# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204803Orig1s000

# STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/BLA #:** | 204-803 |
| **Supplement #:** | SN 0027 |
| **IND #** | 66,086 |
| **Drug Name:** | Posimir (bupivacaine extended-release solution) |
| **Indication(s):** | single-dose instillation into the surgical site to produce post-surgical analgesia |
| **Applicant:** | DURECT Corp. |
| **Date(s):** | Submission Stamp: 6/27/19<br>PDUFA: 12/27/19<br>Primary Review: 12/13/19 |
| **Review Priority:** | Priority (Complete Response to CRL) |
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Keywords: Clinical Studies; Complete Response

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# 1. EXECUTIVE SUMMARY

DURECT originally submitted an NDA for POSIMIR in 2013 seeking an indication for post-surgical analgesia. A Complete Response letter was sent on February 12, 2014. The current application contains the results from additional studies conducted to address issues identified during the original review.

This application contains results from the PERSIST study (C803-028) in subjects undergoing laparoscopic cholecystectomy surgery. This is an abdominal surgery and involves four port incisions to remove the gall bladder. There are two parts of the PERSIST study. Part 1 was designed to address safety concerns from the CR letter and used a saline placebo-control arm rather than the SABER-placebo formulation which had been used in the Phase 2 and 3 studies submitted in the original application. Part 1 was stopped by the applicant voluntarily after approximately 30% of planned enrollment. The comparator arm was changed to active-control bupivacaine HCl 50mg (Amendment #3), and the study was resumed.

The applicant considers neither part of the PERSIST study to be adequate and well-controlled evidence for efficacy because of the change in control arm. I consider the two parts as separate clinical studies, with different objectives. Each was planned and powered to test the superiority comparison of Posimir vs. the control group for efficacy.

Part 1 is a randomized, double-blind, parallel group study in adults undergoing elective outpatient surgery. The comparator arm was saline-placebo, to address safety concerns identified in the CR letter. It was conducted at 17 sites in the U.S. Randomization was stratified by gender within sites. Protocol 1 was designed and powered to test for superiority vs. saline in pain on movement from 0-72 hours post-surgery. The anticipated treatment difference for Posimir vs. saline in determining the sample size was 0.75 units, with a planned sample of 153/group. This study was stopped after 92 subjects (46/group) had been randomized and treated because the sponsor, following advice from the Agency, decided to add an active-control (bupivacaine HCl) arm. The sponsor elected to drop the placebo arm. The results were underpowered to for the comparison to saline-placebo, but the observed treatment difference of 0.79 was in the anticipated range. I consider this as supportive of efficacy of Posimir vs. saline-placebo.

Part 2 was initiated under Protocol Amendment #3 in August 2016. It is a randomized, double-blind, parallel group active-control study, which was designed and powered to test for superiority vs. bupivacaine HCl in pain on movement from 0-48 hours post-surgery, based on an anticipated treatment difference of 0.8 units and 132 subjects/group. The applicant's rationale for the shorter timeframe was that in this surgical setting, the typical decrease in pain from 48-72 hours would make it easier to detect a difference vs. the comparator for the 0-48 hour timeframe than the 0-72 hour timespan in Part 1. A total of 296 subjects were randomized and treated (148/group) in Part 2. The results did not demonstrate superiority (diff=0.37; p-value = 0.12) vs. the active-control.

The applicant discounts this result as not being an adequate and well-controlled study. I consider it suggestive of inconsistent efficacy in the abdominal surgery procedure.

The original submission was reviewed by David Petullo in 2013 (review dated 12/30/13). The applicant submitted six Phase 2 and one Phase 3 studies to support efficacy. The applicant had selected two Phase 2 studies, one in shoulder surgery and one in hernia repair, as primary. The other five studies were labeled as supportive. As Mr. Petullo noted in his review "Studies 803-025, C803-017, CLIN005-0006, CLIN005-0010, and BU-001-IM were indicated as supportive studies. It appears these studies were indicated as supportive as they failed to show a significant treatment effect for Posimir." His conclusion was that the shoulder surgery studies (primary: BU-002-IM; two supportive) did demonstrate efficacy in that surgical procedure, but that the inconsistent results in the two hernia studies (CLIN-803-0006; CLIN005-0010) did not provide sufficient evidence of efficacy for treating post-surgical pain in hernia repair. The supportive studies included one in patients undergoing hysterectomy, and another in patients undergoing major abdominal surgery (open laparotomy; laparoscopic cholecystectomy; or laparoscopic assisted colectomy).

The original application received a Complete Response Letter (CRL) on 2/12/14. The main issues identified were safety (AEs to shoulder joint and surrounding tissue; risk of bruising, hematoma, pruritus, and dehiscence; and an increased risk of neurologically related adverse events). The applicant was advised to conduct additional studies to address these concerns. For each, the advice was the "the treatments need to include SABER-bupivacaine and either bupivacaine HCL or a non-SABER containing placebo (or both). The study needs to be randomized and double-blinded. … Efficacy data must be collected during the study to allow the safety data to be placed in clinical context when the benefit:risk analysis is performed."

PERSIST Part 1 was designed as an adequate and well-controlled placebo-control study. PERSIST Part 2 was designed as an adequate and well-controlled active-control study. They were conducted consecutively, and the common element was the study sites. Amendment #3 designates the change in control, and the redesign with the intent to test superiority vs. the active comparator bupivacaine HCl 50mg. Amendment #3 redefined the timeframe for the primary efficacy endpoint (pain intensity on movement) as 0-48 hours after surgery with the rationale that typically lower pain in the 48-72 hour period would mean it would be easier to detect a difference in the 0-48 hr. period than the 0-72 hr. period used in all previous efficacy studies. The applicant considers the changes made as reason not to consider either part as an adequate and well-controlled study for inclusion in the ISE. I disagree. Each part, if considered independent of the other, was designed as an adequate and well-controlled study to address a specific objective following advice and discussion with DAAAP.

In this submission, the Applicant has revised the intended purpose of two of the formerly "supportive" studies (CLIN005-0006; CLIN005-0010), including the study which Mr. Petullo identified as raising doubt in hernia repair, as "other" and excluded those from the integrated summary of efficacy (ISE). I disagree with the Applicant's reclassification of these studies. Although they were Phase 2 studies, they were designed and powered to test the efficacy (pain)

endpoint and should be considered in the overall body of evidence. I will refer to Mr. Petullo's review of those studies.

The disagreement on classification of the eight efficacy studies, and the resulting conclusions on the strength and consistency of the overall evidence to support a broad indication for treatment of post-surgical pain, was discussed at an Advisory Committee(AC) on January 16, 2020. The committee members' vote (6 yes/ 6 no) indicated a split decision on whether the evidence demonstrated an acceptable risk:benefit.

Based on my review of the PERSIST Part 1 and Part 2 data, along with Mr. Petullo's review of the original submission, and the outcome of the AC, there is not substantial evidence of efficacy to support a broad indication for treatment of post-surgical pain. The body of evidence shows inconsistent efficacy results within and across the four surgical procedures studied.

# 2. INTRODUCTION

## 2.1 Overview

DURECT Corp. is seeking approval for Posimir ™ (SABER-bupivacaine) for the indication of treatment of post-surgical pain. SABER refers to the formulation (Sucrose acetate isobutyrate extended release). The clinical development program included 8 studies of efficacy and safety, shown in Table 1.

Table 1: Clinical Studies conducted by the Applicant

| Surgical Procedure | Study Sites {US} Dates | Phase | Treatment Arms (N) | Pivotal or Supportive [a]; Result |
|---|---|---|---|---|
| Inguinal Hernia | CLIN-803-006-0006<br>5 {0}: AUS, NZ<br>2006 | 2 | Posimir (47)<br><br>SABER-PBO (32 | Pivotal;<br>Posimir superior to SABER-PBO |
| | CLIN005-0010<br>8 {7} NZ<br>2006-07 | 2 | Posimir (54)<br><br>SABER-PBO (35) | Supportive; |
| Arthroscopic Shoulder Surgery | BU-002-IM<br>9 {0} Europe<br>2009-11 | 2 | Posimir (53)<br><br>SABER-PBO (25)<br><br>Bupiv. 50mg (29) | Pivotal;<br>Posimir superior to SABER-PBO;<br><br>Did not show non-inferiority to Bupiv. |
| | C803-017<br>10 {0} AUS, NZ<br>2008-09 | 2b | Posimir (40)<br><br>SABER-PBO (20) | Supportive;<br><br>Did not show superiority to SABER-PBO |
| | CLIN005-0006<br>7 {6} NZ<br>2006-07 | 2 | Posimir (62)<br><br>SABER-PBO (44) | Supportive; |
| Hysterectomy | BU-001-IM<br>13 {0} Europe<br>2009-10 | 2 | Posimir (61)<br><br>SABER-PBO (27)<br><br>Bupiv. 100mg (27) | Supportive; |
| Major Abdominal Surgery | 803-025<br>19 {15} AUS, NZ<br>2009-11 | 3 | Posimir (182)<br><br>SABER-PBO (77) | Supportive;<br>1 of 3 cohorts was designed to test vs. PBO. NSD (p=.06) |

| | | | |
|---|---|---|---|
| | | Bupiv. 75mg (37) | |
| PERSIST Part 1<br>11 All US<br>2015-2016 | 3 | Posimir (46)<br><br>Saline-PBO (46) | Supportive;<br>Underpowered because stopped study at 30% of planned enrollment |
| PERSIST Part 2<br>15 All US<br>2016-2017 | 3 | Posimir (148)<br><br>Bupiv. 75mg (148) | Supportive;<br>Powered to test vs. active-control; Did not demonstrate superiority. |

Source: Reviewer
[a] Applicant's classification

This review will focus on the two parts of the PERSIST study. This study was initially designed to address safety concerns listed in the CR letter. The protocol was submitted in Feb. 26, 2015. In multiple letters and teleconferences during 2015 and 2016, DAAAP advised the sponsor that an active-control arm was needed. Of note, in an Advice Letter on Jan. 11, 2016, DAAAP strongly recommended that the protocol be modified to include bupivacaine treatment group as an active control, and in a teleconference on April 5, 2016, DAAAP advised that, "given the Agency's existing assessment of the balance of safety and efficacy, a demonstration of superiority over active bupivacaine HCL control would almost certainly be required to obtain market approval." I cannot find any record that DAAAP suggested stopping the saline-placebo control arm or replacing that arm with the active-control arm in this study.

### 2.2 Data Sources

All data were supplied by the applicant to the CDER electronic data room (edr) in SAS transport format. The study reports and data in the electronic submission are archived under the network path location: \\Cdsesub1\evsprod\NDA204803\0027. An additional analysis dataset, provided in response to and information request, was submitted on Nov. 20, 2019, and is archived at : \\Cdsesub1\evsprod\NDA204803\0034.

# 3. STATISTICAL EVALUATION

## 3.1 Data and Analysis Quality

The study data were submitted in standard formats, along with all documentation needed to complete my review. I was able to confirm the applicant's efficacy analyses. The data were clearly organized to conduct my own analyses without difficulty.

## 3.2 Evaluation of Efficacy

### 3.2.1 Study C803-028: PERSIST Part 1

#### Study Design and Endpoints

PERSIST Part 1 was a multicenter, randomized, double-blind, parallel group design. It included two treatment arms: Posimir (SABER bupivacaine), and saline-placebo. It was conducted from Nov. 2015 through June 2017 at 22 sites in the U.S. To evaluate the safety and efficacy of SABER-Bupivacaine for alleviating postoperative pain on movement compared with saline placebo in patients undergoing laparoscopic cholecystectomy.

Eligible subjects were adults, age 18 or older, scheduled for elective outpatient laparoscopic cholecystectomy using a convention 4-port procedure. Study treatment was administered by direct instillation into the 4 surgical incisions after the surgical procedure, just prior to closing the incisions with sutures. Following surgery, subjects were monitored in the post-anesthesia care unit (PACU) for a minimum of 2 hours then discharged home. Subjects were contacted by phone on Study Days 2 and 3 (postoperative days [PODs] 1 and 2) for specific postoperative assessments and returned for site visits on Study Days 4, 8, 15, and 29. Rescue medication in the PACU was IV fentanyl 12.5-25 μg upon request. At discharge subjects were provided with acetaminophen 500 mg tablets for mild-to-moderate pain and a prescription for oxycodone 5 mg immediate release tablets for moderate-to-severe pain. Subjects self-administered these medications on an as-needed basis according to written dosing instructions provided by the site investigator or study staff.

Pain intensity on movement (trying to sit up) and at rest were recorded on an 11-point, 0-10 numeric pain rating scale (NPRS). Efficacy, use of rescue medication, and safety assessments were collected using electronic log pads. Pain scores were recorded at predetermined times and prior to any use of rescue. The primary efficacy endpoint was the mean pain on movement for hours 0-72 post-treatment.

Part 1 was originally planned to randomize approximately 320 eligible subjects in a 1:1 ratio to the two treatment arms. This sample size was based on an anticipated difference of 0.75 units for the primary efficacy outcome mean pain on movement from 0-72 hours post-treatment,

with effect size of 0.375, SD=2, and 90% power. Enrollment in Part 1 was stopped after 92 subjects (46 per arm) had been randomized and treated. Subjects were randomized by sex within site.

The modified Intent to Treat (mITT) patient population was defined as all subjects who received study treatment. This was designated as the primary analysis population for efficacy endpoints. Pain assessments were adjusted for use of rescue. If a subject took a rescue medication and then completed a scheduled pain assessment within one half-life of that medication, the value analyzed would be the larger of the scheduled pain assessment and the pre-rescue medication pain assessment.

### Patient Disposition, Demographic and Baseline Characteristics

A total of 94 subjects were randomized to Part 1. Two, both in the Posimir group, did not receive study treatment, for reasons which were not related to treatment. All treated subjects completed the study and are included in the efficacy analyses.

**Table 2. Patient Disposition (PERSIST Part 1)**

| Disposition Category | Posimir | Saline-placebo |
|---|---|---|
| Randomized (ITT) | 48 (100%)* | 46 (100%) |
| Received study treatment (mITT) | 46 (96%) | 46 (100%) |
| Completed study | 46 (96%) | 46 (100%) |
| Discontinued from study | 0 | 0 |

* All percentages are calculated based on Randomized N per group as denominator.
Source: Reviewer
Abbreviations: ITT - intent-to-treat; mITT - modified Intent to Treat

**Baseline Demographics**

The two treatment groups were relatively balanced with respect to relevant demographic and baseline characteristics as shown in Table 2.

**Table 3. Demographic and Baseline Characteristics (PERSIST Part 1)**

| All Treated (MITT) | Posimir N=45* | Saline-placebo N=47 |
|---|---|---|
| Age (years) | | |
| Mean (SD) | 47 (14.3) | 41 (12.9) |
| Range | 22 - 76 | 18 - 67 |
| Gender | | |
| Male | 16 (36%) | 17 (36%) |
| Female | 29 (64%) | 30 (64%) |
| Race | | |
| White | 37 (82%) | 41 (87%) |
| Black | 6 (13%) | 4 (9%) |
| Asian | 2 (4%) | 2 (4%) |
| Other | 0 | 0 |
| Body Mass Index (BMI) kg/$m^2$ | | |
| Mean (SD) | 31 (6.4) | 32 (7.5) |
| Range | 18 - 51 | 21 - 61 |
| ASA physical status classification | | |
| I Normal Healthy | 14 (31%) | 13 (28%) |
| II Mild systemic disease | 27 (60%) | 26 (55%) |
| III Severe systemic disease | 4 (9%) | 8 (17%) |

Source: Reviewer

* One subject randomized to Posimir was actually treated with saline-placebo. The safety analyses used actual treatment received. Efficacy analyses were as randomized.

Abbreviations: ITT - intent-to-treat; mITT - modified Intent to Treat; SD - standard deviation

### Statistical Methodologies

The pain scores were analyzed using a mixed model of repeated measures (MMRM) model with fixed effects for sex, treatment, sex by treatment interaction, time, treatment by time interaction, and study site. Time was a repeating factor within the random effect of subject. The covariance model for the primary analysis was a spatial power model, with distance between observations defined by measurement time. The covariance included a local diagonal term to account for between-subject variability in pain scores. The least squares (LS) mean for each treatment group and corresponding SEs were calculated, along with the difference between the LS means of the treatment groups, the SE of the difference, and 95% CIs for the differences in population means between treatment groups. The primary treatment comparison was based on the test of treatment effect using the LS mean estimate across 72 hours, adjusted for the effects of sex and study site from the type III analysis.

There was relatively little missing data for the 13 scheduled pain assessments. Seventy-five percent of subjects had no missing data, 15% were missing a single pain score, and the remaining 10% were missing 2 or more.

### Results and Conclusions

Table 4 presents the applicant's results for the primary efficacy endpoint, which were confirmed. The results do not show sufficient evidence to conclude superiority to saline due to being underpowered with only 30% of the planned sample size enrolled. The direction and size of the treatment effect are supportive of Posimir.

**Table 4. Efficacy Analysis Results (PERSIST Part 1)**

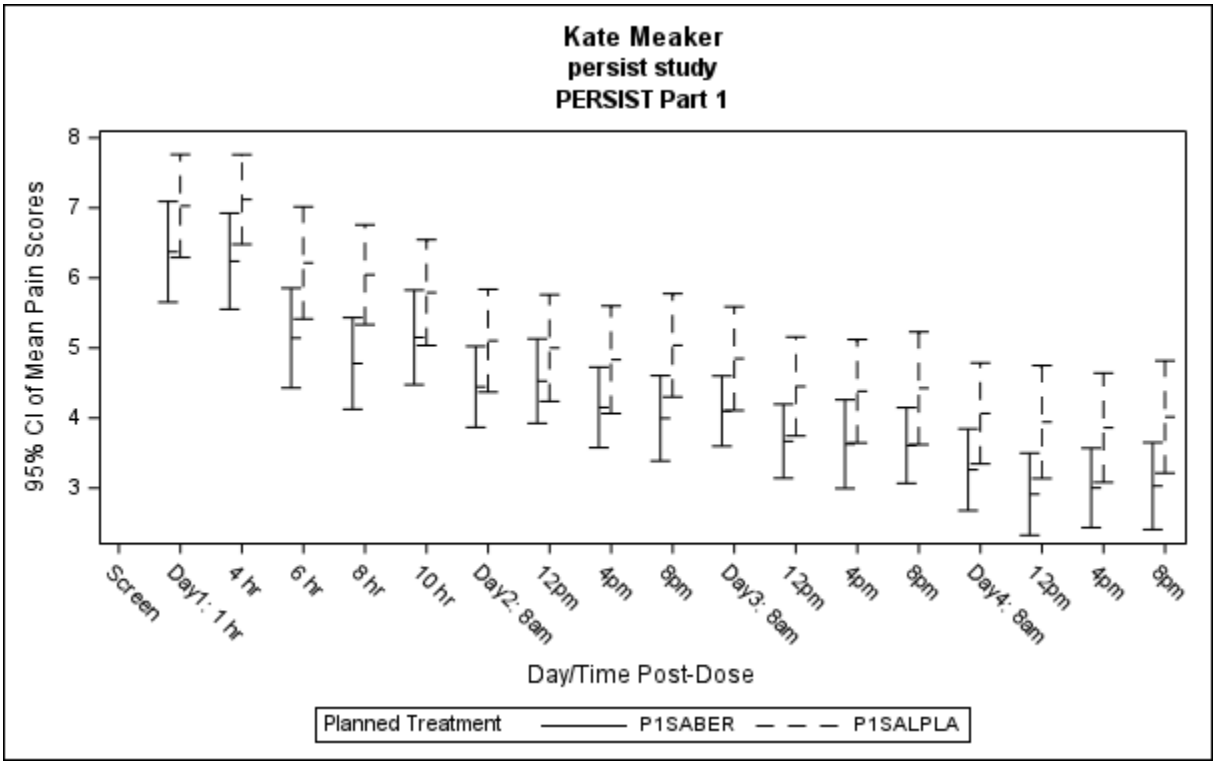
| MITT Patient Population | | Posimir N=46 | Saline-placebo N=46 |
|---|---|---|---|
| **Primary:** Pain Intensity on Movement 0-72 hours Post-treatment | Mean (SE) | 4.4 (0.09) | 5.2 (0.11) |
| | Diff. from placebo | -0.79 | |
| | (95% CI) | (-1.63, 0.06) | |
| | p-value | 0.07 | |

Source: CSR Table 14 and Statistical Report Table 7
Abbreviations: SE – Standard Error; CI - confidence interval;

Secondary endpoints presented by the Applicant were Total IV Morphine-equivalent Dose of Rescue Opioids used for 0-72 hours, Proportion of Subjects Not Taking Opioids after PACU Discharge, and Time to First Opioid Rescue. Drs. Petit-Scott and Van der Clief feel those comparisons in relation to the saline placebo comparator arm are not relevant, as saline-placebo would not be a standard of care option.

Figure 1 displays the mean pain intensity scores at the planned measurement timepoints post-treatment through 72 hours. There is no notable separation in the lines.

**Figure 1. Mean Pain Scores at each measured time point in PERSIST Part 1**




Source: Reviewer

Based on the results, PERSIST Part 1 did not enroll sufficient number of subjects to provide the intended evidence of efficacy vs. saline-placebo. The saline comparator was designed to address safety issues identified in the CR letter, with efficacy to enable consideration of the risk:benefit relationship. The results are not included in the overall body of evidence because the saline-placebo is not an appropriate comparator to support the desired indication.

### 3.2.2 Study C803-028: (PERSIST Part 2)

#### Study Design and Endpoints

PERSIST Part 2 was designed in Amendment #3 (dated June 3, 2016) as a randomized, double-blind, parallel group active-control study. Most aspects were the same as Part 1. Safety assessments during post-surgical recovery in the PACU were refined, and a later (Day 60) safety follow-up was added.

The key change was that the control-arm was changed from saline-placebo (intended to provide reference for safety) to active-control. The objective was to demonstrate superiority of Posimir to bupivacaine HCl 75mg. The primary efficacy endpoint was defined as the mean pain on movement for 0-48 hours post-treatment, rather than the 0-72 hour timeframe used to demonstrate efficacy in all previous studies. The explanation was based on pain data from Study 803-025 Cohort 2 in subjects undergoing laparoscopic cholecystectomy which showed a decline in pain after 48 hours. The Applicant expected to be able to detect a difference more easily using the 0-48 hour timeframe. Using the results from the earlier study, the sample size was powered to detect a difference of 0.8 units in the mean pain on movement NPRS scale with 90% power.

Mean pain on movement for 0-72 hours post-treatment was a secondary endpoint, along with the total IV morphine-equivalent dose of opioid rescue medication used during the first 72 hours post-treatment.

### Patient Disposition, Demographic and Baseline Characteristics

A total of 296 subjects (148/group) were randomized and received treatment in Part 2. Nine subjects were randomized but not treated due to exclusion criteria occurring prior to administration of study treatment. Four subjects (all in the active-control arm) discontinued from the study but all are included in the mITT population for efficacy.

**Table 5. Patient Disposition (PERSIST Part 2)**

| Disposition Category | Posimir | Bupivacaine HCl 75mg |
|---|---|---|
| Randomized (ITT) | 153 (100%)* | 152 (100%) |
| Received study treatment (mITT) | 148 (97%) | 148 (97%) |
| Completed study | 148 (97%) | 144 (95%) |
| Discontinued from study | 0 | 4 |
| Discontinuation Reasons | | |
| Adverse event | 0 | 1 (1%) |
| Death | 0 | 0 |
| Lost to follow-Up | 0 | 1 (1%) |
| Protocol violation | 0 | 0 |
| Withdrew consent | 0 | 0 |
| Other | 0 | 2 (1%) |

* All percentages are calculated based on Randomized N per group as denominator.
Source: Reviewer
Abbreviations: ITT - intent-to-treat; mITT - modified Intent to Treat

**Baseline Demographics**

Demographic and baseline characteristics were similar for both treatment groups and are provided in Table 6 below.

**Table 6. Demographic and Baseline Characteristics (PERSIST Part 2)**

| All Treated (MITT) | Posimir N=148 | Bupivacaine HCl 75mg N=148 |
|---|---|---|
| Age (years) | | |
| Mean (SD) | 45 (13.0) | 45 (13.7) |
| Range | 19 - 74 | 18 - 77 |
| Gender | | |
| Male | 36 (24%) | 34 (23%) |
| Female | 112 (76%) | 114 (77%) |
| Race | | |
| White | 136 (92%) | 131 (89%) |
| Black | 6 (4%) | 9 (6%) |
| Asian | 5 (3%) | 6 (4%) |
| Other | 1 (1%) | 2 (1%) |
| Body Mass Index (BMI) kg/$m^2$ | | |
| Mean (SD) | 31 (7.1) | 32 (6.8) |
| Range | 16 - 59 | 18 - 55 |
| ASA physical status classification | | |
| I Normal Healthy | 87 (59%) | 76 (51%) |
| II Mild systemic disease | 55 (37%) | 63 (43%) |
| III Severe systemic disease | 6 (4%) | 9 (6%) |

Source: Reviewer

* One subject randomized to Posimir was actually treated with saline-placebo. The safety analyses used actual treatment received. Efficacy analyses were as randomized.

Abbreviations: ITT - intent-to-treat; mITT - modified Intent to Treat; SD - standard deviation

### Statistical Methodologies

The pain scores were analyzed using a mixed model of repeated measures (MMRM) model with fixed effects for sex, treatment, sex by treatment interaction, time, treatment by time interaction, and study site. Time was a repeating factor within the random effect of subject. The covariance model for the primary analysis was a spatial power model, with distance between observations defined by measurement time. The covariance included a local diagonal term to account for between-subject variability in pain scores. The least squares (LS) mean for each treatment group and corresponding SEs were calculated, along with the difference between the LS means of the treatment groups, the SE of the difference, and 95% CIs for the differences in population means between treatment groups. The primary treatment comparison was based on the test of treatment effect using the LS mean estimate across 48 hours, adjusted for the effects of sex and study site from the type III analysis. The mean pain for 0-72 hours, a secondary endpoint, was analyzed with the same MMRM approach.

The other secondary endpoint, total IV morphine-equivalent dose of opioid rescue medication used during the first 72 hours post-treatment was to be analyzed by an ANOVA model adjusted for sex if normality assumptions were met or by the van Elteren test (a stratified Wilcoxon Rank Sum test), if normality assumptions were not met. An analysis made prior to data base lock determined that non-parametric methods would be more appropriate to the opioid data collected.

There was relatively little missing data for the 13 scheduled pain assessments. Seventy-one percent of subjects had no missing data, 18% were missing a single pain score, and the remaining 11% were missing 2 or more.

### Results and Conclusions

Table 7 presents the results for the primary and secondary efficacy endpoints. None of the comparisons demonstrate superiority of Posimir to bupivacaine HCl 75mg. The observed treatment effect for mean pain on movement for 0-48 post-treatment was less than half of what the applicant predicted when planning the protocol.

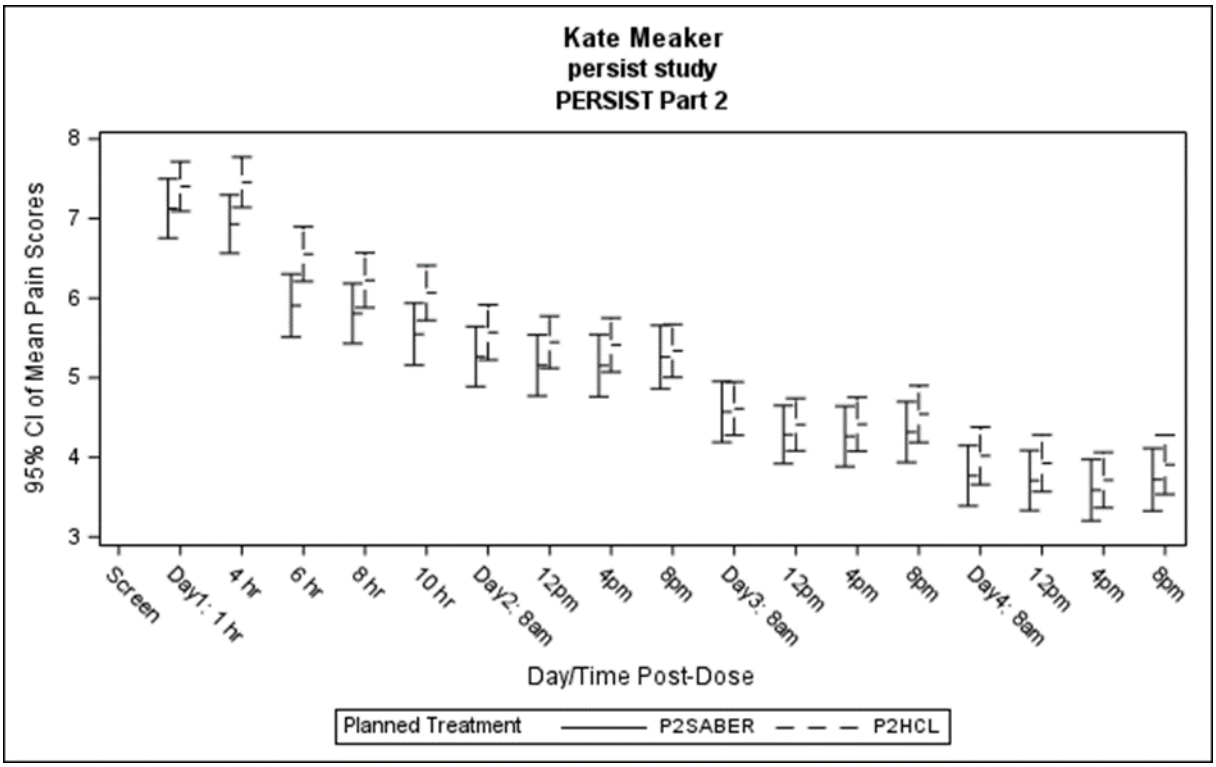
Table 7. Efficacy Analysis Results (PERSIST Part 2)

| MITT Patient Population | | Posimir N=148 | Bupivacaine HCl 75mg N=148 |
|---|---|---|---|
| **Primary:** Pain Intensity on Movement 0-48 hours Post-treatment | Mean (SE)<br>Diff. from bupiv.<br>(95% CI)<br>p-value | 5.6 (0.07)<br>-0.37<br>(-0.84, 0.10)<br>0.12 | 5.9 (0.06) |
| **Secondary:** Pain Intensity on Movement 0-72 hours Post-treatment | Mean (SE)<br>Diff. from bupiv.<br>(95% CI)<br>p-value | 5.1 (0.06)<br>-0.28<br>(-0.76, 0.20)<br>0.26 | 5.4 (0.05) |
| **Secondary:** Total Morphine-Equivalent Dose 0-72 hours Post-treatment (mg) | Mean (SE)<br>Median<br>Median Diff. from bupiv.<br>(95% CI)<br>p-value | 22 (1.6)<br>17<br>-1.2<br>(-5.0, 2.5)<br>0.57 | 23 (1.6)<br>17 |

Source: CSR Table 14 and Statistical Report Tables 6-8
Abbreviations: SE – Standard Error; CI - confidence interval;

Figure 2 shows the mean pain scores at the planned measurement times post-treatment. There is little notable separation after the day of surgery. The vertical division marks the separation between day of surgery (times recorded based on number of hours post-treatment) and the two days after surgery, when pain was recorded at 8am, noon, 4pm, and 8pm. This is an exploratory result only and does not imply statistical significance at any timepoint.

