CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-671

Statistical Review(s)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-671
Drug Name:	SKY0401 (encapsulated morphine)
Indication(s):	Treatment of post-operative pain
Applicant:	SkyePharma Incorporated
Date(s):	Received 07/18/03; user fee (10 months) 05/21/04
Review Priority:	Standard review
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Keywords: NDA review, clinical studies

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

SkyePharma proposed encapsulated morphine (SKY0401) administered by the epidural route for the treatment of post-operative pain. The analgesic effectiveness of SKY0401 was evaluated in five studies of patients experiencing pain from varying surgical procedures. The sponsor concluded that SKY0401 produced greater analgesic efficacy than the control (placebo, low dose SKY0401, or low dose unencapsulated morphine) as measured by a reduction in fentanyl consumption. Based on my evaluation of NDA 21-671, I concluded that statistical evidence supported the use of encapsulated morphine for the proposed indication.

1.2 Brief Overview of Clinical Studies

Morphine sulfate is an opioid analgesic approved for intrathecal and epidural administration. The current proposed product is a novel formulation of morphine manufactured by "microencapsulating an aqueous solution of morphine in microvesicular lipid-based particles (the DepoFoam drug delivery system)." According to the sponsor, "It is intended to provide sustained release of the active agent, morphine, following epidural administration." SKY0401 is investigated in five randomized, double-blind, multi-center trials, namely SKY0401-009, SKY0401-011, SKY0401-012B, SKY0401-15, and SKY0401-017.

Studies SKY0401-009 and SKY0401-011 were conducted in patients undergoing hip arthroplasty. Eligible patients in the former study were randomized to placebo or 10, 20, or 30 mg of SKY0401. Patients in the latter study were randomized to 15, 20, or 25 mg of encapsulated morphine or placebo. Treatments were administered via epidural injection or epidural catheter prior to the induction of general anesthesia at approximately 30 minutes prior to surgery. In both studies, the primary measure of efficacy was the amount of fentanyl used through 48 hours after study drug administration. Analysis of variance (ANOVA) models were utilized to assess treatment group differences. Based on the analysis results, the sponsor concludes that patients receiving SKY0401 used significantly less fentanyl compared to patients receiving placebo.

In Study SKY0401-12B, eligible individuals undergoing lower abdominal surgery were randomized to 5, 10, 15, 20, or 25 mg of encapsulated morphine or 5 mg of unencapsulated morphine. The study design and primary endpoint mimicked those of Study SKY0401-11. The primary analysis assessed the dose response relationship of the SKY0401 treatment groups using a regression model adjusted for the type of anesthesia. A significant trend was observed, suggesting a reduction in fentanyl use with increasing dose. Moreover, fentanyl use significantly decreased among patients in the 10, 20, and 25 mg encapsulated morphine groups compared to patients receiving 5 mg of encapsulated morphine.

Patients scheduled to undergo an elective cesarean section were randomized to 5 mg of unencapsulated morphine or to 5, 10, or 15 mg of encapsulated morphine in study SKY0401-15. An unblinded anesthesiologist administered study treatments by epidural injection following delivery and clamping of the umbilical cord. Subsequent to surgery, patients requesting pain medication were administered acetaminophen with codeine (orally) or IV morphine via PCA pump or as an intermittent bolus. The primary endpoint was the total supplemental opioid analgesic medication used through 48 hours post-dose. An ANOVA model was employed to assess treatment group differences. The sponsor concluded that patients in the 10 and 15 mg SKY0401 treatment groups used significantly less opioid medication compared to patients receiving unencapsulated morphine.

The final study, SKY0401-17, randomized eligible patients undergoing knee arthroplasty to 20 mg of SKY0401, 30 mg of SKY0401, or IV PCA morphine. Treatments were administered (by an unblinded anesthesiologist) via epidural injection prior to the induction of general anesthesia at approximately 30 minutes before surgery. A sham epidural dose injection was given to patients randomized to the IV PCA morphine group. Following surgery, participants randomized to SKY0401 and requesting pain medication received IV hydromorphone until satisfactory pain relief was achieved. Patients then received a PCA pump that administered placebo. According to the sponsor, "If pain control was inadequate following this initial administration, the PCA regime was to be increased and at the same time, the patient was to receive an IV injection of hydromorphone (0.2 mg/ml)." Patients randomized to IV PCA morphine received IV morphine following surgery. Upon experiencing satisfactory pain relief, patients received a PCA pump that administered IV morphine. According to the sponsor, "If pain control was inadequate following this initial administration, the IV morphine PCA regime was to be increased and patients were also to receive an IV placebo injection (mimicking 0.2 mg/mL hydromorphone)." The primary measure of efficacy was pain intensity over 44 hours following the initial 4-hour post-dose assessment and was analyzed via an analysis of variance. An overall treatment effect was not demonstrated.

1.3 Statistical Issues and Findings

The evidence taken collectively from the studies reviewed indicated statistical support favoring SKY0401 for the treatment of post-operative pain through 48 hours. When comparing the varying doses of SKY0401 to placebo or specified active comparator, a significant reduction in fentanyl use was demonstrated in 4 out of 5 of the studies. Study SKY0401-17 failed to demonstrate a treatment effect. The 20 mg dose of encapsulated morphine was included in the design of all studies with the exception of the study in women scheduled to have cesarean sections. An analgesic effect (as measured by a reduction in the amount of post-operative fentanyl use) was shown for patients receiving the 20 mg dose in 3 of the 4 studies. In addition, an effect was shown for patients receiving the 10 and 15 mg doses of encapsulated morphine in various patient populations.

Statistical concerns were discussed and resolved prior to the submission of the NDA. During the course of my review, no additional methodological concerns arose.

2. INTRODUCTION

2.1 Overview

Morphine sulfate is an opioid analgesic approved for intrathecal and epidural administration. The current proposed product, SKY0401, is a novel formulation of morphine manufactured by "microencapsulating an aqueous solution of morphine in microvesicular lipid-based particles (the DepoFoam drug delivery system)." According to the sponsor, "It is intended to provide sustained release of the active agent, morphine, following epidural administration." SKY0401 is also referred to as encapsulated morphine. SkyePharma Incorporated (previously known as DepoTech) introduced the product to the Division of Anesthetic, Critical Care, and Addiction Drug Products via IND 52,113. During the development process, the division provided feedback on numerous submitted protocols. In addition, a pre-NDA meeting occurred on 26 April 2003. Statistical concerns expressed during several correspondences included the definition of the analysis population, the inflation of the type I error due to a sample size adjustment during a proposed interim analysis, and the appropriateness of the proposed methods to handle missing data and multiple comparisons. The concerns were discussed and resolved satisfactorily. SkyePharma submitted NDA 21-671 for encapsulated morphine on 18 July 2003. The submission investigated the safety and efficacy of the product, administered epidurally, for the treatment of post-operative pain.

2.2 Data Sources

Primary support for encapsulated morphine (SKY0401) was derived from five randomized, double-blind, multi-center trials, namely SKY0401-009, SKY0401-011, SKY0401-012B, SKY0401-15, and SKY0401-017. The drug application was electronic. The study reports and data were archived in the Food and Drug Administration internal document room under the network path location \\CDESUB\N21671\N-000\2003-07-18. A summary of the studies is provided in Table 1. The sponsor additionally submitted SKY0401-008, an open label study, to provide supportive efficacy data. This study was not of focus in my review.

