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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Drug Name: SPRIX (Ketorolac tromethamine nasal spray)

Indication(s): Short term management of moderate to severe pain

Applicant: ROXRO PHARMA, Inc.

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The applicant seeks approval to market SPRIX (ketorolac tromethamine nasal spray) for the proposed indication of “short term (up to 5 days) management of moderate to severe pain, as a

(b) (4)

The four controlled efficacy studies collectively indicated that intranasal (IN) ketorolac tromethamine 31.5 mg was better than placebo in the short term management of moderate to severe pain. There is evidence from two Phase 3 studies that IN ketorolac tromethamine reduces pain more (from baseline) through six hours as compared to placebo. Although the results are sensitive to the procedure for handling missing data, there was also evidence of an analgesic effect through 24 and 48 hours.

To evaluate the overall risks and benefits, the review team will need to weigh the strength of the evidence while considering the large proportion of subjects dropping out or taking rescue medication, the use of morphine, and the increased incidence of adverse events due to bleeding noted by the clinical reviewer.

1.2 Brief Overview of Clinical Studies

Ketorolac tromethamine is a non-steroidal, anti-inflammatory drug (NSAID). The intramuscular (IM) injection solution of ketorolac tromethamine has been approved for management of moderate to severe pain in United States for many years. SPRIX is the first IN formulation of ketorolac tromethamine (ketorolac). According to the applicant, “The nasal route has the advantages of rapid absorption of the drug across the nasal mucous membrane and the relative ease of administration.” The development program was discussed between the applicant and the Agency at several meetings. The applicant was advised that multiple-dose studies would be necessary for the evaluation of efficacy.

The applicant conducted 14 clinical studies to evaluate the safety and efficacy of IN ketorolac. Four of the 14 studies were postoperative, randomized, double-blind, placebo-controlled efficacy studies. Two Phase 2 studies were conducted to define the effective dose and establish the safety and efficacy of IN ketorolac for short-term management of acute pain. Two Phase 3 studies were designed primarily to confirm the efficacy of IN ketorolac 31.5 mg (ROX-888) and evaluate the safety for up to 5 days postoperatively.

Study ROX-2001-03 was a Phase 2, single-center and multiple-dose study of IN ketorolac 10 mg and ROX-888 in subjects with pain following major surgery. All subjects had access to morphine sulfate (MS) administered via patient-controlled analgesia (PCA). Subjects were dosed every 8 hours for up to 2 days. A total of 127 subjects with baseline pain intensity (PI) at least 40 mm on a 100-mm visual analog scale (VAS) were randomized to IN ketorolac 10 mg, IN ketorolac 31.5 mg, or placebo. The applicant’s primary endpoint was total MS consumption at 24 hours.

The primary analysis was analysis of variance. There was no multiplicity adjustment for multiple comparisons. Missing data was imputed using applicant's pre-specified rules.

Study ROX-2003-05 was a Phase 2, single-center, single-dose study of ROX-888 in subjects with pain following dental extraction surgery. A total of 80 subjects with baseline pain VAS at least 50 mm were randomized to ROX-888 or placebo. Subjects who used rescue medication were withdrawn from the study at that time. The primary efficacy endpoint was the time-weighted sum of pain intensity difference at 8 hours (SPID8) and analyzed using two-sample t-test. Missing data was imputed using last observation carried forward (LOCF).

Study ROX-2003-01 was a Phase 3, single-center, multiple-dose study of ROX-888 in subjects with postoperative pain. All subjects had access to MS administered via PCA during the multiple-dose portion of the study. The study drug was administered every 8 hours for up to 5 days. A total of 300 subjects with baseline pain VAS at least 40 mm were randomized to ROX-888 or placebo. In order to evaluate the single-dose efficacy, PCA was discontinued 3 hours before the morning dose of the study drug on postoperative Day 1. Subjects who reported a VAS score at least 40 mm in the morning of Day 1 entered the single-dose portion of the study with no access to PCA. The primary efficacy endpoint was SPID6 for subjects who entered the single-dose portion. The primary analysis was analysis of covariance with baseline pain as a covariate. The primary imputation method was LOCF.

Study ROX-2005-01 was a Phase 3, multi-center, multiple-dose study of ROX-888 in subjects with postoperative pain. All subjects had access to MS administered via PCA. Subjects were given study drug every 6 hours for up to 5 days. A total of 321 subjects with baseline PI at least 40 mm were randomized to ROX-888 or placebo. The applicant's primary efficacy endpoint was SPID6 and analyzed using analysis of covariance with baseline pain as a covariate. The primary imputation method was LOCF.

1.3 Statistical Issues and Findings

The applicant's primary efficacy endpoint for the two Phase 3 studies was SPID6, which only evaluated single-dose efficacy. During the review, the Agency requested the applicant submit analyses of the SPID24 and SPID48 endpoints since the proposed indication allows for multiple-dose usage. As a result of the information request, the applicant submitted their analyses of SPID24 and SPID48 using LOCF as the strategy for imputation of missing PI values resulting from a subject dropping out or taking rescue medication in addition to the PCA. I did additional analyses using different imputation methods for all four efficacy studies. The efficacy results for SPID24 and SPID48 of Study ROX-2005-01 were sensitive to the imputation methods. The results of ROX-2003-01 were not sensitive to imputation methods. I identified errors in the derived analysis datasets of Study ROX-2003-01. The analysis results from the updated datasets the applicant submitted differed very little.

There were additional concerns. Specifically, the amount of MS used by some subjects in Study ROX-2005-01 was missing for unknown reasons. For Study ROX-2003-01, the scheduled dosing interval and pain evaluations were interrupted for those subjects who entered the single-dose portion. This resulted in pain assessments for the 16-hour or 24-hour time points being done

within one hour after dosing for some subjects. I was concerned that this could potentially inflate the efficacy of the study drug. Therefore, I re-derived the SPID24 and SPID48 variables using the available pain assessments right before dosing and the actual elapsed time between doses as weights. Based on my analysis, the study drug demonstrated significant superiority. Thus, the concern was alleviated.

2. INTRODUCTION

2.1 Overview

ROX-888 is the first nasal spray containing ketorolac. The first product containing ketorolac was a solution for IM injection, which was developed by Syntex Corporation and marketed under the brand name Toradol.

The development program was discussed at several meetings between the applicant and the division. At the guidance meeting on March 27, 2003, the Agency advised the applicant that (b) (4) was not acceptable as a primary endpoint to show analgesic efficacy and that single-dose efficacy needed to be established for subjects receiving PCA and subjects not receiving PCA. The Agency also advised that there needed to be an evaluation of efficacy in both single and multiple dose settings in order to define the dose and dosing interval.

At the End of Phase 2 meeting on July 16, 2004, the Agency informed the applicant that additional single-dose data was needed from subjects after major surgery, and the dental pain study suggested the dosing interval should be every 6 hours (b) (4). The Agency also suggested that efficacy needed to be established beyond (b) (4) proposed in the draft Phase 3 protocol and that at least two Phase 3 trials needed to be conducted. At another Type B meeting on December 13, 2004, the Agency advised that (b) (4) could not be used as the sole primary endpoint, and that the primary endpoints should address effects on pain in a multiple-dose setting.

At the Pre-NDA meeting on October 4, 2007, the Agency asked the applicant to submit CDISC datasets along with the paper submission.

The development program conducted by the applicant included a total of 14 clinical studies with over 1000 subjects. Four of these studies were randomized, double-blind, placebo-controlled Phase 2 or Phase 3 efficacy studies in which subjects who had undergone major surgery or dental surgery were treated for acute moderate to severe pain, and ten were Phase 1 studies in healthy subjects.

The Phase 2 study, ROX-2001-03, evaluated doses of IN ketorolac 10 mg, ROX-888 or placebo administered every 8 hours for 48 hours with concomitant MS in subjects with postoperative pain following major surgery. Consumption of MS was the primary endpoint in this study and other pain assessments were designated as secondary.

The Phase 2 ROX-2003-05 study was conducted to evaluate the single-dose efficacy of ROX-888 without PCA using a dental pain model.

The two Phase 3 efficacy studies (ROX-2003-01 and ROX-2005-01) were designed to evaluate the analgesic effects of ROX-888 in subjects with postoperative pain following major surgery. The primary objectives of the Phase 3 development program were to confirm the efficacy and safety of ROX-888 demonstrated in the Phase 2 postoperative pain trial and provide additional single-dose efficacy without concomitant opioid therapy.

2.2 Data Sources

The statistical review is based on data submitted for studies ROX-2001-03, ROX-2003-05, ROX-2003-01 and ROX-2005-01.

The electronic data submitted can be found at [\\Fdswa150\nonectd\N22382\N_000](#) under different dated directories. The applicant initially submitted SDTM, ADSL, ADAE, and ADSI datasets on December 5, 2008, which didn't include derived analysis-ready datasets. On January 19, 2009, we requested the applicant submit all analysis-ready and raw datasets for the four efficacy studies. The applicant submitted the requested datasets for each study.

During the review, I identified mistakes in the derivation of the datasets. The applicant submitted corrected datasets on May 4, 2009.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study ROX-2003-05

Study Design and Endpoints

Among the four double-blind, placebo-controlled, and parallel efficacy studies, Phase 2 Study ROX-2003-05 was the only single-dose study and the only study that did not allow concomitant PCA. The study was conducted at a single center in Texas.

In this dental pain study, subjects were randomly assigned to receive ROX-888 or placebo in a 1:1 ratio when their PI ratings after dental extraction equaled at least 50 mm on a 100-mm VAS. PI ratings were not collected after subjects used rescue medication. Subjects were assessed at 20 minutes, 40 minutes, and at 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours after the dose.

The primary efficacy endpoint was time-weighted sum of pain intensity difference from baseline at 8 hours (SPID8). Secondary endpoints included SPID4, SPID6, time to first use of rescue

medication and the proportion of subjects taking rescue medication during the 8-hours post-dose observation period.

Patient Disposition, Demographic and Baseline Characteristics

The demographic and baseline characteristics are provided in the appendix. Subjects in Study ROX-2003-05 were all enrolled after dental extraction. The baseline characteristics were balanced across treatment groups. Overall, 46% were men. The mean age was 24 years.

Table 1 shows the disposition of subjects. Most of the subjects completed the study, with only two subjects lost to follow-up.

Table 1: Subjects' Disposition of ROX-2003-05

| | Placebo | ROX-888 |
|-------------------------|----------------|----------------|
| Number of subjects | 40 | 40 |
| Discontinued Early? | | |
| No | 39 (98%) | 39 (98%) |
| Yes | 1 (3%) | 1 (3%) |
| If yes, primary reason: | | |
| Adverse Event | 0 | 0 |
| Unsatisfactory Response | 0 | 0 |
| Protocol Violation | 0 | 0 |
| Lost to Follow-up | 1 (3%) | 1 (3%) |
| Patient Request | 0 | 0 |
| Investigator Decision | 0 | 0 |
| Death | 0 | 0 |
| Other | 0 | 0 |

(Source: Module 5, Vol. 14)

Statistical Methodologies

The planned primary efficacy variable, SPID8, was analyzed using a two-sample t-test. The primary analysis population included all subjects who received study drug.

The time-related endpoints including time to first perceptible and meaningful relief and time to rescue medication were analyzed using the Kaplan-Meier method.

The applicant calculated SPID8 using the LOCF method for missing PI values. Using the raw data, I re-derived the SPID8 values and couldn't reproduce the applicant's results exactly. Nevertheless, the analysis results were similar.