**Figure 2. Mean Pain Scores at each measured time point in PERSIST Part 2**




Source: Reviewer

Based on these results, PERSIST Part 2 did not provide evidence of superiority to the bupivacaine HCl 75mg active-control group. As noted in the teleconference on April 5, 2016, demonstration of superiority over active bupivacaine HCl control would "almost certainly be required to obtain marketing approval." These results do not provide the strength of evidence needed to show efficacy for Posimir in treatment of post-surgical pain in subjects undergoing laparoscopic cholecystectomy.

### 3.3 Evaluation of Safety

The PERSIST study was intended to address the safety events identified in the CR letter, to better understand the benefit:risk picture. Dr. Petit-Scott will review the body of evidence for safety for the advisory committee.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Age, Gender, and Race

I produced exploratory analyses for the primary efficacy endpoint by age group, gender, race, and body mass index (BMI)(See Tables 8 and 9). These are descriptive analyses only and are not intended for inferential purposes. There were no notable differences in the mean pain intensity on movement across the subgroups in either part of the study.

The applicant anticipated a gender effect for pain, and it was included as a factor in the efficacy models. Overall men reported lower pain scores than women. The majority of subjects in both parts of the study were women (64% in Part 1; 76% in Part 2).

The majority of the subjects (≥90%) were younger than 65 years of age. I used the median age, 45 years, to define the subgroup categories. I used the defined BMI category split at 30 units, with <30 $kg/m^2$ considered not overweight and ≥30 $kg/m^2$ considered overweight. Approximately half the subjects were in each BMI category. There were relatively few subjects of color (POC), only 14 (15%) in Part 1 and 29 (10%) in Part 2, insufficient to make summary statements about the small POC subgroups.

**Table 8. Subgroup Analyses: (PERSIST Part 1) – Reviewer's Results**

| **Primary:** Pain Intensity on Movement 0-72 hours Post-treatment LSMeans (SE) | **PERSIST Part 1** | |
|---|---|---|
| | **Posimir N=46** | **Saline-Placebo N=46** |
| **Age group** | | |
| < 45 years | 4.7 (0.1) | 6.1 (0.1) |
| ≥ 45 years | 4.2 (0.1) | 4.2 (0.1) |
| **Gender** | | |
| Male | 4.0 (0.1) | 4.6 (0.1) |
| Female | 4.8 (0.1) | 5.8 (0.1) |

| | | |
|---|---|---|
| **Race** | | |
| White | 4.3 (0.1) | 5.2 (0.1) |
| People of Color | 5.0 (0.2) | 4.4 (0.3) |
| **Body Mass Index** | | |
| <30 kg/m$^2$ | 4.1 (0.1) | 5.0 (0.1) |
| ≥30 kg/m$^2$ | 4.6 (0.1) | 5.3 (0.1) |

Source: Reviewer

## Table 9. Subgroup Analyses: (PERSIST Part 2) – Reviewer's Results

| **Primary:** Pain Intensity on Movement 0-48 hours Post-treatment LSMeans (SE) | **PERSIST Part 2** | |
|---|---|---|
| | **Posimir N=148** | **Bupiv. HCl 75mg N=148** |
| **Age group** | | |
| < 45 years | 5.6 (0.1) | 6.1 (0.1) |
| ≥ 45 years | 5.5 (0.1) | 5.7 (0.1) |
| **Gender** | | |
| Male | 5.3 (0.1) | 5.7 (0.1) |
| Female | 5.8 (0.1) | 6.1 (0.1) |
| **Race** | | |
| White | 5.5 (0.1) | 5.9 (0.1) |
| People of Color | 6.3 (0.2) | 5.6 (0.2) |
| **Body Mass Index** | | |
| <30 kg/m$^2$ | 5.4 (0.1) | 5.8 (0.1) |
| ≥30 kg/m$^2$ | 5.7 (0.1) | 5.9 (0.1) |

Source: Reviewer

# 5. SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues and Collective Evidence

The Applicant has conducted 8 clinical studies designed to demonstrate efficacy. The two planned and powered as Phase 3 studies did not show superiority of Posimir to the comparator (SABER-Placebo or Bupivacaine active-control). The Applicant has classified the two Phase 2 studies which did demonstrate superiority to SABER-placebo as being pivotal, and discounts the other studies based aspects of the design. The Phase 2 studies were designed appropriately for that purpose, but not as confirmatory studies.

The body of evidence to assess efficacy is inconsistent across the four surgical procedures investigated. Studies on similar surgical procedures provide conflicting results. Only one (arthroscopic shoulder surgery) of the surgical procedures has repeated evidence of efficacy. The Applicant's efforts to highlight the successful 2 studies and discredit the other 6 studies misrepresents the value each contributes to the decision for the desired broad indication for treatment of post-surgical pain.

## 5.2 Conclusions and Recommendations

The PERSIST study was intended to address the concerns regarding safety, and the risk:benefit relationship, in the CR letter after the first submission. The applicant received feedback from DAAAP at an End of Review Type A meeting (9/23/14) and in a Formal Dispute Resolution meeting (12/16/14). Advice was provided on the protocol and amendments through advice letters and teleconferences.

The applicant argues that PERSIST Part 1 is an adequate and well-controlled study but is underpowered to demonstrate efficacy. Both are true. However, demonstrating superiority to saline-placebo for efficacy was not the basis to get approval. While Part 1 is supportive, it is not sufficient evidence for the indication of treatment of post-surgical pain.

The applicant argues that PERSIST Part 2 is not an adequate and well-controlled study because of the changes made in Amendment #3, when the saline-placebo treatment arm was dropped, and the bupivacaine HCl 75mg arm was added. To the contrary, in my opinion what is referred to as Amendment 3 could have been submitted as a new study and has all the necessary criteria to be considered an adequate and well-controlled study. The results do not show superiority to the active-control not because of poor design, but because the observed treatment effect was less than half of what the Applicant anticipated in planning.

The results from the PERSIST study do not clarify the inconsistent efficacy results noted by Mr. Petullo in his review of the seven studies in the initial submission. His conclusion was that only

the shoulder surgery procedure demonstrated sufficient evidence of efficacy for the indication, but not the broad indication the Applicant is seeking. I agree with that conclusion.

This application was presented to an Advisory Committee on January 16, 2020. DAAAP was seeking advice on the risk:benefit relationship as well as the collective body of evidence for efficacy. The committee members' vote (6 yes/ 6 no) indicated a split decision on whether the evidence demonstrated an acceptable risk:benefit.

### 5.3 Labeling Review

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# STATISTICAL MEMORANDUM

| | |
|---|---|
| **NDA/Serial Number:** | NDA 204803/0027 |
| **Drug Name:** | Posimir (sucrose acetate isobutyrate extended-release bupivacaine (SABER-Bupivacaine)) |
| **Indication(s):** | Postoperative analgesia |
| **Objective(s):** | To evaluate the safety of SABER-Bupivacaine for alleviating postoperative pain on movement compared with bupivacaine HCl |
| **Applicant:** | DURECT Corporation |
| **Consult Date:** | January 27, 2020 |
| **Biometrics Division:** | Division of Biometrics VII |
| **Statistical Reviewer:** | Ya-Hui Hsueh, Ph.D. |
| **Concurring Reviewers:** | Eugenio Andraca-Carrera, Ph.D., Team Leader |
| **Medical Division:** | Division of Anesthesiology, Addiction Medicine, amd Pain Medicine (DAAMPM) |
| **Clinical Team:** | Medical Officer: Renee Petit-Scott, M.D.<br>Medical Team Lead: Martha Van Clief, M.D. |
| **Keywords:** | SABER, solicited AE, spontaneously AE |

# 1 INTRODUCTION

DURECT Corporation (the Applicant) submitted the original NDA for posimir (SABER-Bupivacaine) in 2013 as an extended release solution of bupivacaine, an amide local anesthetic, indicated for single-dose instillation into the surgical site to produce post-surgical analgesia. In February 2014, the Agency issued a Complete Response (CR) letter to the Applicant for safety concerns (see NDA 204803 dated 2/12/2014, Complete Response). The Agency advised all additional safety studies need to include SABER-bupivacaine and either bupivacaine HCl or a non-SABER containing placebo, or both. In November 2014, the Applicant submitted a Formal Dispute Resolution Request (FDRR) for additional determination of efficacy and safety of posimir. The FDRR was denied in January 2015. In June 2019, the Applicant resubmitted the NDA along with the updated post hoc safety analyses. An AC meeting on this application was held on January 16, 2020 to discuss the clinical implications of efficacy data and the assessment of safety data in support of the NDA.

Division of Anesthesiology, Addiction Medicine, amd Pain Medicine (DAAMPM) has concerns regarding the adverse events data analyses conducted in the resubmitted NDA. DB7 was consulted to verify data analyses on treatment-emergent adverse events (TEAEs) the Applicant conducted in the trials that compared with immediate-release bupivacaine (bupivacaine HCl) in this resubmission.

**Material Reviewed**

The Applicant submitted electronic documents (integrated summary of safety and clinical study report) and analysis datasets of NDA 204803 on 6/27/2019.

EDR Location: \\cdsesub1\evsprod\nda204803\0027\m5

The applicant submitted responses to the statistics Information Requests (IRs) on 2/28/2020 and 3/13/2020. The links to these IRs are provided below:

EDR Locations: \\cdsesub1\evsprod\nda204803\0040 and \\cdsesub1\evsprod\nda204803\0041

# 2 STATISTICAL COMMENTS

1) The sponsor conducted analyses on incidence of solicited- and spontaneously- reported TEAE in integrated summary of safety (ISS) pooled group A (bupivacaine HCl controlled trials), including trials BU-001-IM, BU-002-IM, C803-025 (Cohorts 1 and 2), and PERSIST Part 2 (Tables 43 and 57 in ISS).

*Reviewer's Comment:*

*The statistical reviewer is able to reproduce these two tables. However, two issues are identified.*

a. *The first issue was the incidence proportions the Applicant calculated. These were simple (or crude) pooling incidence proportions (meaning adding the number of patients receiving the same treatment that experienced the TEAE across the 5 studies and dividing it by the total number of patients on the same treatment). The simple pooling may be misleading in comparing results between the two treatment groups. For pooled group, the study size-adjusted (or standardized) method is more appropriate for presenting the overall incidence proportions. Our calculations of study size-adjusted incidence proportions are presented in Tables 1 and 2.*

b. *The second issue was the inconsistent numbers of TEAEs (both spontaneously- and solicited- reported) observed in the PERSIST part 2 from ISS pooled group A and PERSIST trial Part 2 alone. We sent a statistical information request (IR) regarding this discrepancy to the Applicant for clarification. The Applicant responded that the algorithm used to construct between solicited- and spontaneously- reported TEAEs in the PERSIST trial incorrectly assigned 186 TEAEs to the solicited group in the safety dataset that should have been assigned to the spontaneously-reported group. The Applicant corrected this oversight in the ISS safety dataset (see Applicant's response to information request # 4 on 2/28/2020).*

Table 1. Solicited-Reported TEAEs Incidence in ISS Pooled Group A (Bupivacaine HCl-controlled Studies)*

| System Organ Class /Preferred Term n (Incidence Proportion %) | DB7 Analysis** | | Applicant Analysis | |
|---|---|---|---|---|
| | SABER-Bupivacaine (N=321) | Bupivacaine HCl (N=242) | SABER-Bupivacaine (N=321) | Bupivacaine HCl (N=242) |
| Somnolence | 76 (26.7%) | 66 (23.7%) | 76 (23.7%) | 66 (27.3%) |
| Constipation | 65 (23.1%) | 58 (20.6%) | 65 (20.2%) | 58 (24.0%) |
| Headache | 53 (18.8%) | 49 (17.4%) | 53 (16.5%) | 49 (20.2%) |
| Nausea | 47 (16.2%) | 50 (18.8%) | 47 (14.6%) | 50 (20.7%) |
| Dizziness | 44 (15.0%) | 43 (15.9%) | 44 (13.7%) | 43 (17.8%) |
| Pruritus | 31 (11.0%) | 27 (9.6%) | 31 (9.7%) | 27 (9.9%) |
| Dysgeusia | 31 (11.0%) | 24 (8.5%) | 31 (9.7%) | 24 (11.2%) |
| Paraesthesia | 20 (7.1%) | 21 (7.5%) | 20 (6.2%) | 21 (8.7%) |
| Vomitting | 16 (5.1%) | 20 (7.8%) | 16 (5.0%) | 20 (8.3%) |
| Hypoaesthesia | 8 (2.8%) | 9 (3.2%) | 8 (2.5%) | 9 (3.7%) |

*Bupivacaine HCl studies include BU-001-IM, BU-002-IM, C803-025 (Cohorts 1 and 2), and C803-028 (PERSIST part 2)

**Incidence proportion are calculated based on study size-adjusted method

Table 2. Spontaneously-Reported TEAEs Incidence in ISS Pooled Group A (Bupivacaine HCl-controlled Studies)*

| System Organ Class /Preferred Term n (Incidence Proportion %) | DB7 Analysis** | | Applicant Analysis | |
|---|---|---|---|---|
| | SABER-Bupivacaine (N=321) | Bupivacaine HCl (N=242) | SABER-Bupivacaine (N=321) | Bupivacaine HCl (N=242) |
| Post procedural contusion | 202 (66.7) | 119 (43.2%) | 202 (62.9%) | 119 (49.2%) |
| Nausea | 85 (27.6%) | 79 (31.4%) | 85 (26.5%) | 79 (32.6%) |
| Vomiting | 38 (12.0%) | 27 (11.0%) | 38 (11.8%) | 27 (11.2%) |
| Procedural pain | 34 (11.9%) | 37 (13.4%) | 34 (10.6%) | 37 (15.3%) |
| Headache | 34 (10.8%) | 16 (6.0%) | 34 (10.6%) | 16 (6.6%) |
| Constipation | 27 (9.0%) | 22 (8.7%) | 27 (8.4%) | 22 (9.1%) |
| Dizziness | 27 (8.6%) | 21 (8.3%) | 27 (8.4%) | 21 (8.7%) |
| Pyrexia | 22 (6.5%) | 17 (8.0%) | 22 (6.9%) | 17 (7.0%) |
| Diarrhoea | 19 (6.2%) | 11 (4.4%) | 19 (5.9%) | 11 (4.5%) |
| Somnolence | 18 (6.2%) | 16 (6.2%) | 18 (5.6%) | 16 (6.6%) |
| Dysgeusia | 17 (5.8%) | 10 (3.7%) | 17 (5.3%) | 10 (4.1%) |
| Incision site haemorrhage | 14 (4.7%) | 6 (2.1%) | 14 (4.4%) | 6 (2.5%) |
| Abdominal distension | 13 (4.2%) | 8 (3.4%) | 13 (4.0%) | 8 (3.3%) |
| Post procedural discharge | 12 (4.0%) | 8 (3.0%) | 12 (3.7%) | 8 (3.3%) |
| Incision site haematoma | 11 (3.5%) | 3 (1.2%) | 11 (3.4%) | 3 (1.2%) |
| Hypertension | 11 (3.4%) | 9 (3.6%) | 11 (3.4%) | 9 (3.7%) |
| Incision site erythema | 10 (3.2%) | 5 (1.9%) | 10 (3.1%) | 5 (2.1%) |
| Abdominal pain | 10 (3.2%) | 2 (0.9%) | 10 (3.1%) | 2 (0.8%) |
| Cough | 8 (2.7%) | 4 (1.8%) | 8 (2.5%) | 4 (1.7%) |
| Abdominal pain upper | 8 (2.6%) | 2 (0.7%) | 8 (2.5%) | 2 (0.8%) |
| Back pain | 8 (2.6%) | 17 (6.7%) | 8 (2.5%) | 17 (7.0%) |
| Oropharyngeal pain | 8 (2.6%) | 2 (0.7%) | 8 (2.5%) | 2 (0.8%) |
| Flatulence | 7 (2.3%) | 8 (3.4%) | 7 (2.2%) | 8 (3.3%) |
| Pruritus | 6 (1.9%) | 9 (3.5%) | 6 (1.9%) | 9 (3.7%) |
| Incision site pain | 5 (1.8%) | 8 (2.8%) | 5 (1.6%) | 8 (3.3%) |
| Incision site pruritus | 4 (1.4%) | 8 (2.9%) | 4 (1.2%) | 8 (3.3%) |
| Urinary tract infection | 4 (1.4%) | 6 (2.2%) | 4 (1.2%) | 6 (2.5%) |
| Rash | 3 (1.1%) | 8 (3.3%) | 3 (0.9%) | 8 (3.3%) |

*Bupivacaine HCl studies include BU-001-IM, BU-002-IM, C803-025 (Cohorts 1 and 2), and C803-028 (PERSIST part 2)

**Incidence proportion are calculated based on study size-adjusted method

2) In the PERSIST CSR (page 129/1004), the Applicant conducted the incidence of 6 prespecified wound-related adverse events (Table 23).

*Reviewer's Comments:*

*The statistical reviewer was not able to reproduce the table based on the Applicant-submitted datasets. A statistical IR was sent for clarification. The Applicant clarified the source dataset and the specific variables used to generate the table (see Applicant's response to information request # 5 on 2/28/2020). However, our analyses using the source dataset and the variables listed on the Applicant's response to IR had resulted in difference numbers/incidences. We sent another IR for clarification. The Applicant responded that the source dataset has been corrupted during transfer to the Agency; it includes a large number of missing fields. A replacement for the source dataset is provided along with this response submission (see Applicant's response to information request # 2 on 3/13/2020). The Applicant also confirmed that no other datasets have been corrupted. The statistical reviewer is able to reproduce the table using the replaced dataset.*

# 3 Comments to DAAMPM

The treatment-emergent adverse event data show a consistent signal for increased post procedural confusion/visible bruising in patients treated with SABER-bupivacaine. For central nervous system-related adverse events, the data show some moderate imbalance in AEs between SABER-bupivacaine and bupivacaine HCl.

The data quality in this application was relatively poor. We found numerous inconsistencies between datasets and study reports that required IRs, clarifications, and the re-submission of an originally corrupted dataset. These issues do not necessarily imply data integrity issues or imply potential misrepresentations. However, in our opinion, these issues reduce our confidence in the data and the associated conclusions.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA Serial Number:** 204-803/0000

**Drug Name:** Posimir (extended release bupivacaine)

**Indication(s):** Postsurgical analgesia

**Applicant:** Durect Corporation

**Date(s):** Received: April 12, 2013
PDUFA: February 12, 2014

**Review Priority:** Standard – 10 month

**Biometrics Division:** Division of Biometrics II

**Statistical Reviewer:** David Petullo, M.S.

**Concurring Reviewers:** Janice Derr, Ph.D.

**Medical Division:** Division of Anesthesia, Analgesia, and Addiction Products

**Clinical Team:** Medical Officer: Arthur Simone, M.D., Ph.D.
Deputy Division Director: Rigoberto Roca, M.D.

**Project Manager:** Ayanna Augustus

**Keywords:** clinical studies, NDA review, double-blind, foreign clinical data

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## SUMMARY OF REVISIONS

- Page 9. The following sentence regarding subject (b) (6) who was randomized to treatment, Posimir 330 mg, but did not receive study drug was added to the last paragraph. "One subject randomized to Posimir 330 mg did not receive study drug and was excluded from all analysis."

- Page 10. Table 2 was revised. The number of subjects randomized to Posimir 330 mg was 44 not 43. A footnote was added to the table stating that one subject randomized to Posimir 330 mg did not report a value for race.

- Page 11. Corrected a grammatical error in the third paragraph. Sentences 2 and 3 were revised. "Even though LOCF imputation for subjects that discontinued due to an adverse event may not have been appropriate, there were only four subjects that discontinued. This is not an issue." was changed to "Even though LOCF imputation for subjects that discontinued due to an adverse event may not be appropriate, there were only four subjects that discontinued, therefore this was not an issue."

- Page 11. The following two sentences were added to the results and conclusion section. "Note, one subject treated with Posimir 330mg was administered non-allowed rescue medication during surgery and only had one efficacy assessment post-surgery. This subject was excluded from my efficacy analyses."

- Page 15. Corrected a typographical error in the second sentence of the first paragraph. "In Figure 1 there is clear separation between in the curves for both doses of Posimir and placebo out to approximately 24 hours post-surgery." was changed to "In Figure 1 there is clear separation between the curves for both doses of Posimir and placebo out to approximately 24 hours post-surgery."

- Page 15. Corrected a misquoted reference in the third sentence of the first paragraph. "The non-significance of the comparison of Posimir 330 mg to placebo for $AUC_{72}$ was supported by the results observed in Table 6 where nominal statistical significance was only noted out to 12 hours." was changed to "The non-significance of the comparison of Posimir 330 mg to placebo for $AUC_{72}$ was supported by the results observed in Table 7 where nominal statistical significance was only noted out to 12 hours."

- Page 19. The word LSMEANS in the last sentence of the fourth paragraph was changed to LSMEANs

- Page 22. Corrected a typographical error in the second sentence under Statistical Methodologies. "$AUC_{72}$ was to be tested for non-inferiority (NI) to placebo first, it established, superiority of Posimir to placebo would be tested." was revised to "$AUC_{72}$ was to

be tested for non-inferiority (NI) to placebo first, if established, superiority of Posimir to placebo would be tested."

- Page 27. Correct a misquoted value in the second sentence of the first paragraph. The amount of rescue medication used by Posimir was misquoted should have been 13.7 mg not 12.3 mg.

- Page 28. Corrected a typographical error in the last sentence of the second paragraph. "That being said, Posimir was significantly better than placebo for primary endpoints, bupivacaine was not." Was changed to "That being said, Posimir was significantly better than placebo for the primary endpoints, bupivacaine was not."

- Page 29. The sample size for treatment group 5 in Table 18 was misquoted. It should have been 21 not 35.

- Page 29. A typographical error was corrected in the third paragraph. Categorized was misspelled as "catagorized".

- Page 32. In the first sentence of the second paragraph, the sample size for Study BU-001-IM was misquoted. "Of the 119 subjects randomized and treated, 61 Posimir, 27 placebo, and 27 bupivacaine, 117 completed the study." was revised to "Of the 119 subjects enrolled, 114 were randomized and treated, 60 Posimir, 27 placebo, and 27 bupivacaine. Of these 114 subjects, 113 completed the study."

- Page 32-33. In the last paragraph the sample size for Study C803-025 was misquoted. "A total of 393 subjects were screened in order to randomize 331 subjects. Cohort 1 randomized 32 subjects to Posimir and 23 subjects to bupivacaine, Cohort 2 randomized 30 subjects to Posimir and 20 subjects to bupivacaine, and Cohort 3 randomized 140 to Posimir and 86 subjects to placebo." was changed to "A total of 393 subjects were screened in order to randomize 331 subjects. Of these 26 did not receive treatment. Cohort 1 randomized 30 subjects to Posimir and 18 subjects to bupivacaine, Cohort 2 randomized 30 subjects to Posimir and 20 subjects to bupivacaine, and Cohort 3 randomized 129 to Posimir and 78 subjects to placebo."

- Page 33. Corrected a typographical error in the last sentence of the first paragraph. "The applicants' results the primary analysis are shown in Table 20." was changed to "The applicants' results for the primary analysis are shown in Table 20. "

- Page 33. Corrected a typographical error in the third sentence of the second paragraph. "However, the clinical reviewer felt it was inappropriate to pool the data from these two surgical procedures as they clinically different." was changed to "However, the clinical reviewer felt it was inappropriate to pool the data from these two surgical procedures as they were clinically different."

# 1. EXECUTIVE SUMMARY

Durect Corporation has submitted an application evaluating Posimir, a formulation of bupivacaine that contains an extended-release biodegradable matrix that according to the applicant continuously delivers bupivacaine for 72 hours. Continuous wound perfusion with local anesthetics was developed as a method to extend the duration of action resulting in a reduction of pain and decreased opioid consumption. To support the efficacy of Posimir for treating post-surgical pain, the applicant submitted results from seven clinical trials that evaluated various surgical procedures. Of these seven trials, shown in Table 1, two were identified as pivotal. The applicant claims the analyses of the data from these two studies demonstrated a statistically significant treatment effect in favor of Posimir 660 mg. The other five studies failed to report a statistically significant treatment effect.

Based on my review of the data from the two placebo-controlled clinical trials that were identified as pivotal, CLIN-803-0006-06 (hernia repair surgery) and BU-002-IM (arthroscopic shoulder surgery), there is evidence to support the efficacy of Posimir 660 mg in treating post-surgical pain associated with shoulder surgery. However, I did not find substantial evidence to support the efficacy of Posimir in treating post-surgical pain associated with hernia repair.

In Study BU-002-IM, analyses of the primary efficacy endpoints indicated that subjects treated with Posimir 660 mg on average, had less post-surgical pain and consumed less post-surgical opioid medication than subjects treated with placebo. The evidence of an analgesic effect was further supportive by the analyses of secondary endpoints such as time to first use of rescue medication and amount of opioid rescue medication required during the first 72 hours following surgery. This evidence was further supported by two supportive studies, C803-017 and CLIN005-0006, where results suggested, though not statistically significant, that Posimir 660 mg reduced post-surgical pain associated with shoulder surgery and the amount of post-surgical opioid medication required. However, the clinical benefit beyond 12 hours is unclear. When I examined pain intensity scores by time in Study BU-002-IM, Figure 4, the nominal statistical significance between placebo and Posimir 660 mg was only noted out to approximately 12 hours. This early separation in pain scores could impact the significant difference demonstrated in the comparison of the primary endpoint, $AUC_{72}$.

The benefit of Posimir in treating post-surgical pain associated with hernia repair surgery is not so clear. In the study identified as pivotal, Study CLIN-803-0006-06, the primary analyses indicated that subjects treated with Posimir 660 mg on average, had less post-surgical pain and consumed less post-surgical opioid medication than subjects treated with placebo. However, this effect was not observed in a study identified as supportive, CLIN005-0010. In this study, on average, subjects treated with Posimir 660 mg reported more pain than the placebo subjects and they required more opioid rescue medication. The only notable difference between these two studies was that the Study CLIN005-0010 was conducted mainly in the United States whereas Study CIN-803-0006-06 was conducted in Australia and New Zealand. Based on these results, I do not think there is substantial evidence to support the applicant's claim that Posimir is effective in treating post-surgical pain associated with hernia repair.

# 2. INTRODUCTION

## 2.1 Overview

The applicant states that local anesthetics such as bupivacaine are widely administered as analgesics. However, a significant limitation is their short duration of action, typically 4-6 hours. Continuous wound perfusion with local anesthetics was developed as a method to extend the duration resulting in a reduction of pain and decreased opioid consumption. Posimir is a formulation of bupivacaine that contains an extended-release biodegradable matrix that according to the applicant, continuously releases bupivacaine over 72 hours.

The development program for Posimir was conducted under IND 66,086. The Applicant submitted the results of seven active- and placebo-controlled studies to support efficacy, Table 1. The placebo arm in the below studies refers to the extended-release biodegradable matrix without bupivacaine.

**Table 1. Clinical Studies conducted by the applicant**

| Surgical Procedure | Study | Phase | Control | Pivotal or Supportive | Reviewed in Section |
|---|---|---|---|---|---|
| Inguinal hernia | CLIN-803-006-0006 | 2 | placebo | Pivotal | 3.2.1 |
| | CLIN005-0010 | 2 | placebo | Supportive | |
| Arthroscopic shoulder | BU-002-IM | 2 | active/placebo | Pivotal | 3.2.2 |
| | C803-017 | 2b | placebo | Supportive | |
| | CLIN005-0006 | 2 | placebo | Supportive | |
| Major abdominal | 803-025 | 3 | active/placebo | Supportive | 3.2.3 |
| Hysterectomy | BU-001-IM | 2 | active/placebo | Supportive | |

Source: Reviewer

Study CLIN-803-006-0006 (CLIN-803) and Study BU-002-IM (BU-002) were indicated by the applicant as pivotal studies to establish efficacy. It is unclear why these studies were identified as pivotal other than the fact that they demonstrated a significant treatment effect in favor of Posimir. Study CLIN-803 was conducted from June 2007 to October 2007 at five sites in Australia and New Zealand. Study BU-002 was conducted from April 2009 to February 2011 at nine sites in five countries, Austria, Denmark, Germany, Latvia, Poland, and Sweden. The protocols for these studies were not reviewed by FDA.

Studies 803-025, C803-017, CLIN005-0006, CLIN005-0010, and BU-001-IM were indicated as supportive studies. It appears these studies were indicated as supportive as they failed to show a significant treatment effect for Posimir. The protocols for studies CLIN005-0006 and CLIN005-0010 were reviewed by the clinical team in Jan 2006 but were not reviewed by the statistics team. The results from these supportive studies will be presented and discussed following my review of the pivotal studies.

There were several statistical issues discussed between the applicant and the FDA during the IND stage. During an End-of-Phase 2 meeting held on September 14, 2007, the applicant was informed that area-under-curve (AUC) of pain scores would be acceptable as a primary endpoint. However, the endpoint reduction in opioid use by itself may not have clinical significance unless some additional benefit can be demonstrated, such as fewer opioid-related adverse events. Via a written communication dated March 24, 2009, the applicant was advised that the use of ice

should be standardized and it would not be acceptable to include "use of ice" as a covariate in the primary analyses. The applicant was also informed that missing data should be appropriately accounted for in the statistical analysis plan. A subject that discontinues due to an adverse event should not have a good pain score imputed. Further, the use of rescue medication should be accounted for in the primary efficacy analysis. In a pre-NDA meeting held on July 31, 2012, the applicant was told that whether or not the results from the submitted surgical procedures would support a broad indication would be a review issue and the proposed indication, "extended relief of post-surgical pain," would not be acceptable. Further, it was pointed out that it was not clear that the pivotal studies accounted for the use of rescue medication in the primary efficacy analyses.

### 2.2 Data Sources

All data was supplied electronically by the Applicant as SAS transport files and can be found at the following location in the CDER electronic document room (EDR):

**\\Cdsesub1\EVSPROD\NDA204803\0000\m5\datasets**

## 3. STATISTICAL EVALUATION

Studies CLIN-803 and BU-002 evaluated pain associated with different surgical procedures, hernia repair and arthroscopic shoulder surgery, respectively. These procedures are evaluated separately under Sections 3.2.1 and 3.2.2. Two supportive studies that evaluated pain associated with hysterectomy and major abdominal surgeries are discussed in Section 3.2.3.