Table 1: Table of reviewed studies

Study Number Number of centers (n)	**Study Design**	**Treatment Arms and Number of randomized patients (n)**	**Primary measure of efficacy**
SKY0401-009 Multi-center (16)	Phase 2, randomized, double-blind, placebo-controlled study in patients undergoing hip arthroplasty procedures	•SKY0401 10 mg (34) •SKY0401 20 mg (28) •SKY0401 30 mg (26) •Placebo	Total intravenous fentanyl usage over 48 hours post-dose
SKY0401-011 Multi-center (27)	Phase 3, randomized, double-blind, dose-controlled study in patients undergoing hip arthroplasty procedures	•SKY0401 15 mg (50) •SKY0401 20 mg (49) •SKY0401 25 mg (46) •Placebo (49)	Total intravenous fentanyl usage over 48 hours post-dose
SKY0401-12B Multi-center (63)	Phase 3, randomized, double-blind, placebo-controlled study in patients undergoing lower abdominal surgery	•SKY0401 5 mg (86) •SKY0401 10 mg (70) •SKY0401 15 mg (84) •SKY0401 20 mg (79) •SKY0401 25 mg (83) •Unencapsulated morphine 5 mg (85)	Total intravenous fentanyl usage over 48 hours post-dose
SKY0401-015 Multi-center (7)	Phase 2, randomized, double-blind, active-controlled study of post-op pain following a cesarean section	•SKY0401 5 mg (18) •SKY0401 10 mg (18) •SKY0401 15 mg (18) •Unencapsulated morphine 5 mg (19)	Total supplemental opioid analgesic medication (IV or PO) used through 48 hours post-dose
SKY0401-017 Multi-center (19)	Phase 3, randomized, double-blind, active-controlled study in patients undergoing knee arthroplasty procedures	•SKY0401 20 mg (58) •SKY0401 30 mg (58) •IV PCA morphine (55)	Time weighted pain intensity recall score averaged over 44 hours

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The main body of my evaluation of efficacy will discuss each study individually.

3.1.1 SKY0401-009

Study Design and Endpoints

One hundred and twenty-six patients were randomized to 10, 20, or 30 mg of encapsulated morphine or placebo. Treatments were administered via epidural injection or epidural catheter prior to the induction of general anesthesia at approximately 30 minutes prior to surgery. Intra-operative IV fentanyl was permitted, but the amount was limited. Following surgery, patients experiencing moderate pain were administered fentanyl until satisfactory pain relief was achieved. Patients were subsequently permitted to self-administer fentanyl using a patient controlled analgesia (PCA) pump. Fentanyl use was recorded every 6 hours.

The primary measure of efficacy was the amount of fentanyl used through 48 hours after study drug administration. Secondary measures of efficacy included, but were not limited to, the time to first use of fentanyl, the percentage of patients using no post-op fentanyl, and a patient-rated evaluation of study medication.

Based on previous studies, a sample of size 120 was determined to be sufficient to detect a difference in means of 410 mcg between active and placebo treatments with 89% power. The calculation assumed the total usage in the placebo group was 820 mcg with a standard deviation of 490 mcg. Of note, 16 centers participated in the study; however, only 13 centers enrolled patients.

Patient Disposition, Demographic and Baseline Characteristics

Descriptive information regarding demographic characteristics was summarized using 120 of the 126 randomized patients. The excluded patients did not receive study medication. The ages of patients were between 18 and 75 with a mean age of 56. In the study, 80% of the study participants were Caucasian, 16% of the participants were African American, and 3% of the participants were Hispanic. Females comprised 48% of the patient population. Baseline characteristics included height and weight. Demographic and baseline characteristics did not differ between treatment arms. Detailed tables outlining the composition of the study population with respect to demographic and baseline characteristics are presented in the appendix.

None of the 120 patients receiving study medication withdrew prior to 48 hours post-dose. Six patients discontinued prior to 72 hours; however, these patients did not withdraw due to adverse events.

Statistical Methodologies

The primary analysis assessed treatment group differences using an analysis of variance (ANOVA) model with treatment group and center (pooled) as main effects. An examination of the consistency of the results across centers was conducted via inclusion of a treatment-by-center interaction in the ANOVA model. Multiple comparisons between SKY0401 and placebo treatment groups were conducted using Dunnett's test provided an overall treatment effect was demonstrated. Additionally, the Jonckheere-Terpstra test was utilized to test for a dose-response relationship.

Analyses of secondary endpoints were conducted to provide further support of the effectiveness of the study drug. Fentanyl use at days 1 and 2 was analyzed similar to the primary efficacy measurement. The time to first post-operative fentanyl usage was described via medians and Kaplan-Meier curves and analyzed utilizing a log-rank test. A Cochran-Mantel-Haenszel test was used to investigate the proportion of patients that did not require post-operative fentanyl.

The pre-specified analysis plan proposed the use of a projected total for patients discontinuing prior to 48 hours. The plan to handle missing data was not implemented since no patients withdrew during the 48-hour study duration. According to the sponsor, a pre-specified interim analysis was conducted to confirm the sample size and to plan for future studies. No changes were made as a result of the interim analysis.

Analyses were conducted on all randomized patients receiving study medication. Patient 03-004 was randomized to placebo; however, the patient was administered SKY0401 10 mg.

Results and Conclusions

Table 2: Mean Fentanyl Usage (mcg)

	Placebo (n= 28)	**SKY0401 10 mg (n= 34)**	**SKY0401 20 mg (n=32)**	**SKY0401 30 mg (n=26)**
Total usage 0 to 24 hours				
Mean (SD)	1514 (961)	578 (590)	390 (339)	362 (309)
p-value		<0.0001	<0.0001	<0.0001
Total Usage 24 to 48 hours				
Mean (SD)	919 (683)	744 (939)	515 (665)	291 (576)
p-value		0.799	0.138	0.007
Total Usage 0 to 48 hours				
Mean (SD)	2434 (1539)	1321 (1419)	905 (807)	653 (769)
p-value		0.002	<0.0001	<0.0001

Table 2 depicts the results of the analysis on the primary efficacy variable. The table additionally includes the mean fentanyl use over day 1 and day 2. This information was deemed informative by the medical reviewer, Dr. Lester Schultheis. Of note, the mean values at days 1 and 2 in the table vary slightly from the values presented by the sponsor in the application. I was unable to reproduce the exact values of the sponsor; however, the variations did not seem to affect the overall conclusions. The sponsor concludes that patients in each of the SKY0401 treatment groups used significantly less fentanyl as compared to patients receiving placebo.

Moreover, the amount of fentanyl needed decreased with increasing doses of SKY0401. With regards to the primary efficacy variable, I reanalyzed the data provided applying the same methodology and am in agreement with the sponsor's statistical results and conclusions. In addition, secondary efficacy parameters provided further support of the treatment effectiveness. Specifically, a higher proportion of study participants in the SKY0401 treatment arms required no post-operative fentanyl when compared to the placebo arm, and the time to pain medication was longer for participants receiving SKY0401 as compared to participants receiving placebo.