Results and Conclusions

The group means with standard error for SPID8 and p-values from the two-sample t-test are shown in Table 2. The ROX-888 group had a significantly higher mean SPID8 value.

The median time to perceptible pain relief was 20 minutes for ROX-888 group and 65 for placebo. The median time to meaningful pain relief was 66 minutes for ROX-888 and 90 minutes for placebo. The median time to rescue analgesics was 360 minutes for ROX-888 and 96 minutes for placebo. All of these comparisons for the time-related endpoints were significant with p-values<0.001 based on the log-rank test. No adjustment of p-values for multiple comparisons was made.

There were 22 (55%) subjects in ROX-888 group and 36 (90%) subjects in placebo group who took rescue medication during 8 hours after dosing.

Table 2: Primary Efficacy Results (Study ROX-2003-05)

| Endpoint | Imputation | Placebo | ROX-888 | p-value |
|---------------------|-------------------|----------------|----------------|----------------|
| | | N=40 | N=40 | |
| SPID8 | | | | |
| Applicant's results | | n=40 | n=40 | |
| Mean (SE) | LOCF | -105 (29) | 137 (33) | <0.001 |
| Reviewer's results | | n=40 | n=40 | |
| Mean (SE) | LOCF | -108 (30) | 132 (34) | <0.001 |

(Source: Module 5, vol. 14)

3.1.2 Study ROX-2001-03

Study Design and Endpoints

Study ROX-2001-03 was a single-center (New Zealand) and multiple-dose study. The primary objective of this Phase 2 study was to compare the analgesic efficacy of multiple doses of IN ketorolac 10 mg and ROX-888 with placebo over 2 days in subjects following major surgery (orthopedic or abdominal surgery).

Subjects received study drug every 8 hours and had access to MS via PCA. Subjects were assessed at 30 minutes, 60 minutes, and 2, 3, 4, 5, 6, 8 hours after dosing and every 4 hours thereafter up to 48 hours.

The primary efficacy measure was total MS consumption during the 24-hour period (PCA024) after dosing. Secondary efficacy measures included PCA048, PID scores, SPID scores, quality of analgesia, and global pain control.

Patient Disposition, Demographic and Baseline Characteristics

The demographic and baseline characteristics are provided in the appendix. Subjects were enrolled after abdominal or orthopedic surgery. In the placebo group, 24% of the subjects underwent abdominal surgery, compared with 51% in IN ketorolac 10 mg group and 43% in ROX-888 group. The mean age and percentage of men in the placebo group were higher than those of the other two treatment groups. Other baseline characteristics were similar in three treatment groups. Overall, 33% were men.

Table 3 shows the disposition of subjects. More subjects discontinued from each IN ketorolac group than the placebo group. In the two IN ketorolac groups, four of the 14 subjects who discontinued due to other reasons reported that they refused further nasal spray.

Table 3: Subjects' Disposition of ROX- 2001-03

| | Placebo | IN ketorolac 10 mg | ROX-888 |
|-------------------------|----------|--------------------|----------|
| Number of subjects | 42 | 43 | 42 |
| Discontinued Early? | | | |
| No | 36 (86%) | 32 (74%) | 31 (74%) |
| Yes | 6 (14%) | 11 (26%) | 11 (26%) |
| If yes, primary reason: | | | |
| Adverse Event | 4 (10%) | 5 (12%) | 3 (7%) |
| Unsatisfactory Response | 0 | 0 | 0 |
| Protocol Violation | 0 | 0 | 0 |
| Lost to Follow-up | 0 | 0 | 0 |
| Patient Request | 0 | 0 | 0 |
| Investigator Decision | 0 | 0 | 0 |
| Death | 0 | 0 | 0 |
| Other | 2 (5%) | 6 (14%) | 8 (19%) |

(Source: Module 5, Vol. 13)

Statistical Methodologies

The primary efficacy endpoint, PCA024, was analyzed using analysis of variance (ANOVA). The applicant also did analyses on SPID6, SPID24, and SPID48 using ANOVA. The primary analysis population included all subjects who received study drug. No adjustment of p-values for multiple comparisons was made.

In the clinical study report, the applicant stated the following conventions applied for subjects who withdrew prematurely:

1. If a subject dropped out after 8 hours but prior to 24 hours, data was to be extrapolated to obtain 24-hour MS usage using the average per hour MS usage from the last completed 6-hour block. The 24-48 hour MS use was missing, as was the 0-48 hour MS usage.
2. If a subject dropped out prior to 8 hours after the first dose of ketorolac, the 24-hour MS usage was missing, as were the 24-48 hour MS usage and the 0-48 hour MS usage.
3. If a subject dropped out between 24 and 48 hours, data were to be extrapolated using the average per hour MS usage from the last completed 8-hour block to get 24-48 hour usage and 0-48 hour usage.

In the applicant's response (Study200103_SPID24_48.doc, dated February 26, 2009) to our request for analysis of SPID24 and SPID48, it stated that the following rules were used for extrapolation of PI values:

Pain intensity ratings will be summarized by nominal time point and treatment group for all patients receiving at least the initial dose. The following extrapolation rules will be applied for patients who stopped dosing early. The rules are written in the spirit of the PCA extrapolation rules provided in the protocol.

1. If a patient drops out after receiving only the first dose, the last PI value available will be carried forward through the 8 hour PI score. If PI data is present on the CRF beyond 8 hours, it will be set to missing for the purposes of analysis.
2. If a patient drops out after the first dose but before the 24 hour dose (last dose is 8 or 16 hour dose) then the last PI value available will be carried forward through the 24 hour PI score. If PI data is present on the CRF beyond 24 hours, it will be set to missing for the purposes of analysis.
3. If a patient drops out at or after the 24 hour dose (last dose is 24 or 32 hour dose) then the last PI value available will be carried forward through the 48 hour PI score.

The rules did not allow for extrapolation beyond Hour 6 or 8 if a subject dropped out following the initial dose. For example, Subjects 863, 893, 826 and 906 had missing SPID24 and SPID48 values in the applicant's derived data, though all of the subjects had non-missing SPID6 values. Consequently, I re-derived the SPID6, SPID24 and SPID48 values using both LOCF and BOCF methods to compare with applicants results.

Results and Conclusions

The total mean 24-hour MS consumption was 56 mg in the placebo group, 54 mg in the IN ketorolac 10 mg group, and 38 mg in the ROX-888 group. The difference between the ROX-888 group and the placebo group was statistically significant (p-value = 0.0165). The difference between the ROX-888 group and IN ketorolac 10 mg group was not significant. Four subjects discontinued within 8 hours after the first dose of study drug. Therefore, the PCA024 values were missing for those subjects as specified in the extrapolation rule mentioned previously. I confirmed the applicant's results.

I also replicated the applicant's results on SPID4, SPID6 and SPID8. All of them were in favor of ROX-888. Since the applicant didn't extrapolate beyond 8-hour for subjects withdrawn before the 8-hour time-point, I re-derived and analyzed the results for SPID24 and SPID48. The group means and p-values comparing SPID24 and SPID48 of each ketorolac group to those of the placebo group are shown in Table 4.

The ROX-888 group had significantly higher mean SPID24 results using both BOCF and LOCF methods.

The difference in SPID48 between the ROX-888 group and the placebo group was not statistically significant using the BOCF imputation method.

Table 4: Efficacy Results (Study ROX-2001-03)

| Endpoint | Imputation | Placebo | IN ketorolac 10 mg | ROX-888 | p-value (compared to placebo) | |
|----------------------|------------|---------------------|---------------------|---------------------|-------------------------------|---------------|
| | | | | | IN Ketorolac 10 mg | ROX-888 |
| | | N=42 | N=43 | N=42 | | |
| SPID24 | | | | | | |
| Applicant's Mean(SE) | LOCF | n= 41 665 (60) | n= 41 752 (56) | n= 41 901 (42) | 0.2554 | 0.0023 |
| Reviewer's Mean(SE) | LOCF | n= 42 665 (59) | n= 43 756 (55) | n= 42 887 (44) | 0.2249 | 0.0038 |
| | BOCF | n= 42 654 (58) | n= 43 715 (58) | n= 42 859 (48) | 0.4318 | 0.0093 |
| SPID48 | | | | | | |
| Applicant's Mean(SE) | LOCF | n=39 1578 (109) | n=38 1642 (105) | n=35 2032 (72) | 0.6405 | 0.0016 |
| Reviewer's Mean(SE) | LOCF | n= 42 1530 (117) | n= 43 1631 (97) | n= 42 1903 (86) | 0.4762 | 0.0100 |
| | BOCF | n= 42 1476 (114) | n= 43 1446 (109) | n= 42 1721 (111) | 0.8495 | 0.1218 |

(Source: [\\Fdswa150\nonectd\N22382\N_000\2009-02-27\Additional Analyses\spid2448.doc](#))

3.1.3 Study ROX-2003-01

Study Design and Endpoints

Study ROX-2003-01 was a randomized, double-blind, single-center (New Zealand), Phase 3 study conducted in subjects undergoing major surgery. Subjects were randomized to receive ROX-888 or placebo when postoperative pain ratings equaled at least 40 mm. Study drugs were administered every 8 hours for 48 hours and then 3 times daily for up to 5 days. Subjects were assessed before each dose and had access to MS via PCA starting at the time of the first dose of study drug.

To assess single-dose efficacy without concomitant MS, the PCA morphine was stopped on the morning after surgery. When the VAS score reached at least 40, subjects were given a dose of study drug and pain evaluations were made for 6 hours. The onset of pain relief was measured with a stopwatch and the duration of analgesia was determined by the time to first request to rescue medication or restart of PCA. At the end of this segment, PCA morphine was restarted and the rest of the study was conducted for up to 5 days. Subjects whose PI score didn't reach 40 after discontinuation of PCA continued the originally scheduled multiple-dosing regime and pain assessments.

The primary efficacy endpoint was SPID6 for the single-dose segment of the study. The PCA024, PCA048, the onset of pain relief and duration of analgesia were secondary endpoints.

Patient Disposition, Demographic and Baseline Characteristics

The demographic and baseline characteristics were similar across treatment groups. The detailed information can be found in the appendix.

There were mainly two surgery types in this study, abdominal (52%) and orthopedic (46%). Overall, 69% of the subjects in this study were female.

Subjects disposition are shown in Table 5. A total of 90 subjects (30%) discontinued. Subjects in this study discontinued primarily due to an adverse event or at the subject's request.

The percentages of subjects who discontinued early were similar across treatment groups, but the proportion of subjects who discontinued due to an AE in the ROX-888 group was higher than that of the placebo group (17% vs. 14%).

Table 5: Subjects' Disposition of ROX-2003-01

| | Placebo | ROX-888 |
|------------------------------|-----------------|-----------------|
| Subjects in Efficacy | 101 | 199 |
| Discontinued Early? | | |
| No | 72 (71%) | 138 (69%) |
| Yes | 29 (29%) | 61 (31%) |
| If yes, primary reason: | | |
| Adverse Event | 14 (14%) | 33 (17%) |
| Unsatisfactory Response | 2 (2%) | 0 |
| Need for Analgesia Decreased | 0 | 4 (2%) |
| Protocol Violation | 0 | 0 |
| Subject Request | 8 (8%) | 23 (12%) |
| Investigator Decision | 2 (2%) | 1 (0.5%) |
| Other | 3 (3%) | 0 (0%) |

(Source: Module 5, Vol. 15)

Statistical Methodologies

Although the applicant was advised (End of Phase 2 meeting on July 16, 2004) that efficacy must be assessed beyond 24 hours for multiple-dose studies, the applicant submitted efficacy results using SPID6 as the primary endpoint. Following an information request for assessments beyond 24 hours, the applicant subsequently submitted analysis results for SPID24 and SPID48.

