 12-11-106 was randomized to receive 5-mg SKY0401 for anticipated cystectomy and ileoconduit surgery. However, she did not receive study drug as planned. She developed preoperative respiratory insufficiency that required tracheostomy, renal failure and multiple infections with bacteremia. Her medical team determined that she was not a surgical candidate and she was placed on a palliative morphine infusion until she died from her disease. There is no apparent connection between the study drug and the patient's death.

Patient 16-01-333 was a 60-year-old Caucasian man who received 15 mg of SKY0401 for laparotomy and excision of insulinoma. Shortly before the scheduled visit at 48 hours after study drug administration the patient developed acute dyspnea with cyanosis when transferring from a chair back to his bed. He rapidly decompensated clinically to full cardiopulmonary arrest and expired following extensive resuscitation efforts. Post-mortem examination revealed that the cause of death was pulmonary embolism. The patient's death was related to his underlying disease and possibly related to the type of surgery. It is unlikely that the study drug contributed to his perioperative death.

Patient 17-23-404 was a 67-year-old woman who was treated with 20 mg of SKY0401 for knee replacement. Her preoperative history is notable for hypertension and diabetes. The perioperative course was managed within the protocol except that the patient's beta-blocking medication was inadvertently discontinued. At about 42 hours after study drug administration the patient developed hypotension and tachycardia with clinically significant elevation of cardiac enzymes and EKG changes suggesting silent myocardial injury. After developing angina on the following day the patient underwent cardiac

catheterization which demonstrated high-grade multivessel coronary artery disease. Coronary artery bypass grafting was performed the next day, but her recovery was complicated by respiratory failure and the patient expired from multiorgan system failure about one month after study drug administration. The patient's underlying coronary disease was unknown at the time of her initial orthopedic surgery. Her perioperative myocardial infarction was related to this pathophysiology perhaps compounded by diabetic insensitivity to symptoms of angina and inadvertent withdrawal of beta blockade. The study drug did not appear to be a contributing factor the patient's death.

### 1.6.6.2 Other Serious Adverse Events

One or more SAEs were reported by 11% of all SKY0401-treated patients, compared to 5%, 6% and 9% of placebo, epidural unencapsulated MS and sham epidural with IV PCA MS-treated patients respectively. There was no obvious dose-response across the various SKY0401 doses, although the rate was somewhat higher in the SKY0401 30-mg group (14%).

For SKY0401-treated patients the system organ classes most frequently involved were Gastrointestinal Disorders, Respiratory/Thoracic/Mediastinal Disorders, Cardiac Disorders and Infections/Infestations. The table ( 1.6-5) below illustrates the incidence of serious adverse events associated with SKY0401 compared with control groups according to various body systems.

Table 1.6-5 Serious Adverse Events by Body System Associated with SKY0401 and Comparator Treatments

	Number of Exposures	Patients with Serious AEs	Serious Respiratory	Serious Vascular	Serious Cardiac	Serious Gastrointestinal	Serious Urinary	Serious General	Serious Neurological
Placebo	78	4 (5.1%)	0 (0.0%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unencapsulated Morphine (5 mg)	97	6 (6.2%)	1 (1.0%)	0 (0.0%)	1 (1.0%)	2 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IV PCA	55	5 (9.1%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5 mg SKY0401	121	12 (9.9%)	1 (0.8%)	1 (0.8%)	2 (1.7%)	4 (3.3%)	0 (0.0%)	2 (1.7%)	0 (0.0%)
10 mg SKY0401	141	10 (7.1%)	1 (0.7%)	0 (0.0%)	1 (0.7%)	3 (2.1%)	0 (0.0%)	1 (0.7%)	2 (1.4%)
15 mg SKY0401	197	25 (12.7%)	1 (0.5%)	4 (2.0%)	2 (1.0%)	7 (3.6%)	2 (1.0%)	1 (0.5%)	1 (0.5%)
20 mg SKY0401	224	23 (10.3%)	4 (1.8%)	3 (1.3%)	6 (2.7%)	3 (1.3%)	3 (1.3%)	0 (0.0%)	3 (1.3%)
25 mg SKY0401	132	13 (9.8%)	6 (4.5%)	3 (2.3%)	2 (1.5%)	2 (1.5%)	1 (0.8%)	0 (0.0%)	1 (0.8%)
30 mg SKY0401	90	13 (14.4%)	4 (4.4%)	1 (1.1%)	3 (3.3%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
<b>Total Exposures</b>	<b>1135</b>	<b>111</b>	<b>19</b>	<b>13</b>	<b>18</b>	<b>23</b>	<b>6</b>	<b>4</b>	<b>8</b>

These data were abstracted from sponsor's electronic Integrated Summary of Safety database. IV PCA refers to the group treated with sham epidural and IV PCA. Placebo refers to patients treated with epidural injection of placebo.

Individual events reported in 0.3% or more of All SKY0401- treated patients were paralytic ileus (1.3%), respiratory depression (0.9%), myocardial infarction (0.7%), pulmonary embolism (0.4%), hypoventilation (0.4%), urinary retention (0.4%), somnolence (0.3%), cellulitis (0.3%), gastrointestinal hemorrhage (0.3%), atrial fibrillation (0.3%), cardiac arrest (0.3%), hypotension (0.3%), post-operative wound infection (0.3%), joint dislocation (0.3%), and pyrexia (0.3%), These events are all either expected opioid effects or events expected for the patient population. With the exception

of respiratory adverse events, there is no apparent dose-response across the dose levels of SKY0401 for any of these events.

The only events considered by the sponsor to be possibly related to the study medication involved known opioid effects, notably respiratory depression and paralytic ileus. Respiratory depression events reported as SAEs were generally those requiring administration of an opioid antagonist, intubation or other forms of intensive support or monitoring.

There were only three SAEs that were not resolved by the end of the study. Patient 009-14-001 developed a hip joint infection following revision arthroplasty. Patient 012B-45-109 experienced a cerebral infarct with residual visual effects. Patient 016-01-330 with a history of Crohn's disease developed multiple bowel strictures, one of which was not successfully dilated. The adverse events experienced by these three patients did not appear to be related to SKY0401.

#### **1.6.6.3 Adverse Events Associated with Dropouts**

Six patients out of 905 patients treated with SKY0401 did not complete their protocol because of an adverse event. No patients in the placebo epidural arm, unencapsulated epidural morphine arm or sham epidural with IV PCA arm failed to complete the protocol because of an adverse event.

Four patients treated with SKY0401 died during the study. Patient 012-11-106 has been included among the four deaths even though this patient died one day after the protocol was completed (day 30). These patients are discussed earlier in this review. (One other patient randomized to the SKY0401 arm, but was not treated with SKY0401 also died.)

Two other patients did not complete the protocol because of nonlethal adverse events. Patient 016-01-340, who received 15 mg of SKY0401, was re-hospitalized for progression of pancreatic cancer before the protocol was completed. Patient 009-02-004, who received 10 mg of SKY0401, was observed to be agitated and confused on the day after surgery. The sponsor reports that the patient had a prior history of posttraumatic stress disorder and claustrophobia, which was not previously known to the study staff. The patient's confusion was consistent with his past medical history and not a result of SKY0401.

#### **1.6.6.4 Other Significant Adverse Events**

Other Significant Adverse Events are reviewed according to their associated body system:

Respiratory Serious Adverse Events: The incidence of adverse events coded by the sponsor as serious respiratory depression was no worse with SKY0401 than with alternative treatments. Of the cases of respiratory depression that did occur, 36 patients

treated with SKY0401 (4%) required treatment with a narcotic antagonist but only one patient out of 230 receiving either placebo, unencapsulated morphine or sham epidural with IV PCA require a narcotic antagonist. The patient receiving alternative treatment was treated with unencapsulated epidural morphine. The incidence of receiving narcotic antagonist for respiratory depression was 1 out of 97 (1%) in the unencapsulated morphine group. Among the patients treated with SKY0401 who also received a narcotic antagonist, 7 received 30-mg SKY0401 (8%), 6 patients received 25-mg SKY0401 (4.5%), 13 patients received 20-mg SKY0401 (6%), 5 patients received 15-mg SKY0401 (2.5%), 4 patients received 10-mg SKY0401 (3%), 1 patient received 5-mg SKY0401 (0.8%). These findings suggest a dose-related incidence of respiratory depression requiring narcotic antagonist treatment.

Narcotic-related respiratory depression sufficient to require pharmacological antagonism may indicate that a serious adverse event would have occurred without treatment by an antagonist. These cases may each a “near-miss” for a serious adverse event.

Cardiac Serious Adverse Events: Eight of the 905 SKY0401 patients (1 %) who experienced serious cardiac events had a myocardial infarction or ischemia compared with 3% (2/78) placebo patients. There were 3 additional cases of asystole or ventricular dysrhythmias, but there was no dose relationship of SKY0401 to the incidence of infarction or the combination of dysrhythmias and infarction. One patient experienced an unexplained episode of intraoperative preincisional “asystole” that resolved before treatment. There was one instance of negative pressure pulmonary edema in a 33-year-old treated with SKY0401 (non-cardiac failure). One patient treated with 20 mg SKY0401 and subsequently died experienced nausea and sedation preceding a cardiopulmonary arrest associated with vomit in the airway. Four patients experienced serious supraventricular dysrhythmias.

It is much more likely that myocardial ischemia was not a direct result of SKY0401. Surgery is associated with a generalized inflammatory response that predisposes patients to a hypercoagulable state. Patients with critical coronary artery stenoses are at higher risk in the perioperative period for ischemia and infarction. Morphine, administered intravenously, is an accepted treatment for cardiac ischemia, so it is hard to envision a mechanism for epidural morphine to initiate a cardiac ischemic event. Preincisional asystole can sometimes be related to impaired venous return cause by mechanical ventilation. Negative pressure pulmonary edema is usually a result of vigorous inspiratory effort against an obstructed airway in healthy young individuals.

Vascular Serious Adverse Events: Four of 905 SKY0401 patients (0.4%) experienced pulmonary emboli as did one out of the 78 placebo patients (1%). Two patients experienced DVTs and one experienced a cerebral infarction in the SKY0401 patient population compared with none in the placebo, encapsulated morphine or sham epidural IV PCA arms reported in the ISS. There was no apparent dose dependency of these events. These adverse events were most likely related to the pathophysiology of surgery rather than to SKY0401.

Gastrointestinal Serious Adverse Events: Four out of 904 SKY0401 patients developed gastrointestinal bleeding. Eleven patients developed an ileus (1%, 11/905) compared with

(3%, 3/97) treated with unencapsulated morphine and (1%, 1/78) treated with placebo. One SKY0401 patient developed pancreatitis.

SKY0401 may, like other morphine preparations contribute to bowel dysmotility following surgery. Ileus is a well-known complication of abdominal surgery, but may present after any major surgical procedure. Gastrointestinal bleeding may follow periods of systemic stress, as occurs with surgery. The incidence of these adverse events is typical for the type of procedure and comparable to the comparator populations.

Neurological Serious Adverse Events: 4 of the 905 SKY0401 patients (0.4%) had increased sedation or somnolence classified as serious, 1 patient experienced syncope, 1 experienced worsening of migraine HA. The incidence was comparable in the comparator populations. Patient (0401012B-70-122, described in the narrative below) experienced an exacerbation of weakness in the lower extremities.

Sedation and somnolence are likely related to SKY0410, as they are observed with other morphine preparations. Syncope has many causes and orthostasis resulting from SKY0410 administration should be considered. The clinical course of the patient with worsened lower extremity weakness after SKY0401 is outlined in the following paragraph. A relationship of this complication to SKY0401 cannot be excluded.

Patient 012B-70-122 is a 68-year-old Hispanic male who was enrolled in SKY0401-012B and received a 10-mg dose of SKY0401 on [redacted] preceding surgery for a radical prostatectomy. The patient had a history of diabetes, peripheral neuropathy, hypertension, peripheral edema, mild lower extremity weakness, and a smoker for 25 years. On [redacted] the patient was initiated on gemfibrozil 600 mg daily for the treatment of hyperlipidemia, hydroxyzine 25 mg daily for the treatment of anxiety, Avandia (rosiglitazone) 8 mg daily and Glucovance (glyburide/metformin) 5/500 mg daily for the treatment of diabetes, amitriptyline 25 mg daily for the relief of depression, aspirin 325 mg daily, and Lasix (furosemide) 40 mg daily for the treatment of hypertension. On [redacted] the patient developed an exacerbation of motor weakness [weakness] and sensory loss bilaterally in the lower extremities [hypoesthesia]; however, no lateralized deficits were observed. On [redacted] the patient was re-evaluated by a neurologist and magnetic resonance imaging (MRI) and electromyography (EMG) studies were ordered. A recent seizure was suspected. On [redacted] results from an electroencephalogram (EEG) revealed a mild diffuse disturbance of cerebral activity of uncertain clinical significance. The events resolved on [redacted]

Renal Serious Adverse Events: Four of the 905 SKY0401 patients (0.04%) with serious renal adverse events experienced urinary retention compare with no patients in placebo, unencapsulated morphine or sham epidural IV PCA groups. Three of the patients were treated with 20 mg or higher doses of SKY0401. Two other SKY0401 patients experienced oliguria. Urinary retention is a known complication of opiates including morphine and may be related to SKY0401. The incidence was comparable to comparator groups. Oliguria after surgery has many etiologies and it is not possible to determine a relationship to SKY0401.