### 3.1 Data and Analysis Quality

The electronic data submitted by the Applicant for the two pivotal studies was of sufficient quality to allow a thorough review of the data. I was able to derive the primary and secondary endpoints for each study. The statistical analyses of my derived endpoints were in agreement with the Applicant's analyses.

The Office of Scientific Investigation did not identify any significant issues during the audits of the sites from two studies identified as pivotal.

### 3.2 Evaluation of Efficacy

My review focuses on the studies, pivotal and supportive, submitted to support post-surgical pain associated with hernia repair and shoulder surgery. For each procedure, I thoroughly review the pivotal study and then present the results of the failed supportive studies. Following my review of the individual studies, I present the combined results from both the pivotal and supportive studies and then give my overall conclusion for each procedure.

#### 3.2.1 Inguinal Hernia Repair

##### 3.2.1.1 Pivotal Study

In the study indicated as pivotal, CLIN-803, the applicant appropriately addressed my major concern regarding the use of rescue medication and the need to account for its use when deriving

the primary endpoint, AUC of pain scores out to 72 hours post-surgery. The applicant addressed this concern in a sensitivity analysis.

**Study Design and Endpoints**

Eligible patients that were to undergo an open unilateral tension free Lichtenstein-type inguinal hernia repair were randomized to one of four treatments: Posimir 2.5 mL (330 mg), Posimir 5.0 mL (660 mg), placebo 2.5 mL, or placebo 5.0 mL. This study was conducted in two cohorts. Cohort 1 comprised of the Posimir and placebo administered as 2.5 mL and the second cohort comprised of Posimir and placebo administered as 5.0 mL. Following surgery, a single dose of the study drug was instilled gradually throughout the inguinal canal and the abdominal wall layers to cover all raw surfaces of the wound, filling the subaponeurotic and subcutaneous spaces. Rescue analgesia for break-through pain was allowed upon request. Post-operative efficacy assessments included pain intensity (PI) at rest and during bowel movement, use of rescue medication, time of first bowel movement, post-operative nausea and vomiting, and occurrence of constipation. PI was assessed using an 11-point scale with 0 being no pain and 10 the worst pain and was measured at baseline (prior to surgery), end of general anesthesia, before first dose of rescue medication, and at 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after surgery.

The applicant pre-specified two primary efficacy outcomes; AUC of PI scores out to 72 hours post-surgery ($AUC_{72}$) and the proportion of subjects receiving opioid rescue medication through Day 15. The primary null hypotheses to be tested by the applicant were no difference between treatment groups in terms of AUC and opioid rescue use. The applicant estimated that a sample size of 120 subjects or 60 per cohort would provide 90% power to detect an effect size 0.67 for the difference in $AUC_{72}$. Post-hoc, the applicant changed the proportion of subjects using rescue through Day 15 to Day 3 or 72 hours. The rationale for this change was that 72 hours post-surgery was the time frame utilized for the other primary endpoint, $AUC_{72}$. A pre-specified secondary endpoint was amount of rescue medication used through 72 hours in morphine equivalents, $RES_{72}$. The time to first use of rescue medication was also evaluated.

**Patient Disposition, Demographic and Baseline Characteristics**

This study screened 135 subjects in order to randomize 124 eligible subjects; 32 placebo, 45 Posimir 330 mg, and 47 Posimir 660 mg. One subject randomized to Posimir 330 mg did not receive study drug and was excluded from all analysis. Demographics for all randomized and treated patients are shown in Table 2.

**Table 2. Demographics for Study CLIN-803**

| Characteristic | Treatment | | |
|---|---|---|---|
| | placebo | Posimir 330 mg* | Posimir 660 mg |
| Number of Patients (n) | 32 | 44 | 47 |
| Age in years | | | |
| Mean (SD) | 50 (9) | 46 (12) | 49 (13) |
| Median | 52 | 48 | 50 |
| [range] | [28, 65 ] | [20, 68] | [21, 79] |
| Gender (%) | | | |
| Female | - | 2 (5) | 2 (4) |
| Male | 32 (100) | 42 (95) | 45 (96) |
| Race (%) | | | |
| Caucasian | 30 (94) | 41 (95) | 46 (98) |
| Black | 1 (3) | - | - |
| Multiple | 1 (3) | 2 (5) | - |
| Other | - | - | 1 (2) |

*One subject randomized to Posimir 330 mg did not report race.
Source: Reviewer

This study comprised of mostly male Caucasian subjects with a mean age of approximately 50 years old and was evenly distributed between treatment arms. There were four subjects that did not complete the study, three in the Posimir 330 mg arm and one in the placebo arm. Reasons for discontinuation are shown in Table 3.

**Table 3. Disposition of subjects in Study CLIN-803**

| Reason for Discontinuation | Placebo | Posimir 330 mg | Posimir 660 mg |
|---|---|---|---|
| Multiple surgeries | - | 1 | - |
| Patients best interest | - | 1 | - |
| Underwent surgery for preexisting condition | 1 | - | - |
| Non-allowed medication | - | 1 | - |

Source: Reviewer

Even though these subjects discontinued the study, there was efficacy data for these subjects as they discontinued after 72 hours.

### Statistical Methodologies

The analysis dataset defined by the applicant was all randomized subjects who successfully underwent the surgical procedure without any major deviations. An AUC, similar to a time-weighted average, was calculated for each patient using PI scores measured at 1, 2, 3, 4, 6, 8, and 12 hours following surgery on Day1 and at 8 AM, 12 PM, 4 PM, and 8 PM on Days 2 and 3. This AUC was normalized for each subject by dividing the AUC by 72 hours. This represents the average PI over 72 hours. Missing PI scores were handled as follows.

- If a patient withdrew from the study prior to 72 hours, the last recorded pain score was carried forward (LOCF)

- If a pain measurement was not recoded for a specific visit, the previous maximum pain score was used for the first missing value and any subsequent missing values.

The applicant conducted a sensitivity analysis to examine use of rescue medication. When a scheduled pain score was assessed within one half-life of the rescue medication and the pain score measured prior to using rescue medication was higher, the scheduled pain score was replaced with the rescue pain score. Any missing rescue pain scores were imputed using the worst observation carried forward (WOCF). Half-lives of 5.5, 2, and 4 hours were assumed for tramadol, morphine, and oxycodone, respectively.

The $AUC_{72}$ for each dose of Posimir was compared to placebo using an analysis of variance (ANOVA) model with treatment and site as main effects. It was pre-specified that the placebo groups would be pooled. Dunnett's adjustment was used to account for two comparisons to placebo. The proportion of subjects using rescue medication through Day 3 and Day 15 were compared between treatment arms using a Cochran Mantel Haenszel (CMH) test. To account for the second primary endpoint, a step-down approach was used. If the comparison of $AUC_{72}$ was statistically significant then the proportion of subjects using rescue was tested. The results for $RES_{72}$ were compared between treatment groups using a Wilcoxon rank-sum (WRS) test. Time to first post-operative use of rescue medication was analyzed using Kaplan-Meier methods. A log-rank test was used to compare the survival curves between both doses of Posimir and placebo, and the median time to first use of rescue medication was reported. To account for the two comparisons of Posimir to placebo, I utilized the Sidak adjustment. The Sidak adjustment is slightly more powerful than the Bonferroni adjustment and assumes the individual tests are independent.

Overall, the statistical methodologies utilized by the Applicant for the analyses of the primary and secondary efficacy outcomes were acceptable. Even though LOCF imputation for subjects that discontinued due to an adverse event may not have been appropriate, there were only four subjects that discontinued, therefore it was not an issue. The hypotheses posed by the applicant seemed to indicate that a statistical win would be required for each primary endpoint, $AUC_{72}$ and proportion of subjects using rescue medication. However, with the sequential testing strategy utilized, $AUC_{72}$ was tested first. This would allow for a win on $AUC_{72}$ but not on proportion of subjects using rescue medication.

**Results and Conclusions**

A summary of the applicant's primary analysis and mine for $AUC_{72}$ are shown in Table 4. Both analyses account for missing pain scores and rescue medication. Note, one subject treated with Posimir 330mg was administered non-allowed rescue medication during surgery and only had one efficacy assessment post-surgery. This subject was excluded from my efficacy analyses.

**Table 4. Results from analysis of normalized AUC in Study CLIN-803**

| | Normalized $AUC_{72}$ (PI) - mean (SEM) | | |
|---|---|---|---|
| | Placebo (n=32) | Posimir 330 mg (n=43) | Posimir 660 mg (n=47) |
| Applicant | 3.6 (0.3) | 3.1 (0.3) | 2.5 (0.2) |
| Reviewer | 4.0 (0.3) | 3.3 (0.3) | 2.7 (0.2) |

Source: Reviewer

The point estimates for the difference in LSMEANs between the two doses of Posimir and placebo from my analysis are shown in Table 5. I also present the corresponding 95% confidence intervals (CI) for the difference and associated p-values for the comparison to placebo.

**Table 5. Comparison of Posimir to placebo in Study CLIN-803**

| treatment | Difference | 95 % CI | p-value |
|---|---|---|---|
| Posimir 330 mg | -0.8 | [-1.6, 0.5] | 0.1 |
| Posimir 660 mg | -1.4 | [-2.1, -0.6] | 0.001 |

Source: Reviewer

Note, the AUCs and p-values in my analyses were slightly different from the applicant, although minor. These differences are most likely due to how I handled the use of rescue medication and missing data. I discuss this below. Regardless, my analysis agrees with the applicant: there was a significant difference noted for Posimir 660 mg versus placebo but not for the 330 mg dose.

As an AUC is cumulative and derived from the PI scores measured at each time point, I examined subject level data for missing pain scores. Based on the electronic data submitted by the Applicant, missing data due to discontinuation was not an issue. This was not unexpected as the study was conducted in an inpatient setting and patients only received a single dose of treatment. However, there were some intermittent missing pain scores. The amount of missing data is shown in Table 6.

**Table 6. Missing pain assessments in Study CLIN-803**

| Time-point (hours post-dose) | Number of missing observations (%) | | | |
|---|---|---|---|---|
| | Placebo (n=32) | Posimir 330 mg (n=43) | Posimir 660 mg (n=47) | Combined (n=122) |
| 1 | 3 (9.4) | 1 (2.3) | - | 4 (3.3) |
| 2 | 1 (3.1) | - | 1 (2.1) | 2 (1.6) |
| 3 | - | - | - | - |
| 4 | 1 (3.1) | 1 (2.3) | - | 2 (1.6) |
| 6 | 3 (9.4) | 2 (4.7) | 2 (4.3) | 7 (5.7) |
| 8 | 2 (6.3) | - | 2 (4.3) | 4 (3.3) |
| 10 | 2 (6.3) | 1 (2.3) | 4 (8.5) | 7 (5.7) |
| 12 | 6 (18.8) | 4 (9.3) | 2 (4.3) | 12 (9.8) |
| 22 | 4 (12.5) | - | - | 4 (3.3) |
| 26 | 3 (9.4) | 1 (2.3) | 2 (4.3) | 6 (4.9) |
| 30 | 2 (6.3) | 3 (7.0) | - | 5 (4.1) |
| 34 | 2 (6.3) | - | 1 (2.1) | 3 (2.5) |
| 46 | 2 (6.3) | 2 (4.7) | 4 (8.5) | 8 (6.6) |
| 50 | 2 (6.3) | 1 (2.3) | 4 (8.5) | 7 (5.7) |
| 54 | 4 (12.5) | 3 (7.0) | 2 (4.3) | 9 (7.4) |
| 58 | 1 (3.1) | 2 (4.7) | 3 (6.4) | 6 (4.9) |
| 70 | - | 1 (2.3) | 2 (4.3) | 3 (2.5) |

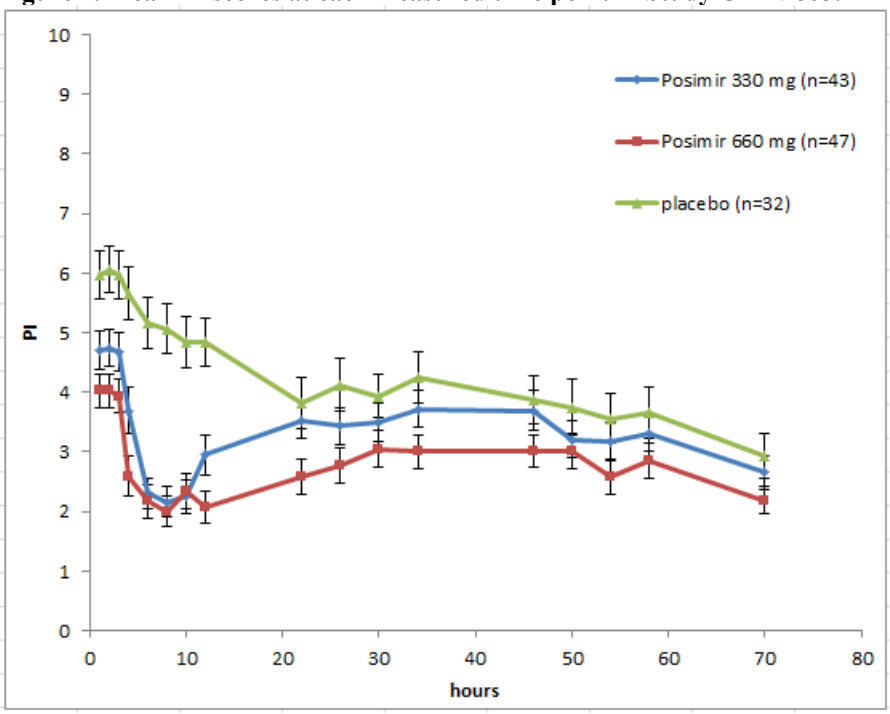
Source: Reviewer

Missing PI scores were less than 10% at all measured time points, with the most missing data being at 12 hours post-surgery. This was not unexpected as it would be the most inconvenient time point to collect. As missing data was fairly low and this was an inpatient study with a single administration of study drug, I decided it was acceptable to use WOCF for missing PI scores when deriving the AUC for each subject. This is in contrast to the applicant who used LOCF.

Next, I accounted for the use of rescue medication. When I only considered medication coded as rescue in the applicant's dataset, there were 511 uses of tramadol and oxycodone. However, when I expanded this to include concomitant medication and surgery medication, there were 714 uses of opioids which included fentanyl, morphine, oxycodone, tramadol, and codeine. In my derivation of $AUC_{72}$ I considered all opioid medication regardless of how classified. If a patient received rescue at time $x$, for any time point within $x + 4$ hours, the highest score from time 0 up until time $x$ was used. If the PI score for the windowed observation was higher than the worst observed score, it was not replaced. I did not consider 592 uses of APAP, although I did examine its use in an exploratory analysis and did not note any significant differences between treatment groups. I discuss this in more detail below.

Using the above methods for missing PI scores and use of rescue medication, the mean PI scores for each treatment group by time are shown in Figure 1. Error bars indicate the 95% CI of the point estimate.

**Figure 1. Mean PI scores at each measured time point in Study CLIN-803.**




Source: Reviewer

I compared each dose of Posimir to placebo at each time point using the same ANOVA model utilized in primary analysis. However, as this was exploratory I did not adjust for multiplicity. Results are shown in Table 7.

**Table 7. Comparisons of PI scores at assessed time point in Study CLIN-803**

| | Difference from placebo (PI) | | | | | |
|---|---|---|---|---|---|---|
| Time point (hrs) | Posimir 330 mg (n=43) | | | Posimir 660 mg (n=47) | | |
| | mean | stder | p-value | mean | stder | p-value |
| 1 | -1.3 | 0.5 | 0.01 | -1.9 | 0.5 | < 0.0001 |
| 2 | -1.3 | 0.5 | 0.01 | -2.0 | 0.5 | < 0.0001 |
| 3 | -1.3 | 0.5 | 0.01 | -2.0 | 0.5 | < 0.0001 |
| 4 | -2.0 | 0.5 | <0.0001 | -2.0 | 0.5 | <0.0001 |
| 6 | -2.9 | 0.5 | <0.0001 | -3.0 | 0.5 | <0.0001 |
| 8 | -2.9 | 0.5 | <0.0001 | -3.0 | 0.5 | <0.0001 |
| 10 | -2.6 | 0.5 | <0.0001 | -2.5 | 0.5 | <0.0001 |
| 12 | -1.9 | 0.5 | 0.0002 | -2.8 | 0.5 | <0.0001 |
| 22 | -0.3 | 0.5 | 0.6 | -1.2 | 0.5 | 0.01 |
| 26 | -0.7 | 0.5 | 0.2 | -1.4 | 0.5 | 0.007 |
| 30 | -0.4 | 0.5 | 0.4 | -0.9 | 0.5 | 0.06 |
| 34 | -0.5 | 0.5 | 0.3 | -1.3 | 0.5 | 0.01 |
| 46 | -0.2 | 0.5 | 0.7 | -0.9 | 0.5 | 0.07 |
| 50 | -0.5 | 0.5 | 0.3 | -0.7 | 0.5 | 0.2 |
| 54 | -0.4 | 0.5 | 0.5 | -1.0 | 0.5 | 0.04 |
| 58 | -0.4 | 0.5 | 0.5 | -0.8 | 0.5 | 0.1 |
| 70 | -0.3 | 0.4 | 0.5 | -0.7 | 0.4 | 0.7 |

Source: Reviewer

The results presented in Figure 1 and Table 7 may help with the clinical interpretation of the effect size observed with the primary endpoint, $AUC_{72}$. In Figure 1 there is clear separation between the curves for both doses of Posimir and placebo out to approximately 24 hours post-surgery. The non-significance of the comparison of Posimir 330 mg to placebo for $AUC_{72}$ was supported by the results observed in Table 7 where nominal statistical significance was only noted out to 12 hours. On the other hand, nominal significance for Posimir 660 mg versus placebo was noted out to approximately 24 hours and the comparison to placebo for $AUC_{72}$ was statistically significant. It should be noted that for both doses of Posimir, the separation from placebo during hours 24 − 72 was not the same magnitude observed during hours 0 − 24. Hence, the significant difference demonstrated in the comparison of $AUC_{72}$ for the Posimir 660 mg arm may be influenced by the early separation in the pains curves.

The results from the proportion of subjects using rescue medication through Day 3 and Day 15 are shown in Tables 8 and 9.

**Table 8. Percent of subjects using opioid rescue medication through Day 15 in Study CLIN-803**

| Treatment | n | Opioids coded as rescue | All Opioids |
|---|---|---|---|
| Placebo | 32 | 72 | 72 |
| Posimir 330 mg | 43 | 65 | 74 |
| Posimir 660 mg | 47 | 49* | 53 |

*p-value=0.04
Source: Reviewer

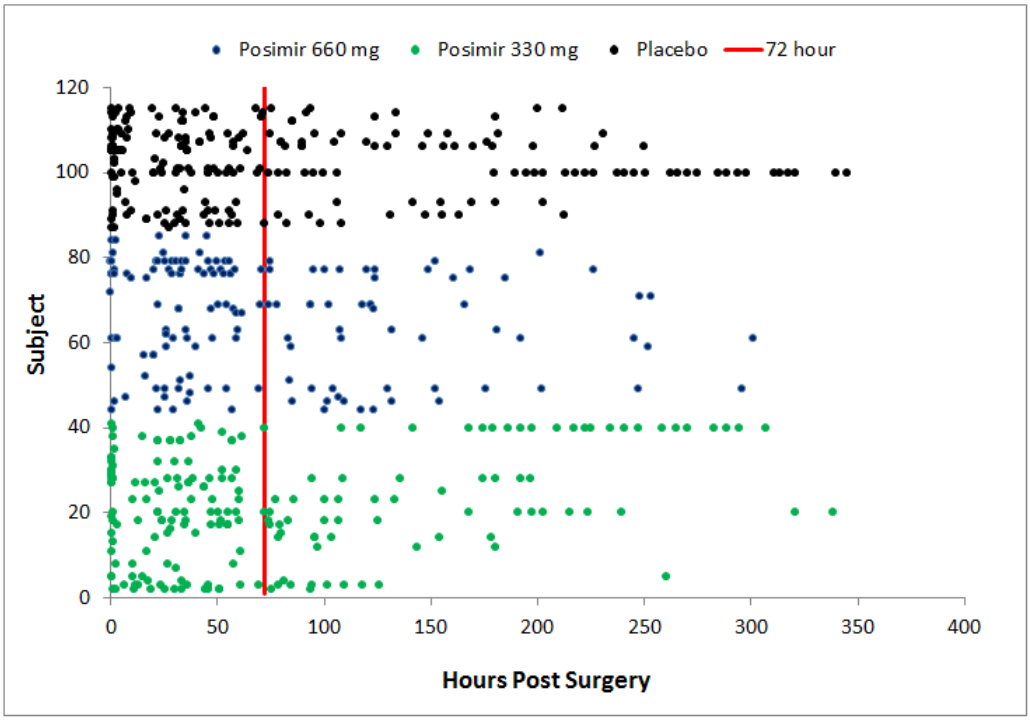
**Table 9. Percent of subjects using opioid rescue medication through Day 3 in Study CLIN-803**

| Treatment | n | Opioids coded as rescue | All Opioids |
|---|---|---|---|
| Placebo | 32 | 72 | 72 |
| Posimir 330 mg | 43 | 63 | 72 |
| Posimir 660 mg | 47 | 49* | 51 |

*p-value=0.04
Source: Reviewer

Regardless of duration, Day 3 or Day 15, when I examined only opioids coded as rescue there was a significant difference noted between placebo and Posimir 660 mg for the percentage of subjects using rescue medication, p-value=0.04. However, when I considered all opioids, not just those coded as rescue, there was no longer a significant treatment effect. Further, regardless of how opioids were coded, I noticed there was very little difference in the results from Day 3 versus Day 15. To explore this, I present subject level use of rescue opioids in Figure 2. I present the data for all opioids regardless of classification. The reference line indicates the 72 hour time point.

**Figure 2. Subject level use of rescue medication after study drug administration in Study CLIN-803**




Source: Reviewer

In Figure 2, if a subject used rescue medication, they used early and often. Hence there was very little difference between the percentages of subjects using through Day 3 versus Day 15.

I also examined the amount of opioid rescue medication (mg morphine equivalent) consumed through 72 hours post-surgery, $RES_{72}$. While not a pre-specified primary endpoint, I considered $RES_{72}$ to be a clinically relevant endpoint. Further, this was a co-primary endpoint in Study BU-002. Medications were converted to morphine equivalents using the conversion table provided by the applicant. It was pre-specified that results would be compared using an ANOVA model with treatment and site if the assumptions of normality and heterogeneity of variance were met. If these assumptions were violated, a non-parametric test would be used. In my analysis and the applicant's these assumptions were violated. A plot of the residuals indicated the data was left skewed and a test for homogeneity of the variance was rejected, p-value < 0.001. Therefore a non-parametric test, Wilcoxon Rank Sum (WRS) test was utilized. Results are shown in Table 10.

**Table 10. Amount of rescue medication consumed through 72 hours post-surgery in Study CLIN-803**

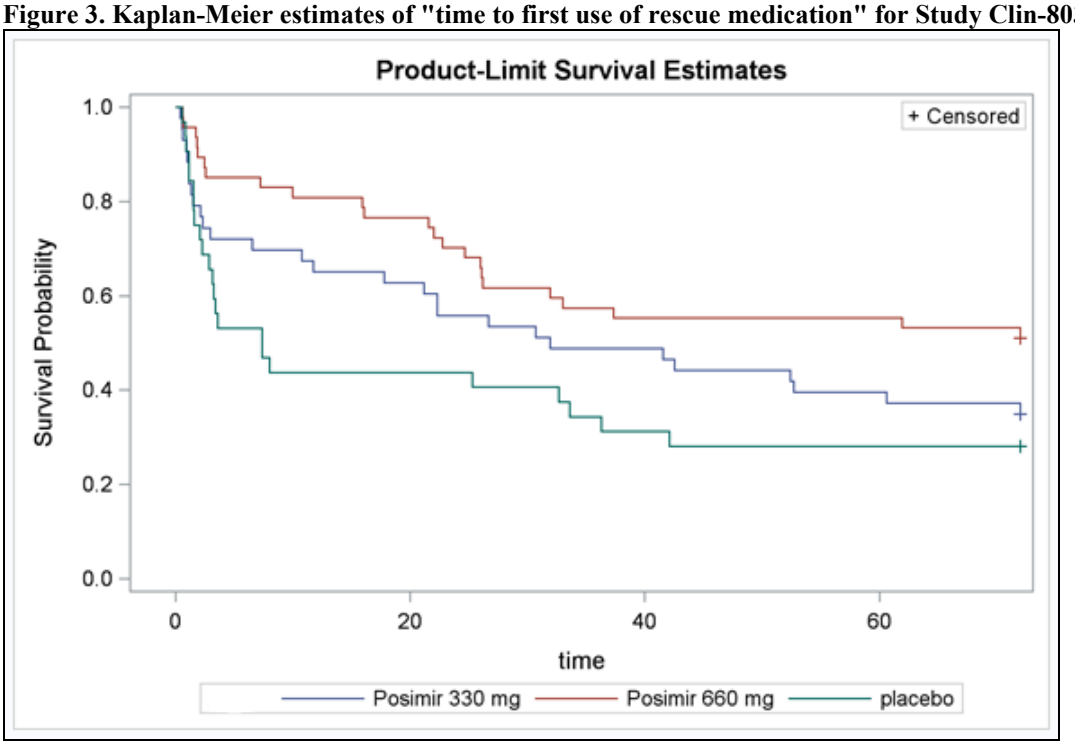
| Treatment | Morphine Equivalent (mg) mean (stdev) | p-value |
|---|---|---|
| Placebo (n=32) | 29.9 (57.6) | - |
| Posimir 330 mg ( n=43) | 13.1 (14.1) | 0.05 |
| Posimir 660 mg (n=47) | 10.4 (13.1) | < 0.01 |

Source: Reviewer

There was a significant difference noted for the comparison of placebo to Posimir 660 mg, p-value < 0.01. However, the comparison of placebo to Posimir 330 mg was borderline significant at the 0.05 level. Regardless of dose, the use of Posimir reduced the amount of opioid medication consumed.

Next I examined the time to first use of rescue medication. In this analysis I considered all post-operative opioids not just those coded as rescue medication. A subject was considered censored if they did not use rescue medication prior to 72 hours post-surgery. The median time to first use of post-operative rescue medication was 7.4 hour hours in the placebo arm, 31.9 hours in Posimir 330 mg, and 72 hours in the Posimir 660 mg treatment arm. Using Kaplan-Meier methods, the survival curves for time to first use of rescue medication for each treatment arm are shown in Figure 3.

**Figure 3. Kaplan-Meier estimates of "time to first use of rescue medication" for Study Clin-803**




Source: Reviewer

Based on the log-rank test adjusted for the two comparisons, a significant difference exists in the distributions of time to first use of rescue medication between Posimir 660 mg and placebo, p-value=0.02 However, the was not a significant difference noted between Posimir 330 mg and placebo, p-value=0.7.

Even though my examination for use of rescue medication did not include approximately 600 uses of APAP, I did explore its use. The percentage of subjects using APAP was similar amongst treatment arms. Approximately 78, 77, and 55 percent of subjects used APAP in the placebo, Posimir 330 mg, and Posimir 660 mg arms, respectively. The average amount of APAP consumed during the first 72 hours post-treatment was also similar between treatment arms; 2.9, 2.8, 2.3 grams for the placebo, Posimir 330 mg, and Posimir 660 mg, respectively. Based on this

information, I decided it was acceptable to exclude the use of APAP from my analyses of rescue medication.

During my exploration of the data for use of rescue medication, I also noted that there was considerable use of medication that could be classified as rescue medication prior to study drug administration. The majority of medication used was fentanyl and morphine and most subjects were involved. In fact only three subjects did not use; two in the placebo arm and one in the Posimir 330 mg arm. The amount of medication in morphine equivalent daily doses was 4.2 mg, 3.1 mg, and 3.4 mg, in the placebo, Posimir 330 mg, and Posimir 660 mg arms, respectively. There were no significant differences noted. Even though pre-treatment use of rescue type medication was not considered in determining the percentage of subjects who used post-treatment rescue medication or amount of post-operative rescue medication, I did consider it when deriving $AUC_{72}$ as it could have influenced the 1 and 2 hour pain assessments. There did not appear to be a difference between treatment arms in the frequency or amount of "rescue" medication used pre-treatment. Further, based on discussions with the medical officer, this use of rescue medication is typical for this type of surgery.

In summary, in this study there was a significance difference noted between placebo and Posimir 660 mg for the first primary endpoint, $AUC_{72}$. This difference was supported when I examined the mean PI scores by time, Figure 1. However, the magnitude of the separation between the curves for placebo and Posimir is diminished after 24 hours. There was no difference noted between Posimir 330 mg and placebo for $AUC_{72}$. For the second primary endpoint, proportion of subjects using rescue medication, when I examined all rescue medication, not just medication coded as rescue, there was not a significant difference between placebo and either dose of Posimir although numerically the numbers were in favor of Posimir. When I examined the amount of rescue medication consumed, $RES_{72}$, there was a significant difference noted in favor of Posimir 660 mg versus placebo but not Posimir 330 mg. This was supported by my analysis of time to first use of rescue medication. Subjects treated with Posimir 660 mg, on average reported less post-surgical pain, required less rescue medication, and waited longer to request it.

#### 3.2.1.1 Supportive Studies

The Applicant submitted the results of a phase 2 trial that evaluated Posimir in subjects undergoing hernia repair surgery, Study CLIN005-0010. The study design and results are presented below. This study failed to show a significant treatment benefit of Posimir in treating post-surgical pain associated with hernia repair surgery.

This was a randomized double-blind, placebo-controlled phase 2 study that evaluated Posimir administered subcutaneous and subaponeurotic to subjects following open hernia repair surgery and was conducted in two cohorts. Subjects were enrolled at seven sites in the United States (California, New York, Pennsylvania, Utah, and Wisconsin) and one site in New Zealand. In Cohort 1, subjects were randomized to one of three treatment arms. In treatment arm 1, placebo was injected into the subaponeurotic space and Posimir 660 mg was administered subcutaneously along the incision line after wound closure. In treatment arm 2, Posimir 660 mg was administered into the subaponeurotic space and placebo was administered subcutaneously along the incision line. In treatment arm 3, placebo was administered in both locations. For Cohort 2, placebo or Posimir 660 mg was instilled into the surgery site prior to wound closure,

treatment arms 4 and 5, respectively. One subject in treatment arm 5 was administered 7.5 mL Posimir (990 mg).