All SPID variables were analyzed using an ANCOVA model with the baseline PI as a covariate and treatment effect in the model. Total MS consumption was analyzed using ANOVA. Note that SPID6 was only defined for subjects who entered the single-dose portion on Day 1, and the corresponding baseline PI was the measurement right before dosing for the single-dose procedure. The onset of pain relief and the duration of analgesia on postoperative Day 1 were analyzed using Kaplan-Meier methods.

The following is an excerpt from the study report about the imputation method used for PI and MS consumption:

Missing data were handled as follows. For the hourly pain evaluations, data were extrapolated using LOCF following the first use of supplemental or backup medication or early withdrawal for other reasons. To examine the sensitivity of the results to the method of extrapolation, a second method was examined. For this alternative method, missing data was handled as follows. For the hourly pain evaluations, data were extrapolated using “baseline observation carried forward” (BOCF) following the first use of supplemental or backup medication or early withdrawal for other reasons. Missing data between time points were linearly interpolated for both methods.

For subjects who withdrew prematurely, the following conventions were applied to the MS consumption analysis:

- a. If a subject dropped out after 4 hours but prior to 24 hours, data were extrapolated to obtain 24-hour MS usage using the average per hour MS usage from the last completed 4-hour block. The 24- to 48-hour MS use remained missing, as did the 0- to 48-hour MS usage.
- b. If a subject dropped out prior to 4 hours after surgery, the 24-hour MS usage was missing, as were the 24- to 48-hour MS usage and the 0- to 48-hour MS usage.
- c. If a subject dropped out between 24 and 48 hours, data were extrapolated using the average per hour MS usage from the last completed 4-hour block to calculate the 24-to 48-hour usage and the 0- to 48-hour usage.

For the additional analyses of SPID24 and SPID48, the applicant defined two analysis populations in the document (Study200301_SPID24_48.doc) submitted on February 16, 2009. Analysis population 1 included those who never made it into the single-dose portion of the study. Analysis population 2 included all subjects with at least one analyzable follow-up time point. For the computation of SPID24 and SPID48 for analysis population 2, the applicant stated the following rule:

For this population, the time points of interest are predose (as shown on the top half of Form 17), 8 hours, 16 hours, 24 hours, 32 hours, 40 hours, 48 hours. If PI evaluations for any of these time points are missing, the dates and times with non-missing PI values provided on the lower half of Form 17 and Form 32 (i.e., 8 hours Post-Op time point) will be reviewed to see if any of those non-missing PI data can be used for the missing PI evaluations in the top half. Data from the closest non-missing time point to the scheduled missing time point will be used. If there are two time points that are equally close to the scheduled time point with missing PI data (i.e., one may be before the schedule time point and the other may be after the scheduled time point), the earlier one will be used. The intention of this approach is to pick the PI data of the time point that is closest to dosing. An example of this case is Subject # 81020. The first dose of the study was taken on 10/Oct at 14:10. The 24-hour time point is missing. The lower half of the form provides evaluations on 11/Oct at 13:40 and 11/Oct at 14:40. Both of these time points are half an hour from the scheduled time point of 11/Oct 14:10 (one is early and the other is late). The earlier evaluation (recorded at 13:40) will be used.

However, I found that the applicant didn't follow the above rule in the actual calculation. The pre-dose PI evaluation in the single-dose portion was excluded for usage as a possible substitution for missing scheduled 16-hour or 24-hour PI evaluation. The corresponding information request and the applicant's corresponding response are quoted below:

For Study 2003-01, the Analysis Rules for Population 2 on page 6 of the file titled “Study200301_SPID24_48.doc” submitted on 16FEB2009, states:

If PI evaluations for any of these time points are missing, the dates and times with non-missing PI values provided on the lower half of Form 17 and Form 32 (i.e., 8 hours Post-Op time point) will be reviewed to see if any of those non-missing PI data can be used for the missing PI evaluations in the top half. Data from the closest non-missing time point to the scheduled missing time point will be used.

There appear to be discrepancies in the data where the above rule was not applied. For example for patient 81090, the pain intensity (PI) value at the 16 hours time point was missing and substituted by the PI evaluation done at 0.5 hour post-op Day 1. However, the assessment at the post-op Day 1 time point appears to be closer to the scheduled 16 hours time point. (The scheduled 16 hours time point was at 9:05 am on (b) (6). The post-op Day 1 assessment was done at 9:00 am on (b) (6). The 0.5 hour post-op Day 1 was at 9:30 am on (b) (6).) Clarify the discrepancies in the data whereby the rule was seemingly not applied.

Response:

The SAS code for the Population 2 analysis didn’t take into account the pre-dose time point in the lower-half of Form 17 for any of the subjects (see sample case report form: *study 200301_Subj81090CRF_Item1.pdf*). The post-op Day 1 assessment that was done at 9:00 was not considered in the selection process for substituting for missing time points in the top half of Form 17.

The applicant submitted the corrected dataset and analysis on May 4, 2009 with records of 27 subjects updated. The applicant conducted analysis on SPID24 and SPID48 using only the LOCF method. I used LOCF, BOCF and LOCF/BOCF method to compare the results. The LOCF/BOCF method is defined as follows: if a PI evaluation was missing for reasons related to an AE or lack of efficacy, the worst value between LOCF and BOCF would be used. Otherwise, LOCF would be used. The LOCF/BOCF method was included at the request of our clinical colleagues .

Another issue was that the original dosing interval and PI evaluation were interrupted for those subjects who entered the single dose portion. Subjects who qualified for entering the single-dose segment were dosed immediately after their PI reached 40 mm on the morning of Day 1. Thus, the pain evaluations at the 16-hour or 24-hour time points for some subjects were done shortly after dosing. In my opinion, this could potentially inflate the efficacy of ROX-888. To alleviate this concern, I also re-derived the SPID24 and SPID48 variables using the pre-dose evaluation and actual elapsed time as the weight. The efficacy results based on the re-derived SPID24 and SPID48 variables supported the efficacy of ROX-888.

Results and Conclusions

There were a total of 74 subjects in the placebo group and 115 subjects in the ROX-888 group who entered the single-dose portion of the study. The applicant’s results for the primary efficacy endpoint, SPID6, are shown in Table 6. The least square means in the table are the within-group means controlling for the baseline value. In the applicant’s dataset, Subject 81709 had a missing SPID6 value when using the LOCF method but a non-missing value when using the BOCF method. This was not correct and resulted in a different number of non-missing SPID6 values in

placebo group using different imputation methods. Nevertheless, the results were similar to my results.

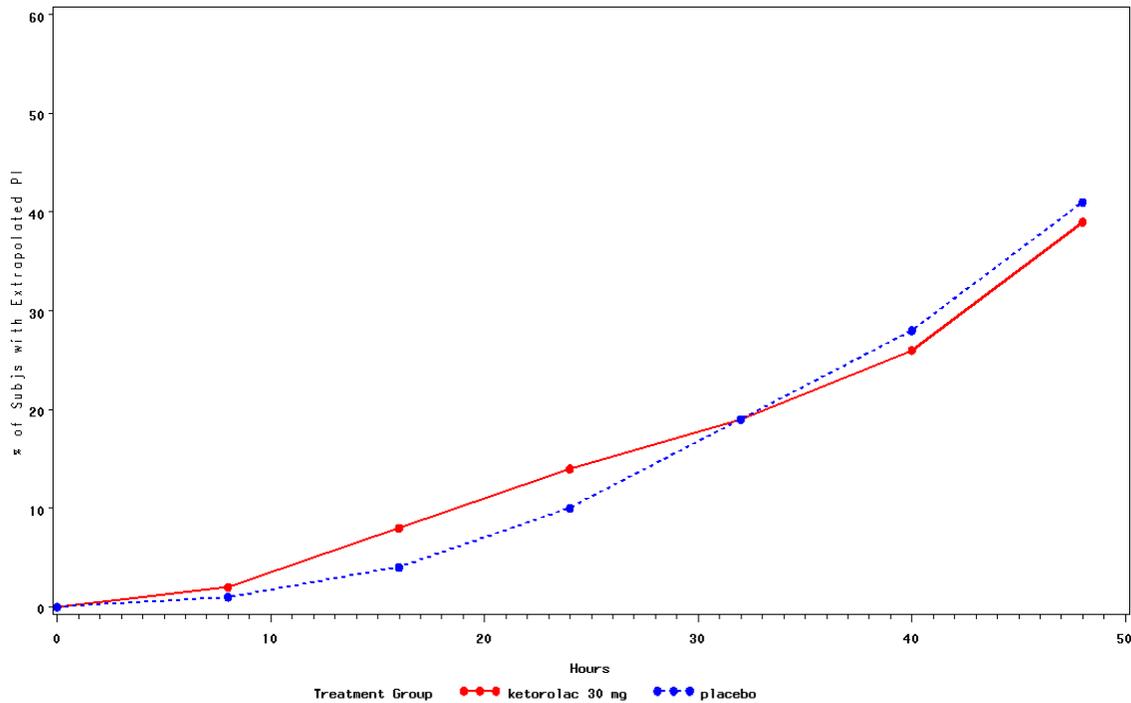
Table 6: Primary Efficacy Results (Study ROX-2003-01)

| Endpoint | Imputation | Stat | Placebo | ROX-888 | p-value |
|----------|------------------|-------------------------|---------|---------|---------|
| SPID6 | Applicant's LOCF | Least square means (SE) | N= 101 | N=199 | |
| | | Difference in means | 35 (13) | 85 (10) | 0.003 |
| | | 95% confidence interval | 17 - 83 | | |
| | BOCF | Least square means (SE) | 49 (10) | 85 (8) | 0.006 |
| | | Difference in means | 36 | | |
| | | 95% confidence interval | 10 - 61 | | |

(Source: Module 5, Vol. 15)

The applicant submitted results for SPID24 and SPID48 using LOCF imputation method. The PI evaluations were extrapolated after a subject dropped out or took additional rescue medication. Figure 1 shows the percentage of subjects with extrapolated PI values at each time point during the first 48 hour for each treatment group. The red line represents ROX-888 and the blue dotted line represents placebo.

Figure 1: Percentage of Subjects with Extrapolated PI (ROX-2003-01)



There were approximately 15% of subjects in the ROX-888 group and 10% of subjects in the placebo group with extrapolated PI at 24 hours. There were approximately 39% of subjects in the ROX-888 group and 41% of subjects in the placebo group with extrapolated PI at 48 hours. Since there were a number of subjects who either took additional rescue medication or withdrew

early, the effect of the imputation method used in the analysis could have potentially been substantial.

Table 7 shows the analysis results for SPID24 and SPID48 using different imputation methods. The applicant didn't include two subjects who had only baseline assessments.