3.1.2 SKY0401-011

Study Design and Endpoints

The design of study SKY0401-011 was similar to that of the previously described phase 2 study (SKY0401-009) with variations in the tested doses and sample sizes. In SKY0401-011, 200 patients scheduled to undergo hip arthroplasty were randomized to 15, 20, or 25 mg of encapsulated morphine or placebo. An unblinded anesthesiologist administered study treatments via epidural injection prior to the induction of general or regional anesthesia at approximately 30 minutes prior to surgery. The maximum recommended amount of fentanyl per patient during surgery was 250 mcg. Following surgery, patients self administered fentanyl using a PCA pump to achieve satisfactory pain relief.

The primary measure of efficacy was the total amount of fentanyl administered over 48 hours post-dose. Secondary measures of efficacy included the time to first use of fentanyl, the percentage of patients using no post-operative fentanyl, and patient-rated evaluations of pain intensity.

Based on phase 2 studies, a sample of size 200 was determined to be sufficient to detect a difference in total fentanyl usage over 48 hours of 400 mcg between active and placebo treatments with 90% power. The calculation assumed the total usage in the placebo group was 820 mcg with a standard deviation of 600 mcg. The study was conducted at 27 sites in the United States; however, only 23 sites enrolled patients.

Patient Disposition, Demographic and Baseline Characteristics

The ages of patients were between 19 and 88 with a mean age of 61. In the study, 88% of study participants were Caucasian, 10% were African American, and 2% were Hispanic. Females comprised 49% of the patient population. Baseline characteristics of interest included height, weight, body mass index (BMI), and American Society of Anesthesiology (ASA) classification. Demographic and baseline characteristics were similar across treatment groups. Detailed tables outlining the composition of the study population with respect to demographic and baseline characteristics are presented in the appendix.

Of the 200 randomized patients, 194 underwent the planned surgery and 183 received study drug. Based on my evaluation, 5 patients withdrew prior to 48 hours. Four patients did not withdraw due to adverse events. According to the patient listings, patient 16006 experienced a serious adverse event; however, the patient was treated as requiring no fentanyl in the submitted

data set. The investigator did not believe that the myocardial infarction was related to the study drug.

Statistical Methodologies

The primary analysis assessed treatment group differences using an ANOVA model with treatment group and type of anesthesia as main effects. If an overall treatment effect was demonstrated, Dunnett's test was used to compare each dose of SKY0401 to placebo. The sponsor pre-specified that a rank transformation would be performed if the critical assumptions of the use of analysis of variance were violated. The total amount of fentanyl used for patients withdrawing prior to 48 hours was a sum of the actual fentanyl utilized prior to withdrawal and a projected amount. The projection was computed as the product of a per-hour average of fentanyl use (prior to withdrawal) and the number of remaining hours in the 48 hour study period.

Analyses of secondary endpoints were conducted to provide further support of the effectiveness of the study drug. Fentanyl use at days 1 and 2 was analyzed similar to the primary efficacy parameter; however, no projections were used for patients discontinuing prior to 48 hours. The time to first post-operative fentanyl usage was analyzed utilizing a log-rank test and described via medians and Kaplan-Meier curves. A Cochran-Mantel-Haenszel test was used to investigate the proportion of patients requiring no post-operative fentanyl. As an exploratory analysis, the sponsor investigated the consistency of the results across centers via inclusion of a treatment-by-center interaction in the ANOVA model described above.

Analyses were conducted on the intent-to-treat (ITT) population consisting of all randomized patients who were followed for use of fentanyl or other opioids. Patients who did not undergo the scheduled surgery were excluded from the ITT population.

Results and Conclusions

Table 3 depicts results of the sponsor's analysis of the total fentanyl used through 48 hours and at days 1 and 2. The sponsor found that the data were not normally distributed and subsequently performed an analysis on the rank transformed data. According to the sponsor, the results (based on ranked and unranked data) were similar; therefore, tables and subsequent conclusions were derived based on the unranked or original data. The sponsor concluded that patients in each of the SKY0401 treatment groups used significantly less fentanyl compared to patients receiving placebo. Based on my independent evaluation of the data, I concur with the results and conclusions. Moreover, the proportion of patients requiring no post-operative fentanyl through 48 hours increased with increasing dose. The time to first post-operative fentanyl was longer for participants receiving SKY0401 when compared to participants receiving placebo. Specifically, the median time to post-operative fentanyl use was 15, 23, and 23 hours for the SKY0401 15, 20, and 25 mg treatment groups respectively. The median time for patients receiving placebo was 4 hours. Of note, 26 of the study participants used an alternate opioid medication. Overall results were consistent across centers.

Table 3: Mean Fentanyl Usage (mcg) - ITT Population

	Placebo (n=49)	SKY0401 15 mg (n=50)	SKY0401 20 mg (n=49)	SKY0401 25 mg (n=46)
Total usage 0 to 24 hours				
Mean (SD)	1282 (985)	295 (342)	210 (210)	201 (325)
p-value		<0.0001	<0.0001	<0.0001
Total Usage 24 to 48 hours				
Mean (SD)	788 (946)	368 (450)	275 (269)	167 (378)
p-value		0.0025	0.0002	<0.0001
Total Usage 0 to 48 hours				
Mean (SD)	2091	663 (715)	485 (715)	371 (675)
p-value		<0.0001	<0.0001	<0.0001

3.1.3 SKY0401-012B

Study Design and Endpoints

Initially, patients undergoing lower abdominal surgery were randomized to placebo or 10, 15, 20, or 25 mg of SKY0401. During the development process, the sponsor amended the study design to exclude the placebo arm and to include a lower dose of the test product (SKY0401 5 mg) along with an active comparator (5 mg of unencapsulated morphine). The study design and endpoints mimicked those of study SKY0401-011.

Five-hundred and forty-six patients were enrolled at 51 of the 63 participating centers in the United States and Australia. The sample size was sufficient to detect a difference of 400 mcg of total fentanyl usage over 48 hours between the higher and lowest doses of encapsulated morphine with at least 90% power.

Patient Disposition, Demographic and Baseline Characteristics

The ages of the 498 patients randomized after the amendment to the study design ranged from 22 to 100 with a mean age of 52. Caucasians comprised 78% of the patient population in the study. Seventy-four percent of the study participants were female. Baseline characteristics of interest included height, weight, BMI, and ASA classification. I found that demographic and baseline characteristics were similar across treatment groups based on my evaluation of 498 patients. The sponsor provided demographic and baseline characteristics for patients randomized before and after the study design was amended. The sponsor found a significant difference between treatment groups among males and females. The sponsor suggested that the difference was the result of the distribution of males across the treatment groups. Specifically, the sponsor assessed the treatment group difference using a Cochran-Mantel-Haenszel test stratifying by type of anesthesia where no male patients received regional anesthesia. The sponsor's summary of the demographic and baseline characteristics is provided in the appendix.

Of the 546 randomized patients, 506 were randomized after the amendment to the study design. After the amendment, 498 participants actually received the scheduled surgical procedure and

480 received the study treatments. Based on my evaluation, 5 patients withdrew prior to completion of the 48-hour study period. None of the patients withdrew due to adverse events.