General Body System Serious Adverse Events: Three of the 905 SKY0401 patients experienced fever and one patient experienced lower extremity weakness. The patient reporting lower extremity weakness (0401012B-70-122) two days after treatment was the same patient who was reported for the same findings in the neurological section. The origin of the patient's symptoms was never determined and resolved spontaneously about thirteen days after onset. Post-operative fever has many etiologies, but these cases do not appear to be related to the study drug.

Test dose administration, gender, race, BMI and type of anesthesia did not appear to influence the rates of SAEs. The type of surgery did not appear to influence the rate of serious adverse events except that reproductive adverse events were more common among patients having cesarean section, cardiac events were more frequent among patients having upper abdominal surgery and pruritis and nausea reported more frequently among volunteers than patients.

### 1.6.7 Common Adverse Events

The percentage of patients reporting one or more adverse event ranged from 93.4% to 100% across the treatment groups. The system organ classes most frequently affected in the All SKY0401 group were, in descending order of frequency, Gastrointestinal Disorders, Skin and Subcutaneous Tissue Disorders, General Disorders and Administration Site Conditions, Nervous System Disorders, Vascular Disorders, Respiratory/Thoracic/Mediastinal Disorders, Renal and Urinary Disorders and Blood and Lymphatic System Disorders.

Individual events reported by more than 10% of patients in the All SKY0401 group included nausea (65.9%), pruritus (54.0%), pyrexia (40.2%), vomiting (32.9%), hypotension (29.9%), anemia (19.0%), headache (15.0%), constipation (12.3%), decreased oxygen saturation (11.9%), urinary retention (11.8%), and dizziness (10.8%). All these events are either expected effects of opioids or would be expected in the patient population. There appeared to be a dose-response for nausea, vomiting, urinary retention, dizziness and decreased oxygen saturation. All of these events are expected dose-related opioid effects.

In the Respiratory/Thoracic/Mediastinal Disorders system organ class, preferred terms relating to respiratory depression included hypoxia, respiratory depression, hypercapnia, dyspnea, apnea and hypoventilation with rates in the All SKY0401 group of 5.4%, 4.3%, 2.4%, 2.2%, 1.0% and 0.8% respectively. There appeared to be a dose-response for hypoxia, respiratory depression and hypercapnia. Also, in the Investigations system organ class, decreased oxygen saturation was reported for 11.9% of patients in the All SKY0401 group and there appeared to be a dose-response. These are expected opioid effects.

The relative incidence of common adverse event by treatment group is listed in Table 1.6-7.

### **1.6.7.1 Applicant's Approach to Eliciting Adverse Events**

In all studies, adverse events (AEs) were reported by the patient or subject and by the investigators in an ongoing manner throughout the study. An adverse event was defined as any unintended, unfavorable clinical sign, symptom, medical complaint or clinically relevant change in laboratory test value, whether or not considered to be test article related. Adverse events were characterized by type, incidence, intensity, and causality. They were graded as mild, moderate, or severe in intensity and coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA) dictionary for the patients in the ISS. (COSTART was used for Study 009 and the open label study 008, but all data in the ISS was coded using MeDRA.) The investigators collected adverse event information from the onset of the trials until designated protocol-established post-treatment endpoints.

A Neurological Assessment Questionnaire was also utilized in collecting neurological adverse in all studies except SKY0401-008 and SKY0401-009. The questions covered the areas of lower limb motor or sensory neuropathy, arachnoiditis, bowel and genitourinary function, seizure and stroke. Consequently the events coded fall into numerous different body systems.

### **1.6.7.2 Adverse Event Categorization and Preferred Terms**

All reported adverse events were categorized by system organ class and preferred term using the MedDRA dictionary. Review of the pooled adverse event data base in the ISS was notable for the following.

In the Respiratory/Thoracic/Mediastinal Disorders system organ class, preferred terms relating to respiratory depression included hypoxia, respiratory depression, hypercapnia, dyspnea, apnea and hypoventilation. This reviewer also examined cases of excessive sedation or somnolence when evaluating adverse events related to respiration. The rationale for including these terms is that impaired consciousness from opiate administration is associated with impaired airway reflexes and potential airway obstruction.

### **1.6.7.3 Incidence of Common Adverse Events**

The incidence of adverse events was examined by this reviewer in terms of body system and surgical procedure as depicted in Table 1.6-6 below. This was performed to identify adverse event relationships to organ systems and differentiate drug effects from effects of surgery. Among SKY0401 treated patients, adverse events were found with decreasing prevalence in the gastrointestinal system (nausea), skin (pruritis), nervous system (sedation), vascular system (hypotension), general body (pyrexia) and respiratory system (respiratory depression). Except for an increased incidence in cardiac and vascular adverse events associated with upper abdominal surgery and an increased incidence of gastrointestinal adverse events with cesarean section no specific pattern was found related to surgical procedure.

Table 1.6-6 Common Adverse Events Listed by Body System and Clinical Trial

Study Number	Hip Surgery		Lower Abdominal Surgery	C-Section	Upper Abdominal Surgery	Knee Surgery	All SKY0401
	9	11	12b	15	16	17	
Vascular Disorders	26 (21.7%)	84 (56.0%)	113 (20.7%)	5 (8.3%)	28 (71.8%)	47 (43.9%)	328 (30.3%)
Skin/Subcutaneous Disorders	67 (55.8%)	72 (48.0%)	238 (43.6%)	28 (46.7%)	15 (38.5%)	67 (62.6%)	538 (49.8%)
Respiratory, Thoracic and Mediastinal Disorders	33 (27.5%)	23 (15.3%)	99 (18.1%)	2 (3.3%)	12 (30.8%)	32 (29.9%)	231 (21.4%)
Reproductive And Breast Disorders	1 (0.8%)	1 (0.7%)	20 (3.7%)	5 (8.3%)	0 (0.0%)	32 (29.9%)	59 (5.5%)
Renal/Urinary Disorders	26 (21.7%)	27 (18.0%)	111 (20.3%)	5 (8.3%)	2 (5.1%)	23 (21.5%)	209 (19.3%)
Psychiatric Disorders	13 (10.8%)	15 (10.0%)	57 (10.4%)	3 (5.0%)	3 (7.7%)	21 (19.6%)	112 (10.4%)
Nervous System Disorders	46 (38.3%)	55 (36.7%)	206 (37.7%)	20 (33.3%)	6 (15.4%)	51 (47.7%)	412 (38.1%)
Musculoskeletal Disorders	9 (7.5%)	12 (8.0%)	37 (6.8%)	8 (13.3%)	6 (15.4%)	8 (7.5%)	81 (7.5%)
Metabolism and Nutrition Disorders	5 (4.2%)	7 (4.7%)	37 (6.8%)	0 (0.0%)	4 (10.3%)	7 (6.5%)	68 (6.3%)
Investigations	42 (35.0%)	26 (17.3%)	44 (8.1%)	4 (6.7%)	4 (10.3%)	38 (35.5%)	158 (14.6%)
Injury, Poisoning and Procedural Complications	5 (4.2%)	17 (11.3%)	28 (5.1%)	2 (3.3%)	2 (5.1%)	3 (2.8%)	57 (5.3%)
Infections and Infestations	3 (2.5%)	6 (4.0%)	35 (6.4%)	6 (10.0%)	3 (7.7%)	10 (9.3%)	63 (5.8%)
General/Administrations Site Disorders	52 (43.3%)	78 (52.0%)	189 (34.6%)	10 (16.7%)	14 (35.9%)	65 (60.7%)	454 (42.0%)
Gastrointestinal Disorders	74 (61.7%)	117 (78.0%)	346 (63.4%)	59 (98.3%)	20 (51.3%)	94 (87.9%)	759 (70.2%)
Cardiac Disorders	11 (9.2%)	18 (12.0%)	57 (10.4%)	3 (5.0%)	13 (33.3%)	18 (16.8%)	126 (11.7%)
Blood/Lymphatic System Disorders	50 (41.7%)	52 (34.7%)	45 (8.2%)	0 (0.0%)	0 (0.0%)	31 (29.0%)	193 (17.9%)

Information in the above table was derived from the electronic database linked to the ISS by this reviewer.

Many of the common adverse events have a known relationship to opiate medication. In order to compare adverse event rates for SKY0401 with rates for the control medications, and to examine the effect of demographic variables and baseline characteristics on adverse event rates, known opioid-related events were selected. These included events representing respiratory depression (decreased oxygen saturation, hypoxia, respiratory depression, hypercapnia, dyspnea, apnea and hypoventilation) and non-respiratory events (nausea, pruritus, vomiting, hypotension, urinary retention, somnolence and paralytic ileus). Also, with the exception of apnea and hypoventilation, all of these events fall into the list of events reported most frequently in the SKY0401 clinical program (events reported by 2% or more of patients in the All SKY0401 group).

Analysis of the adverse events associated with opiate toxicity demonstrates a dose-event relationship with SKY0401 and an increased incidence with SKY0401 compared with the alternative narcotic regimens used as comparators. These findings offer evidence of acute opiate toxicity resulting from SKY0401

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Table 6-7 Summary of Common Adverse Events by Treatment Group

All events (V09, V07, V11, V12, V13, V14, V15)

Number of Patients Who Received Study Drug	5 mg										Total
	Placebo	Unencapsulated Morphine	IV PCA Morphine	SKY0401	10 mg SKY0401	15 mg SKY0401	20 mg SKY0401	25 mg SKY0401	30 mg SKY0401	All SKY0401	
78	97	55	121	141	197	224	132	90	905	1135	
NAUSEA	39 (50.0%)	59 (60.8%)	42 (76.4%)	66 (54.5%)	94 (66.7%)	118 (59.9%)	158 (70.5%)	89 (67.4%)	72 (80.0%)	597 (66.0%)	737 (64.9%)
PRURITUS NOS	13 (16.7%)	37 (38.1%)	9 (16.4%)	51 (42.1%)	79 (56.0%)	98 (49.7%)	134 (59.8%)	70 (53.0%)	57 (63.3%)	489 (54.0%)	548 (48.3%)
VOMITING NOS	14 (17.9%)	25 (25.8%)	19 (34.5%)	30 (24.8%)	44 (31.2%)	55 (27.9%)	86 (38.4%)	38 (28.8%)	46 (51.1%)	299 (33.0%)	357 (31.5%)
HYPOTENSION NOS	25 (32.1%)	25 (25.8%)	16 (29.1%)	17 (14.0%)	28 (19.9%)	76 (38.6%)	79 (35.3%)	42 (31.8%)	29 (32.2%)	271 (29.9%)	337 (29.7%)
OXYGEN SATURATION DECREASED	4 (5.1%)	6 (6.2%)	20 (36.4%)	4 (3.3%)	10 (7.1%)	13 (6.6%)	36 (16.1%)	14 (10.6%)	31 (34.4%)	108 (11.9%)	138 (12.2%)
URINARY RETENTION	4 (5.1%)	4 (4.1%)	6 (10.9%)	4 (3.3%)	13 (9.2%)	23 (11.7%)	31 (13.8%)	19 (14.4%)	18 (20.0%)	108 (11.9%)	122 (10.7%)
HYPOXIA	0 (0.0%)	2 (2.1%)	5 (9.1%)	3 (2.5%)	6 (4.3%)	8 (4.1%)	17 (7.6%)	7 (5.3%)	8 (8.9%)	49 (5.4%)	56 (4.9%)
SOMNOLENCE	2 (2.6%)	3 (3.1%)	5 (9.1%)	1 (0.8%)	5 (3.5%)	6 (3.0%)	12 (5.4%)	6 (4.5%)	14 (15.6%)	44 (4.9%)	54 (4.8%)
RESPIRATORY DEPRESSION	0 (0.0%)	1 (1.0%)	1 (1.8%)	0 (0.0%)	1 (0.7%)	10 (5.1%)	13 (5.8%)	7 (5.3%)	8 (8.9%)	39 (4.3%)	41 (3.6%)
HYPERCAPNIA	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	6 (4.3%)	0 (0.0%)	3 (1.3%)	2 (1.5%)	11 (12.2%)	22 (2.4%)	23 (2.0%)
DYSPNOEA NOS	0 (0.0%)	1 (1.0%)	2 (3.6%)	0 (0.0%)	4 (2.8%)	6 (3.0%)	5 (2.2%)	3 (2.3%)	2 (2.2%)	20 (2.2%)	23 (2.0%)
ILEUS PARALYTIC	1 (1.3%)	3 (3.1%)	1 (1.8%)	4 (3.3%)	3 (2.1%)	4 (2.0%)	3 (1.3%)	3 (2.3%)	2 (2.2%)	19 (2.1%)	24 (2.1%)
APHNOEA	0 (0.0%)	0 (0.0%)	2 (3.6%)	1 (0.8%)	1 (0.7%)	1 (0.5%)	3 (1.3%)	2 (1.5%)	1 (1.1%)	9 (1.0%)	11 (1.0%)
HYPVENTILATION	0 (0.0%)	3 (3.1%)	0 (0.0%)	1 (0.8%)	2 (1.4%)	0 (0.0%)	2 (0.9%)	2 (1.5%)	0 (0.0%)	7 (0.8%)	10 (0.9%)

The use of supplemental opiates to manage pain has the potential to obscure opiate related adverse events related to SKY0401. An analysis of common adverse events in patients treated with SKY0401 who did not receive supplemental narcotics, performed by the sponsor, revealed dose-related increases in the incidence of nausea, pruritis and vomiting.