Table 7: Efficacy Results (Study ROX-2003-01)

| Endpoint | Imputation | Stat | Placebo | ROX-888 | p-value | |
|-------------------------|-------------------|-------------------------|-------------------------|----------------|----------------|-------|
| SPID24 | | | N= 101 | N=199 | | |
| Applicant's | LOCF | Least square means (SE) | 600 (34) | 775 (25) | <0.001 | |
| | | Difference in means | 176 | | | |
| | | 95% confidence interval | 92 - 259 | | | |
| Reviewer's | LOCF | Least square means (SE) | 600 (35) | 767 (25) | <0.001 | |
| | | Difference in means | 168 | | | |
| | | 95% confidence interval | 83 - 252 | | | |
| | BOCF | Least square means (SE) | 572 (36) | 729 (25) | <0.001 | |
| | | Difference in means | 157 | | | |
| | | 95% confidence interval | 71 - 243 | | | |
| | LOCF/BOCF | Least square means (SE) | 576 (36) | 745 (25) | <0.001 | |
| | | Difference in means | 169 | | | |
| | | 95% confidence interval | 83 - 255 | | | |
| | SPID48 | | | | | |
| | Applicant's | LOCF | Least square means (SE) | 1370 (68) | 1627 (28) | 0.002 |
| | | | Difference in means | 257 | | |
| 95% confidence interval | | | 93 - 420 | | | |
| Reviewer's | LOCF | Least square means (SE) | 1371 (69) | 1610 (49) | 0.005 | |
| | | Difference in means | 240 | | | |
| | | 95% confidence interval | 73 - 406 | | | |
| | BOCF | Least square means (SE) | 1154 (73) | 1378 (52) | 0.012 | |
| | | Difference in means | 224 | | | |
| | | 95% confidence interval | 49 - 400 | | | |
| | LOCF/BOCF | Least square means (SE) | 1267 (73) | 1506 (52) | 0.008 | |
| | | Difference in means | 239 | | | |
| | | 95% confidence interval | 63 - 416 | | | |

(Source: [\\Fdswal150\nonectd\N22382\N_000\2009-05-04\Item1\spid2448_p2b.doc](#))

The differences in the SPID24 and SPID48 between the ROX-888 group and the placebo group were statistically significant and not sensitive to the imputation method used.

The applicant's analysis results for total MS consumption are shown in Table 8. Subjects in the ROX-888 group used a significantly smaller amount of MS. I couldn't replicate the numbers in the table, but my results were quite similar.

Table 8: MS Consumption (Study ROX-2003-01)

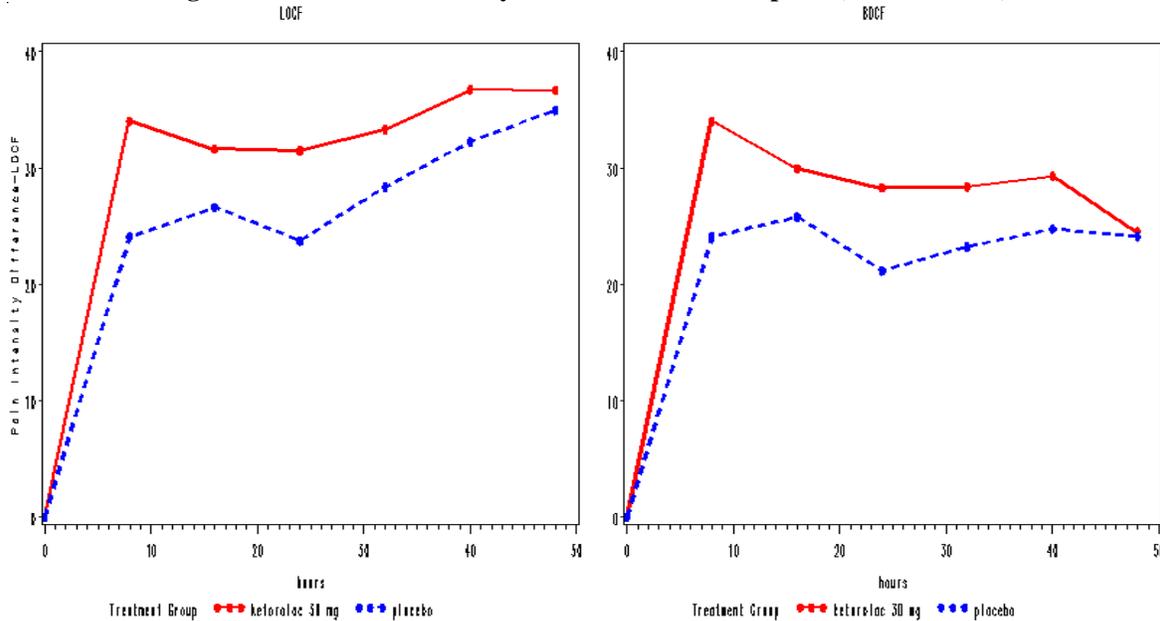
| Amount of Morphine (mg) used During each Time Interval | | | |
|--|--------------------|--------------------|--|
| Assessment Time | Placebo | ROX-888 | P-value |
| 0-24 h, mean (SE) n | 48.4 (2.93) 101 | 34.0 (1.64) 199 | 0.000 ^a 0.000 ^b |
| 24-48 h, mean (SE) n | 29.2 (2.61) 87 | 18.8 (1.51) 166 | 0.000 ^a 0.000 ^b |
| 0-48 h, mean (SE) n | 77.4 (5.28) 87 | 51.4 (2.75) 166 | 0.000 ^a 0.000 ^b |

a. The 1-way ANOVA was used to analyze differences between the 2 treatment groups.
b. The Wilcoxon rank-sum test was used as a nonparametric procedure to analyze differences between the 2 treatment groups.

(Source: Module 2, Vol.2)

Figure 2 shows the mean pain intensity difference (PID) of each treatment group by time point up to 48 hours using LOCF and BOCF. The left panel depicts the PID curves under LOCF with the red line representing ROX-888 and blue dotted line representing placebo. The right panel depicts the PID curves under BOCF. The curves show the separations between treatments from 0 to 48 hours. The PID curves converge at Hour 48.

Figure 2: Mean PID Curves by Treatment Over Timepoint (ROX-2003-01)



The onset of analgesia was quite similar between ROX-888 and placebo. The median time to meaningful analgesia was 0.3 hours for both groups. The time to restart of PCA or rescue medication was 3 hours for ROX-888 and 1.3 hours for placebo, which was in favor of ROX-888.

3.1.4 Study ROX-2005-01

Study Design and Endpoints

Study ROX-2005-01 was a Phase 3, randomized, double-blind, placebo-controlled, multi-center (California, New Zealand, Texas) study in subjects who had undergone abdominal surgery. Eligible subjects were randomized to ROX-888 or placebo. A total of 321 subjects with baseline PI at least 40 mm on a 100-mm VAS were randomized, with 214 subjects to ROX-888. The study drug was administered every 6 hours with for up to 5 days. Subjects additionally had access to MS administered via PCA. Pain was assessed at 20, 40, and 60 minutes, and 2, 3, 4, 5, 6, 12, 18, 24, 30, 36, 42 and 48 hours after the first dose. Thereafter, pain assessments were made immediately before each dosing. Total MS consumption was recorded at 2-hour interval for the first 12 hours and every 6-hour up to 72 hours.

The primary efficacy endpoint was the SPID6. The secondary efficacy endpoints included PCA24 and PCA048.

Patient Disposition, Demographic and Baseline Characteristics

The demographic and baseline characteristics were similar across treatment groups. The majority of the subjects were female (96%). With the exception of one subject, all subjects underwent abdominal surgery. The detailed information can be found in the appendix.

The disposition of subjects is shown in Table 9. A total of 271 subjects (84%) discontinued from Study ROX-2005-01. Subjects in this study discontinued primarily due to a decreased need for analgesia (60%) or an AE (17%).

The percentages of subjects who discontinued were similar across treatment groups, but the proportion of subjects who discontinued due to AEs in the ROX-888 group was much higher than that of the placebo group (20% vs. 12%).

| | Placebo | ROX-888 |
|------------------------------|-----------------|------------------|
| Subjects in Efficacy | 107 | 214 |
| Discontinued Early? | | |
| No | 16 (15%) | 34 (16%) |
| Yes | 91 (85%) | 180 (84%) |
| If yes, primary reason: | | |
| Adverse Event | 13 (12%) | 43 (20%) |
| Unsatisfactory Response | 2 (2%) | 1 (0.5%) |
| Need for Analgesia Decreased | 66 (62%) | 125 (58%) |
| Protocol Violation | 0 | 1 (0.5%) |
| Subject Request | 3 (3%) | 8 (4%) |
| Investigator Decision | 2 (2%) | 1 (0.5%) |
| Other | 5 (5%) | 1 (0.5%) |

(Source: Module 5, Vol. 17)

Statistical Methodologies

As in ROX-2003-01, the applicant’s primary efficacy endpoint was SPID6, and the secondary endpoints included 24-hour and 48-hour total MS consumption. All subjects who had non-missing baseline PI were included in the efficacy analysis. The imputation methods for missing PI and MS consumption were the same as those for analysis population 1 in Study ROX-2003-01.

There were three centers in this study. The SPIDs variables were analyzed using ANCOVA with center and treatment as factors and baseline PI as a covariate. The total MS consumption was analyzed using two-way ANOVA with center and treatment effects in the model.

The applicant conducted analyses on SPID24 and SPID48 using only LOCF method. I used LOCF, BOCF and LOCF/BOCF methods to compare the results.

Results and Conclusions

The applicant’s results for the primary efficacy endpoint SPID6 are shown in Table 10. I replicated the applicant’s result. The difference between the ROX-888 group and the placebo group in terms of SPID6 was significant.

Table 10: Primary Efficacy Results (Study ROX-2005-01)

| Endpoint | Imputation | Stat | Placebo | ROX-888 | p-value |
|----------|---------------------|-------------------------|---------|---------|---------|
| SPID6 | Applicant’s LOCF | Least square means (SE) | N= 107 | N=214 | 0.032 |
| | | Difference in means | 90 (11) | 117 (8) | |
| | | 95% confidence interval | 28 | 2 – 53 | |
| | BOCF | Least square means (SE) | 93 (10) | 116 (7) | 0.048 |
| | | Difference in means | 24 | | |
| | | 95% confidence interval | 0 – 48 | | |

(Source: Module 5, Vol. 17)

As in study ROX-2003-01, the PI evaluations were imputed or extrapolated after a subject dropped out or took additional rescue medication. Figure 3 shows the percentage of subjects with extrapolated PI values at each time point during the first 48 hour for each treatment group. The red line denotes ROX-888 and the blue dotted line denotes placebo.

There were about 41% of subjects in the ROX-888 group and 48% of subjects in the placebo group with extrapolated PI at 24 hours. There were about 85% of subjects in ROX-888 group and 92% of subjects in placebo group with extrapolated PI at 48 hours. A large number of subjects either took additional rescue medication or withdrew early for various reasons. Thus, I was concerned that the analysis results for SPID24 and SPID48 may have been sensitive to the imputation method used.