Statistical Methodologies

The primary analysis (outlined in the statistical analysis plan) assessed the dose-response relationship of the SKY0401 treatment groups using a regression model adjusted for the type of anesthesia. The sponsor additionally conducted an analysis of variance as a supplemental analysis using a protected least significant difference (LSD) test to compare pairs of means. Pairwise comparisons between the 4 higher doses of SKY0401 and the lowest dose of SKY0401 were of primary interest. As a secondary objective, the doses of SKY0401 were compared to the dose of unencapsulated morphine. The sponsor pre-specified that a rank transformation would be performed if the critical assumptions were violated. The methodology for handling missing data outlined in Study SKY0401-011 was also used in SKY0401-12B. Specifically, the total amount of fentanyl used for patients withdrawing prior to 48 hours was a sum of the actual fentanyl utilized prior to withdrawal and a projected amount. The projection was computed as the product of a per-hour average of fentanyl use (prior to withdrawal) and the number of remaining hours in the 48 hour study period. Moreover, the analysis of secondary endpoints of interest mimicked that of Study SKY0401-011.

Efficacy analyses were conducted on the ITT population which included all randomized patients who were enrolled after the amendment to the study design and who underwent the planned surgical procedure.

Results and Conclusions

According to the sponsor, evaluation of the data suggested that the data did not follow a normal distribution; therefore statistical tests were performed on the ranked data. A significant trend was observed, suggesting a reduction in fentanyl use with increasing dose as shown in Figure 1. Moreover, the median total fentanyl use was 645, 760, 590, and 500 mcg in the 10, 15, 20, and 25 mg SKY0401 treatment groups, respectively. The median total fentanyl use was 1005 and 955 mcg in the 5 mg SKY0401 and unencapsulated morphine groups. There was some evidence of a significant reduction in fentanyl usage through 48 hours in the 10, 20, and 25 mg treatment groups as compared to the lower dose group (5 mg SKY0401). Moreover, the time to first post-operative fentanyl use did not vary significantly across treatment groups. Analyses are depicted in Table 4. Of note, my results vary slightly from those of the sponsor for the 10 and 20 mg SKY0401 treatment arms at day 2 due to the exclusion of 2 participants by the sponsor. The variations did not alter the overall conclusions.

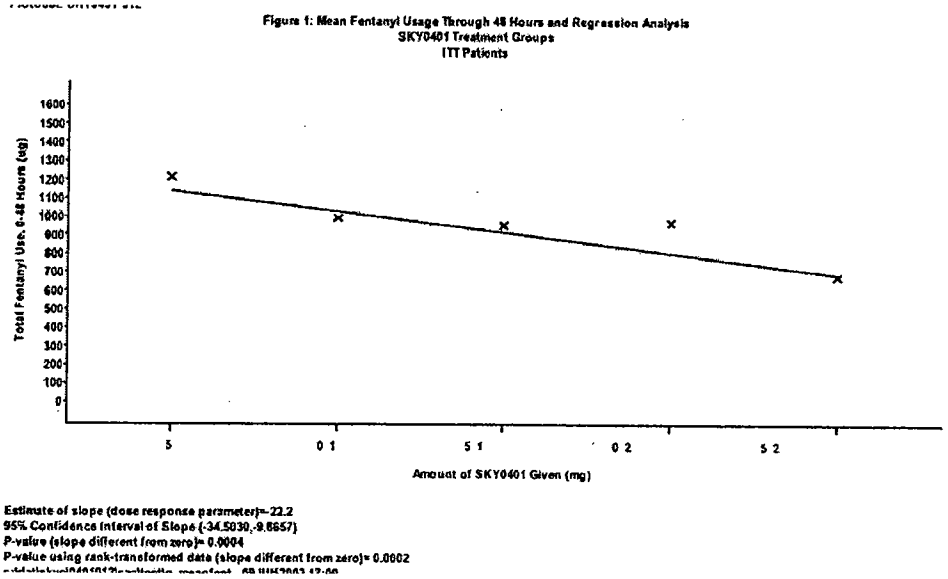

Table 4: Total Fentanyl Usage (mcg) - Rank Transformed Data

	MS 5mg (n=85)	SKY0401 5 mg (n=86)	SKY0401 10 mg (n=70)	SKY0401 15 mg (n=84)	SKY0401 20 mg (n=79)	SKY0401 25 mg (n= 83)
Total usage 0 –24h						
Mean (SD)	677 (504)	662 (557)	559 (529)	592 (446)	599 (557)	404 (318)
Median	506	541	365	475	470	315
p-value*			0.1237	0.5155	0.1715	0.0003
Total Usage 24– 48h						
Mean (SD)	540 (511)	551 (640)	401 (494)	367 (410)	322 (416)	278 (378)
Median	430	323	200	271	130	120
p-value*			0.0899	0.1105	0.0042	0.0005
Total Usage 0– 48h						
Mean (SD)	1218 (894)	1213 (1079)	995 (987)	959 (770)	972(982)	683(620)
Median	1005	955	645	760	590	500
p-value*			0.0447	0.1260	0.0221	<0.0001

* p-values determined using an ANOVA model after a rank transformation of the data.

Dr. Schultheis expressed interest in other opioid use, location of the study drug administration, surgical procedure (incision above the umbilicus), and the presence or absence of a test dose among patients. According to the sponsor, fentanyl was the only opioid permitted during the study duration; however, some violations occurred. Specifically, 51 patients received other opioids in addition to fentanyl. The number of patients receiving other opioids was 13, 7, 3, 9, and 7 in the 5, 10, 15, 20, and 25 mg SKY0401 treatment groups, respectively. Twelve patients randomized to unencapsulated morphine received other opioids. The sponsor converted the alternative opioid medication to an equi-analgesic amount of fentanyl. Analysis of the total opioid usage was subsequently performed. In addition, there were no significant differences among treatment groups regarding location of the study drug administration, surgical procedure (incision above the umbilicus), and the presence or absence of a test dose among patients.

3.1.4 SKY0401-015

Study Design and Endpoints

In this Phase 2 study, patients scheduled to undergo an elective cesarean section were randomized to 5 mg of unencapsulated morphine (MS) or to 5, 10, or 15 mg of encapsulated morphine (SKY0401). An unblinded anesthesiologist administered study treatments by epidural injection following delivery and clamping of the umbilical cord. Subsequent to surgery, patients requesting pain medication were administered acetaminophen with codeine (orally) or IV morphine via PCA pump or as an intermittent bolus.

The primary endpoint was the total supplemental opioid analgesic medication used through 48 hours post-dose. "All opioid medications used were converted to IV morphine equivalents." Secondary endpoints of interest mimicked those of previous studies.

Based on estimates from a prior study, a sample of size 80 was determined to be sufficient to detect a difference in total opioid usage over 48 hours of 69 mg between the encapsulated and unencapsulated treatment groups with 80% power. The calculation assumed the total usage in the active control group was 117 mg with a standard deviation of 78 mg. The study was conducted at 7 sites in the United States.