Table 1.6-8 Summary of Common Adverse Events in Patients Who Did Not Receive Rescue Narcotics by Treatment Group

Number of Patients Who Received Study Drug	5 mg										Total
	Placebo	Encapsulated Morphine	IV PCA Morphine	SKY0401 5 mg	SKY0401 10 mg	SKY0401 15 mg	SKY0401 20 mg	SKY0401 25 mg	SKY0401 30 mg	SKY0401 All	
NAUSEA	1 (1.00%)	1 (1.00%)	0	4 (66.7%)	5 (55.6%)	12 (50.0%)	26 (78.8%)	16 (66.7%)	8 (80.0%)	71 (67.0%)	73 (67.6%)
PRURITUS NOS	1 (1.00%)	0 (0.0%)	NA	2 (33.3%)	0 (0.0%)	14 (58.3%)	23 (69.7%)	13 (54.2%)	7 (70.0%)	59 (55.7%)	60 (55.6%)
VOMITING NOS	0 (0.0%)	0 (0.0%)	NA	2 (33.3%)	3 (33.3%)	6 (25.0%)	14 (42.4%)	11 (45.8%)	7 (70.0%)	43 (40.6%)	43 (39.8%)
HYPOTENSION NOS	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	4 (44.4%)	10 (41.7%)	15 (45.5%)	11 (45.8%)	3 (30.0%)	43 (40.6%)	43 (39.8%)
OXYGEN SATURATION DECREASED	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	0 (0.0%)	2 (8.3%)	4 (12.1%)	3 (12.5%)	7 (70.0%)	16 (15.1%)	16 (14.8%)
URINARY RETENTION	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	0 (0.0%)	6 (25.0%)	5 (15.2%)	4 (16.7%)	0 (0.0%)	15 (14.2%)	15 (13.9%)
HYPOXIA	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	0 (0.0%)	2 (8.3%)	6 (18.2%)	2 (8.3%)	0 (0.0%)	10 (9.4%)	10 (9.3%)
SOMNOLENCE	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	2 (22.2%)	0 (0.0%)	2 (6.1%)	2 (8.3%)	0 (0.0%)	9 (8.5%)	9 (8.3%)
DYSPNOEA NOS	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	2 (22.2%)	0 (0.0%)	2 (6.1%)	2 (8.3%)	0 (0.0%)	9 (8.5%)	9 (8.3%)
RESPIRATORY DEPRESSION	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	0 (0.0%)	1 (4.2%)	2 (6.1%)	1 (4.2%)	1 (10.0%)	5 (4.7%)	5 (4.6%)
HYPERCAEMIA	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	1 (10.0%)	2 (1.9%)	2 (1.9%)
APNOEA	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
HYPVENTILATION	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)

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There were several trends in adverse events that appeared align with demographic groupings. Nausea vomiting and pruritis were more prevalent among patients younger than 65 years and nausea and vomiting were more common among Caucasians than other races. Oxygen desaturation was more common among younger patients than among those over 75 years of age. Somnolence was more prevalent among patients over 65 years old. Men were reported to have a higher incidence of hypotension and urinary retention. Review of the sponsor's analysis of adverse events associated with ASA classification indicated adverse events associated with higher ASA class followed a similar distribution to increasing age except that events related to respiratory dysfunction appeared to be more highly correlated with increased ASA class than advancing age.

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(Sustained-Release Encapsulated Morphine)

Table 1.6-9 Summary of Common Opiate-Related Adverse Events in Patients by Demographic Distributions

Number of Patients Who Received Study Drug	Sex		Age			Race		BMI		
	All SKY0401	Male	Female	< 65	65-75	> 75	Caucasian	Non-Caucasian	<= 30	> 30
NAUSEA	597 (66.0%)	183 (60.0%)	414 (69.0%)	435 (66.7%)	128 (64.0%)	34 (64.2%)	498 (68.9%)	99 (54.4%)	393 (65.3%)	204 (67.3%)
PRURITUS NOS	489 (54.0%)	149 (48.9%)	340 (56.7%)	395 (60.6%)	84 (42.0%)	10 (18.9%)	391 (54.1%)	98 (53.8%)	325 (54.0%)	164 (54.1%)
VOMITING NOS	299 (33.0%)	99 (32.5%)	200 (33.3%)	215 (33.0%)	73 (36.5%)	11 (20.8%)	246 (34.0%)	53 (29.1%)	186 (30.9%)	113 (37.3%)
HYPOTENSION NOS	271 (29.9%)	122 (40.0%)	149 (24.8%)	165 (25.3%)	82 (41.0%)	24 (45.3%)	240 (33.2%)	31 (17.0%)	184 (30.6%)	87 (28.7%)
OXYGEN SATURATION DECREASED	108 (11.9%)	46 (15.1%)	62 (10.3%)	75 (11.5%)	30 (15.0%)	3 (5.7%)	92 (12.7%)	16 (8.8%)	62 (10.3%)	46 (15.2%)
URINARY RETENTION	108 (11.9%)	51 (16.7%)	57 (9.5%)	80 (12.3%)	23 (11.5%)	5 (9.4%)	97 (13.4%)	11 (6.0%)	84 (14.0%)	28 (7.9%)
HYPOXIA	49 (5.4%)	23 (7.5%)	26 (4.3%)	35 (5.4%)	13 (6.5%)	1 (1.9%)	43 (5.9%)	6 (3.3%)	21 (3.5%)	28 (9.2%)
SOMNOLENCE	44 (4.9%)	12 (3.9%)	32 (5.3%)	23 (3.5%)	15 (7.5%)	6 (11.3%)	34 (4.7%)	10 (5.5%)	24 (4.0%)	20 (6.6%)
RESPIRATORY DEPRESSION	39 (4.3%)	9 (3.0%)	30 (5.0%)	18 (2.8%)	18 (9.0%)	3 (5.7%)	30 (4.1%)	9 (4.9%)	27 (4.5%)	12 (4.0%)
HYPERCAPNIA	22 (2.4%)	11 (3.6%)	11 (1.8%)	15 (2.3%)	7 (3.5%)	0 (0.0%)	16 (2.2%)	6 (3.3%)	14 (2.3%)	8 (2.6%)
DYSNOEA NOS	20 (2.2%)	3 (1.0%)	17 (2.8%)	10 (1.5%)	6 (3.0%)	4 (7.5%)	16 (2.2%)	4 (2.2%)	13 (2.2%)	7 (2.3%)
ILEUS PARALYTIC	19 (2.1%)	5 (1.6%)	14 (2.3%)	12 (1.8%)	3 (1.5%)	4 (7.5%)	16 (2.2%)	3 (1.6%)	11 (1.8%)	8 (2.6%)
ARNOEA	9 (1.0%)	7 (2.3%)	2 (0.3%)	4 (0.6%)	5 (2.5%)	0 (0.0%)	9 (1.2%)	0 (0.0%)	6 (1.0%)	3 (1.0%)
HYPVENTILATION	7 (0.8%)	4 (1.3%)	3 (0.5%)	4 (0.6%)	3 (1.5%)	0 (0.0%)	7 (1.0%)	0 (0.0%)	5 (0.8%)	2 (0.7%)

(Sustained-Release Encapsulated Morphine)

Number of Patients Who Received Study Drug	All SKY0401		Anesthesia		ASA Class [1]			Test Dose [2]	
	General	Regional	1	2	3	None	< 15 Min.	>= 15 Min.	
NAUSEA	905	622	283	143	584	150	485	238	176
PRURITUS NOS	597 (66.0%)	390 (62.7%)	207 (73.1%)	104 (72.7%)	378 (64.7%)	96 (64.0%)	314 (64.7%)	156 (65.5%)	123 (69.9%)
VOMITTING NOS	489 (54.0%)	320 (51.4%)	169 (59.7%)	87 (60.8%)	320 (54.8%)	59 (39.3%)	239 (49.3%)	138 (58.0%)	110 (62.5%)
HYPOTENSION NOS	299 (33.0%)	180 (28.9%)	119 (42.0%)	34 (23.8%)	195 (33.4%)	54 (36.0%)	144 (29.7%)	88 (37.0%)	66 (37.5%)
OXYGEN SATURATION DECREASED	271 (29.9%)	178 (28.6%)	93 (32.9%)	27 (18.9%)	186 (31.8%)	53 (35.3%)	109 (22.5%)	79 (33.2%)	78 (44.3%)
URINARY RETENTION	108 (11.9%)	69 (11.1%)	39 (13.8%)	14 (9.8%)	73 (12.5%)	16 (10.7%)	46 (9.5%)	34 (14.3%)	28 (15.9%)
HYPOXIA	108 (11.9%)	79 (12.7%)	29 (10.2%)	16 (11.2%)	77 (13.2%)	14 (9.3%)	51 (10.5%)	34 (14.3%)	22 (12.5%)
SOMNOLENCE	49 (5.4%)	31 (5.0%)	18 (6.4%)	4 (2.8%)	31 (5.3%)	8 (5.3%)	29 (6.0%)	16 (6.7%)	3 (1.7%)
RESPIRATORY DEPRESSION	44 (4.9%)	33 (5.3%)	11 (3.9%)	5 (3.5%)	30 (5.1%)	9 (6.0%)	20 (4.1%)	15 (6.3%)	8 (4.5%)
HYPERCARBIA	39 (4.3%)	23 (3.7%)	16 (5.7%)	5 (3.5%)	25 (4.3%)	9 (6.0%)	18 (3.7%)	15 (6.3%)	6 (3.4%)
DYSRNOEAS NOS	22 (2.4%)	15 (2.4%)	7 (2.5%)	0 (0.0%)	14 (2.4%)	3 (2.0%)	3 (0.6%)	19 (8.0%)	0 (0.0%)
ILEUS PARALYTIC	20 (2.2%)	14 (2.3%)	6 (2.1%)	1 (0.7%)	10 (1.7%)	9 (6.0%)	11 (2.3%)	2 (0.8%)	7 (4.0%)
APNOEA	19 (2.1%)	18 (2.9%)	1 (0.4%)	3 (2.1%)	15 (2.6%)	1 (0.7%)	13 (2.7%)	3 (1.3%)	3 (1.7%)
HYPVENTILATION	9 (1.0%)	9 (1.4%)	0 (0.0%)	2 (1.4%)	6 (1.0%)	1 (0.7%)	2 (0.4%)	7 (2.9%)	0 (0.0%)
	7 (0.8%)	7 (1.1%)	0 (0.0%)	0 (0.0%)	5 (0.9%)	2 (1.3%)	5 (1.0%)	1 (0.4%)	1 (0.6%)

From Sponsor's Table 66-7 Appendix 2.7.4.7 page 419-20

#### 1.6.7.4 Additional Analyses and Explorations

- **Neurological Adverse Events**

One or more neurological event was reported by 7.6% of all SKY0401 patients, compared to 7.8% of the placebo group, 9.5% of the epidural unencapsulated morphine group and 5.5% of the sham epidural IV PCA morphine group. The body system totals in the All SKY0401 group are generally similar to the totals in the three control groups. The events reported most frequently in the "All SKY0401" group were paresthesia (1.5%), erectile dysfunction (1.3%), hypoesthesia (1.1%), urinary incontinence (1.1%), headache (0.9%) and weakness (0.9%). There was no indication of a dose-response relationship across the various dose levels of SKY0401 for any of these events.

The percentage of patients reporting one or more neurological adverse events in the "All SKY0401" group was higher for males (12.2%) compared to females (5.6%). In males the most frequently reported events in SKY0401-treated patients were urinary problems and erectile dysfunction, while in females the most frequent events were paresthesia, headache and weakness. There was no evidence that the frequency of any neurological event was influenced by patient age.

- **Respiratory Adverse Events**

Respiratory depression is the most significant safety hazard with the use of opioid analgesics. As noted above in the sections on serious adverse events, adverse events and vital signs, respiratory depression is a dose-related adverse event associated with SKY0401. This is not unexpected, but in view of the prolonged efficacy of SKY0401 compared to immediate release epidural morphine, the question of late onset of respiratory depression was addressed.

All patients in the integrated safety database who experienced one or more specified adverse event associated with respiratory insufficiency were listed under respiratory depression, hypoxia, hypercapnia, dyspnea, apnea, hypoventilation and decreased oxygen saturation. Sedation and somnolence may also contribute to ventilation disorders but were coded as neurological events.