The primary efficacy endpoints were PI at rest and on movement and pain control as assessed by the subject. PI was assessed using an 11-point NRS and pain control was evaluated using a 5-point scale. For pain control subjects were asked "How would you rate your overall pain control in the last 24 hours?" Responses were poor, fair, good, very good, or excellent. The pre-specified primary endpoints were PI and pain control on Days 0 through 7. For subjects that required supplemental analgesia, pain scores on movement were recoded prior to use. Via a protocol amendment, the primary endpoint was changed to a normalized AUC of PI scores for at rest and on movement at 120 hours post-surgery and were compared between treatment arms using an ANOVA model where the comparison of interest was treatment arm 5 versus pooled placebo, treatment arms 3 and 4. Missing data was imputed using LOCF for monotonic missingness and intermittent missing scores used the average of adjacent scores. The applicant also conducted a sensitivity analysis where pain scores prior to using rescue medication was used in the derivation of the AUC.

The analysis population consisted of all randomized and treated subjects. The number of subjects per treatment arm is shown in Table 11.

**Table 11. Number of subjects per treatment arm in Study CLIN005-0010**

| Treatment Number | Description | Number of subjects randomized and treated |
|---|---|---|
| 1 | Placebo subaponeurotic 5 ml + Posimir SC 5 mL | 14 |
| 2 | Placebo SC 5 mL + Posimir subaponeurotic 5 mL | 13 |
| 3 | Placebo SC 5 mL + Placebo subaponeurotic 5 mL | 18 |
| 4 | Placebo subaponeurotic 5 mL | 21 |
| 5 | Posimir subaponeurotic 5 mL | 22 |
| 5a | Posimir subacromial 7.5 mL | 1 |

SC=subcutaneous
Source: Reviewer

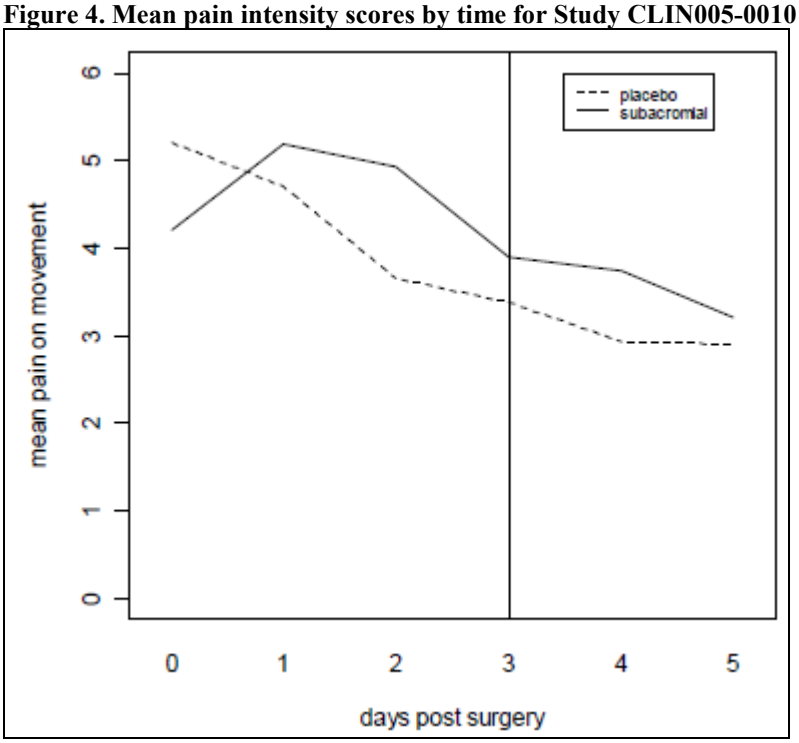
Of the 89 subjects that were randomized and treated, 86 completed the study. There were three subjects that were lost to follow-up, two on active drug and one on placebo. This study mostly evaluated male Caucasian subjects. There were five female subjects randomized, two Asian subjects, one African American subject, and four classified as other. The average age in years was 48 with a range of 21 to 89. The analysis population consisted of all randomized and treated subjects.

The only comparison that demonstrated statistical significance in favor of Posimir was treatment group 5 versus pooled placebo. However, AUC at 120 hours post-surgery was not the endpoint examined in the pivotal study, CLIN-803-006-0006 and the two placebo groups received different volumes of study drug. To compare the results of this study to the pivotal study, I compared mean $AUC_{72}$ for treatment groups 4 and 5 as these treatment arms received the same volume of study drug administered in the pivotal study. The LSMEANs were 4.1 and 4.8 for placebo and Posimir, respectively. The 95% CI for the difference between Posimir and placebo

was [-0.5, 0.8]. The point estimate 0.6, while not significant, was in favor of placebo. This analysis accounted for the use of rescue medication by incorporating pain scores measure prior to using rescue medication when deriving the AUC. Even though this study used LOCF for discontinuations due to AE's they were only two dropouts and none were attributable to an AE.

I next examined the PI scores that were used to generate the AUC's reported above. The pain intensity scores by time are shown in Figure 4. The solid vertical line indicates the 72 hour time point. The solid line in the figure represents Posimir 660 mg, indicated as subacromial in the legend. Note, there is no subacromial space in the abdominal cavity.

**Figure 4. Mean pain intensity scores by time for Study CLIN005-0010**



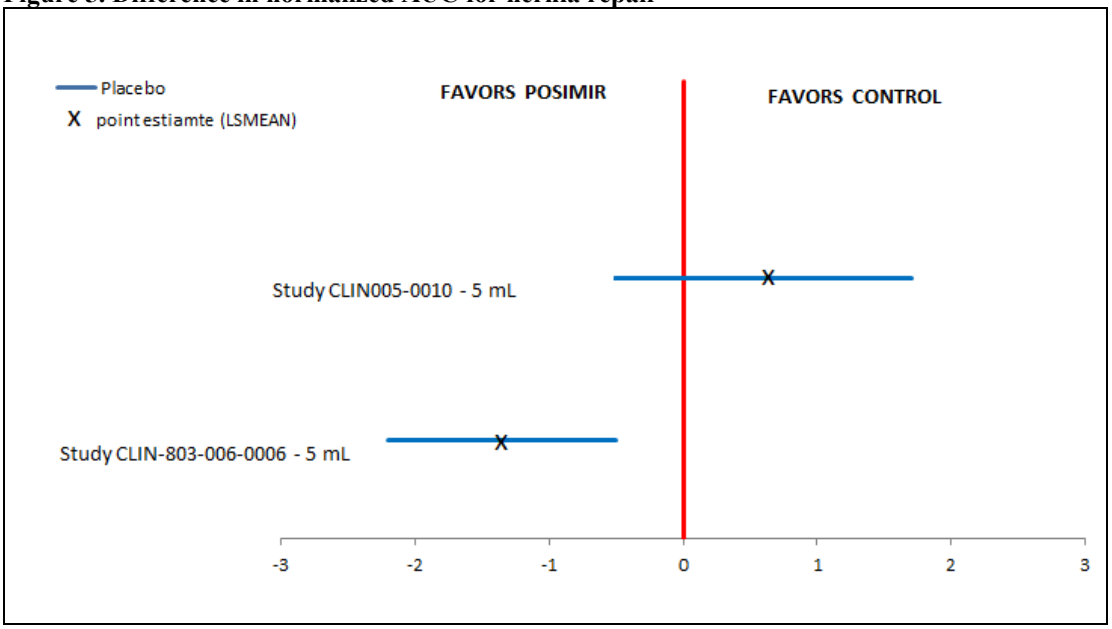

Source: Figure 3 from applicant's CSR

Clearly, the mean pain scores for the Posimir 660 mg treatment arm increased during the first 24 hours. This effect was not observed in the placebo arm. The clinical rationale for this effect is unknown.

Since the point estimate for the difference in $AUC_{72}$ was in the wrong direction, I examined the amount of rescue medication consumed through 72 hours for treatment arms 4 and 5. Results, even though not significant, indicate that subjects in the placebo arm, on average used less rescue medication than subjects in the Posimir 660 mg arm. It seems for this study, placebo subjects had less post-surgical pain and used less rescue medication. There were no differences in the demographics between studies except that this study was mainly conducted in the United States, whereas the successful study was conducted in Australia and New Zealand.
Further examination of these results by site location, United States versus Australia and New Zealand, did not reveal any significant findings. In general the mean $AUC_{72}$ for the Posimir treatment arm was higher than the placebo arm.

I summarize the results of $AUC_{72}$ for the two studies that evaluated post-surgical pain associated with hernia repair surgery. Figure 5 shows the point estimates and 95% CI for difference from placebo for $AUC_{72}$. Note, the 5 mL dose is equal to 660 mg of Posimir.

**Figure 5. Difference in normalized AUC for hernia repair**




Source: Reviewer

I consider these results to be inconclusive. It seems that for the failed supportive study, placebo subjects had less post-surgical pain and used less rescue medication. The only notable difference in demographics between these two studies was the location. The failed study was mainly conducted in the United States, whereas the successful study was conducted in Australia and New Zealand.

## 3.2.2 Arthroscopic Shoulder Surgery

### 3.2.2.1 Pivotal Study

Study BU-002 was identified as pivotal by the applicant. Of the statistical issues identified during IND stage, the applicant addressed my concern regarding use of rescue medication and accounting for it the primary analysis. The applicant conducted a sensitivity analysis where use of rescue medication was accounted for in analysis.

Based on the results of a previous trial in subjects undergoing hernia repair surgery, the applicant estimated 25 placebo subjects and 50 Posimir 660 mg subjects would provide 80% power to detect a significant difference in morphine equivalent doses of 0.6 mg. Additionally, 25 subjects on standard release Bupivacaine were included.

### Study Design and Endpoints

Eligible patients that were to undergo arthroscopic shoulder surgery were randomized to placebo, Posimir 660 mg, or bupivacaine in a 1:2:1 fashion. Following surgery, a single dose of the study drug was administered into the subacromial space. Subjects remained in the hospital at least 48 hours following surgery. Allowed rescue medication during the first 72 hours following surgery was oral morphine and if needed, IV morphine. Since standard bupivacaine and Posimir are different in appearance, dosed at different volumes, and administered differently, a non-blinded surgery team performed the procedure and administered study drug. All other staff involved in post-treatment assessments were blinded. PI was measured (11-point NRS) at 1, 2, 4, 6, 8, and 12 hours post-treatment (Day 0) and at 8:00, 12:00, 16:00, 20:00 on Days 1-7. Subjects were *not* instructed to measure PI scores prior to using rescue medication.

### Patient Disposition, Demographic and Baseline Characteristics

Overall, 126 subjects were screened and 115 were randomized. Eight randomized subjects discontinued prior to surgery and did not receive treatment. Demographics for randomized and treated subjects are shown in Table 12.

**Table 12. Patient demographics for Study BU-002**

| Characteristic | Treatment | | |
|---|---|---|---|
| | placebo | Posimir 660 mg | bupivacaine |
| Number of Patients | 25 | 53* | 29 |
| Age in years | | | |
| Mean (SD) | 49 (10) | 50 (9.5) | 52 (11) |
| Median | 52 | 49 | 52 |
| [range] | [24, 63 ] | [28, 70] | [21, 70] |
| Gender, n (%) | | | |
| Female | 14 (56) | 33 (62) | 17 (59) |
| Male | 11 (44) | 20 (38) | 12 (41) |
| Race, n (%) | | | |
| Caucasian | 24 (96) | 50 (98) | 29 (100) |
| Black | - | - | - |
| Asian | 1 (4) | 1 (2) | - |
| Other | - | - | - |

*2 subjects missing response for race
Source: Reviewer

There were slightly more females than males which was consistent amongst the three treatment arms. The study mainly evaluated Caucasian subjects and as expected, there were no subjects that discontinued from the study.

### Statistical Methodologies

The applicant identified two primary endpoints, $AUC_{72}$ and the amount of opioid rescue medication in morphine equivalent doses used through 72 hours, $RES_{72}$. $AUC_{72}$ was to be tested for non-inferiority (NI) to placebo first, if established, superiority of Posimir to placebo would be tested. The rationale given was that the use of rescue medication may dilute the treatment effect and superiority may not be established. NI was to be declared if the upper limit (UL) for the 95% confidence interval (CI) for the difference between the $AUC_{72}$ for Posimir and placebo was less than or equal to 0.5. Superiority would be tested using an ANOVA model with treatment and pooled country as factors. Rescue medication consumed during the first 72 hours following

treatment was converted to morphine equivalent doses (mg) using the conversion table provided by the sponsor. Results for $RES_{72}$ would be compared between placebo and Posimir using an ANOVA model with treatment and site as effects. If the assumptions of normality and homogeneous variance were not met, a non-parametric test would be used. There would be no formal comparison between Posimir and standard bupivacaine; hence no adjustments for multiplicity were incorporated into the analysis.

This study did not instruct subjects to measure pain scores prior to using rescue medication. To account for this, the applicant proposed a post-hoc sensitivity analysis based on FDA's advice. In this analysis, if a subject used rescue medication on or before a scheduled assessment, within one half-life of the rescue drug, the rescue pain score was considered to be the worst pain score observed prior to its use. This is analogous to worst observation carried forward (WOCF). I took a slightly different approach. Instead of using WOCF when subject used rescue medication, I randomly assigned each subject a moderate pain score, a score 5, 6, or 7. If a subject used rescue medication within 4 hours of a schedule pain assessment, this pain score was used if it larger than the recorded pain score. I used a 4 hour window regardless of the rescue medication used.

The applicant's dataset that contained the pain scores recorded following surgery did not contain the time of assessment. I utilized their derived dataset that contain the time of assessment. Per the applicant's explanation, pain was assessed at pre-specified time points post-surgery and the actual time of assessment was not recorded.

**Results and Conclusions**

The results of the applicant's primary analysis and mine when testing for superiority of Posimir to placebo for $AUC_{72}$ are shown in Tables 13 and 14. The applicant's results presented below were from the sensitivity analysis that accounted for the use of rescue medication. My results are consistent with the applicant. There was a significant treatment effect in favor of Posimir.

**Table 13. Results from analysis of normalized AUC in Study BU-002**

| | Normalized $AUC_{72}$ (PI) - mean (SEM) | | |
|---|---|---|---|
| | Placebo (n=25) | Posimir 660 mg (n=53) | Bupivacaine (n=29) |
| Applicant | 6.3 (0.4) | 5.0 (0.3) | 5.0 (0.4) |
| Reviewer | 6.4 (0.4) | 5.3 (0.3) | 5.5 (0.4) |

Source: Reviewer

The point estimates for the difference in LSMEANs between the Posimir 660 mg and placebo from my analysis are shown in Table 14. I also present the corresponding 95% CI for the difference and the p-values for the comparison to placebo. For interest, I also present the comparison of placebo to bupivacaine.

**Table 14. Comparison of Posimir to placebo in Study BU-002**

| | Difference | 95% CI | p-value |
|---|---|---|---|
| Posimir 660 mg | -1.1 | [-2.1, -0.2] | 0.02 |
| Bupivacaine | -0.2 | [-1.1, 0.7] | 0.1 |

Source: Reviewer

While not used for inferential value, I did compare bupivacaine to Posimir, results not shown. A significant difference was not noted, p-value of 0.7. As the applicant used LOCF, included pooled country in their ANOVA model, and used different windows for the adjustment of rescue medication, my derivation of the mean AUC for each treatment arm differ slightly as I used BOCF and a constant 4 hour window when considering use of rescue medication. The applicant's pre-specified statistical analysis plan indicated they would test for NI of Posimir to placebo first. If NI was established, superiority would be tested. Even though NI was established as indicated by the 95% CI shown in Table 14, there is no clinical interpretation of establishing NI to placebo as a rationale for a NI margin was not established. Regardless, superiority was demonstrated.

As an AUC is cumulative and derived from the PI scores measured at each time point, I examined subject level data for missing PI scores. Similar to Study ClIN-803, monotonic missing data was not an issue as subjects were hospitalized following surgery and none withdrew prior to 72 hours. However, there were some intermittent missing data. The amount of data missing at each time point post-surgery is shown in Table 15.

**Table 15. Missing pain assessments in Study BU-002**

| Time-point (hours post-dose) | Number of missing observations (%) | | | |
|---|---|---|---|---|
| | Placebo (n=25) | Posimir 660 mg (n=53) | Bupivacaine (n=29) | Combined (n=107) |
| 1 | - | - | - | - |
| 2 | 7 (28.0) | 8 (15.1) | 5 (17.2) | 20 (18.7) |
| 4 | 2 (8.0) | 7 (13.2) | 6 (20.7) | 15 (14.0) |
| 6 | 2 (8.0) | 7 (13.2) | 4 (13.8) | 13 (12.1) |
| 8 | 2 (8.0) | 4 (7.5) | 1 (3.4) | 7 (6.5) |
| 12 | 1 (4.0) | - | 1 (3.4) | 2 (1.9) |
| 22 | 4 (16.0) | 8 (15.1) | 5 (17.2) | 17 (15.9) |
| 26 | 2 (8.0) | 5 (9.4) | 3 (10.3) | 10 (9.3) |
| 30 | 1 (4.0) | 5 (9.4) | 5 (17.2) | 11 (10.3) |
| 34 | 1 (4.0) | 3 (5.7) | 3 (10.3) | 7 (6.5) |
| 46 | 3 (12.0) | 8 (15.1) | 3 (10.3) | 14 (13.1) |
| 50 | 3 (12.0) | 3 (5.7) | 2 (6.9) | 8 (7.5) |
| 54 | 1 (4.0) | 6 (11.3) | 2 (6.9) | 9 (8.4) |
| 58 | 3 (12.0) | 4 (7.5) | 3 (10.3) | 10 (9.3) |
| 70 | 3 (12.0) | 5 (9.4) | 4 (13.8) | 12 (11.2) |
| 72 | 2 (2.0) | 9 (17.0) | 4 (13.8) | 15 (14.0) |

Source: Reviewer

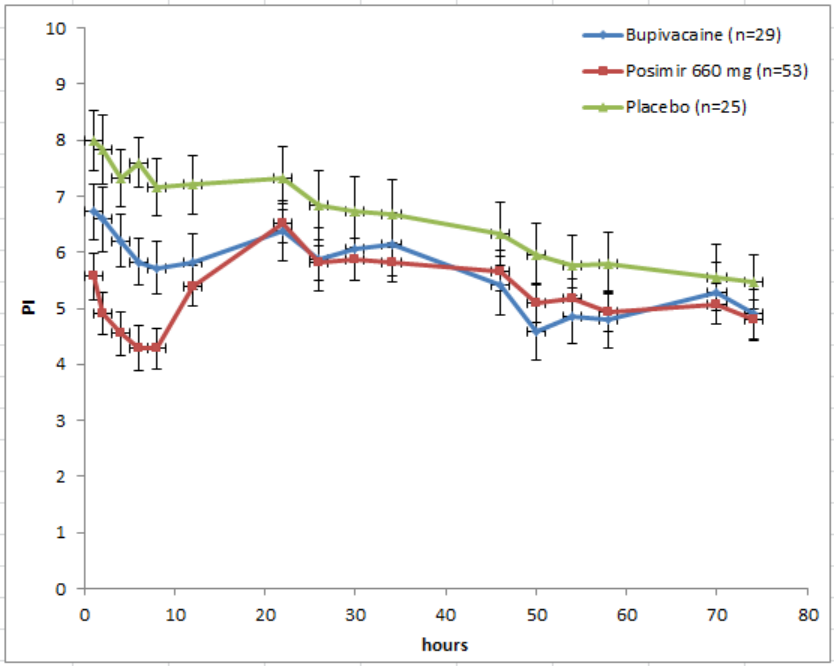
There were more missing PI assessments in this study than in pivotal hernia repair study, CLIN-803. However, in all cases it was less than 20% with the most missing data at the 2, 22, and 72 hour post-treatment time point. Since there were no patterns or trends noted with the missing data and this was an inpatient study with a single administration of study drug, I was not concerned and used WOCF to impute missing pain scores. The applicant used LOCF.

Next, I accounted for the use of rescue medication. When I only considered medication coded as rescue, there were 427 uses of morphine. When I expanded this to include concomitant medication, general anesthesia, and IV medication; there were 697 uses of opioids which

included fentanyl, midazolam, morphine, oxycodone, propofol, and tramadol. In my analysis of PI scores I considered all opioid medication regardless of how classified. As with Study CLIN-803, I did not consider 609 uses of APAP. If a patient received rescue at time *x*, for any time point within *x* + 4 hours, the assigned rescue pain score was used. If the PI score for the windowed observation was higher than the rescue pain score, it was not replaced.

The mean PI scores for each treatment group at each assessed time point are shown in Figure 6. Error bars indicate the 95% CI of the point estimate. This display of the PI scores that were used to generate $AUC_s$ may help with the clinical interpretation of the effect size observed with the primary endpoint, $AUC_{72}$.

**Figure 6. Mean PI scores at each measured time point in Study BU-002-IM**




Source: Reviewer

The above figure demonstrates separation in the curves for Posimir and bupivacaine from placebo out 72 hours. However, the magnitude of the separation from approximately 24 − 72 hours is not the same magnitude observed for hours 1 − 24. This was also observed in Study CLIN-803. It should be noted that regardless of treatment, most subjects had moderate pain throughout the study. Moderate pain is defined as a score between 4 and 7.

Exploring the data that generated the curves above, I compared the mean PI scores of Posimir and bupivacaine to placebo at each time point. As this was exploratory, I did not adjust for multiplicity. Results are shown in Table 16.

**Table 16. Comparison of PI scores by time in Study BU-002**

| Time point (hrs) | Difference from placebo (PI) | | | | | |
|---|---|---|---|---|---|---|
| | Posimir 660 mg (n=53) | | | Bupivacaine (n=29) | | |
| | LSMEAN | stder | p-value | LSMEAN | stder | p-value |
| 1 | -2.4 | 0.7 | 0.0003 | -1.3 | 0.7 | 0.09 |
| 2 | -2.9 | 0.6 | <0.0001 | -1.3 | 0.7 | 0.08 |
| 4 | -2.8 | 0.6 | < 0.0001 | -1.1 | 0.7 | 0.13 |
| 6 | -3.3 | 0.6 | <0.0001 | -1.7 | 0.7 | 0.01 |
| 8 | -2.8 | 0.6 | <0.0001 | -1.4 | 0.7 | 0.03 |
| 12 | -1.8 | 0.6 | 0.004 | -1.4 | 0.7 | 0.05 |
| 22 | -0.8 | 0.6 | 0.19 | -0.9 | 0.7 | 0.18 |
| 26 | -1.0 | 0.6 | 0.09 | -1.0 | 0.7 | 0.16 |
| 30 | -0.9 | 0.7 | 0.19 | -0.7 | 0.9 | 0.38 |
| 34 | -0.8 | 0.6 | 0.18 | -0.5 | 0.7 | 0.47 |
| 46 | -0.7 | 0.6 | 0.29 | -0.9 | 0.7 | 0.20 |
| 50 | -0.9 | 0.6 | 0.16 | -1.4 | 0.7 | 0.05 |
| 54 | -0.6 | 0.6 | 0.34 | -0.9 | 0.7 | 0.20 |
| 58 | -0.9 | 0.6 | 0.16 | -1.0 | 0.7 | 0.15 |
| 70 | -0.5 | 0.6 | 0.45 | -0.3 | 0.7 | 0.69 |
| 72 | -0.7 | 0.6 | 0.25 | -0.6 | 0.7 | 0.39 |

Source: Reviewer

From Table 16, the difference between Posimir and placebo is nominally significant out to 12 hours post-surgery. This indicates that the significant difference noted in the comparison of $AUC_{72}$ may be influenced by the early separation in the curves. There were no significant differences noted between bupivacaine and placebo. Based on the information in Figure 6 and Table 16, the clinical benefit of Posimir 660 mg in reducing post-surgical pain associated with shoulder repair surgery after 12 hours post-surgery is unclear.

Next I examined the second co-primary efficacy endpoint, amount of opioid rescue medication consumed through 72 hours, $RES_{72}$. I considered all opioids used regardless of how the applicant classified the use. It was pre-specified that results would be compared using an analysis of variance (ANOVA) model with treatment and site if the assumptions of normality and heterogeneity of variance were met. If these assumptions were violated, a non-parametric test would be used. In my analysis and the applicant's these assumptions were violated. A plot of the residuals indicated the data was left skewed and a test for homogeneity of variance was rejected, p-value < 0.001. Therefore a non-parametric test, Wilcoxon Rank Sum (WRS), was utilized. Results are shown in Table 17.

**Table 17. Amount of rescue medication consumed through 72 hours post-surgery in Study BU-002**

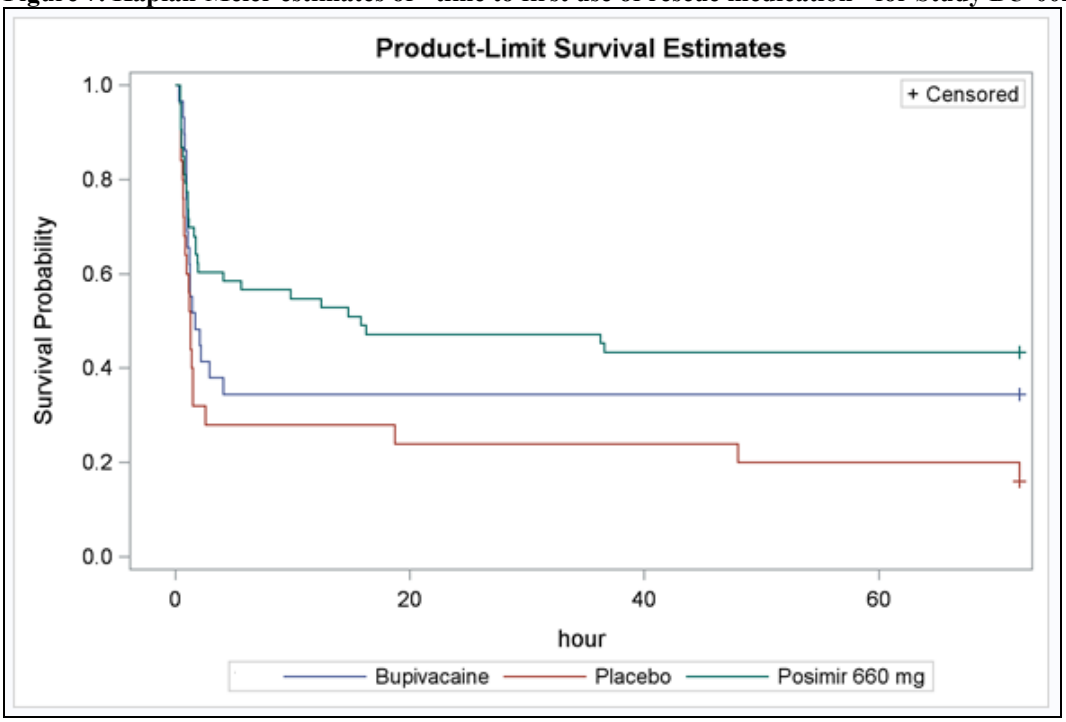
| Treatment | Morphine Equivalent (mg) mean (stdev) | p-value |
|---|---|---|
| Placebo (n=25) | 22.8 (25.8) | - |
| Posimir 660 mg (n=53) | 13.7 (29.1) | 0.01 |
| Bupivacaine (n=29) | 12.3 (17.6) | 0.07 |

Source: Reviewer

There was a significant treatment effect noted for Posimir 660 mg but not for bupivacaine. Subjects treated with Posimir 660 mg, on average used less rescue medication than placebo subjects, 13.7 mg versus 22.8 mg, respectively.

Next I examined time to first use of rescue medication. The median time to first use of post-operative rescue medication was 1.3 hours in placebo subjects, 15.8 hours in Posimir 660 mg treated subjects, and 1.7 hours in subjects treated with bupivacaine. Using Kaplan-Meier methods, the survival curves for time to first use of rescue medication for each treatment arm are shown in Figure 7. In this analysis I considered all post-operative opioids not just those coded as rescue medication. A subject was considered censored if they did not use rescue medication prior to 72 hours post-surgery.

**Figure 7. Kaplan-Meier estimates of "time to first use of rescue medication" for Study BU-002**




Source: Reviewer

Based on the log-rank test, a significant difference exists in the distributions of time to first use of rescue medication between Posimir 660 mg and placebo, p-value=0.01. However, there was not a significant difference between placebo and bupivacaine.

Even though my examination of rescue medication usage did not include 609 uses of APAP, I did explore its use. Every subject regardless of treatment took APAP at some point post-surgery. The average amount of APAP consumed during the first 72 hours post-treatment was also similar between treatment arms; 9.2, 9.8, 9.8 grams for the placebo, Posimir 660 mg, and bupivacaine, respectively. Based on this information, I decided it was acceptable not to include the use of APAP in my analyses of rescue medication.

As in Study CLIN-803 there were some subjects that used rescue medication prior to surgery, 40% in placebo arm, 34% in the Posimir arm, and 38% in the bupivacaine arm. Rescue medication used was mostly fentanyl or morphine. Again, as the clinical team felt this usage was appropriate, I did not include this use when determining the amount of rescue medication consumed through 72 hours. However, as done with Study CLIN-803, I did account for it when deriving AUCs as it could influence early pain scores.

In summary, this study did demonstrate the efficacy of Posimir in treating post-surgical pain associated with shoulder repair. There was a significant difference in favor of Posimir when I examined the pre-specified primary endpoints, $AUC_{72}$ and $RES_{72}$. This was supported by the analysis of secondary endpoints such as pain scores at each time point and time to first use of rescue medication. However, the clinical benefit of Posimir 660 mg in reducing post-surgical pain associated with shoulder repair surgery after 12 hours post-surgery is unclear. Although the study did not demonstrate that it was any better than standard bupivacaine, it was not designed to do so. That being said, Posimir was significantly better than placebo for the primary endpoints, bupivacaine was not.

**3.2.2.2 Supportive Studies**

Two studies, CLIN803-017 and CLIN005-0006, that failed to demonstrate a statistically significant treatment benefit of Posimir in treating post-surgical pain associated with shoulder repair surgery were indicated as supportive by the applicant and are discussed below. Based on the applicants clinical study reports, these studies were conducted prior to the pivotal study. Study CLIN005-0006 was conducted from 2006 to 2007. Study C803-017 was conducted from 2008 to 2009. It is my impression that the applicant conducted these studies in a chronological order until a significant study was obtained.

Study CLIN005-0006: This was a randomized, double-blind, placebo-controlled phase 2 study conducted at six sites in Utah, Georgia, Pennsylvania, California, and Texas and one site in New Zealand. This study was conducted in two cohorts. In cohort 1, eligible subjects were randomized equally to one of three treatment arms. In treatment arm 1, prior to wound closure, 5 mL of placebo was injected into the subacromial space. After wound closure 5 mL of Posimir was administered as two trailing subcutaneous injections along each side of the incision line. In treatment arm 2, prior to wound closure 5 mL of Posimir was injected into the subacromial space. After wound closure 5 mL of placebo was injected along the incision line. In treatment arm 3, placebo was injected into the subacromial space and along the incision line. In cohort 2, subjects were randomized equally to either placebo, treatment arm 4, or Posimir 7.5 mL, treatment arm 5. In Cohort 2 study drug was only injected into the subacromial space. Via a protocol amendment the dose for Cohort 2 was changed from 7.5 mL to 5.0 mL. There were four subjects in treatment arm 4 and three subjects in treatment arm 5 that received the 7.5 mL dose. These treatment arms are referred to as 4a and 5a, respectively. The 5 mL dose of Posimir corresponds to 660 mg active product and the 7.5 mL dose corresponds to 990 mg.