Patient Disposition, Demographic and Baseline Characteristics

The ages of the 75 females included in the efficacy population ranged from 18 to 44 with a mean age of 31. In the study, 64% of study participants were Caucasian, 14% were African American, and 16% were Hispanic. Baseline characteristics of interest included height, weight, pre-pregnancy weight, BMI, and ASA classification. Demographic and baseline characteristics were similar across treatment groups. Detailed tables outlining the composition of the study population with respect to demographic and baseline characteristics are presented in the appendix.

Statistical Methodologies

The primary analysis assessed treatment group differences using an analysis of variance (ANOVA) model with treatment group as the main effect. If an overall treatment effect was demonstrated, Dunnett's test was used to compare each dose of SKY0401 to 5 mg of unencapsulated morphine. The sponsor pre-specified that a rank transformation would be performed if the critical assumptions of the use of an analysis of variance were violated. The analysis plan proposed to use a projected total for patients discontinuing prior to 48 hours. The plan to handle missing data was not implemented since no patients withdrew during the study duration.

Analyses of secondary endpoints were conducted to provide further support of the effectiveness of the study drug. Supplemental opioid use at days 1 and 2 was analyzed similar to the primary efficacy parameter. The time to first post-operative opioid analgesic usage was analyzed

utilizing a log-rank test and described via medians and Kaplan-Meier curves. Fisher's exact test was used to investigate the proportion of patients requiring no post-operative opioid analgesic medication. As an exploratory analysis, the sponsor investigated the consistency of the results across centers via inclusion of a treatment-by-center interaction in the ANOVA model described above.

Patients who did not receive study drug due to the following criteria were excluded from the intent-to-treat population (ITT) population: dural puncture with an epidural needle, experienced any clinically significant complication, received any local anesthetic agent, or received general anesthesia due to the failure of the intrathecal block.

Results and Conclusions

Table 5 depicts results of the sponsor's analysis of the total opioid analgesic medication used through 48 hours and at days 1 and 2. The sponsor found that the data was not normally distributed and performed an analysis on the rank transformed data. The sponsor concluded that patients in the 10 and 15 mg SKY0401 treatment groups used significantly less opioid medication as compared to patients receiving unencapsulated morphine. The time to first post-dose usage of opioid medication was similar between the encapsulated and unencapsulated treatment groups. Moreover, there were no differences among treatment groups in the proportion of patients requiring no post-dose opioid medication. Based on my independent evaluation of the data, I concur with the results and conclusions.

Table 5: Total Opioid Usage (mg) - Rank Transformed Data

	MS 5mg (n=18)	SKY0401 5 mg (n=19)	SKY0401 10 mg (n=19)	SKY0401 15 mg (n=19)
Total usage 0 –24h *				
Mean (SD)	27 (28)	19 (14)	13 (15)	18 (25)
Median	19	15	9	11
Total Usage 24– 48h				
Mean (SD)	20 (12)	16 (14)	12 (9)	11 (21)
Median	16	12	9	6
p-value**		0.0864	0.0134	0.0001
Total Usage 0– 48h				
Mean (SD)	47 (34)	35 (24)	25 (21)	29 (35)
Median	38	31	19	18
p-value**		0.4838	0.0289	0.0178

*The overall test among treatment groups was not significant; therefore, no pairwise evaluations were performed.
**p-values were determined using an ANOVA model after a rank transformation of the data.

3.1.5 SKY0401-017

Study Design and Endpoints

Eligible patients undergoing knee arthroplasty were randomized to 20 mg of SKY0401, 30 mg of SKY0401, or IV PCA morphine. Treatments were administered (by an unblinded

anesthesiologist) via epidural injection prior to the induction of general anesthesia at approximately 30 minutes before surgery. A sham epidural dose injection was given to patients randomized to the IV PCA morphine group. The maximum recommended amount of fentanyl per patient during surgery was 250 mcg. All other opioids were prohibited during surgery.

Following surgery, participants randomized to SKY0401 and requesting pain medication received IV hydromorphone until satisfactory pain relief was achieved. Patients then received a PCA pump that administered placebo. According to the sponsor, "If pain control was inadequate following this initial administration, the PCA regime was to be increased and at the same time, the patient was to receive an IV injection of hydromorphone (0.2 mg/ml)." Patients randomized to IV PCA morphine received IV morphine following surgery. Upon experiencing satisfactory pain relief, patients received a PCA pump that administered IV morphine. According to the sponsor, "If pain control was inadequate following this initial administration, the IV morphine PCA regime was to be increased and patients were also to receive an IV placebo injection (mimicking 0.2 mg/mL hydromorphone)." During the 48-hour post-dose period, all other opioids (excluding IV morphine or hydromorphone) were prohibited. A schematic of the study design is included in the appendix.

The primary measure of efficacy was pain intensity over 44 hours following the initial 4-hour post-dose assessment. The measure was computed as a time weighted average of consecutive assessments of pain intensity (via a visual analog score). Secondary measures of efficacy included time to first use of a post-operative opioid and the proportion of participants not requiring a post-operative opioid.

One-hundred and sixty-eight patients were enrolled at 16 of the 19 participating clinical centers in the United States and Australia. The sample size was sufficient to detect a difference in the mean time-weighted pain intensity of 10 mm between SKY0401 30 mg and IV PCA morphine with at least 90% power.

Patient Disposition, Demographic and Baseline Characteristics

The ages of the 168 randomized patients ranged from 43 to 88 with a mean age of 67. Ninety-eight of the study participants were female, and 153 were Caucasian. Baseline characteristics included height, weight, BMI, and ASA classification. A difference between treatment groups was noted for race. The sponsor did not provide a hypothesis regarding a possible rationale for the difference. Since my post-hoc analysis did not provide evidence of an impact on the treatment efficacy, I did not investigate further. Detailed tables outlining the composition of the sample with respect to demographic and baseline characteristics are presented in the appendix.

Of the 168 randomized patients, 162 received study drug. Moreover, 164 had at least two post-baseline assessments and were included in the analysis population. Based on my evaluations of the data and patient listings, 3 patients withdrew prior to 48 hours. The patients did not withdraw due to adverse events.

Statistical Methodologies

The primary analysis employed an ANOVA model with treatment group and type of anesthesia as main effects. If the primary analysis revealed an overall treatment effect, comparisons between each dose of SKY0401 and IV PCA morphine were conducted using a predefined step-down procedure. The sponsor pre-specified that a rank transformation would be performed if the critical assumptions were violated. Missing values were not imputed for the primary analysis.

According to the sponsor, an interim analysis was conducted during drug development to potentially consider the study as a "pivotal phase 3 study". The purpose of the analysis was to readjust the sample size as needed and to possibly discontinue the 30 mg SKY0401 treatment arm. Of note, the analysis resulted in a change in the sample size.

The secondary measure of efficacy, time to first post-operative opioid use, was analyzed utilizing a log-rank test and estimated using the Kaplan-Meier method. In addition, a Cochran-Mantel-Haenszel test stratified by type of anesthesia was used to investigate the proportion of patients receiving no post-operative opioids. As an exploratory analysis, the sponsor investigated the consistency of the results for the primary efficacy measure across centers via inclusion of a treatment-by-center interaction in the ANOVA model. Efficacy analyses were conducted on the ITT population including all randomized patients having at least two post-randomization pain intensity assessments.