Of all SKY0401-treated patients in controlled trials who received an opiate antagonist, 33.0% (36/109) received an opioid antagonist for the treatment of respiratory depression, as compared to 0.0%, 20.0% (1/5) and 0.0% of patients in the placebo, epidural, unencapsulated morphine and sham epidural with IV PCA morphine groups respectively.

The incidence of respiratory depression as a function of elapsed time after study drug administration was similar among SKY0401 and alternative treatment groups (placebo epidural, unencapsulated epidural morphine and sham epidural with IV PCA). Respiratory depression requiring narcotic antagonism occurred most frequently between 12 and 48 hours after SKY0401 administration compared with less than 12 hours after unencapsulated epidural morphine. The number of patients in the placebo group who

were treated with narcotic antagonists for respiratory depression was too small to assess the timing of onset of respiratory depression.

Use of narcotic antagonists is a clinically significant intervention. It is particularly relevant when used to manage respiratory disturbances because of the acute risk deficiencies in respiratory gas exchange poses to the patient. The incidence of narcotic antagonist administration was examined for respiratory depression, sedation and “narcotic reversal”. The reasons for antagonism were selected because they are potentially related to impaired gas exchange. In particular, instances associated with pruritis, urinary retention, or hypotension, other reasons for narcotic antagonism were excluded. There were no cases of narcotic reversal among the sham epidural with IV PCA or placebo epidural patients for respiratory or related causes.

Table 1.6-10 SKY0401 and Comparator Patients Treated with Narcotic Antagonists

<b>Treatment</b>	<b>Patients Exposed</b>	<b>Patients Treated with Opiate Antagonists for Respiratory Depression, Sedation, or Narcotic Reversal</b>	<b>Percentage of Patients Exposed Patients Treated with Opiate Antagonists for Respiratory Depression, Sedation, or Narcotic Reversal</b>
<b>5-mg Unencapsulated morphine</b>	97	2	2%
<b>5-mg SKY0401</b>	121	2	2%
<b>10-mg SKY0401</b>	141	7	5%
<b>15-mg SKY0401</b>	197	6	3%
<b>20-mg SKY0401</b>	224	20	9%
<b>25-mg SKY0401</b>	132	11	8%
<b>30-mg SKY0401</b>	90	16	18%

Data were abstracted by the reviewer from the electronic dataset linked to the sponsor’s ISS.

The increased incidence of treatment for respiratory depression compared with other reasons for opiate antagonist administration among patients treated with opiate antagonists may point to a higher level of severity associated with SKY0401 than with unencapsulated epidural morphine.

Respiratory depression with SKY0401 was associated with a longer latency than unencapsulated morphine, so that that treatment with a narcotic antagonist may also reflect the requirements of lower intensity nursing care at a later period of the hospital course. In contrast, delayed administration of narcotic antagonists (for respiratory depression) in patients receiving IV PCA may reflect narcotic accumulation with this pain regimen.

### 1.6.8 Less Common Adverse Events

Isolated cases of pulmonary embolism, deep vein thrombosis, cerebral infarction, peripheral edema with genital swelling, orthopedic injury after orthopedic surgery was reported.

Thromboembolic events are a known consequence of the inflammatory processes associated with major surgery and bedrest. There were insufficient numbers of these events to distinguish a relationship of these adverse events to SKY0401 from background effects. The orthopedic injuries reported appear to be surgical complications unrelated to SKY0401. Peripheral edema with genital swelling has been reported as an adverse event associated with unencapsulated morphine administered by epidural injection and may be a result of exposure to SKY0401 in sensitive individuals.

### 1.6.9 Laboratory Findings

#### 1.6.9.1 Overview of Laboratory Testing in the Development Program

The sponsor conducted urine pregnancy testing, typical blood hematological, coagulation, liver function enzymes, chemistry and urinalysis screens typically required as baselines for major surgery and reported these data with findings from the same testing profiles obtained 3 days after surgery. Arterial blood gas analysis was performed in Studies 008 and 009 up to 72 hours after study drug administration. Pharmacokinetic analysis of morphine was performed in Phase 2 studies 008, 009, 018, 016 for 72 hours and in Phase 3 studies 011 and 12b for 48 hours after study drug administration. Reporting appeared to be complete for the patients treated with placebo, but about 20% of the values were not recorded in the ISS for patients treated with unencapsulated morphine and 5-, 10-, 15, and 20-mg doses of SKY0401. Laboratory values for IV PCA patients were not incorporated into the ISS because laboratory testing was not assessed in study (017). Nearly all patients who had screening laboratory values reported also had laboratory testing reported at the 3 day follow-up (F/U) assessment.

Table 1.6-11 Summary Table of Patients Who Had Screening and Follow-up Assessments in the ISS

Treatment	Number of Patients Exposed	Number of Patients Screened	Number of Patients at 3 Day F/U
Placebo epidural	78	78	78
5-mg Unencapsulated Morphine	97	79	78
5-mg SKY0401	121	102	102
10-mg SKY0401	141	123	119
15-mg SKY0401	197	140	138
20-mg SKY0401	224	173	167
25-mg SKY0401	132	132	129
30-mg SKY0401	90	34	34

Data was abstracted by reviewer from electronically linked database to sponsor's ISS

#### **1.6.9.2 Selection of Studies and Analyses for Drug-Control Comparisons of Laboratory Values**

The sponsor examined shifts in laboratory values from screening to day 3 by treatment group. Trends of the mean for each laboratory value measure were reported. The frequency of abnormal laboratory values was compared for SKY0401 treated patients to control groups for each study.

#### **1.6.9.3 Standard Analysis and Explorations of Laboratory Data**

The only finding reported by the sponsor was a trend towards reduction of hemoglobin, hematocrit, red blood cell count, total protein, albumin, calcium, phosphorus and BUN values in all treatment groups. The trends reported by the sponsor were supported by my review of the data, which indicated skewing toward lower values at the 3 day follow-up in comparison to screening values. These findings are consistent with the known effects of surgery and intravenous hydration. There was no apparent dose-response relationship across the SKY0401 dose groups for any of these parameters.

#### **1.6.9.4 Additional Analyses and Explorations**

No additional analyses were performed for general laboratory findings. In the reviewer's examination of the database, additional patterns were not identified in the data that suggested further analysis.

#### **1.6.9.5 Special Assessments**

Two special assessments of performed by the reviewer are reported below.

Although there was a trend toward lower post-operative hemoglobin concentration among all surgical patients, it was not possible to discern a difference between SKY0401 treated patients and comparator groups that might relate to increased surgical bleeding or increased intravascular volume expansion with electrolyte solutions in the perioperative interval. An analysis of hematological adverse events with a focus on anemia and related terms is included below to detect whether intravascular fluid requirements or surgical bleeding may have been altered by the use of SKY0401.

The distribution function of post operative potassium concentrations associated with the highest dose of SKY0401 use and placebo are reported below because of the important relationship potassium concentration has with perioperative cardiac events. Although potassium concentration is carefully monitored in postoperative patients and abnormalities treated aggressively, skewing of the distribution function of post operative potassium concentration may reflect differences in intravascular expansion (shift toward low potassium concentration) or subtle renal hypoperfusion (shift toward high potassium concentration) between treatment groups.

##### **1.6.9.5.1 Analysis of Hematological Adverse Events**

Hematological adverse events were commonly reported, particularly anemia. Association of SKY0401 as a potential contributor to surgical blood loss or electrolyte expansion was investigated in my analysis because epidural narcotics have the potential to affect vascular tone. There was no obvious dose relationship to the incidence of hematological adverse events. Anemia and related key words related to blood loss comprised the largest subset of hematologic adverse events and are shown in Table 1.6-12 below. The incidence of hematological adverse events related to perioperative blood loss with SKY0401 was similar to the incidence observed with treatment alternatives. This means that use of SKY0401 appeared to increase perioperative bleeding compared with standard treatment.

Table 1.6-12 Incidence of Anemia by Treatment Group Across Studies.

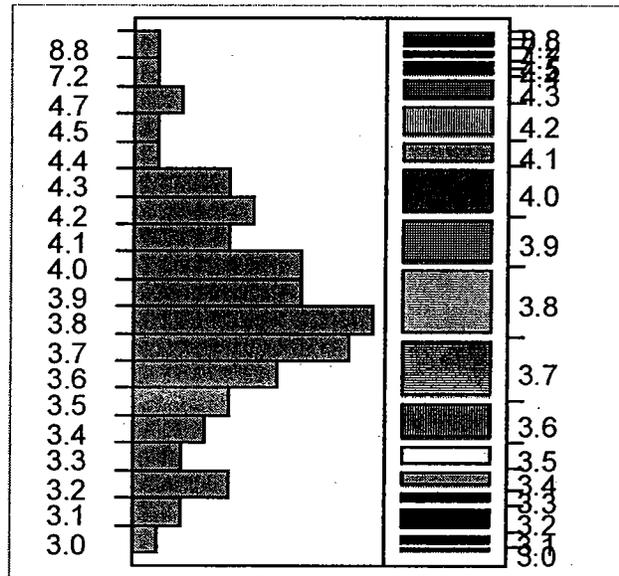
	Number of Exposures	Blood disorders/ Anemia
Placebo	78	32 (41.0%)
Unencapsulated Morphine (5 mg)	97	8 (8.2%)
IV PCA	55	12 (21.8%)
5 mg SKY0401	121	16 (13.2%)
10 mg SKY0401	141	29 (20.6%)
15 mg SKY0401	197	25 (12.7%)
20 mg SKY0401	224	65 (29.0%)
25 mg SKY0401	132	20 (15.2%)
30 mg SKY0401	90	33 (36.7%)
<b>Total Exposures</b>	<b>1135</b>	

This reviewer abstracted the data from the electronic database linked to the sponsor's Integrated Summary of Safety. IV PCA refers to patients treated with sham epidural and IV PCA. Placebo refers to patients treated with epidural injection of placebo.

#### 1.6.9.5.2 Analysis of Serum Potassium Concentration

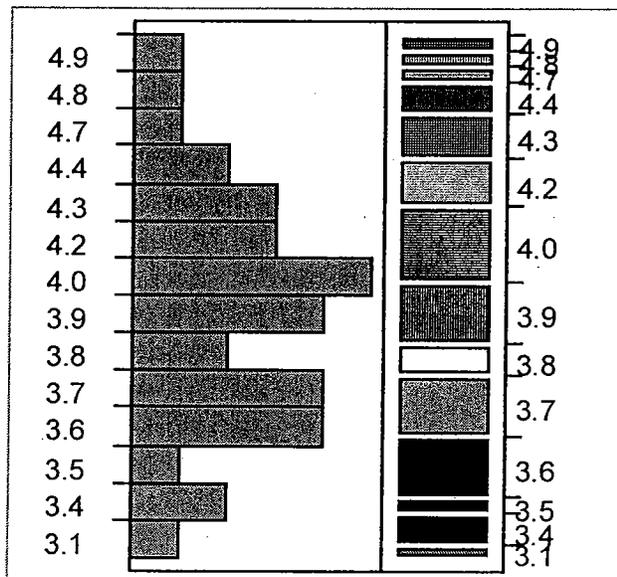
I selected post-operative serum potassium concentration for analysis because of clinically significant changes in potassium often occur following major surgery that require correction in order to prevent life threatening adverse events such as cardiac dysrhythmias. Epidural morphine is associated with vasoactive changes (venodilatation) in the perioperative period that may change intravenous fluid requirements with resultant perturbation of plasma electrolyte balance. Serum potassium concentration was recorded in the preoperative screening panel and on the third postoperative day. Examination of the range of post operative serum potassium levels revealed no skewing of the distribution of serum potassium concentration in the SKY0401 treated patients. There was no evidence that treatment with SKY0401 at the highest dose resulted in a trend toward either low or high serum potassium concentration compared with placebo.

Figure 1.6-13. Placebo epidural : Range of post-operative serum potassium concentration  
 in meq/dL



I abstracted the data from sponsor's electronic database linked to the NDA Integrated Summary of Safety .

Figure 1.6-14. 30-mg SKY0401: Range of post-operative serum potassium concentration  
 in meq/dl



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Abstracted from sponsor's electronic database linked to the NDA Integrated Summary of Safety.

### **1.6.10 Vital Signs**

#### **1.6.10.1 Extent of Vital Sign Testing in the Development Program**

The sponsor collected heart rate, systolic and diastolic blood pressure, body temperature and respiratory rate data. These vital signs were recorded hourly for the first 24 hours and then at 4 hourly intervals for 48 hours. A formal comparison between treatment groups for data completeness was not performed, but my review of the electronic database associated with the ISS indicate that most fields were populated and that there were no apparent differences between SKY0401 patients and comparator groups in terms data completeness.

#### **1.6.10.2 Selection of Studies and Analyses for Overall Drug-Control Comparison**

Pooled data from the sponsor's electronic integrated summary of safety were used to detect changes in mean values and identify patient outliers with gross abnormalities.