Efficacy was assessed using the subjects' evaluation of pain intensity on movement and at rest and pain control collected via the subjects' diary. PI was assessed using an 11-point NRS and pain control was evaluated using a 5-point scale. Subjects were asked "How would you rate your overall pain control in the last 24 hours?" Responses were poor, fair, good, very good, or

excellent. The pre-specified primary endpoints were PI and pain control on Days 0 through 7. For subjects that required supplemental analgesia, pain scores on movement were recoded prior to use. Via a protocol amendment, the primary endpoint was changed to a normalized AUC of PI scores for at rest and on movement at 120 hours post-surgery and were compared between treatment arms using an ANOVA model where the comparison of interest was treatment arm 5 versus pooled placebo, treatment arms 3 and 4. Missing data was imputed using LOCF for monotonic missingness and intermittent missing scores used the average of adjacent scores. The applicant also conducted a sensitivity analysis where pain scores prior to using rescue medication was used in the derivation of the AUC. Post-hoc the applicant examined $AUC_{72}$ and $RES_{72}$.

The analysis population consisted of all randomized and treated subjects. The number of subjects per treatment arm is shown in Table 18.

**Table 18. Number of subjects per treatment arm in Study CLIN005-0006**

| Treatment Number | Description | Number of subjects randomized and treated |
|---|---|---|
| 1 | Placebo subacromial 5 ml + Posimir SC 5 mL | 14 |
| 2 | Placebo SC 5 mL + Posimir subacromial 5 mL | 10 |
| 3 | Placebo SC 5 mL + Placebo subacromial 5 mL | 16 |
| 4 | Placebo subacromial 5 mL | 24 |
| 5 | Posimir subacromial 5 mL | 21 |
| 4a | Placebo subacromial 7.5 mL | 4 |
| 5a | Posimir subacromial 7.5 mL | 3 |

SC=subcutaneous
Source: Reviewer

Overall, there were slightly more male subjects than female, 59% versus 41%, respectively. The average age of subjects was 54 years old with a range of 22 to 82 years old. The majority of subjects were Caucasian with the exception of 7 African American subjects, 2 Asian, and 3 subjects categorized as other. Of the 92 subjects that were randomized and treated, 90 completed the study. Two subjects withdrew consent, one in the active arm and one in the placebo.

This study failed to show a significant difference between placebo and Posimir for AUC of PI scores out to 120 hours post-surgery. In a post-hoc analysis there was a significant difference noted in the $AUC_{72}$ for subjects that received Posimir via a subacromial injection and the pooled placebo group. However the placebo subjects in treatment group 3 received 10 mL of study drug and the placebo subjects in treatment arm 4 received 5 mL of study drug. A more relevant comparison would be treatment groups 4 and 5 as these treatment arms received 5 mL of study drug which was the volume administered in the pivotal study, BU-002-IM. The LSMEANs for $AUC_{72}$ were 5.6 and 5.2 for placebo and Posimir, respectively. The corresponding 95% CI for the difference between Posimir and placebo was [-1.7, 0.5] and failed to show a significant difference. This analysis did account for the use of rescue medication by using the pain scores that were measured prior to using rescue when deriving the AUCs.

Study C803-017: This was a randomized, double-blind, multi-center, placebo-controlled phase 2b study conducted at 8 sites in Australia and 2 sites in New Zealand. Eligible subjects were randomized to receive either placebo or Posimir 660 mg injected interstitially into the

subacromial space upon completion of the procedure. Assessment of efficacy was based on shoulder PI on movement and use of supplemental opioid analgesia. For subjects that required supplemental analgesia, pain scores on movement were recoded prior to use. Two primary efficacy endpoints were identified, normalized $AUC_{72}$ and $RES_{72}$ as measured by morphine equivalent units. The primary null hypotheses were that there were no differences between treatment groups in terms of $AUC_{72}$ and $RES_{72}$.

The analysis population consisted of 20 placebo subjects and 40 Posimir 660 mg subjects which constitute all randomized and treated subjects. A normalized $AUC_{72}$ was calculated for each subject using the standard trapezoidal rule and were compared between treatment groups using an ANCOVA model with treatment, site, and age as factors. Missing data was imputed using BOCF for subjects that discontinued due to an adverse event and LOCF for discontinuations due to any other reason. Intermittent missing data was replaced by using the mean of the values before and after. The mean total opioid dose was computed for each subject and compared between treatment groups using the same ANCOVA model. In case the normality assumption was violated, the applicant also conducted a non-parametric WRS test. To account for two primary endpoints the applicant utilized the Hochberg approach.

Of the 60 subjects randomized to treatment, 59 completed the study. One subject in the placebo withdrew consent. The majority of these subjects were Caucasian; 100% in placebo arm and 93% in the Posimir arm. There was one Aborigine, one Asian, and one other in the Posimir treatment arm. While the placebo arm enrolled equal numbers of male and female subjects, the Posimir treatment arm had slightly more female subjects than male subjects; 58% versus 42%, respectively. Results of the applicant's primary analysis are presented in Table 19. Even though the pain scores we measured prior to using rescue analgesia, the applicant did not utilize them in deriving the $AUC_{72}$.

**Table 19. Applicant's results for the primary analysis in Study C803-017**

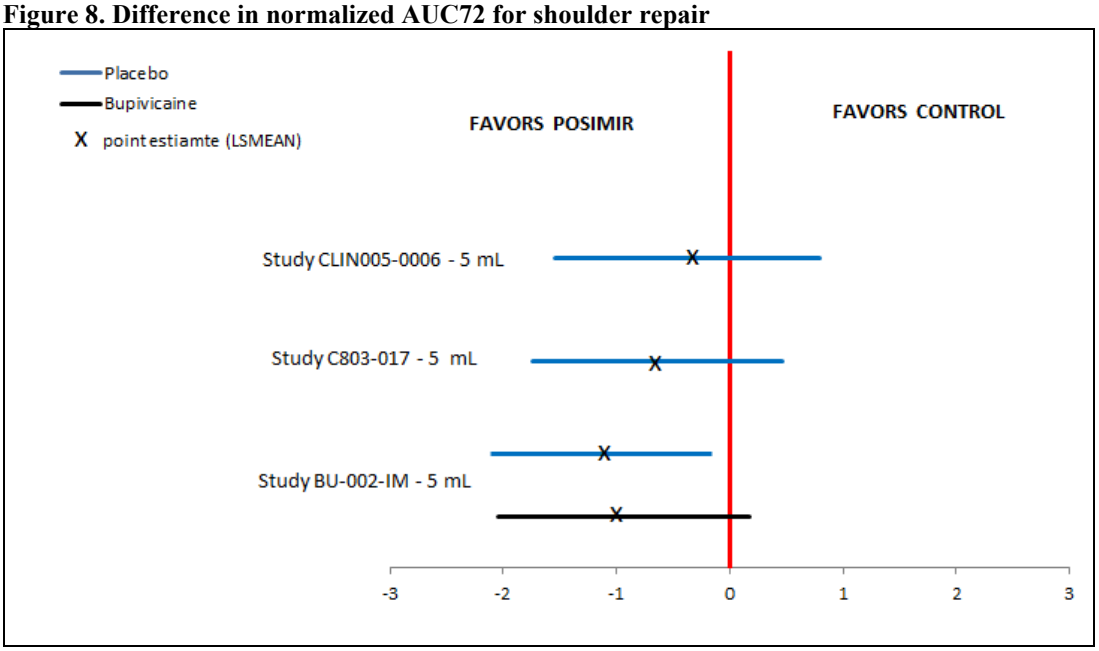
| Endpoint | Placebo (n=20) | Posimir 5 mL (n=40) | Difference (95% CI) | p-value |
|---|---|---|---|---|
| $AUC_{72}$ (pi) | 5.8 | 5.4 | -0.64 [-1.7, 0.47] | 0.3 |
| $RES_{72}$ (mg) | 49.9 | 44.5 | -10.7 (-30.0, 9.6) | 0.3 |

Source: Tables 14.1.8.1 and 14.1.9.1 from applicant's CSR

A significant treatment effect was not observed for either endpoint.

I summarize the results of $AUC_{72}$ for the three studies that evaluated post-surgical pain associated with shoulder repair surgery. Figure 8 shows the point estimates and 95% CI for difference from placebo for $AUC_{72}$. The 5 mL dose is equal to 660 mg of Posimir.

**Figure 8. Difference in normalized AUC72 for shoulder repair**




Source: Reviewer

Unlike the studies that evaluated post-surgical pain associated with hernia repair, all supportive studies, while not significant, supported the treatment benefit of Posimir. The point estimate for $AUC_{72}$ was in the right direction. The comparison of Posimir to bupivacaine in Study BU-002-IM, while not significant, did favor Posimir. Of interest, in this study bupivacaine was not significantly different from placebo in the analyses of the primary and secondary efficacy endpoints.

### 3.2.3 Other Surgical Procedures

The results from two additional studies evaluated post-surgical pain associated with a hysterectomy and major abdominal surgery. Study BU-001-IM was conducted in female subjects undergoing a hysterectomy and Study C803-025 evaluated subjects undergoing a colectomy, laparotomy, or laparoscopic cholecystectomy. Each study is discussed briefly and the applicants' analyses are presented.

Study BU-IM-001: This was a randomized, double-blind, dose-ranging, active- and placebo-controlled phase 2 study that evaluated Posimir in female subjects undergoing a hysterectomy. Subjects were enrolled at 13 sites in 5 countries; France, Germany, Hungary, Latvia, and Sweden. This study was to be conducted in two separate cohorts where Cohort 1 received 5.0 mL of study drug and Cohort 2 received 7.5 mL of study drug. However, Cohort 2 was not conducted. In Cohort 1, subjects were randomized 2:1:1 to either Posimir 5.0 mL, placebo, of 40 mL of bupivacaine. Placebo and Posimir were instilled into the surgery site prior to wound closure. Bupivacaine was injected into the muscle, distal layer and subcutaneously around the surgery site.

The primary efficacy variables were $AUC_{72}$ on movement and $RES_{72}$. Missing pain scores between two non-missing pain scores were not imputed. This is analogous to linear

interpolation. Missing pain scores due to discontinuations were imputed using LOCF. The analysis population was defined as all randomized and treated patients. For $AUC_{72,}$ the applicant tested NI of Posimir 660 mg to placebo using ANOVA model with treatment and pooled site as factors. If the upper bound of the 95% CI for the difference was less than or equal to 0.5, NI was established. This is equivalent to using a NI margin of 0.5. If NI was established, superiority was tested. $RES_{72}$ was computed for each subject by converting amount of rescue medication to morphine equivalent doses. If a subject discontinued prior to 72 hours, the $Res_{72}$ will be calculated as amount of rescue used per hour times 72. Results were compared between placebo and Posimir using an ANOVA model with treatment and pooled site.

Of the 119 subjects enrolled, 114 were randomized and treated, 60 Posimir, 27 placebo, and 27 bupivacaine. Of these 114 subjects, 113 completed the study. One subject in the Posimir arm withdrew consent and one subject in the placebo arm withdrew due to an adverse event. All subjects were female Caucasians with an average age of 46 years old. In the analysis of $AUC_{72}$, NI was claimed as the 95% CI for the difference of Posimir and placebo was [-0.89, 0.35]. The 95% CI for the difference between Posimir and bupivacaine was [-0.68, 0.47]. However, superiority was not established for either comparison, p-value > 0.05. This analysis did not account for use of rescue medication. Additionally, superiority of Posimir 660 mg over placebo for $RES_{72}$ was not established. Placebo subjects, on average used 26.3 mg morphine equivalent units compared to 22.8 mg for the Posimir 660 mg. Bupivacaine treated subjects used an average of 23.9 mg over 72 hours.

Study C803-025: This was a randomized, double-blind, placebo- and active-controlled phase 3 trial that was conducted in three separate cohorts. Cohort 1 randomized subjects undergoing a laparotomy and Cohort 2 randomized subjects undergoing a laparoscopic cholecystectomy. In Cohorts 1 and 2, subjects were randomized 3:2 to Posimir 660 mg or bupivacaine. Cohort 3 was placebo controlled and evaluated subjects receiving a colectomy. Subjects were randomized 3:2 to Posimir 660 mg or placebo. In all cohorts study drug was instilled into the surgery site prior to wound closure. This study was conducted at nine sites in the United States and two sites in Australia.

The primary efficacy variables were $AUC_{72}$ and $RES_{72}$. The analysis population was defined as all randomized subjects that received study drug. An ANCOVA model with treatment, pooled site and incision length as a covariate was used to compare results for both endpoints. Since the results of $RES_{72}$ violated the normality assumptions a non-parametric analysis, WRS, was used. Missing pain scores were handled as follows. If a subject dropped out prior to 72 hours due to an adverse event, the subjects' baseline observation was carried forward. If a subject dropped out for any other reason or had intermittent missing data, a multiple imputation approach was used. The Hochberg approach was utilized to account for two primary endpoints. If the largest p-value was less than 0.05, then both endpoints were declared significant. If the largest p-value was greater than 0.05, the other endpoint will be tested at 0.025. The applicant states that data from Cohorts 1 and 2 will be pooled and summarized but would be non-inferential. The data from Cohort 3 was of interest and would be inferential.

A total of 393 subjects were screened in order to randomize 331 subjects. Of these 26 did not receive treatment. Cohort 1 randomized 30 subjects to Posimir and 18 subjects to bupivacaine,

Cohort 2 randomized 30 subjects to Posimir and 20 subjects to bupivacaine, and Cohort 3 randomized 129 to Posimir and 78 subjects to placebo. Of all randomized subjects, 11 did not complete the study. Six subjects withdrew consent, four in the Posimir arms, one in the bupivacaine arm, and one in the placebo arm. Two subjects, one subject in the Posimir arm and one in the bupivacaine arm discontinued due to an adverse event. The other three reasons were lost to follow-up, investigator decision, and other. The average age of all subjects was 56 years old with a range of 22 to 87. Overall the study enrolled approximately equal numbers of males and females, 48% and 52%, respectively. The applicants' results for the primary analysis are shown in Table 20.

**Table 20. Results of applicants' primary analysis from Study C803-025**

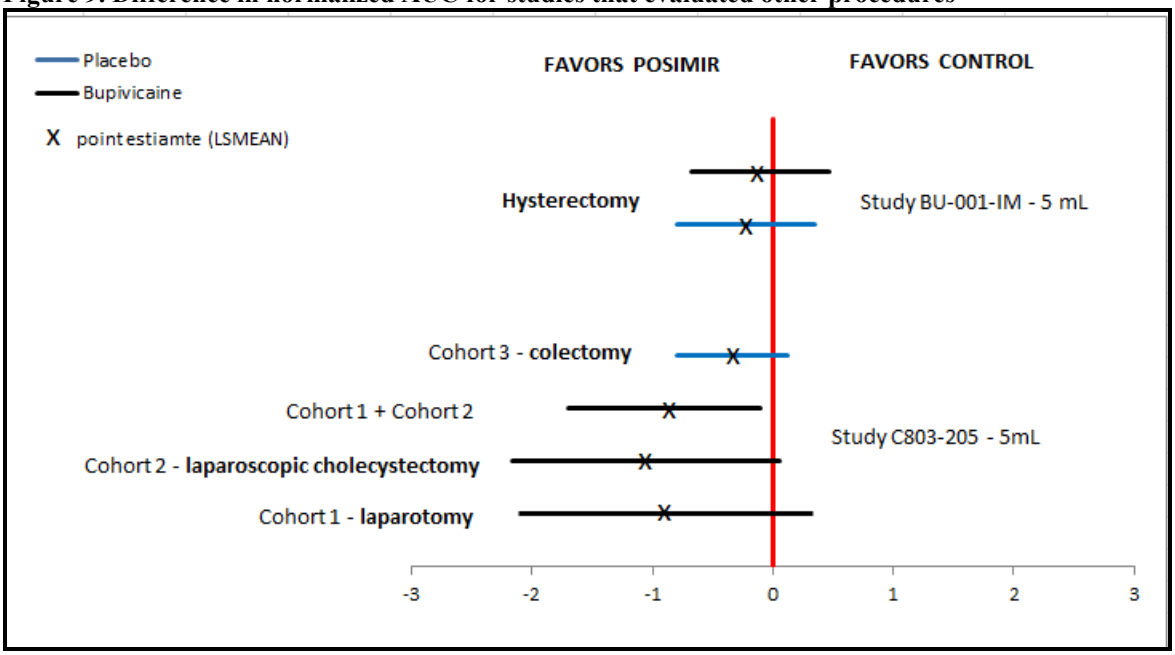
| Cohort | normalized $AUC_{72}$ (pi) | | | p-value |
|---|---|---|---|---|
| | Control | Posimir 5 mL | Difference (95% CI) | |
| 1 | 5.8 | 4.9 | -0.9 (-2.1, 0.3) | 0.15 |
| 2 | 3.9 | 2.8 | -1.1 (-2.2, 0.05) | 0.06 |
| 3 | 5.1 | 4.8 | 0.34 (-0.8, 0.12) | 0.15 |

Source: Table 15 from applicants CSR

The only significant difference noted was when the applicant pooled Cohorts 1 and 2. Superiority of Posimir over bupivacaine was noted, results not shown. However, the clinical reviewer felt it was inappropriate to pool the data from these two surgical procedures as they were clinically different. Further, there were no significant differences noted for the comparison of Posimir to control for $RES_{72}$, results not shown.

Figure 9 shows the point estimates and the 95% CI for the difference of Posimir from control for $AUC_{72}$. I included the two studies that evaluated post-surgical pain associated with hysterectomy, colectomy, laparoscopic cholecystectomy, and laparotomy. While there was not a significant treatment effect noted, in all cases, the point estimate was in favor of Posimir. I included the results from the pooled analysis in Study C803-025 although clinically, it was inappropriate to pool these two procedures.

**Figure 9. Difference in normalized AUC for studies that evaluated other procedures**




Source: Reviewer

Results from these two supportive studies, while not significant, indicated numerically that Posimir was better than placebo.

### 3.3 Evaluation of Safety

The primary medical officer, Dr. Arthur Simone, reviewed the safety data for this application.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, Age, and Geographic Region

The Applicant examined the primary efficacy endpoint, $AUC_{72}$, in Study BU-002 for differences due to age or gender. As this study was conducted mainly in Caucasian subjects, differences due to racial subgroups were not examined. Age was categorized as less than 45 years old or 45 years or older. Since I could not locate a subgroup analysis for CLIN-803 in the applicant's clinical study report, I conducted my own analysis. However, this study was included in a pooled analyses located in the integrated summary of efficacy. Each study will be discussed separately below.

Study CLIN-803

Since the majority of these subjects were male Caucasians, gender and racial subgroups were not examined. I examined the primary endpoint, $AUC_{72}$ for any differences due to age using an ANOVA model with treatment and age. The results for my subgroup analysis for gender are shown in Table 21.

**Table 21. Subgroup analysis for age, gender, and country in Study CLIN-803**

| Subgroup | | $AUC_{72}$ LSMEAN (PI) | | Difference | 95% CI |
|---|---|---|---|---|---|
| | | placebo | Posimir 660 mg | | |
| Age (years) | < 45 (n=) | 5.6 | 3.4 | -2.2 | [-3.4, 0 ] |
| | ≥ 45 (n=) | 3.4 | 2.2 | -1.2 | [-2.8, 0] |

Source: Reviewer

There was not a significant treatment interaction with age when I examined $AUC_{72}$ in Posimir 660 mg and placebo. While not significant, the point estimates were in the right direction.

Study BU-002

The applicant examined $AUC_{72}$ for any treatment interactions with age and gender using an ANOVA model with treatment, site, age, and gender. The 95% CI for the difference of Posimir 660 mg from placebo were presented. The applicant tested for NI and superiority to placebo. The results using my analyses are shown in Table 22.

**Table 22. Subgroup analysis for age and gender in Study BU-002**

| Subgroup | | $AUC_{72}$ LSMEAN (PI) | | Difference | 95% CI |
|---|---|---|---|---|---|
| | | placebo | Posimir 660 mg | | |
| Gender | female (n=47 ) | 6.3 | 5.4 | -0.9 | [-2.2, 0.5] |
| | male (n=33 ) | 6.7 | 5.2 | -1.5 | [-3.1, 0.0] |
| Age (years) | < 45 (n=22) | 6.7 | 5.2 | -1.5 | [-3.3, 0.3] |
| | ≥ 45 (n=55) | 6.3 | 5.4 | -1.0 | [-2.1, 0.2] |

Source: Reviewer

There was not a significant treatment interaction with age or gender and all point estimates, while not significant, were in favor of Posimir. Region of conduct for the seven studies submitted to support efficacy is shown in Table 23.

**Table 23. Geographic location of clinical studies**

| Study | Region | Phase | Type of control | Surgical Procedure |
|---|---|---|---|---|
| CLIN-803-006-0006 | Oceania | 2 | placebo | Inguinal hernia |
| CLIN005-0010 | USA/New Zealand | 2 | placebo | Inguinal hernia |
| BU-002-IM | Europe | 2 | active/placebo | Arthroscopic shoulder |
| C803-017 | Oceania | 2b | placebo | Arthroscopic shoulder |
| CLIN005-0006 | USA/New Zealand | 2 | placebo | Arthroscopic Shoulder |
| 803-025 | Oceania | 3 | active/placebo | Major abdominal |
| BU-001-IM | Europe | 2 | active/placebo | Hysterectomy |

Source: Reviewer

Most of these studies were conducted outside of the United States so I did not examine results for difference in geographic locations. However, the applicant should indicate why they believe these results are applicable to the population in the United States.

### 4.2 Other Special/Subgroup Populations

There were no other subgroups of interest that were identified or analyzed.

# 5. SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues and Collective Evidence

In the three studies that evaluated Posimir 660 mg in treating post-surgical pain associated with arthroscopic shoulder repair, only the pivotal study, BU-002-IM, demonstrated a statistically significant treatment effect in favor of Posimir. The two supportive studies provided additional evidence. Although not statistically significant, results favored Posimir. However, when I examined mean PI scores by time there did not seem to be a clinically relevant difference between Posimir 660 mg and placebo beyond 12 hours. Furthermore, since the pivotal study was conducted entirely in Europe, the Applicant should provide evidence that the surgical procedures in Europe are similar to those conducted in the United States.

In the two studies that evaluated Posimir in treating post-surgical pain associated with hernia repair, only the pivotal study, CLIN-803-006-0006, demonstrated a statistically significant treatment effect in favor of Posimir. The supportive study demonstrated, while not significant, a point estimate that was in the wrong direction. It favored placebo. The only notable difference in the two studies was that the failed study was conducted mainly in the United States whereas the successful study was conducted in Australia and New Zealand.

The three supportive studies that evaluated Posimir in other procedures, while not significant, numerically favored Posimir 660 mg when I examined the primary endpoint $AUC_{72}$.

## 5.2 Conclusions and Recommendations

In Study BU-002-IM, the analyses of the $AUC_{72}$ and $RES_{72}$ yielded significant differences between Posimir 660 mg and placebo for treating post-surgical pain associated with shoulder surgery. This was supported by various secondary endpoints. Although an AUC is acceptable as the primary efficacy endpoint, differences in AUCs have little clinical interpretation when considering treatment effect size. One can examine the pain scores that make up an AUC to aid in the clinical interpretation. Figure 4 is a graph of the mean PI scores by time that supports the statistical significance of the primary efficacy endpoint, $AUC_{72}$. The clinical significance of the treatment beyond 12 hours is unclear. There were no concerns regarding the analysis populations, statistical analyses, or imputation of missing data that could not be addressed. The approach to handling rescue medication in the analysis was appropriate.

In Study CLIN-803-0006-06, the analysis of the primary efficacy endpoints, $AUC_{72}$ and $RES_{72}$ demonstrated a significant treatment effect in favor of Posimir 660 mg. This was supported by the analyses of various secondary endpoints such PI scores by time and time to first use of rescue medication. However, Study CLIN005-0010, did not support this conclusion. Based these results and lack of any rationale as to why one study worked and one study failed and the fact that the failed was conducted mainly in the United States, I do not believe the results from the two studies support an indication for treating post-surgical pain associated with hernia repair.

In conclusion, the efficacy of Posimir 660 mg was demonstrated in treating post-surgical pain associated with shoulder repair surgery as indicated by the significance of the pre-specified primary endpoints and was supported by the significance of various secondary endpoints.

Evidence was also provided in two supportive secondary studies. The applicant should provide evidence that these results are applicable to the population in the United States. In my opinion there was not substantial evidence to support the efficacy of Posimir in treated post-surgical pain associated with hernia repair.

**5.3 Label Review**

Using the label provided in the submission, I have the following comments regarding Section 14. My comments and suggestions follow the Applicant's proposed wording and are italicized. It may be beneficial to include the graph of mean PI scores by time, Figure 4, in the label.

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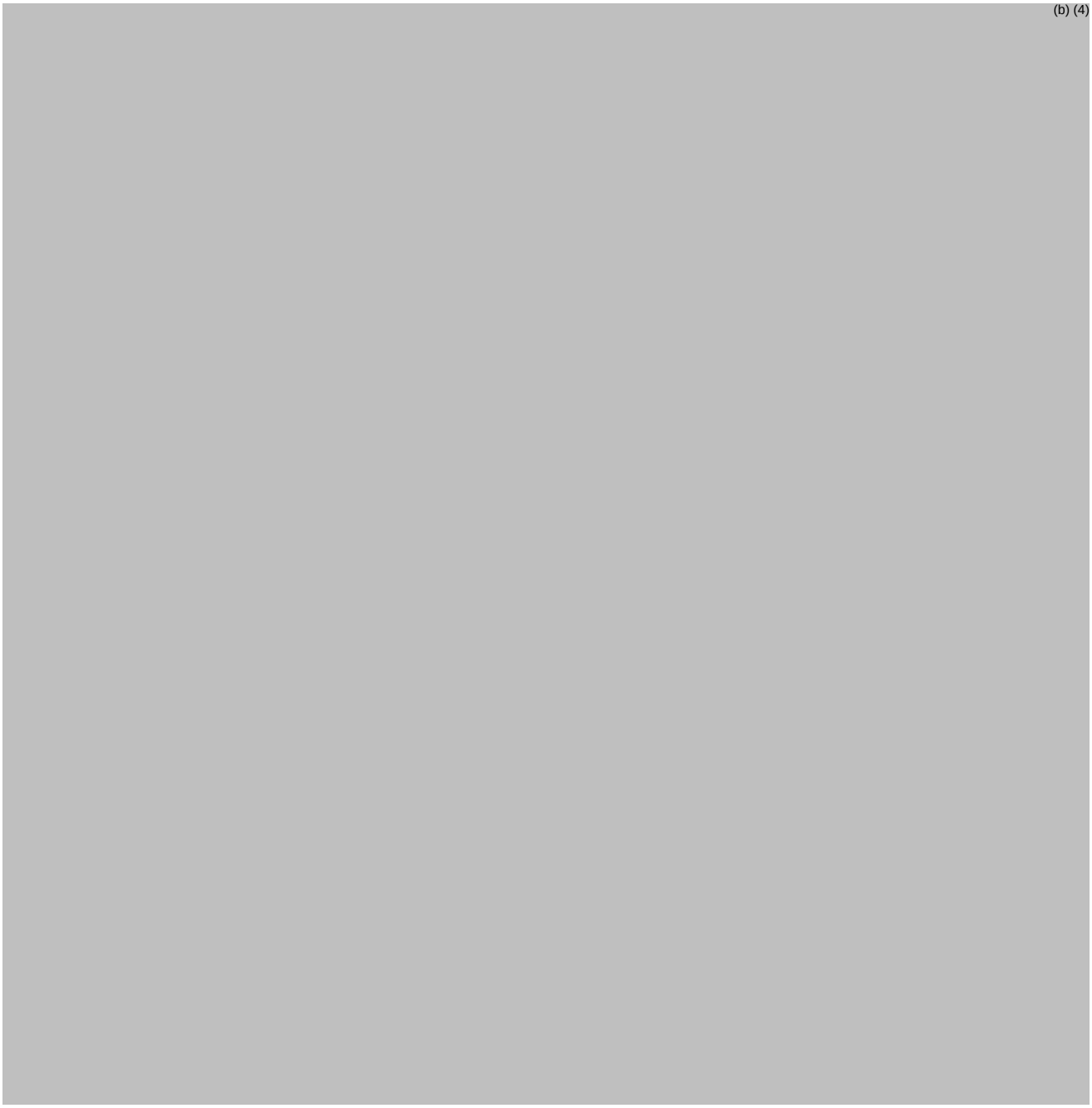



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/s/

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DAVID M PETULLO
02/19/2014

JANICE A DERR
02/19/2014

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA Serial Number:** 204-803/0000

**Drug Name:** Posimir (extended release bupivacaine)

**Indication(s):** Postsurgical analgesia

**Applicant:** Durect Corporation

**Date(s):** Received: April 12, 2013
PDUFA: February 12, 2014

**Review Priority:** Standard – 10 month

**Biometrics Division:** Division of Biometrics II

**Statistical Reviewer:** David Petullo, M.S.

**Concurring Reviewers:** Janice Derr, Ph.D.

**Medical Division:** Division of Anesthesia, Analgesia, and Addiction Products

**Clinical Team:** Medical Officer: Arthur Simone, M.D., Ph.D.
Deputy Division Director: Rigoberto Roca, M.D.

**Project Manager:** Ayanna Augustus

**Keywords:** clinical studies, NDA review, double-blind, foreign clinical data

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# 1. EXECUTIVE SUMMARY

Durect Corporation has submitted an application evaluating Posimir, a formulation of bupivacaine that contains an extended-release biodegradable matrix that according to the applicant continuously delivers bupivacaine for 72 hours. Continuous wound perfusion with local anesthetics was developed as a method to extend the duration of action resulting in a reduction of pain and decreased opioid consumption. To support the efficacy of Posimir for treating post-surgical pain, the applicant submitted results from seven clinical trials that evaluated various surgical procedures. Of these seven trials, shown in Table 1, two were identified as pivotal. The applicant claims the analyses of the data from these two studies demonstrated a statistically significant treatment effect in favor of Posimir 660 mg. The other five studies failed to report a statistically significant treatment effect.