Results and Conclusions

Table 6 depicts the results of the sponsor's analysis on the primary efficacy variable. An overall treatment effect was not demonstrated; therefore, pairwise comparisons were not performed. Due to the lack of a treatment effect, I did not further investigate any additional endpoints.

Table 6: Time-weighted Pain Intensity Recall Scores (as presented by the sponsor)

	IV PCA Morphine	SKY0401		
		20 mg	30 mg	All
Number of Patients	55	51	58	109
Time-Weighted Pain Intensity Recall Score (4 – 48 Hours)				
Mean[1]	39.1	35.0	31.5	33.1
Median	37.0	33.5	27.0	29.3
Min – Max	0.2 – 82.5	5.7 – 78.1	1.8 – 70.0	1.8 – 78.1

P-values were determined using ANOVA including terms for treatment group and type of anesthesia. Pairwise comparisons were evaluated only if the overall treatment group effect was significant.
[1]p-value for overall test among the treatment groups was not significant and therefore pairwise comparisons were not performed.
Min = Minimum; Max = Maximum.

3.2 Evaluation of Safety

The evaluation of safety is deferred to the review of Dr. Lester Schultheis.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Analyses were performed with respect to gender, race, and age for each study. Specifically, the sponsor conducted separate analyses by each subgroup employing models similar to those specified in the primary analyses. I additionally examined the ANOVA models including the subgroup variables as covariates, respectively. I evaluated variation of the treatment effect across each subgroup via inclusion of an interaction term in the ANOVA models. Here, I focus on subgroup analyses for the 4 positive studies.

In SKY0401-009 an analgesic effect, as measured by the total amount of fentanyl usage, was demonstrated in all subgroups with the exception of non-Caucasians. Across subgroups, patients treated with SKY0401 significantly reduced the consumption of fentanyl compared to patients receiving placebo. Moreover among females, Caucasians, and all ages, the amount of fentanyl used decreased with increasing doses of SKY0401. The treatment effect was consistent across all subgroups. Similar results were seen in SKY0401-11 also conducted in the same patient population as SKY0401-009. However, an age effect existed. Older patients used less fentanyl through 48 hours compared to younger patients. Following a more detailed exploration, the sponsor stated " These data indicate that in the older patient population (• •65 years of age), adequate pain management, as evidenced by a decreased requirement for post-operative fentanyl, was achieved with a dose of 15 mg SKY0401 and was comparable with that achieved by 20 mg SKY0401 in younger patient (< 65 years of age)."

Due to the non-normality of the data, the analysis of the primary efficacy measure was conducted on the rank transformed data in study SKY0401-012B. However, subgroup analyses were conducted on the original data. An overall treatment effect was demonstrated among females, Caucasians, and younger individuals (< 65 years of age). The sponsor suggested that the lack of an effect in other subgroups was due to the small number of patients. Additionally, an age effect existed. Specifically, older individuals (• 65) required less fentanyl than younger patients. The sponsor concluded that older patients achieved an analgesic effect via a smaller dose of SKY0401 than required by younger patients.

Study 15 was conducted in females undergoing elective cesarean sections; therefore, subgroup analyses investigated total opioid use by race and age categorized by less than 30 and greater than or equal to 30. An overall treatment effect was demonstrated among non -Caucasians.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The evidence taken collectively from the studies reviewed indicates statistical support favoring SKY0401 for the treatment of post-operative pain through 48 hours. When comparing the varying doses of SKY0401 to placebo or specified active comparator, a significant reduction in fentanyl use was demonstrated in 4 out of 5 of the studies. Study SKY0401-17 failed to demonstrate a treatment effect. The 20 mg dose of encapsulated morphine was included in the design of all studies with the exception of the study in women scheduled to have cesarean sections. An analgesic effect (as measured by a reduction in the amount of post-operative fentanyl use) was shown for patients receiving the 20 mg dose in 3 of the 4 studies. In addition, an effect was shown for patients receiving the 10 and 15 mg doses of encapsulated morphine in various patient populations.

Further investigation of participants undergoing hip arthroplasty suggests a decrease in the amount of fentanyl used from day 1 to day 2 among patients receiving higher doses (i.e. 25 and 30 mg) of encapsulated morphine. A similar decrease was seen across all treatment groups in patients undergoing lower abdominal surgery or cesarean sections. Evidence of an overall treatment effect at day 1 or day 2 (evaluated separately) varied across studies.

Additional support of the treatment effectiveness is garnered from an examination of the proportion of patients not requiring post-operative fentanyl and the time to first post-operative fentanyl use. In studies where the patient population consisted of patients undergoing hip arthroplasty, the median time to first post-operative fentanyl usage was longer for participants receiving SKY0401 as compared to participants receiving placebo. Moreover, the proportion of patients requiring no post-operative fentanyl use through 48 hours increased with increasing doses of encapsulated morphine. The same phenomenon was not consistently demonstrated in other studies.

Statistical concerns were discussed and resolved prior to the submission of the NDA. During the course of my review, no additional methodological concerns arose. A clarification of the data for SKY0401-15 was requested during the review process. I noticed that patients randomized to the 15 mg arm of the product in the efficacy data set were listed as being assigned to the 10 mg arm in other data sets. The sponsor provided a satisfactory explanation for the discrepancy (see appendix).

5.2 Conclusions and Recommendations

The sponsor has proposed encapsulated morphine for the treatment of post-operative pain. The primary claim of the sponsor is that encapsulated morphine produces greater analgesic efficacy (measured by a reduction in fentanyl consumption) compared to placebo or specified comparator. My review of the collective evidence supports SKY0401 for the treatment of post-operative pain.

Issues pertaining to the clinical meaningfulness of the detected differences in fentanyl consumption and the appropriateness of a reduction in fentanyl consumption as a measure of analgesic efficacy are not included in my review. In consultation with Dr. Schultheis, the reduction in fentanyl is an acceptable measure of efficacy; therefore, further discussion is not warranted. Moreover, the review of Dr. Schultheis will explain the clinical meaningfulness of the detected differences and the recommended doses.

5.2.1 Labeling

The draft label describes clinical studies conducted in patients undergoing hip arthroplasty, lower abdominal surgery, or cesarean section. Based on initial consultation with the review team, I have three recommendations. First, I suggest the deletion of [ ] in such phrases as [ ] superior" or "[ ] significant". I believe this deletion throughout the label will not alter the interpretation. Second, I recommend removal of [ ]. Lastly, functional ability is a composite score of four indices reported in the study conducted in women having elective cesarean sections. The validity of the measure is currently unknown; therefore, I do not recommend inclusion of the results of functional ability.

The following table describes the dosing recommendations provided in the label:

Surgical Populations	Age Categories	
	< 65 Years	≥ 65 Years
Hip and knee orthopedic	[ ]	[ ]
Lower abdominal		
Cesarean section		

The statistical evaluation of the evidence suggests effectiveness at the recommended doses; however, the dosing recommendations should be formulated based on the collective evaluation of the efficacy, safety, and pharmacokinetic findings. Thus, the dosing recommendations will be evaluated jointly by the review team.