#### **1.6.10.3 Analyses and Explorations of Vital Signs Data**

For respiratory rate, systolic blood pressure and diastolic blood pressure, the frequencies of vital signs measurements predefined as abnormal were comparable in the control groups and the All SKY0401 group.

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(Sustained-Release Encapsulated Morphine)

Table 1.6-15 Sponsor's Analysis of Abnormal Vital Signs by Treatment Group.

	5 mg		IV PCA Morphine		5 mg SKY0401		10 mg SKY0401		15 mg SKY0401		20 mg SKY0401		25 mg SKY0401		30 mg SKY0401		All SKY0401		Total
	Placebo	Morphine	Morphine	Morphine	SKY0401	SKY0401	SKY0401	SKY0401	SKY0401	SKY0401	SKY0401	SKY0401	SKY0401	SKY0401	SKY0401	SKY0401	SKY0401	SKY0401	
Number of patients with at least 1 abnormal post-dose respiration assessment (< 8 breaths/min)	11/ 78 (14.1%)	5/ 97 (5.2%)	5/ 55 (9.1%)	3/ 121 (2.5%)	23/ 141 (16.3%)	8/ 197 (4.1%)	37/ 224 (16.5%)	15/ 132 (11.4%)	24/ 90 (26.7%)	110/ 905 (12.2%)	131/ 1135 (11.5%)								
Number of patients with at least 1 abnormal post-dose systolic blood pressure assessment (> 25% decrease from baseline)	41/ 78 (52.6%)	44/ 97 (45.4%)	31/ 55 (56.4%)	43/ 121 (35.5%)	73/ 141 (51.8%)	94/ 197 (47.7%)	134/ 224 (59.8%)	72/ 132 (54.5%)	58/ 90 (64.4%)	474/ 905 (52.4%)	590/ 1135 (52.0%)								
Number of patients with at least 1 abnormal post-dose diastolic blood pressure assessment (> 25% decrease from baseline)	49/ 78 (62.8%)	67/ 97 (69.1%)	37/ 55 (67.3%)	80/ 121 (66.1%)	100/ 141 (70.9%)	146/ 197 (74.1%)	181/ 224 (80.8%)	98/ 132 (74.2%)	61/ 90 (67.8%)	666/ 905 (73.6%)	819/ 1135 (72.2%)								
Number of patients with at least 1 abnormal post-dose heart rate assessment (< 40 beats/min)	0/ 78 (0.0%)	0/ 97 (0.0%)	0/ 55 (0.0%)	0/ 121 (0.0%)	0/ 141 (0.0%)	0/ 197 (0.0%)	0/ 224 (0.0%)	0/ 132 (0.0%)	0/ 90 (0.0%)	0/ 905 (0.0%)	0/ 1135 (0.0%)								

From Sponsor's Table 54 Integrated Summary of Safety, page 397.

I reviewed the sponsor's tabular vital sign data for respiration rate systolic and diastolic blood pressure presented in Integrated Summary of Safety Appendix 2.74.7, Tables 50-53 pages 377-397.

There appeared to be a dose response across the doses of SKY0401 for reduction in respiratory rate from 1 hour up to 26 hours post-dose. The highest median reduction in respiratory rate in any treatment group was 6.0 breaths per minute in the placebo group and the SKY0401 30-mg group at 1 hour and in the SKY0401 30-mg group at 16 hours post-dose.

There were no obvious or consistent dose-response patterns in blood pressure. The largest median falls in systolic and diastolic pressure were at one hour post-dose, probably reflecting the effect of surgery and anesthesia.

Up to four hours post-dose median changes in heart rate were toward rate reduction, probably reflecting the effect of anesthesia and surgery. From five hours onwards, median changes were toward rate increase. The highest median change in any SKY0401 group (excluding medians based on single values) was +13.0 bpm in the SKY0401 30-mg group at 30 hours and at 36 hours and in the SKY0401 20-mg group at 48 hours.

The mean/median changes in vital signs seen in these studies are unlikely to be clinically significant for most patients.

#### **1.6.10.3.1 Analyses Focused on Shifts from Normal to Abnormal**

The defined abnormal heart rate of <40 beats/min was not recorded for any patients.

For respiratory rate, systolic blood pressure and diastolic blood pressure, the frequencies of defined abnormal vital signs measurements were comparable in the control groups and the All SKY0401 group.

For respiratory rate and systolic blood pressure, but not for diastolic blood pressure, there appeared to be a dose-response relationship across the dose levels of SKY0401. This may represent an expected opioid effect, although the effect of adequate analgesia in reducing a respiratory rate or systolic blood pressure elevated as a response to pain may be considered.

#### **1.6.10.3.2 Marked Outliers and Dropouts for Vital Signs Abnormalities**

Marked abnormalities in blood pressure have been examined as adverse events in the vascular subsection of body systems above. Hypotension, the predominant abnormality in blood pressure is a known side effect of epidural morphine.

Dysrhythmias and marked changes in heart rate were included in the cardiac subsection of body systems above. Atrial fibrillation and other supraventricular tachydysrhythmias were the predominant rhythm abnormality associated with SKY0401,

but malignant ventricular rhythms were reported in association with myocardial infarction reported under serious adverse events above.

There was no SKY0401 dose relationship to the presentation of supraventricular or malignant ventricular dysrhythmias.

### **1.6.11 Electrocardiograms**

#### **1.6.11.1 Extent of Electrocardiogram Testing in the Development Program**

A 12-lead electrocardiogram was obtained for screening and in the immediate postoperative period unless patients exhibited an adverse event that required further electrocardiographic interpretation. Abnormalities were reported as a brief narrative in the database associated with the ISS.

QRS intervals were not specifically studied and morphine is not known to cause dysrhythmias related to abnormal electrocardiographic intervals such as long QT interval.

#### **1.6.11.2 Selection of Studies and Analyses for Overall Drug-Control Comparison**

Pooled data from the sponsor's integrated summary of safety was used to identify patients with abnormal electrocardiograms. No quantitative analysis was performed on the pooled data.

#### **1.6.11.3 Standard Analyses and Explorations of ECG Data**

Qualitative clinical information was provided in the sponsor's adverse event database. No quantitative information regarding electrocardiographic intervals was reported.

##### **1.6.11.3.1 Marked Outliers and Dropouts for ECG Abnormalities**

Patients with evidence of ischemic cardiac disease have been discussed above under serious cardiac disease and deaths. Supraventricular dysrhythmias such as atrial fibrillation as an adverse event have been discussed above.

### **1.6.12 Immunogenicity**

No immediate hypersensitivity reactions were reported.

### **1.6.13 Human Carcinogenicity**

This was not required because SKY0401 is intended for administration of a single dose.

### **1.6.14 Withdrawal Phenomena / Abuse Potential**

The abuse potential for SKY0401 is expected to be similar to other preparations of morphine for parenteral administration. SKY0401 is intended for use in an in-patient setting. Withdrawal potential was not studied.

### **1.6.15 Human Reproduction and Pregnancy Data**

Studies have not been performed to assess its use in pregnancy. Labeling for other morphine products indicate that opioids cross the placenta and may produce respiratory depression and psychophysiological effects in neonates. Opioids may prolong labor through actions, which temporarily reduce the strength, duration and frequency of uterine contractions. Administration of SKY0401 for pain control during vaginal delivery is contraindicated.

During the cesarean section study (SKY0401-015), the umbilical cord was clamped and the baby delivered before the study drug was administered. In addition, with regard to use in lactating females, no formal studies were conducted.

### **1.6.16 Overdose Experience**

In the clinical trials program, no patients received a higher dose of SKY0401 than that to which they were randomized, either accidentally or deliberately. There is, therefore, no data on "overdose" in that sense.

Out of 905 patients in the ISS treated with SKY0401, 109 patients also received a narcotic antagonist. Treatment with a narcotic antagonist may indicate that overdose with SKY0401 occurred. The use of opiate antagonists is discussed further in sections: Other Significant Adverse Events, Additional Analyses and Explorations, Summary of Selected Drug-Related Adverse Events, Level of Confidence in Dosing and Dose-Toxicity and Dose-Response Relationship.

### **1.6.17 Post-Marketing Experience**

N/A

### **1.6.18 Summary of Selected Drug-Related Adverse Events**

The most serious adverse events associated with SKY0401 are respiratory depression, ileus and hypotension. Nausea and vomiting and pruritis are also associated with SKY0401, but are usually not as serious.

Respiratory depression may occur with administration of any opioid, however SKY0401 unique property of time-release extends the duration after a single dose to 48 hours or in a few cases even longer. SKY0401 is not titratable so that direct respiratory depression or respiratory depression resulting from sedation may be difficult to control. The dose must be selected with careful consideration of the patient's surgery, concomitant medications and comorbidities. Vigilant monitoring will be required for the anticipated duration of risk for respiratory depression. Disposition of patients after treatment with SKY0401 will depend to some degree on institutional culture, but pulse oximetry with alarms and a high nurse to patient ratio are essential for early detection of respiratory depression. The setting should be capable of managing patients with narcotic antagonists and providing rapid institution of mechanical ventilatory support.

Adynamic ileus may be caused by SKY0401 and other opiates. As ileus is a known complication of surgery, especially abdominal surgery, patients should be managed

expectantly following treatment with SKY0401. SKY0401 should not be used in patients with known bowel obstruction.

Nausea and vomiting are associated with SKY0401 and other opiates. While always troublesome, these adverse events can be serious in patients with respiratory depression or sedation. One patient may have expired in clinical trials because of vomiting and sedation with resultant obstruction of the airway. (See deaths.)

Hypotension from SKY0401 may follow reduction in vascular tone associated with many opiates. Orthostasis may result in injury in the early ambulatory perioperative period. It was not possible to demonstrate a dose relationship of perioperative myocardial infarction associated with SKY0401, but hypotension may result in hypoperfusion of vital organs in the setting of critical vascular stenosis.

Pruritis was common after treatment with SKY0401. It is also a well-known complication of other opiates particularly unencapsulated epidural morphine. It is commonly treated with low doses of narcotic antagonists.

#### **1.6.19 General Methodology**

#### **1.6.20 Pooled Data vs. Individual Study Data**

This reviewer used the sponsor's Integrated Summary of Safety electronic database.

#### **1.6.21 Combining Data**

##### **1.6.21.1 Explorations for Predictive Factors**

The sponsor performed an analysis of serious adverse events by patient age. Older patients, as might be expected, had a higher rate of SAEs. In the >75 age group 26.4% of patients in the "All SKY0401" group experienced one or more SAE, as compared to 14.0% of patients in the 65-75 age group and 8.3% of patients in the <65 age group. The rates of SAEs in the Cardiac Disorders body system increased with age. In the >75 age group 13.2% of all SKY0401-treated patients experienced one or more Cardiac SAEs, as compared to 3.0% of patients in the 65-75 age group and 0.5% of patients in the <65 age group.

The sponsor performed analysis of serious adverse events by ASA classification. Patients in ASA Class 3, as might be expected, had a higher rate of SAEs. In the Class 3 group 18.7% of patients in the "All SKY0401" group experienced one or more SAE, as compared to 9.2% in Class 2 and 8.4% in Class 1.

Patient factors that might be useful in predicting an increased likelihood of serious adverse events are elderly age group and ascending ASA classification.

##### **1.6.21.2 Explorations for Dose Dependency for Adverse Findings**

Table 1.6-16 Dose-Dependency of Serious Adverse Events by Body System

	Number of Exposures	Patients with Serious AEs	Serious Respiratory	Serious Vascular	Serious Cardiac	Serious Gastrointestinal	Serious Urinary	Serious General	Serious Neurological
Placebo	78	4 (5.1%)	0 (0.0%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unencapsulated Morphine (5 mg)	97	6 (6.2%)	1 (1.0%)	0 (0.0%)	1 (1.0%)	2 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IV PCA	55	5 (9.1%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5 mg SKY0401	121	12 (9.9%)	1 (0.8%)	1 (0.8%)	2 (1.7%)	4 (3.3%)	0 (0.0%)	2 (1.7%)	0 (0.0%)
10 mg SKY0401	141	10 (7.1%)	1 (0.7%)	0 (0.0%)	1 (0.7%)	3 (2.1%)	0 (0.0%)	1 (0.7%)	2 (1.4%)
15 mg SKY0401	197	25 (12.7%)	1 (0.5%)	4 (2.0%)	2 (1.0%)	7 (3.6%)	2 (1.0%)	1 (0.5%)	1 (0.5%)
20 mg SKY0401	224	23 (10.3%)	4 (1.8%)	3 (1.3%)	6 (2.7%)	3 (1.3%)	3 (1.3%)	0 (0.0%)	3 (1.3%)
25 mg SKY0401	132	13 (9.8%)	6 (4.5%)	3 (2.3%)	2 (1.5%)	2 (1.5%)	1 (0.8%)	0 (0.0%)	1 (0.8%)
30 mg SKY0401	90	13 (14.4%)	4 (4.4%)	1 (1.1%)	3 (3.3%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
<b>Total Exposures</b>	<b>1135</b>	<b>111</b>	<b>19</b>	<b>13</b>	<b>18</b>	<b>23</b>	<b>6</b>	<b>4</b>	<b>8</b>

This reviewer abstracted the data from sponsor's electronic Integrated Summary of Safety database. IV PCA refers to patients treated with sham epidural and IV PCA. Placebo refers to patients treated with placebo epidural injection.