Figure 3: Percentage of Subjects with Extrapolated PI (ROX-2005-01)

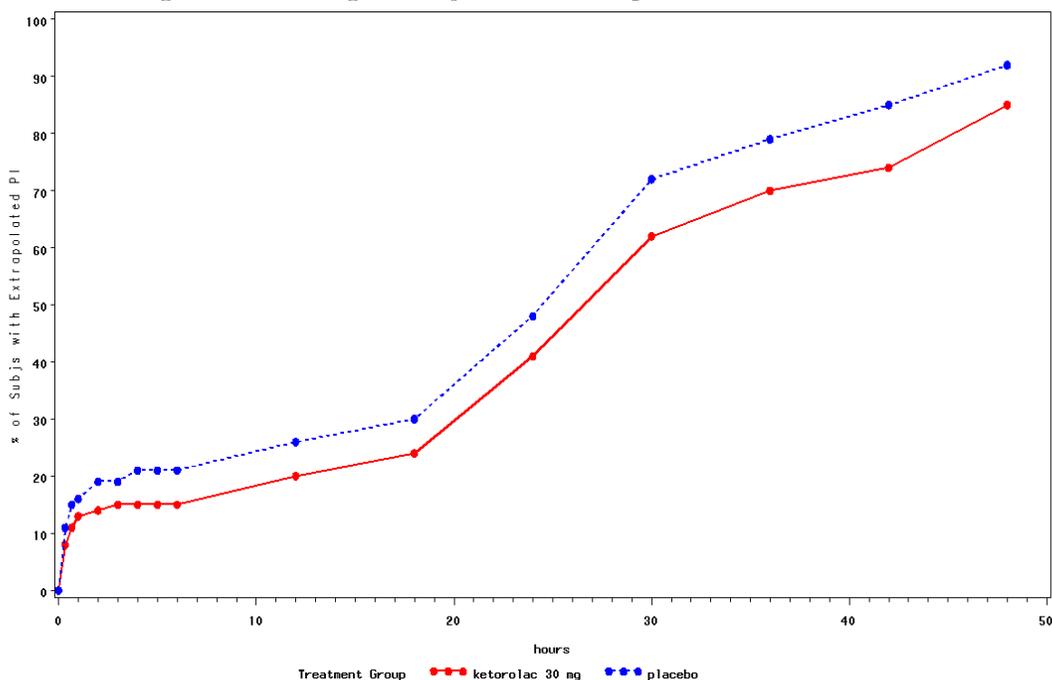


Table 11: Efficacy Results (Study ROX-2005-01)

| Endpoint | Imputation | Stat | Placebo | ROX-888 | p-value |
|---------------|------------|-------------------------|------------|-----------|--------------|
| SPID24 | | | N= 107 | N=214 | |
| Applicant's | LOCF | Least square means (SE) | 515 (47) | 630 (34) | 0.043 |
| | | Difference in means | 116 | | |
| | | 95% confidence interval | 4 - 228 | | |
| Reviewer's | BOCF | Least square means (SE) | 455 (42) | 567 (31) | 0.028 |
| | | Difference in means | 112 | | |
| | | 95% confidence interval | 12 - 212 | | |
| | LOCF/BOCF | Least square means (SE) | 489 (47) | 579 (34) | 0.11 |
| | | Difference in means | 90 | | |
| | | 95% confidence interval | -21 - 201 | | |
| SPID48 | | | | | |
| Applicant's | LOCF | Least square means (SE) | 1097 (101) | 1347 (74) | 0.042 |
| | | Difference in means | 251 | | |
| | | 95% confidence interval | 10 - 491 | | |
| Reviewer's | BOCF | Least square means (SE) | 613 (66) | 856 (48) | 0.002 |
| | | Difference in means | 243 | | |
| | | 95% confidence interval | 86 - 399 | | |
| | LOCF/BOCF | Least square means (SE) | 981 (101) | 1162 (73) | 0.138 |
| | | Difference in means | 180 | | |
| | | 95% confidence interval | -58 - 419 | | |

(Source: [\\Fdswa150\nonectd\N22382\N 000\2009-02-05\Additional Analyses\spid2448.doc](#))

Table 11 shows the analysis results for SPID24 and SPID48 using different imputation methods. The difference between ROX-888 and placebo was not significant using the LOCF/BOCF method for either SPID24 or SPID48. The ROX-888 group failed when using the LOCF/BOCF method because a higher proportion of subjects in this group discontinued because of an AE (see subjects disposition Table 9). The difference was more significant under BOCF than under LOCF because there were a much larger percentage of subjects who had extrapolated PI values especially for SPID48 (see Figure 3) in placebo group.

Figure 4 shows the mean pain intensity difference (PID) of each treatment group by time point up to 48-hour under LOCF and BOCF. There is a clear separation of PID curves between treatments under both BOCF and LOCF methods.

The applicant’s analysis results for total MS consumption are provided in Table 12. I verified the applicant’s results. The ROX-888 group used significantly less MS than the placebo group for time intervals 0 to 24 hours and 0 to 48 hours. The difference between treatment groups was not significant for the time interval 0 to 72 hours.

Figure 4: Mean PID Curves by Treatment Over Timepoint (ROX-2005-01)

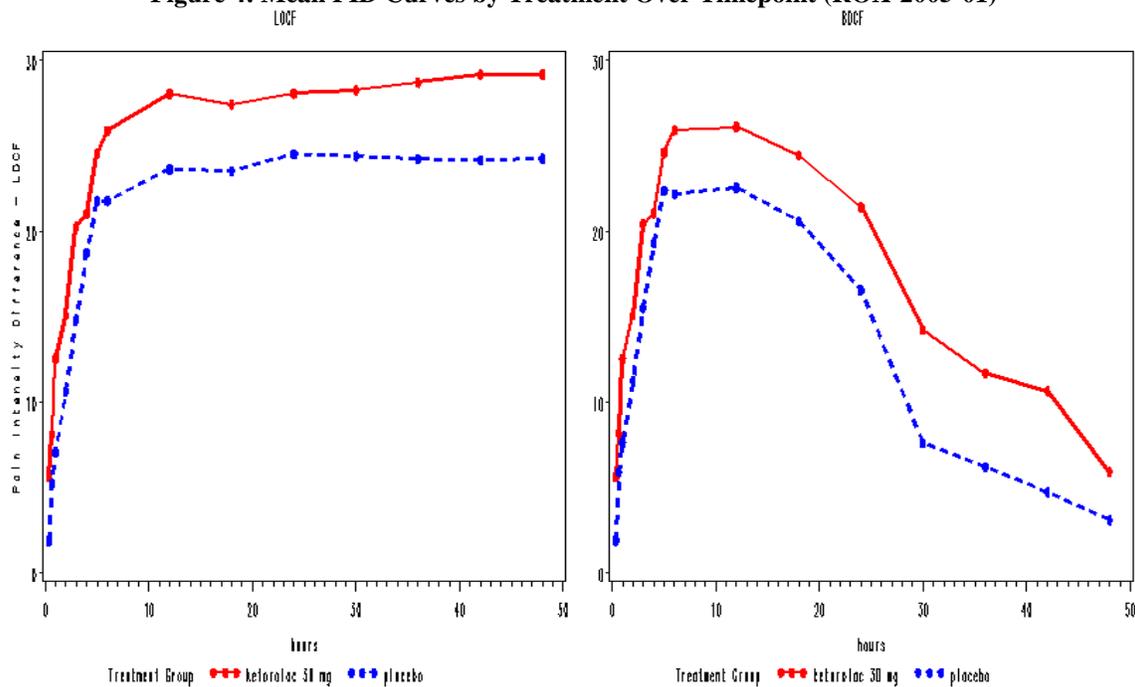


Table 12: Summary of PCA MS Usage (ROX-2005-01)

| Time Interval | Amount of Morphine Used (mg) | | P-value |
|----------------------|-------------------------------------|----------------|--------------------|
| | ROX-888 | Placebo | |
| 0 to 24 h | | | |
| Mean (SE) | 42.4 (2.04) | 54.0 (3.49) | 0.003 ^a |
| n | 210 | 106 | |
| 24 to 48 h | | | |
| Mean (SE) | 23.1 (2.25) | 31.3 (3.53) | 0.041 ^a |
| n | 140 | 80 | |
| 48 to 72 h | | | |
| Mean (SE) | 14.7 (8.84) | 13.0 (6.47) | 0.955 ^a |
| n | 9 | 13 | |
| 0 to 48 h | | | |
| Mean (SE) | 66.7 (4.43) | 89.7 (7.23) | 0.004 ^a |
| n | 140 | 80 | |
| 0 to 72 h | | | |
| Mean (SE) | 81.5 (24.42) | 121.0 (36.44) | 0.304 ^a |
| n | 10 | 13 | |

a. The 2-way ANOVA with factors for treatment and center was used to analyze differences between the 2 treatment groups.

(Source: Module 2, Vol. 2)

3.2 Evaluation of Safety

The evaluation of the safety data was conducted by Dr. Robert Levin. The reader is referred to Dr. Levin's review for information regarding the adverse event profile.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The applicant did subgroup analyses for SPID6 by gender, age, race and type of surgery for pooled subpopulations across studies in the integrated summary report. The subgroup analysis for MS consumption used in the first 6 hours was performed on pooled population across studies ROX-2001-03 and ROX-2005-01. The subgroup analysis for MS consumption used in the first 8 hours was performed on pooled population across studies ROX-2001-03 and ROX-2003-01.

For the four studies, the mean and least square mean values for SPID6 were higher in the ROX-888 group than in the placebo group for both males and females and for both race groups (Caucasian and Non-Caucasian). For all studies except for Study ROX-2005-01, the mean values of SPID6 in the ROX-888 group were higher for both age groups (age < 65 years and ≥ 65 years). Study ROX-2005-01 only included two subjects that were 65 years or older.

I did subgroup analyses for SPID24, SPID48, PCA024 and PCA048 for the individual studies as applicable.

4.1 Gender, Race and Age

ROX-2003-05

No subgroup analysis on age group was done since all subjects were younger than 65 years old. Summary statistics by gender and race for the primary endpoint SPID8 are shown in Table 13.

Table 13: Primary Efficacy Results by Subgroup (Study ROX-2003-05)

| Endpoint | Placebo | | ROX-888 | |
|-------------------------|---------|------------|---------|-----------|
| | n | Mean (SD) | n | Mean (SD) |
| SPID8 | | | | |
| Gender | | | | |
| Female | 22 | -150 (161) | 21 | 166 (198) |
| Male | 18 | -56 (210) | 19 | 94 (229) |
| Race | | | | |
| Caucasian | 21 | -110 (206) | 26 | 88 (215) |
| Non-Caucasian and Other | 19 | -106 (172) | 14 | 214 (191) |

I also did subgroup analyses for other secondary efficacy endpoints including SPID6, time to perceptible and meaningful relief, and time to rescue medication. The subgroup analyses were in favor of ROX-888.

ROX-2001-03

The subgroup summary statistics for the applicant's primary endpoint, PCA024, are shown in Table 14. Notably, there was treatment by gender interaction. The female subjects in both ketorolac groups used less MS than the female subjects in the placebo group. However, the male subjects in both ketorolac groups used more MS from the 0 to 24-hour period than the male subjects in placebo group. The same treatment by gender interaction was also observed for endpoint PCA048.

Table 14: Primary Efficacy Results by Subgroup (Study ROX-2001-03)

| Endpoint | Placebo | | IN Ketorolac 10 mg | | ROX-888 | |
|-------------------------|---------|----------------|--------------------|----------------|---------|----------------|
| | n | Mean (SD) | n | Mean (SD) | n | mean |
| PCA024 | | | | | | |
| Gender | | | | | | |
| Female | 24 | 61 (35) | 30 | 43 (27) | 28 | 31 (19) |
| Male | 17 | 50 (24) | 11 | 86 (55) | 13 | 53 (47) |
| Race | | | | | | |
| Caucasian | 32 | 57(29) | 30 | 52 (36) | 35 | 36 (29) |
| Non-Caucasian and Other | 9 | 53 (37) | 11 | 60 (52) | 6 | 49 (48) |
| Age | | | | | | |
| <65 years | 23 | 67 (33) | 35 | 58 (42) | 28 | 39 (36) |
| ≥ 65 years | 18 | 42 (20) | 6 | 30 (17) | 13 | 35(21) |

The results from subgroup analyses of the endpoints SPID24 and SPID48 were in favor of ROX-888.