APPENDIX

Study SKY0401-009

Demographic and Baseline Characteristics (sponsor's presentation)

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

1. Two-way analysis of variance (ANOVA) with main effects treatment group and study site
2. Cochran-Mantel-Haenszel test for treatment mean row scores (stratified by study site). P-value for race based on two categories (Caucasian, non-Caucasian)

Study SKY0401-011

Demographic and Baseline Characteristics (sponsor's presentation)

Characteristic	Placebo	SKY0401				Total
		15 mg	20 mg	25 mg	All	
Subjects (n)	50	51	50	49	150	200
Age (years)						
Mean (SD)	59.2 (11.5)	63.0 (13.3)	57.8 (12.5)	62.2 (12.1)	61.0 (12.8)	60.6 (12.5)
Median	57.5	64.0	59.0	64.0	62.5	61.0
Min-Max	39 - 85	19 - 86	26 - 77	38 - 88	19 - 88	19 - 88
Sex						
Male	26 (52%)	23 (45%)	28 (56%)	25 (51%)	76 (51%)	102 (51%)
Female	24 (48%)	28 (55%)	22 (44%)	24 (49%)	74 (49%)	98 (49%)
Race						
Caucasian	46 (92%)	44 (86%)	43 (86%)	42 (86%)	129 (86%)	175 (88%)
Black	3 (6%)	6 (12%)	6 (12%)	5 (10%)	17 (11%)	20 (10%)
Asian	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hispanic	1 (2%)	0 (0%)	1 (2%)	2 (4%)	3 (2%)	4 (2%)
Other	0 (0%)	1 (2%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
ASA						
Class 1	2 (4%)	4 (8%)	5 (10%)	4 (8%)	13 (9%)	15 (8%)
Class 2	38 (76%)	37 (73%)	40 (80%)	37 (76%)	114 (76%)	152 (76%)
Class 3	10 (20%)	10 (20%)	5 (10%)	8 (16%)	23 (15%)	33 (17%)

SD = Standard deviation; Min = Minimum; Max = Maximum; ASA = American Society of Anesthesiology.
Sources: Section 14.1, Table 2.x and Appendix 16.2

Study SKY0401-012B

Demographic and Baseline Characteristics (sponsor's presentation)

Characteristic	5 mg MS	SKY0401							Total
		5 mg	10 mg	15 mg	20 mg	25 mg	Combined 10, 15, 20, 25 mg SKY0401	All SKY0401	
Subjects (n)	85	86	70	84	79	83	316	402	487
Age (years)									
Mean (SD)	51.2 (13.6)	50.0 (12.2)	52.2 (15.6)	51.9 (15.2)	53.4 (11.3)	52.2 (13.5)	52.4 (13.9)	51.9 (13.6)	51.8 (13.6)
Median	51.0	48.0	48.5	50.5	52.0	50.0	50.0	50.0	50.0
Min-Max	22 - 87	30 - 91	24 - 84	22 - 90	27 - 77	25 - 99	22 - 99	22 - 99	22 - 99
Age Group (years)									
< 65	70 (82%)	73 (85%)	53 (76%)	64 (76%)	62 (79%)	64 (77%)	243 (77%)	316 (79%)	386 (79%)
65-75	13 (15%)	11 (13%)	11 (16%)	14 (17%)	16 (20%)	17 (21%)	58 (18%)	69 (17%)	82 (17%)
> 75	2 (2%)	2 (2%)	6 (9%)	6 (7%)	1 (1%)	2 (2%)	15 (5%)	17 (4%)	19 (4%)
Gender									
Male	28 (33%)	24 (28%)	14 (20%)	19 (23%)	25 (32%)	19 (23%)	77 (24%)	101 (25%)	129 (27%)
Female	57 (67%)	62 (72%)	56 (80%)	65 (77%)	54 (68%)	64 (77%)	239 (76%)	301 (75%)	358 (73%)
Race									
Caucasian	68 (80%)	57 (66%)	54 (77%)	67 (80%)	61 (77%)	70 (84%)	252 (80%)	309 (77%)	377 (77%)
Black	6 (7%)	17 (20%)	12 (17%)	11 (13%)	11 (14%)	8 (10%)	42 (13%)	59 (15%)	65 (13%)
Asian	1 (1%)	1 (1%)	0 (0%)	2 (2%)	3 (4%)	0 (0%)	5 (2%)	6 (1%)	7 (1%)
Hispanic	9 (11%)	10 (12%)	4 (6%)	4 (5%)	3 (4%)	5 (6%)	16 (5%)	26 (6%)	35 (7%)
Other	1 (1%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (<1%)	2 (<1%)	3 (1%)
ASA									
Class 1	16 (19%)	19 (22%)	14 (20%)	18 (21%)	16 (20%)	19 (23%)	67 (21%)	86 (21%)	102 (21%)
Class 2	57 (67%)	56 (65%)	39 (56%)	50 (60%)	55 (70%)	49 (59%)	193 (61%)	249 (62%)	306 (63%)
Class 3	12 (14%)	11 (13%)	17 (24%)	16 (19%)	8 (10%)	15 (18%)	56 (18%)	67 (17%)	79 (16%)
Class E	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

MS = Unencapsulated morphine sulfate; SD = Standard deviation; ASA = American Society of Anesthesiology.
Source: Section 14.1, Table 5.b and Appendix 16.2, Listing 4

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Study SKY0401-015

Demographic and Baseline Characteristics (sponsor's presentation)

Characteristic	MS	SKY0401				Total
	5 mg	5 mg	10 mg	15 mg	All	
Patients (n)	18	19	19	19	57	75
Age (years)						
Mean (SD)	31.0 (6.0)	30.8 (6.3)	31.2 (6.7)	30.9 (7.6)	31.0 (6.8)	31.0 (6.5)
Median	32.5	32.0	33.0	31.0	31.0	31.0
Min - Max	18 - 39	18 - 39	19 - 39	20 - 44	18 - 44	18 - 44
Race						
Caucasian	12 (67%)	12 (63%)	12 (63%)	12 (63%)	36 (63%)	48 (64%)
Black	5 (28%)	3 (16%)	0 (0%)	2 (11%)	5 (9%)	10 (13%)
Asian	0 (0%)	1 (5%)	2 (11%)	1 (5%)	4 (7%)	4 (5%)
Hispanic	1 (6%)	3 (16%)	5 (26%)	3 (16%)	11 (19%)	12 (16%)
Other	0 (0%)	0 (0%)	0 (0%)	1 (5%)	1 (2%)	1 (1%)
Weight (pounds)						
Pre-Pregnancy, mean (SD)	170 (40)	160 (34)	156 (28)	153 (32)	156 (31)	159 (34)
Screening, mean (SD)	203 (37)	191 (33)	187 (25)	185 (32)	188 (30)	191 (32)

MS = Uncricapsulated morphine sulfate; SD = Standard deviation; Min = Minimum; Max = Maximum.

Clarification regarding data discrepancy

QUESTION from FDA:

The statistician is currently reviewing Study 15 of the SkyePharma application. She has noted that patients randomized to the 15 mg arm of the product in the efficacy dataset are listed as being assigned to the 10 mg arm in other data sets. For example, patient 2201 is assigned to the 15 mg arm in the efficacy dataset and 10 mg in the demographic and adverse events dataset.