There appeared to be a general increase in serious AEs with increasing dose of SKY0401. In particular, there was an increase in incidence of respiratory depression, hypotension, cardiac events, nausea with reduced bowel motility, urine retention and sedation.

### 1.6.21.3 Explorations for Time Dependency for Adverse Findings

The time to resolution of the last respiratory adverse event was broken down into four time periods, <12 hours, 12 to <24 hours, 24 to <48 hours and >48 hours. This data is displayed by treatment group. Of all SKY0401-treated patients with one or more respiratory adverse events, 53/224 (23.7%) experienced an event, which persisted for 48 hours or longer. Of the 53 patients, 8 experienced a serious adverse event.

Table 1.6-17 Serious Respiratory Adverse Events Not Resolved by 48 hours Post-Dosing with SKY0401

Patient Number	Dose of SKY0401	Respiratory Adverse Event(s)	Time of Onset (hr: min)	Time of Resolution (hr: min)	Diagnosis	Investigator-Determined Relationship	Outcome
012-74-132	15 mg	Oxygen saturation decreased Dyspnea	6:00	331:00	Myocardial infarction Pneumonia	Not related	Patient expired
016-01-313	15 mg	Hypoxia	Not >24 hr	69:36	Pulmonary embolus	Not related	Resolved
016-01-320	15 mg	Respiratory Depression	4:02	76:52	Respiratory depression	Related	Resolved
011-16-006	20 mg	Hypoxia	3:12	5 days	Myocardial infarction	Unlikely related	Resolved
011-22-001	25 mg	Hypoventilation Dyspnea Oxygen saturation decreased	11:21	90:06	Hypoventilation and hypotension due to opioid	Related	Resolved
017-03-483	30 mg	Dyspnea Oxygen saturation decreased	4:40	106:00	Cardiac arrhythmia	Not related	Resolved
017-12-454	30 mg	Oxygen saturation decreased Respiratory depression Dyspnea	18:52	5 days	Respiratory depression	Probably related	Resolved
017-23-416	30 mg	Hypercapnia Oxygen saturation decreased	17:30	172:00	Somnolence and hypercapnia due to opioid	Probably related	Resolved

From Sponsor's Table 5. Summary of Clinical Safety 2.7.4, page 16

Three out of four cases of respiratory depression that were related (or possibly related) by investigators to an opioid effect that persisted for longer than 48 hours were associated with a 25-mg or 30-mg dose of SKY0401.

Table 1.6-18 SKY0401-Treated Patients with Respiratory Events with Onset after 48 Hours.

Patient Number	Age/ Gender	Dose of SKY-0401	Surgery Performed	Type of Anesthesia	Respiratory Adverse Event(s)	Time from Dose (hr:min)		Relation- ship	Treatment
						Onset	Reso- lution		
012-19-108	70/F	10mg	Radical hysterectomy	General	Decreased oxygen saturation	89:25	89:35	Possibly	"Pursed lip breathing"
012-73-111	68/F	15mg	Colectomy	General	Dyspnea	114:00	144:00	Unlikely	Oxygen 2 L/min
011-02-001	70/M	20mg	Hip arthroplasty	Regional	Dyspnea	67:44	69:14	Unlikely	None
017-23-415	76/F	20mg	Knee arthroplasty	General	Decreased oxygen saturation	48:05	56:00	Possibly	Oxygen 2 L/min
012-79-102	59/F	25mg	Laporotomy for pelvic mass	General	Dyspnea	120:00	121:00	Unlikely	None

From Sponsor's Table 6. Summary of Clinical Safety, page17.

Two cases out of five reported cases of respiratory adverse events (hypoxemia) presenting 48 hours after SKY0401 administration were considered as "possibly related" by investigators to SKY0401.

Of 905 patients treated with SKY0401 included in the ISS, 106 patients (11.7%) received rescue opioid analgesia, and of these, only 35 reported a respiratory depression adverse event. Among patients treated with SKY0401, 4 patients (0.4%) experienced a serious adverse event with a respiratory component that had not resolved by 48 hours after dosing. These 4 patients responded to treatment with an opioid antagonist and/or intensive supportive care, and the events resolved.

Five patients treated with SKY0401 experienced an adverse respiratory event with a time of onset greater than 48 hours after the dose of study medication. These patients are detailed in Table 1.6-18 above. None of these events were serious. None required an opioid antagonist or other intensive support for respiratory depression. Two events were treated with administration of oxygen by low-flow nasal oxygen. Because use of opioid rescue analgesia was collected systematically only up to 48 hours after the dose of study medication, it cannot be confirmed that rescue opioid analgesia may have contributed to the respiratory event. Samples for morphine blood levels were not collected from any of these patients.

#### 1.6.21.4 Explorations for Drug-Demographic Interactions

No differences were noted with respect to race.

#### 1.6.21.5 Explorations for Drug-Disease Interactions

No specific drug-disease interactions were noted.

### 1.6.22 Causality Determination

Causality could not be determined with every type of adverse event associated with SKY0401. Notable as an exception was the category of respiratory adverse events. The incidence of respiratory adverse events especially respiratory depression was related to the dose of SKY0401. Another category, cardiac adverse events that initially appeared related to SKY0401 did not exhibit dose-dependency for myocardial infarction or angina. Many types of adverse events, such as pruritis have been associated with unencapsulated morphine so a causal relationship to SKY0401 was considered likely. The incidence of adverse events increased with advancing age, however there was insufficient relationship of serious adverse events to dose of SKY0401 to suggest a particular dose limit in the elderly.

### 1.6.23 Safety Conclusions

This reviewer concurs that SKY0401 can be used safely for perioperative pain management. While SKY0401 did have a higher incidence of adverse events than the population receiving treatment alternatives, the benefit of 48 hours of improved pain control is unique in our armamentarium of analgesic regimens for the surgical population. The types of adverse events and their severity is similar to the adverse events associated with unencapsulated morphine for neuraxial application, however the period of risk is longer because of the time-release nature of SKY0401. As clinical experience continues to develop with SKY0401, safety may also be expected to improve by better patient selection and more focused monitoring. Additional investigations may be warranted in clinical populations likely to be exposed in clinical practice including adults having thoracic anesthesia and pediatric patients. The safety and efficacy of SKY0410 with therapeutic doses of epidural local anesthetics has not been studied. More data in elderly patients will be needed to determine whether the incidence of serious adverse events can be related to a dose threshold.

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## 1.7 ADDITIONAL CLINICAL ISSUES

### 1.7.1 Dosing Regimen and Administration

### 1.7.2 Level of Confidence in Dosing

The efficacy and safety findings as they relate to dose selection for SKY0401 for the most important clinical trials will be reviewed briefly to assess the level of confidence one may have in prescribing a dose of SKY0401 for a specific clinical setting.

*Efficacy data to establish appropriate dose: Study 011 of patients having hip arthroplasty*

Phase 3 study 011 (patients having hip surgery), demonstrated efficacy of SKY0401 (15-mg, 20-mg and 25-mg doses) in comparison with placebo epidural injection using mean total supplementary fentanyl as the primary endpoint. In addition, efficacy of each dose of SKY0401 was compared to efficacy of a 5-mg dose of epidurally administered unencapsulated morphine. Dunnett's test was performed to adjust for multiple comparisons for each dose of SKY0401 with unencapsulated morphine. Each dose of SKY0401 exhibited a statistically significant reduction in supplementary pain medication compared with placebo. Over 48 hours the difference in mean total supplemental fentanyl (50 ug/mL) was about 3 mL between the 15-mg dose and 20-mg of SKY0401 and about 3 mL between the 20-mg and 25-mg dose of SKY0401.

In patients  $\geq$  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.

Among all age groups, the differences in supplementary fentanyl between adjacent doses of SKY0401 are of marginal clinical significance. The difference in supplemental fentanyl (6 mL of fentanyl administered over 48 hours) required between the extremes of SKY0401 dosing (15 mg compared with 25 mg of SKY0401) would be considered a large dose in clinical practice and exceeded the dose used by the sponsor in power calculations when designing the study.

*Safety data to establish appropriate dose: Study 011 of patients having hip arthroplasty*

Statistically significant decreases from baseline 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. 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 no 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 within 24 hours post-dose. No SKY0401-treated patients received an opioid antagonist after 48 hours.

Overall, a better safety profile appeared to emerge with 15-mg and 20-mg doses of SKY0401 than the 25-mg dose of SKY0401. It is somewhat disconcerting to have to administer a narcotic antagonist for adverse events in the postoperative patient because of the potential to complicate pain management. In this regard, a 15-mg dose SKY0401 appeared to be no more effective than 20 mg. While the adverse effects of supplemental narcotic cannot be separated from the adverse effects of SKY0401 administration in the study 011, it is possible that for some patients, even the 15-mg and 20-mg dose of SKY0401 were higher than necessary.

*Efficacy data to establish appropriate dosing: Study 009 of patients having hip arthroplasty*

The data from Phase 2 study 009 (patients having hip surgery) generally supported the findings reported for study 011. In study 009, patients treated with SKY0401 received 10 mg, 20 mg or 30 mg. The mean difference in supplementary fentanyl or equivalent opiate between patients receiving 10 mg or 20 mg was about 400 mcg (8 mL at 50 mcg/mL) of fentanyl over 48 hours. Patients treated with 30 mg of SKY0401 received about half the supplementary fentanyl or equivalent opioid narcotic that patients treated with 10 mg received a difference, of about 650 mcg of fentanyl (13 mL). The sponsor's post-hoc analysis (Jonckheere-Terpstra test) indicated statistically significant differences in supplementary fentanyl between the SKY0401 doses studied.

*Safety data to establish appropriate dosing: Study 009 of patients having hip arthroplasty.*

This small study generally supports the findings of Phase 3 study 011 and was used to guide the dosing protocol in study 011. Study 009 identified concerns about the incidence and frequency of adverse events with the 30-mg dose of SKY0401 relating to sedation and respiratory depression. Findings of study 009 also suggested that there were significant differences in efficacy between a 10-mg and a 20-mg dose of SKY0401 for patients undergoing hip surgery.

*Efficacy data to establish appropriate dose: Study 012b, patients having lower abdominal surgery.*

In the amended design of study 012b, abdominal surgery patients were treated with 10 mg, 15 mg, 20 mg, or 25 mg of SKY0401 compared with 5 mg of SKY0401 as a dose comparison or 5 mg of epidural unencapsulated morphine. The discontinued study design included a placebo arm. Evidence of efficacy was demonstrated by an inverse relationship between the dose of SKY0401 and the median supplemental fentanyl administered to patients over 48 hours. An ANOVA of ranked supplemental fentanyl or equivalent opioid narcotic between the 5-mg SKY0401 treatment group and the higher dose regimen treatment groups also indicated statistically significant differences. The sponsor's claims

of statistical significance between 10-, 15-, 20-, and 25-mg doses were not supported by the use of statistical adjustments for repeated measures, but relied on the linear inverse relationship between supplemental fentanyl and SKY0401 dose. However, there was a clear trend demonstrated by a difference in mean supplemental fentanyl between the 10-mg and 25-mg dose of 312 mcg over 48 hours. The difference between the median supplemental fentanyl was 145 mcg. Similar differences in the mean and median total supplementary fentanyl-equivalent narcotic received over 48 hours were found between the treatment groups given 10 mg or 25 mg of SKY0401. Median total fentanyl usage from 24 to 48 hours, was comparable in both the 20- and 25-mg SKY0401 groups (medians of 130.0 and 120.0 mcg, respectively).

Post-operative usage of fentanyl through 48 hours in the patients  $\geq$  65 years of age in the 15-mg SKY0401 treatment group was comparable with that in patients  $<$  65 years of age in the 20-mg SKY0401 group (median usage of 600 mcg versus 619 mcg).

The differences between the supplementary dose of fentanyl required for the 10-mg and the 25-mg dose of SKY0401 are small. Estimating the clinical significance of differences in supplementary fentanyl between doses may be facilitated by consideration of the amount of fentanyl used for other procedures. For example, 500-1000 mcg (10-20 mL at 50 mcg/mL) fentanyl is sufficient narcotic when used with inhalation anesthesia for a cardiac surgical operation lasting 2 to 5 hours in patients of similar age and comorbidity as the patients undergoing hip surgery. Less stressful surgery such as thyroid resection or inguinal hernia repair may require 100 to 200 mcg of fentanyl (2 to 4 mL at 50 mcg/mL) over about 90 minutes of surgery when supplemented with inhalation anesthesia. An infusion of fentanyl used for pain management in a conscious patient in an intensively monitored setting for 48 hours is typically begun at a rate of 1 to 2 mcg/kg/hr. Over the course of 48 hours, a difference of 150 mcg (3 mL at 50 mcg/mL) of fentanyl is small and may not be clinically significant.