ROX-2003-01

Table 15 provides the subgroup summary for the applicant's primary endpoint, SPID6. The subgroup summaries are consistent with the primary analysis. The subgroup analyses for the endpoints SPID24 and SPID48 resulted in same conclusion.

Table 15: Primary Efficacy Results by Subgroup (Study ROX-2003-01)

| Endpoint | Placebo | | ROX-888 | |
|-------------------------|----------------|------------------|----------------|------------------|
| | n | Mean (SD) | n | Mean (SD) |
| SPID6 (LOCF) | | | | |
| Gender | | | | |
| Female | 45 | 40 (120) | 87 | 82 (118) |
| Male | 28 | 33 (93) | 28 | 89 (102) |
| Race | | | | |
| Caucasian | 58 | 21 (94) | 88 | 77 (114) |
| Non-Caucasian and Other | 15 | 98 (146) | 27 | 105 (110) |
| Age | | | | |
| <65 years | 63 | 29 (110) | 98 | 80 (110) |
| ≥ 65 years | 10 | 91 (99) | 17 | 101 (137) |

From Table 16 we can see that Non-Caucasians in the ROX-888 group used more MS than those in the placebo group. The treatment by race interaction for the 48-hour MS consumption was significant suggesting the effect varied among racial groups as shown in Table 16.

Table 16: Efficacy Results by Subgroup (Study ROX-2003-01)

| Endpoint | Placebo | | ROX-888 | |
|-------------------------|----------------|------------------|----------------|------------------|
| | n | Mean (SD) | n | Mean (SD) |
| PCA048 | | | | |
| Gender | | | | |
| Female | 58 | 68 (47) | 123 | 49 (36) |
| Male | 29 | 91 (51) | 43 | 54 (32) |
| Race | | | | |
| Caucasian | 66 | 82 (50) | 124 | 47 (33) |
| Non-Caucasian and Other | 21 | 55 (39) | 42 | 58 (39) |
| Age | | | | |
| <65 years | 75 | 78 (49) | 133 | 54 (36) |
| ≥ 65 years | 12 | 64 (50) | 33 | 35 (26) |

ROX-2005-01

Since 96% of subjects were female and only 2 subjects were older than 65, the gender and age subgroup analyses were not done. Table 17 provides the summary statistics of SPID6, SPID48

and PCA048 for Caucasian and Non-Caucasian. All the subgroup analyses based on race are in favor of ROX-888.

Table 17: Efficacy Results by Race (Study ROX-2005-01)

| Endpoint | Placebo | | ROX-888 | |
|-------------------------|----------------|------------------|----------------|------------------|
| | n | Mean (SD) | n | Mean (SD) |
| SPID6 (LOCF) | | | | |
| Caucasian | 76 | 91 (110) | 154 | 113 (116) |
| Non-Caucasian and Other | 31 | 95 (126) | 59 | 123 (119) |
| SPID48 (LOCF) | | | | |
| Caucasian | 76 | 1062 (1159) | 154 | 1257 (1111) |
| Non-Caucasian and Other | 31 | 1210 (1225) | 59 | 1445 (942) |
| PCA048 | | | | |
| Caucasian | 56 | 93 (72) | 104 | 70 (54) |
| Non-Caucasian and Other | 24 | 83 (42) | 36 | 57 (48) |

4.2 Other Special/Subgroup Populations

ROX-2003-01

The majority of the subjects enrolled in Study ROX-2003-01 underwent abdominal or orthopedic surgery. The summary statistics of SPID6, SPID48 and PCA048 by surgery type are shown in Table 18. The results are in favor of ROX-888.

Table 18: Efficacy Results by Surgery Type (Study ROX-2003-01)

| Endpoint | Placebo | | ROX-888 | |
|----------------------|----------------|------------------|----------------|------------------|
| | n | Mean (SD) | n | Mean (SD) |
| SPID6 (LOCF) | | | | |
| Abdominal | 39 | 48 (124) | 61 | 87 (117) |
| Orthopedic and Other | 34 | 24 (91) | 54 | 79 (111) |
| SPID48 (LOCF) | | | | |
| Abdominal | 54 | 1485 (689) | 102 | 1599 (820) |
| Orthopedic and Other | 47 | 1217 (663) | 97 | 1632 (668) |
| PCA048 | | | | |
| Abdominal | 51 | 62 (43) | 88 | 53 (38) |
| Orthopedic and Other | 36 | 96 (51) | 78 | 46 (32) |

ROX-2005-01

Study ROX-2005-01 was the only multi-center study. The center by treatment interaction was not significant. The summary statistics for SPID6, SPID48 and PCA048 shown in Table 19 are in support of ROX-888.

Table 19: Efficacy Results by Center (Study ROX-2005-01)

| Endpoint | Placebo | | ROX-888 | |
|----------------------|---------|-------------|---------|-------------|
| | n | Mean (SD) | n | Mean (SD) |
| SPID6 (LOCF) | | | | |
| California | 53 | 100 (118) | 107 | 127 (115) |
| New Zealand | 28 | 123 (115) | 54 | 135 (98) |
| Texas | 26 | 44 (94) | 52 | 72 (127) |
| SPID48 (LOCF) | | | | |
| California | 53 | 1192 (1281) | 107 | 1346 (1072) |
| New Zealand | 28 | 1366 (1029) | 54 | 1449 (897) |
| Texas | 26 | 647 (990) | 52 | 1088 (1203) |
| PCA048 | | | | |
| California | 43 | 94 (76) | 76 | 63 (56) |
| New Zealand | 20 | 96 (39) | 38 | 71 (54) |
| Texas | 17 | 71 (56) | 26 | 70 (39) |

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

No statistical issues were identified in the Phase 2 dental pain study ROX-2003-05.

The primary endpoint of Study ROX-2001-03 (Phase 2) was 24-hour MS consumption. (b) (4)

(b) (4) I focused on the analyses of SPID24 and SPID48. The applicant implemented inappropriate imputation methods for calculating SPID24 and SPID48. (b) (4) Therefore, I re-derived the SPID24 and SPID48 endpoints using both LOCF and BOCF methods. ROX-888 failed to demonstrate significant superiority over placebo for SPID48 using the BOCF method. Another issue was that there was a significant treatment by gender interaction for the primary endpoint. The male subjects in ROX-888 group used more MS than males in the placebo group.

Figures 5 and 6 provide an overview of the treatment differences between ROX-888 and placebo for SPID24 and SPID48 from the two Phase 3 studies. The ROX-888 group failed to show superiority over the placebo in Study ROX-2005-01 using the LOCF/BOCF method. The results from Study ROX-2003-01 were in favor of ROX-888 under all the imputation methods used.

The analyses of the total amount of MS usage in both Phase 3 studies were in support of the efficacy of ROX-888. The conclusion was based on the available data provided by the applicant with some subjects having a missing value for the amount of MS usage by PCA.

The result of Study ROX-2005-01 was sensitive to the imputation method because of the high dropout rate (85% for placebo and 84% for ROX-888). ROX-888 demonstrated significance under the BOCF method mainly because BOCF was also conservative for placebo given the use of PCA and the overall dropout rate was similar among treatment arms.

Figure 5: Treatment Comparison on SPID24 for Phase 3 Studies

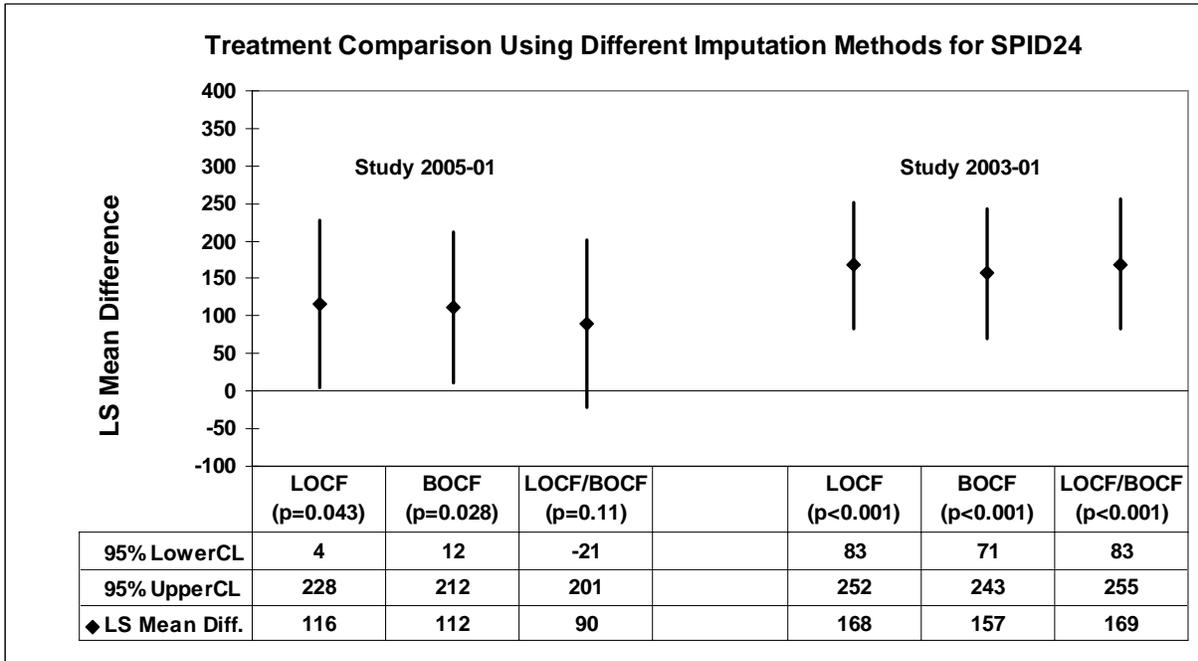
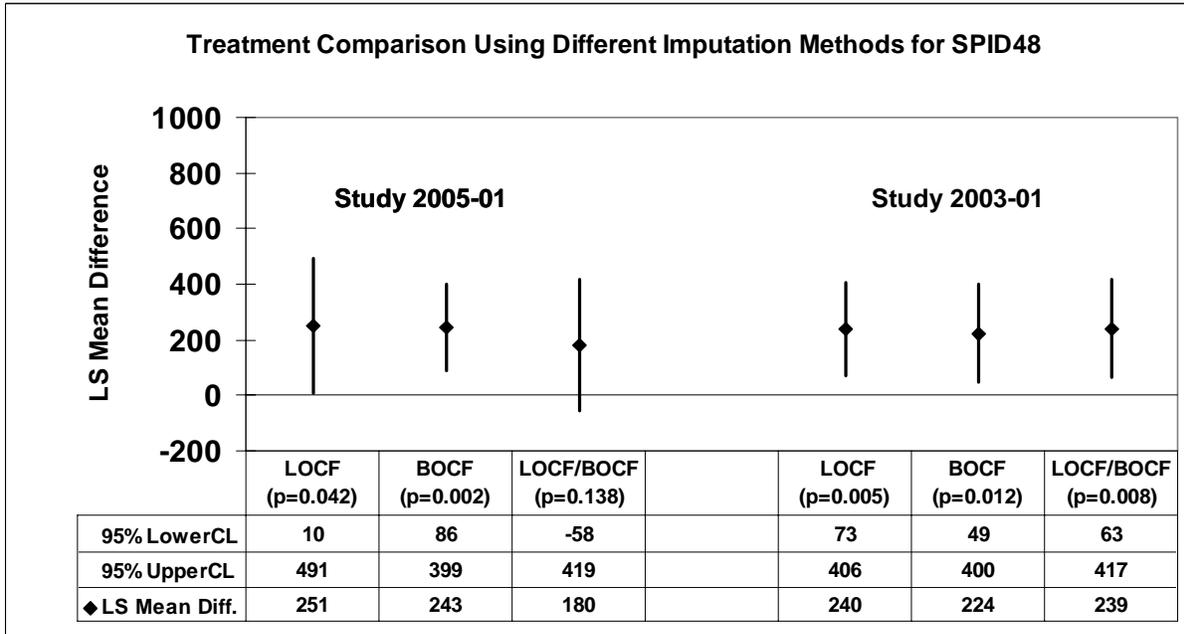


Figure 6: Treatment Comparison on SPID48 for Phase 3 Studies



When the LOCF/BOCF imputation method was used, ROX-888 failed to show efficacy because there was a higher percentage of dropout due to adverse events in the ROX-888 group compared to placebo (20% versus 12%).