RESPONSE:

At the conclusion of Study SKY0401-015 when the study blind was broken, a programming error was made in merging the treatment codes with the CRF datasets. As soon as this error was detected, it was corrected in the programming. All of the datasets and all of the tables, listings and figures for Study SKY0401-015 were regenerated and the CSR was corrected to reflect the accurate treatment assignments. The corrected CSR, tables, listings and figures were submitted in the NDA. At the time the NDA was submitted, it was SkyePharma's understanding that all of the corrected datasets were included in the submission.

During SkyePharma's continuing review of the data submitted in the NDA, the inconsistency in treatment codes between the CRF datasets (e.g., demographics and adverse events) and the derived analysis datasets (i.e., those designated by an "X" prefix) was also recently identified. As follow-up to this finding, SkyePharma performed a thorough investigation of the programming and dataset creation for Protocol SKY0401-015. The findings from the investigation that was completed this week are as follows:

- All datasets were recreated prior to the NDA submission to correct the programming error that impacted the treatment codes.
- The SKY0401-015 CSR, its components (i.e., tables, listings and figures), and any summary safety and efficacy analysis submitted in the NDA were prepared with the corrected datasets.
- The NDA submission included the CRF datasets, containing the treatment code error, but the corrected derived datasets for Study SKY0401-015 because of a miscommunication between data

management and submission publishing. The corrected CRF datasets were available and should have been included in the NDA.

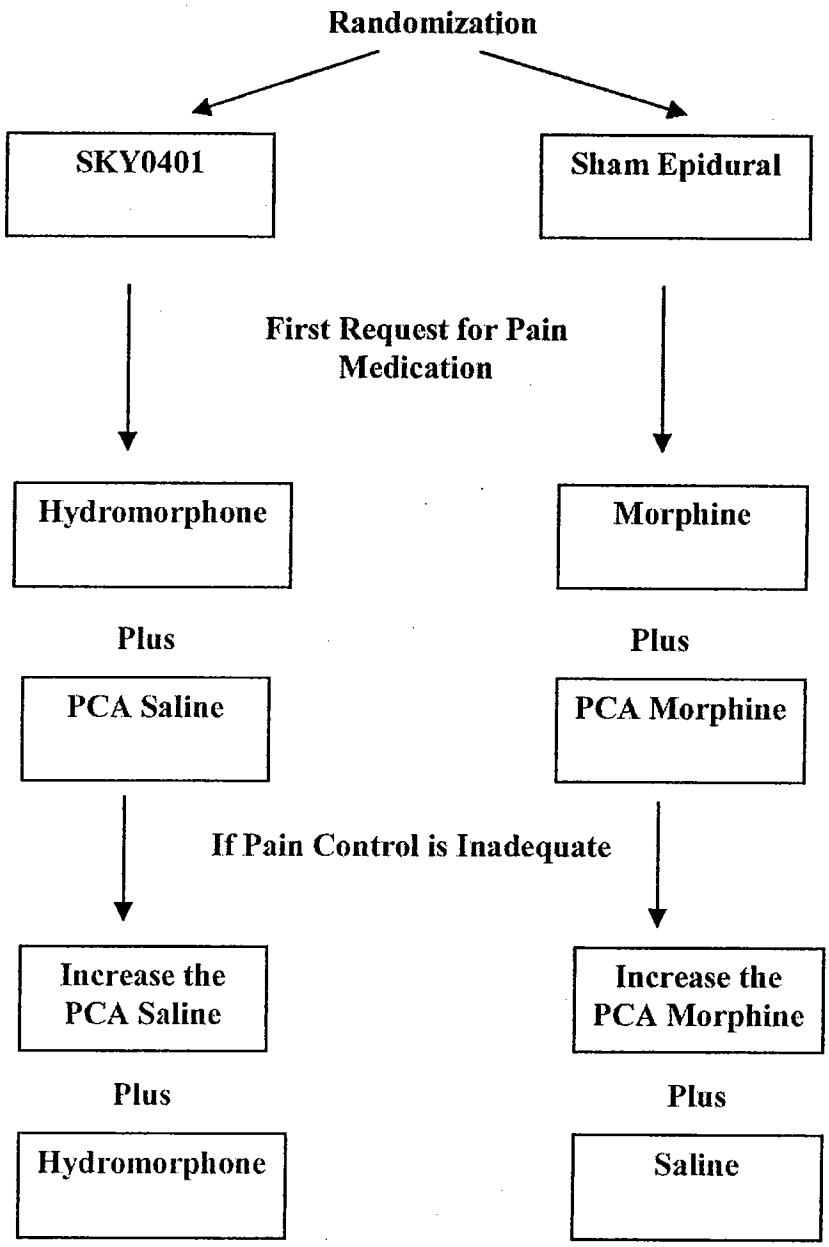
The corrected CRF datasets, with correct treatment codes, will be submitted as an amendment to the NDA.

Also, during the investigation of the data generation for Protocol SKY0401-015, we discovered that some hard codes were employed in the programming. Further inspection indicated that hard codes were also used in other studies. A complete description of the hard codes used in the SKY0401 datasets will be included in the aforementioned amendment to the NDA.

None of the items described above have an impact on the outcome of the clinical studies as reported in the submission. The results reported in the CSR for each protocol are correct.

Study SKY0401-017

Study Design Schematic (sponsor's presentation)



Demographic and Baseline Characteristics (sponsor's presentation)

Characteristic	IV PCA Morphine	SKY0401			Total
		20 mg	30 mg	All	
Patients (n)	55	51	56	107	162
Age (years)					
Mean (SD)	68.0 (9.2)	66.5 (8.9)	65.8 (10.2)	66.1 (9.6)	66.7 (9.4)
Median	69.0	69.0	67.0	68.0	69.0
Min-Max	43 - 85	45 - 81	46 - 88	45 - 88	43 - 88
Age Group (years)					
< 65	16 (29%)	18 (35%)	24 (43%)	42 (39%)	58 (36%)
65 - 75	28 (51%)	25 (49%)	23 (41%)	48 (45%)	76 (47%)
> 75	11 (20%)	8 (16%)	9 (16%)	17 (16%)	28 (17%)
Gender					
Male	25 (46%)	20 (39%)	23 (41%)	43 (40%)	68 (42%)
Female	30 (55%)	31 (61%)	33 (59%)	64 (60%)	94 (58%)
Race					
Caucasian	54 (98%)	49 (96%)	44 (79%)	93 (87%)	147 (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 (11%)	7 (7%)	7 (4%)
BMI					
Mean (SD)	30.7 (5.6)	30.6 (5.0)	31.7 (4.7)	31.1 (4.9)	31.0 (5.1)
Median	30.0	30.0	32.0	31.0	31.0
Min-Max	21 - 45	19 - 42	21 - 40	19 - 42	19 - 45
ASA Classification					
Class 1	4 (7%)	2 (4%)	2 (4%)	4 (4%)	8 (5%)
Class 2	35 (64%)	36 (71%)	38 (68%)	74 (69%)	109 (67%)
Class 3	16 (29%)	13 (26%)	16 (29%)	29 (27%)	45 (28%)

SD = Standard deviation; BMI = Body mass index; ASA = American Society of Anesthesiology; Min = Minimum; Max = Maximum.

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