*Safety data to establish appropriate dose: Study 012b, patients having lower abdominal surgery.*

There was no clear dose relationship to adverse events or serious adverse events in study 012b. The data suggests, however, that there may be an increase in the incidence of treatment with a narcotic antagonist for respiratory depression or sedation among patients treated with 20-mg or 25-mg SKY0401 doses.

Table 1.7-1 Incidence of Adverse Events and Opiate Reversal for Study 012b

Dose of SKY0401 (mg)	Patients exposed	Patients with AE	Patients with Serious AEs	Patients treated with opiate antagonist for respiratory depression or sedation
25	88	62 (70%)	9 (10%)	6 (7%)
20	84	56 (67%)	11 (13%)	5 (6%)
15	91	61 (67%)	12 (13%)	2 (2%)
10	84	56 (67%)	6 (7%)	2 (2%)
5	102	60 (59%)	10 (10%)	2 (2%)

Abstracted from the sponsor's electronic Adverse Events database from study 12b and their electronic narcotic antagonist database in sponsor's Integrated Summary of Safety.

There may be some benefit to choosing the lowest effective dose in this setting with regard to avoiding respiratory depression and sedation that requires treatment with opiate antagonists. The modest increase in efficacy associated with a 20- or 25-mg dose compared with a 10- or 15-mg dose of SKY0401 is offset, in my opinion, by the potential need for respiratory rescue with opiate antagonists. It is also notable that there was a high background incidence of adverse events in this surgical population, perhaps partially obscuring dose-related events associated with SKY0401.

*Efficacy data to establish appropriate dose: Study 015 of patients having cesarean section*

In Phase 2 study 015, patients undergoing cesarean section were randomized to 5 mg, 10 mg, or 15-mg dose of SKY0401 or 5 mg of encapsulated morphine by epidural administration. The primary endpoint was the average total supplemental opioid administered through 48 hours. Analysis of the primary efficacy endpoint demonstrated a statistically significant reduction in average supplemental opioid in the SKY0401 patients compared with the patients who received unencapsulated morphine. Dunnett's test was used to adjust for repeated comparisons between each dose of SKY0401 and unencapsulated morphine. Patient groups receiving either 10 mg or 15 mg of SKY0401 used statistically less opioid on average over 48 hours than the group of patients treated with 5 mg of unencapsulated morphine. The mean supplemental opioid use was slightly higher in the patient group treated with 15 mg of SKY0401 than in the patient group treated with 10 mg SKY0401.

The 15-mg dose was associated with slightly higher supplemental morphine administration than the 10-mg dose, the opposite of what would be expected if efficacy increases with increasing doses of SKY0401. Practically, the difference in efficacy between the 10-mg and 15-mg dose was very small, so that the inverted dose response relationship may be attributed to experimental variation. The conclusion of this reviewer is that the 10 and 15-mg doses are essentially identical in efficacy. The 10-mg dose of SKY0401 appears to be superior to the control group and comparable to the 15-mg dose of SKY0401.

*Safety data to establish appropriate dose: Study 015 of patients having cesarean section*

Nearly every patient experienced an adverse event, but only 4 adverse events were serious. The serious adverse events were related to the surgical wound. The safety profile among the doses of SKY0401 appears similar.

Study 017 failed to demonstrate efficacy in the primary endpoint and will not be discussed in terms of confidence in the dose/regimen. Data from study 017 is included for the evaluation of dose toxicity in Section 1.7.3 below.

### 1.7.3 Dose-toxicity and dose-response relationships

There were two cases of prolonged respiratory depression lasting 5 days associated the 30-mg SKY0401 dose. Toxicity of the 30-mg dose and efficacy of the 20-mg and 10-mg doses of SKY0401 compared with placebo observed in Study 009, prompted further study of SKY0401 in doses of 15-mg, 20-mg and 25-mg in Study 011. Further review of the dose-response data from Study 009 indicated that there are statistically significant and clinically relevant differences in efficacy between 10 and 20 mg of SKY0401 in pain management of hip arthroplasty. The 15-mg dose of SKY0401 may be considered to be the lowest dose of SKY0401 demonstrated to be effective in both studies. The 15-mg dose of SKY0401 was evaluated directly in Study 011 and indirectly in Study 09 by evaluation of 10-mg and 20-mg doses, thereby bracketing the 15-mg dose. The 20-mg and 25-mg doses of SKY0401 were somewhat more effective in Study 011 than 15 mg in reducing supplemental narcotic requirements, but they were also associated with a higher rate of administration of a narcotic antagonist to treat adverse events. This means that a modest dose-response related to efficacy was also associated with increased toxicity.

The 10-mg and 20-mg doses of SKY0401 met the sponsor's statistical criteria for superiority in the analysis of their primary efficacy endpoint in study 12b. The sponsor reported that IV fentanyl usage through 48 hours post-dose was significantly lower in the 10-, 20-, and 25-mg SKY0401 groups compared with the 5-mg SKY0401 group, and in the 10-, 15-, 20-, and 25-mg SKY0401 groups compared with the MS group. The sponsor indicated that the lack of significance ( $p = 0.1$ ) of the 15-mg SKY0401 group compared with the 5-mg SKY0401 group was a result of the higher median value (760 mcg) compared with that of the 10-, 20-, and 25-mg SKY0401 groups (645, 590, and 500 mcg, respectively).

For patients having abdominal surgery (Study 12b), the median differences in supplemental narcotic administered to patients receiving 10 mg, 15 mg, 20 mg or 25 mg of SKY0401 were rather small in practical terms and may not be operationally important in reducing supplementary pain treatment to patients. There was no clear relationship between dose of SKY0401 and adverse events in Study 12b, however doses of 10 mg and 15 mg were associated with a lower incidence of narcotic antagonist administration. If a higher dose of SKY0401 increases the incidence that narcotic antagonists will be required (Table 1.6-10) or that respiratory adverse events will occur (Table 8-02), then the benefit of the higher dose may not be worth the increased risk. These findings suggest that a 10-mg dose may be safer than higher doses without significantly compromising efficacy in abdominal surgery.

In the setting of cesarean section, 10-mg and 15-mg doses of SKY0401 appeared to have comparable efficacy and adverse event profiles. It is notable that nearly every patient exhibited some form of adverse event, although relationship to study drug was not established for all events. For cesarean section, the evidence suggests that a 10-mg dose of SKY0401 appears to be safe and effective.

The table relating dose dependency to serious adverse events by body system is reproduced here from Section 1.6 of the NDA to facilitate comparison of the various doses studied in the sponsor's clinical trials.

Table 1.7-2 Dose-Dependency of Serious Adverse Events by Body System

	Number of Exposures	Patients with Serious AEs	Serious Respiratory	Serious Vascular	Serious Cardiac	Serious Gastrointestinal	Serious Urinary	Serious General	Serious Neurological
Placebo	78	4 (5.1%)	0 (0.0%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unencapsulated Morphine (5 mg)	97	6 (6.2%)	1 (1.0%)	0 (0.0%)	1 (1.0%)	2 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IV PCA	55	5 (9.1%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5 mg SKY0401	121	12 (9.9%)	1 (0.8%)	1 (0.8%)	2 (1.7%)	4 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
10 mg SKY0401	141	10 (7.1%)	1 (0.7%)	0 (0.0%)	1 (0.7%)	3 (2.1%)	0 (0.0%)	1 (0.7%)	2 (1.4%)
15 mg SKY0401	197	25 (12.7%)	1 (0.5%)	4 (2.0%)	2 (1.0%)	7 (3.6%)	2 (1.0%)	1 (0.5%)	1 (0.5%)
20 mg SKY0401	224	23 (10.3%)	4 (1.8%)	3 (1.3%)	6 (2.7%)	3 (1.3%)	3 (1.3%)	0 (0.0%)	3 (1.3%)
25 mg SKY0401	132	13 (9.8%)	6 (4.5%)	3 (2.3%)	2 (1.5%)	2 (1.5%)	1 (0.8%)	0 (0.0%)	1 (0.8%)
30 mg SKY0401	90	13 (14.4%)	4 (4.4%)	1 (1.1%)	3 (3.3%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
<b>Total Exposures</b>	<b>1135</b>	<b>111</b>	<b>19</b>	<b>13</b>	<b>18</b>	<b>23</b>	<b>6</b>	<b>4</b>	<b>8</b>

Abstracted from data in the sponsor's electronic Integrated Summary of Safety database.

Placebo refers to epidural injection of placebo and IV PCA refers to sham epidural and IV PCA.

There appeared to be a general increase in serious AEs with increasing dose of SKY0401. In particular, there was an increase in incidence of respiratory depression, hypotension, cardiac events, nausea with reduced bowel motility, urine retention and sedation. Possible dose adjustments for elderly patients are reviewed below.

#### 1.7.4 Relationship To Known Pharmacology

The pharmacokinetics of morphine release from liposomal encapsulation indicate higher blood levels within the first hour after administration of SKY0401 when a test dose containing lidocaine is given within 10 minutes of SKY040. There was no apparent pharmacodynamic effect established related to a shorter than 15 minute latency between test dose administration and SKY0401. It is important to note that the patients studied were in the noisy environment of the operating room during the first hour after SKY0401 administration and subtle effects of early release of morphine from encapsulation may not have been apparent. For example, a slight exaggeration of the hypotension associated with induction of anesthesia may not have been recognized. The sponsor's plan to recommend a 15-minute latency between administration of a test dose and SKY0401 is reasonable especially in the setting where epidural drugs are administered outside a well monitored setting (e.g. operating room holding area).

#### 1.7.5 Dose Modification Recommendations

In the Phase 3 trial of hip surgery (Study 011), the 15-mg dose of SKY0401 was more effective than epidural placebo. The sponsor did not evaluate 15 mg of SKY0401 in the Phase 2 Study (009), but determined that 10 mg and 20 mg were more effective than placebo, thereby effectively bracketing the 15-mg dose.

In the sponsor's study of patients undergoing lower abdominal surgery SKY0401 in doses between 10 mg and 25 mg was determined to be superior to 5 mg of SKY0401. The 15-mg dose of SKY0401 was not found by the sponsor to be more effective than 5 mg of SKY0401, however, no adjustment for repeated measures was used when comparing 10-mg, 15-mg, 20-mg and 25-mg to 5-mg doses, individually. Moreover a regression model demonstrated an inverse linear relationship between dose and the primary efficacy variable despite the slight deviation of data associated with the 15-mg dose.

The study of patients undergoing cesarean section, a low pelvic incision in most cases, demonstrated superiority of the 10-mg dose of SKY0401 compared to a 5-mg dose of unencapsulated morphine.

Table 1.7-3 Summary of Effective Doses

Study	Effective Doses					Comparator
	10 mg	**	20 mg		30 mg	
009 Hip Surgery	10 mg	**	20 mg		30 mg	Placebo
011 Hip Surgery		15 mg	20 mg	25 mg		Placebo
012b Lower Abdominal Surgery	10 mg	15 mg*	20 mg	25 mg		5 mg SKY0401
015 Cesarean Section	10 mg	15 mg				5-mg unencapsulated morphine

Abstracted from data in the sponsor's study reports.

\*\* The 15-mg dose was not evaluated directly in Study 09.

\*The sponsor did not demonstrate a statistically significant difference the primary efficacy endpoint between patient groups treated with 15-mg and 5-mg doses of SKY0401 in Study 012b, however a dose response relationship was shown in a linear regression model.

The data indicate that 15 mg is a sufficient dose for hip surgery and 10 mg is sufficient for abdominal and pelvic surgery in the general population. The sponsor has adequately demonstrated safety and efficacy for the 10-mg dose for cesarean section, but this reviewer feels that cesarean section and abdominal surgery may be grouped together. The clinical trials of lower abdominal surgery and cesarean section have similar incisions and involve visceral manipulation. My conclusions are based upon the sponsor's findings of efficacy, the incidence and type of adverse events associated with each dose, and the median difference in supplemental fentanyl used between dose groups. Even when statistically significant differences in efficacy between doses were claimed by the sponsor, a small savings in supplemental fentanyl associated with a higher dose of SKY0401 was either not clinically relevant or outweighed by an increased incidence in certain adverse events.

While some elderly patients will benefit from the use of SKY0401 in managing their perioperative pain, this reviewer's opinion is that the label should clearly indicate that older sicker patients are at higher risk of serious adverse events. An individual risk-benefit analysis will have to be employed to determine whether the analgesic benefits of SKY0401 outweigh its risk in a patient who is elderly, classified as ASA 3 or higher, or has known heart disease, baseline respiratory dysfunction or depressed consciousness. The

data were limited, however they did not demonstrate that higher doses increased the incidence of serious adverse events in older patients. Safe use of SKY0401 in the elderly will depend on individualized patient evaluation, selection and careful monitoring.