Based on my review of the data from the two placebo-controlled clinical trials that were identified as pivotal, CLIN-803-0006-06 (hernia repair surgery) and BU-002-IM (arthroscopic shoulder surgery), there is evidence to support the efficacy of Posimir 660 mg in treating post-surgical pain associated with shoulder surgery. However, I did not find substantial evidence to support the efficacy of Posimir in treating post-surgical pain associated with hernia repair.

In Study BU-002-IM, analyses of the primary efficacy endpoints indicated that subjects treated with Posimir 660 mg on average, had less post-surgical pain and consumed less post-surgical opioid medication than subjects treated with placebo. The evidence of an analgesic effect was further supportive by the analyses of secondary endpoints such as time to first use of rescue medication and amount of opioid rescue medication required during the first 72 hours following surgery. This evidence was further supported by two supportive studies, C803-017 and CLIN005-0006, where results suggested, though not statistically significant, that Posimir 660 mg reduced post-surgical pain associated with shoulder surgery and the amount of post-surgical opioid medication required. However, the clinical benefit beyond 12 hours is unclear. When I examined pain intensity scores by time in Study BU-002-IM, Figure 4, the nominal statistical significance between placebo and Posimir 660 mg was only noted out to approximately 12 hours. This early separation in pain scores could impact the significant difference demonstrated in the comparison of the primary endpoint, $AUC_{72}$.

The benefit of Posimir in treating post-surgical pain associated with hernia repair surgery is not so clear. In the study identified as pivotal, Study CLIN-803-0006-06, the primary analyses indicated that subjects treated with Posimir 660 mg on average, had less post-surgical pain and consumed less post-surgical opioid medication than subjects treated with placebo. However, this effect was not observed in a study identified as supportive, CLIN005-0010. In this study, on average, subjects treated with Posimir 660 mg reported more pain than the placebo subjects and they required more opioid rescue medication. The only notable difference between these two studies was that the Study CLIN005-0010 was conducted mainly in the United States whereas Study CIN-803-0006-06 was conducted in Australia and New Zealand. Based on these results, I do not think there is substantial evidence to support the applicant's claim that Posimir is effective in treating post-surgical pain associated with hernia repair.

# 2. INTRODUCTION

## 2.1 Overview

The applicant states that local anesthetics such as bupivacaine are widely administered as analgesics. However, a significant limitation is their short duration of action, typically 4-6 hours. Continuous wound perfusion with local anesthetics was developed as a method to extend the duration resulting in a reduction of pain and decreased opioid consumption. Posimir is a formulation of bupivacaine that contains an extended-release biodegradable matrix that according to the applicant, continuously releases bupivacaine over 72 hours.

The development program for Posimir was conducted under IND 66,086. The Applicant submitted the results of seven active- and placebo-controlled studies to support efficacy, Table 1. The placebo arm in the below studies refers to the extended-release biodegradable matrix without bupivacaine.

**Table 1. Clinical Studies conducted by the applicant**

| Surgical Procedure | Study | Phase | Control | Pivotal or Supportive | Reviewed in Section |
|---|---|---|---|---|---|
| Inguinal hernia | CLIN-803-006-0006 | 2 | placebo | Pivotal | 3.2.1 |
| | CLIN005-0010 | 2 | placebo | Supportive | |
| Arthroscopic shoulder | BU-002-IM | 2 | active/placebo | Pivotal | 3.2.2 |
| | C803-017 | 2b | placebo | Supportive | |
| | CLIN005-0006 | 2 | placebo | Supportive | |
| Major abdominal | 803-025 | 3 | active/placebo | Supportive | 3.2.3 |
| Hysterectomy | BU-001-IM | 2 | active/placebo | Supportive | |

Source: Reviewer

Study CLIN-803-006-0006 (CLIN-803) and Study BU-002-IM (BU-002) were indicated by the applicant as pivotal studies to establish efficacy. It is unclear why these studies were identified as pivotal other than the fact that they demonstrated a significant treatment effect in favor of Posimir. Study CLIN-803 was conducted from June 2007 to October 2007 at five sites in Australia and New Zealand. Study BU-002 was conducted from April 2009 to February 2011 at nine sites in five countries, Austria, Denmark, Germany, Latvia, Poland, and Sweden. The protocols for these studies were not reviewed by FDA.

Studies 803-025, C803-017, CLIN005-0006, CLIN005-0010, and BU-001-IM were indicated as supportive studies. It appears these studies were indicated as supportive as they failed to show a significant treatment effect for Posimir. The protocols for studies CLIN005-0006 and CLIN005-0010 were reviewed by the clinical team in Jan 2006 but were not reviewed by the statistics team. The results from these supportive studies will be presented and discussed following my review of the pivotal studies.

There were several statistical issues discussed between the applicant and the FDA during the IND stage. During an End-of-Phase 2 meeting held on September 14, 2007, the applicant was informed that area-under-curve (AUC) of pain scores would be acceptable as a primary endpoint. However, the endpoint reduction in opioid use by itself may not have clinical significance unless some additional benefit can be demonstrated, such as fewer opioid-related adverse events. Via a written communication dated March 24, 2009, the applicant was advised that the use of ice

should be standardized and it would not be acceptable to include "use of ice" as a covariate in the primary analyses. The applicant was also informed that missing data should be appropriately accounted for in the statistical analysis plan. A subject that discontinues due to an adverse event should not have a good pain score imputed. Further, the use of rescue medication should be accounted for in the primary efficacy analysis. In a pre-NDA meeting held on July 31, 2012, the applicant was told that whether or not the results from the submitted surgical procedures would support a broad indication would be a review issue and the proposed indication, "extended relief of post-surgical pain," would not be acceptable. Further, it was pointed out that it was not clear that the pivotal studies accounted for the use of rescue medication in the primary efficacy analyses.

### 2.2 Data Sources

All data was supplied electronically by the Applicant as SAS transport files and can be found at the following location in the CDER electronic document room (EDR):

**\\Cdsesub1\EVSPROD\NDA204803\0000\m5\datasets**

## 3. STATISTICAL EVALUATION

Studies CLIN-803 and BU-002 evaluated pain associated with different surgical procedures, hernia repair and arthroscopic shoulder surgery, respectively. These procedures are evaluated separately under Sections 3.2.1 and 3.2.2. Two supportive studies that evaluated pain associated with hysterectomy and major abdominal surgeries are discussed in Section 3.2.3.

### 3.1 Data and Analysis Quality

The electronic data submitted by the Applicant for the two pivotal studies was of sufficient quality to allow a thorough review of the data. I was able to derive the primary and secondary endpoints for each study. The statistical analyses of my derived endpoints were in agreement with the Applicant's analyses.

The Office of Scientific Investigation did not identify any significant issues during the audits of the sites from two studies identified as pivotal.

### 3.2 Evaluation of Efficacy

My review focuses on the studies, pivotal and supportive, submitted to support post-surgical pain associated with hernia repair and shoulder surgery. For each procedure, I thoroughly review the pivotal study and then present the results of the failed supportive studies. Following my review of the individual studies, I present the combined results from both the pivotal and supportive studies and then give my overall conclusion for each procedure.

#### 3.2.1 Inguinal Hernia Repair

##### 3.2.1.1 Pivotal Study

In the study indicated as pivotal, CLIN-803, the applicant appropriately addressed my major concern regarding the use of rescue medication and the need to account for its use when deriving

the primary endpoint, AUC of pain scores out to 72 hours post-surgery. The applicant addressed this concern in a sensitivity analysis.

**Study Design and Endpoints**

Eligible patients that were to undergo an open unilateral tension free Lichtenstein-type inguinal hernia repair were randomized to one of four treatments: Posimir 2.5 mL (330 mg), Posimir 5.0 mL (660 mg), placebo 2.5 mL, or placebo 5.0 mL. This study was conducted in two cohorts. Cohort 1 comprised of the Posimir and placebo administered as 2.5 mL and the second cohort comprised of Posimir and placebo administered as 5.0 mL. Following surgery, a single dose of the study drug was instilled gradually throughout the inguinal canal and the abdominal wall layers to cover all raw surfaces of the wound, filling the subaponeurotic and subcutaneous spaces. Rescue analgesia for break-through pain was allowed upon request. Post-operative efficacy assessments included pain intensity (PI) at rest and during bowel movement, use of rescue medication, time of first bowel movement, post-operative nausea and vomiting, and occurrence of constipation. PI was assessed using an 11-point scale with 0 being no pain and 10 the worst pain and was measured at baseline (prior to surgery), end of general anesthesia, before first dose of rescue medication, and at 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after surgery.

The applicant pre-specified two primary efficacy outcomes; AUC of PI scores out to 72 hours post-surgery ($AUC_{72}$) and the proportion of subjects receiving opioid rescue medication through Day 15. The primary null hypotheses to be tested by the applicant were no difference between treatment groups in terms of AUC and opioid rescue use. The applicant estimated that a sample size of 120 subjects or 60 per cohort would provide 90% power to detect an effect size 0.67 for the difference in $AUC_{72}$. Post-hoc, the applicant changed the proportion of subjects using rescue through Day 15 to Day 3 or 72 hours. The rationale for this change was that 72 hours post-surgery was the time frame utilized for the other primary endpoint, $AUC_{72}$. A pre-specified secondary endpoint was amount of rescue medication used through 72 hours in morphine equivalents, $RES_{72}$. The time to first use of rescue medication was also evaluated.

**Patient Disposition, Demographic and Baseline Characteristics**

This study screened 135 subjects in order to randomize 124 eligible subjects; 32 placebo, 45 Posimir 330 mg, and 47 Posimir 660 mg. Demographics for all randomized and treated patients are shown in Table 2.

**Table 2. Demographics for Study CLIN-803**

| Characteristic | Treatment | | |
|---|---|---|---|
| | placebo | Posimir 330 mg | Posimir 660 mg |
| Number of Patients (n) | 32 | 43 | 47 |
| Age in years | | | |
| Mean (SD) | 50 (9) | 46 (12) | 49 (13) |
| Median | 52 | 48 | 50 |
| [range] | [28, 65 ] | [20, 68] | [21, 79] |
| Gender (%) | | | |
| Female | - | 2 (5) | 2 (4) |
| Male | 32 (100) | 41 (95) | 45 (96) |
| Race (%) | | | |
| Caucasian | 30 (94) | 40 (95) | 46 (98) |
| Black | 1 (3) | - | - |
| Multiple | 1 (3) | 2 (5) | - |
| Other | - | - | 1 (2) |

Source: Reviewer

This study comprised of mostly male Caucasian subjects with a mean age of approximately 50 years old and was evenly distributed between treatment arms. There were four subjects that did not complete the study, three in the Posimir 330 mg arm and one in the placebo arm. Reasons for discontinuation are shown in Table 3.

**Table 3. Disposition of subjects in Study CLIN-803**

| Reason for Discontinuation | Placebo | Posimir 330 mg | Posimir 660 mg |
|---|---|---|---|
| Multiple surgeries | - | 1 | - |
| Patients best interest | - | 1 | - |
| Underwent surgery for preexisting condition | 1 | - | - |
| Non-allowed medication | - | 1 | - |

Source: Reviewer

Even though these subjects discontinued the study, there was efficacy data for these subjects as they discontinued after 72 hours.

### Statistical Methodologies

The analysis dataset defined by the applicant was all randomized subjects who successfully underwent the surgical procedure without any major deviations. An AUC, similar to a time-weighted average, was calculated for each patient using PI scores measured at 1, 2, 3, 4, 6, 8, and 12 hours following surgery on Day1 and at 8 AM, 12 PM, 4 PM, and 8 PM on Days 2 and 3. This AUC was normalized for each subject by dividing the AUC by 72 hours. This represents the average PI over 72 hours. Missing PI scores were handled as follows.

- If a patient withdrew from the study prior to 72 hours, the last recorded pain score was carried forward (LOCF)

- If a pain measurement was not recoded for a specific visit, the previous maximum pain score was used for the first missing value and any subsequent missing values.

The applicant conducted a sensitivity analysis to examine use of rescue medication. When a scheduled pain score was assessed within one half-life of the rescue medication and the pain score measured prior to using rescue medication was higher, the scheduled pain score was replaced with the rescue pain score. Any missing rescue pain scores were imputed using the worst observation carried forward (WOCF). Half-lives of 5.5, 2, and 4 hours were assumed for tramadol, morphine, and oxycodone, respectively.

The $AUC_{72}$ for each dose of Posimir was compared to placebo using an analysis of variance (ANOVA) model with treatment and site as main effects. It was pre-specified that the placebo groups would be pooled. Dunnett's adjustment was used to account for two comparisons to placebo. The proportion of subjects using rescue medication through Day 3 and Day 15 were compared between treatment arms using a Cochran Mantel Haenszel (CMH) test. To account for the second primary endpoint, a step-down approach was used. If the comparison of $AUC_{72}$ was statistically significant then the proportion of subjects using rescue was tested. The results for $RES_{72}$ were compared between treatment groups using a Wilcoxon rank-sum (WRS) test. Time to first post-operative use of rescue medication was analyzed using Kaplan-Meier methods. A log-rank test was used to compare the survival curves between both doses of Posimir and placebo, and the median time to first use of rescue medication was reported. To account for the two comparisons of Posimir to placebo, I utilized the Sidak adjustment. The Sidak adjustment is slightly more powerful than the Bonferroni adjustment and assumes the individual tests are independent.

Overall, the statistical methodologies utilized by the Applicant for the analyses of the primary and secondary efficacy outcomes were acceptable. Even though LOCF imputation for subjects that discontinued due to an adverse event may not be appropriate, there were only four subjects that discontinued. This is not an issue. The hypotheses posed by the applicant seemed to indicate that a statistical win would be required for each primary endpoint, $AUC_{72}$ and proportion of subjects using rescue medication. However, with the sequential testing strategy utilized, $AUC_{72}$ was tested first. This would allow for a win on $AUC_{72}$ but not on proportion of subjects using rescue medication.

**Results and Conclusions**

A summary of the applicant's primary analysis and mine for $AUC_{72}$ are shown in Table 4. Both analyses account for missing pain scores and rescue medication.

**Table 4. Results from analysis of normalized AUC in Study CLIN-803**

| | Normalized $AUC_{72}$ (PI) - mean (SEM) | | |
|---|---|---|---|
| | Placebo (n=32) | Posimir 330 mg (n=43) | Posimir 660 mg (n=47) |
| Applicant | 3.6 (0.3) | 3.1 (0.3) | 2.5 (0.2) |
| Reviewer | 4.0 (0.3) | 3.3 (0.3) | 2.7 (0.2) |

Source: Reviewer

The point estimates for the difference in LSMEANs between the two doses of Posimir and placebo from my analysis are shown in Table 5. I also present the corresponding 95% confidence intervals (CI) for the difference and associated p-values for the comparison to placebo.

**Table 5. Comparison of Posimir to placebo in Study CLIN-803**

| treatment | Difference | 95 % CI | p-value |
|---|---|---|---|
| Posimir 330 mg | -0.8 | [-1.6, 0.5] | 0.1 |
| Posimir 660 mg | -1.4 | [-2.1, -0.6] | 0.001 |

Source: Reviewer

Note, the AUCs and p-values in my analyses were slightly different from the applicant, although minor. These differences are most likely due to how I handled the use of rescue medication and missing data. I discuss this below. Regardless, my analysis agrees with the applicant: there was a significant difference noted for Posimir 660 mg versus placebo but not for the 330 mg dose.

As an AUC is cumulative and derived from the PI scores measured at each time point, I examined subject level data for missing pain scores. Based on the electronic data submitted by the Applicant, missing data due to discontinuation was not an issue. This was not unexpected as the study was conducted in an inpatient setting and patients only received a single dose of treatment. However, there were some intermittent missing pain scores. The amount of missing data is shown in Table 6.

**Table 6. Missing pain assessments in Study CLIN-803**

| Time-point (hours post-dose) | Number of missing observations (%) | | | |
|---|---|---|---|---|
| | Placebo (n=32) | Posimir 330 mg (n=43) | Posimir 660 mg (n=47) | Combined (n=122) |
| 1 | 3 (9.4) | 1 (2.3) | - | 4 (3.3) |
| 2 | 1 (3.1) | - | 1 (2.1) | 2 (1.6) |
| 3 | - | - | - | - |
| 4 | 1 (3.1) | 1 (2.3) | - | 2 (1.6) |
| 6 | 3 (9.4) | 2 (4.7) | 2 (4.3) | 7 (5.7) |
| 8 | 2 (6.3) | - | 2 (4.3) | 4 (3.3) |
| 10 | 2 (6.3) | 1 (2.3) | 4 (8.5) | 7 (5.7) |
| 12 | 6 (18.8) | 4 (9.3) | 2 (4.3) | 12 (9.8) |
| 22 | 4 (12.5) | - | - | 4 (3.3) |
| 26 | 3 (9.4) | 1 (2.3) | 2 (4.3) | 6 (4.9) |
| 30 | 2 (6.3) | 3 (7.0) | - | 5 (4.1) |
| 34 | 2 (6.3) | - | 1 (2.1) | 3 (2.5) |
| 46 | 2 (6.3) | 2 (4.7) | 4 (8.5) | 8 (6.6) |
| 50 | 2 (6.3) | 1 (2.3) | 4 (8.5) | 7 (5.7) |
| 54 | 4 (12.5) | 3 (7.0) | 2 (4.3) | 9 (7.4) |
| 58 | 1 (3.1) | 2 (4.7) | 3 (6.4) | 6 (4.9) |
| 70 | - | 1 (2.3) | 2 (4.3) | 3 (2.5) |

Source: Reviewer

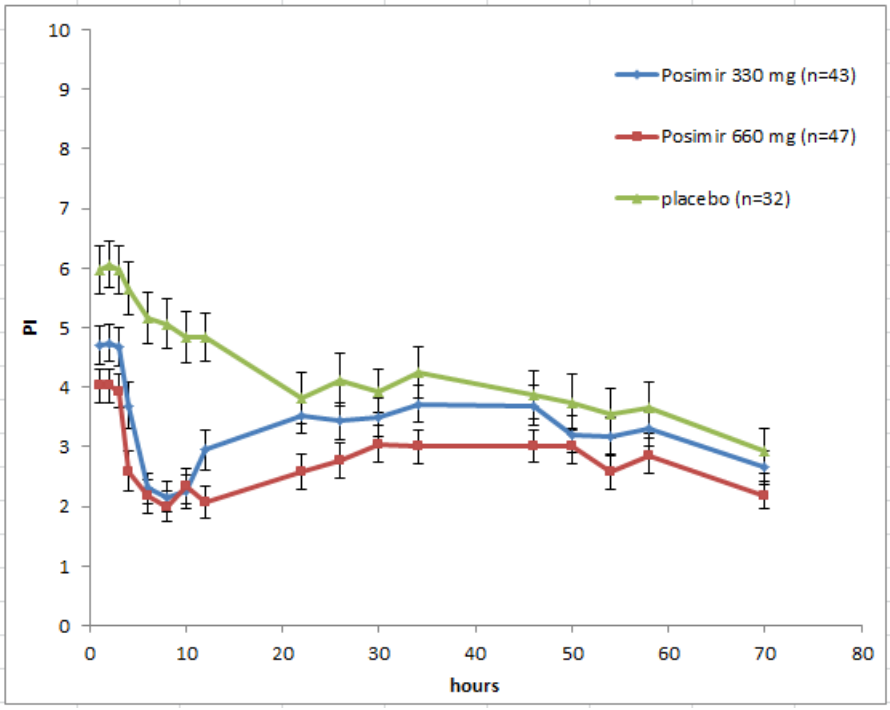
Missing PI scores were less than 10% at all measured time points, with the most missing data being at 12 hours post-surgery. This was not unexpected as it would be the most inconvenient

time point to collect. As missing data was fairly low and this was an inpatient study with a single administration of study drug, I decided it was acceptable to use WOCF for missing PI scores when deriving the AUC for each subject. This is in contrast to the applicant who used LOCF.

Next, I accounted for the use of rescue medication. When I only considered medication coded as rescue in the applicant's dataset, there were 511 uses of tramadol and oxycodone. However, when I expanded this to include concomitant medication and surgery medication, there were 714 uses of opioids which included fentanyl, morphine, oxycodone, tramadol, and codeine. In my derivation of $AUC_{72}$ I considered all opioid medication regardless of how classified. If a patient received rescue at time $x$, for any time point within $x + 4$ hours, the highest score from time 0 up until time $x$ was used. If the PI score for the windowed observation was higher than the worst observed score, it was not replaced. I did not consider 592 uses of APAP, although I did examine its use in an exploratory analysis and did not note any significant differences between treatment groups. I discuss this in more detail below.

Using the above methods for missing PI scores and use of rescue medication, the mean PI scores for each treatment group by time are shown in Figure 1. Error bars indicate the 95% CI of the point estimate.

**Figure 1. Mean PI scores at each measured time point in Study CLIN-803.**




Source: Reviewer

I compared each dose of Posimir to placebo at each time point using the same ANOVA model utilized in primary analysis. However, as this was exploratory I did not adjust for multiplicity. Results are shown in Table 7.

**Table 7. Comparisons of PI scores at assessed time point in Study CLIN-803**

| Time point (hrs) | Difference from placebo (PI) | | | | | |
|---|---|---|---|---|---|---|
| | Posimir 330 mg (n=43) | | | Posimir 660 mg (n=47) | | |
| | mean | stder | p-value | mean | stder | p-value |
| 1 | -1.3 | 0.5 | 0.01 | -1.9 | 0.5 | < 0.0001 |
| 2 | -1.3 | 0.5 | 0.01 | -2.0 | 0.5 | < 0.0001 |
| 3 | -1.3 | 0.5 | 0.01 | -2.0 | 0.5 | < 0.0001 |
| 4 | -2.0 | 0.5 | <0.0001 | -2.0 | 0.5 | <0.0001 |
| 6 | -2.9 | 0.5 | <0.0001 | -3.0 | 0.5 | <0.0001 |
| 8 | -2.9 | 0.5 | <0.0001 | -3.0 | 0.5 | <0.0001 |
| 10 | -2.6 | 0.5 | <0.0001 | -2.5 | 0.5 | <0.0001 |
| 12 | -1.9 | 0.5 | 0.0002 | -2.8 | 0.5 | <0.0001 |
| 22 | -0.3 | 0.5 | 0.6 | -1.2 | 0.5 | 0.01 |
| 26 | -0.7 | 0.5 | 0.2 | -1.4 | 0.5 | 0.007 |
| 30 | -0.4 | 0.5 | 0.4 | -0.9 | 0.5 | 0.06 |
| 34 | -0.5 | 0.5 | 0.3 | -1.3 | 0.5 | 0.01 |
| 46 | -0.2 | 0.5 | 0.7 | -0.9 | 0.5 | 0.07 |
| 50 | -0.5 | 0.5 | 0.3 | -0.7 | 0.5 | 0.2 |
| 54 | -0.4 | 0.5 | 0.5 | -1.0 | 0.5 | 0.04 |
| 58 | -0.4 | 0.5 | 0.5 | -0.8 | 0.5 | 0.1 |
| 70 | -0.3 | 0.4 | 0.5 | -0.7 | 0.4 | 0.7 |

Source: Reviewer

The results presented in Figure 1 and Table 7 may help with the clinical interpretation of the effect size observed with the primary endpoint, $AUC_{72}$. In Figure 1 there is clear separation between in the curves for both doses of Posimir and placebo out to approximately 24 hours post-surgery. The non-significance of the comparison of Posimir 330 mg to placebo for $AUC_{72}$ was supported by the results observed in Table 6 where nominal statistical significance was only noted out to 12 hours. On the other hand, nominal significance for Posimir 660 mg versus placebo was noted out to approximately 24 hours and the comparison to placebo for $AUC_{72}$ was statistically significant. It should be noted that for both doses of Posimir, the separation from placebo during hours 24 − 72 was not the same magnitude observed during hours 0 − 24. Hence, the significant difference demonstrated in the comparison of $AUC_{72}$ for the Posimir 660 mg arm may be influenced by the early separation in the pains curves.

The results from the proportion of subjects using rescue medication through Day 3 and Day 15 are shown in Tables 8 and 9.

**Table 8. Percent of subjects using opioid rescue medication through Day 15 in Study CLIN-803**

| Treatment | n | Opioids coded as rescue | All Opioids |
|---|---|---|---|
| Placebo | 32 | 72 | 72 |
| Posimir 330 mg | 43 | 65 | 74 |
| Posimir 660 mg | 47 | 49* | 53 |

*p-value=0.04
Source: Reviewer

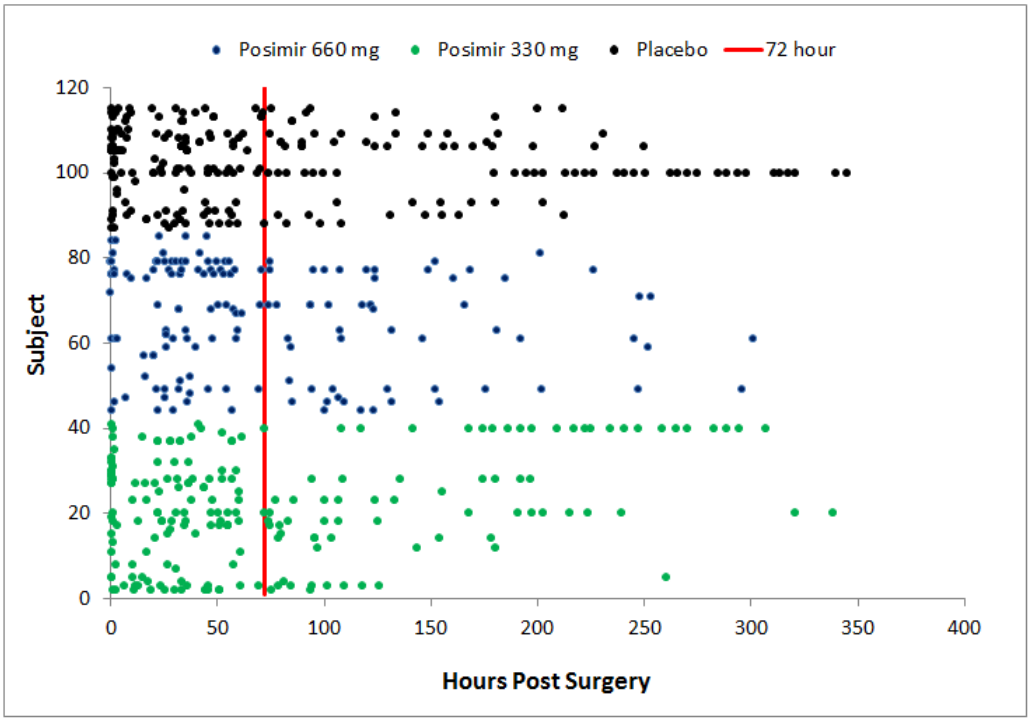
**Table 9. Percent of subjects using opioid rescue medication through Day 3 in Study CLIN-803**

| Treatment | n | Opioids coded as rescue | All Opioids |
|---|---|---|---|
| Placebo | 32 | 72 | 72 |
| Posimir 330 mg | 43 | 63 | 72 |
| Posimir 660 mg | 47 | 49* | 51 |

*p-value=0.04
Source: Reviewer

Regardless of duration, Day 3 or Day 15, when I examined only opioids coded as rescue there was a significant difference noted between placebo and Posimir 660 mg for the percentage of subjects using rescue medication, p-value=0.04. However, when I considered all opioids, not just those coded as rescue, there was no longer a significant treatment effect. Further, regardless of how opioids were coded, I noticed there was very little difference in the results from Day 3 versus Day 15. To explore this, I present subject level use of rescue opioids in Figure 2. I present the data for all opioids regardless of classification. The reference line indicates the 72 hour time point.

**Figure 2. Subject level use of rescue medication after study drug administration in Study CLIN-803**




Source: Reviewer

In Figure 2, if a subject used rescue medication, they used early and often. Hence there was very little difference between the percentages of subjects using through Day 3 versus Day 15.

I also examined the amount of opioid rescue medication (mg morphine equivalent) consumed through 72 hours post-surgery, $RES_{72}$. While not a pre-specified primary endpoint, I considered

$RES_{72}$ to be a clinically relevant endpoint. Further, this was a co-primary endpoint in Study BU-002. Medications were converted to morphine equivalents using the conversion table provided by the applicant. It was pre-specified that results would be compared using an ANOVA model with treatment and site if the assumptions of normality and heterogeneity of variance were met. If these assumptions were violated, a non-parametric test would be used. In my analysis and the applicant's these assumptions were violated. A plot of the residuals indicated the data was left skewed and a test for homogeneity of the variance was rejected, p-value < 0.001. Therefore a non-parametric test, Wilcoxon Rank Sum (WRS) test was utilized. Results are shown in Table 10.

**Table 10. Amount of rescue medication consumed through 72 hours post-surgery in Study CLIN-803**

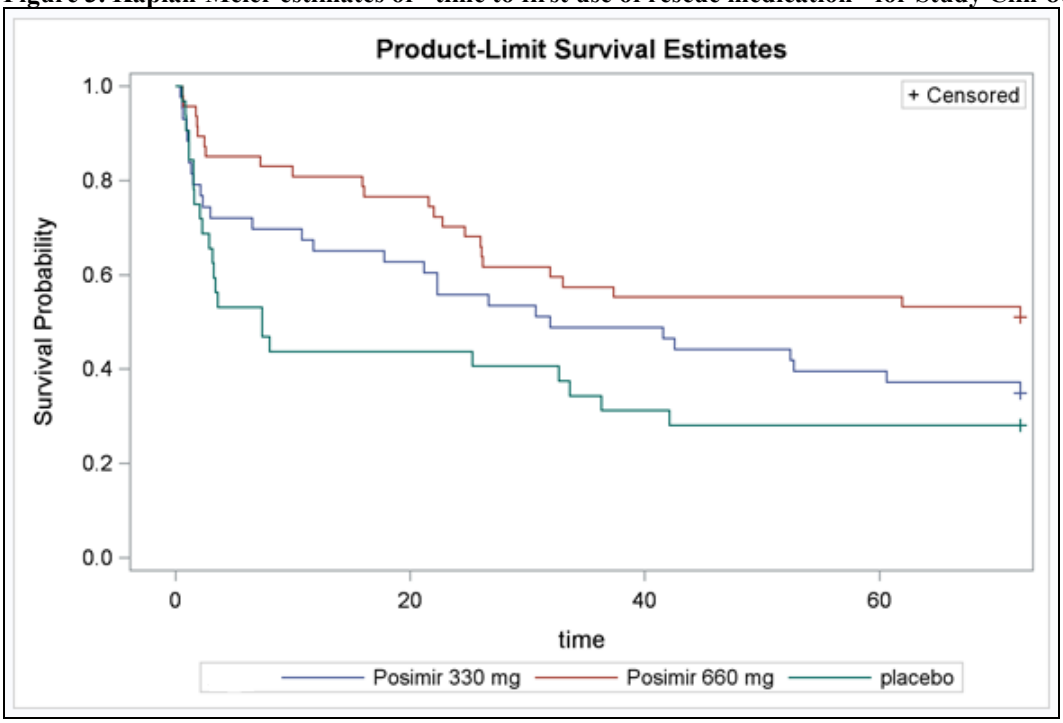
| Treatment | Morphine Equivalent (mg) mean (stdev) | p-value |
|---|---|---|
| Placebo (n=32) | 29.9 (57.6) | - |
| Posimir 330 mg ( n=43) | 13.1 (14.1) | 0.05 |
| Posimir 660 mg (n=47) | 10.4 (13.1) | < 0.01 |

Source: Reviewer

There was a significant difference noted for the comparison of placebo to Posimir 660 mg, p-value < 0.01. However, the comparison of placebo to Posimir 330 mg was borderline significant at the 0.05 level. Regardless of dose, the use of Posimir reduced the amount of opioid medication consumed.