For Study ROX-2003-01, in addition to the PI extrapolation issues mentioned previously, there were several subjects dosed and has pain evaluated off-schedule. The information request we sent out and the applicant's corresponding response are quoted below:

- 2. According to the clinical study report (CSR) for Study 2003-01, patients were assessed immediately before the study drug administration and immediately before each subsequent dose during the first 48 hours of the study, ie, at 8, 16, 24, 32, 40, and 48 hours.**

However for some patients, assessments were made after doses were administered. For example for patient 81087, the 3rd dose (16 hours) was given at 8:50 am on 15JUN2004 and the PI at 16 hours time point was evaluated at 9:45 am on 15JUN2004, which was about 1 hour after dosing. Clarify the discrepancies.

Response:

The protocol originally provided for assessments to be done before each dose at 8-hour intervals. During a June 5, 2003 meeting with the Division of Anti-inflammatory, Analgesic and Ophthalmologic Drug Products, ROXRO was instructed to add an evaluation of IN ketorolac vs. placebo in a "single-dose" fashion, i.e., to stop the PCA morphine and then administer a single dose of study drug followed by hourly assessments with no backup analgesic medication. Protocol amendment 1 accommodated this change. Entering subjects into the single-dose part of the study temporarily disrupted the schedule of assessments and dosing, so the regular 8-hourly program was suspended and then reinstated after the single-dose segment was completed. The insertion of the single-dose evaluation occurred on the morning of the first postoperative day (the day after surgery and the start of dosing), so the dosing intervals affected were usually the 16-hour and/or the 24-hour time points. In the example cited of Subject 81087, the assessment performed at 8:50 was actually the initial (pre-dose) assessment of the single-dose segment, which was then followed by hourly assessments following the dose of study drug.

5.2 Conclusions and Recommendations

There was significant evidence that ROX-888 provided single-dose efficacy as measured by endpoint SPID6 in the Phase 2 and 3 studies. Overall, ROX-888 also demonstrated efficacy through 24 or 48 hours based on the data submitted.

5.2.1 Labeling

[Redacted] (b) (4)

[Redacted] (b) (4)

I recommend the applicant convey the claims in text instead of the proposed tables. It should be noted that the applicant has focused on SPID6 for this multiple-dose drug. I recommend the conclusions be based on the SPID values associated with multiple-dose use. Since Study D is a Phase 2, single-dose dental pain study and SPRIX is proposed for multiple-dose use, the applicant's claims based on the dental pain study should not be included. In consultation with our clinical colleagues, I also recommend the applicant not include the claims from Study A since the study was a Phase 2 exploratory study (b) (4)

(b) (4) The study, while supportive, does not add information to the label beyond that of Study B and Study C.

APPENDICES

Summary of Demographics and Baseline Characteristics

Study ROX-2001-03 (Source: Module 5, Vol. 13)

| | PLACEBO | 10 MG IN KETOROLAC | 30 MG IN KETOROLAC | TOTAL |
|--------------------|---------------|--------------------|--------------------|---------------|
| NUMBER OF PATIENTS | 42 | 43 | 42 | 127 |
| AGE | | | | |
| MEAN (SEM) | 56.7 (2.5) | 49.7 (2.1) | 52.8 (2.5) | 53.0 (1.4) |
| MEDIAN | 61.0 | 47.0 | 53.0 | 54.0 |
| RANGE | 19 - 78 | 22 - 78 | 24 - 80 | 19 - 80 |
| SEX | | | | |
| MALE | 18 (42.9%) | 11 (25.6%) | 13 (31.0%) | 42 (33.1%) |
| FEMALE | 24 (57.1%) | 32 (74.4%) | 29 (69.0%) | 85 (66.9%) |
| ETHNICITY | | | | |
| ASIAN | 0 (0.0%) | 2 (4.7%) | 0 (0.0%) | 2 (1.6%) |
| BLACK | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| CAUCASIAN | 32 (76.2%) | 31 (72.1%) | 34 (81.0%) | 97 (76.4%) |
| HISPANIC | 0 (0.0%) | 0 (0.0%) | 1 (2.4%) | 1 (0.8%) |
| POLYNESIAN | 10 (23.8%) | 10 (23.3%) | 7 (16.7%) | 27 (21.3%) |
| OTHER | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| HEIGHT (cm) | | | | |
| MEAN (SEM) | 166.81 (1.56) | 166.62 (1.46) | 167.27 (1.27) | 166.90 (0.82) |
| MEDIAN | 167.00 | 165.00 | 166.45 | 166.40 |
| RANGE | 134.6 - 183.0 | 152.4 - 197.0 | 150.0 - 188.0 | 134.6 - 197.0 |
| WEIGHT (kg) | | | | |
| MEAN (SEM) | 79.65 (2.55) | 81.40 (2.79) | 79.21 (2.35) | 80.10 (1.48) |
| MEDIAN | 77.20 | 83.00 | 78.00 | 80.00 |
| RANGE | 49.4 - 115.0 | 50.0 - 124.0 | 50.0 - 117.0 | 49.4 - 124.0 |

Study ROX-2003-05 (Source: Module 5, Vol. 14)

| | PLACEBO | KETOROLAC 30 mg | TOTAL |
|----------------------------------|-------------|--------------------|-------------|
| NUMBER OF SUBJECTS | 40 | 40 | 80 |
| AGE | | | |
| MEAN (SE) | 23.5 (0.8) | 24.6 (1.1) | 24.1 (0.7) |
| MEDIAN | 22.0 | 22.5 | 22.0 |
| RANGE | 18.0-43.0 | 18.0-47.0 | 18.0-47.0 |
| N | 40 | 40 | 80 |
| SEX | | | |
| FEMALE | 22 (55.0%) | 21 (52.5%) | 43 (53.8%) |
| MALE | 18 (45.0%) | 19 (47.5%) | 37 (46.3%) |
| N | 40 | 40 | 80 |
| ETHNICITY | | | |
| ASIAN | 4 (10.0%) | 0 (0.0%) | 4 (5.0%) |
| BLACK OR AFRO-AMERICAN | 5 (12.5%) | 7 (17.5%) | 12 (15.0%) |
| OTHER: | 1 (2.5%) | 0 (0.0%) | 1 (1.3%) |
| WHITE (HISPANIC OR LATINO) | 9 (22.5%) | 7 (17.5%) | 16 (20.0%) |
| WHITE (NON-HISPANIC AND NON-LAT) | 21 (52.5%) | 26 (65.0%) | 47 (58.8%) |
| N | 40 | 40 | 80 |
| WEIGHT | | | |
| MEAN (SE) | 190.4 (7.9) | 176.3 (6.8) | 183.3 (5.2) |
| MEDIAN | 177.5 | 171.5 | 176.0 |
| RANGE | 115.0-318.0 | 117.0-279.0 | 115.0-318.0 |
| N | 40 | 40 | 80 |
| HEIGHT | | | |
| MEAN (SE) | 68.0 (0.6) | 67.6 (0.6) | 67.8 (0.4) |
| MEDIAN | 68.0 | 67.0 | 67.3 |
| RANGE | 62.0-75.0 | 61.0-77.0 | 61.0-77.0 |
| N | 40 | 40 | 80 |

Study ROX-2003-01 (Source: Module 5, Vol. 15)

| | PLACEBO | 30 MG IN KETOROLAC | TOTAL | P-VALUE |
|---------------------------------------|--------------|--------------------|--------------|-----------|
| NUMBER OF SUBJECTS | 101 | 199 | 300 | |
| AGE | | | | |
| MEAN (SE) | 51.0 (1.20) | 51.7 (0.92) | 51.5 (0.73) | 0.681 [a] |
| MEDIAN | 49.5 | 50.3 | 50.0 | |
| RANGE | 22 - 73 | 19 - 81 | 19 - 81 | |
| N | 101 | 199 | 300 | |
| SEX | | | | |
| MALE | 37 (36.6%) | 55 (27.6%) | 92 (30.7%) | 0.110 [b] |
| FEMALE | 64 (63.4%) | 144 (72.4%) | 208 (69.3%) | |
| N | 101 | 199 | 300 | |
| ETHNICITY | | | | |
| ASIAN | 2 (2.0%) | 2 (1.0%) | 4 (1.3%) | 0.641 [c] |
| WHITE (NON-HISPANIC AND NON-LAT.) | 78 (77.2%) | 147 (73.9%) | 225 (75.0%) | |
| WHITE (HISPANIC OR LATINO) | 0 (0.0%) | 4 (2.0%) | 4 (1.3%) | |
| POLYNESIAN (INCLUDES MAORI/PAC. ISL.) | 20 (19.8%) | 44 (22.1%) | 64 (21.3%) | |
| OTHER | 1 (1.0%) | 2 (1.0%) | 3 (1.0%) | |
| N | 101 | 199 | 300 | |
| HEIGHT (cm) | | | | |
| MEAN (SE) | 169.2 (0.99) | 167.1 (0.70) | 167.8 (0.58) | 0.081 [a] |
| MEDIAN | 167.3 | 166.4 | 167.0 | |
| RANGE | 151 - 198 | 135 - 198 | 135 - 198 | |
| N | 100 | 199 | 299 | |
| WEIGHT (kg) | | | | |
| MEAN (SE) | 86.8 (1.82) | 82.2 (1.26) | 83.7 (1.04) | 0.037 [a] |
| MEDIAN | 85.8 | 80.0 | 82.0 | |
| RANGE | 49 - 140 | 45 - 133 | 45 - 140 | |
| N | 101 | 199 | 300 | |
| TEMPERATURE (°C) | | | | |
| MEAN (SE) | 36.6 (0.04) | 36.6 (0.03) | 36.6 (0.02) | 0.404 [a] |
| MEDIAN | 36.6 | 36.6 | 36.6 | |
| RANGE | 35 - 37 | 36 - 38 | 35 - 38 | |
| N | 101 | 199 | 300 | |
| SYSTOLIC BP (mmHg) [d] | | | | |
| MEAN (SE) | 141.1 (2.56) | 135.0 (1.43) | 137.1 (1.29) | 0.024 [a] |
| MEDIAN | 138.0 | 135.0 | 136.5 | |
| RANGE | 99 - 229 | 94 - 190 | 94 - 229 | |
| N | 101 | 199 | 300 | |
| DIASTOLIC BP (mmHg) [d] | | | | |
| MEAN (SE) | 81.2 (1.38) | 76.2 (0.74) | 77.9 (0.69) | 0.001 [a] |
| MEDIAN | 81.0 | 76.0 | 78.0 | |
| RANGE | 53 - 120 | 50 - 103 | 50 - 120 | |
| N | 101 | 199 | 300 | |
| PULSE RATE (beats/min) | | | | |
| MEAN (SE) | 72.4 (1.14) | 73.4 (0.86) | 73.1 (0.69) | 0.468 [a] |
| MEDIAN | 72.0 | 72.0 | 72.0 | |
| RANGE | 49 - 112 | 48 - 128 | 48 - 128 | |
| N | 101 | 199 | 300 | |
| RESPIRATION (breaths/min) | | | | |
| MEAN (SE) | 15.9 (0.14) | 16.1 (0.11) | 16.1 (0.09) | 0.333 [a] |
| MEDIAN | 16.0 | 16.0 | 16.0 | |
| RANGE | 12 - 20 | 12 - 22 | 12 - 22 | |
| N | 101 | 199 | 300 | |
| TYPE OF SURGERY | | | | |
| ABDOMINAL | 54 (53.5%) | 102 (51.3%) | 156 (52.0%) | 0.068 [c] |
| ORTHOPEDIC | 43 (42.6%) | 96 (48.2%) | 139 (46.3%) | |
| OTHER | 4 (4.0%) | 1 (0.5%) | 5 (1.7%) | |
| N | 101 | 199 | 300 | |
| TYPE OF ANESTHESIA | | | | |
| GENERAL ONLY | 80 (79.2%) | 152 (76.4%) | 232 (77.3%) | 0.844 [c] |
| SPINAL ONLY | 19 (18.8%) | 40 (20.1%) | 59 (19.7%) | |
| GENERAL AND SPINAL | 2 (2.0%) | 7 (3.5%) | 9 (3.0%) | |
| N | 101 | 199 | 300 | |