### **1.7.6 Unresolved Dosing Issues**

The contribution of excessive supplemental narcotic to adverse events cannot be ruled out in the clinical trials studied. Supplemental fentanyl doses or other opioid schedules may need modification especially in the 24-48 hour period after treatment with SKY0401.

## **1.8 DRUG-DRUG INTERACTIONS**

Benzodiazepines, sedatives, antihistaminics or psychotropic drugs are known in the broad clinical practice environment to potentiate the sedative and respiratory depressant action of other opiates and may exert a similar influence on patients treated with SKY0401. Other opiates may be expected to compound the side effects of SKY0401. Based upon experience with neuraxial administration of Duramorph® (unencapsulated morphine), patients with reduced hepatic metabolism or renal clearance may develop high blood morphine levels several days after administration. (See Duramorph label.)

## **1.9 USE IN SPECIAL POPULATIONS**

### **1.9.1 Adequacy of By-Gender Investigation and Analyses**

The sponsor has included adequate numbers of subjects and patients of both genders in the clinical development program. The sponsor has also performed adequate by-gender analyses for both the efficacy data and the safety data. Demographically, it was noted that overall, the subjects were predominantly female and Caucasian.

### **1.9.2 Elderly Population**

A total of 337 subjects 65 years of age and older participated in the trials included in the ISS dataset. They comprised 30% of the subjects evaluable for safety. Of these, 253 subjects received treatment with the SKY0401; 28% of all SKY0401 treated subjects. The ages ranged from 65 to 99 years old. Therefore, a sufficient range and number of elderly subjects was included in evaluation of safety and efficacy to allow appropriate labeling of use in this population.

The type of adverse event by body system varied with age group, as did the incidence of serious adverse events. Patients younger than 65 years old tended to exhibit nausea, vomiting and pruritis while older patients exhibited more sedation, respiratory depression and cardiac events. Older patients tended to be in ASA class 3 rather than ASA 1 or 2, indicating a higher incidence of serious concurrent disease than in the younger patients studied.

The dose-related incidence of serious adverse events is presented in Table 1.7-4 below. There did not appear to be a strong relationship between the dose of SKY0401 and the incidence of serious adverse events, suggesting that most of the serious adverse events did not result from administration of SKY0401, but were a consequence of the age and

associated comorbidities of the patient. It could not be determined from the limited data available whether elderly patients treated with SKY0401 were at higher risk for serious adverse events than elderly patients treated with alternatives such as IV PCA after sham epidural or 5 mg of unencapsulated morphine (MS).

The sponsor indicated that, in patients over the age of 65 years treated with 15 mg of SKY0401, requirements for supplemental narcotics were similar to patients younger than 65 years treated with 20 mg of SKY0401. On the basis of similar efficacy, they recommended a 15-mg dose in elderly patients having the same surgeries as patients less than 65 years of age. While the sponsor's argument has some merit, chronological age chosen for a threshold dose adjustment may not be a sufficiently sensitive indicator of the relevant physiological differences between patients. For example, there was no clear dose relationship to the frequency of serious adverse events on the basis of age alone. Lower doses may be appropriate in the elderly patient population, but the severity of comorbidities may be more important than age in adjusting the dose of SKY0401.

Table 1.7-4 Serious Adverse Event Frequency in Elderly Patients Compared with General Population by Treatment Group

	<b>Pts with SAE &lt; 65 years old</b>	<b>Pts with SAE 65 to 74 years old</b>	<b>Pts with SAE &gt; 75 years old</b>
IV PCA (Sham epidural)	1, (6%)	3, (11%)	1, (8%)
Placebo epidural	1, (2%)	2, (9%)	1, (13%)
5 mg unencapsulated MS	4, (5%)	1, (10%)	1, (25%)
5 mg SKY0401	8, (8%)	3, (21%)	1, (50%)
10 mg SKY0401	6, (5%)	2, (13%)	2, (22%)
15 mg SKY0401	17, (12%)	4, (11%)	4, (21%)
20 mg SKY0401	13, (9%)	7, (11%)	3, (23%)
25 mg SKY0401	5, (5%)	4, (13%)	4, (40%)
30 mg SKY0401	6, (12%)	4, (14%)	3, (27%)
Total SKY0401	55, (8%)	24, (13%)	17, (27%)
Total number of pts	61, (8%)	30, (12%)	19, (22%)

Data abstracted from the sponsor's electronic database in the Integrated Summary of Safety.

Carefully selected and monitored elderly patients may benefit from SKY0401 despite a higher incidence of serious adverse events than in younger patients. Careful preoperative evaluation and intensive intraoperative/post operative monitoring of respiratory and cardiac status may improve clinical outcomes. Elderly patients who are treated with SKY0401, but have their surgical procedure cancelled may be at particular risk for sedation, delayed respiratory depression, and vomiting with airway obstruction and cardiac arrest. There does not appear to be a threshold dose, below which the

incidence of adverse events is reduced in this population, so use of the lowest possible effective dose should be encouraged.

### 1.10 PEDIATRIC PROGRAM EVALUATION

This product was not studied in pediatric patients. Lumbar epidural anesthesia is not commonly used in children, because the technique requires a high level of patient cooperation and the spinal cord extends more caudad than in adults. Caudal epidural anesthesia is commonly used in pediatric patients, especially infants because the immature caudal cornu has not fused and the procedure may be performed safely in patients under general anesthesia.

The sponsor was granted a pediatric deferral at the End of Phase 2 meeting, pending completion of the studies with adults. The sponsor agreed to perform clinical trials in a pediatric population within 2 years of approval for an indication in adults.

Pediatric patients including infants may benefit from SKY0401. Further development of the product should be completed to facilitate safe use in pediatric patients.

### 1.11 ABUSE LIABILITY

This product has the same abuse liability as intravenous morphine. Morphine is a Schedule II narcotic under the United States Controlled Substance Act (21 U.S.C. 801-886). The product is expected to be used exclusively in a controlled hospital setting.

### 1.12 120-DAY SAFETY UPDATE

The sponsor reported the findings of a Phase 1 pharmacokinetic trial (PROTOCOL SKY0401-018) as the only component of their 120-day safety update. The trial is summarized briefly below.

#### Study 018

**Title:** 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.

**Objective:** 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.

**Population:** N= 35

**Summary:**

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  $C_{max} > 20$  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.)

Protocol Amendment No. 1 August 15 2003, 18 subjects were randomised 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.

**Safety:**

Of the 35 subjects enrolled in the study, 34 were evaluated for safety; one subject (Subject 102) did not receive SKY0401 due to an unsuccessful epidural block. The most commonly reported adverse events were gastrointestinal disorders (10/34, 29.4%), nervous system disorders (3/34, 8.8%), and renal and urinary disorders (2/34, 5.9%). The majority of AEs were consistent with opioid-related or local anesthetic-related side effects and were considered mild; 23.1% (3/13) were considered moderate in severity.

The data indicates that a therapeutic dose of lidocaine (300 mg) with epinephrine (100mcg) preceding epidural SKY0401 was associated with increased blood morphine levels compared with SKY0401 alone. Even longer latencies between administration of anesthetic doses of lidocaine with epinephrine and SKY0401 may be required compared with a lidocaine/epinephrine test dose and SKY0401.

• **Serious Adverse Event:**

One SAE was reported: an episode of bradycardia in a 32-year-old Black male with no significant medical history reported by the investigator as severe and unlikely related to study drug. Approximately 35-37 minutes post epidural injection of 20 mL of 1.5% lidocaine with epinephrine (1:200,000) and 5-7 minutes post epidural injection of SKY0401 15 mg, the subject had an acute episode of bradycardia (39 bpm) with hypotension and respiratory depression.

The subject was immediately treated by atropine 1 mg IV push, followed by an ephedrine 5-mg IV push and a second atropine 1-mg IV push. The subject's vital signs returned to the normal range and the subject remained stable thereafter.

**Final Assessment:**

The new data provided in the 120-Day Safety Update does not significantly alter the safety profile demonstrated by the earlier data.

**REVIEW OF PACKAGE INSERT**

On the basis of this review, the following changes to the label are proposed:

Pharmacokinetics

- Removal of the description of the pharmacokinetic study of SKY0401 with a therapeutic dose of lidocaine and epinephrine because the safety and efficacy of a therapeutic dose of local anesthetic was not studied in adequate and well controlled clinical trials.
- In the subsection describing pharmacokinetics of SKY0401 with a test dose of lidocaine with epinephrine: Indicate that the Cmax of morphine was comparable between the no test dose group and the group having a delay of 15 minutes between SKY0401 and the test dose.

CLINICAL STUDIES

- Indicate that efficacy was shown in four clinical trials with the number of patients in the ITT analysis.
- Remove [ ] was not shown in this clinical trial of patients having knee arthroplasty.
- In the presentation describing Study 015 in cesarean section, remove [ ]

INDICATIONS AND USAGE

- Indicate that administration of SKY0401 in the thoracic epidural space has not been evaluated and is not recommended.

CONTRAINDICATIONS

- Include increased intracranial pressure and circulatory shock.

WARNINGS

- Include statement reflecting that patients must be observed in a monitored setting for 48 hours after administration of SKY0401 with staff able to resuscitate patients from opiate overdose.
- In subsection on respiratory depression:
- Indicate that respiratory depression occurred more than 48 hours after SKY0401 administration occasionally.

## PRECAUTIONS

### Nursing mothers

- A cautionary statement should be included indicating that the excretion in milk is unknown and that a clinical decision to discontinue nursing or not administer SKY0401 should be made.

### Pediatric Use

- A statement indicating that SKY0401 has not been tested and is not recommended in patients younger than 18 should be included.

### Use in the Elderly

- The number of patients presented should be the number of patients studied for efficacy in the ITT population. A cautionary statement suggesting that careful evaluation of comorbid conditions is made before administration of SKY0401.

### Intravenous or Intramuscular Administration

- Remove discussion of [ ]

### Drug Interactions

- Remove discussion of therapeutic doses of local anesthesia except to indicate that use of therapeutic doses of epidural local anesthetics with epinephrine (for conduction anesthesia) have not been studied in clinical trials.

### CNS Depressants:

- Remove [ ] replace with advice to employ vigilant monitoring.

### Muscle Relaxants:

- Include statement to indicate that use of SKY0401 in patient treated with neuromuscular blocking agents may delay recovery of spontaneous ventilation.

## ADVERSE EVENTS

- Order listed adverse events in terms of their relative morbidity. Include a statement indicating the incidence of treatment of respiratory depression with narcotic antagonists among SKY0401 patients.

## OVERDOSAGE

- Indicate that administration of supplemental narcotics should be done cautiously to avoid precipitating respiratory depression.

## DOSAGE AND ADMINISTRATION

- Change the recommended dose of SKY0401 from 15 mg to 15 mg for patients having hip surgery and from 10 mg to 10 mg for patients having lower abdominal surgery.
- Replace [redacted] with advice to use caution in treating elderly patients with SKY0401.
- Change the recommended delay between administration of a test dose and SKY0401 from 15 minutes to 15 minutes.

**Appears This Way  
On Original**

## CONCLUSIONS

This product is approvable. There should be clear warnings about the potential for associated serious adverse events, especially delayed respiratory depression in the label. The duration of action of SKY0401 is longer than with unencapsulated morphine so the label should indicate that the period of vigilant monitoring should be extended. Special warning should be offered for care of patients with comorbidities that may be disproportionately exacerbated by side effects of SKY0401 such as bowel dysmotility, hypotension or respiratory depression. For example, patients with suspected bowel obstruction, critical vascular stenosis to vital organs or elevations of intracranial pressure are expected to be at increased risk from SKY0401 associated adverse events.

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cc: Division File  
Original NDA

**APPENDICES**

**American Society of Anesthesia Classification system**

ASA Physical Status	Description	Examples
1	A normal, healthy patient without organic, physiologic, or psychiatric disturbance	Healthy with good exercise tolerance
2	A patient with controlled medical conditions without significant systemic effects	Controlled hypertension, controlled diabetes mellitus without systemic effects, cigarette smoking without evidence of COPD, anemia, mild obesity, pregnancy, or aged < 1 or > 70 years
3	A patient having medical conditions with significant systemic effects intermittently associated with significant functional compromise	Controlled CHF, stable angina, old MI, poorly controlled hypertension, morbid obesity, bronchospastic disease with intermittent symptoms, chronic renal failure
4	A patient with a medical condition that is poorly controlled, associated with significant dysfunction and is a potential threat to life	Unstable angina, symptomatic COPD, symptomatic CHF, hepatorenal failure
5	A patient with a critical medical condition that is associated with little chance of survival with or without the surgical procedure	Multiorgan failure, sepsis syndrome with hemodynamic instability, hypothermia, poorly controlled coagulopathy
6	A patient who is brain dead and is undergoing anesthesia care for the purposes of organ donation	
E	This modifier is added any of the above classes to signify a procedure that is being performed as an emergency and may be associated with a suboptimal opportunity for risk modification	

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/s/

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Lester Schultheis  
5/18/04 08:08:05 PM  
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Bob Rappaport  
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for Rigoberto Roca, M.D.