Next I examined the time to first use of rescue medication. In this analysis I considered all post-operative opioids not just those coded as rescue medication. A subject was considered censored if they did not use rescue medication prior to 72 hours post-surgery. The median time to first use of post-operative rescue medication was 7.4 hour hours in the placebo arm, 31.9 hours in Posimir 330 mg, and 72 hours in the Posimir 660 mg treatment arm. Using Kaplan-Meier methods, the survival curves for time to first use of rescue medication for each treatment arm are shown in Figure 3.

**Figure 3. Kaplan-Meier estimates of "time to first use of rescue medication" for Study Clin-803**




Source: Reviewer

Based on the log-rank test adjusted for the two comparisons, a significant difference exists in the distributions of time to first use of rescue medication between Posimir 660 mg and placebo, p-value=0.02 However, the was not a significant difference noted between Posimir 330 mg and placebo, p-value=0.7.

Even though my examination for use of rescue medication did not include approximately 600 uses of APAP, I did explore its use. The percentage of subjects using APAP was similar amongst treatment arms. Approximately 78, 77, and 55 percent of subjects used APAP in the placebo, Posimir 330 mg, and Posimir 660 mg arms, respectively. The average amount of APAP consumed during the first 72 hours post-treatment was also similar between treatment arms; 2.9, 2.8, 2.3 grams for the placebo, Posimir 330 mg, and Posimir 660 mg, respectively. Based on this information, I decided it was acceptable to exclude the use of APAP from my analyses of rescue medication.

During my exploration of the data for use of rescue medication, I also noted that there was considerable use of medication that could be classified as rescue medication prior to study drug administration. The majority of medication used was fentanyl and morphine and most subjects were involved. In fact only three subjects did not use; two in the placebo arm and one in the Posimir 330 mg arm. The amount of medication in morphine equivalent daily doses was 4.2 mg, 3.1 mg, and 3.4 mg, in the placebo, Posimir 330 mg, and Posimir 660 mg arms, respectively. There were no significant differences noted. Even though pre-treatment use of rescue type medication was not considered in determining the percentage of subjects who used post-treatment rescue medication or amount of post-operative rescue medication, I did consider it when deriving $AUC_{72}$ as it could have influenced the 1 and 2 hour pain assessments. There did

not appear to be a difference between treatment arms in the frequency or amount of "rescue" medication used pre-treatment. Further, based on discussions with the medical officer, this use of rescue medication is typical for this type of surgery.

In summary, in this study there was a significance difference noted between placebo and Posimir 660 mg for the first primary endpoint, $AUC_{72}$. This difference was supported when I examined the mean PI scores by time, Figure 1. However, the magnitude of the separation between the curves for placebo and Posimir is diminished after 24 hours. There was no difference noted between Posimir 330 mg and placebo for $AUC_{72}$. For the second primary endpoint, proportion of subjects using rescue medication, when I examined all rescue medication, not just medication coded as rescue, there was not a significant difference between placebo and either dose of Posimir although numerically the numbers were in favor of Posimir. When I examined the amount of rescue medication consumed, $RES_{72}$, there was a significant difference noted in favor of Posimir 660 mg versus placebo but not Posimir 330 mg. This was supported by my analysis of time to first use of rescue medication. Subjects treated with Posimir 660 mg, on average reported less post-surgical pain, required less rescue medication, and waited longer to request it.

#### 3.2.1.1 Supportive Studies

The Applicant submitted the results of a phase 2 trial that evaluated Posimir in subjects undergoing hernia repair surgery, Study CLIN005-0010. The study design and results are presented below. This study failed to show a significant treatment benefit of Posimir in treating post-surgical pain associated with hernia repair surgery.

This was a randomized double-blind, placebo-controlled phase 2 study that evaluated Posimir administered subcutaneous and subaponeurotic to subjects following open hernia repair surgery and was conducted in two cohorts. Subjects were enrolled at seven sites in the United States (California, New York, Pennsylvania, Utah, and Wisconsin) and one site in New Zealand. In Cohort 1, subjects were randomized to one of three treatment arms. In treatment arm 1, placebo was injected into the subaponeurotic space and Posimir 660 mg was administered subcutaneously along the incision line after wound closure. In treatment arm 2, Posimir 660 mg was administered into the subaponeurotic space and placebo was administered subcutaneously along the incision line. In treatment arm 3, placebo was administered in both locations. For Cohort 2, placebo or Posimir 660 mg was instilled into the surgery site prior to wound closure, treatment arms 4 and 5, respectively. One subject in treatment arm 5 was administered 7.5 mL Posimir (990 mg).

The primary efficacy endpoints were PI at rest and on movement and pain control as assessed by the subject. PI was assessed using an 11-point NRS and pain control was evaluated using a 5-point scale. For pain control subjects were asked "How would you rate your overall pain control in the last 24 hours?" Responses were poor, fair, good, very good, or excellent. The pre-specified primary endpoints were PI and pain control on Days 0 through 7. For subjects that required supplemental analgesia, pain scores on movement were recoded prior to use. Via a protocol amendment, the primary endpoint was changed to a normalized AUC of PI scores for at rest and on movement at 120 hours post-surgery and were compared between treatment arms using an ANOVA model where the comparison of interest was treatment arm 5 versus pooled placebo, treatment arms 3 and 4. Missing data was imputed using LOCF for monotonic

missingness and intermittent missing scores used the average of adjacent scores. The applicant also conducted a sensitivity analysis where pain scores prior to using rescue medication was used in the derivation of the AUC.

The analysis population consisted of all randomized and treated subjects. The number of subjects per treatment arm is shown in Table 11.

**Table 11. Number of subjects per treatment arm in Study CLIN005-0010**

| Treatment Number | Description | Number of subjects randomized and treated |
|---|---|---|
| 1 | Placebo subaponeurotic 5 ml + Posimir SC 5 mL | 14 |
| 2 | Placebo SC 5 mL + Posimir subaponeurotic 5 mL | 13 |
| 3 | Placebo SC 5 mL + Placebo subaponeurotic 5 mL | 18 |
| 4 | Placebo subaponeurotic 5 mL | 21 |
| 5 | Posimir subaponeurotic 5 mL | 22 |
| 5a | Posimir subacromial 7.5 mL | 1 |

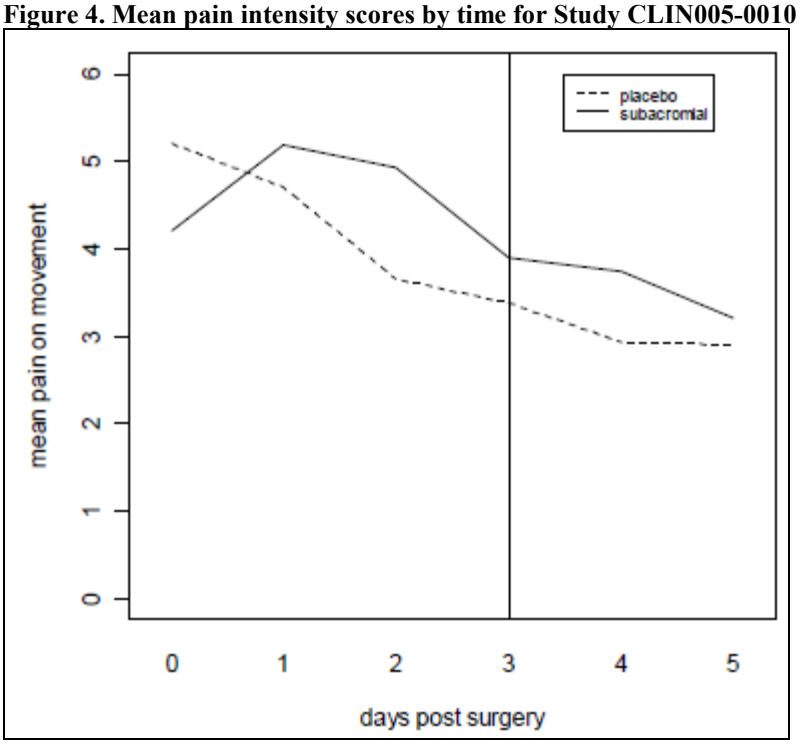
SC=subcutaneous
Source: Reviewer

Of the 89 subjects that were randomized and treated, 86 completed the study. There were three subjects that were lost to follow-up, two on active drug and one on placebo. This study mostly evaluated male Caucasian subjects. There were five female subjects randomized, two Asian subjects, one African American subject, and four classified as other. The average age in years was 48 with a range of 21 to 89. The analysis population consisted of all randomized and treated subjects.

The only comparison that demonstrated statistical significance in favor of Posimir was treatment group 5 versus pooled placebo. However, AUC at 120 hours post-surgery was not the endpoint examined in the pivotal study, CLIN-803-006-0006 and the two placebo groups received different volumes of study drug. To compare the results of this study to the pivotal study, I compared mean $AUC_{72}$ for treatment groups 4 and 5 as these treatment arms received the same volume of study drug administered in the pivotal study. The LSMEANS were 4.1 and 4.8 for placebo and Posimir, respectively. The 95% CI for the difference between Posimir and placebo was [-0.5, 0.8]. The point estimate 0.6, while not significant, was in favor of placebo. This analysis accounted for the use of rescue medication by incorporating pain scores measure prior to using rescue medication when deriving the AUC. Even though this study used LOCF for discontinuations due to AE's they were only two dropouts and none were attributable to an AE.

I next examined the PI scores that were used to generate the AUC's reported above. The pain intensity scores by time are shown in Figure 4. The solid vertical line indicates the 72 hour time point. The solid line in the figure represents Posimir 660 mg, indicated as subacromial in the legend. Note, there is no subacromial space in the abdominal cavity.

**Figure 4. Mean pain intensity scores by time for Study CLIN005-0010**



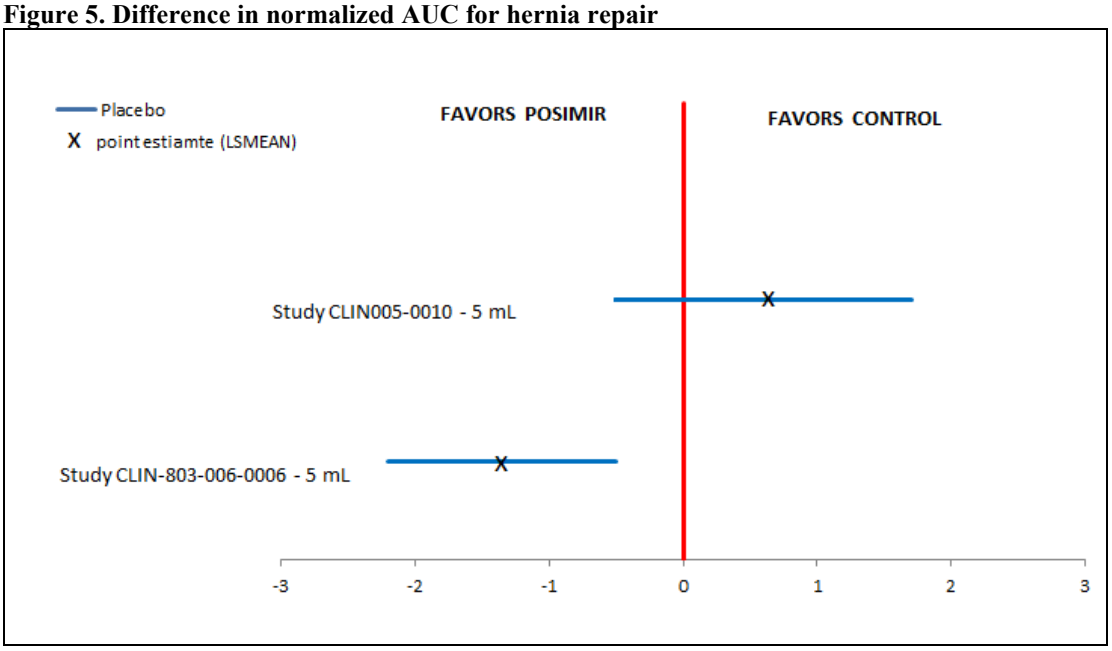

Source: Figure 3 from applicant's CSR

Clearly, the mean pain scores for the Posimir 660 mg treatment arm increased during the first 24 hours. This effect was not observed in the placebo arm. The clinical rationale for this effect is unknown.

Since the point estimate for the difference in $AUC_{72}$ was in the wrong direction, I examined the amount of rescue medication consumed through 72 hours for treatment arms 4 and 5. Results, even though not significant, indicate that subjects in the placebo arm, on average used less rescue medication than subjects in the Posimir 660 mg arm. It seems for this study, placebo subjects had less post-surgical pain and used less rescue medication. There were no differences in the demographics between studies except that this study was mainly conducted in the United States, whereas the successful study was conducted in Australia and New Zealand.
Further examination of these results by site location, United States versus Australia and New Zealand, did not reveal any significant findings. In general the mean $AUC_{72}$ for the Posimir treatment arm was higher than the placebo arm.

I summarize the results of $AUC_{72}$ for the two studies that evaluated post-surgical pain associated with hernia repair surgery. Figure 5 shows the point estimates and 95% CI for difference from placebo for $AUC_{72}$. Note, the 5 mL dose is equal to 660 mg of Posimir.

**Figure 5. Difference in normalized AUC for hernia repair**




Source: Reviewer

I consider these results to be inconclusive. It seems that for the failed supportive study, placebo subjects had less post-surgical pain and used less rescue medication. The only notable difference in demographics between these two studies was the location. The failed study was mainly conducted in the United States, whereas the successful study was conducted in Australia and New Zealand.

## 3.2.2 Arthroscopic Shoulder Surgery

### 3.2.2.1 Pivotal Study

Study BU-002 was identified as pivotal by the applicant. Of the statistical issues identified during IND stage, the applicant addressed my concern regarding use of rescue medication and accounting for it the primary analysis. The applicant conducted a sensitivity analysis where use of rescue medication was accounted for in analysis.

Based on the results of a previous trial in subjects undergoing hernia repair surgery, the applicant estimated 25 placebo subjects and 50 Posimir 660 mg subjects would provide 80% power to detect a significant difference in morphine equivalent doses of 0.6 mg. Additionally, 25 subjects on standard release Bupivacaine were included.

**Study Design and Endpoints**

Eligible patients that were to undergo arthroscopic shoulder surgery were randomized to placebo, Posimir 660 mg, or bupivacaine in a 1:2:1 fashion. Following surgery, a single dose of the study drug was administered into the subacromial space. Subjects remained in the hospital at least 48 hours following surgery. Allowed rescue medication during the first 72 hours following surgery was oral morphine and if needed, IV morphine. Since standard bupivacaine and Posimir are

different in appearance, dosed at different volumes, and administered differently, a non-blinded surgery team performed the procedure and administered study drug. All other staff involved in post-treatment assessments were blinded. PI was measured (11-point NRS) at 1, 2, 4, 6, 8, and 12 hours post-treatment (Day 0) and at 8:00, 12:00, 16:00, 20:00 on Days 1-7. Subjects were *not* instructed to measure PI scores prior to using rescue medication.

**Patient Disposition, Demographic and Baseline Characteristics**

Overall, 126 subjects were screened and 115 were randomized. Eight randomized subjects discontinued prior to surgery and did not receive treatment. Demographics for randomized and treated subjects are shown in Table 12.

**Table 12. Patient demographics for Study BU-002**

| Characteristic | Treatment | | |
|---|---|---|---|
| | placebo | Posimir 660 mg | bupivacaine |
| Number of Patients | 25 | 53* | 29 |
| Age in years | | | |
| Mean (SD) | 49 (10) | 50 (9.5) | 52 (11) |
| Median | 52 | 49 | 52 |
| [range] | [24, 63 ] | [28, 70] | [21, 70] |
| Gender, n (%) | | | |
| Female | 14 (56) | 33 (62) | 17 (59) |
| Male | 11 (44) | 20 (38) | 12 (41) |
| Race, n (%) | | | |
| Caucasian | 24 (96) | 50 (98) | 29 (100) |
| Black | - | - | - |
| Asian | 1 (4) | 1 (2) | - |
| Other | - | - | - |

*2 subjects missing response for race
Source: Reviewer

There were slightly more females than males which was consistent amongst the three treatment arms. The study mainly evaluated Caucasian subjects and as expected, there were no subjects that discontinued from the study.

**Statistical Methodologies**

The applicant identified two primary endpoints, $AUC_{72}$ and the amount of opioid rescue medication in morphine equivalent doses used through 72 hours, $RES_{72}$. $AUC_{72}$ was to be tested for non-inferiority (NI) to placebo first, it established, superiority of Posimir to placebo would be tested. The rationale given was that the use of rescue medication may dilute the treatment effect and superiority may not be established. NI was to be declared if the upper limit (UL) for the 95% confidence interval (CI) for the difference between the $AUC_{72}$ for Posimir and placebo was less than or equal to 0.5. Superiority would be tested using an ANOVA model with treatment and pooled country as factors. Rescue medication consumed during the first 72 hours following treatment was converted to morphine equivalent doses (mg) using the conversion table provided by the sponsor. Results for $RES_{72}$ would be compared between placebo and Posimir using an ANOVA model with treatment and site as effects. If the assumptions of normality and homogeneous variance were not met, a non-parametric test would be used. There would be no formal comparison between Posimir and standard bupivacaine; hence no adjustments for multiplicity were incorporated into the analysis.

This study did not instruct subjects to measure pain scores prior to using rescue medication. To account for this, the applicant proposed a post-hoc sensitivity analysis based on FDA's advice. In this analysis, if a subject used rescue medication on or before a scheduled assessment, within one half-life of the rescue drug, the rescue pain score was considered to be the worst pain score observed prior to its use. This is analogous to worst observation carried forward (WOCF). I took a slightly different approach. Instead of using WOCF when subject used rescue medication, I randomly assigned each subject a moderate pain score, a score 5, 6, or 7. If a subject used rescue medication within 4 hours of a schedule pain assessment, this pain score was used if it larger than the recorded pain score. I used a 4 hour window regardless of the rescue medication used.

The applicant's dataset that contained the pain scores recorded following surgery did not contain the time of assessment. I utilized their derived dataset that contain the time of assessment. Per the applicant's explanation, pain was assessed at pre-specified time points post-surgery and the actual time of assessment was not recorded.

**Results and Conclusions**

The results of the applicant's primary analysis and mine when testing for superiority of Posimir to placebo for $AUC_{72}$ are shown in Tables 13 and 14. The applicant's results presented below were from the sensitivity analysis that accounted for the use of rescue medication. My results are consistent with the applicant. There was a significant treatment effect in favor of Posimir.

**Table 13. Results from analysis of normalized AUC in Study BU-002**

| | Normalized $AUC_{72}$ (PI) - mean (SEM) | | |
|---|---|---|---|
| | Placebo (n=25) | Posimir 660 mg (n=53) | Bupivacaine (n=29) |
| Applicant | 6.3 (0.4) | 5.0 (0.3) | 5.0 (0.4) |
| Reviewer | 6.4 (0.4) | 5.3 (0.3) | 5.5 (0.4) |

Source: Reviewer

The point estimates for the difference in LSMEANs between the Posimir 660 mg and placebo from my analysis are shown in Table 14. I also present the corresponding 95% CI for the difference and the p-values for the comparison to placebo. For interest, I also present the comparison of placebo to bupivacaine.

**Table 14. Comparison of Posimir to placebo in Study BU-002**

| | Difference | 95% CI | p-value |
|---|---|---|---|
| Posimir 660 mg | -1.1 | [-2.1, -0.2] | 0.02 |
| Bupivacaine | -0.2 | [-1.1, 0.7] | 0.1 |

Source: Reviewer

While not used for inferential value, I did compare bupivacaine to Posimir, results not shown. A significant difference was not noted, p-value of 0.7. As the applicant used LOCF, included pooled country in their ANOVA model, and used different windows for the adjustment of rescue medication, my derivation of the mean AUC for each treatment arm differ slightly as I used BOCF and a constant 4 hour window when considering use of rescue medication. The

applicant's pre-specified statistical analysis plan indicated they would test for NI of Posimir to placebo first. If NI was established, superiority would be tested. Even though NI was established as indicated by the 95% CI shown in Table 14, there is no clinical interpretation of establishing NI to placebo as a rationale for a NI margin was not established. Regardless, superiority was demonstrated.

As an AUC is cumulative and derived from the PI scores measured at each time point, I examined subject level data for missing PI scores. Similar to Study ClIN-803, monotonic missing data was not an issue as subjects were hospitalized following surgery and none withdrew prior to 72 hours. However, there were some intermittent missing data. The amount of data missing at each time point post-surgery is shown in Table 15.

**Table 15. Missing pain assessments in Study BU-002**

| Time-point (hours post-dose) | Number of missing observations (%) | | | |
|---|---|---|---|---|
| | Placebo (n=25) | Posimir 660 mg (n=53) | Bupivacaine (n=29) | Combined (n=107) |
| 1 | - | - | - | - |
| 2 | 7 (28.0) | 8 (15.1) | 5 (17.2) | 20 (18.7) |
| 4 | 2 (8.0) | 7 (13.2) | 6 (20.7) | 15 (14.0) |
| 6 | 2 (8.0) | 7 (13.2) | 4 (13.8) | 13 (12.1) |
| 8 | 2 (8.0) | 4 (7.5) | 1 (3.4) | 7 (6.5) |
| 12 | 1 (4.0) | - | 1 (3.4) | 2 (1.9) |
| 22 | 4 (16.0) | 8 (15.1) | 5 (17.2) | 17 (15.9) |
| 26 | 2 (8.0) | 5 (9.4) | 3 (10.3) | 10 (9.3) |
| 30 | 1 (4.0) | 5 (9.4) | 5 (17.2) | 11 (10.3) |
| 34 | 1 (4.0) | 3 (5.7) | 3 (10.3) | 7 (6.5) |
| 46 | 3 (12.0) | 8 (15.1) | 3 (10.3) | 14 (13.1) |
| 50 | 3 (12.0) | 3 (5.7) | 2 (6.9) | 8 (7.5) |
| 54 | 1 (4.0) | 6 (11.3) | 2 (6.9) | 9 (8.4) |
| 58 | 3 (12.0) | 4 (7.5) | 3 (10.3) | 10 (9.3) |
| 70 | 3 (12.0) | 5 (9.4) | 4 (13.8) | 12 (11.2) |
| 72 | 2 (2.0) | 9 (17.0) | 4 (13.8) | 15 (14.0) |

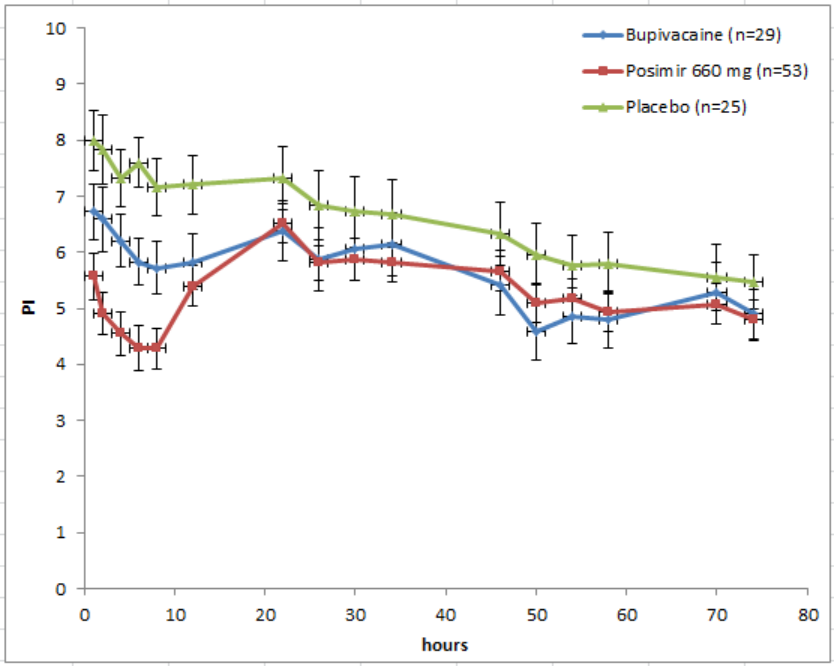
Source: Reviewer

There were more missing PI assessments in this study than in pivotal hernia repair study, CLIN-803. However, in all cases it was less than 20% with the most missing data at the 2, 22, and 72 hour post-treatment time point. Since there were no patterns or trends noted with the missing data and this was an inpatient study with a single administration of study drug, I was not concerned and used WOCF to impute missing pain scores. The applicant used LOCF.

Next, I accounted for the use of rescue medication. When I only considered medication coded as rescue, there were 427 uses of morphine. When I expanded this to include concomitant medication, general anesthesia, and IV medication; there were 697 uses of opioids which included fentanyl, midazolam, morphine, oxycodone, propofol, and tramadol. In my analysis of PI scores I considered all opioid medication regardless of how classified. As with Study CLIN-803, I did not consider 609 uses of APAP. If a patient received rescue at time $x$, for any time point within $x + 4$ hours, the assigned rescue pain score was used. If the PI score for the windowed observation was higher than the rescue pain score, it was not replaced.

The mean PI scores for each treatment group at each assessed time point are shown in Figure 6. Error bars indicate the 95% CI of the point estimate. This display of the PI scores that were used to generate $AUC_s$ may help with the clinical interpretation of the effect size observed with the primary endpoint, $AUC_{72}$.

**Figure 6. Mean PI scores at each measured time point in Study BU-002-IM**




Source: Reviewer

The above figure demonstrates separation in the curves for Posimir and bupivacaine from placebo out 72 hours. However, the magnitude of the separation from approximately 24 − 72 hours is not the same magnitude observed for hours 1 − 24. This was also observed in Study CLIN-803. It should be noted that regardless of treatment, most subjects had moderate pain throughout the study. Moderate pain is defined as a score between 4 and 7.

Exploring the data that generated the curves above, I compared the mean PI scores of Posimir and bupivacaine to placebo at each time point. As this was exploratory, I did not adjust for multiplicity. Results are shown in Table 16.

**Table 16. Comparison of PI scores by time in Study BU-002**

| Time point (hrs) | Difference from placebo (PI) | | | | | |
|---|---|---|---|---|---|---|
| | Posimir 660 mg (n=53) | | | Bupivacaine (n=29) | | |
| | LSMEAN | stder | p-value | LSMEAN | stder | p-value |
| 1 | -2.4 | 0.7 | 0.0003 | -1.3 | 0.7 | 0.09 |
| 2 | -2.9 | 0.6 | <0.0001 | -1.3 | 0.7 | 0.08 |
| 4 | -2.8 | 0.6 | < 0.0001 | -1.1 | 0.7 | 0.13 |
| 6 | -3.3 | 0.6 | <0.0001 | -1.7 | 0.7 | 0.01 |
| 8 | -2.8 | 0.6 | <0.0001 | -1.4 | 0.7 | 0.03 |
| 12 | -1.8 | 0.6 | 0.004 | -1.4 | 0.7 | 0.05 |
| 22 | -0.8 | 0.6 | 0.19 | -0.9 | 0.7 | 0.18 |
| 26 | -1.0 | 0.6 | 0.09 | -1.0 | 0.7 | 0.16 |
| 30 | -0.9 | 0.7 | 0.19 | -0.7 | 0.9 | 0.38 |
| 34 | -0.8 | 0.6 | 0.18 | -0.5 | 0.7 | 0.47 |
| 46 | -0.7 | 0.6 | 0.29 | -0.9 | 0.7 | 0.20 |
| 50 | -0.9 | 0.6 | 0.16 | -1.4 | 0.7 | 0.05 |
| 54 | -0.6 | 0.6 | 0.34 | -0.9 | 0.7 | 0.20 |
| 58 | -0.9 | 0.6 | 0.16 | -1.0 | 0.7 | 0.15 |
| 70 | -0.5 | 0.6 | 0.45 | -0.3 | 0.7 | 0.69 |
| 72 | -0.7 | 0.6 | 0.25 | -0.6 | 0.7 | 0.39 |

Source: Reviewer

From Table 16, the difference between Posimir and placebo is nominally significant out to 12 hours post-surgery. This indicates that the significant difference noted in the comparison of $AUC_{72}$ may be influenced by the early separation in the curves. There were no significant differences noted between bupivacaine and placebo. Based on the information in Figure 6 and Table 16, the clinical benefit of Posimir 660 mg in reducing post-surgical pain associated with shoulder repair surgery after 12 hours post-surgery is unclear.

Next I examined the second co-primary efficacy endpoint, amount of opioid rescue medication consumed through 72 hours, $RES_{72}$. I considered all opioids used regardless of how the applicant classified the use. It was pre-specified that results would be compared using an analysis of variance (ANOVA) model with treatment and site if the assumptions of normality and heterogeneity of variance were met. If these assumptions were violated, a non-parametric test would be used. In my analysis and the applicant's these assumptions were violated. A plot of the residuals indicated the data was left skewed and a test for homogeneity of variance was rejected, p-value < 0.001. Therefore a non-parametric test, Wilcoxon Rank Sum (WRS), was utilized. Results are shown in Table 17.