[a] The one-way analysis of variance was used to compare differences between the two treatment groups.
[b] Treatment comparison was statistically analyzed using the chi-square test.
[c] Treatment comparison was statistically analyzed using the Fisher's exact test.
[d] Blood pressures were taken while the subject was either supine or sitting.

Study ROX-2005-01 (Source: Module 5, Vol. 17)

| | PLACEBO | 30 MG IN KETOROLAC TOTAL | | P-VALUE |
|-------------------------------------|--------------|--------------------------|--------------|-----------|
| NUMBER OF SUBJECTS | 107 | 214 | 321 | |
| AGE | | | | |
| MEAN (SE) | 46.4 (0.87) | 45.6 (0.58) | 45.9 (0.48) | 0.451 [a] |
| MEDIAN | 46.8 | 45.5 | 45.7 | |
| RANGE | 28 - 70 | 22 - 64 | 22 - 70 | |
| N | 107 | 214 | 321 | |
| SEX | | | | |
| MALE | 4 (3.7%) | 8 (3.7%) | 12 (3.7%) | 1.000 [b] |
| FEMALE | 103 (96.3%) | 206 (96.3%) | 309 (96.3%) | |
| N | 107 | 214 | 321 | |
| ETHNICITY | | | | |
| NON-HISPANIC AND NON-LATINO | 88 (82.2%) | 182 (85.0%) | 270 (84.1%) | 0.517 [b] |
| HISPANIC OR LATINO | 19 (17.8%) | 32 (15.0%) | 51 (15.9%) | |
| N | 107 | 214 | 321 | |
| RACE | | | | |
| AMERICAN INDIAN OR ALASKA NATIVE | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0.549 [c] |
| ASIAN | 9 (8.4%) | 24 (11.2%) | 33 (10.3%) | |
| BLACK OR AFRICAN AMERICAN | 11 (10.3%) | 23 (10.7%) | 34 (10.6%) | |
| NATIVE HAWAIIAN OR OTHER PACIFIC IS | 11 (10.3%) | 12 (5.6%) | 23 (7.2%) | |
| WHITE | 76 (71.0%) | 154 (72.0%) | 230 (71.7%) | |
| OTHER | 0 (0.0%) | 1 (0.5%) | 1 (0.3%) | |
| N | 107 | 214 | 321 | |
| HEIGHT (CM) | | | | |
| MEAN (SE) | 165.1 (0.84) | 164.0 (0.50) | 164.4 (0.43) | 0.253 [a] |
| MEDIAN | 165.0 | 164.0 | 164.0 | |
| RANGE | 147 - 191 | 145 - 188 | 145 - 191 | |
| N | 107 | 214 | 321 | |
| WEIGHT (KG) | | | | |
| MEAN (SE) | 79.7 (1.71) | 77.0 (1.29) | 77.9 (1.03) | 0.223 [a] |
| MEDIAN | 79.8 | 73.0 | 74.8 | |
| RANGE | 49 - 126 | 45 - 141 | 45 - 141 | |
| N | 107 | 214 | 321 | |
| TEMPERATURE (CENTIGRADE) | | | | |
| MEAN (SE) | 36.6 (0.04) | 36.7 (0.03) | 36.6 (0.02) | 0.544 [a] |
| MEDIAN | 36.7 | 36.7 | 36.7 | |
| RANGE | 36 - 38 | 35 - 38 | 35 - 38 | |
| N | 105 | 209 | 314 | |
| SYSTOLIC BP (MMHG) [d] | | | | |
| MEAN (SE) | 126.6 (1.73) | 126.1 (1.27) | 126.3 (1.02) | 0.847 [a] |
| MEDIAN | 124.0 | 124.5 | 124.0 | |
| RANGE | 96 - 185 | 90 - 220 | 90 - 220 | |
| N | 107 | 214 | 321 | |
| DIASTOLIC BP (MMHG) [d] | | | | |
| MEAN (SE) | 72.4 (1.25) | 73.1 (0.83) | 72.9 (0.69) | 0.547 [a] |
| MEDIAN | 72.0 | 73.0 | 73.0 | |
| RANGE | 34 - 101 | 40 - 120 | 34 - 120 | |
| N | 107 | 214 | 321 | |
| PULSE RATE (BEATS/MIN) | | | | |
| MEAN (SE) | 75.2 (1.10) | 78.3 (0.88) | 77.3 (0.70) | 0.034 [a] |
| MEDIAN | 76.0 | 77.0 | 77.0 | |
| RANGE | 48 - 113 | 54 - 124 | 48 - 124 | |
| N | 107 | 214 | 321 | |
| RESPIRATION (BREATHS/MIN) | | | | |
| MEAN (SE) | 16.7 (0.20) | 17.1 (0.15) | 17.0 (0.12) | 0.189 [a] |
| MEDIAN | 16.0 | 16.0 | 16.0 | |
| RANGE | 8 - 22 | 10 - 24 | 8 - 24 | |
| N | 105 | 213 | 318 | |
| TYPE OF SURGERY | | | | |
| ABDOMINAL | 107 (100.0%) | 213 (99.5%) | 320 (99.7%) | 1.000 [c] |
| OTHER | 0 (0.0%) | 1 (0.5%) | 1 (0.3%) | |
| N | 107 | 214 | 321 | |
| TYPE OF ANESTHESIA | | | | |
| GENERAL ONLY | 105 (98.1%) | 211 (98.6%) | 316 (98.4%) | 0.738 [c] |
| SPINAL ONLY | 0 (0.0%) | 1 (0.5%) | 1 (0.3%) | |
| OTHER ONLY | 1 (0.9%) | 1 (0.5%) | 2 (0.6%) | |
| GENERAL AND SPINAL | 1 (0.9%) | 0 (0.0%) | 1 (0.3%) | |
| GENERAL AND OTHER | 0 (0.0%) | 1 (0.5%) | 1 (0.3%) | |
| N | 107 | 214 | 321 | |

[a] The 2-way analysis of variance with factors for treatment and center was used to compare differences between the two treatment groups. The center-by-treatment interaction term was not included in the model since it was not statistically significant ($p > 0.100$).

[b] Treatment comparison was statistically analyzed using the chi-square test.

[c] Treatment comparison was statistically analyzed using the Fisher's exact test.

[d] BP was taken while supine or sitting. See Table 26 for a summary of vital signs collected at predose and follow-up.

| Linked Applications | Submission Type/Number | Sponsor Name | Drug Name / Subject |
|---------------------|------------------------|--------------|---------------------------------------|
| NDA 22382 | ORIG 1 | | KETOROLAC TROMETHAMINE NASAL SPRAY |

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

/s/

FENG LI
08/07/2009

THOMAS J PERMUTT
08/10/2009
concur

DIONNE L PRICE
08/10/2009
Concur

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 22-382 Applicant: Roxro Pharma, Inc. Stamp Date:
Drug Name: Ketorolac NDA/BLA Type: S Indication:
Tromethamine Nasal Spray

On **initial** overview of the NDA/BLA application for RTF:

| | Content Parameter for RTF | Yes | No | NA | Comments |
|----|--|------------|-----------|-----------|--|
| 1A | Paper Submission: Index is sufficient to locate necessary reports, tables, data, etc. | X | | | |
| 1B | Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc. | | | | |
| 2 | ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.) | X | | | |
| 3 | Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated. | X | | | |
| 4 | Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets). | | | X | During filing review, data sets are not located in EDR |

THE STATISTICAL SECTION OF THE APPLICATION [IS/IS NOT] FILEABLE:

This NDA from a statistical perspective is fileable.

| Content Parameter (possible review concerns for 74-day letter) | Yes | No | NA | Comment |
|---|------------|-----------|-----------|--|
| Designs utilized are appropriate for the indications requested. | X | | | |
| Endpoints and methods of analysis are specified in the protocols/statistical analysis plans. | X | | | |
| Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available. | | | X | |
| Appropriate references for novel statistical methodology (if present) are included. | | | X | |
| Safety data organized to permit analyses across clinical trials in the NDA/BLA. | | | X | During filing, the datasets are not in EDR |
| Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate. | | | | |

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Requests to the Applicant for the 74-day letter or as an information request are listed here.

1. You submitted SDTM datasets which generally conform to a specific format. The format may not include variables denoting the efficacy assessments from the case report forms. For Studies 2001-03, 2003-02, 2003-05, and 2005-01, we therefore request that you submit raw datasets for all efficacy assessments taken from the case report form and analysis-ready datasets which should be derived from the raw data. For each study, at least two analysis-ready datasets should be submitted. One should contain subject-level efficacy (i.e. one record per subject), and another analysis-ready dataset should contain assessment-level efficacy (i.e. one record per subject per assessment time -- example, subject 1, pain intensity difference at time 0 is 5, pain intensity difference at time 0.5 hours is 4, etc...). The analysis-ready datasets should include all derived variables used to generate the results presented in the study reports. Most importantly, your primary and secondary endpoints should be included.

Provide a data definition file for these datasets with detailed information on how the variables are derived (i.e. formula) and which variables in the raw data or case report form were used in the calculation of the variables.

2. Perform analyses on SPID 24 and SPID 48 using the same analytical approaches applied to your primary endpoint (i.e. SPID 6)

Reviewing Statistician

Date

Supervisor/Team Leader

Date

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

/s/

Joan Buenconsejo
2/25/2009 12:24:34 PM
BIOMETRICS

Dionne Price
3/3/2009 03:40:34 PM
BIOMETRICS