**Table 17. Amount of rescue medication consumed through 72 hours post-surgery in Study BU-002**

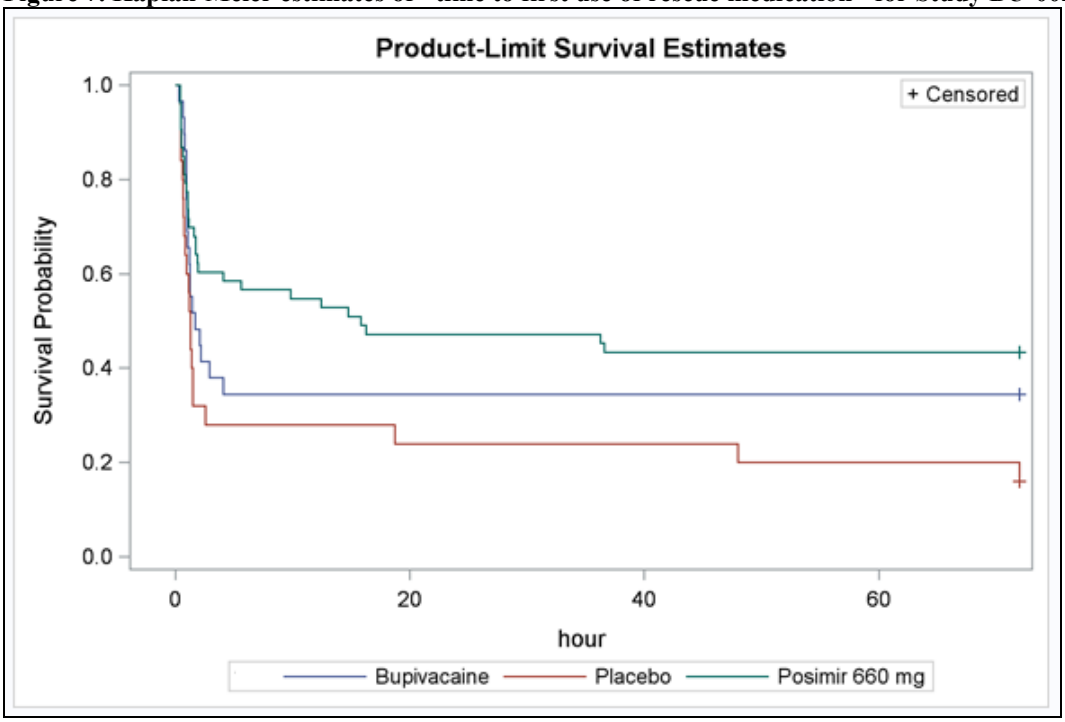
| Treatment | Morphine Equivalent (mg) mean (stdev) | p-value |
|---|---|---|
| Placebo (n=25) | 22.8 (25.8) | - |
| Posimir 660 mg (n=53) | 13.7 (29.1) | 0.01 |
| Bupivacaine (n=29) | 12.3 (17.6) | 0.07 |

Source: Reviewer

There was a significant treatment effect noted for Posimir 660 mg but not for bupivacaine. Subjects treated with Posimir 660 mg, on average used less rescue medication than placebo subjects, 12.3 mg versus 22.8 mg, respectively.

Next I examined time to first use of rescue medication. The median time to first use of post-operative rescue medication was 1.3 hours in placebo subjects, 15.8 hours in Posimir 660 mg treated subjects, and 1.7 hours in subjects treated with bupivacaine. Using Kaplan-Meier methods, the survival curves for time to first use of rescue medication for each treatment arm are shown in Figure 7. In this analysis I considered all post-operative opioids not just those coded as rescue medication. A subject was considered censored if they did not use rescue medication prior to 72 hours post-surgery.

**Figure 7. Kaplan-Meier estimates of "time to first use of rescue medication" for Study BU-002**




Source: Reviewer

Based on the log-rank test, a significant difference exists in the distributions of time to first use of rescue medication between Posimir 660 mg and placebo, p-value=0.01. However, there was not a significant difference between placebo and bupivacaine.

Even though my examination of rescue medication usage did not include 609 uses of APAP, I did explore its use. Every subject regardless of treatment took APAP at some point post-surgery. The average amount of APAP consumed during the first 72 hours post-treatment was also similar between treatment arms; 9.2, 9.8, 9.8 grams for the placebo, Posimir 660 mg, and bupivacaine, respectively. Based on this information, I decided it was acceptable not to include the use of APAP in my analyses of rescue medication.

As in Study CLIN-803 there were some subjects that used rescue medication prior to surgery, 40% in placebo arm, 34% in the Posimir arm, and 38% in the bupivacaine arm. Rescue medication used was mostly fentanyl or morphine. Again, as the clinical team felt this usage was appropriate, I did not include this use when determining the amount of rescue medication consumed through 72 hours. However, as done with Study CLIN-803, I did account for it when deriving AUCs as it could influence early pain scores.

In summary, this study did demonstrate the efficacy of Posimir in treating post-surgical pain associated with shoulder repair. There was a significant difference in favor of Posimir when I examined the pre-specified primary endpoints, $AUC_{72}$ and $RES_{72}$. This was supported by the analysis of secondary endpoints such as pain scores at each time point and time to first use of rescue medication. However, the clinical benefit of Posimir 660 mg in reducing post-surgical pain associated with shoulder repair surgery after 12 hours post-surgery is unclear. Although the study did not demonstrate that it was any better than standard bupivacaine, it was not designed to do so. That being said, Posimir was significantly better than placebo for primary endpoints, bupivacaine was not.

**3.2.2.2 Supportive Studies**

Two studies, CLIN803-017 and CLIN005-0006, that failed to demonstrate a statistically significant treatment benefit of Posimir in treating post-surgical pain associated with shoulder repair surgery were indicated as supportive by the applicant and are discussed below. Based on the applicants clinical study reports, these studies were conducted prior to the pivotal study. Study CLIN005-0006 was conducted from 2006 to 2007. Study C803-017 was conducted from 2008 to 2009. It is my impression that the applicant conducted these studies in a chronological order until a significant study was obtained.

Study CLIN005-0006: This was a randomized, double-blind, placebo-controlled phase 2 study conducted at six sites in Utah, Georgia, Pennsylvania, California, and Texas and one site in New Zealand. This study was conducted in two cohorts. In cohort 1, eligible subjects were randomized equally to one of three treatment arms. In treatment arm 1, prior to wound closure, 5 mL of placebo was injected into the subacromial space. After wound closure 5 mL of Posimir was administered as two trailing subcutaneous injections along each side of the incision line. In treatment arm 2, prior to wound closure 5 mL of Posimir was injected into the subacromial space. After wound closure 5 mL of placebo was injected along the incision line. In treatment arm 3, placebo was injected into the subacromial space and along the incision line. In cohort 2, subjects were randomized equally to either placebo, treatment arm 4, or Posimir 7.5 mL, treatment arm 5. In Cohort 2 study drug was only injected into the subacromial space. Via a protocol amendment the dose for Cohort 2 was changed from 7.5 mL to 5.0 mL. There were four subjects in treatment arm 4 and three subjects in treatment arm 5 that received the 7.5 mL dose. These treatment arms are referred to as 4a and 5a, respectively. The 5 mL dose of Posimir corresponds to 660 mg active product and the 7.5 mL dose corresponds to 990 mg.

Efficacy was assessed using the subjects' evaluation of pain intensity on movement and at rest and pain control collected via the subjects' diary. PI was assessed using an 11-point NRS and pain control was evaluated using a 5-point scale. Subjects were asked "How would you rate your overall pain control in the last 24 hours?" Responses were poor, fair, good, very good, or

excellent. The pre-specified primary endpoints were PI and pain control on Days 0 through 7. For subjects that required supplemental analgesia, pain scores on movement were recoded prior to use. Via a protocol amendment, the primary endpoint was changed to a normalized AUC of PI scores for at rest and on movement at 120 hours post-surgery and were compared between treatment arms using an ANOVA model where the comparison of interest was treatment arm 5 versus pooled placebo, treatment arms 3 and 4. Missing data was imputed using LOCF for monotonic missingness and intermittent missing scores used the average of adjacent scores. The applicant also conducted a sensitivity analysis where pain scores prior to using rescue medication was used in the derivation of the AUC. Post-hoc the applicant examined $AUC_{72}$ and $RES_{72}$.

The analysis population consisted of all randomized and treated subjects. The number of subjects per treatment arm is shown in Table 18.

**Table 18. Number of subjects per treatment arm in Study CLIN005-0006**

| Treatment Number | Description | Number of subjects randomized and treated |
|---|---|---|
| 1 | Placebo subacromial 5 ml + Posimir SC 5 mL | 14 |
| 2 | Placebo SC 5 mL + Posimir subacromial 5 mL | 10 |
| 3 | Placebo SC 5 mL + Placebo subacromial 5 mL | 16 |
| 4 | Placebo subacromial 5 mL | 24 |
| 5 | Posimir subacromial 5 mL | 35 |
| 4a | Placebo subacromial 7.5 mL | 4 |
| 5a | Posimir subacromial 7.5 mL | 3 |

SC=subcutaneous
Source: Reviewer

Overall, there were slightly more male subjects than female, 59% versus 41%, respectively. The average age of subjects was 54 years old with a range of 22 to 82 years old. The majority of subjects were Caucasian with the exception of 7 African American subjects, 2 Asian, and 3 subjects catagorized as other. Of the 92 subjects that were randomized and treated, 90 completed the study. Two subjects withdrew consent, one in the active arm and one in the placebo.

This study failed to show a significant difference between placebo and Posimir for AUC of PI scores out to 120 hours post-surgery. In a post-hoc analysis there was a significant difference noted in the $AUC_{72}$ for subjects that received Posimir via a subacromial injection and the pooled placebo group. However the placebo subjects in treatment group 3 received 10 mL of study drug and the placebo subjects in treatment arm 4 received 5 mL of study drug. A more relevant comparison would be treatment groups 4 and 5 as these treatment arms received 5 mL of study drug which was the volume administered in the pivotal study, BU-002-IM. The LSMEANs for $AUC_{72}$ were 5.6 and 5.2 for placebo and Posimir, respectively. The corresponding 95% CI for the difference between Posimir and placebo was [-1.7, 0.5] and failed to show a significant difference. This analysis did account for the use of rescue medication by using the pain scores that were measured prior to using rescue when deriving the AUCs.

Study C803-017: This was a randomized, double-blind, multi-center, placebo-controlled phase 2b study conducted at 8 sites in Australia and 2 sites in New Zealand. Eligible subjects were randomized to receive either placebo or Posimir 660 mg injected interstitially into the

subacromial space upon completion of the procedure. Assessment of efficacy was based on shoulder PI on movement and use of supplemental opioid analgesia. For subjects that required supplemental analgesia, pain scores on movement were recoded prior to use. Two primary efficacy endpoints were identified, normalized $AUC_{72}$ and $RES_{72}$ as measured by morphine equivalent units. The primary null hypotheses were that there were no differences between treatment groups in terms of $AUC_{72}$ and $RES_{72}$.

The analysis population consisted of 20 placebo subjects and 40 Posimir 660 mg subjects which constitute all randomized and treated subjects. A normalized $AUC_{72}$ was calculated for each subject using the standard trapezoidal rule and were compared between treatment groups using an ANCOVA model with treatment, site, and age as factors. Missing data was imputed using BOCF for subjects that discontinued due to an adverse event and LOCF for discontinuations due to any other reason. Intermittent missing data was replaced by using the mean of the values before and after. The mean total opioid dose was computed for each subject and compared between treatment groups using the same ANCOVA model. In case the normality assumption was violated, the applicant also conducted a non-parametric WRS test. To account for two primary endpoints the applicant utilized the Hochberg approach.

Of the 60 subjects randomized to treatment, 59 completed the study. One subject in the placebo withdrew consent. The majority of these subjects were Caucasian; 100% in placebo arm and 93% in the Posimir arm. There was one Aborigine, one Asian, and one other in the Posimir treatment arm. While the placebo arm enrolled equal numbers of male and female subjects, the Posimir treatment arm had slightly more female subjects than male subjects; 58% versus 42%, respectively. Results of the applicant's primary analysis are presented in Table 19. Even though the pain scores we measured prior to using rescue analgesia, the applicant did not utilize them in deriving the $AUC_{72}$.

**Table 19. Applicant's results for the primary analysis in Study C803-017**

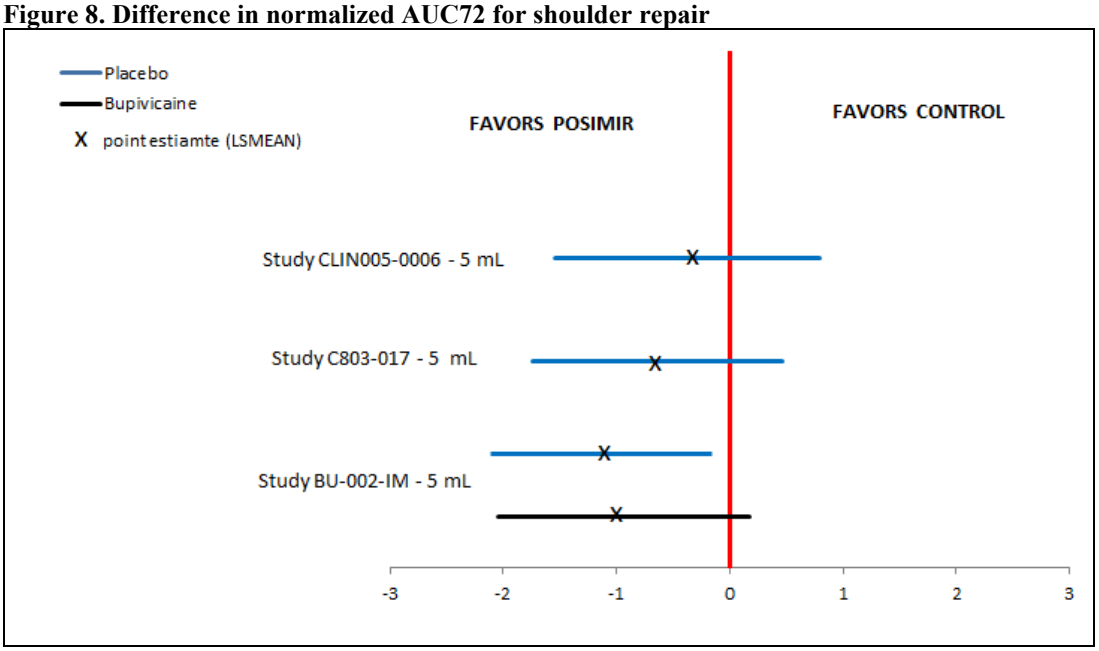
| Endpoint | Placebo (n=20) | Posimir 5 mL (n=40) | Difference (95% CI) | p-value |
|---|---|---|---|---|
| $AUC_{72}$ (pi) | 5.8 | 5.4 | -0.64 [-1.7, 0.47] | 0.3 |
| $RES_{72}$ (mg) | 49.9 | 44.5 | -10.7 (-30.0, 9.6) | 0.3 |

Source: Tables 14.1.8.1 and 14.1.9.1 from applicant's CSR

A significant treatment effect was not observed for either endpoint.

I summarize the results of $AUC_{72}$ for the three studies that evaluated post-surgical pain associated with shoulder repair surgery. Figure 8 shows the point estimates and 95% CI for difference from placebo for $AUC_{72}$. The 5 mL dose is equal to 660 mg of Posimir.

**Figure 8. Difference in normalized AUC72 for shoulder repair**




Source: Reviewer

Unlike the studies that evaluated post-surgical pain associated with hernia repair, all supportive studies, while not significant, supported the treatment benefit of Posimir. The point estimate for $AUC_{72}$ was in the right direction. The comparison of Posimir to bupivacaine in Study BU-002-IM, while not significant, did favor Posimir. Of interest, in this study bupivacaine was not significantly different from placebo in the analyses of the primary and secondary efficacy endpoints.

### 3.2.3 Other Surgical Procedures

The results from two additional studies evaluated post-surgical pain associated with a hysterectomy and major abdominal surgery. Study BU-001-IM was conducted in female subjects undergoing a hysterectomy and Study C803-025 evaluated subjects undergoing a colectomy, laparotomy, or laparoscopic cholecystectomy. Each study is discussed briefly and the applicants' analyses are presented.

Study BU-IM-001: This was a randomized, double-blind, dose-ranging, active- and placebo-controlled phase 2 study that evaluated Posimir in female subjects undergoing a hysterectomy. Subjects were enrolled at 13 sites in 5 countries; France, Germany, Hungary, Latvia, and Sweden. This study was to be conducted in two separate cohorts where Cohort 1 received 5.0 mL of study drug and Cohort 2 received 7.5 mL of study drug. However, Cohort 2 was not conducted. In Cohort 1, subjects were randomized 2:1:1 to either Posimir 5.0 mL, placebo, of 40 mL of bupivacaine. Placebo and Posimir were instilled into the surgery site prior to wound closure. Bupivacaine was injected into the muscle, distal layer and subcutaneously around the surgery site.

The primary efficacy variables were $AUC_{72}$ on movement and $RES_{72}$. Missing pain scores between two non-missing pain scores were not imputed. This is analogous to linear

interpolation. Missing pain scores due to discontinuations were imputed using LOCF. The analysis population was defined as all randomized and treated patients. For $AUC_{72,}$ the applicant tested NI of Posimir 660 mg to placebo using ANOVA model with treatment and pooled site as factors. If the upper bound of the 95% CI for the difference was less than or equal to 0.5, NI was established. This is equivalent to using a NI margin of 0.5. If NI was established, superiority was tested. $RES_{72}$ was computed for each subject by converting amount of rescue medication to morphine equivalent doses. If a subject discontinued prior to 72 hours, the $Res_{72}$ will be calculated as amount of rescue used per hour times 72. Results were compared between placebo and Posimir using an ANOVA model with treatment and pooled site.

Of the 119 subjects randomized and treated, 61 Posimir, 27 placebo, and 27 bupivacaine, 117 completed the study. One subject in the Posimir arm withdrew consent and one subject in the placebo arm withdrew due to an adverse event. All subjects were female Caucasians with an average age of 46 years old. In the analysis of $AUC_{72}$, NI was claimed as the 95% CI for the difference of Posimir and placebo was [-0.89, 0.35]. The 95% CI for the difference between Posimir and bupivacaine was [-0.68, 0.47]. However, superiority was not established for either comparison, p-value > 0.05. This analysis did not account for use of rescue medication. Additionally, superiority of Posimir 660 mg over placebo for $RES_{72}$ was not established. Placebo subjects, on average used 26.3 mg morphine equivalent units compared to 22.8 mg for the Posimir 660 mg. Bupivacaine treated subjects used an average of 23.9 mg over 72 hours.

Study C803-025: This was a randomized, double-blind, placebo- and active-controlled phase 3 trial that was conducted in three separate cohorts. Cohort 1 randomized subjects undergoing a laparotomy and Cohort 2 randomized subjects undergoing a laparoscopic cholecystectomy. In Cohorts 1 and 2, subjects were randomized 3:2 to Posimir 660 mg or bupivacaine. Cohort 3 was placebo controlled and evaluated subjects receiving a colectomy. Subjects were randomized 3:2 to Posimir 660 mg or placebo. In all cohorts study drug was instilled into the surgery site prior to wound closure. This study was conducted at nine sites in the United States and two sites in Australia.

The primary efficacy variables were $AUC_{72}$ and $RES_{72}$. The analysis population was defined as all randomized subjects that received study drug. An ANCOVA model with treatment, pooled site and incision length as a covariate was used to compare results for both endpoints. Since the results of $RES_{72}$ violated the normality assumptions a non-parametric analysis, WRS, was used. Missing pain scores were handled as follows. If a subject dropped out prior to 72 hours due to an adverse event, the subjects' baseline observation was carried forward. If a subject dropped out for any other reason or had intermittent missing data, a multiple imputation approach was used. The Hochberg approach was utilized to account for two primary endpoints. If the largest p-value was less than 0.05, then both endpoints were declared significant. If the largest p-value was greater than 0.05, the other endpoint will be tested at 0.025. The applicant states that data from Cohorts 1 and 2 will be pooled and summarized but would be non-inferential. The data from Cohort 3 was of interest and would be inferential.

A total of 393 subjects were screened in order to randomize 331 subjects. Cohort 1 randomized 32 subjects to Posimir and 23 subjects to bupivacaine, Cohort 2 randomized 30 subjects to Posimir and 20 subjects to bupivacaine, and Cohort 3 randomized 140 to Posimir and 86 subjects

to placebo. Of all randomized subjects, 11 did not complete the study. Six subjects withdrew consent, four in the Posimir arms, one in the bupivacaine arm, and one in the placebo arm. Two subjects, one subject in the Posimir arm and one in the bupivacaine arm discontinued due to an adverse event. The other three reasons were lost to follow-up, investigator decision, and other. The average age of all subjects was 56 years old with a range of 22 to 87. Overall the study enrolled approximately equal numbers of males and females, 48% and 52%, respectively. The applicants' results the primary analysis are shown in Table 20.

**Table 20. Results of applicants' primary analysis from Study C803-025**

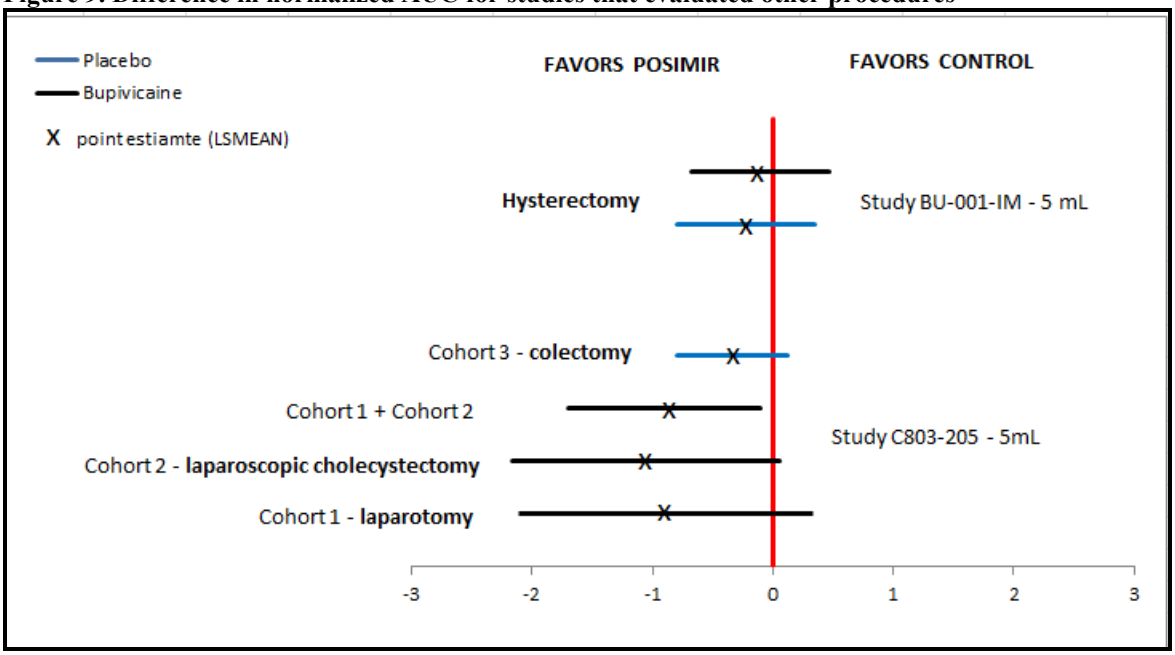
| Cohort | normalized $AUC_{72}$ (pi) | | | p-value |
|---|---|---|---|---|
| | Control | Posimir 5 mL | Difference (95% CI) | |
| 1 | 5.8 | 4.9 | -0.9 (-2.1, 0.3) | 0.15 |
| 2 | 3.9 | 2.8 | -1.1 (-2.2, 0.05) | 0.06 |
| 3 | 5.1 | 4.8 | 0.34 (-0.8, 0.12) | 0.15 |

Source: Table 15 from applicants CSR

The only significant difference noted was when the applicant pooled Cohorts 1 and 2. Superiority of Posimir over bupivacaine was noted, results not shown. However, the clinical reviewer felt it was inappropriate to pool the data from these two surgical procedures as they clinically different. Further, there were no significant differences noted for the comparison of Posimir to control for $RES_{72}$, results not shown.

Figure 9 shows the point estimates and the 95% CI for the difference of Posimir from control for $AUC_{72}$. I included the two studies that evaluated post-surgical pain associated with hysterectomy, colectomy, laparoscopic cholecystectomy, and laparotomy. While there was not a significant treatment effect noted, in all cases, the point estimate was in favor of Posimir. I included the results from the pooled analysis in Study C803-025 although clinically, it was inappropriate to pool these two procedures.

**Figure 9. Difference in normalized AUC for studies that evaluated other procedures**




Source: Reviewer

Results from these two supportive studies, while not significant, indicated numerically that Posimir was better than placebo.

### 3.3 Evaluation of Safety

The primary medical officer, Dr. Arthur Simone, reviewed the safety data for this application.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, Age, and Geographic Region

The Applicant examined the primary efficacy endpoint, $AUC_{72}$, in Study BU-002 for differences due to age or gender. As this study was conducted mainly in Caucasian subjects, differences due to racial subgroups were not examined. Age was categorized as less than 45 years old or 45 years or older. Since I could not locate a subgroup analysis for CLIN-803 in the applicant's clinical study report, I conducted my own analysis. However, this study was included in a pooled analyses located in the integrated summary of efficacy. Each study will be discussed separately below.

Study CLIN-803

Since the majority of these subjects were male Caucasians, gender and racial subgroups were not examined. I examined the primary endpoint, $AUC_{72}$ for any differences due to age using an ANOVA model with treatment and age. The results for my subgroup analysis for gender are shown in Table 21.

**Table 21. Subgroup analysis for age, gender, and country in Study CLIN-803**

| Subgroup | | $AUC_{72}$ LSMEAN (PI) | | Difference | 95% CI |
|---|---|---|---|---|---|
| | | placebo | Posimir 660 mg | | |
| Age (years) | < 45 (n=) | 5.6 | 3.4 | -2.2 | [-3.4, 0 ] |
| | ≥ 45 (n=) | 3.4 | 2.2 | -1.2 | [-2.8, 0] |

Source: Reviewer

There was not a significant treatment interaction with age when I examined $AUC_{72}$ in Posimir 660 mg and placebo. While not significant, the point estimates were in the right direction.

Study BU-002

The applicant examined $AUC_{72}$ for any treatment interactions with age and gender using an ANOVA model with treatment, site, age, and gender. The 95% CI for the difference of Posimir 660 mg from placebo were presented. The applicant tested for NI and superiority to placebo. The results using my analyses are shown in Table 22.

**Table 22. Subgroup analysis for age and gender in Study BU-002**

| Subgroup | | $AUC_{72}$ LSMEAN (PI) | | Difference | 95% CI |
|---|---|---|---|---|---|
| | | placebo | Posimir 660 mg | | |
| Gender | female (n=47 ) | 6.3 | 5.4 | -0.9 | [-2.2, 0.5] |
| | male (n=33 ) | 6.7 | 5.2 | -1.5 | [-3.1, 0.0] |
| Age (years) | < 45 (n=22) | 6.7 | 5.2 | -1.5 | [-3.3, 0.3] |
| | ≥ 45 (n=55) | 6.3 | 5.4 | -1.0 | [-2.1, 0.2] |

Source: Reviewer

There was not a significant treatment interaction with age or gender and all point estimates, while not significant, were in favor of Posimir. Region of conduct for the seven studies submitted to support efficacy is shown in Table 23.

**Table 23. Geographic location of clinical studies**

| Study | Region | Phase | Type of control | Surgical Procedure |
|---|---|---|---|---|
| CLIN-803-006-0006 | Oceania | 2 | placebo | Inguinal hernia |
| CLIN005-0010 | USA/New Zealand | 2 | placebo | Inguinal hernia |
| BU-002-IM | Europe | 2 | active/placebo | Arthroscopic shoulder |
| C803-017 | Oceania | 2b | placebo | Arthroscopic shoulder |
| CLIN005-0006 | USA/New Zealand | 2 | placebo | Arthroscopic Shoulder |
| 803-025 | Oceania | 3 | active/placebo | Major abdominal |
| BU-001-IM | Europe | 2 | active/placebo | Hysterectomy |

Source: Reviewer

Most of these studies were conducted outside of the United States so I did not examine results for difference in geographic locations. However, the applicant should indicate why they believe these results are applicable to the population in the United States.

### 4.2 Other Special/Subgroup Populations

There were no other subgroups of interest that were identified or analyzed.

# 5. SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues and Collective Evidence

In the three studies that evaluated Posimir 660 mg in treating post-surgical pain associated with arthroscopic shoulder repair, only the pivotal study, BU-002-IM, demonstrated a statistically significant treatment effect in favor of Posimir. The two supportive studies provided additional evidence. Although not statistically significant, results favored Posimir. However, when I examined mean PI scores by time there did not seem to be a clinically relevant difference between Posimir 660 mg and placebo beyond 12 hours. Furthermore, since the pivotal study was conducted entirely in Europe, the Applicant should provide evidence that the surgical procedures in Europe are similar to those conducted in the United States.

In the two studies that evaluated Posimir in treating post-surgical pain associated with hernia repair, only the pivotal study, CLIN-803-006-0006, demonstrated a statistically significant treatment effect in favor of Posimir. The supportive study demonstrated, while not significant, a point estimate that was in the wrong direction. It favored placebo. The only notable difference in the two studies was that the failed study was conducted mainly in the United States whereas the successful study was conducted in Australia and New Zealand.

The three supportive studies that evaluated Posimir in other procedures, while not significant, numerically favored Posimir 660 mg when I examined the primary endpoint $AUC_{72}$.

## 5.2 Conclusions and Recommendations

In Study BU-002-IM, the analyses of the $AUC_{72}$ and $RES_{72}$ yielded significant differences between Posimir 660 mg and placebo for treating post-surgical pain associated with shoulder surgery. This was supported by various secondary endpoints. Although an AUC is acceptable as the primary efficacy endpoint, differences in AUCs have little clinical interpretation when considering treatment effect size. One can examine the pain scores that make up an AUC to aid in the clinical interpretation. Figure 4 is a graph of the mean PI scores by time that supports the statistical significance of the primary efficacy endpoint, $AUC_{72}$. The clinical significance of the treatment beyond 12 hours is unclear. There were no concerns regarding the analysis populations, statistical analyses, or imputation of missing data that could not be addressed. The approach to handling rescue medication in the analysis was appropriate.

In Study CLIN-803-0006-06, the analysis of the primary efficacy endpoints, $AUC_{72}$ and $RES_{72}$ demonstrated a significant treatment effect in favor of Posimir 660 mg. This was supported by the analyses of various secondary endpoints such PI scores by time and time to first use of rescue medication. However, Study CLIN005-0010, did not support this conclusion. Based these results and lack of any rationale as to why one study worked and one study failed and the fact that the failed was conducted mainly in the United States, I do not believe the results from the two studies support an indication for treating post-surgical pain associated with hernia repair.

In conclusion, the efficacy of Posimir 660 mg was demonstrated in treating post-surgical pain associated with shoulder repair surgery as indicated by the significance of the pre-specified primary endpoints and was supported by the significance of various secondary endpoints.

Evidence was also provided in two supportive secondary studies. The applicant should provide evidence that these results are applicable to the population in the United States. In my opinion there was not substantial evidence to support the efficacy of Posimir in treated post-surgical pain associated with hernia repair.

**5.3 Label Review**

Using the label provided in the submission, I have the following comments regarding Section 14. My comments and suggestions follow the Applicant's proposed wording and are italicized. It may be beneficial to include the graph of mean PI scores by time, Figure 4, in the label.

(b) (4)



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

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/s/

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DAVID M PETULLO
12/27/2013

JANICE A DERR
12/30/2013